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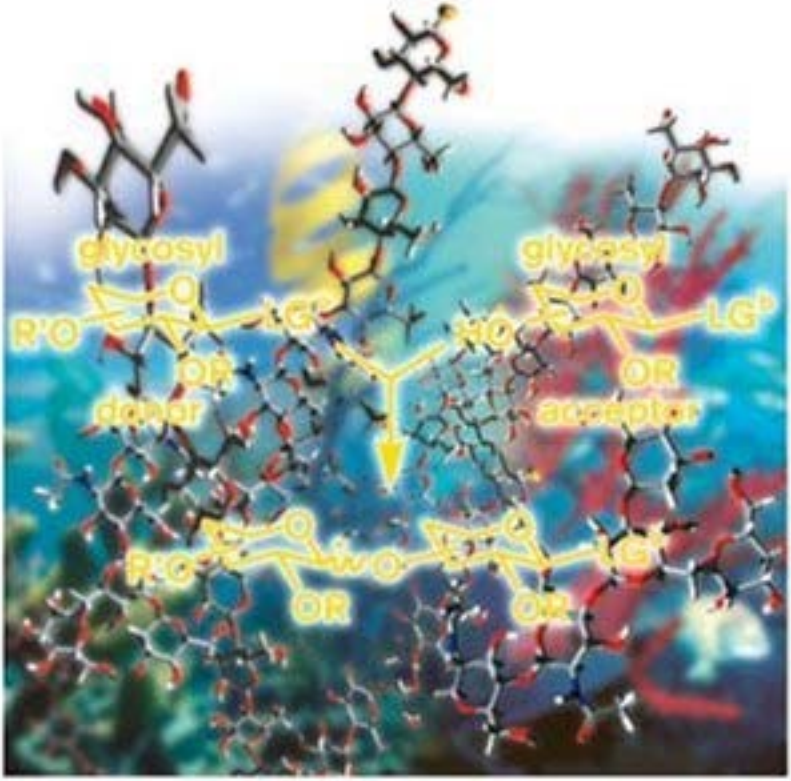
Handbook of Chemical Glycosylation

Advances in Stereoselectivity and Therapeutic Relevance



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Contents

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Preface

Carbohydrates are the most abundant biomolecules on Earth. Although information about these fascinating natural compounds is not yet complete, we have already learned about some crucial aspects of the carbohydrate involvement in damaging cellular processes such as bacterial and viral infections, development and growth of tumors, metastasis, septic shock that are directly associated with deadly diseases of the twenty-first century, such as AIDS, cancer, meningitis and septicemia. The tremendous medicinal potential of glycostructures has already been acknowledged by the development of synthetic carbohydrate-based vaccines and therapeutics. The elucidation of the mechanisms of carbohydrate involvement in disease progression would be further improved if we could rely on the detailed knowledge of the structure, conformation and properties of the carbohydrate molecules. Therefore, the development of effective methods for the isolation and synthesis of complex carbohydrates has become critical for the field of glycosciences. Although significant improvements of the glycoside and oligosaccharide synthesis have already emerged, a variety of synthetic targets containing challenging glycosidic linkages cannot yet be directly accessed.

A vast majority of biologically and therapeutically active carbohydrates exist as polysaccharides (cellulose, chitin, starch, glycogen) or complex glycoconjugates (glycolipids, glycopeptides, glycoproteins) in which monosaccharide units are joined via glycosidic bonds. This linkage is formed by a glycosylation reaction, most commonly a promoter-assisted nucleophilic displacement of the leaving group (LG) of the glycosyl donor with the hydroxyl moiety of the glycosyl acceptor. Other functional groups on both the donor and the acceptor are temporarily masked with protecting groups (P). These reactions are most commonly performed in the presence of an activator: promoter or catalyst. As the new glycosidic linkage creates a chirality center, particular care has to be taken with regard to the stereoselectivity. Although in the natural environment specificity and selectivity of an enzyme ensure the stereoselectivity of glycosylation, synthesis of synthetic carbohydrate faces a major challenge in comparison to the synthesis of other natural biopolymers, that is proteins and nucleic acids.

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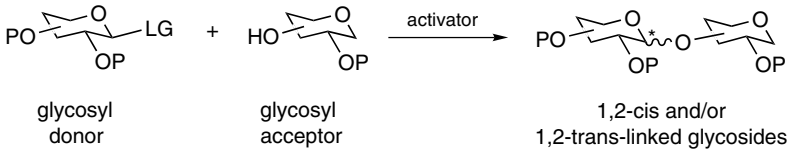

Although mechanistic studies of the glycosylation reaction are scarce, certain conventions have already been established. Pioneering mechanistic work of Lemieux was enriched by recent studies by Bols, Boons, Crich, Gin, Kochetkov, Schmidt, Whitfield and others. 1,2-*trans* Glycosides are often stereoselectively obtained with the assistance of the 2-acyl neighboring participating group. In case of ether-type nonparticipating substituents, the glycosylation proceeds with poorer stereocontrol that results in mixtures of diastereomers, which makes the synthesis of 1,2-*cis* glycosides a notable challenge.

Since the first attempts at the turn of the twentieth century, enormous progress has been made in the area of the chemical *O*-glycoside synthesis. However, it is only in the past two–three decades that the scientific world has witnessed a dramatic improvement in the methods used for glycosylation. Recently, an abundance of glycosyl donors that can be synthesized under mild reaction conditions and that are sufficiently stable toward purification, modification and storage have been developed. Convergent synthetic strategies enabling convenient and expeditious assembly of oligosaccharides from properly protected building blocks with the minimum synthetic steps have also become available.

As it stands, many of the recent developments in the area of chemical glycosylation still remain compromised when applied to the stereoselective synthesis of difficult glycosidic linkages. These special cases include the synthesis of 1,2-*cis* glycosides, especially β-mannosides and *cis*-furanosides, 2-amino-2-deoxyglycosides, 2-deoxyglycosides and α-sialosides. In spite of the considerable progress and the extensive effort in this field, no universal method for the synthesis of targets containing these types of linkages has yet emerged. Therefore, these difficult cases will be discussed individually.

This book summarizes the recent advances in the area of chemical glycosylation and provides updated information regarding the current standing in the field of synthetic carbohydrate chemistry. An expansive array of methods and strategies available to a modern synthetic carbohydrate chemist is discussed. The first chapter (Chapter 1) discusses major principles of chemical glycosylation, reaction mechanisms, survey methods for glycosylation and factors influencing the reaction outcome, as well as describes the strategies for expeditious synthesis of oligosaccharide. Each subsequent chapter discusses a certain class of glycosyl donors. Methodologies developed to date are classified and discussed based on the type of the anomeric leaving group: halogens (Chapter 2), oxygen-based derivatives (Chapter 3) and sulfur/selenium-based derivatives (Chapter 4). Bicyclic compounds, 1,2-dehydro derivatives, miscellaneous glycosyl donors and indirect synthetic methods are discussed in Chapter 5. Each chapter will discuss the following aspects of a particular methodology or approach, wherever it is applicable:

(1) Introduction (relevant to this class of glycosyl donors/methods)
(2) Synthesis of glycosyl donor
(3) Glycosylation (major activators/promoters, particulars of the reaction mechanism, examples of both 1,2-*cis* and 1,2-*trans* glycosylations)
(4) Application to target/total synthesis (oligosaccharides, glycoconjugates, natural products)
(5) Special topics (synthesis of β-mannosides, furanosides, sialosides, glycosides of aminosugars and deoxysugars, if applicable)
(6) Conclusions and future directions
(7) Typical experimental procedures
(8) References.

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1
General Aspects of the Glycosidic Bond Formation

Alexei V. Demchenko

1.1
Introduction

Since the first attempts at the turn of the twentieth century, enormous progress has been made in the area of the chemical synthesis of *O*-glycosides. However, it was only in the past two decades that the scientific world had witnessed a dramatic improvement the methods used for chemical glycosylation. The development of new classes of glycosyl donors has not only allowed accessing novel types of glycosidic linkages but also led to the discovery of rapid and convergent strategies for expeditious oligosaccharide synthesis. This chapter summarizes major principles of the glycosidic bond formation and strategies to obtain certain classes of compounds, ranging from glycosides of uncommon sugars to complex oligosaccharide sequences.

1.2
Major Types of *O*-Glycosidic Linkages

There are two major types of *O*-glycosides, which are, depending on nomenclature, most commonly defined as α- and β-, or 1,2-*cis* and 1,2-*trans* glycosides. The 1,2-*cis* glycosyl residues, α-glycosides for D-glucose, D-galactose, L-fucose, D-xylose or β-glycosides for D-mannose, L-arabinose, as well as their 1,2-*trans* counterparts (β-glycosides for D-glucose, D-galactose, α-glycosides for D-mannose, etc.), are equally important components in a variety of natural compounds. Representative examples of common glycosides are shown in Figure 1.1. Some other types of glycosides, in particular 2-deoxyglycosides and sialosides, can be defined neither as 1,2-*cis* nor as 1,2-*trans* derivatives, yet are important targets because of their common occurrence as components of many classes of natural glycostructures.

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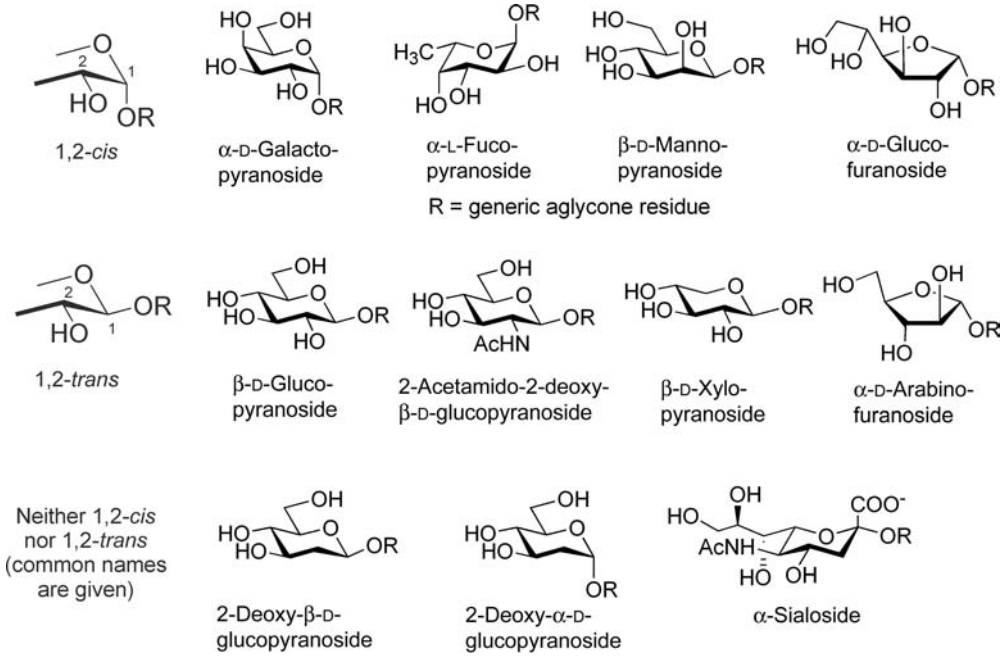


Figure 1.1 Common examples of *O*-glycosides.

1.3 Historical Development: Classes of Glycosyl Donors

The first reactions performed by Michael (synthesis of aryl glycosides from glycosyl halides) [1] and Fischer (synthesis of alkyl glycosides from hemiacetals) [2] at the end of the nineteenth century showed the complexity of the glycosylation process. The discovery of the first controlled, general glycosylation procedure involving the nucleophilic displacement of chlorine or bromine at the anomeric center is credited to Koenigs and Knorr [3]. The glycosylations were performed in the presence of Ag_2CO_3, which primarily acted as an acid (HCl or HBr) scavenger. At that early stage, glycosylations of poorly nucleophilic acceptors such as sugar hydroxyls were sluggish and inefficient; hence, even the synthesis of disaccharides represented a notable challenge. The first attempts to solve this problem gave rise to the development of new catalytic systems that were thought to be actively involved in the glycosylation process [4]. Thus, Zemplen and Gerecs [5] and, subsequently, Helferich and Wedermeyer [6] assumed that the complexation of the anomeric bromides or chlorides with more reactive, heavy-metal-based catalysts would significantly improve their leaving-group ability. This approach that has become a valuable expansion of the classic Koenigs–Knorr method made it possible to replace Ag_2CO_3 or Ag_2O by more active mercury(II) salt catalysts. The early attempts

to improve the glycosylation process have revealed the necessity to find a delicate balance between the reactivity and stereoselectivity [7,8]. Indeed, it was noted that faster reactions often result in a decreased stereoselectivity. At around the same time, the first attempts to involve other classes of anomeric leaving groups (LGs) resulted in the investigation of peracetates as glycosyl donors [9].

Seminal work of Lemieux [10] and Fletcher and coworkers [11,12] has led to the appreciation that the reactivity of the glycosyl halides and the stereoselectivity of glycosylation are directly correlated to the nature of the protecting groups, especially at the neighboring C-2 position. From early days, it has been acknowledged that peracylated halides often allow stereoselective formation of 1,2-*trans* glycosides. Later, this phenomenon was rationalized by the so-called participatory effect of the neighboring acyl substituent at C-2. Although occasionally substantial amounts of 1,2-*cis* glycosides were obtained even with 2-acylated glycosyl donors, the purposeful 1,2-*cis* glycosylations were best achieved with a nonparticipating ether group at C-2, such as methyl or benzyl. Further search for suitable promoters for the activation of glycosyl halides led to the discovery of Ag-silicate that proved to be very efficient for direct β-mannosylation, as these reactions often proceed via a concerted S_N2 mechanism [13,14].

For many decades classic methods, in which anomeric bromides, chlorides, acetates or hemiacetals were used as glycosyl donors, had been the only procedure for the synthesis of a variety of synthetic targets ranging from simple glycosides to relatively complex oligosaccharides (Figure 1.2). Deeper understanding of the reaction mechanism, driving forces and principles of glycosylation have stimulated the development of other methods for glycosylation, with the main effort focusing on the development of new anomeric leaving groups [15,16]. During the 1970s to early 1980s, a few new classes of glycosyl donors were developed. The following compounds are only the most representative examples of the first wave of the leaving-group development: thioglycosides by Ferrier *et al.* [17], Nicolaou *et al.* [18], Garegg *et al.* [19] and others [20]; cyanoethylidene and orthoester derivatives by Kochetkov and coworkers [21,22]; *O*-imidates by Sinay and coworkers [23] and Schmidt and Michel [24]; thioimidates including *S*-benzothiazolyl derivatives by Mukaiyama *et al.* [25]; thiopyridyl derivatives by Hanessian *et al.* [26] and Woodward *et al.* [27] and glycosyl fluorides by Mukaiyama *et al.* [28] (Figure 1.2). Many glycosyl donors introduced during that period gave rise to excellent complimentary glycosylation methodologies. Arguably, trichloroacetimidates [29,30], thioglycosides [31–33] and fluorides [34,35] have become the most common glycosyl donors nowadays.

A new wave of methods arose in the end of the 1980s, among which were glycosyl donors such as glycosyl acyl/carbonates [36–38], thiocyanates [39], diazirines [40], xanthates [41], glycals [42,43], phosphites [44,45], sulfoxides [46], sulfones [47], selenium glycosides [48], alkenyl glycosides [49–51] and heteroaryl glycosides [52] (Figure 1.2). These developments were followed by a variety of more recent methodologies and improvements, among which are glycosyl iodides [53], phosphates [54], Te-glycosides [55], sulfonylcarbamates [56], disulfides [57], 2-(hydroxycarbonyl) benzyl glycosides [58] and novel thio- [59,60] and *O*-imidates [61,62] (Figure 1.2). In

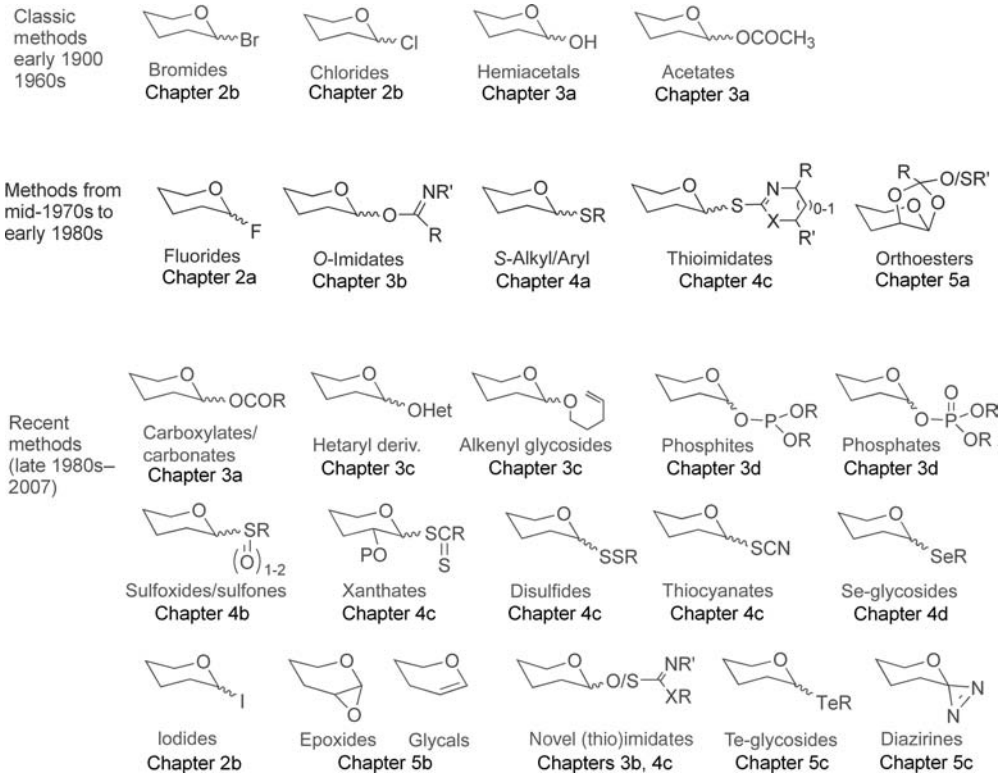
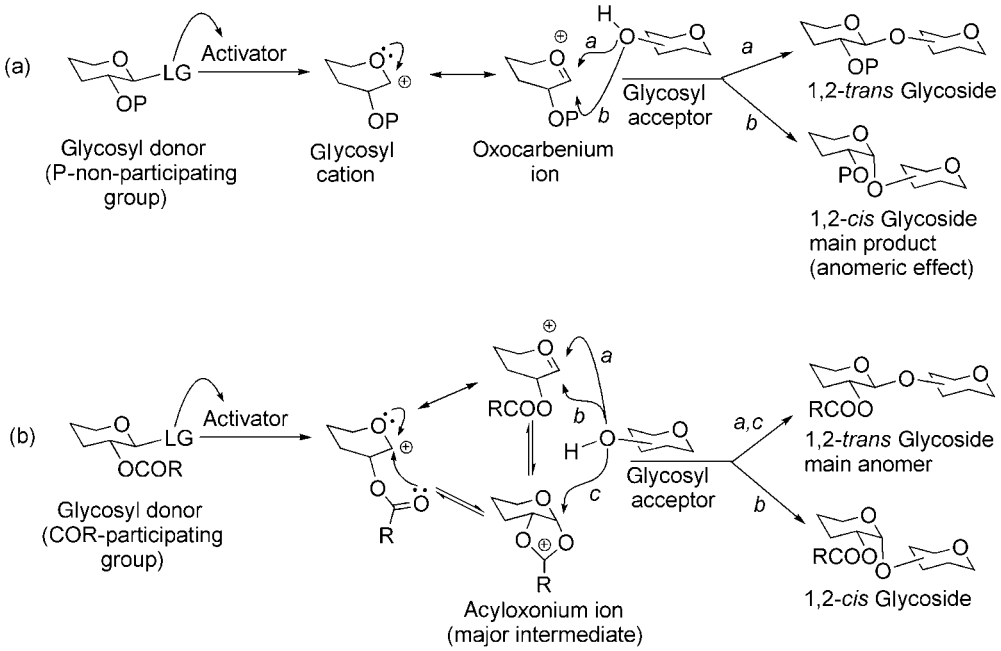


Figure 1.2 Survey of glycosyl donors.

addition, a variety of new recent methodologies bring the use of classic glycosyl donors such as hemiacetals to entirely different level of flexibility and usefulness [63]. These innovative concepts will be discussed in the subsequent chapters dealing with particular classes of clycosyl donors..

1.4 General Reaction Mechanism

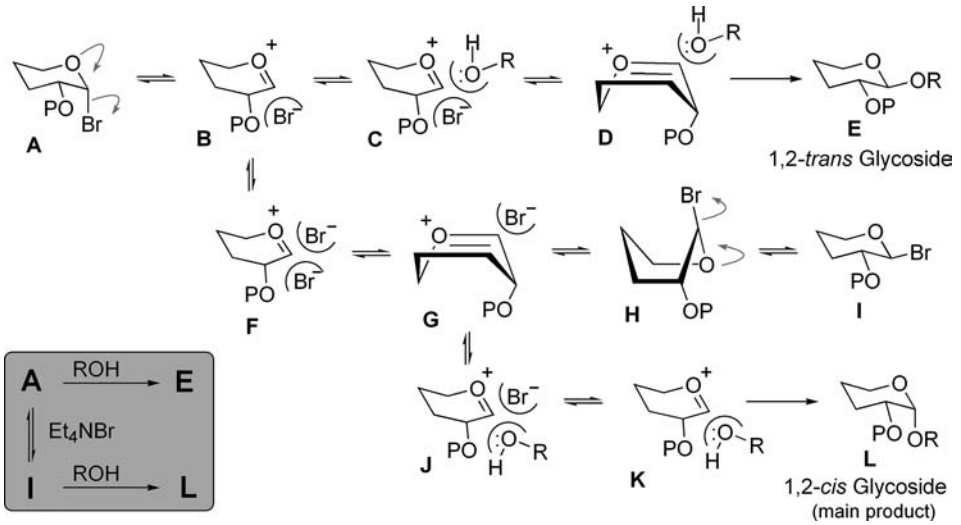
Detailed glycosylation mechanism has not been elucidated as yet; therefore, speculations and diagrams presented herein are a commonly accepted prototype of the glycosylation mechanism. Most commonly, the glycosylation reaction involves nucleophilic displacement at the anomeric center. As the reaction takes place at the secondary carbon atom with the use of weak nucleophiles (sugar acceptors), it often follows a unimolecular S_N1 mechanism. Glycosyl donors bearing a nonparticipating and a participating group will be discussed separately (Scheme 1.1a and b, respectively). In most cases, an activator (promoter or catalyst) assisted departure of the anomeric leaving group results in the formation of the glycosyl cation. The only



Scheme 1.1

possibility to intramolecularly stabilize glycosyl cation formed from the glycosyl donor bearing a non-participating group is by resonance from O-5 that results in oxocarbenium ion (Scheme 1.1a). The most commonly applied nonparticipating groups are benzyl (OBn) for neutral sugars and azide (N_3) for 2-amino-2-deoxy sugars; however, other moieties have also been occasionally used. The anomeric carbon of either resonance contributors is sp^2 hybridized; hence, the nucleophilic attack would be almost equally possible from either the top (*trans*, β- for the D-gluco series) or the bottom face (*cis*, α-) of the ring. Even though the α-product is thermodynamically favored because of the so-called anomeric effect (discussed in the subsequent section) [64], a substantial amount of the kinetic β-linked product is often obtained owing to the irreversible character of glycosylation of complex aglycones. Various factors such as temperature, protecting groups, conformation, solvent, promoter, steric hindrance or leaving groups may influence the glycosylation outcome (discussed below) [65,66].

1,2-*trans* Glycosidic linkage can be stereoselectively formed with the use of anchimeric assistance of a neighboring participating group, generally an acyl moiety such as *O*-acetyl (Ac), *O*-benzoyl (Bz), 2-phthalimido (NPhth) and so on [67–69]. These glycosylations proceed primarily via a bicyclic intermediate, the acyloxonium ion (Scheme 1.1b), formed as a result of the activator-assisted departure of the leaving group followed by the intramolecular stabilization of the glycosyl cation. In this case, the attack of a nucleophile (alcohol, glycosyl acceptor) is only possible from the top face of the ring (pathway c), therefore allowing stereoselective formation of a 1,2-*trans* glycoside. Occasionally, substantial amounts of 1,2-*cis*-linked products are also



Scheme 1.2

formed, most often when unreactive alcohols are used as the substrates and/or poorly nucleophilic participatory substituents are present at C-2. In these cases, glycosylation assumingly proceeds via oxocarbenium ion, via pathways a and b (Scheme 1.1b), resulting in the formation of 1,2-*trans* and 1,2-*cis* glycosides, respectively, or most commonly mixtures thereof.

Seminal work by Lemieux on the halide-ion-catalyzed glycosidation reaction involved extensive theoretical studies that gave rise to a more detailed understanding of the reaction mechanism [70]. Thus, it was postulated that a rapid equilibrium could be established between a relatively stable α-halide **A** and its far more reactive β-counterpart **I** by the addition of tetraalkylammonium bromide (Et_4NBr, Scheme 1.2). In this case, a glycosyl acceptor (ROH) would preferentially react with the more reactive glycosyl donor (**I**) in an S_N2 fashion, possibly via the tight ion-pair complex **K**, providing the α-glycoside **L**. It is likely that the energy barrier for a nucleophilic substitution **I** → **L** (formation of the α-glycoside) is marginally lower than that for the reaction **A** → **E** (formation of a β-glycoside). If the difference in the energy barrier were sufficient, it should be possible to direct the reaction toward the exclusive formation of α-anomers.

Therefore, to obtain complete stereoselectivity, the entire glycosylation process has to be performed in a highly controlled manner. In this particular case, the control is achieved by the use of extremely mild catalyst (R_4NBr), although very reactive substrates and prolonged reaction at times are required.

Other common approaches to control the stereoselectivity of glycosylation will be discussed in the subsequent sections. In addition to the apparent complexity of the glycosidation process, there are other competing processes that cannot be disregarded. These reactions often cause the compromised yields of the glycosylation products and further complicate the studies of the reaction mechanism.

Elimination, substitution (formation of unexpected substitution products or hydrolysis at the anomeric center), cyclization (inter- and intramolecular orthoesterification), migration and redox are only a few to mention [71].

1.5
Anomeric Effects

A basic rule of conformational analysis known from the introductory organic chemistry is that an *equatorial* substituent of cyclic six-membered hydrocarbons is energetically favored. Hence, it is more stable owing to 1,3-diaxial interactions that would have occurred if a large substituent were placed in the *axial* position (Figure 1.3). For sugars, this rule is only applicable to hemiacetals (1-hydroxy derivatives) that are stabilized in β-orientation via intramolecular hydrogen-bond formation with O-5. Other polar substituents such as halide, OR or SR attached to the anomeric center of pyranoses/pyranosides prefer the axial orientation, which would be exclusive if the equilibrium at the anomeric center could be achieved. This phenomenon, which was first observed by Edward [72] and defined as *anomeric effect* by Lemieux [73], is partially responsible for the stereochemical outcome of processes taking place at the anomeric center of sugars [64,74,75].

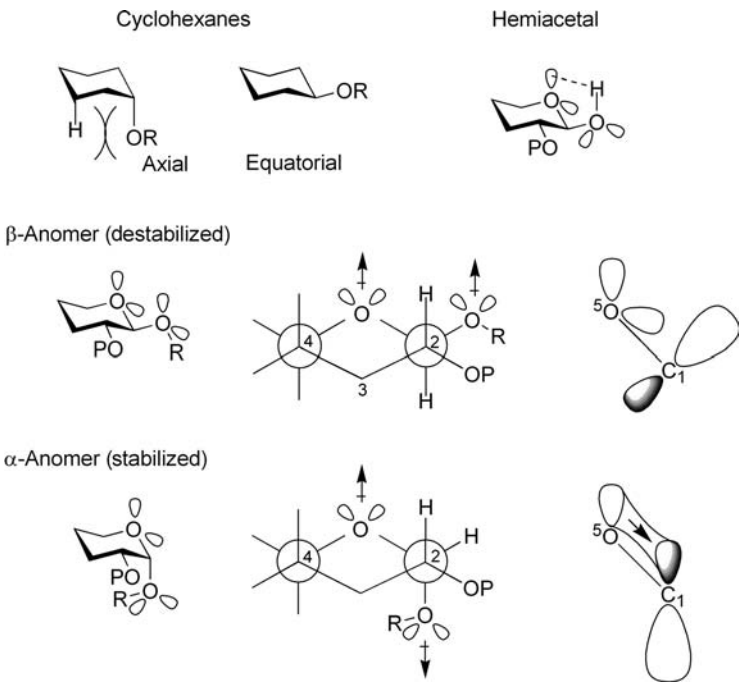


Figure 1.3 Anomeric effect.

What are the origins of the anomeric effect, sometimes referred to as *endo*-anomeric effect? In this context, the so-called *exo*-anomeric effect dealing with the stabilization of the β-anomer is of somewhat lesser influence on the overall process and will not be discussed herein [64]. One factor is that the substituent on the atom bonded to the ring at C-1 has lone-pair electrons, which would have repulsive interactions with those of the ring oxygen (O-5) if the anomeric substituent is in the equatorial position (β-position for D-sugars in $^4C_1$ conformation) but not if it is in the axial position (Figure 1.3). In addition, an electron-withdrawing axial substituent (α-anomer for D-sugars in $^4C_1$ conformation) is stabilized via hyperconjugation owing to the periplanar orientation of both nonbonding orbital of O-5 and antibonding orbital of C-1. This does not occur with the β-anomer, as the nonbonding orbital of O-5 and antibonding orbital of C-1 are in different planes and therefore are unable to interact.

1.6 Stereoselectivity of Glycosylation

As noted above, it is a general experience of carbohydrate synthesis that stereoselective preparation of 1,2-*cis* glycosides is more demanding than that of 1,2-*trans* glycosides. The formation of 1,2-*trans* glycosides is strongly favored by the neighboring-group participation (generation of intermediate acyloxonium ion). Typically, the use of a participating substituent at C-2 is sufficient to warrant stereoselective 1,2-*trans* glycosylation.

One of the factors affecting the stereochemical outcome of glycosidation of glycosyl donors bearing a nonparticipating substituent at C-2 is the anomeric effect, which favors α-glycoside formation (1,2-*cis* for the D-gluco series). However, because of the irreversible character of glycosylation, the role of the anomeric effect is diminished and other factors affecting the orientation of the new glycosidic bond (discussed below) often come to the fore. Although variation of reaction conditions or structural elements of the reactants may lead to excellent 1,2-*cis* stereoselectivity, no successful comprehensive method for 1,2-*cis* glycosylation has emerged as yet.

1.6.1 Structure of the Glycosyl Donor

1.6.1.1 Protecting Groups

The most powerful impact on the stereoselectivity is produced from the neighboring group at C-2. Neighboring-group participation is one of the most powerful tools to direct stereoselectivity toward the formation of a 1,2-*trans*-linked product. The neighboring substituent at C-2 is also responsible for the 'armed–disarmed' chemoselective glycosylation strategy [76]. The effects of the remote substituents are of lesser importance; however, there is strong evidence that a substituent at C-6 position may influence the stereochemical outcome of glycosylation dramatically. Although experimental proof has not emerged as yet, a possibility for the long-range 6-*O*-acyl or carbonate

group assistance resulting in the preferential formation of α-glucosides cannot be overruled [77–81]. It was also found that the steric bulkiness or strong electron-withdrawing properties of a substituent at C-6 are beneficial for 1,2-*cis* glucosylation, most likely because of shielding (sterically or electronically) the top face of the ring and, therefore, favoring the nucleophilic attack from the opposite side [14,82–88].

Although the effect of the C-6 substituent was found to be of minor importance for the derivatives of the D-galacto series [89], a remote effect is sufficiently strong when a participating moiety is present at C-4 [90,91]. Thus, the use of *p*-methoxybenzoyl (anisoyl) [91] and diethylthiocarbamoyl [81] groups was found to be exceptionally beneficial for the formation of α-galactosides. Similar effects (including C-3 participation) were also detected for the derivatives of the L-fuco [92,93], L-rhamno [94], D-manno and D-gluco [14,82,95] series [96]. It was noted that when the unprotected hydroxyl is present at C-4 of the sulfamidogalacto donor, the expected β-glycosyl formation occurs. However, when the hydroxyl group is blocked with benzyl or acyl, the process unexpectedly favors α-glycoside formation. This phenomenon was rationalized via the formation of the intramolecular hydrogen bonding (C4−O−H···O−C5), destabilizing oxocarbenium ion contribution to the reaction mechanism that favors α-glycosylation (pathway b, Scheme 1.1a). Torsional effects induced by the cyclic acetal protecting groups may also strongly affect the stereoselectivity at the anomeric center; however, these effects remain unpredictable at this stage [88,97–99].

1.6.1.2 **Leaving Group**

There are a large number of publications describing the comparison of various glycosylation methods applied for particular targets. However, only few principles could be reliably outlined. It has been unambiguously demonstrated that halides activated in the presence of a halide ion (from, e.g. Bu_4NBr) often provide the highest ratios of α-/β-glycosides [100–104]. Since in most cases the glycosylation reactions proceed via unimolecular S_N1 mechanism, the orientation of the leaving group at the anomeric center is of lesser importance. However, the glycosylation reactions occasionally proceed via bimolecular S_N2 mechanism with the inversion of the anomeric configuration. In this context, glycosyl donors with 1,2-*cis* orientation form 1,2-*trans* glycosides: for example glycosyl halides with insoluble catalysts (also used for β-mannosylation) [105], α-imidates in the presence of boron trifluoride etherate (BF_3–Et_2O) at low temperature [106] and 1,2-anhydro sugars [107]. Conversely, 1,2-*trans*-oriented glycosyl donors stereospecifically afford 1,2-*cis* glycosides, for example highly reactive β-glucosyl halides [70], glycosyl thiocyanates [39,108] and anomeric triflates formed *in situ* were found superior for the synthesis of β-mannosides [109,110].

1.6.2
Structure of the Glycosyl Acceptor

1.6.2.1 **Position of the Hydroxyl**

Alcohol reactivity is typically inversely correlated with the 1,2-*cis* stereoselectivity – the most reactive hydroxyls give the lowest α-/β-ratios – the stronger the nucleophile,

the faster the reaction, and hence the more difficult it is to control. Regarding the sugar or aliphatic glycosyl acceptors, the general rule normally states that glycosylation of more reactive primary hydroxyl provides poorer stereoselectivity in comparison to that when the secondary hydroxyls are involved [111]. The same principles are applicable for the synthesis of glycopeptides; thus, the glycosylation of the secondary hydroxyl of threonine typically gives higher α-stereoselectivity than when primary hydroxyl group of serine is glycosylated with 2-azido-2-deoxy-galactosyl bromide or trichloroacetimidates [112,113]. Occasionally, primary hydroxyls provide somewhat higher 1,2-*cis* stereoselectivity in comparison to that of the secondary hydroxyl groups. This can serve as an indirect evidence of the glycosylation reaction proceeding via the bimolecular mechanism, at least partially.

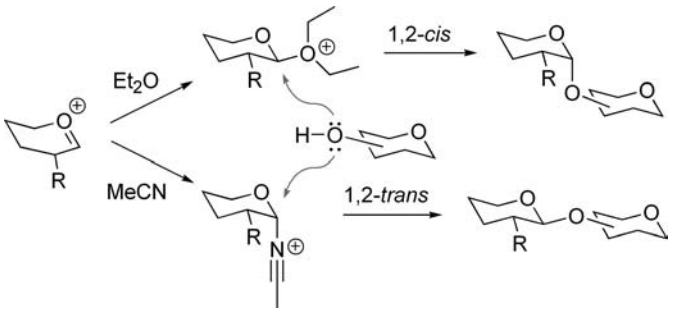
1.6.2.2 **Protecting Groups**

It is well established that ester-electron-withdrawing substituents reduce electron density of the neighboring hydroxyl group by lowering its nucleophilicity [88,105,114]. This may improve stereoselectivity, as the reaction can be carried out in a more controlled manner. As an example, glycosylation of axial 4-OH of galactose often gives excellent 1,2-*cis* stereoselectivity, especially in combination with electron-withdrawing substituents (e.g. *O*-benzoyl, OBz) [115]. However, poorly reactive hydroxyls can lose their marginal reactivity completely when surrounded by the deactivating species, resulting in lower glycosylation yields.

1.6.3
Reaction Conditions

1.6.3.1 **Solvent Effect**

Another important factor that influences the stereoselectivity at the anomeric center is the effect of the reaction solvent. In general, polar reaction solvents increase the rate of the β-glycoside formation via charge separation between O-5 and β-O-1. If the synthesis of α-glycosides is desired, CH_2Cl_2, $ClCH_2CH_2Cl$ or toluene would be suitable candidates as reaction solvents. However, there are more powerful forces than simple solvation that have to be taken into consideration. The so-called participating solvents, such as acetonitrile and diethyl ether, were found to be the limiting cases for the preferential formation of β-D- and α-D-glucosides, respectively [78]. These observations were rationalized as follows: if the reactions are performed in acetonitrile, the nitrilium cation formed *in situ* exclusively adopts axial orientation, allowing stereoselective formation of equatorially substituted glycosides (Scheme 1.3). This approach allows obtaining 1,2-*trans* glucosides with good stereoselectivity even with glycosyl donors bearing a nonparticipating substituent. On the contrary, ether-type reaction solvents such as diethyl ether, tetrahydrofuran [116] or dioxane [117] can also participate in the glycosylation process. Differently, in these cases the equatorial intermediate is preferentially formed, leading toward the axial glycosidic bond formation [85,86,118–120]. Nitroethane was also employed as a suitable solvent for 1,2-*cis* glycosylation [121].



Scheme 1.3

1.6.3.2 Promoter (Catalyst), Additions

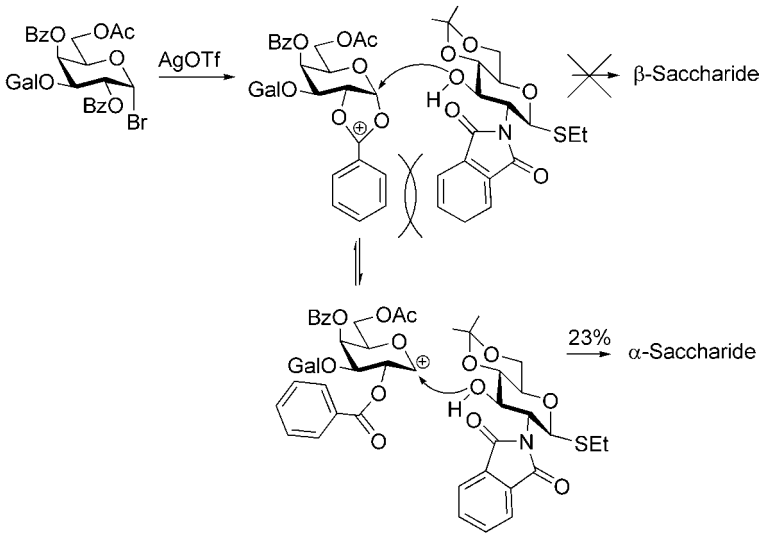
Milder activating conditions are generally beneficial for 1,2-*cis* glycosylation. Thus, halide-ion-catalyzed reactions give the best results for the glycosylation with glycosyl halides [70]; thioglycosides perform better when activated with a mild promoter, such as iodonium dicollidine perchlorate (IDCP) [122,123]; whereas trichloroacetimidates are best activated with the strong acidic catalysts, such as trimethylsilyl trifluoromethanesulfonate (TMS-triflate, TMSOTf) or triflouromethanesulfonic acid (triflic acid, TfOH) [106]. Various additions to the promoter systems often influence the stereochemical outcome of the glycosylation. Among the most remarkable examples is the use of perchlorate ion additive that was found to be very influential in 1,2-*cis* glycosylations [118,124].

1.6.3.3 Temperature and Pressure

High pressure applied to the reactions with participating glycosyl donors further enhances 1,2-*trans* selectivity [125]; when the high-pressure conditions were applied for glycosylations with a nonparticipating glycosyl donor, remarkable increase in the reaction yield was noted with only marginal changes in stereoselectivity [126]. Kinetically controlled glycosylations at lower temperatures generally favor 1,2-*trans* glycoside formation [100,120,127–130], although converse observations have also been reported [131,132].

1.6.4 Other Factors

Unfavorable steric interactions that occur between glycosyl donor and acceptor in the transition state or other factors or conditions may unexpectedly govern the course and outcome of the glycosylation process. One of the most remarkable effects, the so-called 'double stereodifferentiation' takes place when stereochemical interactions between bulky substituents in glycosyl donor and glycosyl acceptor prevail the stereodirecting effect of a neighboring participating group. The pair of reagents where these interactions occur is called a 'mismatched pair'. Thus, only α-linked product was unexpectedly formed with 2-phthalimido glycosyl acceptor (Scheme 1.4). [133]. A coupling of the same glycosyl donor with conformationally



Scheme 1.4

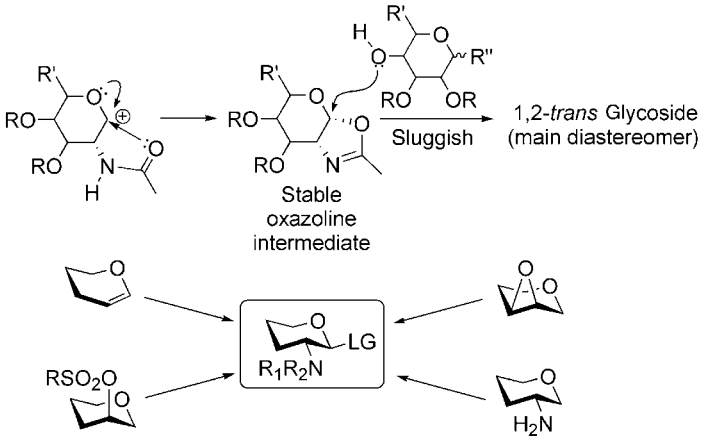
modified 1,6-anhydro acceptor afforded β-linked oligosaccharide with 75% yield. It was also demonstrated that if this effect takes place with a sugar of the D-series, its L-enantiomer forms a matched pair with the same glycosyl acceptor.

1.7
Special Cases of Glycosylation

This section outlines special cases of glycosylation, not necessarily uncommon, which do not follow general conventions discussed above. It is not unusual when general glycosylation methods do not work or cannot be applied to the synthesis of glycosides described herein. The synthesis of each of these classes of compounds requires careful selection of techniques, their modification or design of conceptually new approaches. Sometimes special indirect or total synthesis based technologies have been developed and applied specifically to the synthesis of these targets.

1.7.1
Aminosugars

Glycosides of 2-amino-2-deoxy sugars are present in the most important classes of glycoconjugates and naturally occurring oligosaccharides, in which they are connected to other residues via either 1,2-*cis* or, more frequently, 1,2-*trans* glycosidic linkage [134–136]. In particular, 2-acetamido-2-deoxyglycosides, most common of the D-gluco and D-galacto series, are widely distributed in living organisms as glycoconjugates (glycolipids, lipopolysaccharides, glycoproteins) [134], glycosaminoglycans (heparin,



Scheme 1.5

heparin sulfate, dermatan sulfate, chondroitin sulfate, hyaluronic acid) [137] and so on [138,139]. Special efforts for the synthesis of glycosyl donors of 2-amino-2-deoxy sugars have been focusing on the development of simple, efficient, regio- and stereoselective procedures.

As a vast majority of naturally occurring 2-amino-2-deoxy sugars are *N*-acetylated, from the synthetic point of view, a 2-acetamido-2-deoxy substituted glycosyl donor would be desirable to minimize protecting-group manipulations. For this type of glycosyl donors, however, the oxocarbenium ion rearranges rapidly into an oxazoline intermediate (Scheme 1.5). Even under harsh Lewis acid catalysis, this highly stable oxazoline intermediate does not exert strong glycosyl-donor properties. Although the synthesis of 1,2-*trans* glycosides is possible with the use of this type of glycosyl donors, the synthesis of 1,2-*cis* glycosides is a burden. As a matter of fact, the participating nature of the *N*-acetyl moiety presents an obvious hindrance when the formation of the α-linkage is desired. A minimal requirement for the synthesis of 1,2-*cis* glycosides would be the use of a C-2 nonparticipating moiety.

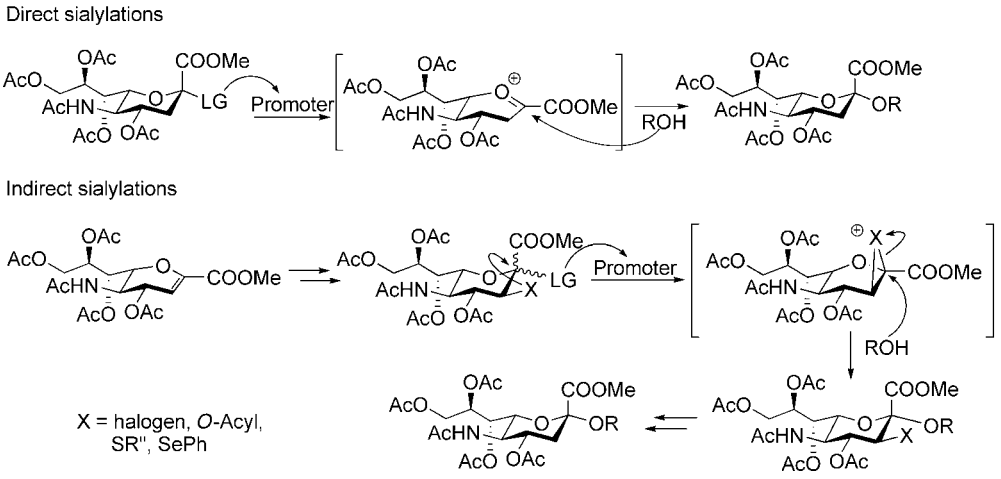
Nowadays, a variety of synthetic approaches to the synthesis of 2-amino-2-deoxyglycosides have been developed, and progress in this area has been reviewed [140–142]. These syntheses are started either from a glycosamine directly or by the introduction of nitrogen functionality to glycose or glycal derivatives. To this end, various glycosamine donors with modified functionalities have been investigated; in particular, those bearing an N-2 substituent capable of either efficient participation via acyloxonium, but not (2-methyl) oxazoline, intermediate for 1,2-*trans* glycosylation or a nonparticipating moiety for 1,2-*cis* glycosylation.

1.7.2 Sialosides

Sialic acids are nine-carbon monosaccharides involved in a wide range of biological phenomena. Their unique structure is characterized by the presence of a carboxylic

group (ionized at physiological pH), deoxygenated C-3, glycerol chain at C-6 and differently functionalized C-5. Among the 50 derivatives reported so far, *N*-acetylneuraminic acid (5-acetamido-3, 5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid, Neu5Ac) is the most widespread. The natural equatorial glycosides and their unnatural axial counterparts are classified as α- and β-glycosides, respectively. In spite of extensive efforts and notable progress, the chemical synthesis of sialosides remains a significant challenge [143–146]. The presence of a destabilizing electron-withdrawing carboxylic group and the lack of a participating auxiliary often drive glycosylation reactions toward competitive elimination reactions, resulting in the formation of a 2,3-dehydro derivative and in poor stereoselectivity (β-anomer). To overcome these problems, a variety of leaving groups and activation conditions for direct sialylations have been developed. It was also demonstrated that the *N*-substituent at C-5 plays an influential role in both stereoselectivity of sialylation and the reactivity of sialyl donors [147].

Along with these studies, a variety of indirect methods for chemical sialylation have been developed. Several glycosyl donors derived from Neu5Ac have been prepared that possess an auxiliary at C-3. This auxiliary should control the anomeric selectivity of glycosylation by neighboring-group participation, leading to the formation of 2,3-*trans*-glycosides [143]. Thus, α-glycosides are favored in the case of equatorial auxiliaries (Scheme 1.6), whereas β-glycosides are preferentially formed when the participating auxiliary is axial. The auxiliaries also help in preventing 2,3-elimination that often constitutes a major side reaction in the direct *O*-sialylations. One of the most important requirements is that an auxiliary should be easily installed prior to, and removed after, glycosylation. Usually, the auxiliaries are introduced by a chemical modification of the readily accessible 2,3-dehydro derivative of Neu5Ac [148]. These transformations can be performed



Scheme 1.6

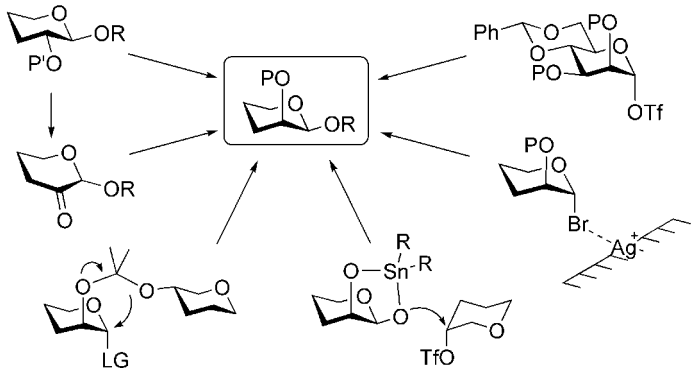
either through a 2,3-oxirane derivative or by a direct addition reaction to the double bond.

1.7.3 Synthesis of 2-Deoxyglycosides

2-Deoxyglycosides are important constituents of many classes of antibiotics. The development of reliable methods for stereoselective synthesis of both α- and β-2-deoxyglycosides has become an important area of research and development of new classes of drugs and glycomimetics [149,150]. It should be noted that because of the lack of anchimeric assistance of the substituent at C-2, the synthesis of both types of linkages represents a notable challenge. On one hand, the direct glycosylation of 2-deoxy glycosyl donors often results in the formation of anomeric mixtures. Similar to that of conventional glycosylation, the solvent and promoter effects play important stereodirecting roles in the synthesis. On the other hand, similar to that discussed for the sialosides, a participating auxiliary can be used to add to the stereoselectivity of glycosylation. Usually this moiety is introduced through 1,2-dehydro derivatives with concomitant or sequential introduction of the anomeric leaving group. The methods employing both axial and equatorial substituents are known to result in the formation of 1,2-*trans* glycosides, which upon 2-deoxygenation can be converted into the respective targets. Although this latter approach requires additional synthetic steps, it is often preferred because it provides higher level of stereocontrol.

1.7.4 Synthesis of β-Mannosides

β-Mannosyl residues are frequently found in glycoproteins. The chemical synthesis of 1,2-*cis*-β-mannosides cannot be achieved by relying on the anomeric effect that would favor axial α-mannosides at the equilibrium. In addition, it is further disfavored by the repulsive interactions that would have occurred between the axial C-2 substituent and the nucleophile approaching from the top face of the ring. For many years the only direct procedure applicable to β-mannosylation – Ag-silicate promoted glycosidation of α-halides – was assumed to follow bimolecular S_N2 mechanism [13,14]. The difficulty of the direct β-mannosylation was addressed by developing a variety of indirect approaches such as C-2 oxidation-reduction, C-2 inversion, anomeric alkylation and intramolecular aglycone delivery (Scheme 1.7) [151–155]. This was the standing in this field before Crich and coworkers discovered that 4,6-*O*-benzylidene protected sulfoxide [109] or thiomannoside [110] glycosyl donors provide excellent β-manno stereoselectivity. Mechanistic and spectroscopic studies showed that anomeric α-*O*-triflates generated *in situ* as reactive intermediates can be stereospecifically substituted. On a similar note, 2-(hydroxycarbonyl)benzyl glycosides have proven to be versatile glycosyl donors for the synthesis of β-mannosides via anomeric triflate intermediates [58].



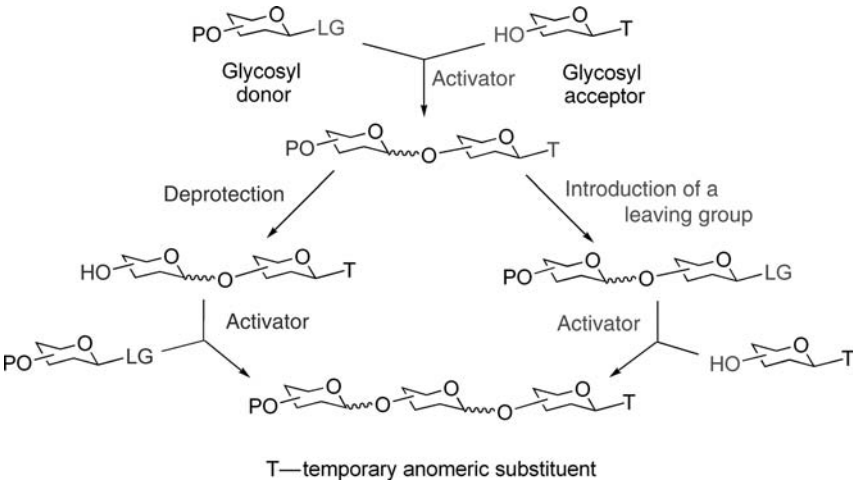
Scheme 1.7

1.7.5
Synthesis of Furanosides

In comparison to their six-membered ring counterparts, furanosides are relatively rare. Nevertheless, their presence in a variety of glycostructures from bacteria, parasites and fungi makes this type of glycosidic linkage an important synthetic target [156,157]. The synthesis of 1,2-*trans* furanosides is relatively straightforward and, similar to that of pyranosides, can be reliably achieved with the use of glycosyl donors bearing a participating group at C-2. In contrast, the construction of 1,2-*cis*-glycofuranosidic linkage is difficult, even more so than with pyranosides, because the stereocontrol in glycofuranosylation cannot be added by the anomeric effect owing to the conformational flexibility of the five-membered ring. In fact, both stereoelectronic and steric effects favor the formation of 1,2-*trans* glycofuranosides. Despite some recent progress, stereoselective synthesis of 1,2-*cis* glycofuranosides has been one of the major challenges of synthetic chemistry. General glycosylation methods, involving glycosyl fluorides [158], trichloroacetimidates [159], and thioglycosides [156,160] along with less common and indirect techniques [161–164], were applied to 1,2-*cis* furanosylation. More recently, a notable improvement in stereoselectivity of 1,2-*cis* furanosylation was achieved by using glycosyl donors in which the ring has been locked into a single conformation. These examples include 2,3-anhydro [165–169], 3,5-*O*-(di-*tert*-butylsilylene) [170,171] and 3,5-*O*-tetraisopropyldisiloxanylidene [172] protected bicyclic glycosyl donors.

1.8
Glycosylation and Oligosaccharide Sequencing

Stereoselective glycosylation is only a part of the challenge that synthetic chemists confront during the synthesis of oligosaccharides. Regardless of the efficiency of a single glycosylation, a traditional stepwise approach requires subsequent conversion of the disaccharide derivative into the second-generation glycosyl acceptor or glycosyl



Scheme 1.8 Linear oligosaccharide synthesis.

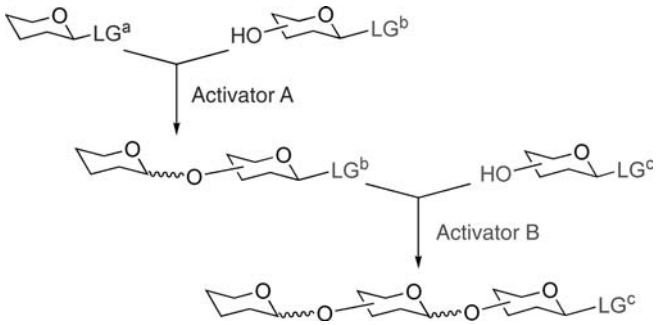
donor (see Scheme 1.8). The modified disaccharides are then coupled with a glycosyl donor (or acceptor) to obtain a trisaccharide. This reaction sequence is then repeated again until oligosaccharide of the desired chain length is obtained.

It has become apparent that the linear approach is too inefficient and lengthy, especially when applied to the synthesis of large oligosaccharides. As a result, the past two decades have witnessed a dramatic improvement in the methods and strategies used for oligosaccharide synthesis. The first attempt to address challenges associated with the linear stepwise approach was the development of a convergent approach [105,173,174]. According to this approach, oligosaccharide building blocks are obtained separately and then coupled together, which, in comparison to the linear approach, allows formation of larger saccharides faster. It is especially advantageous if the synthesis of two or more sequential repeat units is desired for the introduction of a 'difficult' linkage, such as 1,2-*cis*, at an earlier stage of the saccharide assembly to avoid complicated diastereomer separation at the later stage.

When the arsenal of the glycosylation techniques was limited to Fischer and Koenigs–Knorr approaches (or their variations), the oligosaccharide assembly was limited to the linear and block techniques. However, when stable glycosyl donors such as thioglycosides or *O*-alkenyl glycosides emerged, a question of selective or chemoselective activation arose. In brief, most recently developed strategies fit into three broad categories: leaving-group-based (selective or orthogonal activation), preactivation-based and protecting-group-based (armed–disarmed) strategies [175].

1.8.1
Leaving-Group-Based Strategies

The schematic outline of the stepwise selective activation is shown in Scheme 1.9; thus, a glycosyl donor, bearing a reactive LG[a], is coupled with a glycosyl acceptor,



Scheme 1.9 Stepwise selective activation.

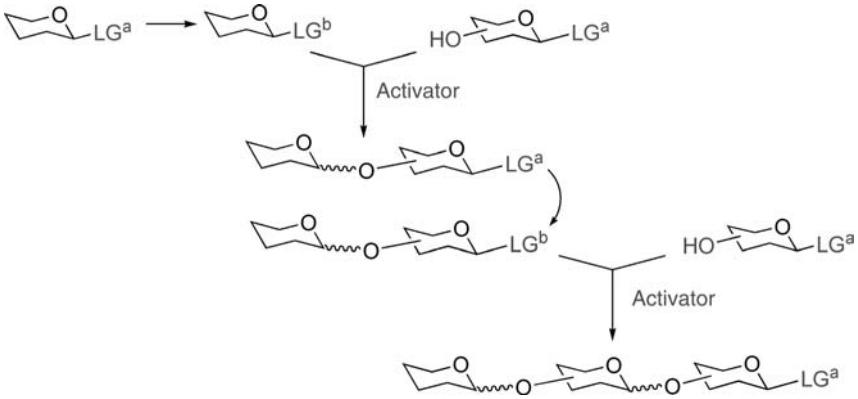
bearing a relatively stable LG^b at the anomeric center. The major requirement for this reaction to take place is the use of a suitable activator that would selectively activate LG^a but not LG^b (Activator A). Early studies involved the activation of alkyl halides over *S*-alkyl/aryl glycosides [173,176–179]. Subsequently, other examples of suitable LG^a for selective activations have become available: trichloroacetimidates, phosphite, phosphate, thioimidate, hemiacetal, sulfoxide, selenoglycoside, orthoester and so on [175]. Many of these couplings were performed with the use of either *S*-alkyl/aryl or *O*-alkenyl/hetaryl moieties as LG^b. In principle, the activation sequence can be continued providing that there is an LG^c that would withstand reaction conditions for the LG^b activation (Activator B). However, these elongated multistep sequences are not yet routinely available. Few available examples include the following three-step activation sequences: bromide as LG^a, Se-phenyl as LG^b, and *S*-ethyl as LG^c [180]; *S*-benzoxazolyl (SBox) as LG^a, *S*-ethyl as LG^b, and *O*-pentenyl as LG^c [181]; SBox as LG^a, *S*-thiazolinyl (STaz) as LG^b, *S*-ethyl as LG^c [182] and so on [183].

The combination of two chemically distinct glycosylation reactions, in which one of the leaving groups is activated while the other one remains intact and vice versa, has led to the discovery of the orthogonal glycosylation strategy [184]. This unique and virtually one of the most advanced techniques for oligosaccharide synthesis requires the use of orthogonal glycosyl donors [185]. Typically, phenyl thioglycosides are selectively activated over glycosyl fluorides and vice versa [184,186,187]. Recently, it has been discovered that a combination of *S*-ethyl and *S*-thiazolinyl glycosides also allows orthogonal activation [188].

A one-pot technique, combining two or more glycosylation steps based on activation of one donor over another, have also been developed [182,189–191]. This one-pot technique is virtually a variation of a simple stepwise selective activation strategy, which allows further improvement in the efficiency of the synthesis by avoiding the necessity for isolation (and purification) of the intermediates.

1.8.2
Two-Step Activation and Preactivation Strategies

According to the two-stage activation (or preactivation) approach, both glycosyl donor and glycosyl acceptor initially bear the same type of a leaving group (LG^a).



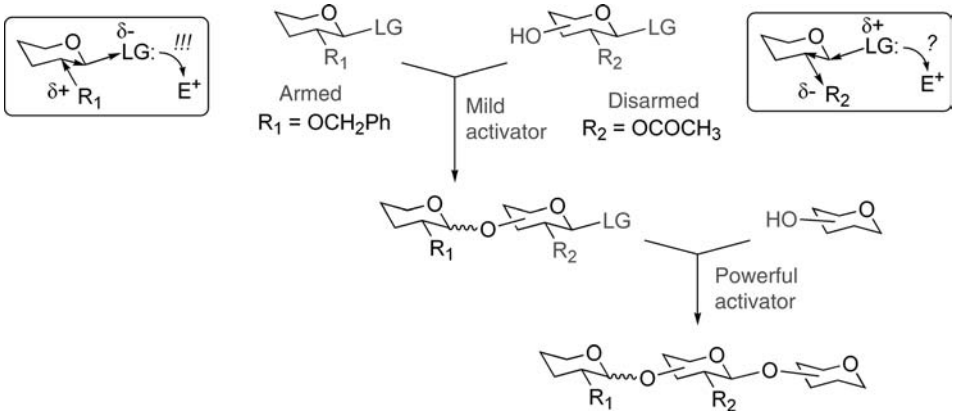
Scheme 1.10 Two-step activation concept.

However, to couple these two reactants, the LG^a of the potential glycosyl donor unit is first converted into an LG^b, which is then selectively activated over LG^a of the glycosyl acceptor in the presence of a selective activator (Activator B, Scheme 1.10). This two-step activation sequence can be reiterated; for this purpose the leaving group of the obtained disaccharide LG^a is again converted into LG^b and so on. This concept was discovered for *S*-ethyl (LG^a) and bromo (LG^b) moieties [173] and further explored for other systems [176,192–194]. The same principle was applied by Danishefsky in the reiterative glycal assembly approach [43,195,196]. This technique involves the transformation of glycals into 1,2-anhydro sugars, which can be easily glycosidated with partially protected glycal-based glycosyl acceptors. Recently, the versatility of the two-step activation was demonstrated by a one-pot preactivation procedure [197,198], according to which *S*-tolyl glycosides are converted *in situ* into a reactive intermediate.

Similar principle is executed in the active–latent approach that has been applied to a number of systems [51,193,199,200]. It is important to note that the conversion between LG^a and LG^b in the active–latent approach does not involve substitution at the anomeric center; instead, a simple modification of the leaving group itself is executed. Recently, the application of this technique was enhanced by the discovery that 2-(benzyloxycarbonyl)benzyl glycosides are perfectly stable compounds, whereas the corresponding 2-(hydroxycarbonyl)benzyl moiety, obtained by the selective hydrogenolysis is an excellent leaving group that can be readily activated [58]. This and other conceptually similar recent discoveries [56,201] open new exciting perspectives for further development of the active–latent strategy.

1.8.3
Protecting-Group-Based Strategies

Another efficient strategy, the armed–disarmed approach, developed by Fraser-Reid is based on the chemoselectivity principle [193,202]. According to this



Scheme 1.11 Armed–disarmed strategy.

technique, a benzylated (electronically activated, armed) glycosyl donor is chemoselectively activated over the acylated (electronically deactivated, disarmed) derivative bearing the same type of LG in the presence of a mild promoter (Scheme 1.11). At the first step a 1,2-*cis*-linked disaccharide is preferentially obtained because of the use of the ether-type arming substituent, a nonparticipating group (*O*-benzyl). The obtained disaccharide can then be used for 1,2-*trans* glycosylation directly in the presence of a more potent promoter, capable of activating the disarmed LG.

Initially developed for *O*-pentenyl glycosides, this concept was further explored for the chemoselective glycosidations of ethyl thioglycosides, selenoglycosides, fluorides, phosphoroamidates, substituted thioformimidates, glycals, benzoxazolyl and thiazolinyl glycosides [175]. The chemoselective activation has become the basis of programmable multistep reactivity-based technique, including highly efficient one-pot approaches [203,204]. Further insights into the armed–disarmed approach came with the observation of the unusual reactivity pattern of the SBox glycosides. Thus, it was demonstrated that glycosyl donors with 2-*O*-benzyl-3,4,6-tri-*O*-acyl protecting-group pattern are even more deactivated than the corresponding 'disarmed' peracyl derivatives [205]. Although the exact nature of this so-called *O*-2/*O*-5 cooperative interesting effect is not yet understood, it has been postulated that the intermediate carbocation stabilization via the acyloxonium ion of the peracylated donor is favored over the oxocarbenium ion stabilization of the 2-*O*-benzyl-3,4,6-tri-*O*-acylated donors. Another interesting concept is the use of 2-*O*-picolyl substituent as an arming participating group. According to this so-called inverse armed–disarmed method, the 1,2-*trans* glycosidic linkage can be chemoselectively introduced at the first glycosylation step [206].

1.9 Conclusions and Outlook

The progress in the area of chemical glycosylation has significantly improved our ability to synthesize various glycosidic linkages with impressive yields and stereoselectivity. But, can we conclude that we have entirely solved the problem of chemical glycosylation? Unfortunately not, and hopefully this chapter introduced the reader to the challenge of chemical glycosylation, a variety of factors, conditions, and driving forces influencing all aspects of this complex chemical reaction as well as prepared for studying more specialized material dedicated to particular methods and strategies employed in modern carbohydrate chemistry. Recent progress made in the area of development of new coupling methods and highly efficient strategies for expeditious oligosaccharide synthesis will ultimately provide an efficient and trouble-free access to complex saccharides. This goal cannot be achieved without the comprehensive knowledge of the glycosylation mechanism and driving forces of glycosylation and competing side processes. It is likely that the consecutive scientific development in this field will be focusing on studying the fundamental mechanistic aspects of glycosylation rather than developing additional anomeric leaving groups.

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2
Glycoside Synthesis from Anomeric Halides

2.1
Glycosyl Fluorides

Shin-ichiro Shoda

2.1.1
Background

Selection of an appropriate glycosyl donor is of great importance in planning strategies for glycoside syntheses (see Section 1.3). Factors to be considered regarding the structure of glycosyl donors used in glycosylations are the chemical character and stereochemistry of leaving groups, the stability of protecting groups among others. The following two characteristics are preferred for the glycosyl donors to be employed in practical glycoside syntheses (Figure 2.1). First, the covalent bond between the leaving group (X) and the anomeric center should possess a moderate thermal stability, because the use of an unstable glycosyl donor often results in difficulty in its handling as well as low reaction yields. Second, the Lewis acid (LA) that promotes glycosylation by cleaving the C−X bond must have a weak acidity so that acid-sensitive functional groups in the glycosyl donors are not damaged during the glycosylation reactions. Glycosyl donors should fulfill these requirements to be employed practically for glycosylation reactions.

Recently, glycosyl fluorides (X = F, Figure 2.1) [1–4] have become one of the most useful glycosyl donors that fulfill the above-mentioned requirements. Fluorine has the smallest covalent radius among the halogens and the largest electronegativity among all elements [5] (Table 2.1). Because of the large bond-dissociation energy of the C−F bond (552 kJ mol^{-1}), it had been believed that glycosyl fluorides were too stable to be used for glycosidic bond formations. These beliefs influenced chemists for a long time and resulted in glycosyl fluorides playing a less significant role than other glycosyl halides in carbohydrate chemistry, until the first publication of the glycosyl fluoride method appeared in 1981 [6]. In fact, glycosyl halides employed in glycoside synthesis had been restricted to relatively unstable glycosyl chlorides and

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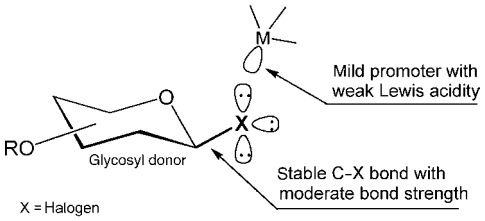


Figure 2.1 Preferred characteristics of glycosyl donors: stability of C−X bond and mildness of promoter.

bromides, and successful results could not always be expected with regard to either yields and/or stereoselectvity.

The first glycosylation reaction by using a glycosyl fluoride was based on the hypothesis that if the chlorine or bromine atom at the anomeric center of glycosyl donors were replaced by fluorine, it would make the glycosyl donor more stable, which would potentially lead to higher yields. Once it was disclosed that the C−F bond of glycosyl fluorides could be activated by a weak Lewis acid, stannous chloride ($SnCl_2$), the large bond-dissociation energy of the C−F bond became inconsequential. On the contrary, the following merits of using glycosyl fluorides as glycosyl donors have emerged: (a) the ease of preparation under a variety of mild reaction conditions, (b) relatively high stability toward chromatography on silica gel, (c) a variety of suitable promoters available for coupling with glycosyl acceptors, (d) orthogonality of the conditions required for the activation of glycosyl fluorides over other glycosyl donors, for example thioglycosides, (e) application to 'armed–disarmed concept' for convergent synthesis of oligosaccharides (see Sections 1.8.3 and 2.1.3.6), (f) possibility to be used in chemoenzymatic glycosylations and (g) ease of monitoring the reaction of glycosyl fluorides by NMR spectroscopy as the spin number of the naturally occurring isotope of ^{19}F is 1/2.

Table 2.1 Physical data for elements that can be used to change the chemical character of the leaving groups on the anomeric center of glycosyl donors.

	Covalent radius (nm)	Electronegativity (Pauling)	C−halogen bond-dissociation energy (kJ mol^{-1}) [5]	H−halogen bond-dissociation energy (kJ mol^{-1}) [5]
F	0.064	3.98	552	570
Cl	0.099	3.16	397	432
Br	0.114	2.96	280	366

The bond-dissociation energy is defined as the standard enthalpy change of the reaction in which the bond is broken: $R:X \rightarrow R + X$.

As a result of the extensive research on glycosylations using glycosyl fluorides during the past 25 years, an enormous amount of experience has been gained concerning reactions and manipulations of glycosyl fluorides [2–4]. This chapter deals with advances in the synthesis of glycosyl fluorides, glycosylation reactions with glycosyl fluoride donors promoted by various activators and applications to natural product synthesis. Several special topics relevant to glycosidic bond-forming reactions that use glycosyl fluorides will also be discussed.

2.1.2 Synthesis of Glycosyl Fluoride Donors

2.1.2.1 Fluorinating Reagents

The number of publications on the synthesis of glycosyl fluorides dramatically increased as many researchers started to use glycosyl fluorides for glycosylation in the early 1980s. The synthesis can be achieved by substitution or addition reactions with many types of fluorinating reagents (Figure 2.2), such as 2-fluoro-1-methylpyridinium tosylate **1** [7], diethylaminosulfur trifluoride (DAST) **2** [8,9], CF_3ZnBr–TiF_4 [10], diethyl azodicarboxylate (DEAD)–PPh_3 (Mitsunobu reagent)/$Et_3O^+BF_4^-$ [11], 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) **3** [12], bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) **4** [13], *N,N*-diisopropyl(1-fluoro-2-methyl-1-propenyl)amine **5** [14], HF [15], HF-pyridine [16], HF–MeCN–Ac_2O [17], AgF [1,18], $AgBF_4$ [19], KHF_2 [20], ZnF_2 [21], Et_3N–HF [22], CF_3ZnBr [10], DAST*N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) [23,24], 4-methyl(difluoroiodo)benzene **6** [25,26], tetrabutylammonium fluoride (TBAF) [27], $PhI(OAc)_2$–SiF_4 [28], XeF_2 [29], *N,N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine (DFMBA) **7** [30], Bu_4NBF_4 (electrochemical) [31] and BF_3–OEt_2 [32].

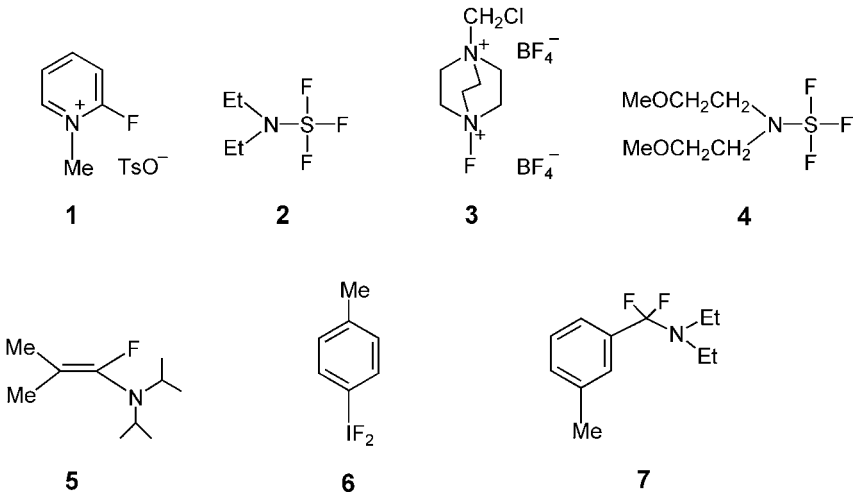
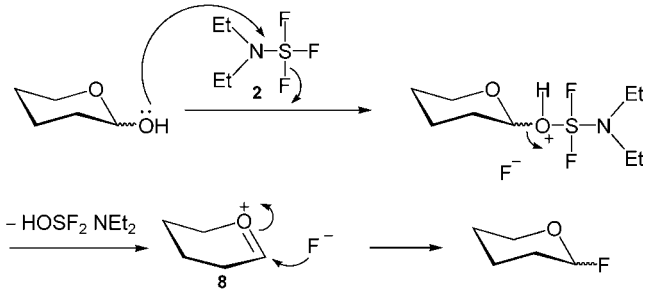


Figure 2.2 Typical fluorinating reagents.



Scheme 2.1

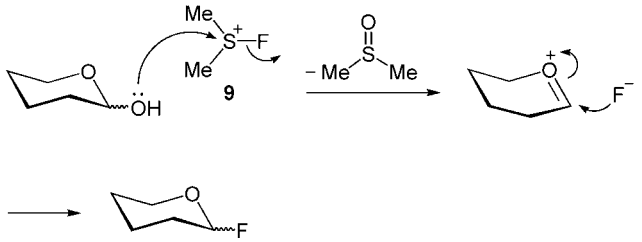
In general, a synthetic route that involves glycosylation processes strongly depends on the availability of the precursors. Taking this into consideration, fluorination reactions are classified according to synthetic precursors as follows: hemiacetals, glycosyl halides, glycosyl esters, *S*-glycosides and other derivatives. Comprehensive reviews on the synthesis of glycosyl fluorides are available and are highly recommended to the reader [33,34].

2.1.2.2 Glycosyl Fluorides from Hemiacetals

Various hemiacetals can be converted into the corresponding glycosyl fluorides with diethylaminosulfur trifluoride **2** as the fluorinating reagent. The reaction proceeds presumably via a process that involves an oxocarbenium ion intermediate **8** (Scheme 2.1). Commonly used hydroxyl-protecting groups such as benzyl, benzoyl and acetonide functionalities do not interfere with the fluorinations. The α/β ratio of the resulting glycosyl fluorides depends on the solvent. For example, when 2,3,5-tri-*O*-benzyl-D-ribose is treated with DAST in THF, the α/β ratio of the resulting fluoride is 1/9.9, which becomes 1/2.0 when CH_2Cl_2 is used [8]. A nonexplosive reagent Deoxo-Fluor ($(MeOCH_2CH_2)_2NSF_3$) **4** was developed for the kilogram scale usage [13].

Trifluoromethylzinc bromide (CF_3ZnBr)–TiF_4 is also an effective reagent that has been used to replace the anomeric hydroxyl group by fluorine. For example, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose can be converted into the corresponding glycosyl fluoride in 83% yield (α/β = 40/60) [10]. *N*,*N*-Diisopropyl(1-fluoro-2-methyl-1-propenyl)amine **5** is an effective reagent for the conversion of 1-hydroxy furanose and pyranose derivatives into the corresponding glycosyl fluorides. For example, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride is obtained from the corresponding 1-hydroxy sugar as a mixture of anomers (α/β = 7/18) [14]. As fluorination occurs under neutral conditions, this reagent does not interfere with protecting groups such as benzyl, benzoyl, acetyl, acetonide or silyl functionalities.

The transformation of 1-hydroxy sugars to the corresponding glycosyl fluorides can be achieved by a mixture of Selectfluor **3** (Figure 2.2) and methyl sulfide presumably through a fluorosulfonium ion **9**, which then reacts with the anomeric



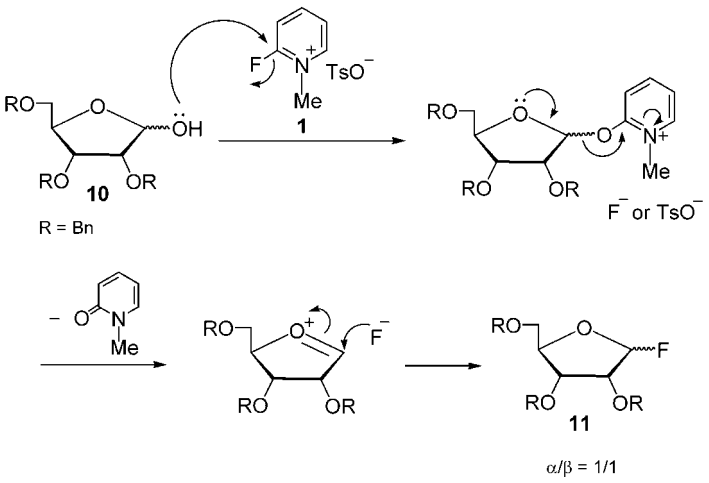
Scheme 2.2

hydroxyl group of the 1-hydroxy sugar followed by the displacement of the intermediate sulfoxide moiety by fluoride ion (Scheme 2.2) [12].

Some dehydrating reagents are also effective for the fluorination of 1-hydroxy sugars. For example, 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose can be converted into the corresponding fluoride under modified Mitsunobu conditions by using diethyl azodicarboxylate–$PPh_3/Et_3O^+BF_4^-$ reagent [11]. 2-Fluoro-1-methylpyridinium tosylate **1** was found to be effective for the synthesis of glycofunanosyl fluoride **11** starting from the corresponding 1-hydroxy sugar **10** (Scheme 2.3) [7].

2.1.2.3 Glycosyl Fluorides from Glycosyl Esters

The classical method for introducing the fluorine atom to the anomeric center is to treat per-*O*-acetylated sugars with hydrogen fluoride [15], using which α-glycosyl fluorides can be prepared stereoselectively, however, the procedure is incompatible with any acid-sensitive functionalities present in the molecule. In addition, hydrogen fluoride is highly corrosive, which makes this method unattractive to many



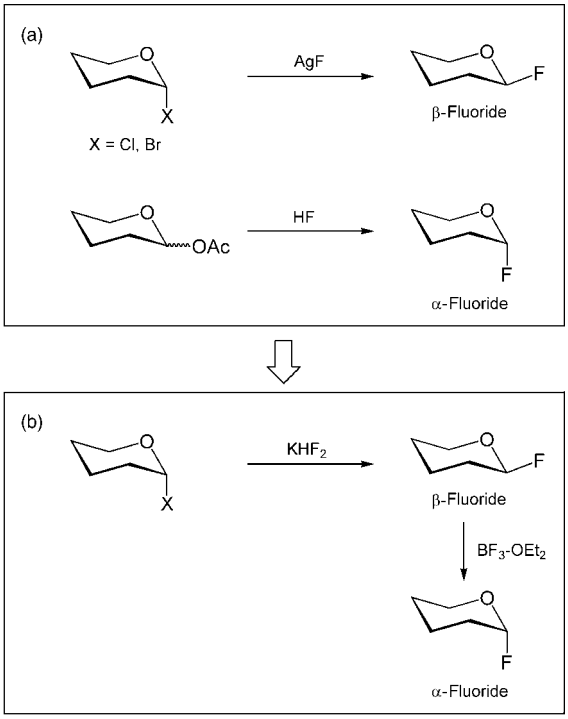
Scheme 2.3

researchers. A much milder procedure for the formation of α-glycosyl fluorides from 1-acyl derivatives uses pyridinium poly(hydrogen fluoride) [35,36].

2.1.2.4 Glycosyl Fluorides from Glycosyl Halides

Isomers of both α-glycosyl fluoride and β-glycosyl fluoride in their protected forms are prepared starting from glycosyl chlorides or bromides by the following two procedures. β-Glycosyl fluorides are prepared by the displacement of the corresponding per-*O*-acylated glycosyl chlorides or bromides with silver fluoride via an S_N2-type reaction (Scheme 2.4a). The synthetic route to β-fluorides can be replaced by another route that involves a nucleophilic substitution of α-glycosyl bromide with potassium hydrogen fluoride (KHF_2) (Scheme 2.4b) [20]. The opposite anomer (α-glycosyl fluoride) can be prepared via the anomerization of the β-fluoride by the action of BF_3–OEt_2 (Scheme 2.4b) [7]. For laboratory scale experiments, the use of KHF_2 and BF_3–OEt_2 is recommended instead of silver fluoride, because the experimental procedures for the reactions without the involvement of a silver salt or hydrogen fluoride are much simpler and more environmentally benign.

Trifluorozincbromide reagent (CF_3ZnBr) is employed for the synthesis of glycosyl fluorides from glycosyl bromides. When 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl



Scheme 2.4

bromide was treated with this reagent, the corresponding fluoride was obtained in a β-selective manner. This result can be explained by assuming an acyloxonium ion intermediate resulted from the neighboring-group participation at C-2 [10].

2.1.2.5 Glycosyl Fluorides from *S*-Glycosides

Some of the most significant progress concerning glycosyl fluoride synthesis is the development of conversion methods starting from thioglycoside derivatives. Phenyl thioglycosides can be converted into the corresponding glycosyl fluorides by the combined use of DAST **2** and NBS [23]. Selectfluor **3** is also able to convert thioglycosides into glycosyl fluorides [12]. The fact that the anomeric alkylthio group can be converted into the fluorine atom enables one to design an efficient synthetic route for oligosaccharides based on a two-step activation concept (see Figure 2.7 in Section 2.1.3.5).

2.1.2.6 Glycosyl Fluorides from Other Anomeric Moieties

The triazole derivative **12**, prepared from the corresponding glycosyl azide, can be converted into the corresponding glycosyl fluoride by the action of HF-pyridine (Figure 2.3a) [37]. The [1-phenyl-1*H*-tetrazol-5-yl]glycosides **13** were also used to produce the corresponding fluorides with HF-pyridine (Figure 2.3b) [38].

The per-*O*-benzylated 1,2-anhydro-α-D-hexopyranose **14**, prepared by epoxidation of a glycal, reacts with tetrabutylammonium fluoride to give the corresponding glycosyl fluoride with β-configuration (Figure 2.4a) [27]. The hydroxyfluorination of glycal derivative **15** using $PhI(OAc)_2$–SiF_4 proved to be a stereoselective route to α-glycosyl fluorides (Figure 2.4b) [28].

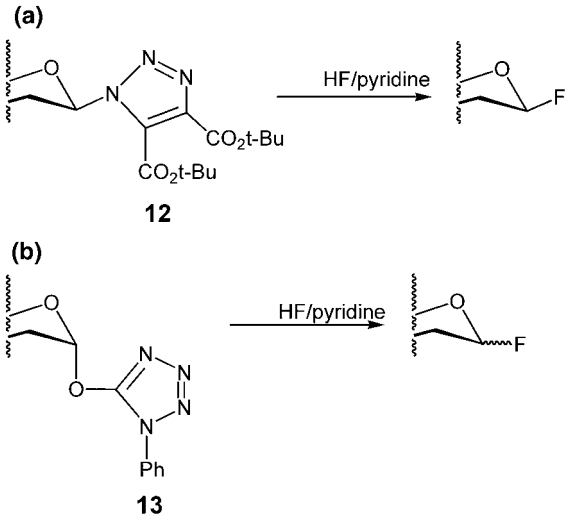


Figure 2.3 Use of triazole and tetrazole derivatives for glycosyl fluoride synthesis.

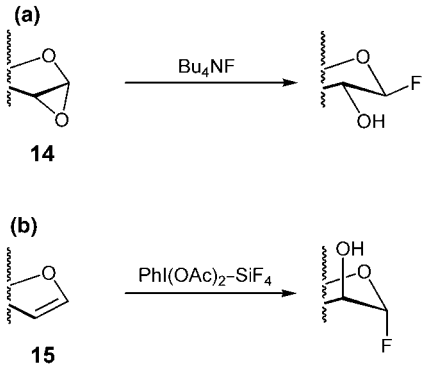


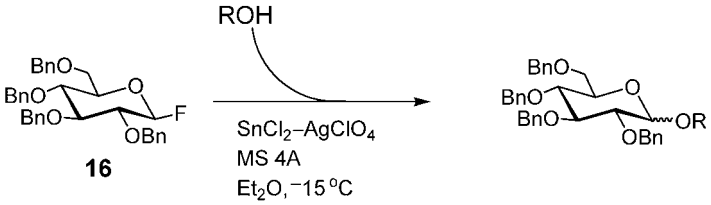
Figure 2.4 Synthesis of glycosyl fluorides from 1,2-anhydro sugars and glycal derivatives.

2.1.3 Glycosylation Using Glycosyl Fluorides as Glycosyl Donors

2.1.3.1 A Weak Lewis Acid Cleaves the C–F Bond. How Was the Glycosyl Fluoride Method Discovered?

The discovery of the glycosyl fluoride method originates from two unexpected findings made during early experiments. The first finding was the realization of a new synthetic route to glycosyl fluorides by using a dehydrating reagent, 2-fluoro-1-methylpyridinium tosylate **1** (Scheme 2.3). In the course of investigating nucleoside synthesis using the dehydrating reagent **1**, glycosyl fluoride **11** was formed as the by-product in good yield starting from the hemiacetal **10**. In the early 1980s, the synthesis of glycosyl fluorides was a problem because preparative methods usually included the use of hazardous anhydrous hydrogen fluoride. As the fluorination reaction using **1** required no hazardous reagents, this method triggered extensive investigations of glycosyl fluorides as glycosyl donors.

The second unexpected finding occurred during the course of examining various Lewis acids as potential promoters for the coupling reaction of glycosyl fluorides and alcohols. Interestingly, the desired glycosylation reaction proceeded smoothly with $SnCl_2$, a fairly weak Lewis acid at room temperature, giving rise to 1,2-*cis* glycosides that are difficult to prepare compared to the 1,2-*trans* glycosides [6]. When the reaction was carried out in the presence of silver perchlorate as a copromoter in diethyl ether, the 1,2-*cis* selectivity further increased. Various 1,2-*cis* glucosides were prepared in a stereoselective manner by the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **16** with alcohols including sterically hindered ones, such as methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside and *t*-butyl alcohol (Scheme 2.5, Table 2.2) [6]. The tendency of predominant formation of 1,2-*cis* glycosides in diethyl ether can be explained by the preferential formation of the equatorial intermediate because of solvent participation as described in Section 1.6.3.

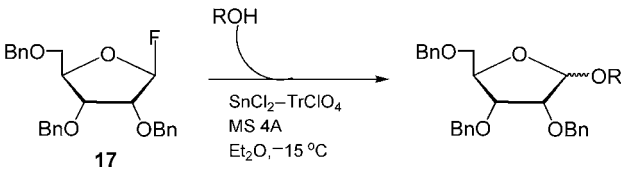


Scheme 2.5

This method was also found to be applicable to the synthesis of 1,2-*cis* glycofuranosides. 2,3,5-Tri-*O*-benzyl-β-glucofuranosyl fluoride **17** was found to react with various alcohols, including sterically hindered *t*-butyl alcohol, in the presence of $SnCl_2$–$TrClO_4$ (Tr = Ph_3C), thereby affording a good route to 1,2-*cis* furanosides that are difficult to obtain by other means (Scheme 2.6, Table 2.2) [7].

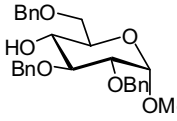
The characteristic feature of the divalent tin compounds is that they have both a vacant orbital and a lone pair of electrons (Figure 2.5). In this glycosylation reaction, it is assumed that $SnCl_2$ behaves as a Lewis acid, where the vacant orbital accepts one of the three lone pairs in the fluorine atom of the glycosyl fluoride. As a result of this interaction, the C−F bond cleaves to give the oxocarbenium ion intermediate that is then attacked by an alcohol to give the glycoside.

It is noteworthy that the addition of strong Lewis acids is not necessary to promote the glycosylation; the use of relatively weak Lewis acids like $SnCl_2$ is sufficient to activate the considerably strong C−F bond of glycosyl fluorides. All of these results



Scheme 2.6

Table 2.2 Synthesis of 1,2-*cis*-glycosides by using glycosyl fluorides as glycosyl donors promoted by $SnCl_2$–$AgClO_4$ [6] or $SnCl_2$–$TrClO_4$ [7].

R–OH	Fluoride	Yield (%)	α/β	Fluoride	Yield (%)	α/β
3β-Cholestanol	**16**	96	92/8	**17**	88	81/19
	**16**	91	80/20	**17**	96	85/15
t-BuOH	**16**	87	81/19	**17**	90	85/15

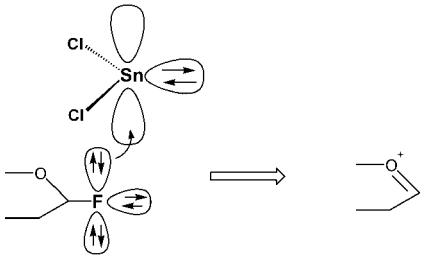


Figure 2.5 Activation of the C−F bond of glycosyl fluoride by the divalent tin species, giving rise to oxocarbenium ion intermediate.

clearly show that the fluorophilic character of Lewis acids is much more important than their Lewis acidities [39]. These basic findings have greatly stimulated the development of a series of new glycosylation reactions in these years, where a variety of combinations of glycosyl fluorides and Lewis acids have been designed on the basis of the fluorophilicity of the promoters [39].

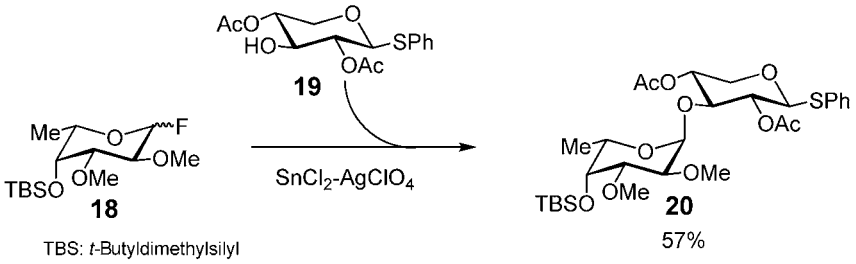
2.1.3.2 Various Promoters Employed in Glycosylation by the Glycosyl Fluoride Method

The promoters found for the activation of glycosyl fluorides are as follows: $SnCl_2$–$AgClO_4$ [6], $SnCl_2$–$TrClO_4$ (Tr = Ph_3C) [7], $SnCl_2$–AgOTf [40,41], SiF_4 [42], Me_3SiOTf (Tf = trifluoromethanesulfonyl) [42], BF_3–OEt_2 [43–46], TiF_4 [47], SnF_4 [48], Cp_2MCl_2–$AgClO_4$ (M = Ti, Zr, Hf; Cp = cyclopentadiene) [49–53], Cp_2ZrCl_2–$AgBF_4$ [54], Cp_2HfCl_2–AgOTf [54–57], $Bu_2Sn(ClO_4)_2$ [58], Me_2GaCl [59], Tf_2O [60,61], Li-ClO_4 [62–64], $Yb(OTf)_3$ [65], $La(ClO_4)_3$–nH_2O [66], $La(ClO_4)_3$–nH_2O/$Sn(OTf)_2$ [67], Yb-Amberlyst 15 [68], sulfated zirconia [69,70], $TrB(C_6F_5)_4$ [71], TfOH [72–77], HB$(C_6F_5)_4$ [73–77], carbocationic species paired with $B(C_6F_5)_4^-$ and TfO^- [78], $SnCl_2$–$AgB(C_6F_5)_4$ [79], $SnCl_4$–$AgB(C_6F_5)_4$ [80], $Ce(ClO_4)_3$ [81], ytterbium(III)tris[bis(perfluorobutylsulfonyl)amide] ($Yb[N(SO_2CF_2CF_2CF_2CF_3)_2]_3$) [82] and $Cu(OTf)_2$ [83]. Among these promoters, tin(II) species (SnX_2), bis(cyclopentadienyl)metal derivatives (Cp_2MCl_2), BF_3–OEt_2 and protic acids are the most frequently employed. Several examples using these promoters will be described in the following section.

2.1.3.3 Glycosylations Promoted by Various Promoters

$SnCl_2$–AgX The L-fucosyl fluoride derivative **18** reacts with glycosyl acceptor **19** in the presence of $SnCl_2$–$AgClO_4$ to give the corresponding disaccharide **20** as α-anomer only (Scheme 2.7) [84].

The coupling reaction of glycosyl fluoride of *N*-acetylneuraminic acid derivative **21**, possessing an equatorial auxiliary at C-3, and a sugar alcohol **22** promoted by $SnCl_2$–AgOTf leads to the corresponding α-linked disaccharide **23** as the major product (Scheme 2.8) [85]. The phenylthio auxiliary acts as a participating group to control the stereochemical course of the glycosylation, giving rise to a naturally occurring sialoside derivative.

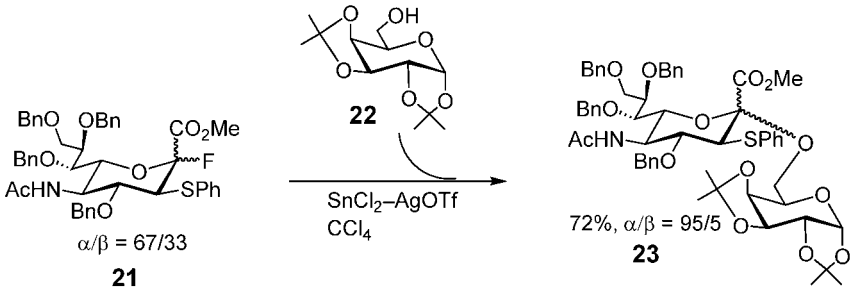


TBS: *t*-Butyldimethylsilyl

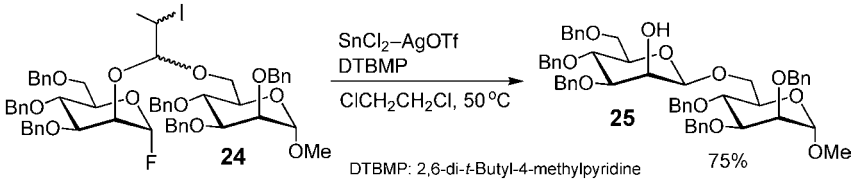
Scheme 2.7

The β-selective mannosylation is a challenging topic in glycoside synthesis because the formation of β-glycosidic linkage is stereoelectronically disfavored (see Section 1.7.4). Several approaches so far have been tried aiming at the preferential formation of β-mannnosides by changing the structure of promoters. The principle of the intramolecular aglycon delivery [86–89] has been applied to glycosyl fluoride **24** by the use of $SnCl_2$–AgOTf in dichloroethane, giving rise to a 1,2-*cis*-mannoside derivative **25** (Scheme 2.9) [90].

Bis(cyclopentadienyl)metal-Based Promoters (Cp_2MCl_2)–AgX A combination of bis (cyclopentadienyl) metal dichloride and silver perchlorate acts as a powerful pro-

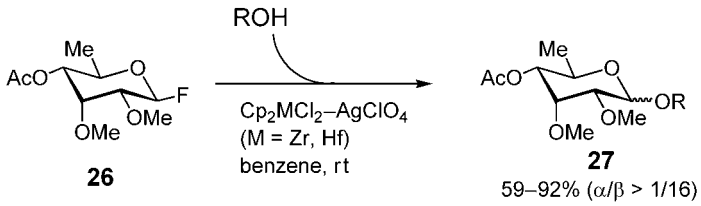


Scheme 2.8



DTBMP: 2,6-di-*t*-Butyl-4-methylpyridine

Scheme 2.9

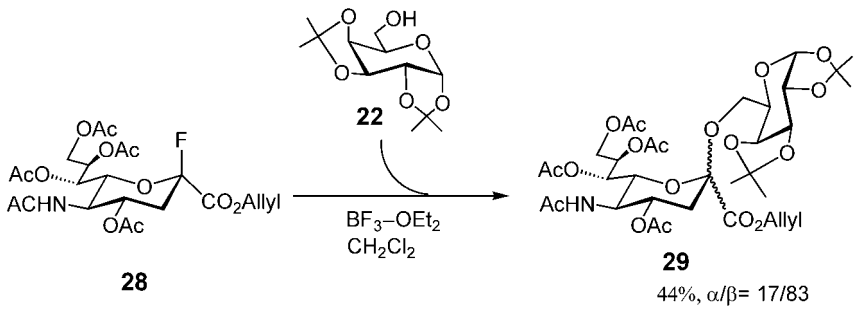


Scheme 2.10

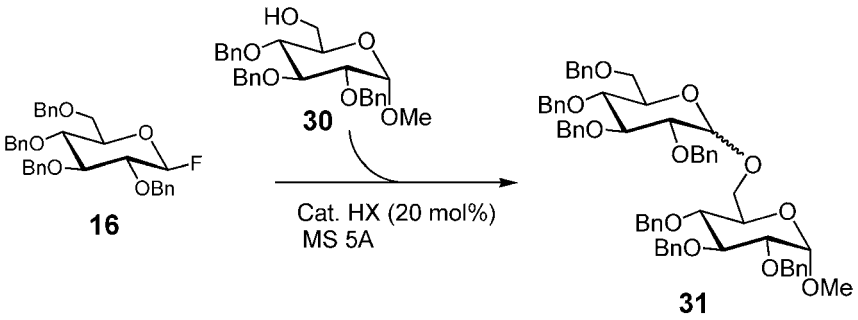
moter for the glycosylation of glycosyl fluoride. For example, the promoter system of Cp_2MCl_2–$AgClO_4$ (M = Zr, Hf) is effective for the activation of glycosyl fluoride **26**, which enables highly β-selective formation of D-mycinoside **27** in benzene (Scheme 2.10) [49]. The use of Cp_2HfCl_2–$AgClO_4$ in 1 : 2 molar ratio rather than 1 : 1 molar ratio provides much higher reactivity for the activation of glycosyl fluoride, where some implication for the involvement of $Cp_2Hf(ClO_4)_2$ is obtained [52].

BF_3–OEt_2 Unnatural β-sialoside derivatives are produced preferentially by using *O*-acetylated glycosyl fluoride donor and BF_3–OEt_2 as the promoter. When β-sialyl fluoride derivative **28** was reacted with acceptor **22** in the presence of BF_3–OEt_2 in dichloromethane, the β-sialoside **28** was obtained in a mixture of anomers (α/β 17/83) (Scheme 2.11) [44].

Protic Acids According to hard and soft acids and bases (HSAB) principle, proton is considered to be fluorophilic because of its hard character and because it has higher dissociation energy for H—F bond than for H—Cl and H—Br (Table 2.1) [91]. Various protic acid catalysts can promote stereoselective glycosylation of alcohols using glycosyl fluoride donors in the presence of MS 5 Å in an appropriate solvent [72–77]. For example, when glycosyl fluoride was reacted with various alcohols in CH_2Cl_2 at room temperature in the presence of a catalytic amount of trifluoromethansulfonic acid (TfOH), the corresponding glycoside is obtained in good yields [73–75].



Scheme 2.11



Scheme 2.12

Donors possessing other halogens as leaving groups, such as glycosyl chloride and bromide, are not effectively activated in contrast to glycosyl fluoride.

When strong acid catalysts are generated *in situ* (supernatant) and used for the coupling of **16** with the glycosyl acceptor **30** either in Et_2O at room temperature or in benzotrifluoride (BTF)/^{t}BuCN (5 : 1) at 0 °C, the corresponding α- or β-linked disaccharides **31**, respectively, is obtained in high yields (Scheme 2.12 and Table 2.3). Interestingly, the stereoselectivity varies as the combination of catalyst and solvent is switched.

2.1.3.4 Glycosylation of Silylated Compounds as Glycosyl Acceptors

Glycosyl fluorides can be coupled with silylated glycosyl acceptors in place of compounds with a free hydroxyl by using a catalytic amount of Lewis acid as the promoter. In this reaction, an oxocarbenium ion **32** is first generated from a glycosyl fluoride in the presence of a Lewis acid (Figure 2.6) [92]. The resulting ion is then attacked by the silylated oxygen atom of the acceptor **33** to form the *O*-glycoside by liberating $R_3Si–F$ and LA. As no acid is generated during the glycosylation, it is not necessary to add a base to the reaction mixture, which often favors the formation of

Table 2.3 Effect of solvent and counteranion of protic acids on stereoselectivity of formation of **31** [76].

Catalyst	Yield (%) (Et_2O, rt)	α/β	Yield (%) (BTF—^{t}BuCN(5:1)0 °C)	α/β
HOTf	98	88/12	Quant	47/53
HOTf	96	88/12	99	49/51
$HClO_4$	98	92/8	Quant	60/40
$HOSO_2C_4F_9$	99	88/12	96	47/53
$HNTf_2$	Quant	49/51	99	9/91
$HNTf_2$	Quant	50/50	Quant	9/91
$HSbF_6$	99	56/44	Quant	12/88
$HB(C_6F_5)_4$	95	55/45	99	7/93

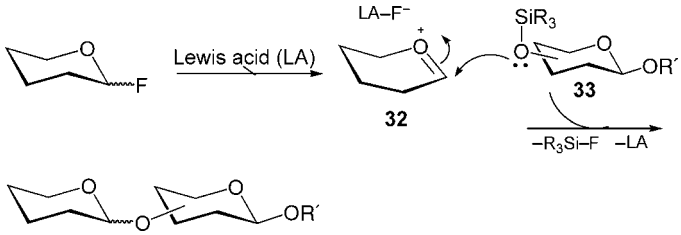
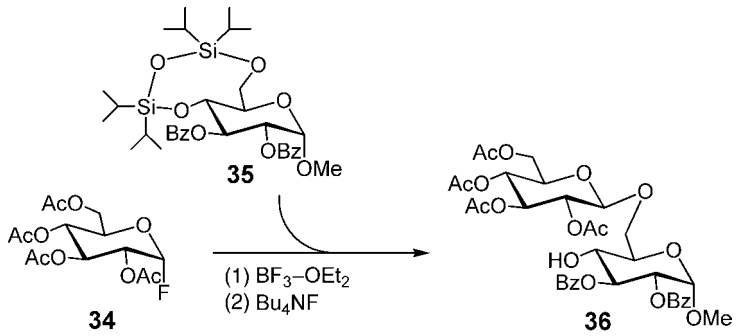


Figure 2.6 Glycosyltion of silylated acceptor by glycosyl fluoride.

orthoesters in the classical Koenigs–Knorr reactions. Trimethylsilyl triflate (TMSOTf) effectively promotes the coupling reaction of various silyl ethers and glycosyl fluorides [42]. When the glycosyl fluoride **34** is reacted with the 4,6-TIPS-protected methyl glucoside **35** in the presence of a catalytic amount of BF_3–OEt_2, a regioselective β(1–6) glycosylation is observed, affording the gentiobioside **36** (Scheme 2.13) [93].

2.1.3.5 Two-Stage Activation Procedure

The strategy of combining the chemistry of glycosyl fluorides with that of thioglycosides (see Section 4.1) for the synthesis of oligosaccharides was first suggested in 1984 (see Section 2.7) (Figure 2.7) [23]. In the first activation stage, the phenylthio group of compound **37** is converted into the corresponding glycosyl fluoride **38** by treating it with DAST and NBS (see Section 2.1.2.5). In the second activation stage, the resulting glycosyl fluoride **38** is coupled to a glycosyl acceptor **39**, which may carry a phenylthio group at the reducing end for further propagation of the oligosaccharide chain. The disaccharide **40** obtained may then be deprotected at the desired position to give an acceptor **42** or converted into a glycosyl fluoride **41** that may be used as a new glycosyl donor. Reiteration of the process can produce the desired target oligosaccharide.



Scheme 2.13

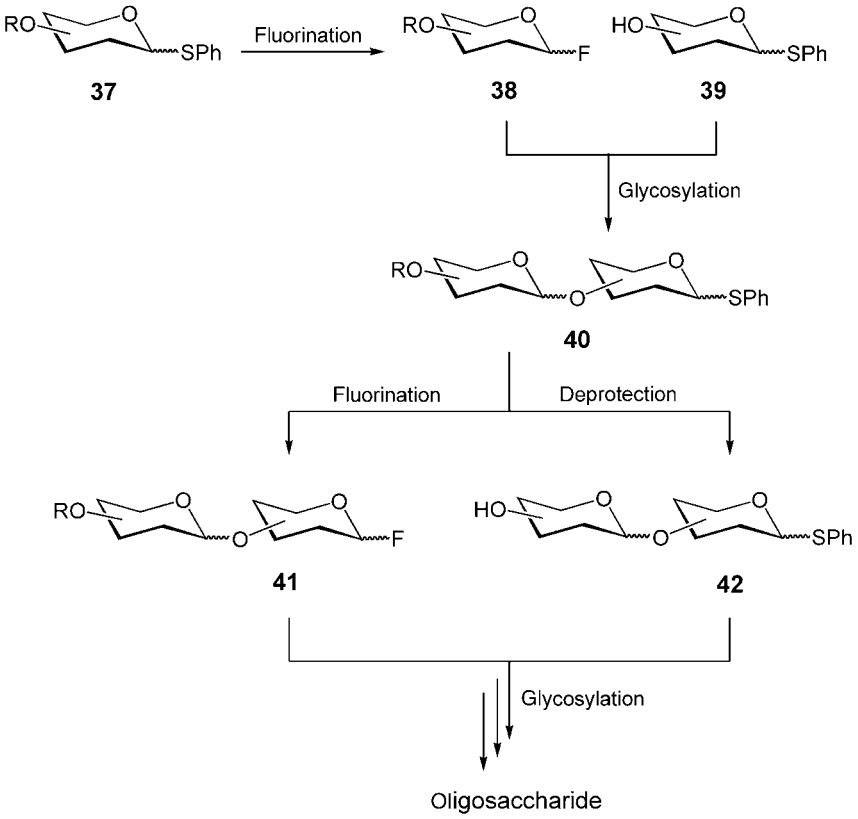
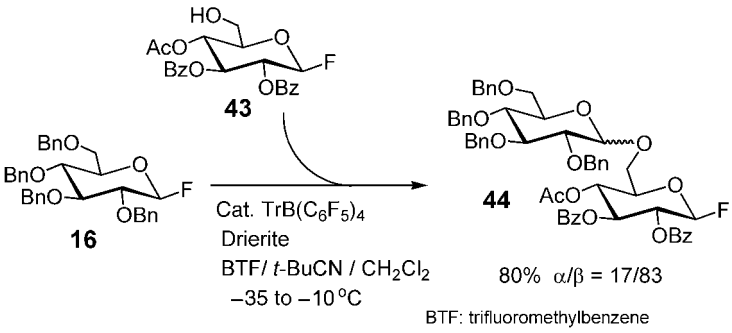
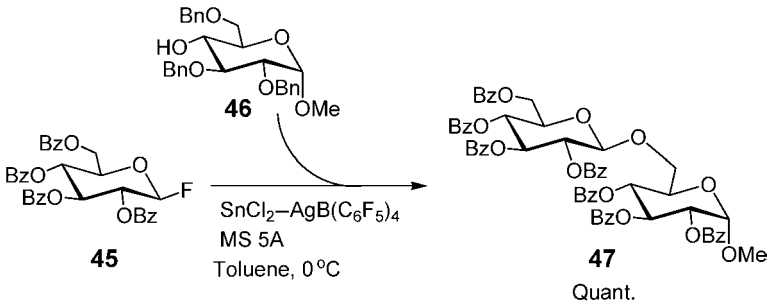


Figure 2.7 Two-stage activation procedure using glycosyl fluoride and thioglycoside as glycosyl donor.



Scheme 2.14



Scheme 2.15

2.1.3.6 **Protecting-Group-Based Strategy**

The chemoselective activation of glycosyl fluorides based on the 'armed–disarmed concept' (see Section 1.8.4) has been described (Scheme 2.14) [94]. The catalytic glycosylation of the disarmed glycosyl fluoride **43** with the armed glycosyl fluoride **16** was promoted by trityl tetrakis(pentafluorophenyl)borate ($TrB(C_6F_5)_4$) in trifluoromethylbenzene (BTF)–pivalonitorile–CH_2Cl_2 (5 : 1 : 1) to give the corresponding disaccharide **44** in good yield and β-selectivity [72,72].

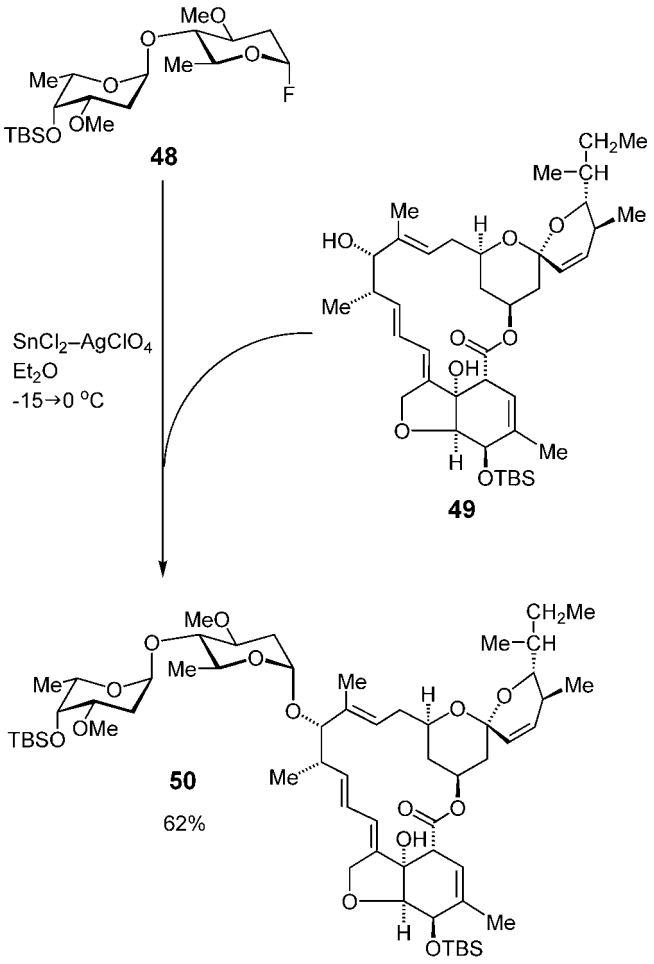
On the contrary, activation of the disarmed glycosyl fluoride **45** by the combined use of $SnCl_2$ and silver tetrakis(pentafluorophenyl)borate ($AgB(C_6F_5)_4$) could be achieved to afford β-D-disaccharide **47** in excellent yields even in the cases of using acceptor **46** having secondary alcohol that generally exhibit low nucleophilicity (Scheme 2.15) [79]. These reactions are the first examples of catalytic glycosylation using armed and disarmed glycosyl fluorides with various glycosyl acceptors having free hydroxyl groups.

2.1.4
Application to Natural Product Synthesis

In the previous section, several glycosylation reactions have been described, showing a variety of promoters employed in the glycosyl fluoride method. Applications to natural product synthesis that build on these basic reactions will be described herein. The promoters most frequently employed for natural product synthesis are $SnCl_2$–AgX (X = ClO_4, OTf), Cp_2MCl_2–AgX (M = Hf, Zr, X = ClO_4, OTf), BF_3–OEt_2 and a protic acid (HOTf).

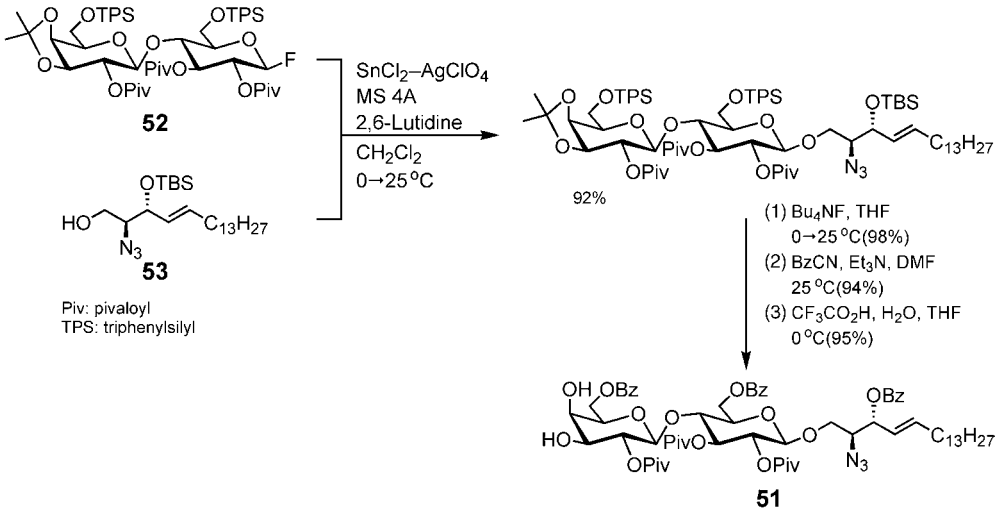
In the synthesis of avermectin B_{1a}, the disaccharide fluoride **48** is prepared and coupled with avermectin aglycon **49** in the presence of $SnCl_2$–$AgClO_4$ in dry ether to give protected avermectin B_{1a}**50** in 62% yield (Scheme 2.16) [23].

As the reaction proceeds under mild reaction conditions, this original promoter, $SnCl_2$–$AgClO_4$, can also be employed in the synthesis of complex glycosides such as rhynchosporosides [95], cyclodextrin [41,96], trimeric Le^x [55,97], globotriaosylceramide (Gb_3) [98] or Elfamycin [99]. As a representative example, the synthetic route



Scheme 2.16

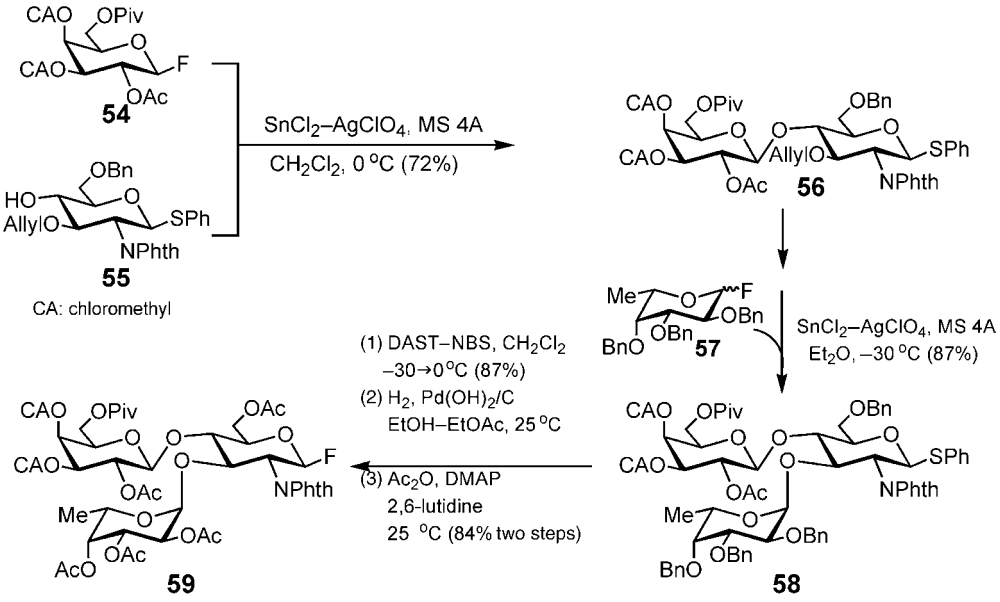
to the trimeric Le^x**61** is illustrated in Schemes 2.17–2.19. The lactosyl sphingosine acceptor **51** is constructed by coupling the disaccharide fluoride donor **52** and the alcohol **53** in the presence of $SnCl_2$–$AgClO_4$, followed by the regioselective deprotection. However, the coupling of galactosyl fluoride derivative **54** with the sugar acceptor **55** affords the corresponding β-glycoside **56** stereoselectively. After selective deprotection, the resulting disaccharide alcohol can be coupled with the glycosyl fluoride **57** using the $SnCl_2$–$AgClO_4$ promoter system, giving rise to the trisaccharide derivative **58**. The trisaccharide **58** is then converted into the corresponding fluoride donor **59** and coupled with the disaccharide sphingosine derivative **51** by using the Cp_2HfCl_2–AgOTf promoter to afford the pentasaccharide derivative **60**.



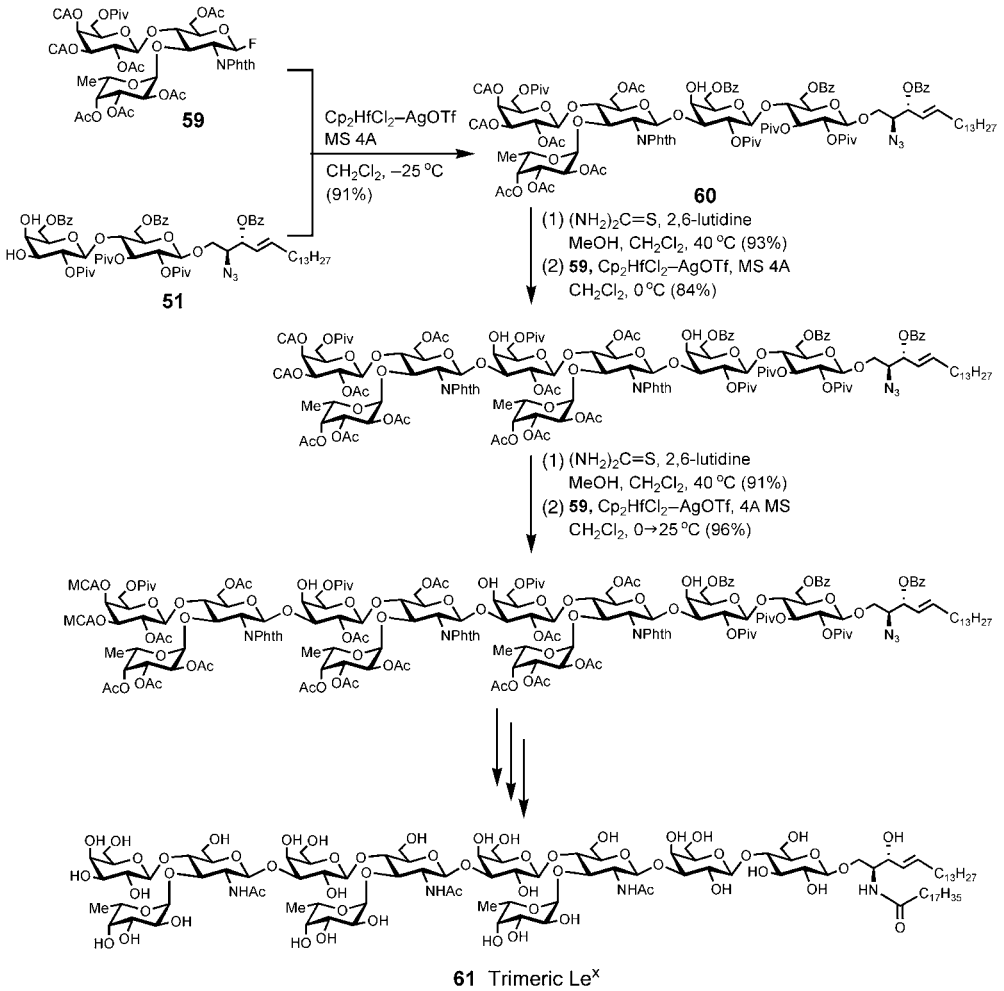
Scheme 2.17

The glycosylation process by using the trisaccharide fluoride is repeated twice to give trimeric Le^x**61** after deprotections.

The total synthesis of agelagalastatins **62a** and **62b**, an antineoplastic glycosphingolipid, has been achieved by using an α-selective glycosylation of the ceramide



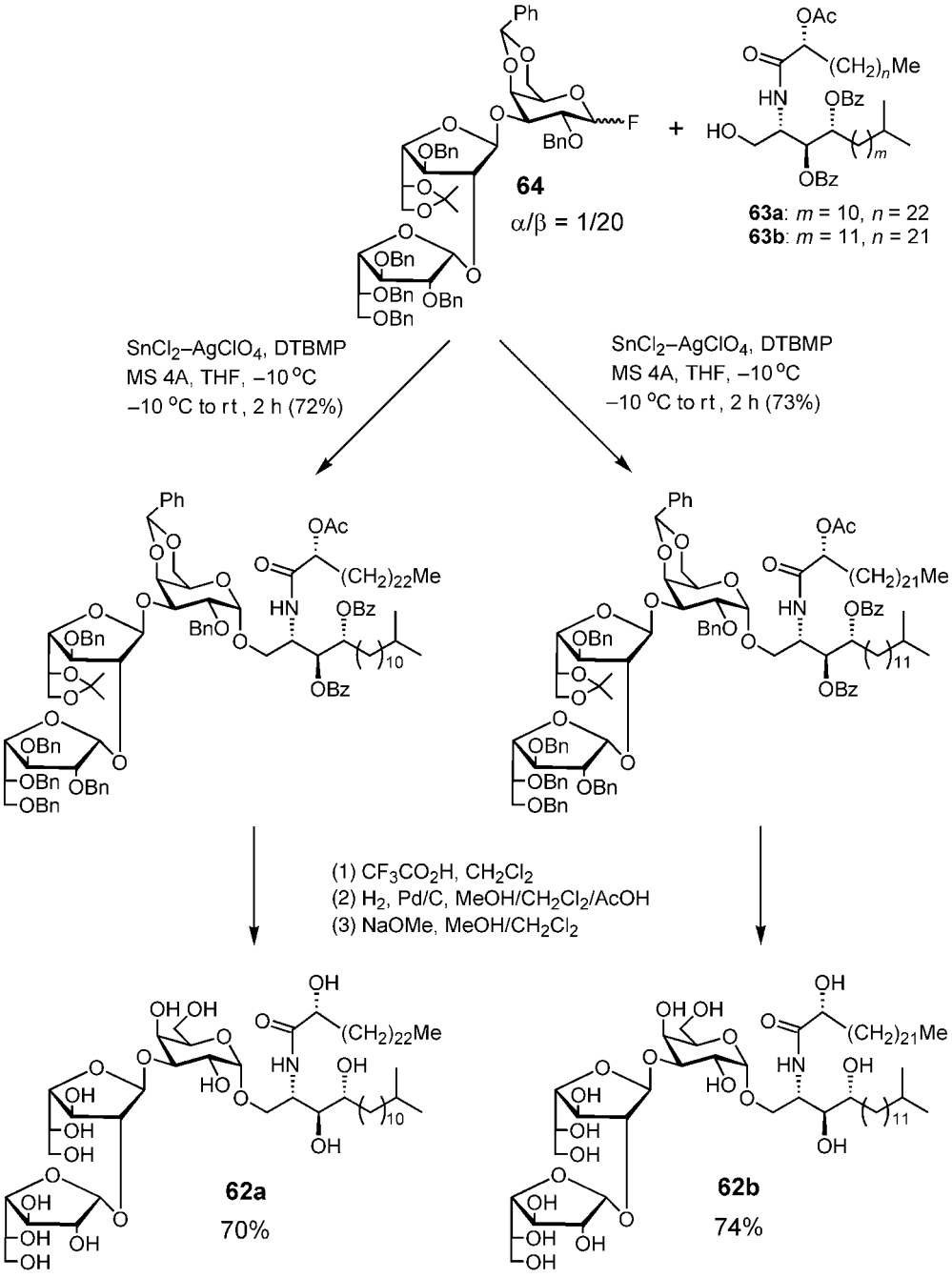
Scheme 2.18



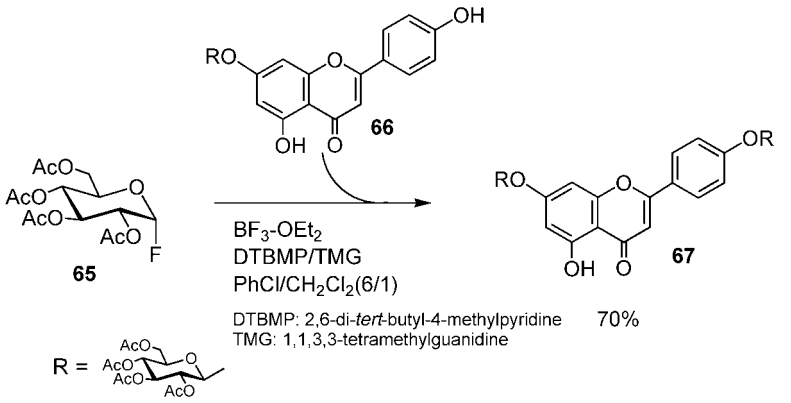
Scheme 2.19

derivatives **63a** and **63b** with the trisaccharide fluoride **64** promoted by $SnCl_2$–$AgClO_4$ (Scheme 2.20) [100].

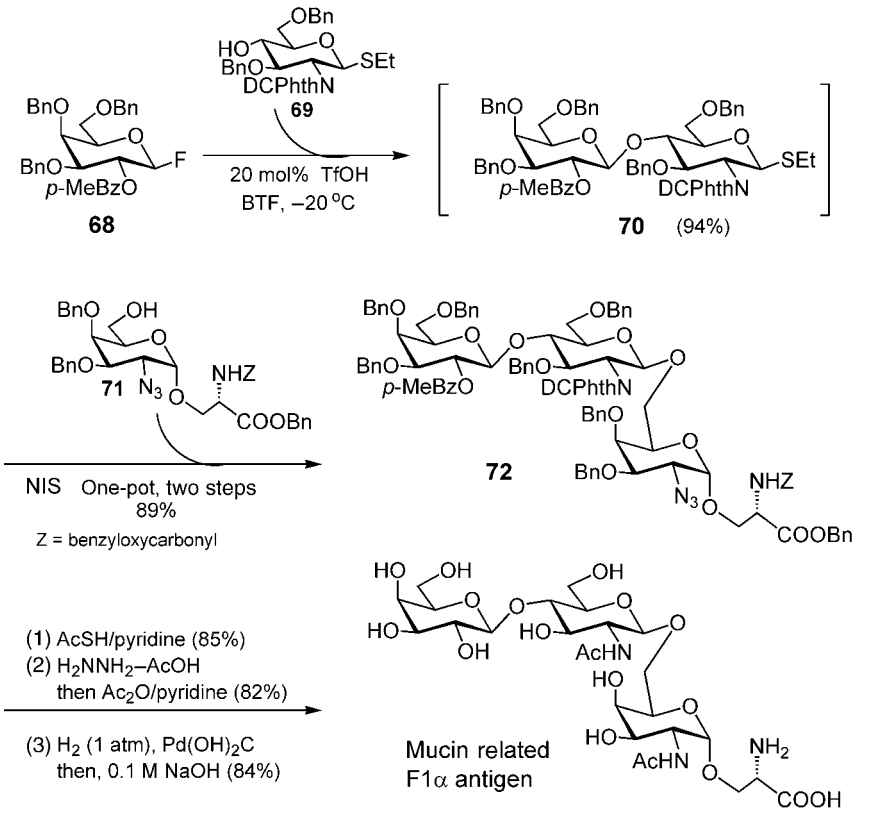
The usefulness of the Cp_2MCl_2–AgX system (M = Hf, Zr, X = ClO_4, OTf) can be also seen in the total synthesis of various natural products. The $[Cp_2MCl_2]$–$AgClO_4$ (M = Zr, Hf) promoters were used for the total synthesis of mycinamicin IV [51]. The first total synthesis of neohancosides A and B, monoterpene diglycosides isolated from *Cynanchum hancockianum*, has been achieved using a glycosyl fluoride as a glycosyl donor. The key step involves the coupling of glycosyl fluoride and linalool in the presence of $[Cp_2ZrCl_2]$–$AgClO_4$ [101].


64
α/β = 1/20
63a: m = 10, n = 22
63b: m = 11, n = 21
SnCl2–AgClO4, DTBMP
MS 4A, THF, –10 °C
–10 °C to rt, 2 h (72%)
SnCl2–AgClO4, DTBMP
MS 4A, THF, –10 °C
–10 °C to rt, 2 h (73%)
(1) CF3CO2H, CH2Cl2
(2) H2, Pd/C, MeOH/CH2Cl2/AcOH
(3) NaOMe, MeOH/CH2Cl2
62a
70%
62b
74%

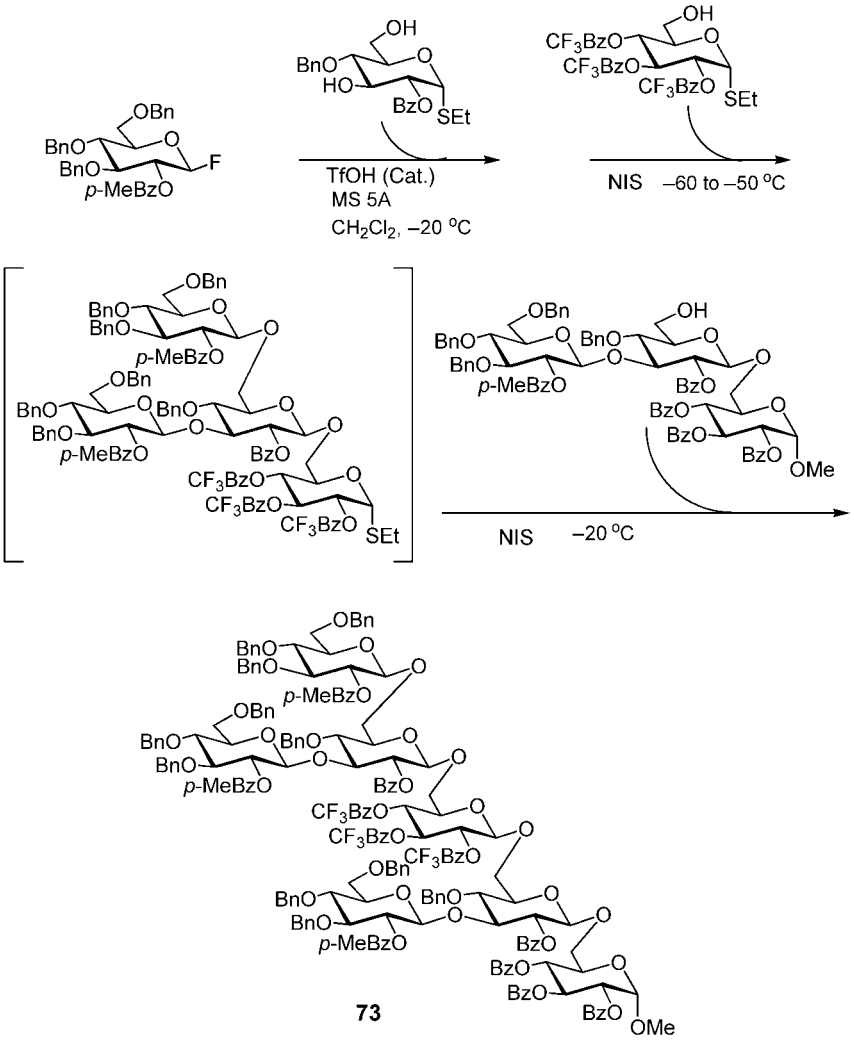
Scheme 2.20



Scheme 2.21



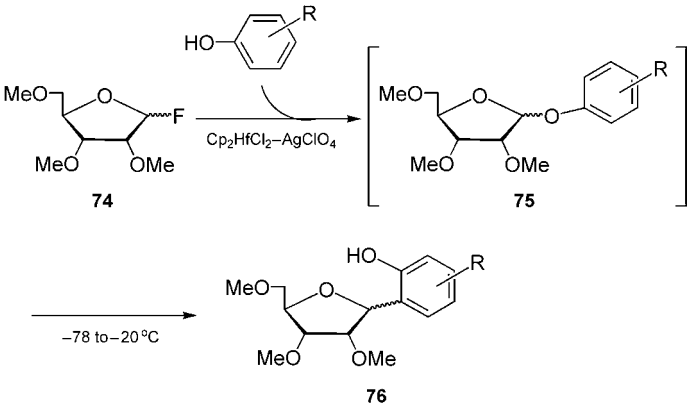
Scheme 2.22



Scheme 2.23

The glycosyl fluoride glycosylation promoted by BF_3–OEt_2 is applied in the key step of the total synthesis of ipopolysaccharide (LPS) derivative [102] and D-*myo*-inositol monomannoside [103]. Also, glycosylation of 4′-OH of **66** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride **65** is achieved using a BF_3–OEt_2/2,6-di-*tert*-butyl-4-methylpyridine/1,1,3,3-tetramethylguanidine system in 70% yield (Scheme 2.21). The resulting glycoside **67** is converted into apigenin glucopyranoside derivative, a component of blue flower pigment of *Salvia patens* [104].

The one-pot sequential glycosylation strategy is applied to the convergent total synthesis of the F1α antigen (Scheme 2.22) [105]. The glycosyl fluoride **68** is first



Scheme 2.24

reacted with thioglycoside **69** in the presence of a catalytic amount of TfOH to afford disaccharide **70**. The β-selectivity of the reaction can be controlled by the neighboring-group participation of the *p*-MeBz moiety at the C-2 position. Second glycosylation of glycopeptide **71** with **70** occurs by subsequently adding NIS in a one-pot fashion, and fully protected trisaccharide derivative **72** is obtained stereoselectively in 89% yield.

Moreover, the one-pot sequential glycosylation method has been applied successfully to the rapid assembly of a branched heptasaccharide **73** (Scheme 2.23) [106].

2.1.5 Special Topics

2.1.5.1 *C*-Glycoside Synthesis via *O*-Glycosylation

Glycosyl fluorides have also proved useful in the synthesis of *C*-glycosides, *N*-glycosides and *S*-glycosides, so that a broad application is guaranteed for this class of glycosyl donors [107–109]. Here, a *C*-glycosylation reaction that involves a rearrangement of *O*-glycoside is described as a representative example (Scheme 2.24). When glycosyl fluoride donor **74** is reacted with a phenol derivative in the presence of $CpHfCl_2$–$AgClO_4$, the *O*-glycosylation takes place rapidly at −78 °C. After the formation of the *O*-glycoside **75**, gradual warming results in the formation of *C*-glycoside **76** via rearrangement [110]. This reaction was successfully applied to the total synthesis of Veneomycine B_2 [111].

2.1.5.2 Glycosyl Fluorides for the Synthesis of a Combinatorial Library

The use of a single glycosylating tool is not enough to accomplish the synthesis of a complex oligosaccharide. It is often necessary to combine a glycosylation reaction with other glycosylation reactions. The principle of the orthogonal strategy [112] by

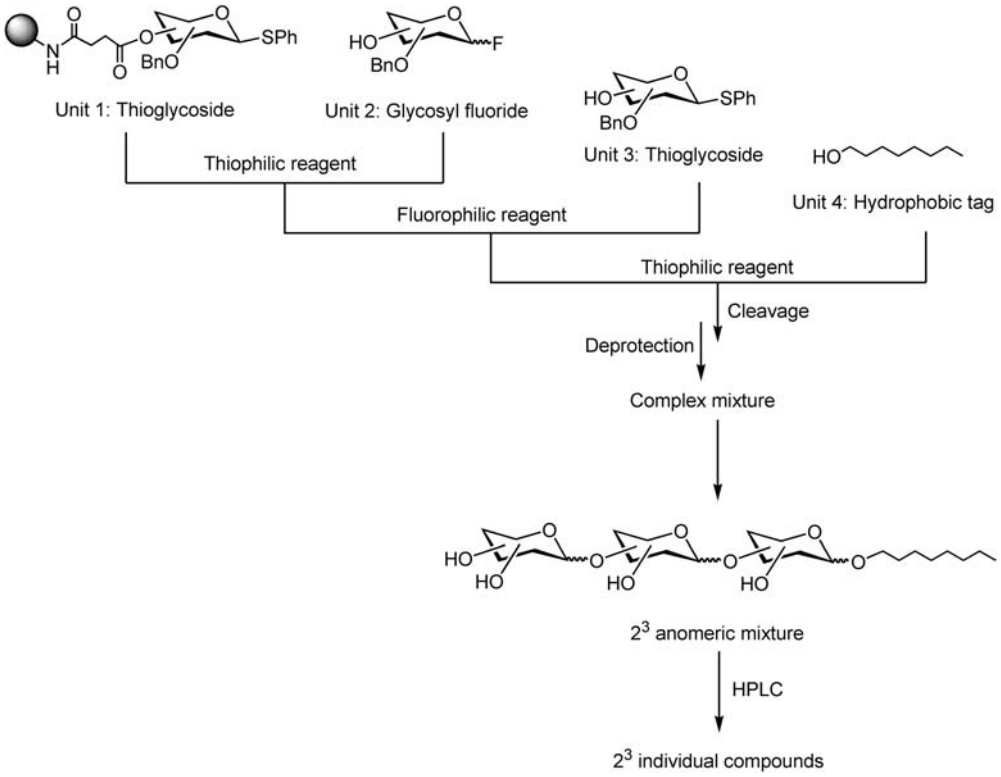


Figure 2.8 Orthogonal synthesis leading to combinatorial library of trisaccharides.

the combination of two types of glycosylation reactions, in which one of the leaving groups is activated while the other one remains intact and vice versa, will be discussed.

A new method of orthogonal oligosaccharide synthesis leading to a combinatorial library of trisaccharides, α/β-L-Fuc-(1–6)-α/β-D-Gal-(1–2/3/4/6)-α/β-D-Glc-octyl, has been developed [113]. This method is based on the combined use of a stationary solid-phase reaction, in which no mechanical mixing is required, an orthogonal glycosylation strategy [112] and solid-phase extraction (Figure 2.8). The glycosyl fluoride method plays the key role in the synthesis. Four individual synthetic equivalents were sequentially coupled by means of the orthogonal-glycosylation strategy. The last component introduced acts as a hydrophobic tag that facilitates rapid isolation of the products after cleavage of the substances accumulated on the support and the deprotection reactions. The trisaccharides obtained were finally isolated by reverse-phase HPLC [113].

2.1.5.3 Glycosyl Fluorides as Glycosyl Donors for Chemoenzymatic Synthesis

Unlike any of the other protected glycosyl halides, glycosyl fluorides can be deprotected without the loss of the halide function. This makes glycosyl fluorides very rare

compounds that can be used as glycosyl donors in aqueous solutions as well as in organic solvents. Several efficient glycosylations have been demonstrated catalyzed by glycosidases [114–116] and glycosynthases [117].

2.1.6 Conclusions and Future Directions

The glycosyl fluoride method, which was developed in the early 1980s, has now reached a stage at which it has become possible to produce extremely complex glycosides while controlling their stereochemistry. Although the history of glycosyl fluoride method is much shorter than that of the classical Koenigs–Knorr glycosylation, many applications to natural product synthesis have already been demonstrated, clearly indicating its great utility in the field of carbohydrate chemistry. The reason why glycosyl fluorides have been so frequently employed as glycosyl donors is that they show higher activities in the presence of various promoters as well as ease of handling because of their thermal stability. Almost all elements that can activate the C−F bond of glycosyl fluoride donors are located in the region of hard elements with higher fluorophilicity in the periodic table. It can easily be predicted that other Lewis acids that promote glycosylations using glycosyl fluorides will be found in future on the basis of the concept of fluorophilicity. It should also be noted that various macromolecular catalysts of well-defined structures would be designed and prepared for chemoenzymatic glycosylation on a larger scale based on rapid advances in genetic engineering [118].

2.1.7 Typical Experimental Procedures

2.1.7.1 Preparation of the Glycosyl Donors

Fluorination with Bis(2-Methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) from 1-Hydroxy Sugar [13] A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (10 mmol) in dry CH_2Cl_2 (3.0 ml) was added at room temperature under nitrogen to a solution of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) **4** (11 mmol) in CH_2Cl_2 (2.0 ml). The resulting mixture was poured into saturated $NaHCO_3$ (25 ml), extracted with the help of CH_2Cl_2 (3×15 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography (silica gel, hexane/ethyl acetate) afforded the pure product of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride (98%, $\alpha/\beta = 28:72$).

Fluorination with Silver Fluoride from Glycosyl Bromide [17] A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (5 g) and anhydrous silver fluoride (5 g) in dry acetonitrile (25 ml) was shaken under argon overnight. The resulting solution was filtered and aqueous sodium chloride was added to precipitate any silver ions from the solution. The mixture was filtered and concentrated to a syrup that was

dissolved in chloroform, extracted with water, dried (Na_2SO_4) and evaporated under reduced pressure at 35 °C, with precautions to exclude moisture. The residue was dissolved in boiling diethyl ether. Subsequently, crystallization was completed by the addition of light petroleum (bp 65–110 °C), giving rise to 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride (80%).

Fluorination with Pyridinium Poly(hydrogen fluoride) from Glycosyl Ester [16] Pyridinium poly(hydrogen fluoride) (4 ml) was added dropwise to an ice-cooled solution of 1,2-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (2.5 mmol) in dry toluene (5 ml). The mixture was left at 0 °C for 5 h. Ether (10 ml) and saturated KI solution (30 ml) were added to the reaction mixture, which was then extracted with a mixture of ether and hexane (3 : 1, 3 × 30 ml) and the organic layer was washed with brine (30 ml), dried (Na_2SO_4) and filtered and the solvent was removed *in vacuo* to give white solid particles. Recrystallization from ethanol gave 2-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranosyl fluoride as white needles (30%).

Fluorination with DAST–NBS from Thioglycoside [23] Carefully dried thioglycoside (0.3 mmol) was dissolved in CH_2Cl_2 (3 ml) under argon and cooled to −15 °C. The stirred solution was then treated with DAST (60 µl, 0.45 mmol) and allowed to stir for 2 min before NBS (0.39 mmol) was added. After 25 min, the reaction mixture was diluted with CH_2Cl_2 (25 ml) and poured into a cold saturated $NaHCO_3$ solution (3 ml). The organic phase was separated and washed with saturated $NaHCO_3$ solution (3 ml) and brine (3 ml), before being dried ($MgSO_4$) and evaporated. The oily product was subjected to flash column chromatography (silica gel, ether–petroleum ether mixtures) to afford pure fluoride (85%). R_f 0.26 (60% ether in petroleum ether).

2.1.7.2 Glycosylation Using Glycosyl Fluorides as Glycosyl Donors

$SnCl_2$–$AgClO_4$ Promoter [6] A solution of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (0.2 mmol) and 3β-chlostanol (0.17 mmol) in ether (4 ml) was added to a mixture of stannous chloride (0.2 mmol), silver perchlorate (0.2 mmol) and 4 Å molecular sieves at −15 °C, and the reaction mixture was stirred at the indicated temperature for 24 h. After filtration, the filtrate was washed with cold saturated $NaHCO_3$ solution and dried (Na_2SO_4). After the removal of the solvent, the residue as purified by preparative TLC (silica gel) to give 3β-chloestanyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (88%) and the corresponding β-anomer (8%).

$SnCl_2$–$TrClO_4$ Promoter [7] A solution of 3β-cholestanol (1.7 mmol) and 2,3,5-tri-*O*-benzyl-β-ribofuranosyl fluoride (2.0 mmol) in ether (4 ml) was added to a stirred suspension of stannous chloride (2.0 mmol), trityl perchlorate (2.0 mmol) and 4 Å molecular sieves in ether (1 ml) at −15 °C. After the reaction was completed, saturated $NaHCO_3$ solution was added to the reaction mixture. The mixture was filtered through Celite and extracted with ether. The organic layer was dried (Na_2SO_4), the

solvent was removed under reduced pressure and the residue was purified by preparative TLC to give 3β-cholestanyl 2,3,5-tri-*O*-benzyl-α-ribofuranoside (71%) and the corresponding β-anomer (17%).

Bis(cyclopentadienyl)metal Derivatives (Cp_2ZrCl_2) Promoter [49] Cp_2ZrCl_2 (271 mmol) and $AgClO_4$ (271 mmol) were added to a mixture of D-mycinosyl fluoride **26** (54.2 mmol) and cyclohexylmethanol (108 mmol) and powdered molecular sieves 4 Å (approximately 100 mg) in benzene (2.5 ml), and the mixture was stirred for 10 min at room temperature. After the addition of saturated $NaHCO_3$ solution and filtration through a pad of Celite, the mixture was extracted with ethyl acetate, and washed with saturated aqueous $NaHCO_3$ solution and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by preparative TLC (hexane : ether = 1 : 1) to give the corresponding glycoside **27** (92%, α/β = 1/16).

Glycosylation of a Silylated Glycosyl Acceptor Using SiF_4 Promoter [42] An acetonitrile solution of SiF_4 (0.08 M, 7 ml, 0.57 mmol) was added to a mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (1.9 mmol) and cyclohexyl trimethylsilyl ether (1.9 mmol) in acetonitrile (3 ml) at 0 °C. The mixture was stirred for 4 h at the same temperature and poured into a mixture of KF (5 g) and 0.1 M phosphate buffer solution (pH 7.4, 30 ml). The resulting mixture was extracted with ether–hexane (2 : 1, 60 ml), and the organic layer was washed with a saturated $NaHCO_3$ solution (30 ml), a mixture of saturated $NaHCO_3$ solution and brine (1 : 5, 30 ml), and dried (Na_2SO_4). After evaporation, the residue was purified by chromatography (silica gel, 15 g, ether : hexane = 1 : 2) to give cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides (90%, α/β = 15/85). Separation of the anomers was done by medium-pressure column chromatography (silica gel, ethyl acetate : $CHCl_3$ = 1 : 6).

TfOH Promoter [71] TfOH (3.0 mg in toluene, 0.2 ml, 0.020 mol) was added to a stirred suspension of MS 5 Å (300 mg), a glycosyl fluoride (0.12 mmol), and a glycosyl acceptor (0.10 mmol) in ether (2.5 ml) at 0 °C. After completion of the glycosylation reaction by monitoring TLC, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (2 ml). Then, the mixture was diluted with ethyl acetate and 1 M HCl, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, and was dried ($MgSO_4$). After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to afford the corresponding glycoside.

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2.2
Glycosyl Chlorides, Bromides and Iodides

Suvarn S. Kulkarni, Jacquelyn Gervay-Hague

2.2.1
Background

Since the advent of Koenigs–Knorr glycosylation in 1901 [119], glycosyl bromides are among the most popular glycosyl donors that continue to find wide application in oligosaccharide and natural product synthesis [120,121]. Glycosyl chlorides, on the contrary, have been used for specific applications but their general use is limited owing to their reduced activity [121]. In contrast, for much of the twentieth century, glycosyl iodides were thought to be unstable and too reactive for any useful purposes. This notion has been refuted and over the past decade glycosyl iodide chemistry has enjoyed a renaissance, with increasing reports on the preparation and use of glycosyl iodides since last reviewed in 1998 [122]. The chemistry of glycosyl chlorides and bromides was reviewed by Nitz and Bundle [121]. *O*-Glycosylations of glycosyl bromides and chlorides with applications in total synthesis was also reviewed by Pellissier [120]. Along with these reports, virtually every review article on stereoselective glycosylations includes examples of bromides and chlorides as glycosyl donors. In this chapter, we will first briefly discuss major advances in the twenty-first century pertaining to the preparation and use of glycosyl chlorides and bromides and devote the major part of the discussion to the novel chemistry of glycosyl iodides.

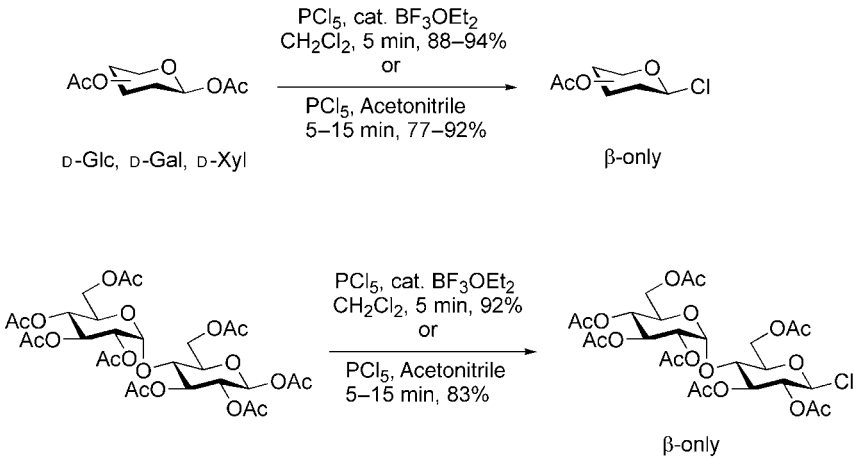
2.2.2 Glycosyl Chlorides

2.2.2.1 Preparation of Glycosyl Chlorides

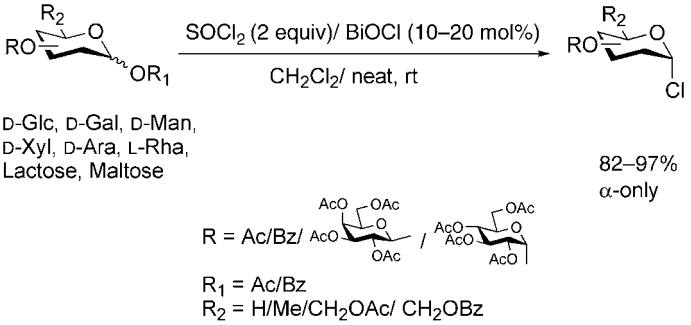
Anomeric halides follow the typical reactivity order F < Cl < Br < I for nucleophilic substitutions. They have been used in stereoselective *O*-glycosylation, nucleophilic displacement, and carbanion as well as in radical reactions.

There are several procedures for the selective preparation of anomerically pure α- and β-glycosyl chlorides. Thermodynamically unstable 1,2-*trans*-isomers (β-isomers of D-glucose and D-galactose) are usually prepared via neighboring-group participation from 1,2-*trans*-glycosyl acetates using various chlorinating agents such as anhydrous tin tetrachloride ($SnCl_4$), titanium tetrachloride ($TiCl_4$) and aluminum trichloride ($AlCl_3$) in nonpolar solvents or by the action of HCl in dry ether. Combinations of dichloromethyl methyl ether–BF_3OEt_2 and thionyl chloride with acetic acid are also used. The aforementioned methods have recently been compared to Ibatullin's method [123], which utilizes phosphorous pentachloride (PCl_5) in the presence of a catalytic amount of BF_3OEt_2 (Scheme 2.25). This methodology has been shown to give consistently high yields and selectivity [124] in the presence of $AlCl_3$ or in the absence of any catalyst when conducted in polar solvents such as acetonitrile. 1,2-*cis* Acetates do not react with PCl_5. Moreover, cleavage of interglycosidic linkage does not occur under these conditions. An alternative method to generate β-glycosyl chlorides is by the chlorination of alkyl or aryl thioglycosides using iodine monochloride (ICl) [125]. Similarly, the use of IBr generates the corresponding α-glycosyl bromide under mild conditions that tolerate sensitive protecting groups on the sugar substrate [125].

A few methods exist for the formation of 1,2-*cis* isomers. Protic acids such as HCl or AcOH in conjunction with thionyl chloride ($SOCl_2$) furnish β-chlorides from



Scheme 2.25

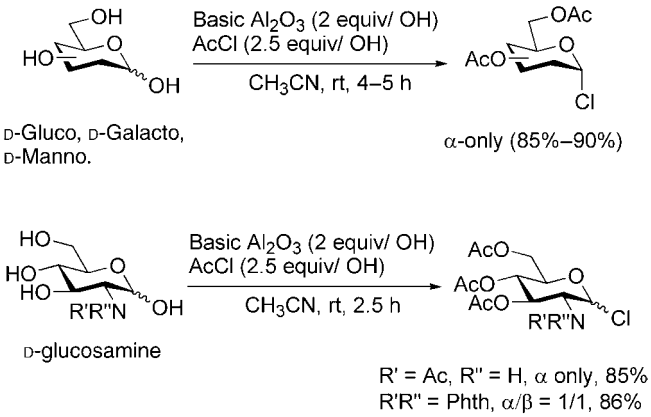


Scheme 2.26

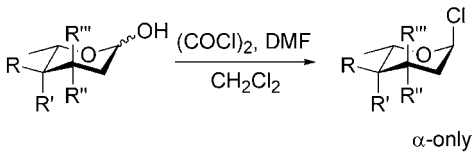
glycosyl acetates, whereas Lewis acids such as $ZnCl_2$ or $BiCl_3$ reverse the selectivity. A recent solvent-free protocol, amenable to large-scale preparation, involves the reaction of glycosyl peracetates (mono- and disaccharides; α or β) with $SOCl_2$ and $BiCl_3$, generated *in situ* from an amount of 10–20 mol% of a procatalyst BiOCl to afford α-anomeric chlorides in high yields and selectivity (Scheme 2.26) [126]. The reaction probably proceeds through a concerted mechanism without neighboring-group participation to give α-chlorides.

Very recently, it has been shown that unprotected reducing sugars can be directly converted into acetylated α-glycosyl chlorides using AcCl and basic Al_2O_3 on solid support (Scheme 2.27) [127]. The reaction conditions are mild and generally the yields and selectivity are high. Even, *N*-acetyl D-glucosamine can be converted into glycosyl chloride using this method.

Yet another method involves the treatment of a hemiacetal with oxalyl chloride in DMF. The protocol allows for an efficient preparation of α-chlorides of 2-deoxy-L-hexopyranosides (Scheme 2.28) [128].



Scheme 2.27



R = OAc, R' = H, R'' = N_3, R''' = H
R = H, R' = OAc, R'' = N_3, R''' = H
R = H, R' = OAc, R'' = OAc, R''' = H
R = OAc, R' = H, R'' = H, R''' = H
R = H, R' = OAc, R'' = N_3, R''' = CH_3
R = OAc, R' = H, R'' = N_3, R''' = CH_3

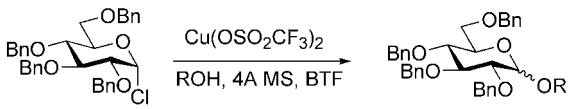
Scheme 2.28

2.2.2.2 Reactions of Glycosyl Chlorides

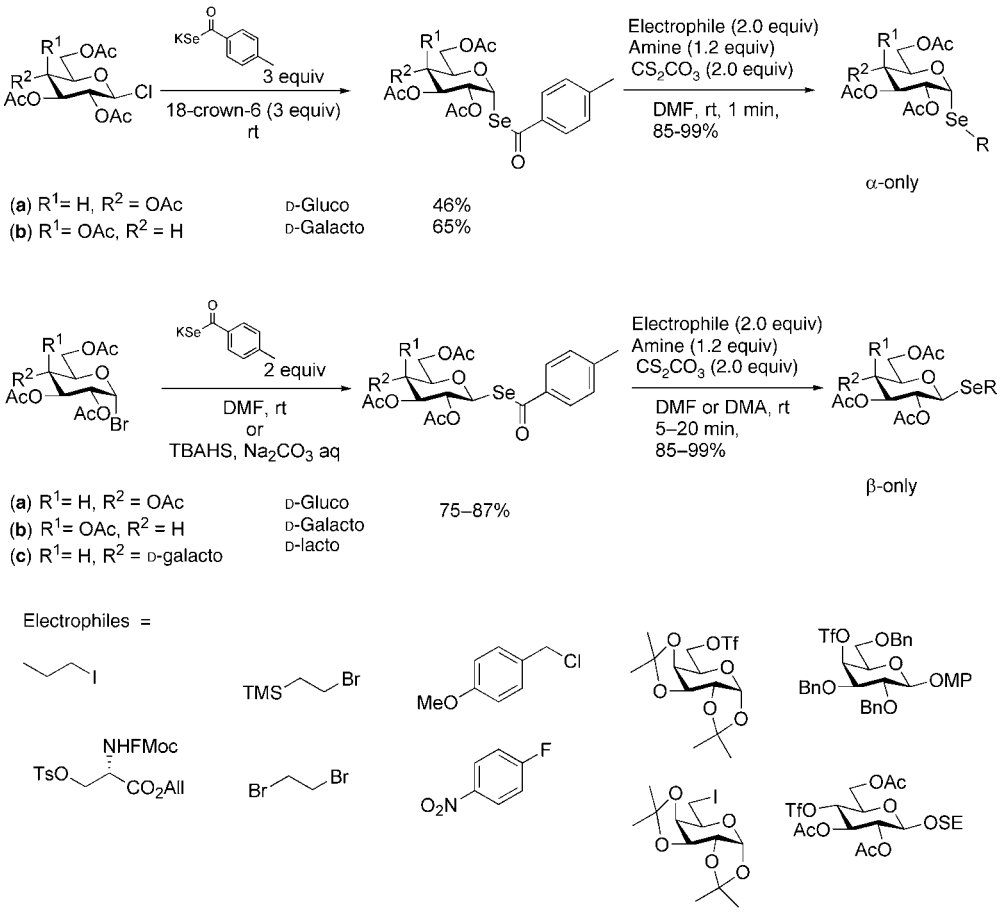
Glycosylation Classical Koenigs–Knorr reaction involves the coupling of a glycosyl bromide or chloride with glycosyl acceptors using heavy metal ion, typically mercury or silver [119–121]. Over the years, Lewis acid catalysis and phase transfer catalysis (PTC) have been introduced as useful variations of this process. Generally, glycosyl bromides are preferred over chlorides in these glycosylations. Copper(II) trifluoromethanesulfonate in benzotrifluoride ($C_6H_5CF_3$, BTF) has been shown to promote glycosylation of chlorides along with other glycosyl donors such as glycosyl fluorides, acetates, trichloroacetimidates and hemiacetals, although the yields and the selectivities are moderate (Scheme 2.29) [129].

S_N2 Reactions Owing to their inherent stability, glycosyl chlorides are appropriate candidates for S_N2 reactions offering complementary stereoselectivity compared to that of bromides and iodides. They are therefore useful precursors for various glycosyl donors. The following examples are noteworthy.

Selenoglycosides Monophasic reactions of acetylated β-glucosyl or galactosyl chlorides with potassium *p*-methylselenobenzoate in the presence of 18-crown-6 furnish a mixture of α- and β-isomers together with an unidentified product that upon purification affords α-isomer in modest yields (Scheme 2.30) [124]. In contrast, S_N2 reactions of the corresponding α-bromides (α-D-Glc, α-D-Gal, α-D-Lac) work well under monophasic as well as biphasic conditions to afford the corresponding β-isomers [130]. These α-and β-*p*-methylbenzoyl selenoglycosides react rapidly with various electrophiles to produce a diverse array of α-and β-selenoglycosides, respectively.



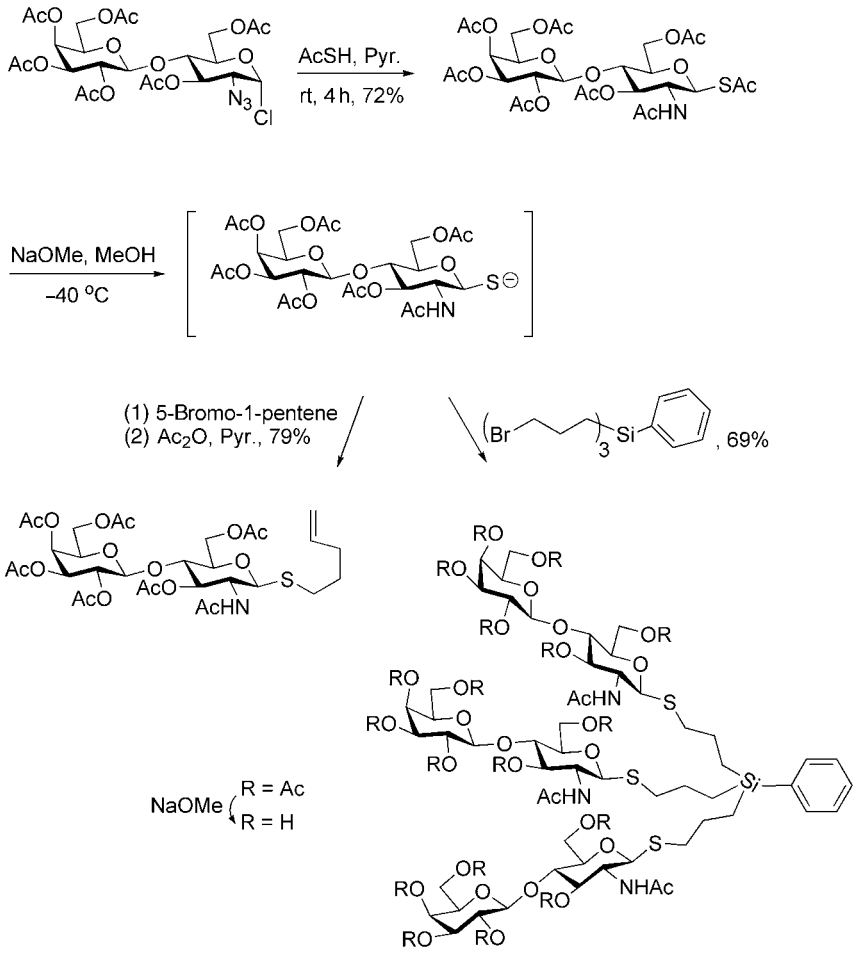
Scheme 2.29



Scheme 2.30

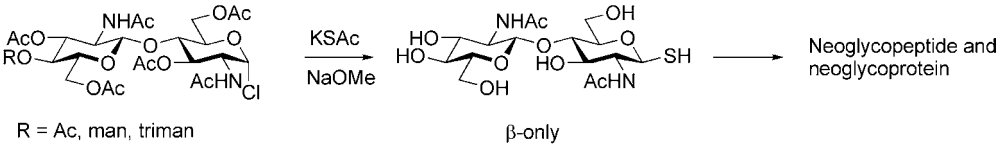
Thioglycosides α-Anomeric chlorides can be displaced smoothly in an S_N2 manner by thioacetate anions to produce β-anomeric thioacetates in high yields. For example, 2-azido lactosyl α-chloride reacts with excess thioacetic acid in the presence of pyridine to yield β-thioacetate with concomitant reductive acetamidation of the azide group [131]. The thioacetate could be reacted further to provide *S*-glycosides in high yields and subsequently transformed into a new class of glycoclusters (Scheme 2.31). Watt and Boons [132] used this reaction in their convergent synthesis of *N*-glycan core oligosaccharide thioaldoses (Scheme 2.32). The corresponding per-*O*-acetylated α-glycosyl chlorides were displaced with thioacetate to afford β-thioacetates in high yields and selectivity, which upon saponification gave the target oligosaccharides to be used for site-specific glycosylation of peptides and proteins bearing free cysteine.

Glycosyl Phosphates Deoxy sugars, which are vital components of various biomolecules such as vancomycin, erythromycin and daunomycin are difficult to be

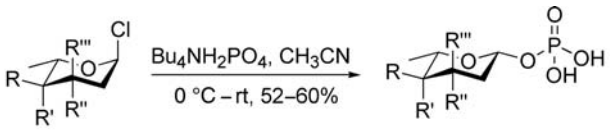


Scheme 2.31

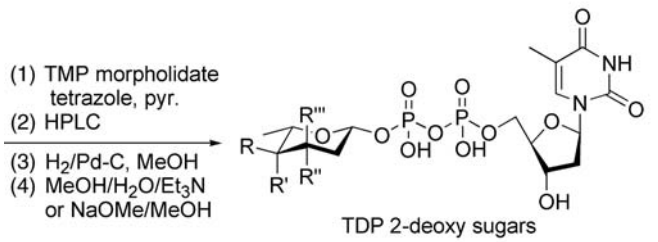
stereoselectively synthesized. β-Selectivity is hard to control without neighboring-group participation as α-linked products are favored. Kahne and coworkers [128] reported a stereoselective method to synthesize 2-deoxy-β-L-glycosyl phosphates from glycosyl chlorides via mainly S_N2 displacement with $Bu_4NH_2PO_4^-$ ($\alpha/\beta = 1:5–1:9$). It should be emphasized that more reactive glycosyl iodides and bromides



Scheme 2.32



R = OAc, R' = H, R'' = N_3, R''' = H	α/β = 1:5
R = H, R' = OAc, R'' = N_3, R''' = H	α/β = 1:5
R = H, R' = OAc, R'' = OAc, R''' = H	α/β = 1:9
R = OAc, R' = H, R'' = H, R''' = H	α/β = 1:9
R = H, R' = OAc, R'' = N_3, R''' = CH_3	α/β = 1:5
R = OAc, R' = H, R'' = N_3, R''' = CH_3	α/β = 1:5



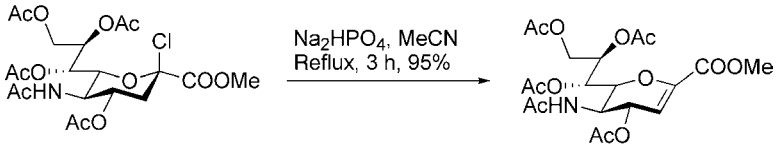
TDP 2-deoxy sugars

L-Acosamine	R = OH, R' = H, R'' = NH_2, R''' = H, 30%
L-Daunosamine	R = H, R' = OH, R'' = NH_2, R''' = H, 33%
2-Deoxy L-fucose	R = H, R' = OH, R'' = OH, R''' = H, 42%
L-Vancosamine	R = H, R' = OH, R'' = NH_2, R''' = CH_3, 35%
L-*epi*-Vancosamine	R = OH, R' = H, R'' = NH_2, R''' = CH_3, 28%

Scheme 2.33

give α-isomers as major products through S_N1-like reactions (α/β = 2 : 1), whereas stable chlorides shift the mode of the reaction toward S_N2 providing a range of β-deoxy sugar phosphates. Subsequent reaction of the glycosyl phosphates with TMP (thymidine monophosphoryl) morpholidate, followed by a careful HPLC separation from the minor α-isomer, azide reduction and deprotection of acetates gave 2-deoxy-β-TDP sugars in good yields (Scheme 2.33).

Elimination – Glycal Formation Sialic-acid-containing oligosaccharides play vital roles in living systems. Stereoselective sialylations typically require a stereodirecting group at C-3 that can be introduced to a 2,3-glycal (Neu5Ac glycal), which is also a key intermediate in the synthesis of the anti-influenza drug Relenza. Neu5Ac Glycal is obtained by eliminating the corresponding glycosyl chloride under various conditions. According to a recent protocol [133], a treatment of the peracetylated *N*-acetylneuraminic acid glycosyl chloride with anhydrous Na_2HPO_4 in refluxing acetonitrile quantitatively affords glycal (Scheme 2.34). The product can be isolated by simple filtration and evaporation of solvent thus obviating the need for chromatographic purification. Notably, no glycal formation takes place at room temperature.



Scheme 2.34

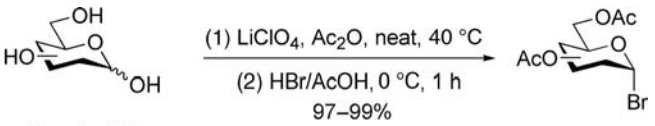
2.2.3 Glycosyl Bromides

As stated earlier, glycosyl bromides possess activity and stability intermediate to that of other halides; they are more reactive than fluorides or chlorides but more stable than iodides. Their popularity is largely attributed to controlled *O*-glycosylation via Koenigs–Knorr and related methods, phase transfer catalysis, solvolysis and displacement reactions. In this section, new methods of preparing glycosyl bromides and their modes of reactions are discussed. Their recent applications in oligosaccharide, glycoconjugate and natural product synthesis since 2001 are also presented.

2.2.3.1 Preparation of Glycosyl Bromides

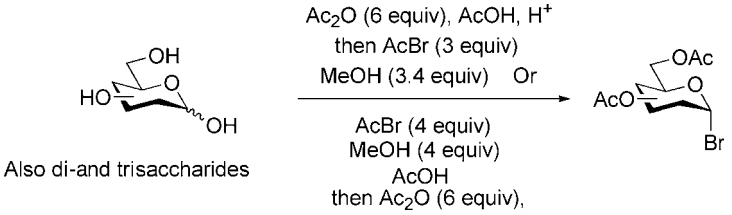
Earlier established methods for the generation of glycosyl bromides include the treatment of free reducing sugars with AcBr, AcBr–AcOH, AcBr–MeOH, PBr_3, Ac_2O–HBr–AcOH, or treatment of peracetylated sugars with HBr–AcOH or $BiBr_3$–TMSBr [134]. A recently reported two-step one-pot procedure workable on a large scale, affords α-anomeric bromides from free sugars (D-glucose, D-mannose, D-lactose, D-cellobiose, D-maltose) almost quantitatively (Scheme 2.35) [135]. Sequential treatment of a free sugar with Ac_2O (1.05 equiv per OH) in the presence of $LiClO_4$ (0.1 equiv per OH) followed by bromination using 33% HBr/AcOH solution furnishes acetylated glycosyl bromides.

Hunsen's procedures [134] use a combination of AcBr and MeOH for *in situ* generation of HBr (Scheme 2.36). Thus, free sugars including mono- (D-Glc, D-Man), β-linked disaccharides (D-cellobiose, D-lactose) and α-linked di- and trisaccharides (D-maltose, D-maltotriose) could be effortlessly converted into α-glycosyl bromides by treatment with Ac_2O and cat $HClO_4$ for peracetylation, followed by AcBr and MeOH. Alternatively, premixing of AcBr and MeOH in AcOH, to generate HBr, followed by the addition of sugar and Ac_2O affords the title compounds. The former protocol works better for galactose and maltotriose.

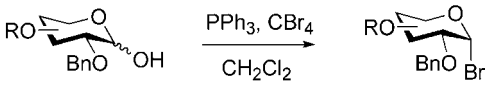


Also disaccharides

Scheme 2.35



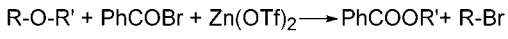
Scheme 2.36

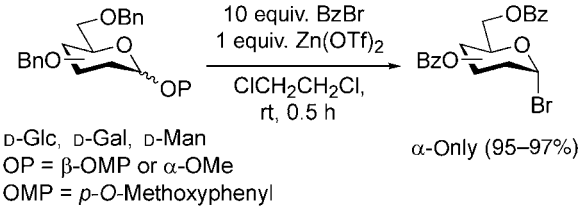


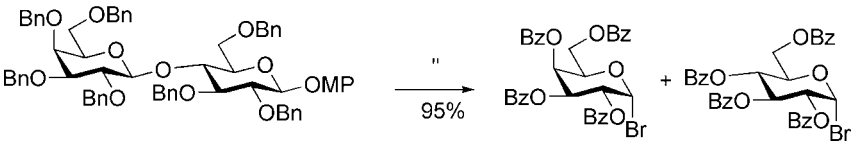
Scheme 2.37

The treatment of 2-*O*-benzylated hemiacetal sugars with Appel agents, triphenylphosphine/carbon tetrabromide ($PPh_3 + CBr_4$), in dichlormethane generates the corresponding 2-OBn α-glycosyl bromides, which are too reactive to purify (Scheme 2.37) [136]. The addition of diethyl ether to the reaction mixture precipitates the side product triphenylphosphine oxide (Ph_3PO), which can be filtered and the crude bromide is then obtained by evaporation.

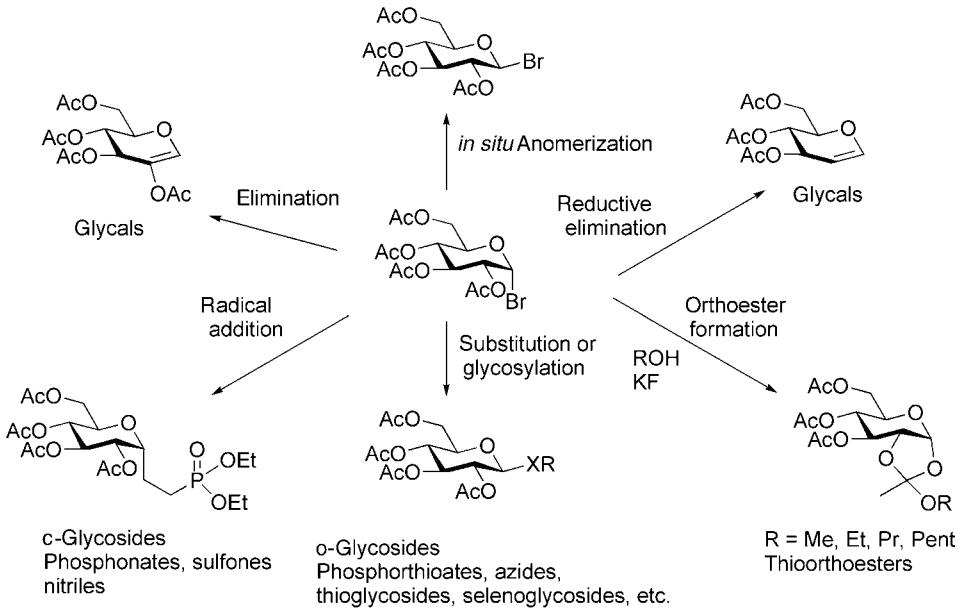
Polat and Linhardt reported a unique reagent combination of zinc triflate and benzoyl bromide for one-pot conversion of benzyl ethers to the corresponding benzoates. In these reactions, methyl or *p*-methoxyphenyl (OMP) glycosides were converted into perbenzoylated glycosyl bromides in near quantitative yields (Scheme 2.38) [137]. Per-*O*-benzylated lactose however underwent cleavage of both glycoside bonds generating per-*O*-benzoylated α-galactosyl and α-glucosyl bromides.







Scheme 2.38



Scheme 2.39

2.2.3.2 **Reactivity Patterns and Some Useful Reactions of Glycosyl Bromides**

Apart from direct glycosylations, glycosyl bromides can be converted into a panoply of synthons for diverse applications (Scheme 2.39). For example, glycals are useful synthetic precursors for the synthesis of glycosides (via Ferrier glycosylation or epoxides), aminoglycosides and oligosaccharides. Acetylated glycosyl bromides (pyranose, furanose mono- and disaccharides) form glycals via reductive elimination under various conditions [138] including a simple electrochemical setup [139]. Glycosyl bromides are susceptible to halide-assisted anomerization. Alternatively, bromides can be converted into 1,2-orthoesters, yet another synthetically useful entity, generated conventionally in the presence of a sterically hindered base or more recently by using potassium fluoride in acetonitrile at 50 °C [140].

Acetylated α-glycosyl bromides can be converted into β-anomeric azides or thioglycosides using NaN_3 or RSH in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) via a one-pot protocol starting from free sugars under phase transfer catalysis [141]. Azidolysis has also been shown to be accelerated under sonication-mediated conditions (5–10 min, 99%) [142]. The 1-azido derivatives can be subsequently transformed into dipeptides by incorporating sugar amino acids [143] and novel β-linked *N*-glycoside neoglycotrimers employing the Staudinger–aza-Wittig process or click chemistry [144].

Anomeric bromides can be converted into other important common glycosyl donors such as 1,2-*trans* selenoglycosides with indium(I) iodide-mediated cleavage of diselenides [145]. Seleno- and thioglycosides are also obtained from zinc/zinc chloride mediated cleavage of dichalconides [146], through thiophenolysis under

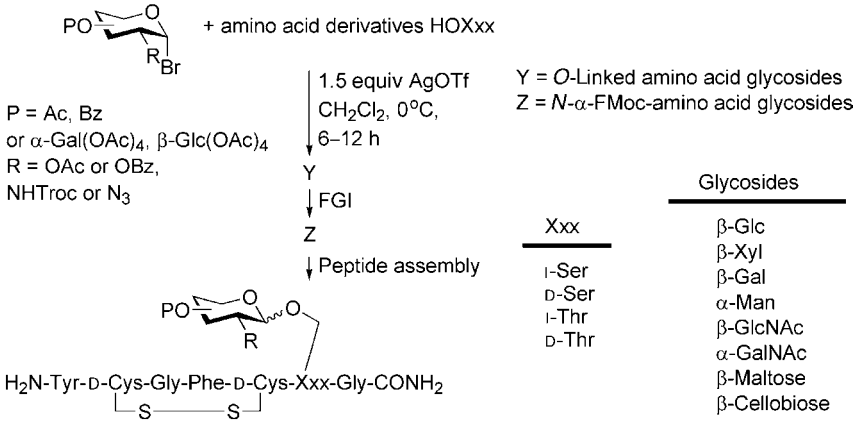
phase transfer [141,147] as well as homogeneous conditions [148], and *n*-pentenyl glycosides [149]. Glycosyl bromides have also been transformed into phosphorothioates using microwave techniques [150]. Various *S*- [151] and *N*-glycosylated [151,152] heterocycles have been accessed through glycosyl bromides as well.

Tin-catalyzed radical reactions of glycosyl bromides (D-Glc, D-Gal and L-Fuc) with diethyl vinylphosphonate have been shown to proceed in a diastereoselective fashion leading to the formation of corresponding α-linked *C*-glycosides [153], which were elaborated to the *C*-glycosyl analogs of natural NDP sugars as glycosyltransferase inhibitors [154]. Radical reactions of glycosyl bromides with benzothiazoyl vinyl sulfone afford α-C-glycoside sulfones with 60–73% yields [155].

2.2.3.3 Stereoselective Glycosylations Employing Glycosyl Bromides and Applications

Since the introduction of the first stereoselective glycosylation protocol more than a century ago, the Koenigs–Knorr reaction [119], glycosyl bromides have remained the most extensively used donors in glycosidation reactions. Anomeric selectivity is mainly controlled by the nature of the C-2 substituent; an ether-type group allows the formation of 1,2-*cis* glycosides owing to the anomeric effect, whereas ester-type groups lead to the formation of 1,2-*trans* glycosides through neighboring-group participation. Other factors such as solvent participation, temperature and metal chelation also play an important role.

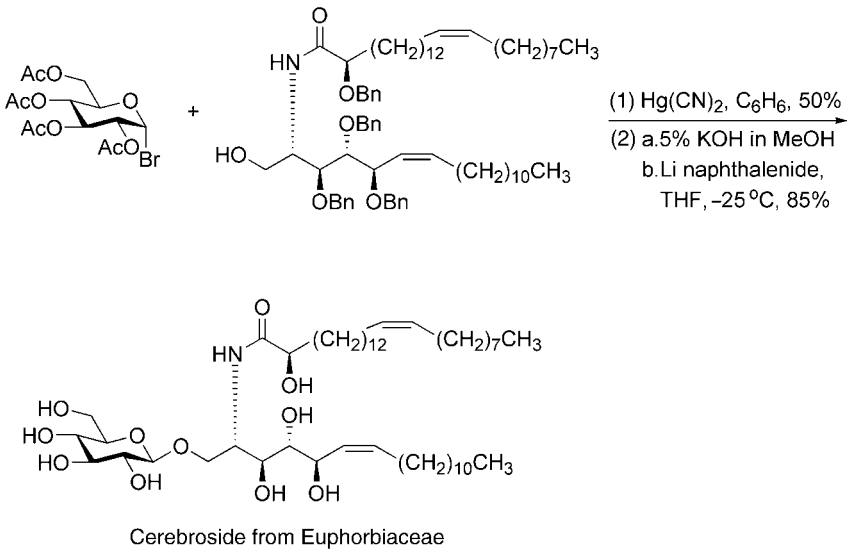
Over the years, several modifications including the use of Hg(II) salts and AgOTf as catalysts have been incorporated into the protocol that originally involved Ag_2CO_3 as an acid scavenger. These catalysts are especially suitable for solid-phase synthesis as exemplified by the synthesis of *O*-linked glycopeptide analogs of Enkephalin (Scheme 2.40) [156]. The synthesis of 18 *N*-α-Fmoc-amino acid glycosides, for solid-phase glycopeptide assembly, was carried out from either the corresponding O'Donnell Schiff bases or the *N*-α-Fmoc-amino-protected serine or threonine and the appropriate glycosyl bromide using Hanessian's modification of the Koenigs–Knorr method utilizing AgOTf. The observed differences in the



Scheme 2.40

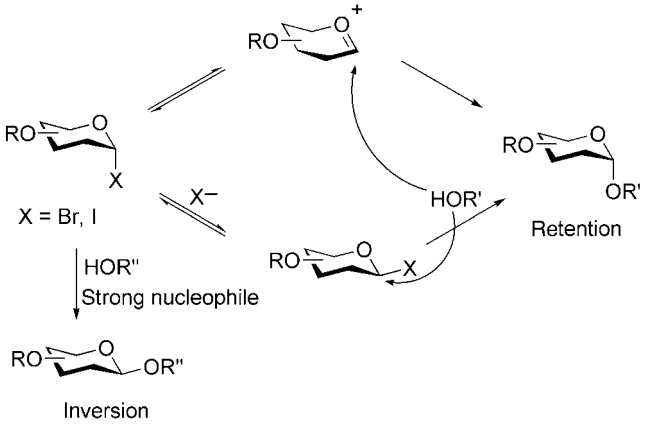
reaction rates of D-glycosyl bromides with the L- and D-forms of serine and threonine were rationalized in terms of the steric interactions within the two types of diastereomeric transition states for the D/L and D/D reactant pairs. The *N*-α-Fmoc-protected glycosides [monosaccharides Xyl, Glc, Gal, Man, GlcNAc and GalNAc; disaccharides Gal-β-(1–4)-Glc (lactose), Glc-β-(1–4)-Glc (cellobiose) and Gal-α-(1–6)-Glc (melibiose)] were incorporated into 22 enkephalin glycopeptide analogs. Fluorobenzoyl groups have been successfully used as alternatives to benzoyl or acetyl groups in solid-phase synthesis, suppressing β-elimination of base-sensitive *O*-serine-linked glycopeptides during base-catalyzed deacylation [157]. AgOTf-catalyzed glycosylations also work well in solution, as exemplified by syntheses of the spacer-armed pentasaccharide sialyl lacto-*N*-neoteraose and sialyl lacto-*N*-tetraose. In a systematic study of glycosylating *N*-trichloroacetyl-D-glucosamine derived mono- and disaccharide donors with disarmed acceptors (galactose, lactose, and lactosamine), AgOTf-activated acetylated glycosyl bromide donors displayed the best results among other types of donors [158].

Another modification of the Koenigs–Knorr method that uses $HgCN_2$ has continued to find applications in the synthesis of challenging *O*-disaccharides including 3-β-D-glucopyranosyl-D-glucitol [159] and more recently in the total synthesis of a bioactive cerebroside (Scheme 2.41) [160]. $Hg(CN)_2$ promoted coupling of acetylated glucosyl bromide with a fully functionalized ceramide acceptor afforded β-linked *O*-glycoside (50% yield), which upon global deprotection afforded the target cerebroside. Recently, glycosylations of acetylated glycosyl bromides were shown to be promoted with Lewis acid catalysis using $InCl_3$ under essentially neutral conditions, affording 1,2-*trans* glycosides and disaccharides in good yields [161].



Cerebroside from Euphorbiaceae

Scheme 2.41

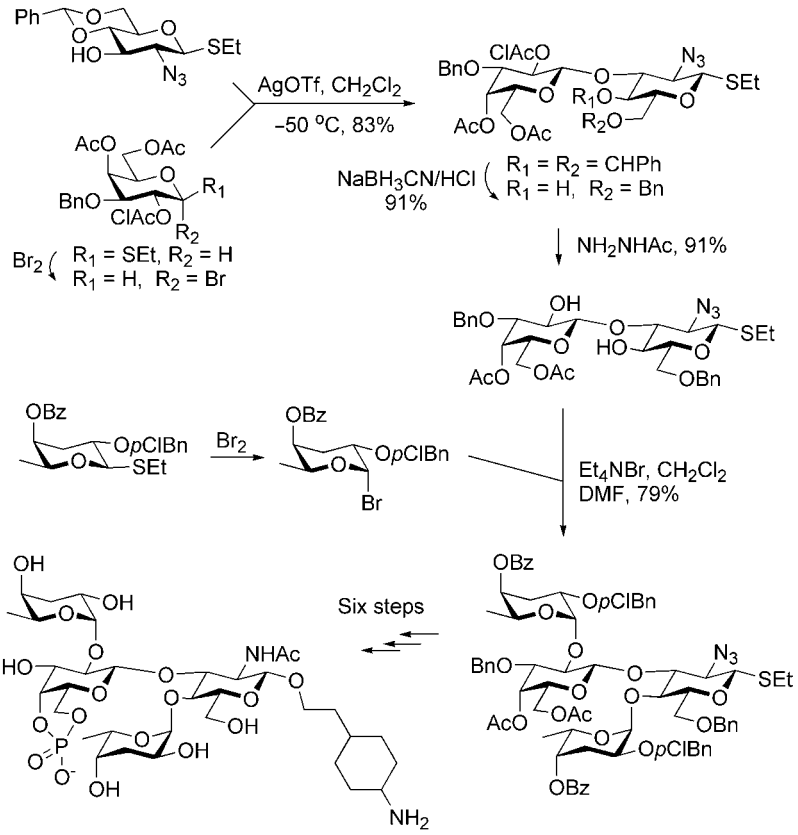


Scheme 2.42

Installation of a 1,2-*cis*-glycosidic bond is more challenging as compared to the 1,2-*trans* linkage [162]. Although, a nonparticipating group at C-2 of a glycosyl donor favors the formation of 1,2-*cis* glycoside by virtue of the anomeric effect, α-selectivity is often only moderate. In principle, S_N2 displacement of a 1,2-*trans* donor should furnish a 1,2-*cis* glycoside. However, this is often complicated by partial intervention of S_N1-like transition states giving α/β-mixtures. Pioneering work by Lemieux *et al.* [163] revealed new pathways for stereoselective 1,2-*cis* glycosylation through halide-catalyzed *in situ* anomerization. Accordingly, reactions of thermodynamically stable α-glycosyl bromides with tetrabutylammonium bromide generated the more reactive β-glycosyl bromides, which reacted with various alcohols under neutral conditions to afford α-glycosides, stereoselectively (Scheme 2.42).

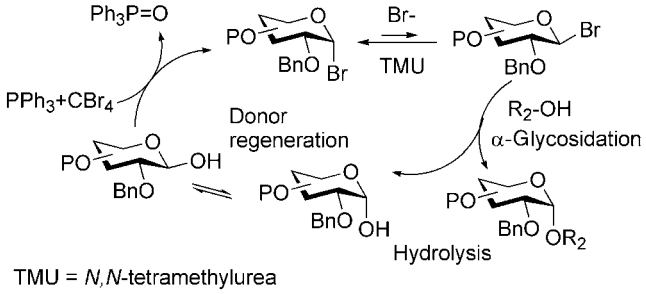
Stable thioglycosides can be readily converted into α-glycosyl bromides, which upon *in situ* anomerization could be coupled with thioglycoside acceptors with high α-selectivity or, conversely, with high β-selectivity using AgOTf via neighboring-group participation. This two-stage activation provides a useful tool for stereoselective orthogonal glycosylation, the merits of which can be gauged from Oscarson's recent syntheses of monodeoxy analogs of an α-linked branched trisaccharide Glc*p* (1 → 3)-α-D-Man*p*(1 → 2)- α-D-Man*p*OMe [164]. This approach was further exploited in the synthesis of oligosaccharides corresponding to *Vibrio cholerae* – a spacer equipped tetrasaccharide α-L-Col*p*-(1 → 2)-β-D-Gal*p*(1 → 3)-[α-L-Col*p*-(1 → 4)]-β-D-Glc*p*-NAc (colitose = 3,6-dideoxy-L-*xylo*-hexose), containing a 4,6-cyclic phosphate in the galactose residue (Scheme 2.43) [165]. Thus, galactose β-thioglycoside was first converted into an α-anomeric bromide and subsequently coupled with a glucosyl thioglycoside acceptor in the presence of AgOTf to obtain a β-linked disaccharide. Selective deacylation and reductive ring opening of the benzylidene acetal at O-4 afforded a diol acceptor that underwent double glycosylation with a L-colitose donor under *in situ* anomerization conditions affording a protected tetrasaccharide with high α-stereoselectivity and good yields.

Two alternate protocols for the *in situ* anomerization procedure have been introduced by Kobayashi and Nishida, both involving Appel agents [166–168]. According to

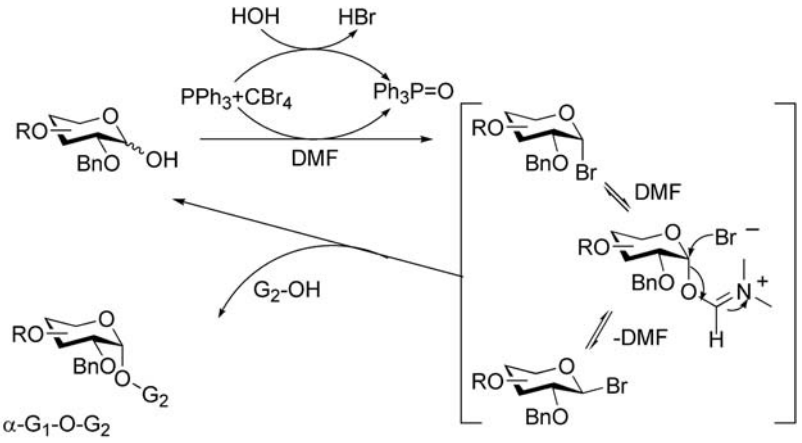


Scheme 2.43

the first pathway (Scheme 2.44), the reaction of a 2-*O*-benzyl-1-hydroxy sugar with CBr_4 and PPh_3 generates a reactive glycosyl bromide *in situ* [136], which is subsequently coupled with an acceptor in the presence of Br^- and *N,N*-tetramethylurea (TMU) at room temperature to afford α-glycoside quantitatively [166]. This reagent



Scheme 2.44

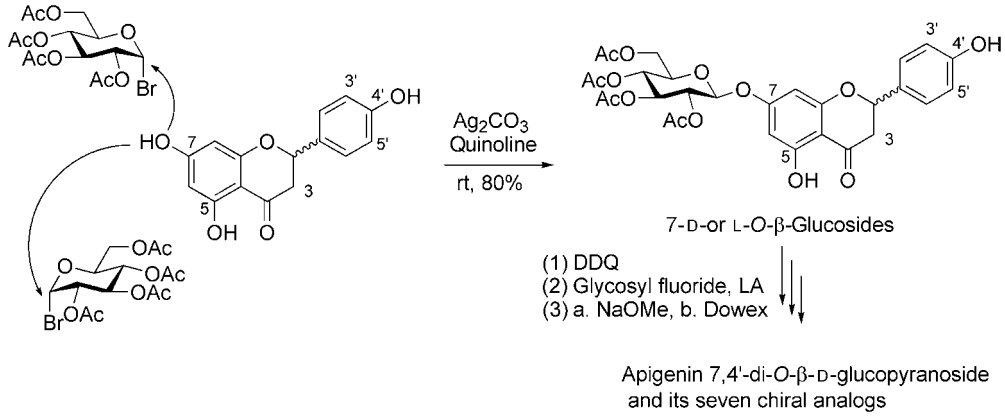


Scheme 2.45

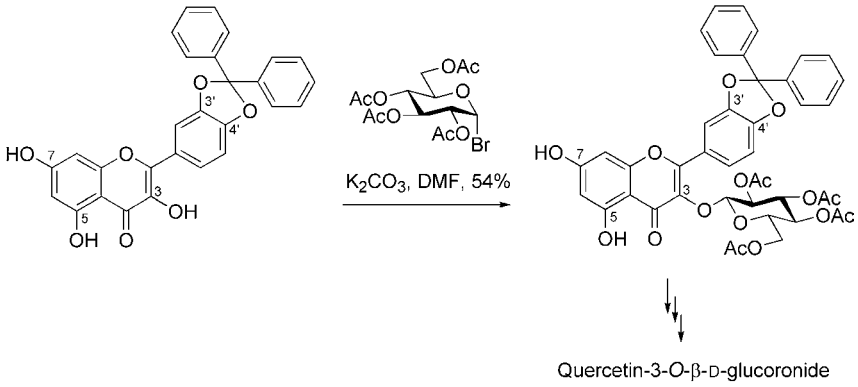
combination plays multiple roles including the glycosyl bromide formation, *in situ* anomerization and glycosylation. It also serves to scavenge water allowing the reactions to be performed without special attention to moisture. The reaction works well for D-gluco, D-galacto and L-fuco donors using various acceptors. The second dehydrative protocol employs DMF as a solvent, which obviates the necessity to add TMU (Scheme 2.45) [167]. On the basis of NMR studies, a DMF–glycosyl adduct (cationic α-glycosyl imidate-like [168] intermediate with Br^- counterion) is implicated in this reaction.

Glycosyl bromides have also proven to be excellent donors for highly regioselective glycosylation of flavonols leading to a total synthesis of numerous natural products [120]. For example, peracetylglucosyl bromide was regioselectively coupled with naringenin (Scheme 2.46) under classical Konigs–Knorr conditions resulting in 80% yield [169]. Consecutive coupling with a glucosyl fluoride also proceeded regioselectively at O-4′. On the basis of these results, Kondo and coworkers reported the first total synthesis of apigenin 7,4′-di-*O*-β-D-glucopyraoside, a component of the blue pigment, protodelphin, along with seven chiral analogs [169,170]. Partially protected quercetin (Scheme 2.47) was regioselectively coupled with a glucosyl bromide at O-3 under basic conditions to afford the 3-*O*-β-D-glycoside in 54% yield. The glycoside was further transformed into quercetin-3-*O*-β-D-glucuronide via benzylation, deacetylation, TEMPO oxidation and hydrogenation [171]. Yu [172], and subsequently Linhardt [173], employed phase transfer conditions to effect regioselective O-3 glycosylation of 3,5,3′ and 3,5,4′-triols of the quercetin nucleus using various mono- and disaccharide glycosyl bromides (Scheme 2.48) [172–176]. Phase transfer conditions have also been used for the coupling of glycosyl bromides in solid-phase synthesis [177].

Very recently, direct displacement of acylated glycosyl bromides (D-Man and L-Fuc) with nucleotide 5′-diphosphates has been shown to proceed stereoselectively



Scheme 2.46

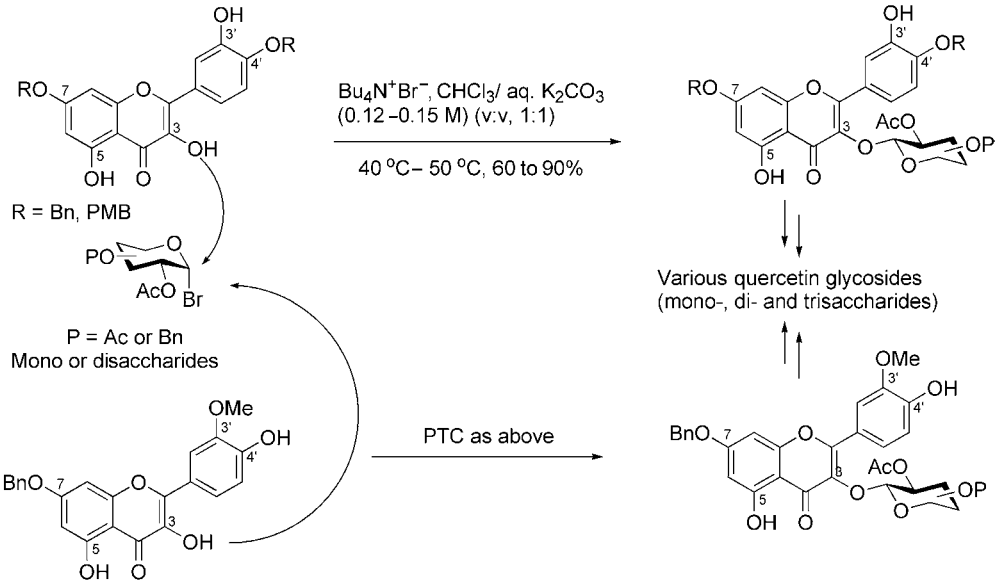


Scheme 2.47

through classical neighboring-group participation. This route is utilized for the preparation of diastereomerically pure α-D-manno and β-L-fuco-linked sugar nucleotide diphosphates UDP and GDP (Scheme 2.49) [178].

2.2.4
Glycosyl Iodides

Over the past decade, glycosyl iodides [122] have clearly become an important reactive intermediate in carbohydrate synthesis. Their reactivity and stability can be tuned by altering the protecting-group pattern. Thus, per-*O*-silylated iodides, which are usually generated *in situ*, are on the extreme high side of the reactivity scale, partially benzylated iodides possess intermediate reactivity and can be stored for longer times at subzero temperatures, whereas per-*O*-acylated glycosyl iodides are stable crystalline solids with long shelf life. The unique reactivity profile of

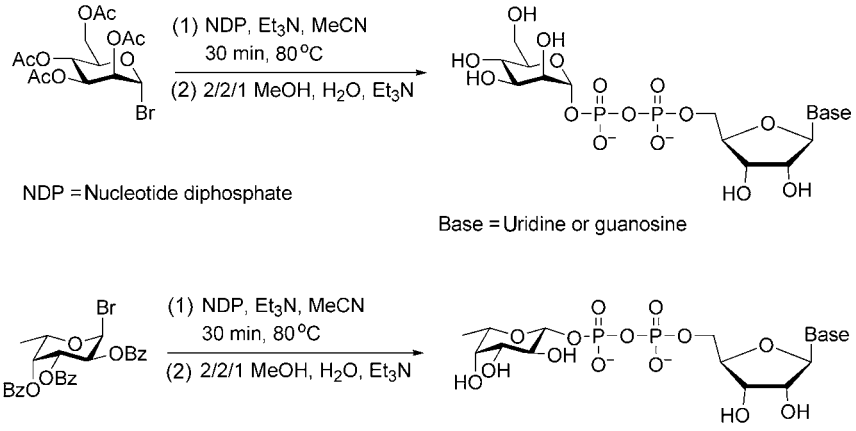


Scheme 2.48

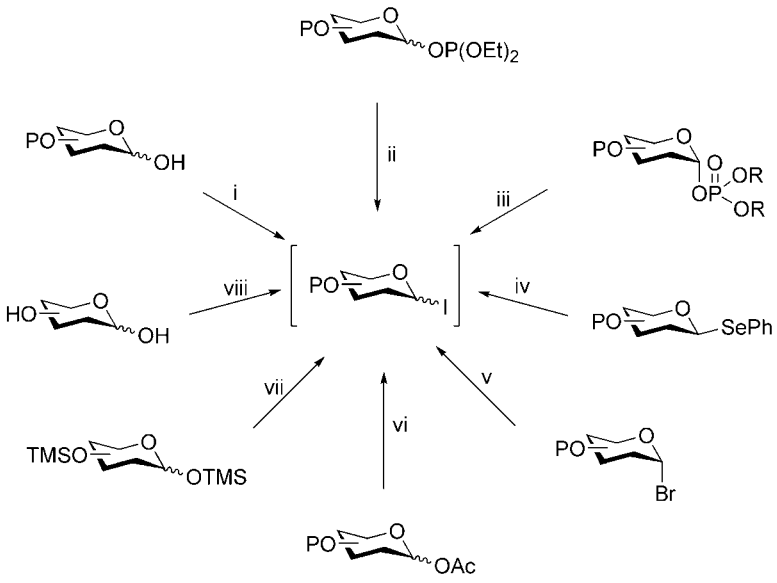
glycosyl iodides can be advantageously exploited for solvolysis and stereospecific S_N2 glycosylations.

2.2.4.1 Preparation of Glycosyl Iodides

Several methods are available to access glycosyl iodides (Scheme 2.50). Anomeric hemiacetals bearing diverse protecting groups (Bn, Bz, Ac, N_3, CMe_2) upon treatment with a polymer-bound triphenylphosphine–iodine complex and imidazole can be converted into α-glycosyl iodides [179]. The precipitated by-products,



Scheme 2.49



(i) -C_6H_4-PPh_2-I_2, ImH or PPh_3-I_2, ImH
(ii) DTBPI, 4 Å MS, CH_2Cl_2
(iii) 1M $LiClO_4$, Li(Na)I, 4 A MS, CH_2Cl_2
(iv) I_2, $CDCl_3$
(v) I_2 or IBr or ICl or NIS
(vi) TMSI or I_2/Et_3SiH or HI (I_2 + RSH)
(vii) TMSI, CH_2Cl_2
(viii) a. Ac_2O, cat. I_2; b. I_2, HMDS (TMSI)

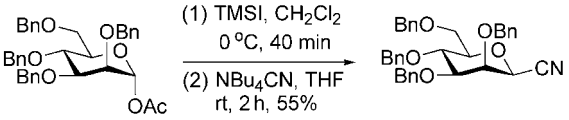
Scheme 2.50

that is excess imidazole and solid polymer-bound phosphine oxide, can be removed by filtration through Celite yielding iodides that are pure enough to be used for further reaction. Per-*O*-benzylated glycosyl diethylphosphites (D-Glc, D-Gal, L-Fuc) have also been used to generate glycosyl iodides using 2,6-di-*tert*-butyl pyridinium iodide (DTBPI) in CH_2Cl_2 at ambient temperature [180]. Waldman's method [181] employs per-*O*-benzylated glycosyl phosphates as precursors to glycosyl iodides generated by the reaction of LiI in 1 M solution of $LiClO_4$ in organic solvents, such as CH_2Cl_2 or CH_3CN. Selenoglycosides provide the corresponding iodides upon treatment with molecular I_2. NMR monitoring experiments revealed that per-*O*-benzylated (armed) selenoglucosides are rapidly converted (5 min) into the corresponding iodides, whereas the disarmed counterpart takes 4 days [182]. Acylated bromosugars can be converted into glycosyl iodides by its reaction with iodine [183] or other reagents such as IBr, ICl and NIS [184].

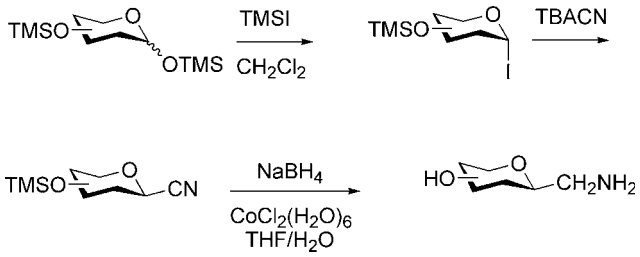
One of the most reliable and commonly used methods to prepare glycosyl iodides involves the treatment of anomeric acetates with TMSI. Thiem and Meyer introduced this method to generate iodides from anomeric acetates, acetals, methyl glycosides or anhydro sugars [185]. In this reaction, the acetate is first activated by silylation and concomitantly undergoes displacement to generate anomeric iodide. In the first mechanistic studies with glycosyl iodides [186], it was shown that α-iodides are stereoselectively formed from β-anomeric acetates. Conversely, β-glycosyl iodides are the initial products derived from α-acetates but β-iodide readily converts into the thermodynamically more stable α-anomer. Per-*O*-acetates of mono- and disaccharides can also be transformed into α-glycosyl iodides upon treatment with HI, generated *in situ* by the reaction of solid iodine and thiol [187], or by I_2/triethylsilane [188]. Per-*O*-trimethylsilylated mono- [189,190] and disaccharides [191] also undergo conversion to the corresponding glycosyl iodides upon treatment with TMSI. A recent procedure for one-pot preparation of glycosyl iodides from free hexoses involves per-*O*-acetylation followed by the treatment with I_2/hexamethyl disilane (TMSI generated *in situ*) [192]. Among all these procedures, TMSI is often the reagent of choice due to the ease of removing volatile by-products (TMSOMe, TMSOTMS or TMSOAc), which can compete as acceptors if left in the reaction mixture.

2.2.4.2 Reactions of Glycosyl Iodides

Nucleophilic Anionic Substitutions Classical Koenigs–Knorr glycosylation and variants thereof involves metal chelation for halide activation and often proceeds through oxonium ion formation, allowing the stereochemical outcome to be dictated by the C-2 substituent on the donor sugar. Alternatively, glycosyl iodides undergo direct displacement through an S_N2-like mechanism. In an attempt to develop efficient nonmetal-catalyzed glycosylations, anionic additions to glycosyl iodides were studied [193]. These reactions proceeded with inversion of configuration at the anomeric center to give β-glycosides even in the absence of a C-2 participating group, with the following order of reactivity –2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl iodide > 2,3,4,6-tetra-*O*-benzyl- α-D-glucosyl iodide > 2,3,4,6-tetra-*O*-benzyl- α-D-mannosyl iodide. Glycal formation was observed with glucosyl and galactosyl iodides when highly basic anions were employed whereas no elimination took place with mannosyl iodides. A variety of nucleophiles such as malonate, CN^-, N_3, phthalimide, phenoxide and acetate anions were stereoselectively added to glycosyl iodides to afford β-linked *C*-, *N*- and *O*-glycosides in good yields. The formation of the β-mannosyl cyanate was particularly noteworthy (Scheme 2.51).



Scheme 2.51

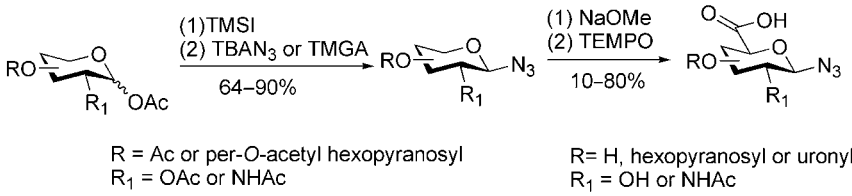


Scheme 2.52

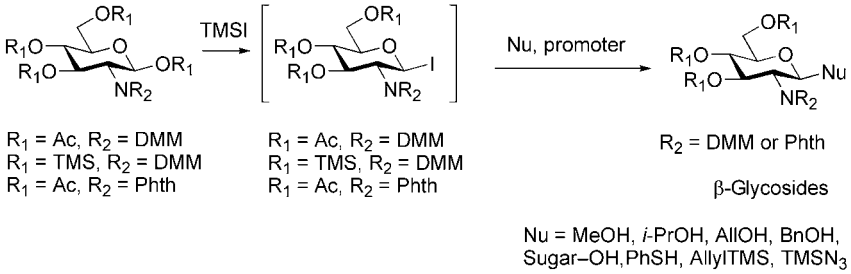
Similarly, per-*O*-trimethylsilylated mono- and β-linked disaccharides (lactose and cellobiose, not melibiose) could be converted into the corresponding α-glycosyl iodides, which upon S_N2 displacement with CN^- using TBACN mainly afforded β-cyano derivatives in good overall yields [191]. The cyanoglycosides were transformed into aminomethyl glycosides via reduction under mild conditions (Scheme 2.52).

These methods were extended to include disarmed glycosyl iodides as a general method for the synthesis of glycopyranosyluronic acid azides (Scheme 2.53) [194]. Peracetylated mono- (D-Glc, D-Gal and D-Man) and disaccharides (cellobiose, lactose, melibiose) were first treated with TMSI to generate the corresponding glycosyl iodides, which were then reacted with $TBAN_3$ or tetramethylguanidium azide (TMGA) in CH_2Cl_2 to afford β-anomeric azides in good yields. These azides were transformed into the corresponding uronic acids after deacetylation and low-temperature TEMPO oxidation. Along similar lines, glycosyl iodides of dimethylmaleolyl (DMM) or phthaloyl (Phth)-protected D-glucosamine were generated and coupled with various nucleophiles (alcohols – MeOH, AllOH, *i*-PrOH and BnOH without promoter, sugar-OH with AgOTf, PhSH, and allyl-TMS as well as $TMSN_3$ with $BF_3{\cdot}OEt_2$) to obtain β-linked *O*-, *S*-, *C*-, and *N*-glycosides in good yields (Scheme 2.54) [195]. This reaction goes through the intermediacy of an unstable β-iodide as evidenced by NMR studies. The stereochemical outcome of the glycosylation is believed to be controlled by neighboring-group participation of the C-2 functionality.

S_N2 reactions of glycosyl iodides have proven especially advantageous in the synthesis of 2-deoxy β-*O*-aryl-D-glycosides. This is a challenging linkage to make, as there is no neighboring group to participate. Sometimes, stereochemistry is



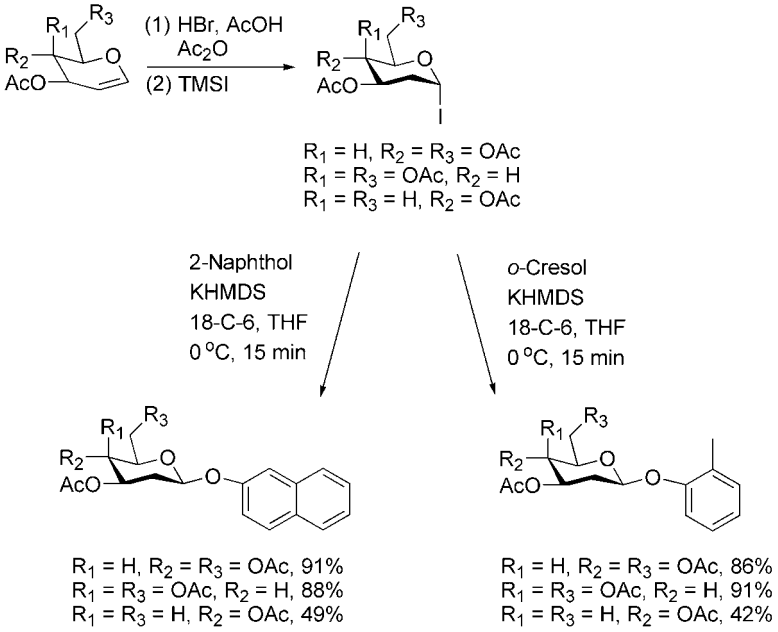
Scheme 2.53



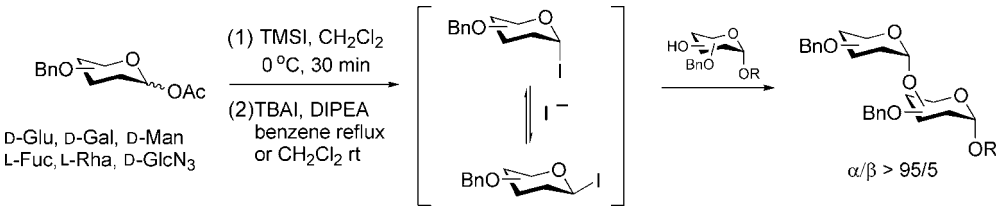
Scheme 2.54

controlled by temporary introduction of a stereo-directing functionality at C-2, and the C-2 functional group is removed after glycosylation. Direct displacement of α-glycosyl iodides obviated the necessity for a C-2 directing group. The conversion of glycals to 2-deoxy glycosyl acetates followed by the reaction with TMSI readily afforded the corresponding α-glycosyl iodides, which underwent facile S_N2 reactions with aryl alkoxy anions (*o*-crysol or 2-naphthol) to provide aryl β-2-deoxy-glycosides in good yields (Scheme 2.55) [196].

Stereoselective Glycosylations of Glycosyl Iodides General methods for α-selective glycosylation of glycosyl iodides via *in situ* anomerization have been established [197]. Armed glycosyl iodides undergo the reaction in the presence of tetrabutylammonium iodide (TBAI) and Hünig's base (diisopropyl ethylamine DIPEA) with



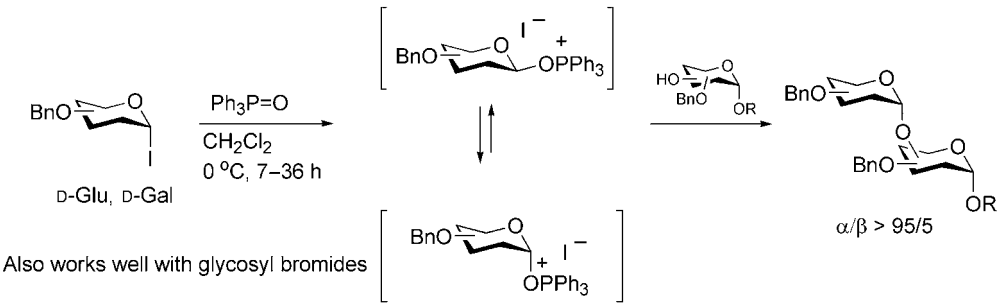
Scheme 2.55



Scheme 2.56

various acceptors (Scheme 2.56), including hemiacetals, 6-OH and sterically hindered secondary sugar acceptors. Under these conditions, the first formed α-iodide undergoes attack by I^- to generate the thermodynamically unstable β-iodide, which being orders of magnitude more reactive than the corresponding α-iodide instantaneously reacts with nucleophilic acceptors to form α-glycosidic linkages. Such glycosylations involving anomeric iodides were found to offer advantages over the corresponding bromides in terms of time, yield and overall efficiency. The donor iodides follow the following order of reactivity: L-Fuc > D-Gal > D-Man > D-Glc. Thus, glucosyl iodides show higher reactivity than mannosyl iodides in direct nucleophilic displacement reactions, whereas this order is reversed in TBAI-promoted glycosylations. Solvent effects have also been observed in these glycosylations when using acetonitrile as a participating solvent and allyl alcohol as an acceptor. Intriguingly, per-*O*-benzylated glucosyl iodide afforded the corresponding β-allyl glucoside as the major isomer ($\alpha/\beta = 1:10$), whereas per-*O*-benzylated galactosyl iodide rapidly and exclusively generated α-galactoside in acetonitrile. The mannosyl iodide furnished 1/1 α/β mixture under identical conditions [197]. These observations could be rationalized on the basis of the relative rate of formation of oxonium ion versus nitrilium ion intermediates.

Analogous to the *in situ* anomerization method, α-selectivity is also achieved by adding triphenylphosphine oxide in place of TBAI as a promoter, as first established with glycosyl iodides [198,199] (Scheme 2.57) and subsequently with glycosyl bromides [200]. Upon treatment with Ph_3PO, benzylated glycosyl iodides are believed to generate transient glycosyl phosphonium iodides. Glycosyl acceptors predominantly react with the β-form to afford α-disaccharides in very high yields and with high

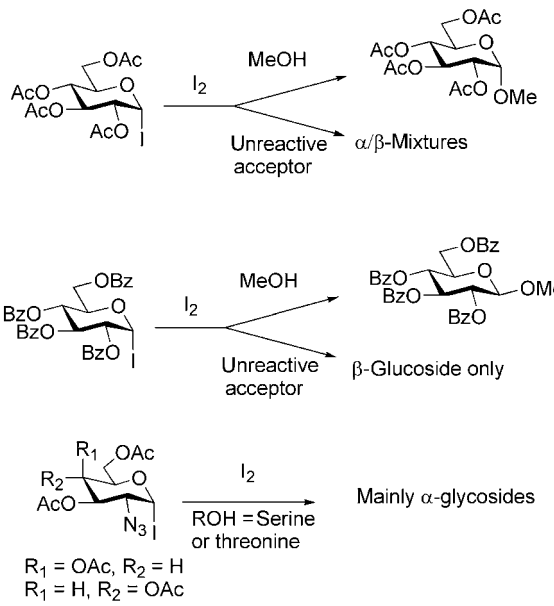


Scheme 2.57

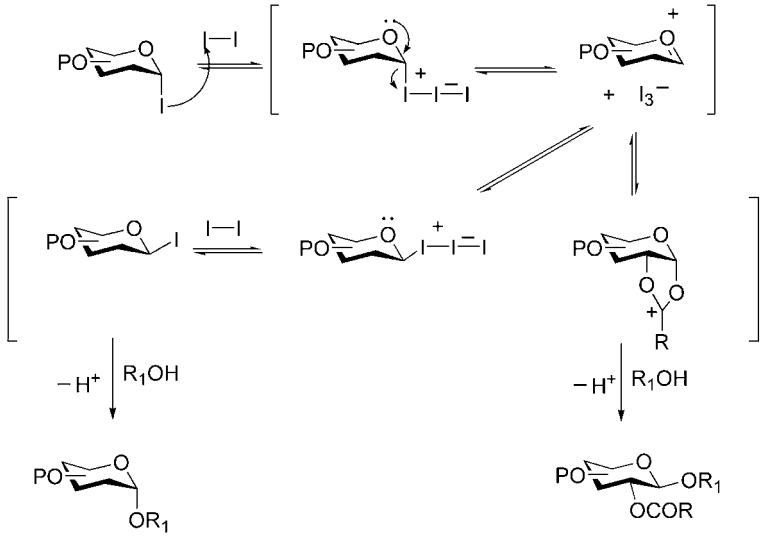
stereoselectivity. This procedure also works well with glycosyl bromides but requires longer reaction times.

Field and coworkers [201] used iodine for the activation of per-*O*-acetylated glycosyl iodides. Although disarmed glycosyl iodides are activated by I_2, the stereochemical outcome is dominated by the nature of the O-2 protecting group and the reactivity of the acceptor. For example, glycosylations between acetate protected donors and reactive acceptors like methanol gave exclusively α-product, whereas per-*O*-benzoylated iodides gave only β-linked products. Good α-selectivity was also observed with 2-deoxy-2-azido donors using serine and threonine acceptors (Scheme 2.58). The α-linked products in per-*O*-acetate sugars presumably arise through S_N2 displacement of an β-iodide existing at equilibrium in the reaction mixture (Scheme 2.59). Per-*O*-benzoylated donors have more effective neighboring-group participation yielding β-isomers. Donors bearing nonparticipating azides at C-2 mainly give α-isomers, and the selectivity decreases with decreasing reactivity of the acceptor.

Per-*O*-acylated glycosyl iodides are stable at room temperature and can be purified on a silica gel column and stored at 0 °C. Stachulski and coworkers [202] synthesized methyl 2,3,4-tri-*O*-pivaloyl-glucopyranuroate iodide, which is a stable solid at 20 °C and can be stored for months at room temperature or for more than a year at 0 °C. The X-ray crystal structure of this compound, the first one of this class, shows a typical chair structure. Importantly, such a disarmed and stable iodide can be coupled with primary and secondary steroidal alcohols using I_2 as a promoter, as demonstrated by the synthesis of morphine-6-glucuronide, an analgesic [202]. The glycosyl donor ability

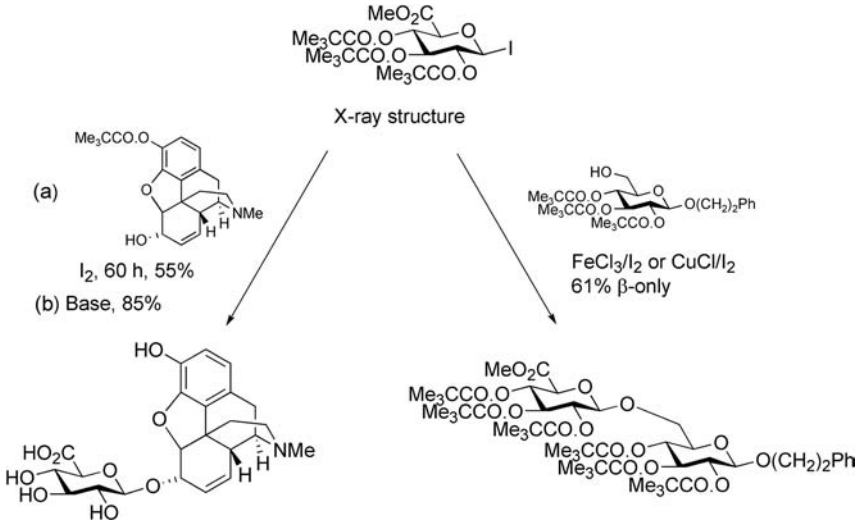


Scheme 2.58

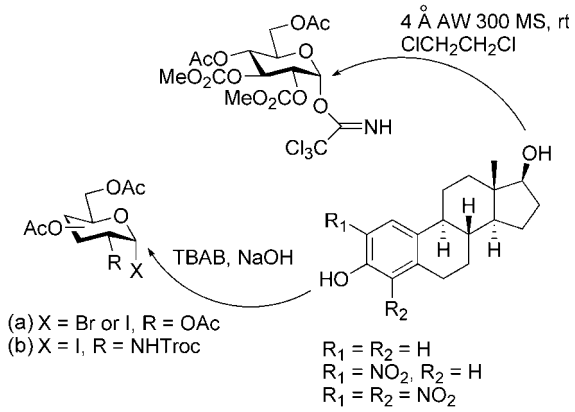


Scheme 2.59

of the iodide is contrasted with the corresponding bromide, which gives a yield of only 20% for the coupling with 3-*O*-pivaloyl morphine acceptor compared to 55% yield obtained with the iodide. This iodide donor could also be coupled with several other steroidal alcohols using NIS or metal salts as promoters [203]. In a similar fashion, the iodide glycosyl donor can be coupled with disarmed sugar acceptors in the presence of NIS/I_2/TMSOTf, $FeCl_3/I_2$ or $CuCl/I_2$ to obtain β-linked disaccharides in good yields (Scheme 2.60) [204]. Disarmed glycosyl iodides (and bromides) have also been used to



Scheme 2.60

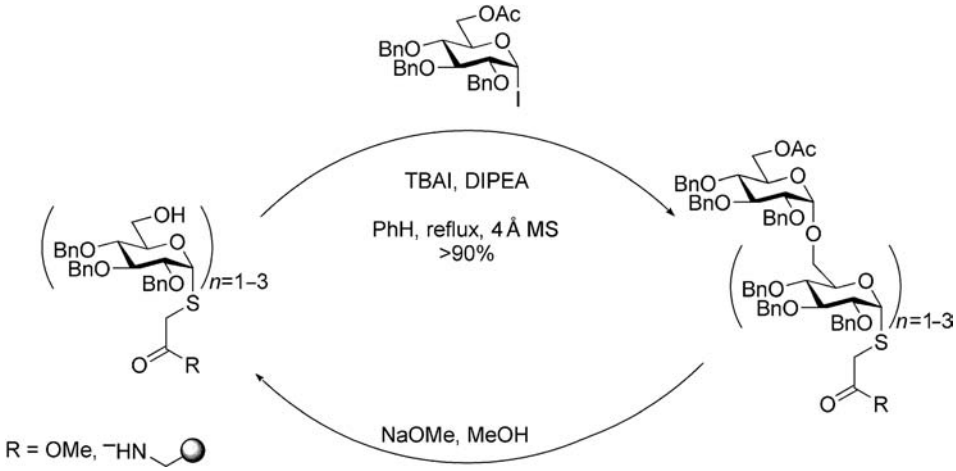


Scheme 2.61

achieve regioselectivity in the glycosylation of 17β-estradiol and its derivatives [205]. Glycosyl iodides undergo regioselective glycosylation of the phenolic alcohol under phase transfer catalysis conditions, whereas trichloroacetimidates selectively couple with the carbinol under mild activation with 4 Å acid-washed molecular sieves (Scheme 2.61).

α-Selective Glycosylation: Applications to Oligosaccharide and Glycolipid Synthesis *In situ* anomerization has been successfully applied in α-glycosylations of orthogonally protected armed glycosyl iodides for oligosaccharide synthesis under solution- [206–209] and solid-phase [207] conditions. α-(1 → 6)-Linked glucosyl homooligomers (isomaltobiose) were synthesized with high yields (84–94% for each coupling), giving α-glycoside as the only product in each step. A $1+1+1$ iterative coupling strategy utilizing a 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl glucopyranoside monomeric unit and convergent $2+2+2$ and $2+4$ couplings was equally successful [206,207]. Notably, the corresponding glycosyl iodide could be stored under argon in benzene solution in the refrigerator for a month without significant degradation. Solution-phase synthesis via $1+1+1$ strategy began with the glucosyl iodide donor that was first coupled with a 6-OH thioglucoside acceptor to afford α-1 → 6-linked disaccharide, which upon selective de-*O*-acetylation generated the corresponding 6-OH disaccharide acceptor. Iterative coupling with the same iodide donor furnished tri- and tetrasaccharides in very high yields (Scheme 2.62) [206]. Under solid-phase conditions, the 6-OH thioglucoside acceptor was first linked to tentagel NH_2 resin via amide bond formation with the anomeric thioglycolic acid and then the coupling–deacetylation sequence was repeated [207].

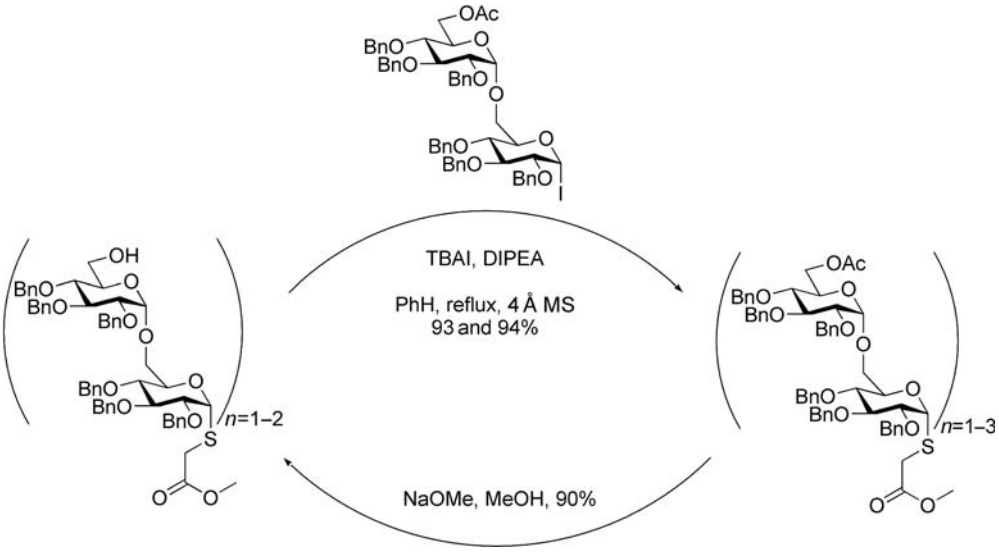
In the $2+2+2$ strategy, the α-1 → 6-inked disaccharide was first assembled from the glucosyl iodide donor and 6-OH glucoside acceptor bearing an anomeric acetate. This disaccharide was then used to generate iodide, which was employed in the coupling with the disaccharide thioglycoside acceptor. Repetitive coupling and deactylation sequences on the tetrasaccharide afforded hexasaccharide as only the



Scheme 2.62

α-anomer in high yield (Scheme 2.63). Similarly, the 2 + 4 strategy furnished the corresponding hexasaccharide in high yields.

It should be emphasized that under these conditions, neither cleavage of interglycoside bond by TMSI was observed nor β-isomer was detected in any of the couplings. Although the solid-phase strategy was advantageous in terms of ease of purification, it required the use of excess donor (7.5 equiv per coupling) and longer reaction times (12 h for each coupling) [207]. In contrast, solution-phase reactions

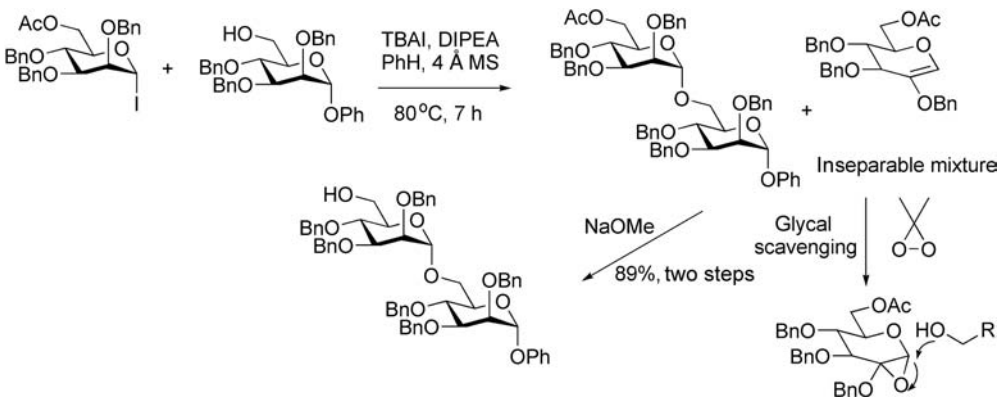


Scheme 2.63

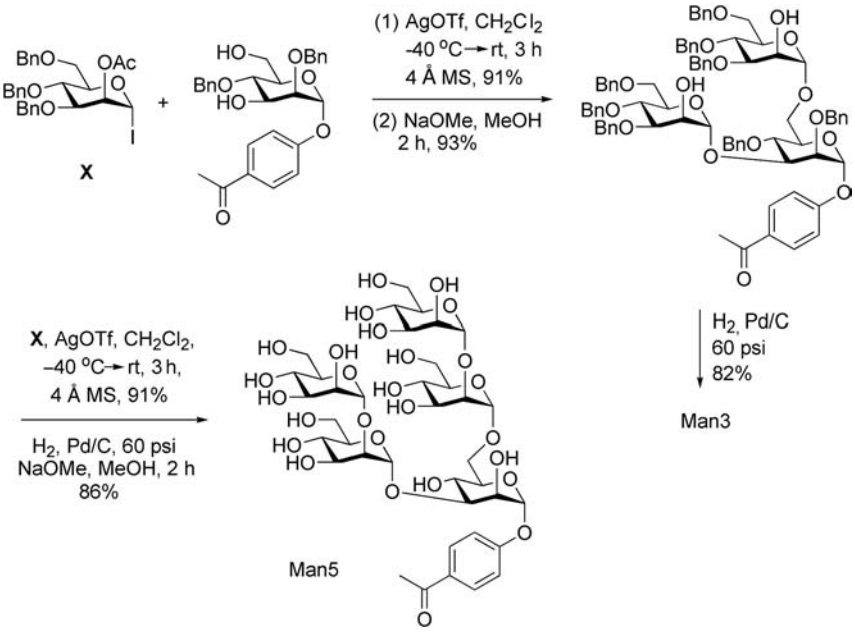
utilized only 2.5 equiv of donor and required 2–3 h for the completion of each glycosylation reaction, making solution phase the preferred strategy for oligomer synthesis.

These studies were extended to develop a highly efficient synthesis of HIV-1-associated glycoprotein (gp120) mannose di-, tri- and pentasaccharides (Man-3 and Man-5). The α-(1 → 6)-linked disaccharide constructs could be prepared in solution from glycosyl iodide precursors with only a slight excess of the iodide donor [208], and this process offers advantages over solid-phase methods that require more than 5 equiv of donor. During the TBAI-assisted reaction, excess glycosyl iodide is converted into a glycal that is not easily separable from the desired disaccharide. This problem could be overcome using a scavenging protocol involving selective epoxidation of the intervening glycal followed by nucleophilic attack (Scheme 2.64) [208]. Alternatively [209], glycosylation of a *O*-2-acetyl mannosyl iodide donor in the presence of silver triflate at −40 °C furnished the desired disaccharide along with the orthoester, which could be rearranged to the disaccharide by simply warming the reaction to room temperature. The methodology was applied in the synthesis of pentasaccharide (Man-5). Through double glycosylation of a 3,6-dihydroxy acceptor, high mannose sugars were readily obtained in nearly quantitative yields (Scheme 2.65).

The glycosyl iodide methodology has worked especially well in more challenging α-galactosylations [210–212], as demonstrated by the synthesis of a potent immunostimulator α-galactosyl ceramide KRN7000 (Scheme 2.66) [210]. Commonly employed donors such as fluorides, trichloroacetimidates, phosphites and hemiacetals usually furnish difficult-to-separate α-/β-mixtures with yields typically ranging from 30 to 70%. In contrast, (2*S*,3*S*)-2-azido-3-*para*-methoxybenzyl sphingosine and (2*S*,3*S*,4*R*)-2-azido-3,4-*para*-methoxybenzyl phytosphingosine react with per-*O*-benzylated galactosyl iodide affording only α-*O*-glycosidic linkages with yields over 90%. Subsequent conversion of azido groups to an amine, followed by fatty acid coupling and debenzylation along with the reduction of double bond under hydrogenolysis conditions afforded pure KRN7000 and 4-deoxy-KRN7000.



Scheme 2.64

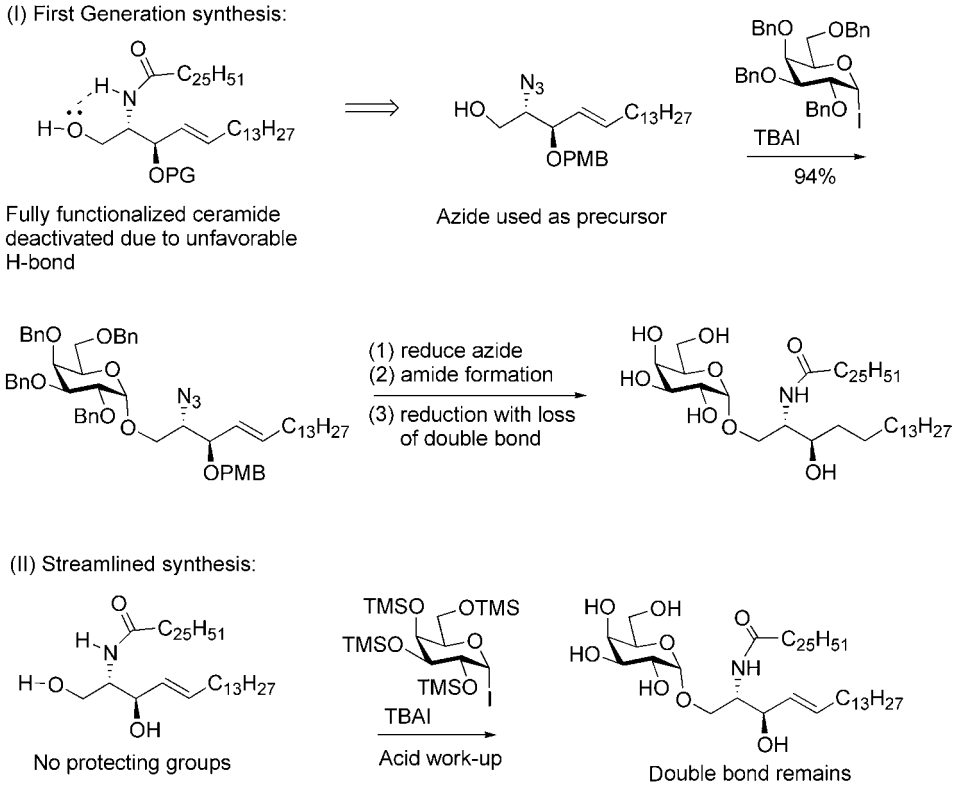


Scheme 2.65

Although this method offered advantages over existing technology, it required several steps to prepare the glycolipid for coupling. A higher degree of efficiency and simplicity was achieved by using per-*O*-trimethylsilylated (*O*-TMS) sugars as precursors to glycosyl iodides in a one-pot endeavor [211]. Under these conditions, per-*O*-TMS galactosyl iodides underwent α-glycosidation with fully functionalized glyceride and ceramide acceptors producing α-linked glycolipids (Schemes 2.42 and 2.43). The treatment of the crude product in the same reaction vessel with acidic resin in methanol afforded biologically relevant biomolecules in high yields and with high stereoselectivity. This mild one-pot protocol allows the synthesis of pure α-anomeric glycolipids bearing various sensitive functionalities such as esters, amides and double bonds (Scheme 2.67) [212]. Microwave radiation has proven useful in these reactions when utilizing lipids having limited solubility.

Hindsgaul and Uchiyama also used *in situ*-generated per-*O*-TMS fucosyl iodides for α-L-fucosylation [189]. Beau and coworkers employed anomeric-TMS sugars for the synthesis of 1,2-*trans*-*C*-glycosyl compounds via reductive samariation of glycosyl iodides [190]. Very recently, the first synthesis of indigo *N*-glycosides (blue sugars) was reported from the reaction of dehydroindigo with *in situ*-generated per-*O*-TMS L-rhamnosyl, D-glucosyl and D-mannosyl iodides [213].

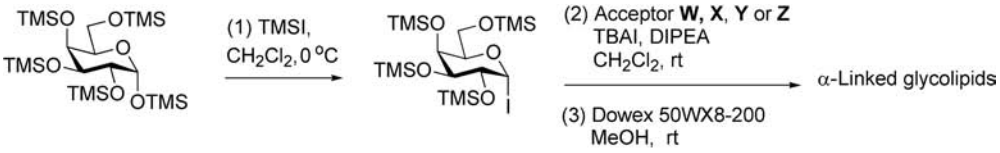
A useful extension of the *in situ* anomerization process involves the employment of C-nucleophiles such as vinyl and allyl magnesium bromides. Grignard reactions to per-*O*-benzylated glycosyl iodides proceed stereoselectively when a strong nucleophile like allyl magnesium bromide is used, giving β-*C*-allyl fucosides (95% β-only)



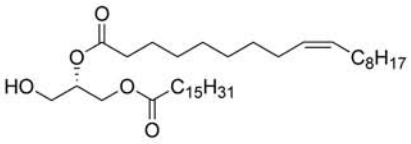
Scheme 2.66

and galactosides (85% β-only) in high yields [214]. In contrast, reactions of benzylated α-D-galactosyl iodides with vinyl magnesium bromide generate an α/β mixture favoring the α-isomer. The scenario is reversed when the reaction is carried out under *in situ* anomerization conditions using TBAI in toluene at reflux, in which case the α-isomer is formed in high yields (79%, α/β = 12/1) [215]. This methodology proved useful in the first synthesis of a α-linked *C*-glycolipid corresponding to the immunoreactive bacterial glycolipid BbGL2 (Scheme 2.68).

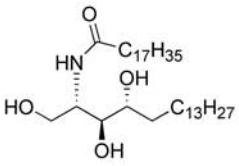
β-Mannosylation Using Glycosyl Iodides The unique reactivity of glycosyl iodides was further revealed when glucosyl, galactosyl and mannosyl iodide donors were treated with strained oxacycloalkane acceptors to afford *O*-glycosides with high β-selectivity (Scheme 2.69) [216]. These reactions proceed without donor activation in CH_2Cl_2 and are highly β-selective with reactive acceptors, such as propylene oxide and trimethylene oxide. Glycosyl iodides are unique in this respect, as analogous reactions with the corresponding bromides failed. These reactions were used for the synthesis of β-thiomannosides from thiocycloalkane acceptors. In the absence of neighboring-group participation, β-selectivity is thought to arise from direct nucleophilic displacement of the α-iodide, whereas the minor α-product may result from



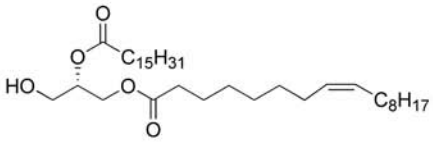
Acceptors



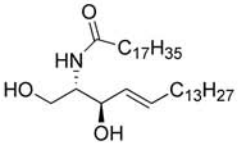
W



Y

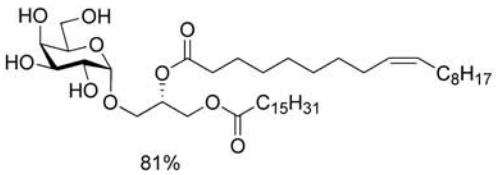


X

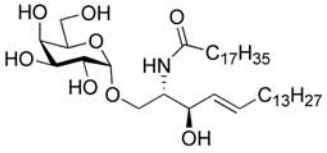


Z

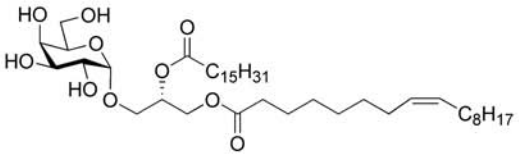
Glycolipids



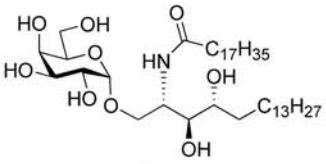
81%



77%

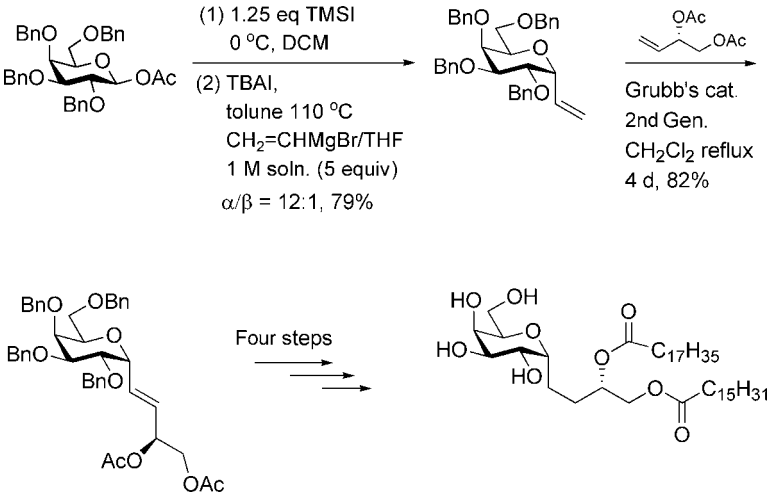


72%

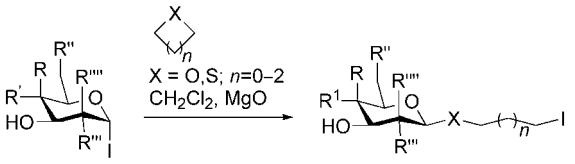


67%
(With microwave)

Scheme 2.67



Scheme 2.68



Glc: R, R'''' = H; R', R'', R''' = OBn
Gal: R', R'''' = H; R, R'', R''' = OBn
Man: R, R'''' = H; R', R'''' = OBn, R'' = OAc

Scheme 2.69

nucleophilic attack on the β-iodide formed by *in situ* anomerization by the action of liberated I^-. Limiting the *in situ* anomerization is required to drive the reaction mechanism toward the exclusive formation of β-glycoside [217]. Achieving β-selectivity is particularly difficult in D-mannosides as the anomeric effect as well as the C2-acyl directing group favor the formation of the α-isomer. Studies further indicated that β-selectivity could be improved using the reverse thermal effect [218].

2.2.5 Conclusions

Over the years, glycosyl halides have been the most utilized donors in stereoselective glycosylations. *In situ* anomerization is a powerful way of introducing 1,2-*cis* glycosides under neutral conditions, whereas direct displacement of anomeric halides typically leads to 1,2-*trans* glycosylations in the absence of neighboring-group participation. Glycosyl iodide donors offer several advantages over previously reported chloride or bromide donors, as reactions employing iodides are faster, highly

stereoselective, and high yielding. In many cases, solution-phase reactions and purification can be carried out faster than solid-phase reactions. Current literature dispels the notion that glycosyl iodides are too reactive to be synthetically utilized. Instead, glycosyl iodides have emerged as important players in stereoselective glycoconjugate synthesis. Glycosylations using iodides, *in situ* generated from per-*O*-TMS sugars, are even more advantageous, as the final target molecules can be accessed in a one-pot manner after a single-column chromatography purification. This feature is especially attractive for rapidly synthesizing diverse analogs of oligosaccharides, glycoconjugates and glycolipids for structure–activity relationships (SARs) studies. Recent developments streamline complex oligosaccharide assembly providing powerful tools for drug discovery.

2.2.5.1 **General Procedure for One-Pot Glycosylation Using Glycosyl Iodides**

TMSI (30 mg, 0.15 mmol) is added to a solution of 1,2,3,4,6-penta-*O*-trimethylsilyl-D-galactopyranose (81 mg, 0.15 mmol) in CH_2Cl_2 (2 ml) at 0 °C and the reaction is stirred for 20 min. Anhydrous benzene (5 ml) is added and solvents are azeotroped twice on rotary evaporator. The yellowish oil is dissolved in CH_2Cl_2 (2 ml) and kept under argon. In a separate flask, molecular sieves (MS, 4 Å, 100 mg), TBAI (165 mg, 0.45 mmol), acceptor (0.05 mmol) and DIPEA (58 mg, 0.45 mmol) are added to CH_2Cl_2 (2 ml). The mixture is stirred under argon at room temperature. The glycosyl iodide solution is cannulated into the reaction mixture and stirring is continued at room temperature. After the completion of the reaction, as indicated by TLC (12–48 h), the solvent is evaporated and EtOAc is added. Precipitated TBAI and other solid materials are filtrated through Celite and the solvent is evaporated. MeOH (10 ml) and Dowex 50WX8-200 ion-exchange resin (0.5 g) are added and the reaction is stirred at ambient temperature for 4 h. The resin is filtered and the solvent is removed *in vacuo*. The resulting residue is purified by column chromatography on silica gel (gradient MeOH–CH_2Cl_2) to obtain the product (typical range 65–90%) as a white solid.

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3
Glycoside Synthesis from 1-Oxygen Substituted Glycosyl Donors

3.1
Hemiacetals and *O*-Acyl/Carbonyl Derivatives

Daniel A. Ryan, David Y. Gin

3.1.1
Introduction

This chapter outlines the development, achievements and limitations of glycosylation methods that rely on C1-hemiacetal donors and C1-*O*-acyl donors. These are among the simplest glycosyl donors to prepare in standard *O*-glycosylation reactions. As such, developments in the use of these donors constitute valuable advances in the field of synthetic carbohydrate chemistry.

3.1.2
Dehydrative Glycosylation via Electrophilic Activation of C1-Hemiacetals

Glycosylation with C1-hemiacetal donors offers a notable variation from most of the other glycosylation strategies, in that it combines the steps of anomeric derivatization and activation/glycosylation into a one-pot procedure (Scheme 3.1). In this process, the hemiacetal donor **1** is exposed to an electrophilic reagent (El^+) that activates the hemiacetal by converting it to a potent leaving group for expulsion from the anomeric center. With the introduction of a glycosyl acceptor (NuH) to the activated intermediate **2**, the desired glycoside **3** is formed directly, wherein the controlled extraction of 1 equiv of water mediates the union of glycosyl donor and acceptor.

An attractive feature of this dehydrative coupling approach is that it avoids the need for isolation of intermediate glycosyl donors. This can be desirable if a glycosyl donor is not stable to isolation or purification. Moreover, the use of a hemiacetal donor reduces the number of synthetic manipulations of the carbohydrate donor by avoiding hemiacetal derivatization to alternative donor types. In this way, the approach has the potential to streamline time and labor-intensive multiglycosylation sequences. Although there increasingly have been reports of these direct dehydrative

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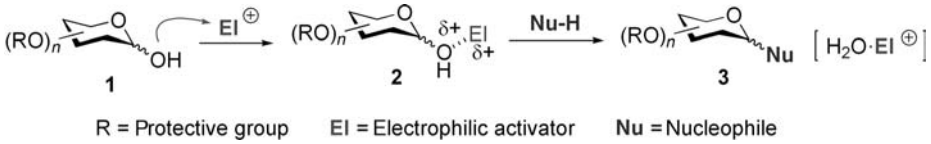


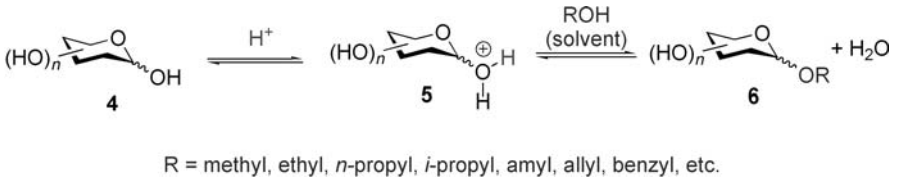
Scheme 3.1 Electrophilic activation of hemiacetals for dehydrative glycosylation.

glycosylations having performed with high synthetic utility, the methods that employ derivatized hemiacetal donors are more commonly practiced. This stems from unique challenges posed by hemiacetal donors, given that the hemiacetal can also serve as a nucleophilic acceptor. As a result, any process that generates an activated hemiacetal intermediate **2** in the presence of unreacted hemiacetal **1** is in danger of promoting self-condensation to generate the corresponding 1,1′-linked anhydro dimer as an unwanted side product. Thus, hemiacetal activation relies on either transient activation (i.e. via acid) with thermodynamic control over the acetal exchange process, or electrophiles that efficiently form irreversible complexes with the hemiacetal hydroxyl to initiate the water extraction process.

The preparation of C1-hemiacetal glycosyl donors follows many of the traditional strategies for selective anomeric functionalization. Although many synthetic sequences can be envisioned for the preparation of a selectively protected C1-hemiacetal donor, one of the two general synthetic approaches is employed. The first approach involves a complete and indiscriminate protection of all hydroxyl groups (including the hemiacetal hydroxyl) on a furanose or pyranose substrate, and then reliance on the differential reactivity of the acetal functionality to expose the anomeric hydroxyl in **1**. These synthetic sequences include hydroxyl peralkylation and anomeric hydrolysis [1], hydroxyl perbenzylation and anomeric hydrogenolysis [2], and hydroxyl peracylation and anomeric deacylation [3,4]. The second, perhaps more common, approach involves an initial acid promoted hemiacetal-to-acetal exchange at the anomeric center of a pyranose or furanose to effect selective protection at the C1-position (i.e. Fischer glycosylation, see below). Subsequent orthogonal protection of the periphery hydroxyl groups on the carbohydrate sets the stage for the final, selective anomeric deprotection to C1-hemiacetal donor **1** [5].

3.1.3
Acid Activation of C1-Hemiacetals

The Fischer glycosylation is among the earliest chemical glycosylations and involves acid-catalyzed reaction with an unprotected hemiacetal donor **4** (Scheme 3.2) [6,7]. Because the reaction is under thermodynamic control, it is conducted with a large excess of glycosyl acceptor alcohol (ROH) to drive the equilibrium to glycoside **6**. Consequently, the Fischer glycosylation is best employed with simple alcohol solvents. In addition, the reaction typically requires high temperatures and/or long reaction times, which are not ideal conditions for complex or sensitive substrates. Not surprisingly, anomeric selectivity in the glycosylation process is usually dictated

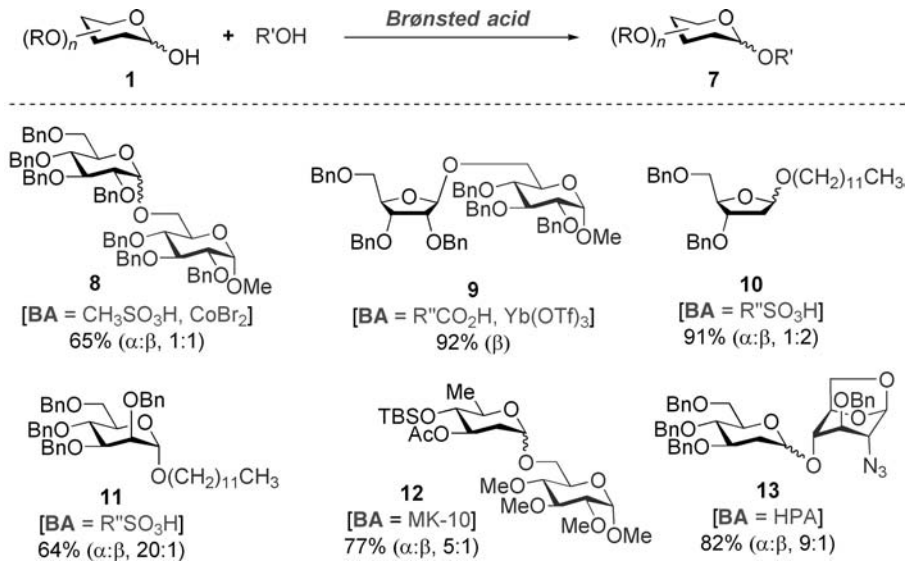


Scheme 3.2 Fischer glycosylation.

by the relative ground-state energies of the product glycoside anomers. Despite these constraints, the Fischer glycosylation remains indispensable, in that it directly provides unprotected glycosidic products [8]. The importance of this reaction is reflected in the application of the Fischer glycosylation in the industrial preparation of surfactants used in consumer goods.

Recent investigations have revealed new acid promoters for the preparation of more complex glycosides from *selectively protected* C1-hemiacetal donors such as **1**. In the presence of a desiccant, several types of acid promote glycosylation typically without the requirements for excess glycosyl acceptor and high temperatures. Because of the reversible nature of acid coordination to hydroxyl groups, this class of reactions generally allows for activation of the hemiacetal donor to occur in the presence of the glycosyl acceptor alcohol.

Classically, Brønsted acids are the promoters of the Fischer glycosylation. Though substrate complexity is still limited in scope, recent developments in these reagents more commonly allows for disaccharide synthesis (Scheme 3.3). For instance, Koto *et al.* have reported that the combination of methanesulfonic acid (30 mol%) and



Scheme 3.3 Brønsted acid promoted dehydrative glycosylations.

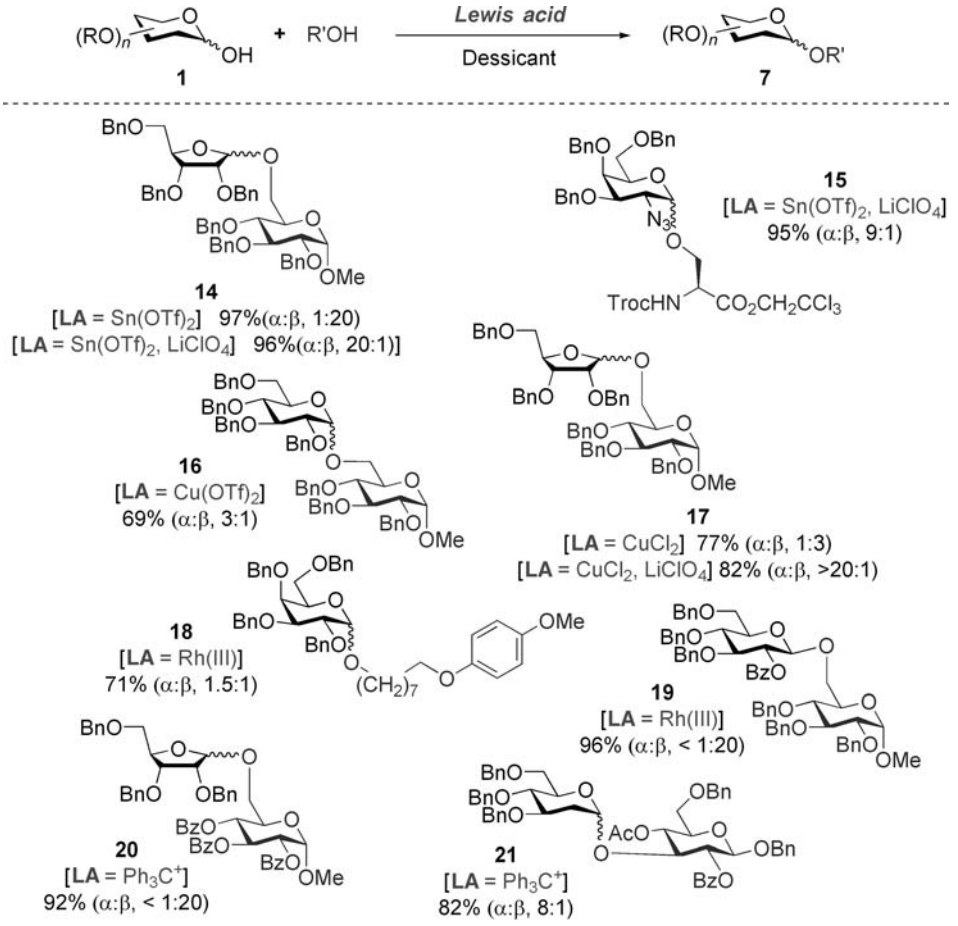
cobalt(II) bromide ($CoBr_2$, 1 equiv) promotes glycosidic bond formation from hemiacetal donor **1** and acceptor alcohol (1 equiv) in just 2 h at 25 °C. Cobalt(II) bromide functions as both a desiccant and a latent source of hydrobromic acid, allowing for generation of a glycosyl bromide intermediate. From this reaction, disaccharide **8** was prepared in 65% [9,10]. Inanaga *et al.* reported that the combination of methoxyacetic acid and $Yb(OTf)_3$ (10 mol% each) with 4 Å molecular sieves yields glycosides in good yields [11]. Control experiments indicated that both Lewis and Brønsted acids are necessary. Using this procedure, the ribosyl disaccharide **9** was obtained with high 1,2-*trans* selectivity, though the degree of stereoselectivity was generally substrate dependent.

Kobayashi and coworkers have advanced the use of sulfonic acids in Fischer-type glycosylations with the discovery that surfactant sulfonic acids catalyze the dehydrative glycosylation of hemiacetals using water as the reaction solvent [12]. It was proposed that long-chain acid and alcohol acceptors form emulsions in water with hydrophobic interiors, which promote dehydration within this emulsion. Thus, furanose and pyranose hemiacetals reacted with C-5 to C-12 long-chain alcohol acceptors (1.5 equiv) in the presence of 10 mol% of dodecylbenzenesulfonic acid to afford glycosides such as **10** or **11** with good conversion at elevated temperatures. The method has been extended to the synthesis of aryl *C*-glycosides in water [13].

Toshima and coworkers found that the heterogeneous, layered-silicate acid catalyst Montmorillonite K-10 (MK-10) effectively promotes stereoselective glycosylation with olivoside (2,6-dideoxyglucopyranose) donors [14]. One of the benefits of heterogeneous catalysis is the ability to obtain product by simply filtering the catalyst from the reaction medium, which avoids neutralization steps and salt formation. In the reaction, the dehydrated clay presumably acts as both acid and desiccant. For instance, the treatment of an olivose hemiacetal with a monosaccharide acceptor and MK-10 (150 wt%) at 25 °C provided glycoside **12** in 77% yield. Other reports have appeared wherein 4 Å molecular sieves function as the sole heterogeneous additive to effect *N*-glycoside bond formation [15].

An uncommon approach to in dehydrative glycosylations was detailed by Toshima *et al.*, wherein a heteropoly acid was used to promote the reaction [16]. Heteropoly acids (HPA), such as $H_4SiW_{12}O_{40}$ used in this study, are strong Brønsted acids with octahedral metal-oxygen core structural units [17]. The researchers comment that $H_4SiW_{12}O_{40}$ acid is easily dehydrated by heating and acts as both a desiccant and a strong Brønsted acid, thus making it a conspicuous choice for use in dehydrative glycosylations with hemiacetal donors. Using this acid, glycosylation of the secondary alcohol acceptor (1.5 equiv) provided disaccharide **13** in 82% yield after only 1 h at 25 °C. In this investigation, the reaction was applied to various pyranose hemiacetal donors with good results.

In addition to Brønsted acid promoted Fischer-type glycosylations, Lewis acids have been investigated (Scheme 3.4). A variety of Lewis acids promote glycosylation under mild conditions, often in substoichiometric amounts. The earliest examples include $ZnCl_2$ [18] and $FeCl_3$ [19], although these reactions were demonstrated only for preparation of trehalose-type disaccharides. Mukaiyama *et al.* have very recently developed metal triflate catalysts for the dehydrative glycosylation with



Scheme 3.4 Lewis acid promoted dehyrative glycosylations.

hemiacetal donors. Tin(II), ytterbium(III) and lanthanum(III) triflates are all viable catalysts at 1 mol% loading. In combination with hexamethyldisiloxane as desiccant, these systems provide glycoside products in a few hours at room temperature [20]. Preliminary investigations suggested that $Sn(OTf)_2$ was the most effective catalyst, which was used in the preparation of disaccharide **14** (97%), favoring the β anomer by 20 : 1. The anomeric stereoselectivity of this reaction was reversed by addition of lithium perchlorate (1.5 equiv) to the reaction to effect 96% yield of the α anomer, favored by 20 : 1. The role of lithium perchlorate was proposed to be sterically guided formation of a β-anomeric perchlorate intermediate, which directs nucleophilic addition to the opposite face. Using this modification, the *O*-linked glycopeptide precursor **15** was achieved in 95% yield (α : β, 9 : 1). Although the reaction scope has not been extended to secondary alcohols or to more complex substrates, the high yields

and stereoselectivity ingrain this catalyst/desiccant combination among the most efficient Lewis acid systems reported to date.

Cu(II) Lewis acids also promote Fischer-type glycosylations. Yamada and Hayashi have reported that Cu(II) triflate (1.1 equiv) in the presence of 4 Å molecular sieves yields disaccharides such as **16** in moderate yield [21]. Benzotrifluoride solvent, introduced by Ogawa and Curran as a less-toxic alternative to dichloromethane [22], gave optimal yields in this reaction. A catalytic Cu(II) system composed of $CuCl_2$, bis (diphenylphosphino)ferrocene and silver perchlorate (1 : 1 : 2 mol composition) was effective at 5 mol% loading with calcium sulfate desiccant. The application of this system provided disaccharide **17** with moderate β-selectivity [23]. Again, it was found that the anomeric stereoselectivity could be reversed with the addition of $LiClO_4$, which provided the α anomer of **17** in greater than a 20 : 1 ratio. The role of lithium perchlorate was suggested to be analogous to that of Mukaiyama's work, which invokes either the intermediacy of a β-anomeric perchlorate [20], or lithium perchlorate affecting *in situ* product anomerization, depending on the activating protocol used [24,25].

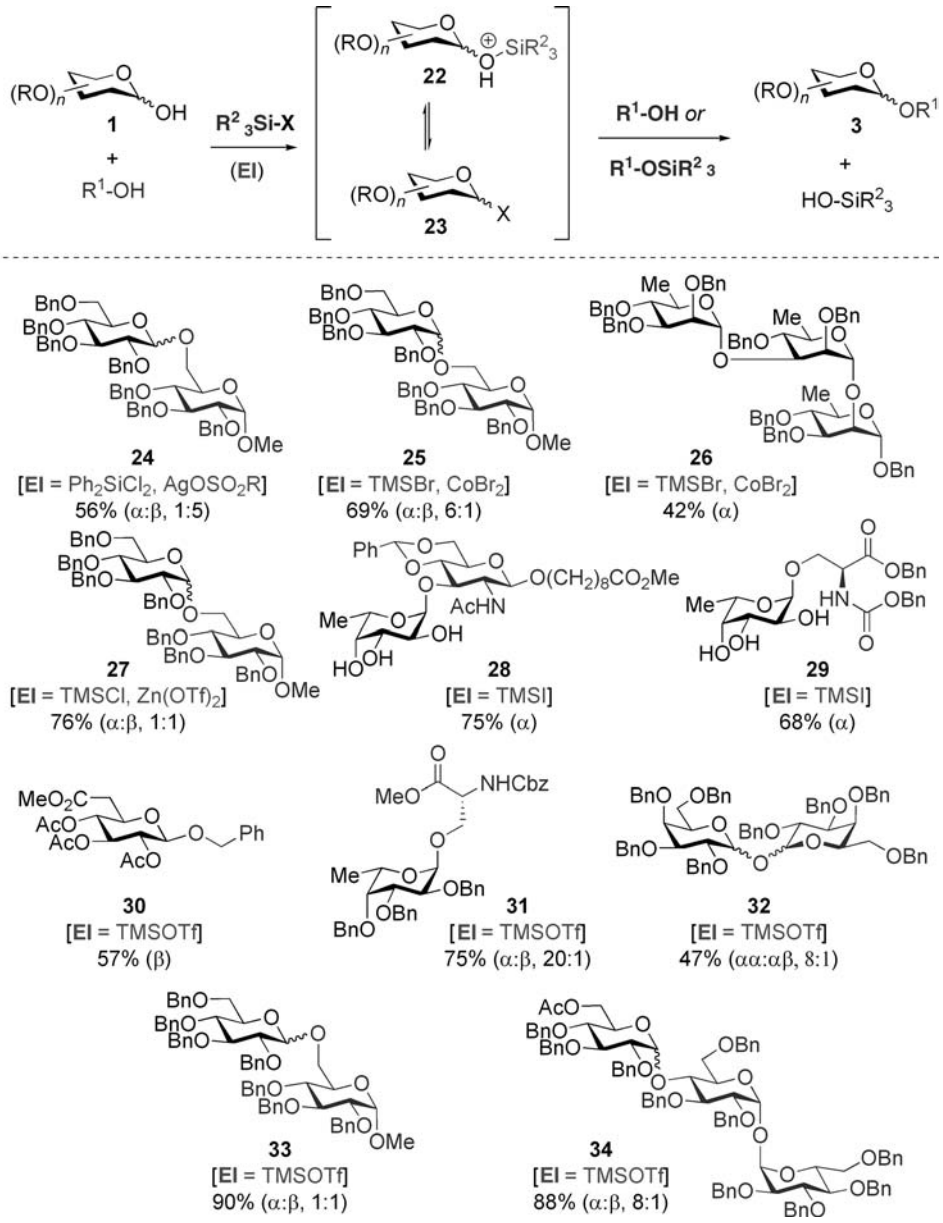
Indeed, a variety of Lewis acids have been shown to effect glycosylation with hemiacetal donors. Ernst and coworkers have used 5 mol% of [Rh(III)$(MeCN)_3$ (triphos)] tris(triflate) with 4 Å molecular sieves to prepare glycoconjugates **18** and **19** [26]. Mukaiyama's group has used trityl tetrakis(pentafluorophenyl)borate (3–5 mol%) with Drierite in the preparation of disaccharides **20** and **21** [27,28]. In the synthesis of **21**, the α-selectivity was shown to arise from *in situ* anomerization of the β-pyranoside over time.

As illustrated by the above examples, a number of Brønsted and Lewis acids promote Fischer-type glycosylation of hemiacetal donors allowing access to more complex glycosides. The application to oligosaccharide synthesis, or even glycosylation of less-reactive alcohol acceptors, is still uncommon. Beyond these reactions significant contributions have been made to the classic Fischer glycosylation with unprotected glycosyl donors. Some of these innovations include the effect of calcium or strontium cations on product isomer distribution [29], the use of $FeCl_3$ or $BF_3{\cdot}OEt_2$ to provide furanoside or pyranoside products using only slight excess of acceptor [30–33], microwave acceleration of the reaction [34] and new developments in the preparation of long-chain alkyl glycosides using heterogeneous acids [35–39].

3.1.4
Hemiacetal Activation with Silicon Electrophiles

Silicon presents an attractive option among electrophilic activating and dehydrating agents of hemiacetals because of the wide commercial availability of electrophilic silicon sources. The two main classes of silicon electrophiles used, namely silyl halides and silyl sulfonates, have been demonstrated to promote a variety of glycosylations including some examples of oligosaccharide synthesis.

One of the earliest reports of silicon-based electrophilic activation comes from the Koto laboratory on the use of silyl halide electrophiles to promote the dehydrative glycosylation with hemiacetal donors [40,41]. In the reaction (Scheme 3.5),



Scheme 3.5 Silicon activators in dehydrative glycosylation.

diphenyldichlorosilane (1 equiv) and silver sulfonate salts (2 equiv) effect the coupling of glycosyl donor **1** and acceptor (R^1OH).

Diphenyldichlorosilane is thought to react with hemiacetal **1** to afford silyl hemiacetal **22** and thereby liberate HCl to perpetuate the reaction. The investigators design

that, upon glycosylation of the acceptor, the chlorosilanol by-product polymerizes as an effective mode of dehydration. The role of the silver salt is to facilitate anomeric substitution in the event of anomeric chloride intermediates (23, X = Cl). Specifically, with silver toluenesulfonate and silver triflate additives at 0 °C, this procedure provided disaccharide **24** in 56% yield (α : β 1 : 5) [40]. Although the demonstrated reaction efficiency is only moderate, this early study laid the groundwork for later developments with silyl halide promoters.

The reagent combination of trimethylsilyl bromide and cobalt(II) bromide also promotes dehydrative glycosylation with hemiacetal donors and is notable for its use in oligosaccharide synthesis. The activation of the hemiacetal donor, which proceeds in the presence of the acceptor alcohol (R^1OH), results in glycosyl bromide intermediate **23** (X = Br). Mechanistic pathways may include silylation of the hemiacetal, silylation of the hydroxyl acceptor or both. In control experiments, it was shown that a preformed silyl hemiacetal was capable of transformation to the glycosyl bromide; independently, a silyl ether was shown to be a capable acceptor of glycosyl bromide donors. With the addition of tetrabutylammonium bromide to promote halide-catalyzed glycosidic bond formation, disaccharide **25** was produced in 69% yield (α : β, 6 : 1) over 16 h at 25 °C [42]. The trisaccharide repeat unit **26** of the *O*-specific polysaccharide of *Pseudomonades* pathogens was synthesized in 42% yield from a disaccharide hemiacetal donor [43]. In related work, Susaki has found that the combination of trimethylsilyl choride and zinc(II) triflate also effects glycosylation. Using this protocol, disaccharide **27** was formed in 76% as a 1 : 1 anomeric mixture [44].

Trimethylsilyl halides have been used as the sole activator/desiccator in Fischer-type glycosylations. Uchiyama and Hindsgaul reported that the treatment of unprotected L-fucose with excess trimethylsilyl chloride and triethylamine allowed for a quantitative preparation of a tetra-TMS protected fucose donor, which was isolated upon extraction with pentane [45]. A solution of this silylated donor was then treated with a trimethylsilyl iodide (TMSI) promoter and the alcohol acceptor (0.3 equiv) to effect glycosylation in less than 30 min at room temperature. In this way, disaccharide **28** was obtained in 75% yield, exclusively as the α anomer after a work up with methanol. Similarly, the glycopeptide **29** was isolated in 68% yield. Although this reaction involves isolation of the tetra-TMS derivatized donor, it is a notable development using silicon electrophiles to promote Fischer-type glycosylations. Vigorita and coworkers have applied this reaction to unprotected xylopyranose and arabinopyranose donors [46]. Fukase and coworkers have prepared propargyl and allyl glycosides in good yield and selectivity using only TMSCl, a procedure that does not entail isolation of the silylated donor [47].

Trialkylsilyl sulfonates, especially trimethylsilyl triflate (TMSOTf), represent the other broad class of silicon electrophiles used to promote direct dehydrative glycosylations (Scheme 3.5). Among the earliest reports, Nudelman and coworkers found that hemiacetal donor **1** and glycosyl acceptor (R^1OH) can be coupled under the agency of TMSOTf (1 equiv) to provide *O*-alkyl glycosides in a matter of hours at temperatures below 20 °C [48]. Again, the possibility of nonselective silylation between the glycosyl donor and the acceptor exists, though to no deleterious effect.

In fact, other studies have shown that TMSOTf catalyzes the glycosylation of a silylated acceptor with a silylated hemiacetal donor [49]. Nudel man's procedure was applied to the synthesis β-glucuronide **30**, isolated in 57% yield. Kiyoi and Kondo have applied the TMSOTf activation protocol to protected L-fucose hemiacetal donors for glycopeptide synthesis and obtained glycopeptide fragment **31** in 74% yield (α : β, 20 : 1) [50]. Posner and Bull have developed a procedure that uses excess TMSOTf in the presence of molecular sieves (SYLOSIV A4) to synthesize various 1,1′-linked disaccharides such as the galactopyranose dimer **32** [51,52].

Koto's group reported the use of TMSOTf in one of the rare examples of oligosaccharide synthesis using this class of activators [53]. Activation of the donor and acceptor using TMSOTf (5 equiv) and pyridine (3 equiv) at −45 °C provides glycoside products after a few hours at 0 °C. For instance, disaccharide **33** was isolated in 90% yield (α : β, 1 : 1.3). Further, extension of reaction scope was accomplished with the synthesis trisaccharide **34** in 88%, favoring the α anomer (8 : 1). In this case, the C-6 acetate of the glycosyl donor was believed to direct the α-selectivity through long-range participation.

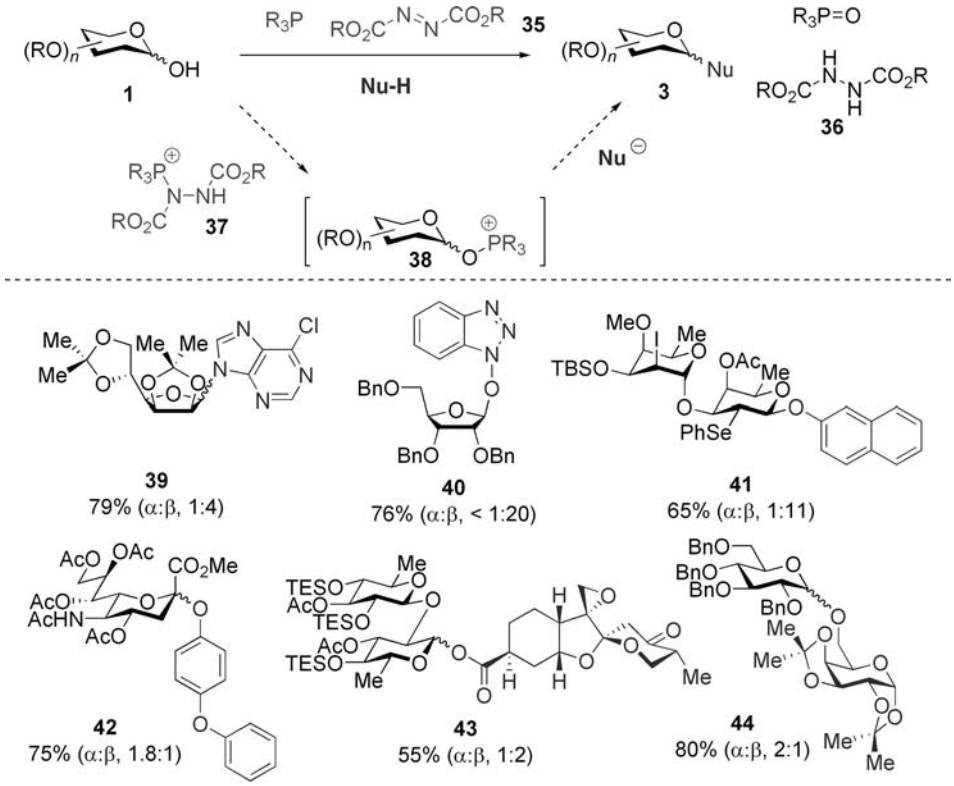
In addition to the silicon-based *in situ* activation of hemiacetal donors, there has been a significant body of work that uses electrophilic silicon activation of preformed C-1 silyl hemiacetal donors [54–67]. However, this work is outside the scope of this discussion.

3.1.5
Hemiacetal Activation with Phosphorus Electrophiles

Phosphorus-based activating agents present an attractive option among electrophilic activation of hemiacetal glycosyl donors. The relatively high bond strength of the phosphorus–oxygen bond provides ample thermodynamic driving force for C1-hydroxyl activation and subsequent dehydration via formation of phosphine oxide in the glycosylation event [68]. Three main modes of electrophilic phosphorus activation exist, and together they exhibit a wide variety of accessible substrate classes in direct dehydrative glycosylations.

Shortly after the discovery of the Mitsunobu reaction in the late 1960s [69], phosphonium activation of hemiacetals was reported using the reagent combination of a phosphine and a dialkyl azodicarboxylate **35** (Scheme 3.6). The reaction between the phosphine and **35** affords *N*-betaine intermediate **37**, which serves as a potent electrophilic activator for hemiacetal **1**. From this activation step, the glycosyl oxophosphonium intermediate **38** is generated along with the liberation of the dialkyl hydrazinedicarboxylate by-product **36**. Subsequent nucleophilic addition of the acceptor occurs to expel phosphine oxide from the anomeric center with formation of the new, anomeric bond. Much like the original Mitsunobu reaction, the successful application of the Mitsunobu protocol to glycosylation typically requires relatively acidic glycosyl acceptors such as imides, hydroxyphthalimides, carboxylic acids and phenols.

Szarek *et al.* were the first to develop this mode of glycosylation, which was demonstrated for ribonucleoside synthesis. In the reaction, a protected mannofuranose



Scheme 3.6 Dehydrative glycosylation via the Mitsunobu protocol.

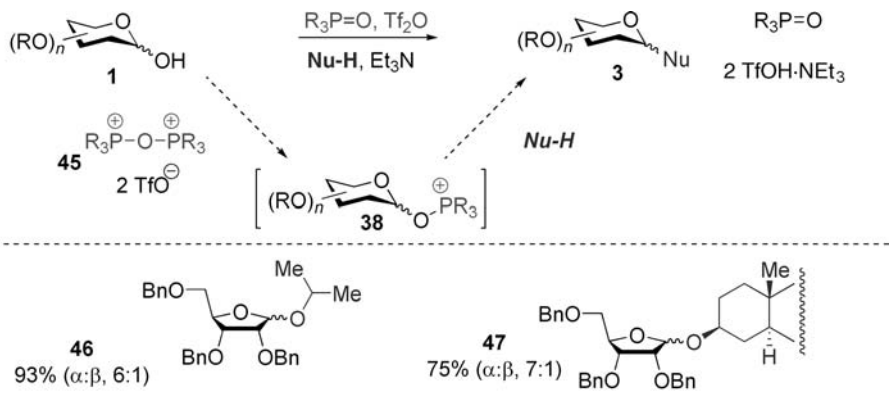
hemiacetal donor was added to an equimolar solution of methyldiphenylphosphine, diethyl azodicarboxylate, and the 6-chloropurine glycosyl acceptor at ambient temperature. The resulting *N*-glycoside **39** was isolated in 79% yield, favoring the natural β anomer [70]. This general method has been applied to pyranose hemiacetal donors and other *N*-acceptors [71–75]. It was later demonstrated that *N*-hydroxy nucleophiles are efficient glycosyl acceptors in this reaction [76], as evidenced by the formation of riboside **40** in 76% yield with high α-selectivity [77]. The results generally show good stereoselectivity for the 1,2-*trans* riboside, although the stereoselectivity can be reversed when either a trityl or a *tert*-butyldimethylsilyl protective group is used on the C-5 hydroxyl of the ribofuranose donor. Although *O*-*N*-glycosides are not a common class of glycosidic bond, this method has been successfully applied to the synthesis of the glycosyl-oxyamine linkage in calicheamicin [78,79].

The glycosylation based on the Mitsunobu reaction has been most commonly directed to the synthesis of *O*-aryl glycosides, a structural motif found in a variety of natural products [80–82]. Early work by Grynkiewicz [83,84], among others [85–87], established the viability of triphenylphosphine and diethylazodicarboxylate to promote the glycosylation of phenol acceptors at ambient temperature. More recently, Roush and coworkers have discovered that the glycosylation performed well in the

stereoselective synthesis of *O*-aryl glycosides *en route* to 2-deoxy sugars. In synthetic efforts to the antitumor natural products olivomycin and mithramycin, Mitsunobu glycosylation of 2-naphthol provided disaccharide **41** in 65% yield with high β-selectivity [88–90]. Although the hemiacetal donor predominantly favors the α-form and the Mitsunobu reaction generally favors an S_N2 pathway, the participation of the C-2 phenylselenyl group could not be ruled out as the stereocontrolling element. Ernst *et al.* also found that the sialyl glycoside **42** could be obtained in good yield (75%), but with little stereocontrol [91]. This example is notable because of the congested steric environment of sialic acid C-2 hemiketal donors. Not surprisingly, glycosyl esters have also been prepared under similar conditions. In their synthesis of the antitumor natural product phyllanthoside [92,93], Smith and coworkers found that the synthesis of glycoconjugate **43** was not possible by direct esterification of the hemiacetal using an acyl chloride aglycon, as this experiment provided the undesired α-glycoside. Accordingly, the problem was addressed with the Mistunobu glycosylation, thereby capitalizing on a proposed S_N2 pathway via an α-oxophosphonium intermediate. Thus, the glycosyl ester **43** was formed in 55% yield, with increased β-selectivity (α : β, 1 : 2). Advances in the synthesis of *O*-aryl β-glucuronides have also appeared [94].

Although aliphatic alcohols are typically poor acceptors in the Mitsunobu-type glycosylation, Szarek and coworkers have highlighted one advance to this end [95]. For the triphenylphosphine and diethylazodicarboxylate promoted glycosylation of a monosaccharide acceptor, the addition of mercuric bromide is necessary to promote the reaction. For example, the (1,6)-disaccharide **44** was obtained in 80% yield using this modified Mitsunobu protocol. Unlike previous examples with phenol or *N*-acceptors, preactivation of the hemiacetal donor was performed for 10 min at room temperature prior to addition of the aliphatic alcohol nucleophile.

In 1975, Hendrickson and Schwartzman reported a different mode of phosphorus-based hydroxyl activation using bis(phosphonium) electrophiles $(R_3P{-}O{-}PR_3)^{2+}$. These highly reactive electrophiles are generated from the reagent combination of phosphine oxide and trifluoromethanesulfonic (triflic) anhydride [96]. Mukaiyama



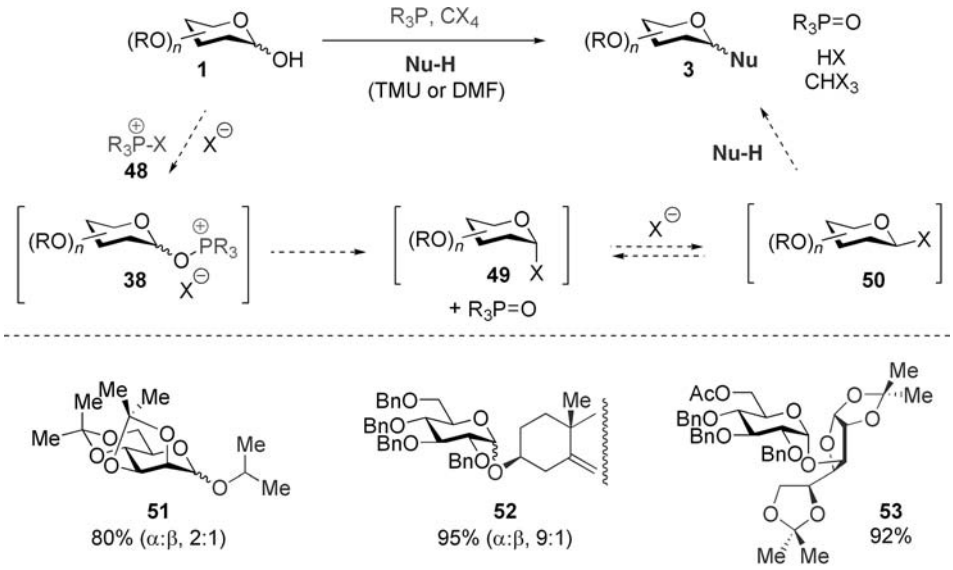
Scheme 3.7 Dehydrative glycosylation with $[R_3PO]_2{\cdot}Tf_2O$.

and Sudha later discovered that bisphosphonium electrophiles effectively promote dehydrative glycosylation with hemiacetal donors (Scheme 3.7) [97]. In this method, a hemiacetal **1** is activated by the bis(phosphonium) ditriflate salt **45** for *in situ* generation of the anomeric oxophosphonium intermediate **38**, a species observed by ^{31}P NMR and ^{13}C NMR. With the introduction of a nucleophile, phosphine oxide is expelled from the anomeric center as the glycosidic bond in **3** is formed.

This method has been used only a few times, despite the high yields reported. In the procedure, the hemiacetal was activated with tributylphosphine oxide (4.5 equiv) and triflic anhydride (2.1 equiv) for 2 h at 0 °C, followed by an addition of the glycosyl acceptor. As a result, the isopropyl riboside **46** was prepared in 93% and the cholestanyl riboside **47** was prepared in 75%, both with α-anomeric selectivity.

The reaction of phosphines and alkyl halides presents an alternative way to generate phosphonium electrophiles (Scheme 3.8). In particular, the combination of a phosphine and carbon tetrabromide (the Appel reaction) allows for *in situ* formation of a phosphonium dibromide salt (**48**, X = Br). Treatment of a hemiacetal donor **1** with the phosphonium halide **48** initially provides the oxophosphonium intermediate **38** (X = Br). However, the oxophosphonium intermediate **38** can react with bromide ion to form the anomeric bromide intermediate **49** (X = Br) with concomitant generation of phosphine oxide. With the aid of bromide ion catalysis (i.e. reversible, catalytic formation of the more reactive β-anomeric bromide **50**) [98], the nucleophile displaces the anomeric bromide to form the desired glycoside product **3**. The hydrobromic acid by-product is typically buffered by the presence of tetramethyl urea (TMU).

In 1980, Gross and coworkers first applied this concept to a direct dehydrative glycosylation using tris(dimethylamino)phosphine and carbon tetrachloride [99].

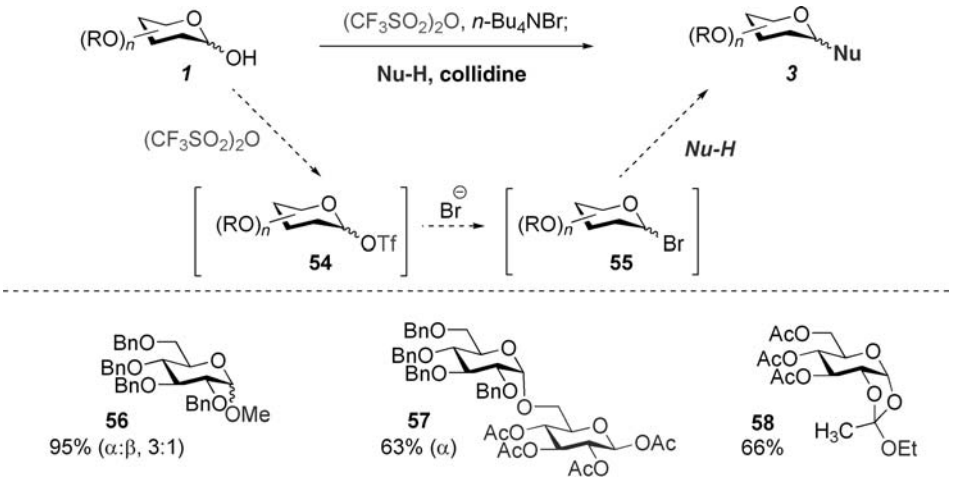


Scheme 3.8 Dehydrative glycosylation with $R_3P{\cdot}CX_4$.

With these reagents, the corresponding anomeric oxophosphonium intermediate **38** (X = Cl) is formed, allowing for its direct displacement with the nucleophilic acceptor. This reaction afforded the isopropyl glycoside **51** (80%). It was noted that control of the reaction temperature at −40 °C in the presence of silver salts precludes glycosyl chloride formation (**49**, X = Cl) during hemiacetal activation. More recently, the groups of Nifant'ev [100] and Kobayashi [101] have developed a modified Appel method for glycosidic bond formation. In the early work, the Appel glycosylation involved *in situ* generation of glycosyl bromide **49**, which was subjected to halide ion catalysis by addition of tetrabutylammonium bromide and tetramethyl urea. Further reaction insights revealed that the addition of an external halide source is unnecessary, and high yields and selectivities for the 1,2-*cis* α-glycoside are still obtained [102]. In the event, activation of the hemiacetal with triphenylphosphine and carbon tetrabromide for 3 h at 0 °C, followed by addition of the acceptor, provided glycoside products such as cholesteryl glucoside **52** (95%, α : β, 9 : 1) or the (1,3)-disaccharide **53** (92%, α). The higher α selectivity in the formation of **53** was thought to arise from long-range participation of the C-6 acetate. Despite the use of 3 equiv of glycosyl acceptor, the stereoselective formation of 1,2-*cis* α-glycosides from hemiacetal donors with C-2 nonparticipatory protective groups is a notable feature of the method. Interestingly, when the reaction was run in *N*,*N*-dimethylformamide (DMF) solvent, glycosyl imidate intermediates were detected by ^{1}H NMR, and shorter reaction times were observed [103,104].

3.1.6
Hemiacetal Activation with Sulfur Electrophiles

The first direct dehydrative glycosylation promoted by sulfur electrophiles was reported by Leroux and Perlin [105]. In this reaction (Scheme 3.9), activation of



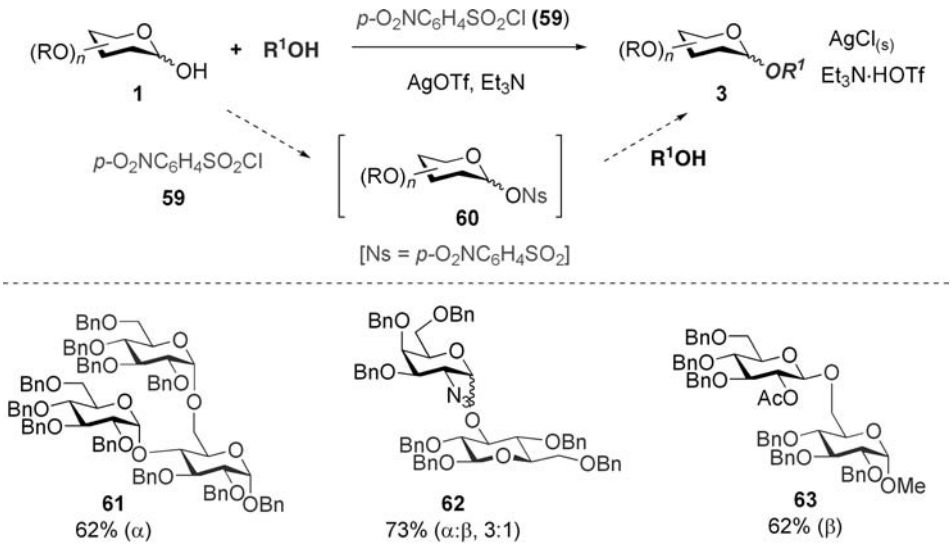
Scheme 3.9 Dehydrative glycosylation with Tf_2O.

hemiacetal **1** ensues with triflic anhydride in the presence of the sterically hindered base 2,4,6-collidine at −70 °C to provide the anomeric triflate intermediate **54**. Although the authors report identifying this intermediate by NMR, its exposure to even simple alcohol acceptors led to low yields of product. Increases in reaction efficiency occur with the introduction of tetrabutylammonium bromide, allowing for rapid displacement of the anomeric triflate **54** to form the more stable glycosyl bromide intermediate **55**. Subsequent introduction of a glycosyl acceptor (NuH) provides the desired glycoside **3**.

This method has allowed for the synthesis of methyl glycoside **56** (95%, α : β, 3 : 1) [105] and (1,6)-disaccharide **57** (63%) [106]. The preference for the 1,2-*cis* glycosidic bond in these examples was thought to be the consequence of halide ion catalysis [98]. A limitation of this method was the finding that with a C-2 ester substituted hemiacetal donor, orthoester **58** was isolated as the principal product in the presence of ethanol. Thus, stereoselective formation of β-glycosides appears to be challenging by this approach. Later developments by Pavia and coworkers showed that in the absence of a base and bromide source, self-condensation of the donor occurs to form the 1,1′-linked disaccharide [107–109], although the use of excess acceptor avoids glycosyl donor self-condensation and provides glycoconjugates [110].

Sulfonyl chloride hemiacetal activating agents were first investigated by Leroux and Perlin in the stereoselective synthesis of *O*-alkyl glycosides using methanesulfonyl chloride [106] and later by Szeja using toluenesulfonyl chloride under phase-transfer conditions [111]. These pioneering studies have not yet been extended to the disaccharide synthesis. In 1980, Koto *et al.* reported that a mixture of a hemiacetal glycosyl donor **1** and alcohol acceptor (R^1OH) could be treated with the ternary mixture of *para*-nitrobenzenesulfonyl chloride **59**, triethylamine and silver triflate (AgOTf) chloride scavenger to promote glycosidic bond formation at low temperatures (Scheme 3.10) [112]. The activated hemiacetal donor, in the form of anomeric *p*-nitrobenzenesulfonate **60**, reacts with the acceptor to provide the desired glycoside **3**. Unlike most of the direct dehydrative glycosylations that involve pretreatment of the glycosyl donor with the activating reagents prior to the addition of the alcohol acceptor, in this case, the donor and acceptor are both present when the activating reagents are introduced.

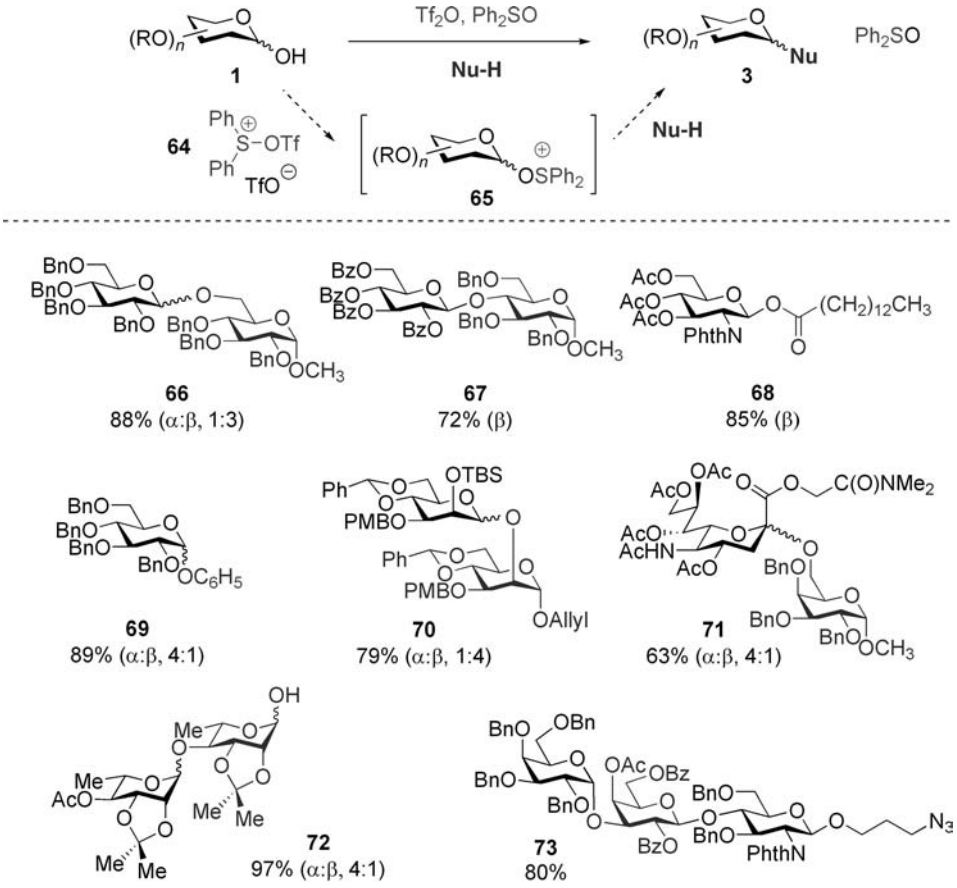
The stereochemistry of the glycosylation was initially found to be highly substrate dependent [113,114]. Advances were made to improve efficiency and generality, whereby addition of *N*,*N*-dimethylacetamide to the reaction provided optimal α-selectivity without compromising the yield [115]. With this advance, the branched trisaccharide **61** could be obtained in 62%, with α selectivity. Similarly, a C-2 azido galactose hemiacetal, an important class of glycosyl donor in *O*-linked glycopeptide synthesis, reacted to provide disaccharide **62** in 73% [116]. Stereoselectivity in the synthesis of β-glycosides was best achieved by the use of a C-2 participatory group, illustrated by the formation of disaccharide **63** (62%) [117]. Koto and coworkers have applied this stereoselective method to the synthesis of pentosides [118], C-2 aminoglycosides [119] and multiple oligosaccharides [120–125]. The use of common and shelf-stable reagents makes this protocol an attractive choice for glycosylations.



Scheme 3.10 Dehydrative glycosylation with sulfonyl halides.

Gin and coworkers have developed a sulfonium-based electrophilic activation of hemiacetals (Scheme 3.11). Treatment of diphenyl sulfoxide (2.8 equiv) with triflic anhydride (1.4 equiv) allows for *in situ* formation of the highly reactive sulfonium bistriflate **64** [126]. This putative species engages in efficient activation of hemiacetal **1** over 1 h at −40 °C to provide the activated anomeric oxosulfonium intermediate **65**, which was verified by ^{1}H NMR [127]. With the introduction of a glycosyl acceptor, the glycosidic bond formation occurs to provide glycoside **3**, along with the regeneration of diphenyl sulfoxide. More recent developments have allowed for the use of substoichiometric quantities of sulfoxide reagent, wherein di-(*n*-butyl)sulfoxide (0.2 equiv) can be employed with benzenesulfonic anhydride as the stoichiometric dehydrating reagent [128,129].

Using the diphenyl sulfoxide protocol, a variety of glycoconjugates can be prepared (e.g. **66**–**69**) [126,127]. The anomeric stereochemistry with nonparticipating C-2 benzyl protective groups is moderate and substrate dependent; however, good 1,2-*trans* β-selectivity is achieved with C-2 ester or C-2 amide directing groups. A number of reports have appeared that extend the method. Seeberger and coworkers have found that glycosylation with a hemiacetal donor incorporating the 4,6-benzylidene directing group [130], allowes for the formation of β-mannosides in moderate to good selectivity [131]. For example, disaccharide **70** was prepared in 79% yield (α : β, 1 : 4). In other developments, (*p*-nitrophenyl)(phenyl) sulfoxide and triflic anhydride were found to be suitable activating reagents for C-2 hemiketal glycosyl donors. Using a C-1 *N*,*N*-dimethyl glycolamide directing group [132], the sialyl disaccharide **71** was obtained in 63% yield favoring the desired α anomer [133]. The $Ph_2SO{\cdot}Tf_2O$ glycosylation has recently been used to establish multiple glycosidic bonds in the synthesis of complex saponin adjuvants for vaccine development [134].



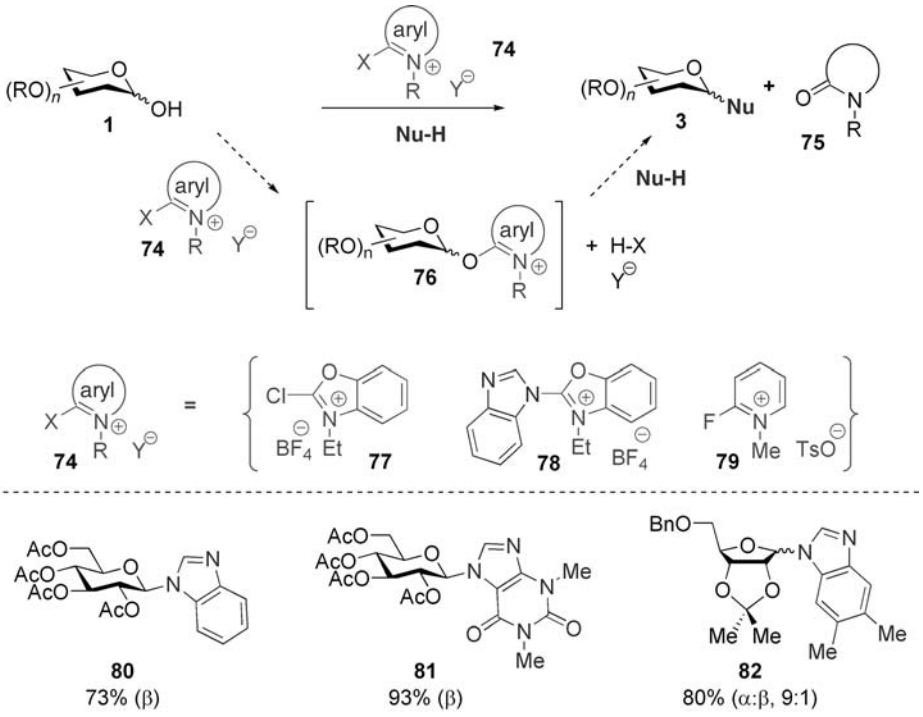
Scheme 3.11 Dehydrative glycosylation with $Ph_2SO{\cdot}Tf_2O$.

Iterative approaches to oligosaccharide formation by this method have also been advanced. A $Ph_2SO{\cdot}Tf_2O$ mediated glycosylation of a rhamnopyranose acceptor incorporating both a C-4 hydroxyl and a C-1 hemiacetal was performed, and the C-4 hydroxyl was glycosylated preferentially to form (1,4)-disaccharide **72** in high yield [135]. The disaccharide product **72** presents a hemiacetal that is immediately available for subsequent glycosylation, requiring no additional anomeric protective group manipulations. Recently, a one-pot, three-component trisaccharide synthesis using sulfonium activation of hemiacetals was reported by van der Marel and associates [136]. The $Ph_2SO{\cdot}Tf_2O$ dehydration method was used to glycosylate a C-3 hydroxyl acceptor for the *in situ* formation of an α(1,3)-disaccharide, which contains a latent sulfide donor at the reducing-end. A further addition of triflic anhydride at this time allows for activation of this thioglycoside donor and subsequent glycosylation, forming trisaccharide **73** in 80% yield.

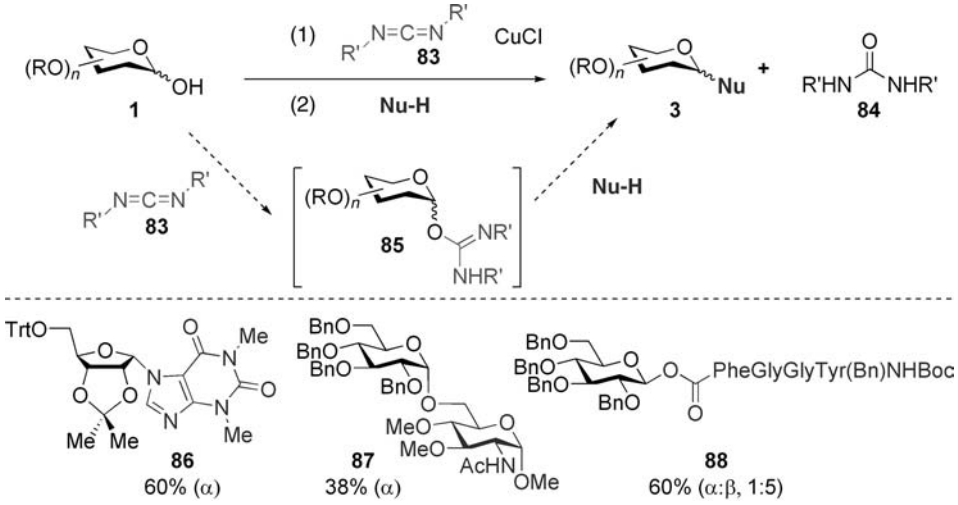
3.1.7
Hemiacetal Activation with Carbon Electrophiles

The earliest examples of carbon-based activation of hemiacetals in a direct dehydrative glycosylation employ hetaryl onium salts, reagents that had previously been used to convert hemiacetals to glycosyl halides [137,138]. In the general approach (Scheme 3.12), the hemiacetal **1** is treated with an *N*-alkyl hetaryl onium salt **74**, which acts as a *C*-electrophile for hemiacetal activation. The resulting *O*-aryl intermediate **76** is susceptible to reaction with a glycosyl acceptor (NuH), leading to the displacement of the anomeric leaving group to form the desired glycoside **3** and the 2-pyridone-derived by-product **75**.

In an early example, Mukaiyama and coworkers used hetaryl onium salts for nucleoside synthesis. The active hetaryl onium salt is generated *in situ* from the reaction of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **77** and the glycosyl acceptor. With benzimidazole as glycosyl acceptor, the resulting 2-(1-benzimidazoyl)benzoxazolium tetrafluoroborate **78** was obtained. The reaction between the hetaryl onium salt **78** and hemiacetal donor **1** occurs at 60 °C to activate the hemiacetal and thereby reveal the glycosyl acceptor. This procedure led to the formation of nucleoside **80** with exclusive 1,2-*trans* selectivity [139]. The nucleoside **81** was similarly prepared. Alternatively, 2-fluoro-1-methylpyridinium tosylate **79** directly



Scheme 3.12 Dehydrative glycosylation with hetaryl onium salts.



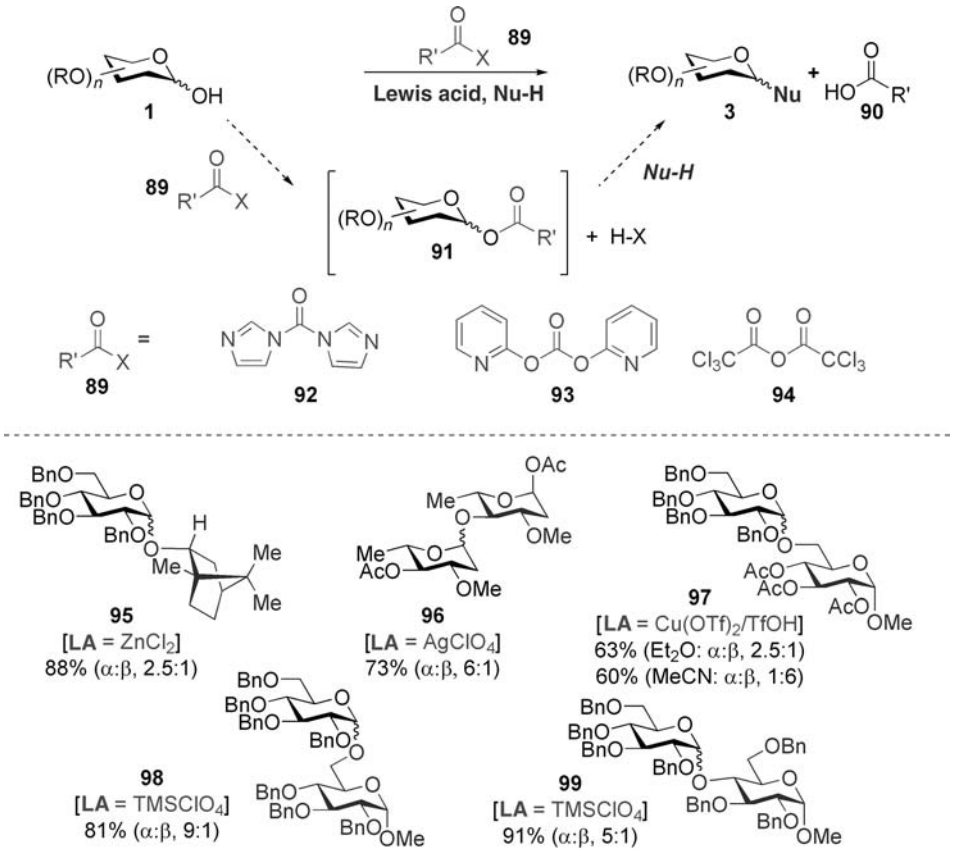
Scheme 3.13 Dehydrative glycosylation with carbodiimides.

promotes dehydrative glycosylations of hemiacetals, providing, for example ribonucleoside **82** in 80% yield [140]. Although research in this area has focused only on the preparation of *N*-glycosides, it nevertheless illustrates an early and intriguing method for dehydrative glycosylation.

In an extension beyond hetaryl onium salt promoted hemiacetal activation, Ishido and coworkers have reported the carbodiimide activation of hemiacetals [141]. In the method (Scheme 3.13), the hemiacetal donor **1** is treated with a carbodiimide electrophile **83** and copper(I) chloride to provide glycosyl isourea intermediate **85**. Highly susceptible to hydrolysis, the isourea **85** was not isolated but could be detected by ^{13}C NMR and IR spectroscopy [142,143]. Accordingly, the reaction between intermediate **85** and the glycosyl acceptor (NuH) provides glycoside product **3**, along with urea by-product **84**.

A typical procedure calls for reaction of the hemiacetal donor with dicyclohexyl carbodiimide and copper(I) chloride (0.1 equiv) at 80 °C, followed by an addition of the acceptor and continued heating. As an early demonstration of this protocol, α-riboside **86** was prepared in moderate yield but with exclusive stereoselectivity [141]. Further measures were required for the glycosylation of monosaccharide acceptors, such as addition of *p*-toluenesulfonic acid (0.1 equiv) to promote the formation of disaccharide **87** [144]. The method was more suitably applied to the synthesis of *O*-acyl glycopeptides, as evidenced by the formation of **88** in 60% yield [143,144]. Various peptides with non-nucleophilic side chains were found to be amenable to this stereoselective reaction. The β-selectivity was suggested to arise from a preponderance of the α-isourea intermediate **85** in the activation step.

Another mode of carbon-based activation of hemiacetals relies on carbonyl-centered electrophiles **89** (Scheme 3.14). These reagents have demonstrated the highest efficiency for disaccharide synthesis among electrophilic carbon activating agents. In the event, the hemiacetal **1** is activated with electrophile **89** for *in situ*



Scheme 3.14 Dehydrative glycosylation with carbonyl activators.

generation of the glycosyl *O*-carbonyl intermediate **91**. With Lewis acid assistance, addition of a glycosyl acceptor allows for displacement of the anomeric carboxylate of **91** to give glycoside product **3**. In the case that the active intermediate **91** is a glycosyl carbonate or glycosyl carbamate, carbon dioxide is expelled from the by-product **90** providing added entropic driving force to the reaction.

The earliest examples of one-pot direct dehydrative glycosylations involving this mode of activation was reported by Ford and Ley [145]. Treatment of hemiacetal **1** with 1,1′-carbonyldiimidazole **92** rapidly provides the glycosyl (1-imidazolylcarbonyl) intermediate **91**. The glycosyl carbamate serves as a capable donor with zinc(II) bromide promotion (1 equiv) at elevated temperatures. Through this procedure, the glycosylation of a sterically hindered secondary alcohol afforded glucoside **95** in 88% yield. The method was also applied, with slight modification, in the synthesis of Avermectin B1a, wherein glycoside **96** was formed in 73% yield using silver perchlorate activation [146,147].

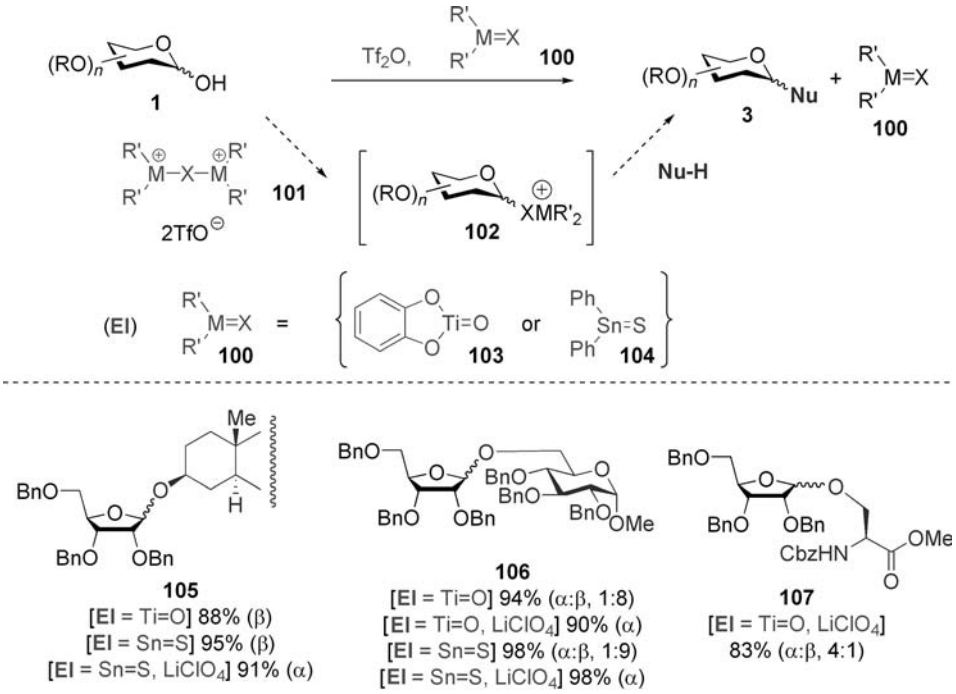
Hanessian and coworkers have used a one-pot glycosylation in their development of 2-pyridylcarbonate donors, which were found to be unstable to chromatography

[148]. Hemiacetal **1** is activated with bis(2-pyridyl) carbonate **93** (1.2 equiv) and catalytic *N,N*-dimethyl 4-aminopyridine (DMAP) to allow for *in situ* formation of the corresponding glycosyl carbonate intermediate **91**. This intermediate reacts with alcohol acceptors in the presence of copper(II) triflate (2.5 equiv) and triflic acid (0.5 equiv) to give disaccharides, such as **97**, in moderate yields. The addition of triflic acid was necessary to reduce the amount of unreacted α-glycosyl carbonate, seemingly the less reactive anomeric carbonate intermediate in the glycosylation. The stereoselectivity of this reaction could be reversed by exchanging the reaction solvent from diethyl ether to acetonitrile. In this case, the formation of disaccharide **97** was achieved with a 1 : 6 α : β ratio in 60% yield. This solvent effect was attributed to the ability of acetonitrile to form an α-glycosyl nitrilium intermediate [149], whereas ether solvents favor β-coordination, and the reaction proceeds through the respective intermediate to β or α glycoside product [150,151].

Kusumoto and coworkers have found that the treatment of hemiacetal **1** with trifluoro- or trichloroacetic anhydride **94** (1 equiv) and trimethylsilyl perchlorate (0.2 equiv) selectively provides the corresponding anomeric ester intermediate **91** [152]. Hemiacetal acylation occurs even in the presence of the alcohol acceptor. With Lewis acid assistance, the glycosyl ester intermediate is displaced to provide disaccharide products in good yields. This transformation allowed the synthesis of disaccharides **98** (81%) and **99** (91%). In some cases, acetic anhydride has been used as the electrophilic activator of hemiacetal donors and the reaction with thiol acceptors yields *S*-linked glycosides [153,154].

3.1.8 Other Methods

Activation of hemiacetals with titanium-oxo and tin-sulfide reagents presents an alternative mode of electrophilic activation of hemiacetal donors, though not fundamentally unlike many of the previous methods (Scheme 3.15). Mukaiyama's group has developed much of the chemistry for titanium- and tin-based glycosylation, which has been applied to furanose hemiacetal donors. The original paper reports the use of a [1,2-benzenediolato(2-)-*O,O′*]oxotitanium reagent **103** (catechol titanium oxide, 4 equiv) with triflic anhydride (2 equiv) to provide the postulated titanium bistriflate activating agent **101** [155,156]. The hemiacetal donor **1** reacts with the bis(titanium) complex **101** for over 2 h at −23 °C to form the active glycosyl intermediate **102**. A silyl ether glycosyl acceptor (4 equiv) is then added to the reaction, which in the presence of cesium fluoride, produces riboside products in high yields and anomeric selectivity. For example, the ribosides **105** and **106** were formed in 88 and 94% yields, respectively, favoring the β anomer. It was postulated that coordination of the anomeric oxotitanium moiety of intermediate **102** to the *cis* C-2 oxygen substituent further aided selectivity for the 1,2-*trans* β-glycoside. The reaction was rendered stereoselective upon the introduction of lithium perchlorate (4 equiv) [157], allowing for the generation of disaccharide **106** in 90% yield (α). The lithium perchlorate was proposed to promote dissociation of anomeric oxotitanium species **102**, allowing nucleophiles access to the α-face. Similarly, glycopeptide **107**

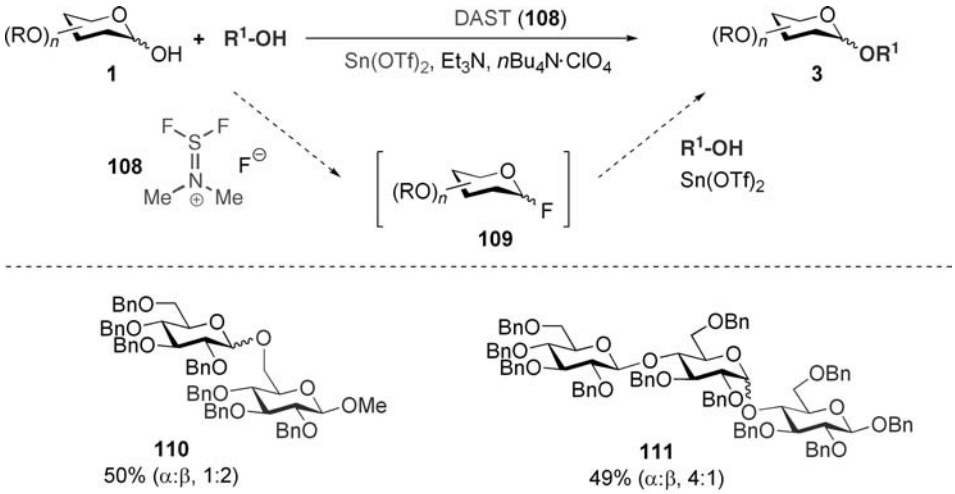


Scheme 3.15 Metal oxide and metal sulfide-promoted glycosylations.

was formed from the glycosylation of the silylated serine acceptor in 83% yield, favoring the α anomer (4 : 1).

Following from this work, Mukaiyama *et al.* were able to improve the yields and stereoselectivity using diphenyltin sulfide **104** (1.5 equiv) and triflic anhydride (1.2 equiv) activating agents [158]. Several glycosides were obtained in excellent yield and stereoselectivity, as exemplified by the ribosyl cholesterol **105** (95%, β) and the disaccharide **106** (98%, 1 : 9 α : β). The α-selective glycosylations with lithium perchlorate additive were equally impressive. The cholesteryl riboside **105** was produced in 91% and the disaccharide **106** in 98% yield. In later work, it was demonstrated that diphenyltin sulfide in combination with silver perchlorate (in the absence of Tf_2O) catalyzed the formation of glycosides, albeit with moderate β-selectivity [159]. It was also noted that the combination of Lawesson's reagent and silver salts also effectively catalyzed this transformation. Although these methods have only been demonstrated on ribose hemiacetal donors, the excellent yields and stereoselectivity suggest alluring prospects for the other substrate classes.

Despite the high utility of glycosyl fluorides as stand-alone glycosyl donors, there has been only one example of a direct dehydrative glycosylation whereby hemiacetal activation proceeds through a glycosyl fluoride intermediate. Hirooka and Koto have detailed the use of diethylaminosulfur trifluoride (DAST) for dehydrative glycosylations with hemiacetal donors (Scheme 3.16) [160]. Treatment of a mixture of hemiacetal **1** and alcohol acceptor (R^1OH) with DAST **108** (2 equiv) at 0 °C provides the



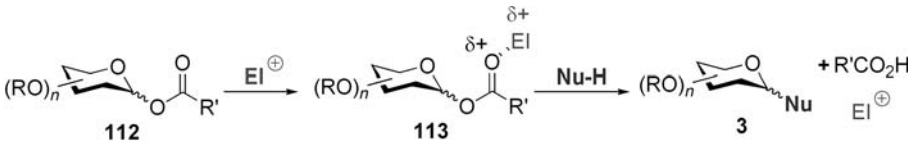
Scheme 3.16 DAST-promoted dehydrative glycosylations.

glycosyl fluoride intermediate **109**. After screening various promoters, an efficient *in situ* conversion of the glycosyl fluoride **109** to glycoside product **3** occurs with $Sn(OTf)_2$. Triethylamine and tetrabutylammonium perchlorate are used in the reaction to minimize the self-condensation of the donor and increase the β-selectivity, respectively.

This procedure has been demonstrated to provide moderate yields and anomeric selectivity in oligosaccharide synthesis. For instance, the disaccharide **110** was obtained in 50% yield as a 1 : 2 α : β ratio. The reaction side products were mainly the self-condensed donor (10–25%) and unreacted hemiacetal (5–10% or higher). Alternatively, the α-linked glycosides were favored with diethyl ether solvent. In this way, trisaccharide **111** was prepared from the disaccharide hemiacetal donor in 49% yield, favoring the α-anomer by 4 : 1.

3.1.9
Glycosylation with Anomeric Esters

Glycosylation with anomeric ester donors is one of the most convenient and simplest approaches to glycosidic bond construction. Advantages of using glycosyl ester donors include their easy preparation and chemical stability, which are characteristics that typically allow these compounds to be prepared in large quantities and stored and handled with relative ease. This presents a practical and convenient option when selecting an approach to glycoside bond formation. In the general reaction (Scheme 3.17), the glycosyl ester **112** is subjected to electrophilic activation of the carbonyl group to provide the reactive intermediate **113**. Subsequent displacement of the anomeric ester by the glycosyl acceptor (NuH) provides the desired glycoside product **3**. A consideration with this class of donor is the anomeric configuration of the starting ester **112**, which can significantly affect the reactivity



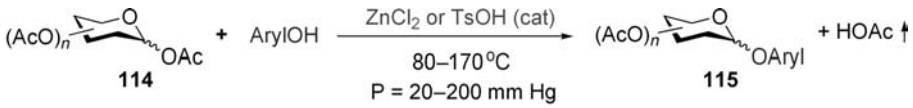
Scheme 3.17 Glycosylations with glycosyl ester donors.

of the glycosyl donor. Indeed, the 1,2-*trans* anomeric ester is most often used in glycosylations, and its higher reactivity is attributed to anchimeric assistance by the C-2 participatory group. Related to this, the nature of the promoter would be expected to play a defining role in the reaction efficiency. Discoveries in the synthesis of glycosides using glycosyl ester donors are discussed below.

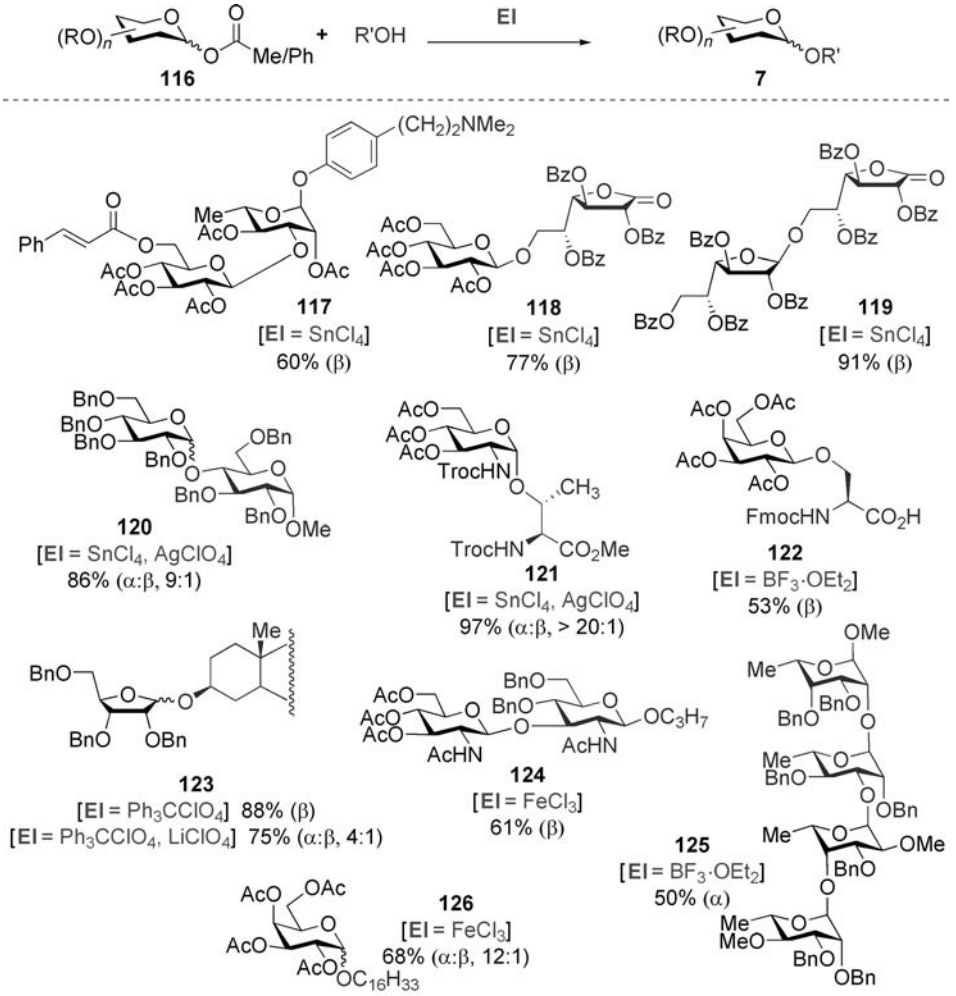
3.1.9.1 Glycosyl Acetate and Glycosyl Benzoate Donors

The glycosylation with glycosyl acetate donors was demonstrated by Helferich and Schmitz-Hillerbrecht [161]. In their method (Scheme 3.18), a peracetyl sugar, such as β-D-glucose pentaacetate **114**, is combined with phenol and either zinc(II) chloride or toluenesulfonic acid catalyst. At high temperature and reduced pressure in the absence of solvent, *O*-aryl glycoside **115** is obtained. The method has been used extensively in the early literature (e.g. [162–166]). For several carbohydrate donors, including glucopyranose, galactopyranose [167], *N*-acetyl glucosamine, *N*-acetyl galactosamine [168] and allopyranose [169], the reaction has been reported as being stereoselective, with the outcome depending on the identity of the catalyst and the reaction temperature. Typically, toluenesulfonic acid is used in the reaction at 80–100 °C to favor the 1,2-*trans* β-anomer; however, zinc(II) chloride at higher temperatures leads to the 1,2-*cis* α-anomer even in the presence of a C-2 participatory group. In the latter case, the formation of the α-anomer arises from thermodynamic equilibration under the reaction conditions. A few reports on the preparation of *O*-aryl disaccharides have been documented [170–175], and the reaction has been used in the synthesis of tyrosine *O*-aryl glycopeptides [176], ribofuranose nucleosides [177–184] and *S*-glycosides [185–188]. In these investigations, a diverse set of acid promoters have been successfully employed.

Significant practical advances were made in adapting the process to solution-phase couplings with the appropriate choice of Lewis acid (Scheme 3.19). One of the most commonly used Lewis acids in the solution-phase Helferich glycosylation is tin tetrachloride ($SnCl_4$) [189], which successfully promotes glycosylation with a range of glycosyl acetate donors **116** and acceptors. For instance, the $SnCl_4$ promoted Helferich glycosylation has allowed for the preparation of a variety of *O*-aryl glycosides [190–192], including the hordenine glycoalkaloid **117** isolated after



Scheme 3.18 Helferich glycosylation.



Scheme 3.19 Lewis acid activation of glycosyl ester donors.

24 h at 0 °C [193]. Disaccharides have also been synthesized under similar conditions [194–197], exemplified by the formation of 1,2-*trans* disaccharide **118** in 77% yield [198]. Although less commonly used than anomeric acetate donors, anomeric benzoates have also been activated with stoichiometric $SnCl_4$ [199–201]. With this donor type, disaccharide **119** was obtained in 91% yield after 5 h at ambient temperature [202]. In all of the above examples, the products have been obtained with the expected 1,2-*trans* configurations in high stereoselectivity. Mimicking the thermodynamic control over anomeric stereoselectivity of the original Helferich reaction, it was discovered that employing $SnCl_4$ at elevated temperatures and longer durations can even favor the 1,2-*cis* anomer [190,203–208]. Following this principle, Mukaiyama and coworkers have developed a general protocol to efficiently access 1,2-*cis*

α-glycosides. The combination of $SnCl_4$ and AgOTf (20 mol%) catalyzes the glycosylation with anomeric ester donors and silyl alcohol acceptors to provide good yields of product with high 1,2-*cis* α-stereoselectivity [209–212]. In control experiments, it was shown that the Lewis acid catalyst, postulated to be $SnCl_3^+ ClO_4^-$, isomerizes the 1,2-*trans* *O*-alkyl glycoside to the 1,2-*cis* glycoside. In this way, disaccharide **120** was prepared in 86% yield (α : β, 9 : 1) over 24 h at 0 °C. Notably, the reaction provides a high 1,2-*cis* α-selectivity even in the presence of C-2 participatory groups. The C2-trichloroethoxycarbonyl (Troc) aminoglycoside **121** was generated in excellent yield and stereoselectivity. It was found that reduction of catalyst loading from 20 to 10% and shortening the reaction time provides the corresponding 1,2-*trans*-linked glycosides in high yield and selectivity. This stereoselective reaction has been adopted for disaccharide and trisaccharide synthesis [213,214]. Taken together, the $SnCl_4$ and $SnCl_4$/Ag-ClO_4 mediated glycosylations have demonstrated a significant substrate scope. Apart from the examples described above, various *O*-alkyl glycosides (e.g. [215–219]) and nucleosides [220–228] have also been achieved by using $SnCl_4$ promotion of the solution-phase Helferich glycosylation.

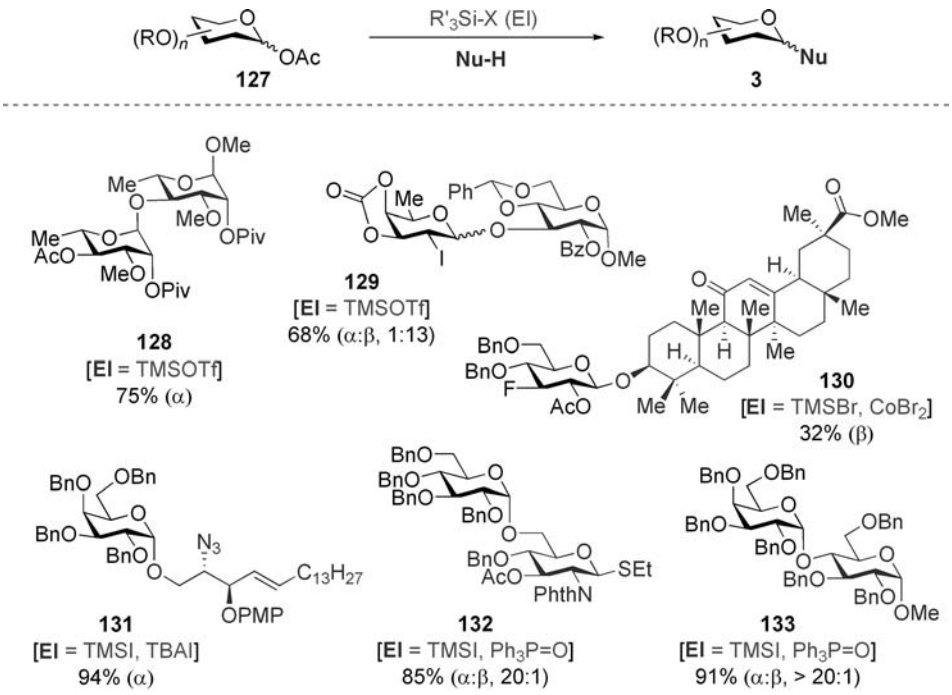
Boron trifluoride diethyletherate ($BF_3{\cdot}OEt_2$) is another commonly used Lewis acid in solution-phase Helferich glycosylations and was reported as early as 1949 [229,230]. Like $SnCl_4$, $BF_3{\cdot}OEt_2$ promotes glycosylation of phenols with peracetyl donors with high efficiency [231–238]. $BF_3{\cdot}OEt_2$ has also been found to effect *C*-aryl glycoside formation with armed donors and electron-rich aromatic rings [82,239]. A distinct application of the $BF_3{\cdot}OEt_2$ promoted reaction was demonstrated by Kihlberg and coworkers in a convenient method to glycopeptide fragments by glycosylation of an amino acid alcohol acceptor that incorporates an unprotected C-terminal carboxylate [240,241]. In this reaction, excess $BF_3{\cdot}OEt_2$ (3 equiv) was added to a solution of pentaacetyl galactose and *N*-Fmoc-serine acceptor (1 equiv) to provide the glycoconjugate **122** in 53% yield after 1 h at ambient temperature [242]. By comparison, in the synthesis of L-fucose glycopeptides the use of 6 equiv of $BF_3{\cdot}OEt_2$ over 2 d was demonstrated to reverse the stereoselectivity and provide 1,2-*cis* α-fucosides (35–45% yield) [243]. The 1,2-*cis* stereoselectivity was the result of product anomerization, which has only been reported for L-fucose glycopeptides. A number of other researchers have adopted this general method for glycopeptide bond formation [244–250]. The $BF_3{\cdot}OEt_2$ activation of a glycosyl acetate donors has also been used in oligosaccharide synthesis [251–253]. Gurjar and Viswanadham, in their convergent synthesis of a mycobacterial glycolipid, prepared tetrasaccharide **125** in 50% yield from the coupling of a disaccharide acceptor with a disaccharide acetate donor at 0 °C [254]. Most of the examples with $BF_3{\cdot}OEt_2$ activation result in exclusive formation of the 1,2-*trans* isomer and the formation of 1,2-*cis* glycosides is rare and the efficiency appears to be low [238].

Trityl perchlorate ($TrClO_4$) is a relatively new promoter of the solution phase Helferich glycosylation, though it has shown promising activity for a number of substrates. Early work by Mukaiyama *et al.* established that glycosyl acetate activation with trityl perchlorate (1 equiv) at 0 °C provided ribofuranoside **123** in 88% yield [24]. In this reaction it was observed that the α anomer was first generated and then isomerized to the β anomer under the agency of $TrClO_4$. The authors hypothesized

that addition of a mild base would suppress this anomerization without compromising Lewis acid activation of the donor. Interestingly, it was found that addition of $LiClO_4$ and 4 Å molecular sieves provided the corresponding α glycoside of **123** in 75% as a 4 : 1 α : β mixture. The method has been extended to 1,2-*cis* selective glycosylation of glucopyranose acetate donors with C-2 nonparticipatory groups, as well as the synthesis of 1,2-*cis* *C*-glycosides using a polymer-supported $TrClO_4$ derivative [255]. Trityl perchlorate mediated glycosylation has also been used in the total synthesis of Lepidicin A [256] and Spinosyn A [257].

A number of reports have appeared using $FeCl_3$ activation of anomeric ester donors, though most often with donors incorporating a C-2 amide functionality. Kiso and Anderson advanced the use of $FeCl_3$ for glycosylation with C-2 amide glycosyl acetate donors [258], following from earlier work by Matta and Bahl on the use of $FeCl_3$ for oxazoline synthesis from anomeric acetates [259]. It is widely held that Lewis acid coordinated oxazolines (oxazolinium cations) are the reactive intermediates in glycosylations with these acetate donors [260]. In one example, $FeCl_3$ (1.5 equiv) in combination with $CaSO_4$ and tetramethylurea (TMU) promoted the formation of disaccharide **124** in 61% yield over 2–3 d [261]. The long reaction times are indicative of the low reactivity of C-2 acetamido glycosyl donors, an established challenge with this class of molecules. To aid in the glycosylation of secondary alcohol acceptors, procedures involving excess quantities of both $FeCl_3$ and glycosyl donor have been used [262]. This general method has been adopted by a number of researchers [263–265]. In addition, $FeCl_3$ has been applied to other C-2 amide derivatives, such as *N*-phthaloyl or *N*-chloroacetyl glycosyl acetate donors, wherein electronic tuning of the amide substituent allows for more efficient glycosylations [260,266]. It should be noted that other Lewis acids, such as $SnCl_4$ [267], $BF_3{\cdot}OEt_2$ [268], TMSOTf [269–273] and camphor sulfonic acid [274], have all been used to activate C-2 amide glycosyl acetate donors with seemingly comparable efficiency, though TMSOTf was effective at low temperatures. The application of $FeCl_3$ to other, non-C-2 amide donors has provided some interesting results [275,276]. Chatterjee and Nuhn have discovered that the use of $FeCl_3$ at ambient temperature predominately provided the α-galactoside **126** in 68% yield, even with a C-2 ester participatory group in the glycosyl donor.

Trimethylsilyl triflate, a recently developed promoter of glycosyl ester donors, has proven to be generally useful as a consequence of its high electrophilicity [272,277–279]. In these reactions (Scheme 3.20), TMSOTf often can be used in substoichiometric quantities to promote glycosylation with anomeric ester donors (**127**). To this end, the 1,2-*trans*-linked disaccharide **128** was obtained in 75% yield by the action of TMSOTf (0.6 mol equiv) at −78 °C [280]. This reagent has been further applied to the synthesis of the 2-deoxy galactose segment of the aureolic acid antibiotics. In this work, Durham and Roush reported that the TMSOTf activation (0.2 mol equiv) of a glycosyl acetate donor at 0 °C provided disaccharide **129** in 68% yield (α : β, 1 : 13) [281]. TMSOTf has also been demonstrated in the glycosylation with perbenzoyl glycosyl donors and simple alcohol acceptors [282]. Other silyl triflates have been successfully used as activators, including *tert*-butyldimethylsilyl triflate (TBSOTf) [283], the catalyst system composed of $SiCl_4$ and AgOTf for



Scheme 3.20 Silicon activation of glycosyl ester donors.

nucleoside synthesis [212], and a polymer-supported silyl triflate for deoxyglycoside synthesis [284]. The utility of the silyl triflate protocol is reflected in its use in the synthesis of natural products [82,285,286] and oligosaccharides [287,288].

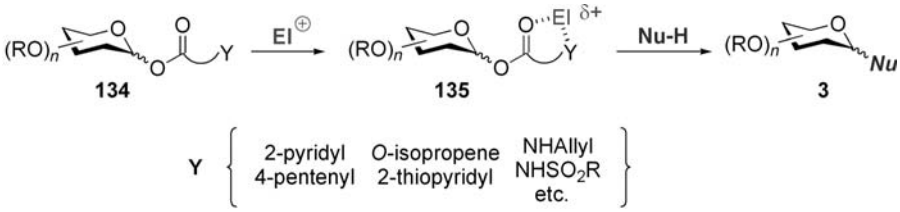
A variation in electrophilic silicon activation of glycosyl esters includes the use of a nucleophilic promoter to aid in displacement of the anomeric ester (Scheme 3.20). In an early report, Morishima and Mori found that the application of their reagent system used for direct dehydrative glycosylation of hemiacetal donors (Section 3.1.4), namely trimethylsilyl bromide (2 equiv) and cobalt(II) bromide (3 equiv), also promotes glycosylation of ester donors. This protocol first converts the glycosyl ester **127** to a glycosyl bromide intermediate, which in turn reacts with the glycosyl acceptor (NuH) to form glycoside products **3** at room temperature. For example, from this procedure β-glucoside **130** was obtained, but the yield was low (32%) [289]. Gervay-Hague and coworkers have significantly contributed to this approach by intercepting glycosyl iodide intermediates through the action of trimethylsilyl iodide on glycosyl acetate donors. In the reaction, the iodide counterion of the silicon electrophile is sufficiently nucleophilic to displace the activated ester [290]. Thus, the glycosyl iodide intermediate is obtained without purification, and then treated with the acceptor and tetrabutylammonium iodide. From this procedure, glycoside **131** was obtained in 94% after 1.5 h at 65 °C [291]. The efficient formation of the 1,2-*cis* α-glycosides with C-2 nonparticipatory groups results from halide ion catalysis of the intercepted glycosyl iodide intermediate [292]. The method has been extended to solution- and solid-phase

oligosaccharide synthesis [293,294], as well as preparation of *S*-, *N*- and *C*-glycosides [67,295,296]. Mukaiyama and coworkers have employed the combination of TMSI and phosphine oxide to effect glycosylation with a glycosyl acetate donor via a proposed anomeric oxophosphonium intermediate [297]. Although the glycosyl oxophosphonium intermediate was not observed by NMR, the phosphine oxide nucleophilic catalysis in glycosidic bond formation was independently demonstrated. The treatment of the glycosyl acetate donor **127** with TMSI, triphenylphosphine oxide and the glycosyl acceptor provides disaccharides after 21 h at room temperature. From this procedure, disaccharides such as **132** or **133** could be obtained in high yield and selectivity. Other researchers have found that in certain cases, silicon activation is not required to access the reactive glycosyl iodide intermediate. Schmid and Waldmann have shown that anomeric trifluoroacetate glycosyl donors undergo displacement by the sole action of lithium iodide (1 equiv) to promote the formation of disaccharides under neutral conditions [298]. In addition, an intriguing report has appeared that uses natural phosphate doped with potassium iodide to promote the reaction of a ribofuranose acetate donor with various silylated nucleobase acceptors [299].

The Helferich glycosylation has been used extensively in carbohydrate chemistry and only the main classes of activating agents are surveyed in this chapter. Besides the acids documented above, many different Brønsted acids (e.g. $HClO_4$ [300], NH_2SO_3H [301], TfOH [302], MK-10 [303]), Lewis acids (e.g. $Sc(OTf)_3$ [304], $Yb(OTf)_3$ [305], $Yb[N(Tf)_2]_3$ [306], $SiCl(OTf)_3$ [307], $AlCl_3$ [220] and Tf_2O [308]) and acid combinations (e.g. $BF_3{\cdot}OEt_2 + Bi(OTf)_3$ [309], $TMSCl + Zn(OTf)_2$ [310], $TsOH + Yb(OTf)_3$ [311]) have been used to similar effect. In terms of variability of the glycosyl ester donor, reports have detailed the use of halogen-substituted acetate donors [24,312], anomeric pivaloate donors [313] and anomeric *p*-nitrobenzoate donors [314–322] in this reaction.

3.1.10
Activation of *O*-Carbonyl Derivatives

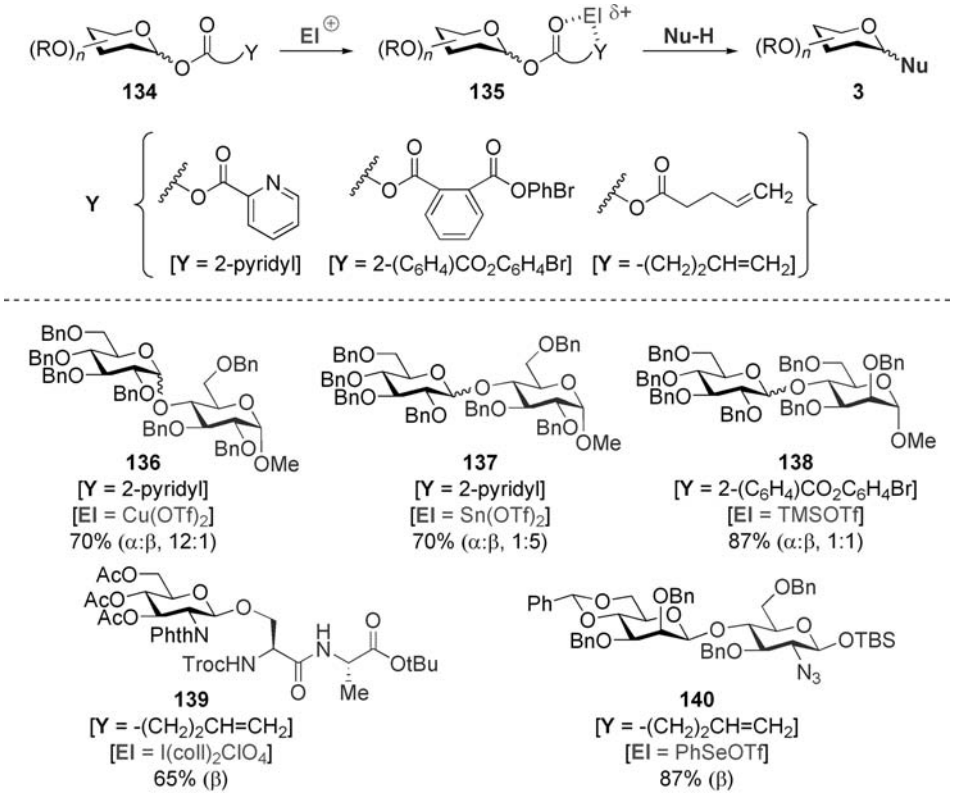
Apart from glycosyl acetate and benzoate donors, more elaborate *O*-carbonyl derivatives offer potential for distinct modes of anomeric leaving group activation. Many of these donors (Scheme 3.21) involve activation of an anomeric *O*-carbonyl derivative **134** at a remote functional group (Y). The activated remote functionality, in turn,



Scheme 3.21 Remote activation of C1-*O*-carbonyl donors.

promotes loss of the anomeric leaving group by an intramolecular reaction with the carbonyl oxygen or through chelated coordination as in intermediate **135**. In the presence of a glycosyl acceptor (NuH), the leaving group is displaced and the glycoside product **3** is formed. This conceptual approach, forwarded by Hanessian and coworkers [323], has the inherent benefit of being able to design a chemoselective pairing of the activating agent and the remote functionality. Consequently, greater possibilities for orthogonal glycosylation are established. In the following section, glycosylation with donors derived from glycosyl esters, *O*-glycosyl thiocarbonates, glycosyl carbamates and glycosyl carbonates will be summarized.

Glycosyl esters with remote functionality constitute a relatively new class of *O*-carbonyl glycosyl donors, which fulfill the prospect of mild and chemoselective activation protocols (Scheme 3.22). For example, Kobayashi and coworkers have developed a 2-pyridine carboxylate glycosyl donor **134** (Y = 2-pyridyl), which is activated by the coordination of metal Lewis acid (El^+) to the Lewis basic pyridine nitrogen atom and ester carbonyl oxygen atom [324]. In the event, 2-pyridyl(carbonyl) donor **134** and the monosaccharide acceptor were treated with copper(II) triflate (2.2 equiv) in diethyl ether at −50 °C, providing the disaccharide **136** in 70% (α : β,

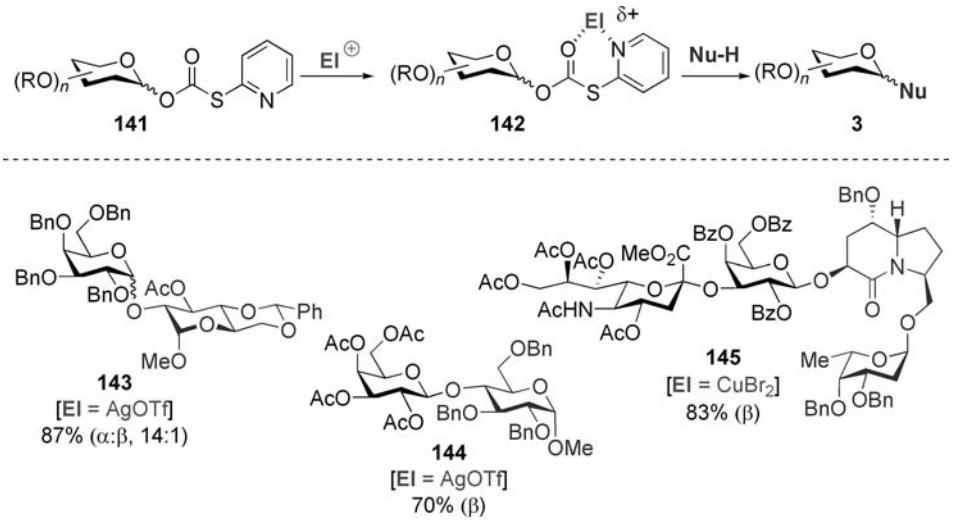


Scheme 3.22 Remote activation of C1-*O* carbonyl donors.

12 : 1) [325]. Interestingly, it was found that by varying the nature of the Lewis acid and solvent, stereoselectivity could be reversed. Using tin(II) triflate in acetonitrile, 70% yield of disaccharide **137** was isolated, this time favoring the β anomer by 5 : 1. Kim and coworkers have reported glycosylation with glycosyl phthalate donors **134** [Y = 2-(C_6H_4)$CO_2C_6H_4$Br] [326]. The glycosyl phthalate **134** can be activated with TMSOTf (0.5 equiv) at −78 °C to promote the formation of a variety of disaccharides, including **138** (87%, α : β, 1 : 1). Limited stereoselectivity was observed for most of the substrates [327]. Kunz and coworkers have demonstrated the usefulness of anomeric 4-pentenoyl glycosyl donors **134** [Y = −$(CH_2)_2$CH = CH_2] [328], arising from Fraser-Reid's established method using *O*-pentenyl glycoside donors [329,330]. The 4-pentenoyl glycosyl donors reportedly display increased reactivity relative to *O*-pentenyl donors. In the reaction, the 4-pentenoyl donor **134** was treated with iodonium di-*sym*-collidine perchlorate at ambient temperature to activate the distal alkene. This remote activation step, in turn, causes γ-lactonization with the anomeric ester carbonyl oxygen of **135** and subsequent expulsion of lactone in the glycosidic bond forming event. From this procedure glycopeptide **139** was obtained in 65% yield with the acid-sensitive *tert*-butyl ester intact. Kim and coworkers have also developed a stereoselective synthesis of β-mannosides by using 4-pentenoyl donor **134** protected with the 4,6-benzylidene stereodirecting group [331,332]. In the reaction, the glycosyl donor is activated with excess phenylselenyl triflate (PhSeOTf) and silver triflate for 15 min at −78 °C, followed by an addition of the acceptor. Glycosylation takes place below 0 °C to provide disaccharides such as **140** in 87% yield, exclusively as the β-anomer. The β-selectivity using the 4-pentenoate glycosyl donors was, in general, high. Innovative methods that use alkynoate ester donors have also been developed to access disaccharides in good yield [333,334].

Through their pioneering efforts in this field, Hanessian's group has devised a number of effective donors in the remote activation approach [8,335]. Covering the topic of remote activation in full is beyond the scope of this chapter, as some of the most useful glycosyl donors include *O*-heteroaryl glycoside and various *S*-glycoside donors. However, one relevant class to this discussion is the 2-thiopyridylcarbonate (TOPCAT) donors, compounds such as **141** that are reportedly stable and easily obtainable molecules (Scheme 3.23) [336,337]. It was anticipated that the activation of TOPCAT donor **141** with a Lewis acid (El^+) allows for chelation of the Lewis acid to both the thiopyridyl nitrogen and the carbonyl ester oxygen of intermediate **142**. This two-point coordination aids the displacement of the thiocarbonate moiety to afford the targeted glycoside **3**.

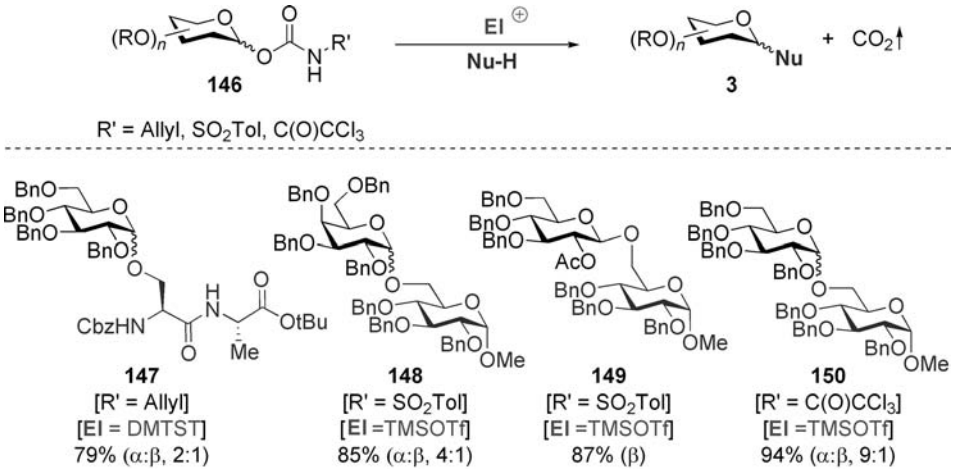
In an early report [335], it was shown that glycosylation with the 2-thiopyridylcarbonate donor **141** and a monosaccharide acceptor proceeds under the promotion of AgOTf (3 equiv) at 0 °C. In diethyl ether cosolvent, this reaction afforded disaccharide **143** in 87%, favoring the α anomer (14 : 1). The TOPCAT donor is also amenable to glycosyl ester protected carbohydrate donors, thereby providing a convenient route to β-linked disaccharides such as **144** with complete anomeric selectivity. The method has been applied to the synthesis of oligosaccharides and sialyl Lewis X mimetics [338–340]. A TOPCAT disaccharide donor was employed with $CuBr_2$ activation to form glycoconjugate **145** in 83%, exclusively as the β anomer



Scheme 3.23 Remote activation of 2-thiopyridylcarbonate donors.

[341]. The high yields, stereochemical control and mild reaction conditions make this class of *O*-carbonyl donors an attractive option.

Carbamate glycosyl donors are another useful class of compounds, which pre sent significant variability in chemical structures (Scheme 3.24). In an early example by Kunz and Zimmer, the *N*-allyl carbamate donors were used in a remote activation protocol to furnish pyranoside and furanoside products. In this reaction, the *N*-allyl carbamate donor **146** is activated with dimethyl methylthiosulfonium

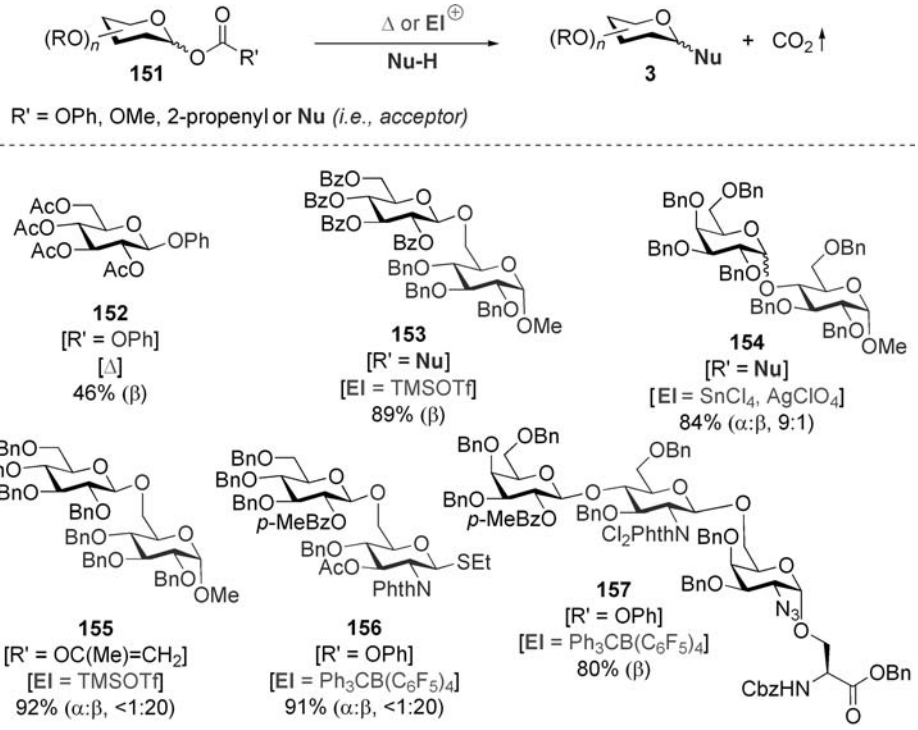


Scheme 3.24 Remote activation of C1-*O*-carbamate donors.

triflate (DMTST) at room temperature. Subsequent introduction of the glycosyl acceptor affords glycosidic product, such as glycopeptide **147** in 79% yield (α : β, 2 : 1) [342]. High stereoselectivity for 1,2-*trans* glycosides was achieved in this reaction using C-2 ester participatory groups. Hinklin and Kiessling have reported on the glycosylation with a variety of *N*-sulfonylcarbamate glycosyl donors activated by TMSOTf [343]. In the reaction, the *N*-toluenesulfonyl donor **146** is activated with TMSOTf (1.1 equiv), and upon addition of the monosaccharide acceptor, the desired **3** is obtained. With this protocol, disaccharide **148** was synthesized in 85% yield (α : β, 4 : 1). It was also shown that the incorporation of a C-2 ester in the glycosyl donor allows for high yields of the β anomer, illustrated by the preparation of disaccharide **149** in 87% yield. Beyond considerations of anomeric stereoselectivity, further investigations showed that substitution on the sulfonamide nitrogen allowed the reactivity of the glycosyl donor to be tuned. In related work, a variety of substituted carbamate donors and Lewis acid activators were systematically investigated by Redlich's group and others [344,345]. In one example, an *N*-trichloroacetyl carbamate was activated with TMSOTf (1 equiv) at 0 °C to provide disaccharide **150** in 94% yield (α : β, 9 : 1) [346]. Although this example does not react in a remote activation pathway, the ability to tune the electronic character of the glycosyl donor with different substituents again illustrates a beneficial aspect of this donor class.

Glycosyl carbonates constitute another class of glycosyl *O*-carbonyl donors, which in certain cases show distinct reactivity in the glycosylation event (Scheme 3.25) [347,348]. The carbonate leaving group, upon expulsion of CO_2, has been found to act as the glycosyl acceptor in the reaction. Ishido and coworkers [349–351] first described the heating of the glycosyl phenyl carbonate **151** (R′ = OPh) to 170 °C, which effected decarboxylation to provide the phenyl glycoside **152** in 46% yield along with mixed carbonate by-products. Following the pioneering work by Descotes and coworkers [352], Ikegami and coworkers demonstrated that Lewis acids promote decarboxylation and glycosidic bond formation of bis(mannosyl) carbonates **151** (R′ = Nu = acceptor), even at ambient temperatures [353,354]. Accordingly, disaccharide **153** was prepared in 89% by the treatment of the corresponding mixed carbonate **151** with TMSOTf (1.1 equiv) [355]. A 1,2-*cis* variation of this reaction can be achieved by using the catalyst system composed of $SnCl_4$ and $AgClO_4$ (20 mol %) in diethyl ether solvent. This procedure afforded the α-linked disaccharide **154** in 84% yield as a 9 : 1 α : β ratio [356]. Scheffler and Schmidt have studied the TMSOTf promoted decarboxylative glycosylation through competition experiments between mixed carbonates, and it was concluded that the reaction is an intermolecular process [357].

Simple alkyl carbonates have also been used as glycosyl donors with the addition of an external glycosyl acceptor. Sinay and coworkers have reported that 2-propenyl carbonate donors, such as **151** (R′ = 2-propenyl), are activated with TMSOTf at −25 °C to afford good yields of disaccharide products [358]. Disaccharide **155** was obtained in high yield and α-stereoselectivity after 30 min. Similarly, Mukaiyama *et al.* have used phenyl (R′ = OPh) or methyl (R′ = OMe) carbonates



Scheme 3.25 Glycosylation with C1-*O*-carbonate donors.

151 as glycosyl donors [359]. By using substoichiometric trityl tetrakis(pentafluorophenyl)borate (10 mol%) as an activator of a phenyl carbonate donor, disaccharide **156** was formed in 91% yield with exclusive β selectivity over 6 h at −20 °C [360]. The stability of the product disaccharide **156**, with a latent ethylsulfide leaving group at the reducing end, allowed for the development of one-pot procedures for trisaccharide synthesis [361,362]. In the event, the trisaccharide glycopeptide **157** was prepared by using the trityl perchlorate activation of a galactosyl phenyl carbonate donor to glycosylate a C-4 hydroxyl acceptor, then subsequent *in situ* activation of the latent sulfide donor by addition of *N*-iodosuccinimide and addition of the C-6 hydroxyl glycopeptide acceptor. This one-pot three-component assembly achieved trisaccharide **157** in 80% yield [363]. Other modes of electrophilic activation of alkyl carbonate donors have been developed, including $SnCl_2$, SbI_3 and TeI_4 [364,365]. In particular, methyl carbonate donors have been activated by the catalyst system composed of either diphenyl tin sulfide and a silver salt or Lawesson's reagent and a silver salt for the preparation of 1,2-*trans*-linked ribonucleosides with good efficiency [366–368]. Trichloromethyl carbonate donors have also been used with TMSOTf or $BF_3{\cdot}OEt_2$ activation to effect 1,2-*cis* *O*-aryl galactopyranosides [369].

3.1.11 Conclusion

There has been a considerable development in glycosylations with C1-hydroxyl donors beyond the classic Fischer glycosylation. These methods employ a wide range of chemistry to effectively deal with the established challenges of the approach, and this is achieved in many cases with good stereocontrol and reaction efficiency. There are many methods that display promising reactivity, but comparatively a few have exhi bited expansive substrate scope in the proving ground of oligosaccharide and complex molecule synthesis. It is expected that with continuing developments in this area, the advantages of the direct dehydrative glycosylation will be more fully realized, leading to more efficient reactions with greater contributions to multiglycosylation sequences.

Glycosylations with anomeric acetate and benzoate donors have maintained steady occurrence in the literature. The great advantage of their use is the ease of preparation and stability of the donor. Glycosyl acetate donors have been applied to complex molecule synthesis, though their use in this context has been relatively limited in number. The exploration of anomeric *O*-carbonyl donors has paved the way for new reactivity in this field. In particular, the remote activation approach allows for mild, chemoselective promotion of various glycosyl donors. The potential of these glycosylations has already been realized in one-pot, iterative oligosaccharide synthesis.

3.1.12 Representative Experimental Procedures

3.1.12.1 Representative Procedure for Preparation of C1-Hemiacetal Donors Through a Peracylation-Selective Anomeric Deacylation Sequence [3,4]

Acetic anhydride (20 equiv) was slowly added to a solution of D-galactose (16.65 mmol, 1 equiv) in dry pyridine (33 ml) at 0 °C. The reaction was stirred at 0 °C for 1 h and then 4-(*N*,*N*-dimethylamino)pyridine (0.1 equiv) was added and the reaction was brought to room temperature. After 6 h the reaction mixture was slowly poured into 500 ml of stirring ice water and extracted with ethyl acetate (75 ml). After the evaporation of the ethyl acetate portion and repeated evaporations from toluene, pentaacetyl D-galactose was obtained in 89% yield. The pentaacetyl D-galactose is also widely available from commercial sources. A solution of the peracetyl sugar (12.8 mmol, 1 equiv) and benzylamine (1.5 equiv) in tetrahydrofuran (30 ml) was stirred at room temperature overnight. The mixture was diluted with cold water and extracted with chloroform (3×50 ml). The chloroform portion was washed with ice-cold dilute HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, water and then dried (Na_2SO_4), filtered and concentrated. The crude reaction concentrate was purified by silica gel chromatography to provide the acetyl protected C1-hemiacetal.

3.1.12.2 Representative Procedure for Brønsted Acid Promoted Glycosylation with C1-Hemiacetal Donors Using Methoxyacetic Acid [11]

A mixture of hemiacetal donor (1 mmol), glycosyl acceptor (1.2 equiv), methoxya-cetic acid (0.1 equiv) and $Yb(OTf)_3$ (0.1 equiv) in dichloromethane (40 ml) was

refluxed for 3–5 h under argon through a column of activated 4 Å molecular sieves (28 g).

3.1.12.3 Representative Procedure for Lewis Acid Promoted Glycosylation with C1-Hemiacetal Donors Using $Sn(OTf)_2$ and $LiClO_4$ [20]

The reaction was carried out under an argon atmosphere. Tin(II) trifluoromethanesulfonate and anhydrous calcium sulfate (Drierite) were dried at 100 °C under reduced pressure (0.1 mmHg) for 1 h prior to use. To a stirred suspension of Sn $(OTf)_2$ (0.01 equiv), Drierite (750 mg), $LiClO_4$ (1.5 equiv) and hexamethyldisiloxane (0.10 equiv) in $MeNO_2$ (2 ml) was added a solution of glycosyl donor (0.40 mmol, 1 equiv) and alcohol acceptor (1.2 equiv) in $MeNO_2$ (4 ml) at room temperature. Upon completion of the reaction, as indicated by TLC analysis, saturated aqueous $NaHCO_3$ was added and the mixture was filtered. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel.

3.1.12.4 Representative Procedure for Silicon Promoted Glycosylation with C1-Hemiacetal Donors Using Me_3SiBr and $CoBr_2$ [42]

The glycosyl donor, glycosyl acceptor, $CoBr_2$, *n*-Bu_4NBr were stored *in vacuo* over P_2O_5 prior to use. Me_3SiBr was used without any pretreatments. Me_3SiBr (1 equiv) was stirred into a mixture of glycosyl donor (0.17 mmol, 1 equiv), the glycosyl acceptor (0.8 equiv), $CoBr_2$ (1 equiv), *n*-Bu_4NBr (1 equiv) and 4 Å molecular sieves (180 mg) in CH_2Cl_2 (0.45 ml). The resulting mixture was stirred at ambient temperature (22–28 °C). Upon completion of the reaction, the reaction mixture was filtered and the filtrate evaporated and purified by silica gel chromatography.

3.1.12.5 Representative Procedure for Mitsunobu-Type Glycosylation with C1-Hemiacetal Donors and Phenol Glycosyl Acceptors [90]

The reaction was conducted in flame-dried glassware under a dry nitrogen atmosphere. A solution of glycosyl donor (0.200 mmol, 1 equiv), phenol (1.4 equiv) and Ph_3P (1.5 equiv) in toluene (3 ml) was stirred with 4 Å molecular sieves (~100 mg) for 0.5 h and cooled to 0 °C. DEAD (2 equiv) was added, and the reaction mixture was stirred overnight. The mixture was then diluted with EtOAc and filtered. The purification of the reaction mixture was performed by Kieselgel flash chromatography and preparative TLC.

3.1.12.6 Representative Procedure for Appel-Type Glycosylation with C1-Hemiacetal Donors [102]

Reactions were carried out in a glass vessel closed with a septum cap. Neither molecular sieve nor drying gas was used. The glycosyl donor (0.41 mmol, 1 equiv) in CH_2Cl_2 (3 ml) was treated with Ph_3P (3 equiv) and CBr_4 (3 mol equiv) and stirred for 3 h at room temperature. Then, the *N,N*-tetra-methylurea (300 µl) and the glycosyl acceptor (3 equiv) were added and stirred at room temperature. The reaction was monitored by TLC analysis until the bromide donor was

completely consumed. The reaction mixture was then diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solution and then dried (Na_2SO_4) and concentrated. The product was purified by silica gel column chromatography.

3.1.12.7 Representative Procedure for Nosyl Chloride Promoted Glycosylation with C1-Hemiacetal Donors [115]

A mixture of a glucosyl acceptor (0.33 mmol, 1 equiv), glycosyl donor (1.3 equiv), 4-nitrobenzenesulfonyl chloride (2.5 equiv), silver trifluoromethanesulfonate (2.5 equiv) and dichloromethane (1.8 ml) was successively treated with *N,N*-dimethylacetamide (2.5 equiv for secondary alcohol acceptor or 5 equiv for primary alcohol acceptor) and triethylamine (2.5 equiv) under stirring at −40 °C bath temperature. The bath temperature was gradually raised to 0 °C over 1 h and then the reaction was stirred overnight at 0 °C. At this time, solid $NaHCO_3$ was added and the reaction was brought to room temperature with stirring. The reaction mixture was filtered and concentrated, then purified by silica gel chromatography. Contamination of any trace nitrogenous compounds in the glucosides was removed by rechromatography on silica gel in hexane–ethyl acetate.

3.1.12.8 Representative Procedure for Diphenyl Sulfoxide and Triflic Anhydride Promoted Glycosylation with C1-Hemiacetal Donors [127]

The reaction was performed in flame-dried modified Schlenk (Kjeldahl shape) flask fitted with a glass stopper or rubber septum under a positive pressure of argon. Trifluoromethanesulfonic anhydride (1.4 equiv) was added to a solution of glycosyl donor (0.191 mmol, 1 equiv) and diphenyl sulfoxide (2.8 equiv) in a mixture of toluene and dichloromethane (8 ml, 3 : 1 vol/vol) at −78 °C. The reaction mixture was stirred at this temperature for 5 min and then at −40 °C for 1 h. At this time, 2-chloropyridine (5.0 equiv) and the glycosyl acceptor (3.0 equiv) were added sequentially at −40 °C. The solution was stirred at this temperature for 1 h, then at 0 °C for 30 min and finally at 23 °C for 1 h before the addition of excess triethylamine (10 equiv). The reaction was diluted with dichloromethane (100 ml) and was washed sequentially with saturated aqueous sodium bicarbonate solution (2 × 100 ml) and saturated aqueous sodium chloride (100 ml). The organic layer was dried (sodium sulfate) and concentrated. The residue was purified by silica gel flash column chromatography.

3.1.12.9 Representative Procedure for Carbodiimide Promoted Glycosylation with C1-Hemiacetal Donors [144]

A mixture of glycosyl donor (2.0 mmol, 1 equiv), *N,N′*-dicyclohexylcarbodiimide (1 equiv) and copper(I) chloride (0.01 equiv) was fused for 0.5 h at 80 °C. The glycosyl acceptor (0.5 equiv) was added to the resulting melt, which was further heated for 1 h at 80 °C. The melt was dissolved in dichloromethane (40 ml) and the *N,N′*-dicyclohexylurea was removed by filtration. The filtrate was evaporated and the residue was purified by silica gel column chromatography to provide product glycoside.

3.1.12.10 Representative Procedure for Carbonyl Promoted Glycosylation with C1-Hemiacetal Donors Using Trichloroacetic Anhydride [152]

To a suspension of glycosyl donor (1.5 mmol, 1 equiv), glycosyl acceptor (0.7 equiv) and 5 Å molecular sieves (500 mg) in dry diethyl ether (4 ml), $AgClO_4$ (0.2 equiv), $(CCl_3CO)_2O$ (1 equiv) and TMSCl (0.2 equiv) was added under a N_2 atmosphere. The mixture was stirred at room temperature for 8 h. Ethyl acetate and saturated aqueous $NaHCO_3$ solution were added to the mixture and 5 Å molecular sieves were removed by filtration. The organic later was washed with aqueous NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

3.1.12.11 Representative Procedure for Lewis Acid Promoted Glycosylation with Glycosyl Acetate Donors Using $SnCl_4$ [198]

A solution of the glycosyl donor (0.51 mmol, 1 equiv) in MeCN (6 ml) was chilled at 0 °C (ice water bath) and $SnCl_4$ (0.5 mmol, 1 equiv) was added. The solution was stirred for 10 min at 0 °C and the glycosyl acceptor (1 equiv) was added. The reaction was monitored by TLC until no starting material remained. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with saturated aqueous $NaHCO_3$ (2×30 ml) and water, then dried ($MgSO_4$) and evaporated. The residue obtained was purified by column chromatography on silica gel. The product glycoside thus obtained could be further purified by dissolution in Et_2O and precipitation by the addition of hexane. The resulting syrup was dissolved in hot EtOH and the product glycoside was crystallized upon cooling with seed crystals.

3.1.12.12 Representative Procedure for Iodotrimethylsilane and Phosphine Oxide Promoted Glycosylation with Glycosyl Acetate Donors [297]

The reaction was carried out under an argon atmosphere in dried glassware. To a stirred suspension of 5 Å molecular sieves (240 mg) and glycosyl acetate donor (0.12 mmol, 1 equiv) in CH_2Cl_2 (1.2 ml) was added iodotrimethylsilane (1 equiv) at 0 °C. After stirring for 30 min, $Ph_3P{=}O$ (2 equiv) and then glycosyl acceptor (0.7 equiv) were added. The reaction mixture was stirred at room temperature until TLC analysis indicated that the reaction was completed. The reaction mixture was then diluted with EtOAc, filtered through Celite and evaporated. The resulting residue was purified by preparative TLC on silica gel.

3.1.12.13 Representative Procedure for Lewis Acid Promoted Glycosylation with TOPCAT Glycosyl Donor Using Silver Triflate [335]

The reaction was performed under an argon atmosphere. A mixture of the glycosyl donor (0.185 mmol, 1 equiv), glycosyl acceptor (0.7 equiv) and activated powdered 4 Å molecular sieves (200 mg) in 6 ml of Et_2O–CH_2Cl_2 (5 : 1 vol/vol) was stirred overnight at room temperature and then cooled to 0 °C. Silver triflate (3 equiv) was added to the reaction mixture and stirred for 5 h at 0 °C. The resulting suspension was then treated with a few drops of pyridine, filtered through Celite and concentrated. Purification was performed by flash column chromatography on silica gel.

3.1.12.14 Representative Procedure for TMS Triflate Promoted Glycosylation with Glycosyl N-Tosyl Carbamate Donors [343]

Reaction was carried out in an oven-dried glassware under a nitrogen atmosphere. Prior to reaction, the glycosyl donor (0.10 mmol, 1 equiv) and glycosyl acceptor (1.5 equiv) were azeotroped three times with dry toluene. The resulting residue was dissolved in dry Et_2O (1.0 ml) and TMOTf (1.1 equiv) was added dropwise, followed by stirring under nitrogen for 1.5 h. The reaction was quenched by adding solid $NaHCO_3$ and the Et_2O was removed under reduced pressure. The residue was purified using silica gel flash column chromatography.

3.1.12.15 Representative Procedure for Trityl Salt Promoted Glycosylation with Glycosyl Phenyl Carbonate Donors [360]

To a stirred suspension of trityl tetrakis (pentafluorophenyl) borate (4.6 mg, 0.005 mmol) and Drierite (250 mg) in a mixture of pivalonitrile and dichloromethane (0.45 ml, 2 : 1 vol/vol), a solution (pivalonitrile : dichloromethane = 2 : 1, 0.8 ml) of glycosyl acceptor (1.2 equiv) and glycosyl donor (0.05 mmol, 1 equiv) at −20 °C was successively added. After the reaction mixture was stirred for 6 h at −20 °C, it was quenched by adding saturated aqueous $NaHCO_3$ (10 ml). The mixture was filtered through Celite and extracted with dichloromethane (three times, each of 20 ml). The combined organic layers were washed with brine (5 ml) and the organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by preparative TLC on silica gel.

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3.2
Glycoside Synthesis from 1-Oxygen-Substituted Glycosyl Imidates

Xiangming Zhu, Richard R. Schmidt

3.2.1
Introduction

Of the various synthetic strategies developed to date, glycoside syntheses based on glycosyl imidates are probably the most popular. This is because usually only catalytic amounts of a promoter are required to provide very high glycosyl-donor properties of glycosyl imidates whereas other glycosyl donors, such as glycosyl halides, thioglycosides, generally require at least equimolar amounts of a promoter system, which is often associated with disadvantages of various kinds.

In 1980, Schmidt introduced the corresponding trichloroacetimidates [370], which have become one of the most widely used glycosyl donors in contemporary carbohydrate chemistry [371–381]. Glycosyl trichloroacetimidates can be easily prepared by a base-catalyzed addition of an anomeric hydroxyl group to trichloroacetonitrile (Cl_3CCN) using either inorganic or organic bases. This reaction is generally high yielding and, because of its reversibility, high anomeric control can often be achieved. In addition, competing reactions with nonanomeric hydroxyl groups are quite slow. In a typical Schmidt glycosidation reaction, a catalytic amount of Lewis acid, such as trimethylsilyl triflate (TMSOTf) or boron trifluoride etherate ($BF_3{\cdot}OEt_2$), is most commonly used as the promoter. Glycosyl trichloroacetimidates exhibit outstanding donor properties in terms of ease of formation, stability, reactivity and general applicability and usually result in high product yields and high anomeric stereocontrol. The anomeric stereochemistry is derived from the anomeric configuration of glycosyl

trichloroacetimidates (inversion or retention), anchimeric assistance, the influence of solvents or thermodynamic or kinetic effects. As the *O*-glycosyl *N*-methyl acetimidates [382], introduced by Sinay, required lengthy preparation procedures and exhibited low reactivity, they did not gain broad application.

In 1983, Schmidt reported another type of glycosyl imidates, trifluoroacetimidates [383], as glycosyl donors. Afterward, a series of different *N*-substituted glycosyl trifluoroacetimidates were also prepared from the corresponding glycosyl hemiacetals and *N*-substituted trifluoroacetimidoyl chlorides [384]. Initial experiments revealed that glycosylations with trifluoroacetimidates were generally less efficient than those with trichloroacetimidates in terms of product yields. Later, Yu and Tao [385] and Iadonisi and coworkers [386] explored the application of glycosyl *N*-phenyl trifluoroacetimidates and reported particularly good reactivity for some specific glycosylation reactions. On the whole, trifluoroacetimidate donors exhibit reduced reactivity compared to the corresponding trichloroacetimidate donors presumably because of the lower *N*-basicity or the presence of an *N*-substituent or smaller trifluoromethyl-group-caused conformational change [387].

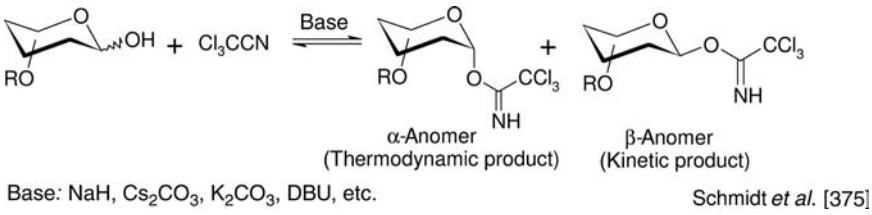
This review covers the recent advances in the use of *O*-glycosyl imidates in oligosaccharide and glycoconjugate synthesis, with emphasis on literature published between 1999 and 2006. However, because of the large volume of work in this area, only the most representative applications will be presented. One can refer to the similar preceding review [381] published in 2000 and another quite comprehensive review [375] on trichloroacetimidate method published in 1994 for earlier application of glycosyl trichloroacetimidates. Trifluoroacetimidate method will be discussed separately in this review in the light of its less popularity in carbohydrate chemistry.

3.2.2 Methodological Aspects

3.2.2.1 Preparation of Anomeric *O*-Trichloroacetimidates

Conventionally, the use of NaH or Cs_2CO_3 as a base for the reaction of glycosyl hemiacetals with Cl_3CCN often yields the thermodynamically favored α-glycosyl trichloroacetimidates, whereas the use of K_2CO_3 often yields kinetically controlled β-glycosyl trichloroacetimidates (Scheme 3.26). The use of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) often provides α/β mixtures, mostly favoring α-products.

Recently, two independent groups reported almost at the same time that polymer-supported DBU [388] and TBD [389] (1,5,7-triazabicyclo[4.4.0]dec-5-ene) were



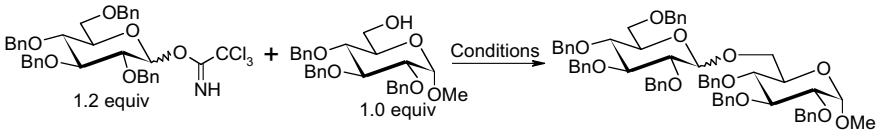
Scheme 3.26

efficient reagents for the preparation of trichloroacetimidates, affording excellent yields of pure products after simple filtration and evaporation. This was found to be particularly useful when the formed trichloroacetimidate donors were highly labile [388]. Another investigation disclosed that the polymer-bound DBU was the most efficient under substoichiometric conditions and was, therefore, the reagent of choice for the general preparation of this important class of glycosyl donors [390].

3.2.2.2 Glycosidation of *O*-Glycosyl Trichloroacetimidates

As mentioned above, TMSOTf and $BF_3{\cdot}OEt_2$ are the most commonly used catalysts for the Schmidt glycosidation. Several new catalysts for the activation of trichloroacetimidate donors have also been reported in the past years. Catalytic amount of $Sm(OTf)_3$ activated armed glycosyl trichloroacetimidates under very mild conditions [391], whereas disarmed trichloroacetimidate could be activated effectively by Yb $(OTf)_3$ [392]. These trivalent lanthanide triflates are generally stable salts that can be easily stored without particular precautions. AgOTf was also reinvestigated recently as a catalyst and proved to be a mild and, in some cases, more efficient catalyst in TMSOTf-sensitive glycosidation reactions [393]. In addition, the nature of the counteranion in catalysts is very influential in controlling the stereoselectivity of the Schmidt glycosidation, as reflected by comparing entries 1 and 2, or 3 and 4 in Table 3.1 [394], but how the anions work has not yet been understood. Appropriately functionalized acyl sulfonamides were also employed as catalysts for trichloroacetimidate glycosidations [395]. More recently, silica-supported perchloric acid ($HClO_4$–SiO_2) has been used as a convenient and efficient promoter in various glycosylation reactions, with trichloroacetimidates as glycosyl donors [396]. Also, the use of $HClO_4$–SiO_2 for 'on-column' glycosylation and subsequent '*in situ*' separation provided a novel and robust method for glycoside synthesis [397]. Trichloroacetimidate donors were also promoted by precise microwave heating in the absence of strong Lewis acids, giving the desired products in good yields [398]. A few papers were devoted to the use of ionic liquids as solvents to perform Schmidt glycosylations, in which the reactions proceeded at room temperature under mild conditions and, in some cases, avoided the use of Lewis acid catalyst [399–401].

Table 3.1



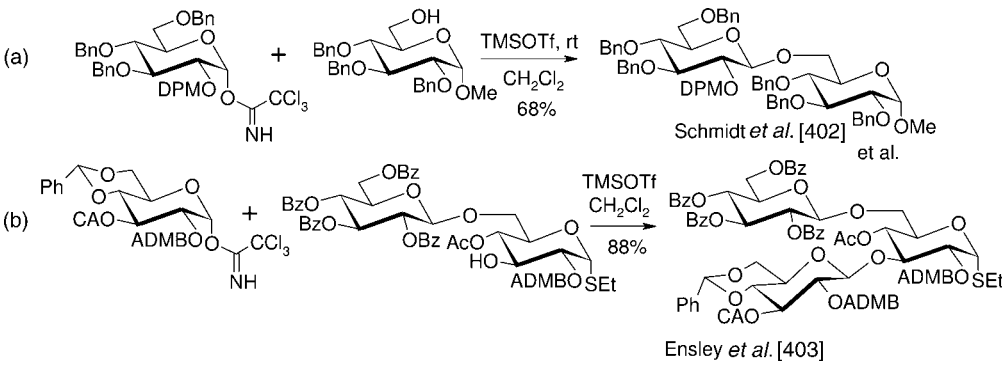
Entry	Conditions	Yield (%)	α/β Ratio
1	$HClO_4$, Et_2O	99	91 : 9
2	$HB(C_6F_5)_4$, Et_2O	97	43 : 57
3	$HClO_4$, BTF–^{t}BuCN	95	54 : 46
4	$HB(C_6F_5)_4$, BTF–^{t}BuCN	97	10 : 90

3.2.3
Synthesis of Oligosaccharides

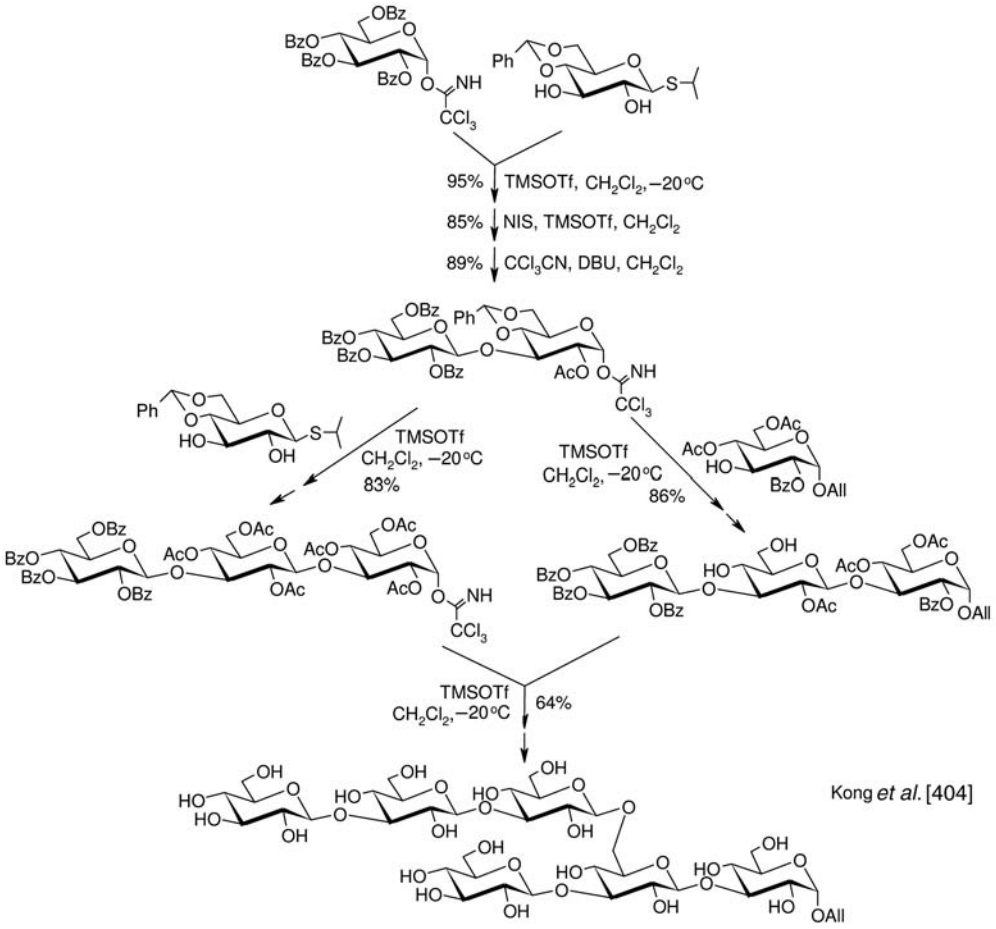
3.2.3.1 β-Glucosides, β-Galactosides, α-Mannosides and Others

The use of neighboring-group participation of 2-*O*-acyl-protected glycosyl trichloroacetimidates usually allows the synthesis of 1,2-*trans* glycosides such as β-glucosides, β-galactosides, α-mannosides, α-rhamnosides, β-xylosides and so on. A new ether-type protecting group, diphenylmethyl (DPM), was recently introduced into glucose 2-OH position, and interestingly, the resulting glucosyl trichloroacetimidate exclusively gave β-glucosides (Scheme 3.27a) [402]. The steric bulk of this group exerts anchimeric assistance on the anomeric stereocontrol through neighboring-group participation, as an acyl group does. Also, the use of 4-acetoxy-2,2-dimethylbutanoyl (ADMB) protecting group for 2-OH of glucose prevented the orthoester formation during glucosidation reactions, thereby allowing the selective formation of β-glucosides, as shown in Scheme 3.27b [403]. Recently, a glucohexaose was synthesized convergently as its allyl glycoside using trichloroacetimidate method (Scheme 3.28) [404], wherein the glycosylation steps are highly regioselective and high yielding. Similarly, β-(1 → 6)-linked glucooctaose was also synthesized employing glycosyl trichloroacetimidates as donors and partially protected sugars as acceptors [405]. A general approach based on trichloroacetimidate donor for the synthesis of 3,6-branched glucooligosaccharides has also been developed [406]. By this approach, a phytoalexin elicitor glucohexaose was prepared on a 100-g scale [407] and a tetradecasaccharide was also synthesized efficiently [408].

Syntheses of a series of galactans, including a decasaccharide, consisting of a β-(1 → 3)-linked galactosyl backbone and β-(1 → 6)-linked side chains of different size attached at the C-6 were achieved with glycosyl trichloroacetimidates as donors [409]. The β-(1 → 6)-linked galactans branched with α-arabinofuranose, that is arabinogalactan, were also synthesized in the same laboratories [410]. Again, glycosyl trichloroacetimidate was the sole donor used in the whole synthesis (Scheme 3.29). Other arabinogalactan-derived oligosaccharides have also been prepared on the basis of the trichloroacetimidate method [411,412].

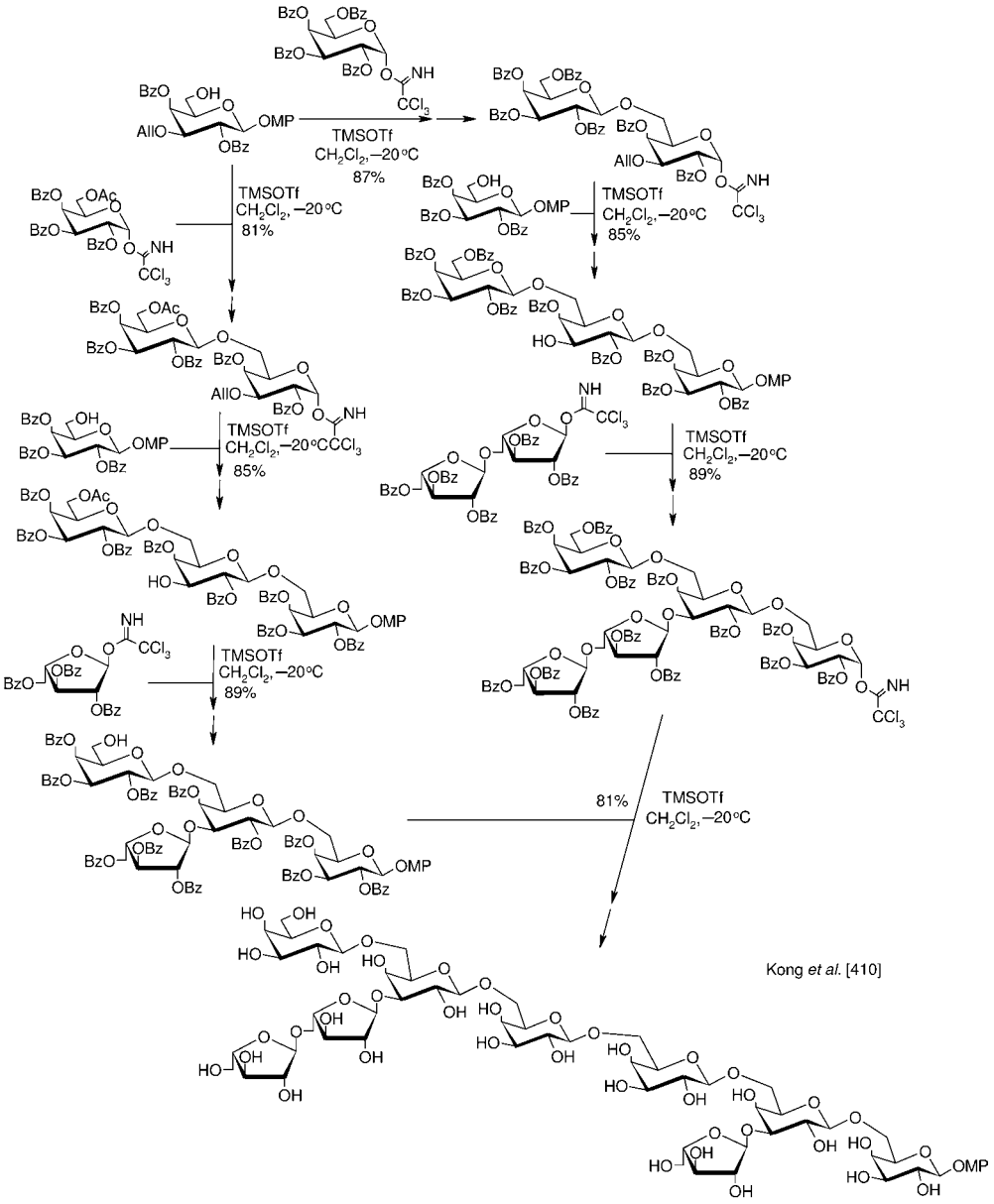


Scheme 3.27



Scheme 3.28

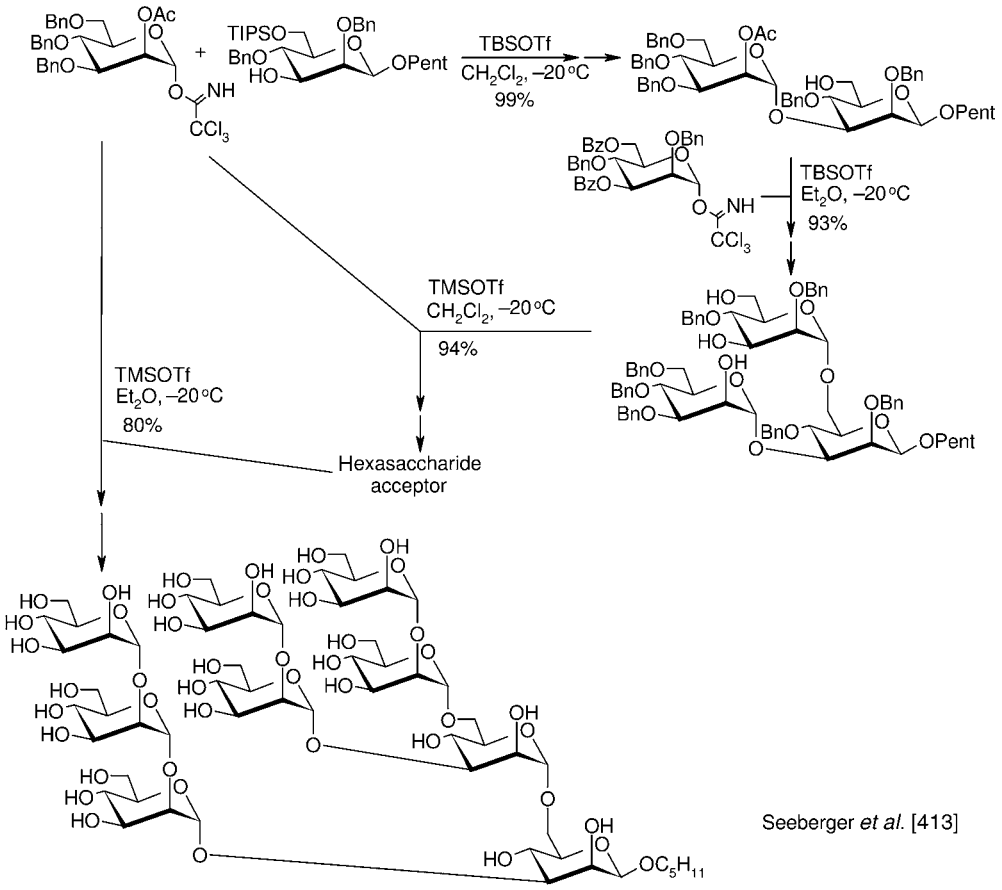
The synthesis of high-mannose-type cell surface glycans, which are found in nature as *N*-linked glycoconjugates, has been explored for the past two decades. Glycosyl trichloroacetimidates have often been exploited in the synthesis of this type of structures [413–421]. Recently, a linear synthesis of a typical triantennary high-mannose nonasaccharide was accomplished in four high-yielding Schmidt glycosidation events [413], as shown in Scheme 3.30. Also, a convergent procedure has been developed recently for the synthesis of oligosaccharides consisting of α-(1 → 2)- and α-(1 → 3)-linked rhamnan backbones and additional sugar side chains via di- and tetrasaccharides that could be converted either into glycosyl donors by deallylation and transformation into trichloroacetimidates or into acceptors by deacetylation. The efficiency of this procedure was demonstrated by the assembly of a decasaccharide carrying two GlcNAc residues derived from lipopolysaccharides (LPS) of phytopathogenic bacteria (Scheme 3.31) [422]. Trichloroacetimidate method



Scheme 3.29

has also been used in the synthesis of other rhamnooligosaccharides branched with different sugars [423–428].

In addition, oligomers of other monosaccharides, such as arabinofuranose [429], galactofuranose [430,431] and xylose [432], were also synthesized efficiently by taking advantage of the Schmidt glycosylation procedure.

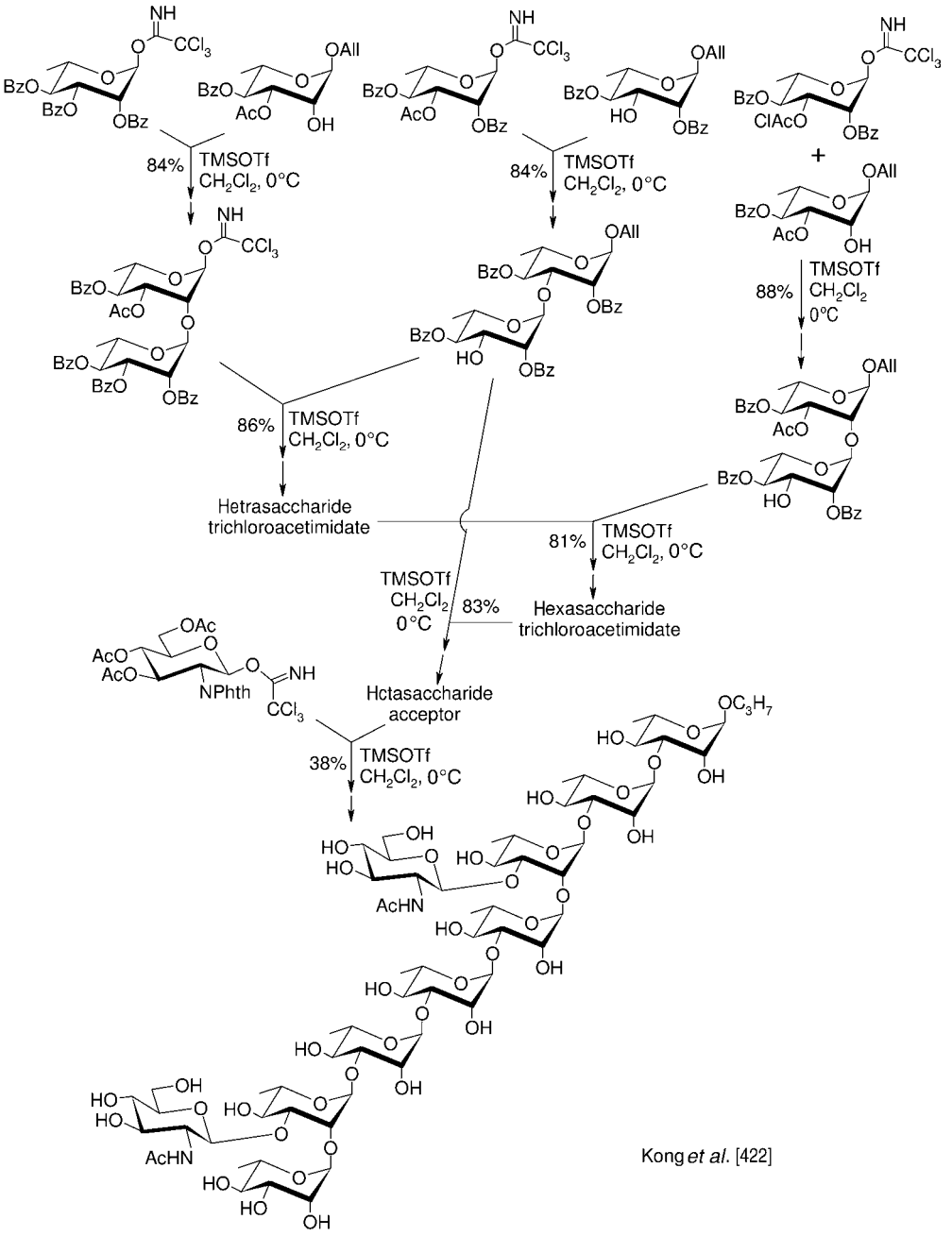


Scheme 3.30

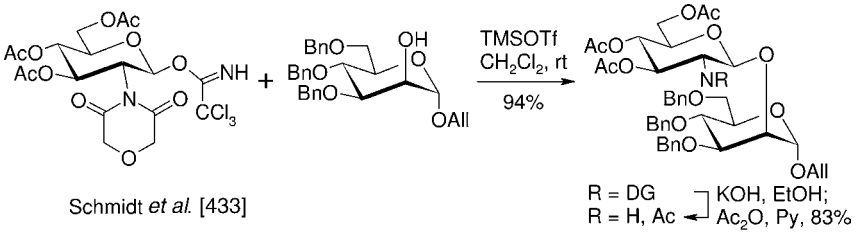
3.2.3.2 Aminosugar-Containing Oligosaccharides

A large number of oligosaccharides of biological significance contain aminosugar units. Therefore, considerable attention has been paid to the synthesis of aminosugar-containing oligosaccharides in the past years. A few new *N*-protecting groups have been proposed and tested in aminosugar glycoside synthesis [433]. Satisfactory results were obtained with *N*-diglycolyl (DG) group, which could be easily introduced and removed under basic conditions in high yields, and glycosylation reactions with *N*-DG-protected trichloroacetimidates gave high yields and β-stereoselectivities (Scheme 3.32) [433].

Chitooligosaccharides, the oligomers of *N*-acetylglucosamine, have been synthesized recently. In the synthesis, dimethylmaleoyl (DMM) group was used as amino protecting group (Scheme 3.33) [434]. Because of the anchimeric assistance and the electron-withdrawing character of the DMM group, the corresponding trichloroacetimidates were also excellent glycosylating agents to introduce β-aminosugars.


84%
TMSOTf
CH2Cl2, 0°C
84%
TMSOTf
CH2Cl2, 0°C
88%
TMSOTf
CH2Cl2
0°C
86%
TMSOTf
CH2Cl2, 0°C
Hetrasaccharide
trichloroacetimidate
81%
TMSOTf
CH2Cl2, 0°C
TMSOTf
CH2Cl2
0°C
83%
Hexasaccharide
trichloroacetimidate
Hctasaccharide
acceptor
38%
TMSOTf
CH2Cl2, 0°C
Kong et al. [422]

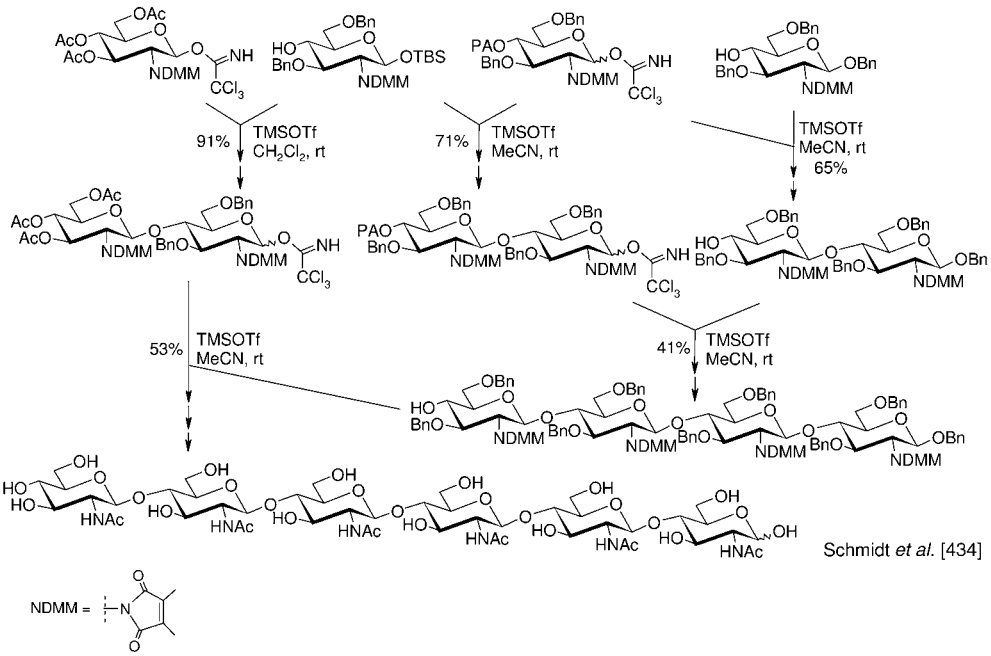
Scheme 3.31



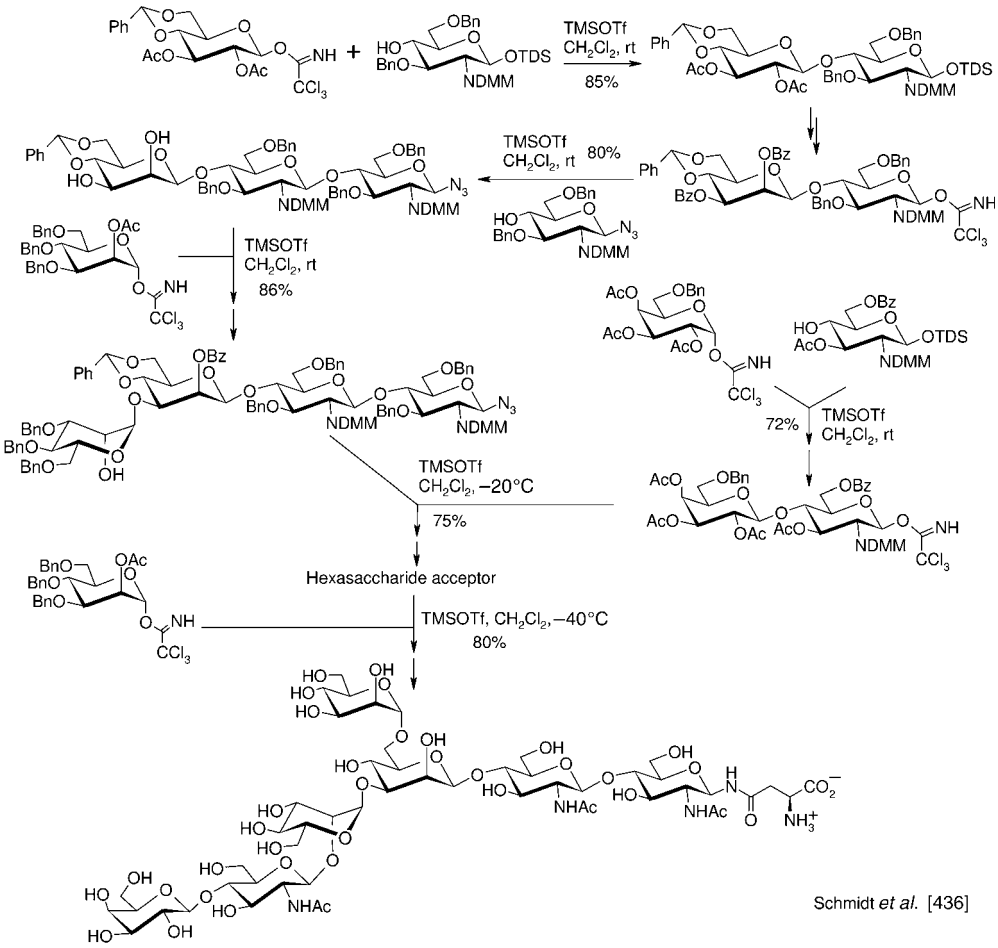
Scheme 3.32

The same approach has also been employed in the synthesis of lacto-*N*-tetraose and lacto-*N*-neotetraose [435] that represent core structural elements of more complex oligosaccharides in human milk, glycolipids and glycoproteins. An *N*-glycan fragment, asparagine-linked heptasaccharide consisting of the pentasaccharide core structure and one *N*-acetyllactosamine residue, was also assembled successfully using DMM group as the amino protecting group and glycosyl trichloroacetimidates as powerful donors (Scheme 3.34) [436].

The trichloroacetimidate method has also been used to prepare bivalent Le^X oligosaccharides to study the conformational details of carbohydrate clusters by NMR spectroscopy [437]. Two Le^X trisaccharides were covalently linked through the 6-hydroxy group or through the anomeric oxygen to yield the corresponding dimers. The synthesis of anomerically linked dimer was performed with



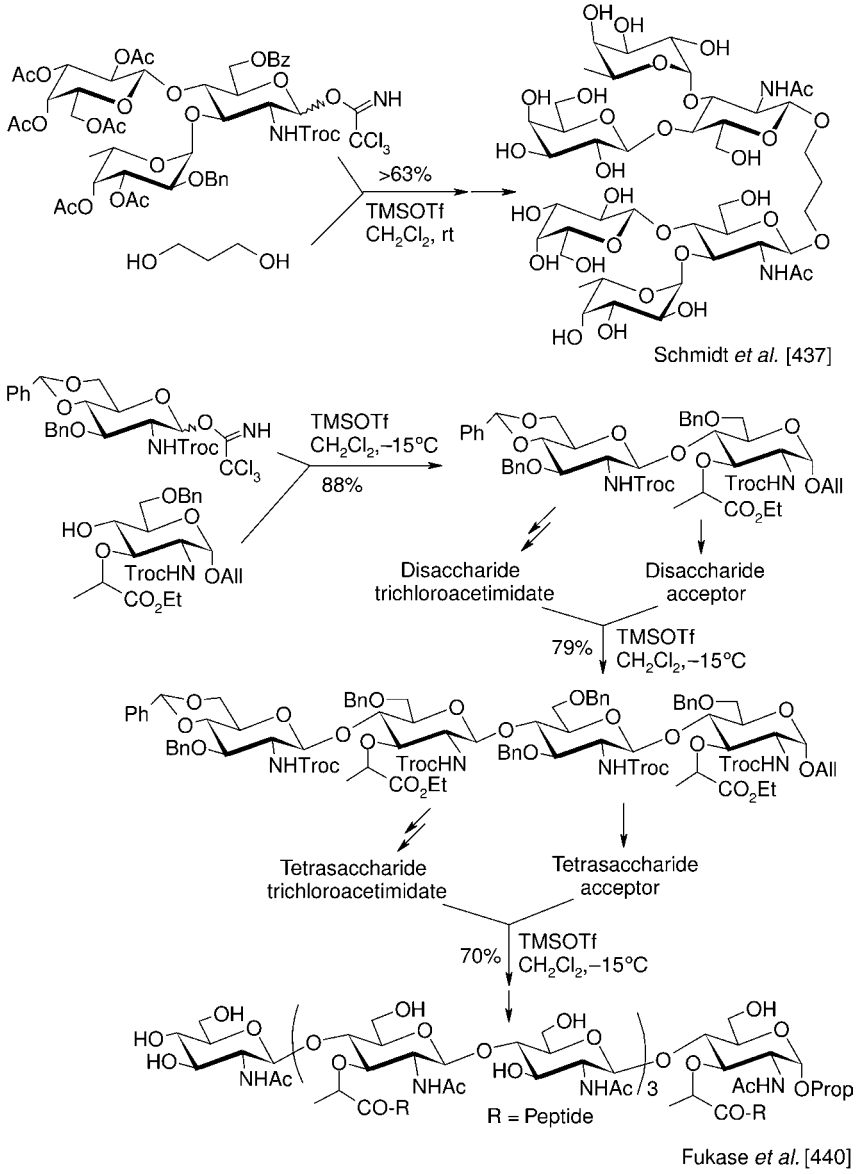
Scheme 3.33



Scheme 3.34

N-trichloroethoxycarbonyl (Troc)-protected aminosugar trichloroacetimidate as the glycosyl donor (Scheme 3.35) [437]. It should be mentioned that the Troc group has often been used in the synthesis of aminosugar glycosides because of its high stability under most reaction conditions, and it could be removed under specific conditions [438,439]. High-yielding and stereoselective glycosylations with *N*-Troc-protected trichloroacetimidates were also achieved in the synthesis of peptidoglycan fragments, as shown in Scheme 3.35 [440].

In the past years, many syntheses have been described for the glycosaminoglycan (GAG) oligosaccharides [441–450], such as heparin and chondroitin structures, to investigate their biological function in greater detail. One frequently encountered problem in the synthesis of heparin structures is the stereocontrol in the construction of α-glucosamine linkages. Recently, syntheses of a group of heparin oligosaccharides including a nonasaccharide were achieved using the trichloroacetimidate

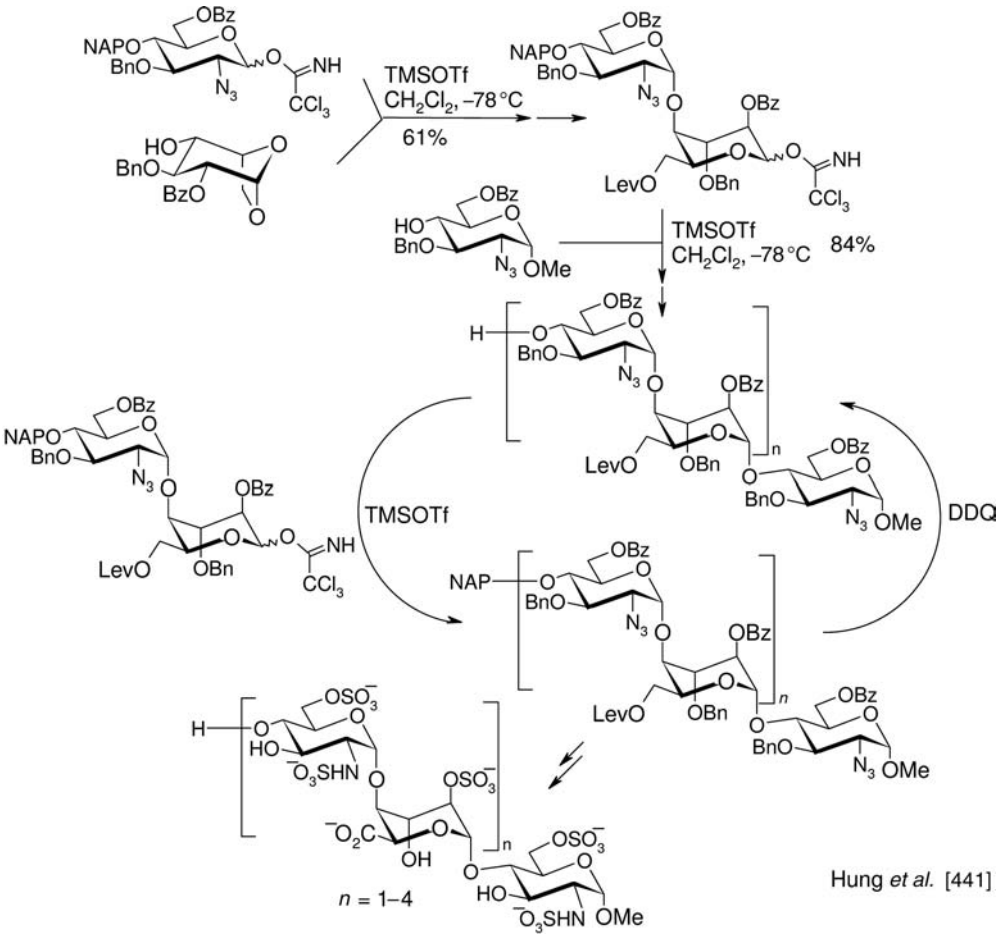


Scheme 3.35

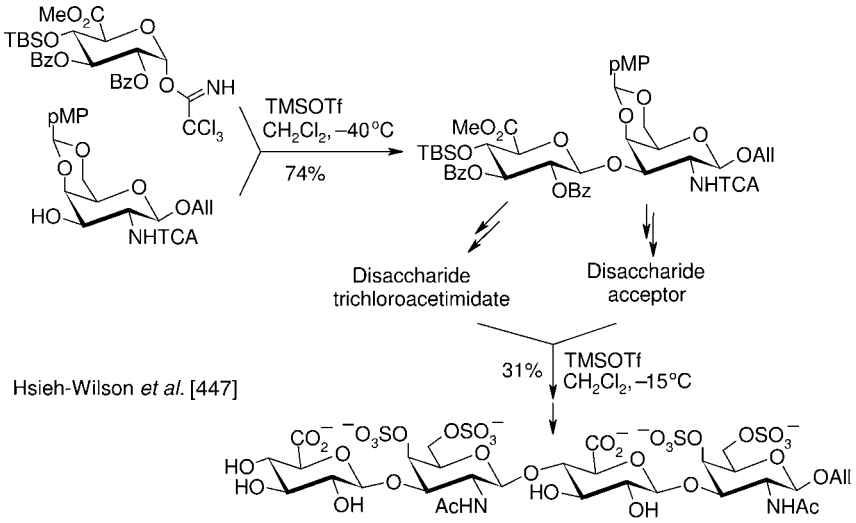
method [441], in which the most commonly used 2-azidoglucosyl trichloroacetimidates were employed to introduce the requisite α-glucosamine linkages (Scheme 3.36). The chain elongation sequence, involving the removal of 2-naphthylmethyl group (NAP) by using DDQ and subsequent glycosylation with the key disaccharide trichloroacetimidate, was repeated to assemble the penta-, hepta- and nonasaccharides, respectively. Also, a group of heparin tetrasaccharides, differing in

their sulfation pattern at position C-6 of the glucosamine units, was also synthesized from two common disaccharide precursors by the Schmidt glycosylation procedure [442]. In addition, the stereochemistry of glycosylation reactions with 2-azidoglycosyl trichloroacetimidates has been investigated very recently using a series of *chiro*-inositol derivatives as glycosyl acceptors [443]. The results indicated that the influence of the absolute configuration, the orientation of the acceptor OH group and the conformational constraint of the acceptor on the stereochemical outcome of the reaction are difficult to be assessed. To achieve good stereocontrol of these glycosylations, extensive experimentation is still required.

Chondroitin sulfates (CS) are ubiquitous components of extracellular matrices of all connective tissues such as the artery and tendon and exhibit a variety of biological functions. They are linear copolymers made up of dimeric units composed of glucuronic acid and *N*-acetyl galactosamine. The first biological investigation



Scheme 3.36

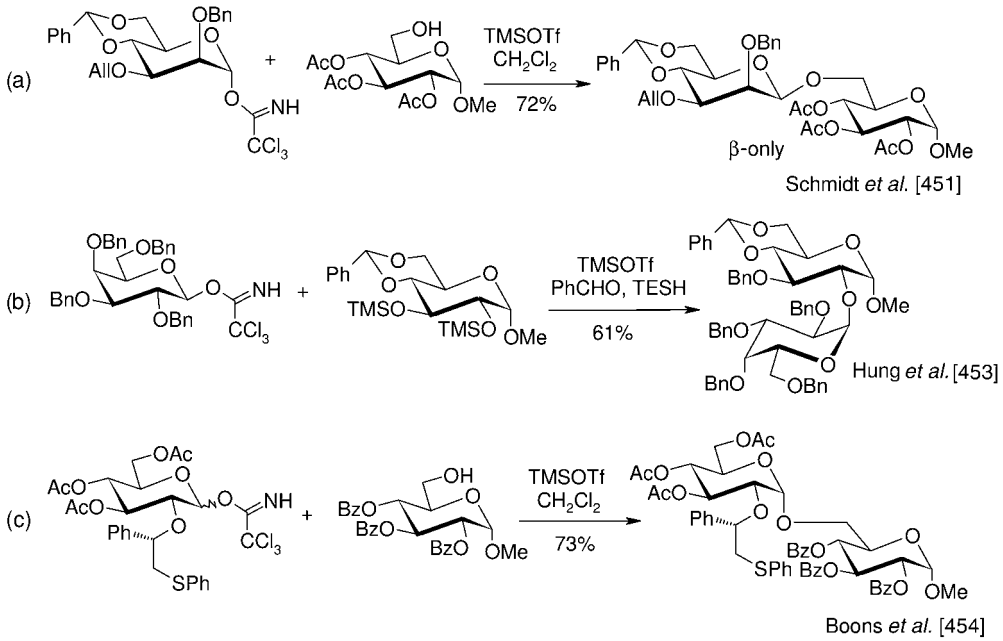


Scheme 3.37

of synthetic chondroitin molecules was carried out very recently, in which a tetrasaccharide fragment was defined as a minimal motif required for activity [447]. A convergent route for the synthesis of this tetrasaccharide, based on the efficient stereocontrolling effect of trichloroacetimido group associated with trichloroacetimidate activation, was developed (Scheme 3.37).

3.2.3.3 1,2-*cis* Glycosides

The presence of 1,2-*cis* glycosides in various natural products led to the search for efficient methodologies for constructing this type of glycosidic linkage. Again, trichloroacetimidate chemistry plays a very important role in this context [451–455]. Recently, preferential β-mannoside formation was achieved with 4,6-*O*-benzylidene-protected mannosyl trichloroacetimidates as glycosyl donors and catalytic amounts of TMSOTf as the promoter [451]; hence, another convenient procedure was available for the preparation of β-mannosides, as shown in Scheme 3.38a. For the reaction course, the intermediacy of a twist-boat-type structure was proposed. β-Mannosides were also prepared conveniently and efficiently with mannosyl trichloroacetimidates possessing a strongly electron-withdrawing benzylsulfonyl group at the O-2 position as glycosyl donors [452]. These donors, upon activation, favor the generation of a flattened twist-boat intermediate conformation because of a strong dipole effect, which is preferentially attacked from the β side to form β-mannosides. Moreover, the benzylsulfonyl group could be easily removed after glycosylation. Biologically interesting *cis*-(1 → 2)-linked disaccharide derivatives were prepared by a regioselective one-pot benzylation–glycosylation strategy based on the TMSOTf-catalyzed Schmidt glycosylation procedure (Scheme 3.38b) [453]. The high regioselectivity was deemed to be induced not only by the steric hindrance between the



Scheme 3.38

anomeric methoxy group and 2-OTMS group but also by the inductive effect of the two anomeric oxygen atoms that cause a decrease in the nucleophilicity of 2-oxygen.

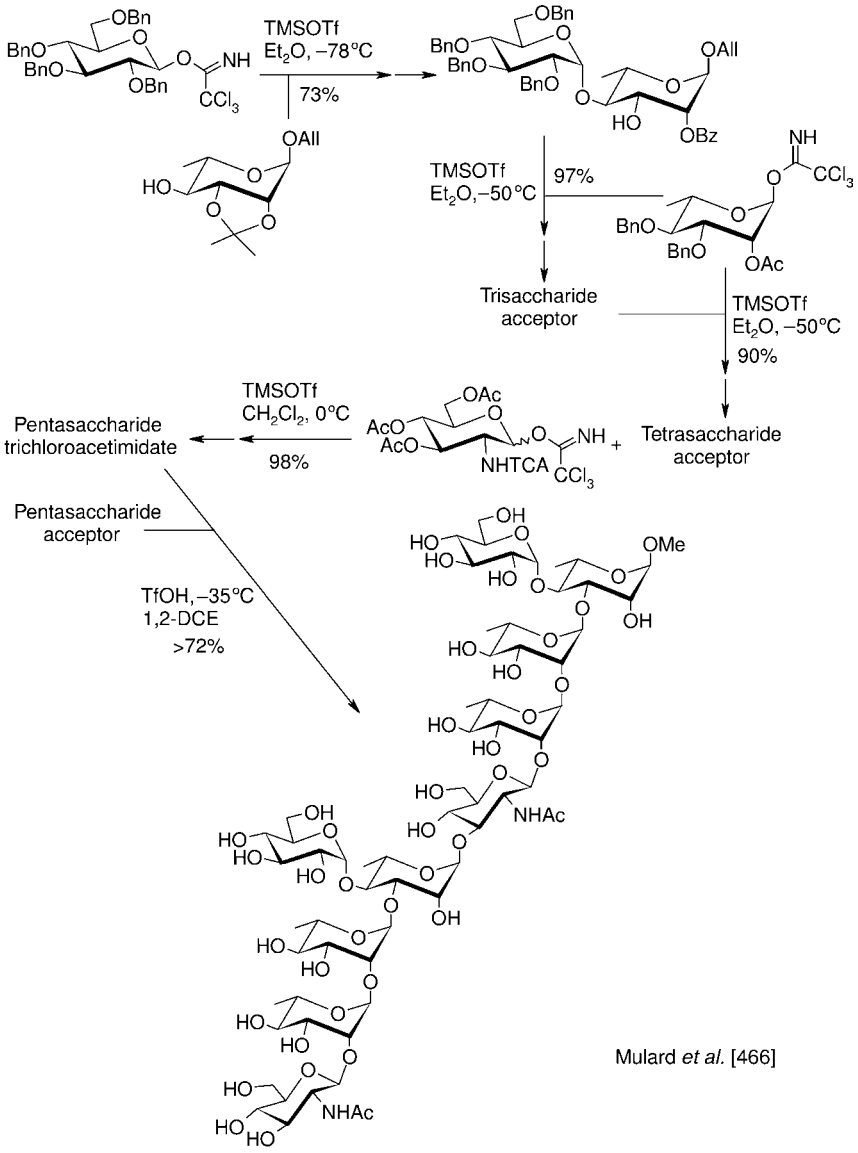
A new strategy for the stereoselective introduction of 1,2-*cis* glycosidic linkages has also been developed recently based on glycosyl trichloroacetimidates with a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl group at O-2 position (Scheme 3.38c). These donors reacted through an unusual pathway, whereby the phenylsulfanyl moiety of the chiral auxiliary performed the neighboring-group participation to give a quasistable anomeric sulfonium ion with *trans*-decalin conformation. Thus, an acceptor could only approach this sulfonium ion intermediate from the bottom face leading to α-glycosides [454]. Nevertheless, relatively harsh conditions were required to install and cleave this auxiliary.

Besides the applications in the above-mentioned methodologies, trichloroacetimidate chemistry has also been used in the past years to construct various oligosaccharides containing 1,2-*cis* linkages [456–465]. In some examples, notably by Kong and coworkers [460], 1,2-*cis* stereoselectivity was influenced by the glycosidic bonds originally present in either the donor or the acceptor.

3.2.3.4 Miscellaneous Oligosaccharides

The trichloroacetimidate method has also found wide applications in the synthesis of various complex oligosaccharides. In the course of the development of chemically defined glycoconjugate vaccines against shigellosis, a decasaccharide, corresponding to two consecutive repeating units of the *O*-specific polysaccharide of *Shigella*

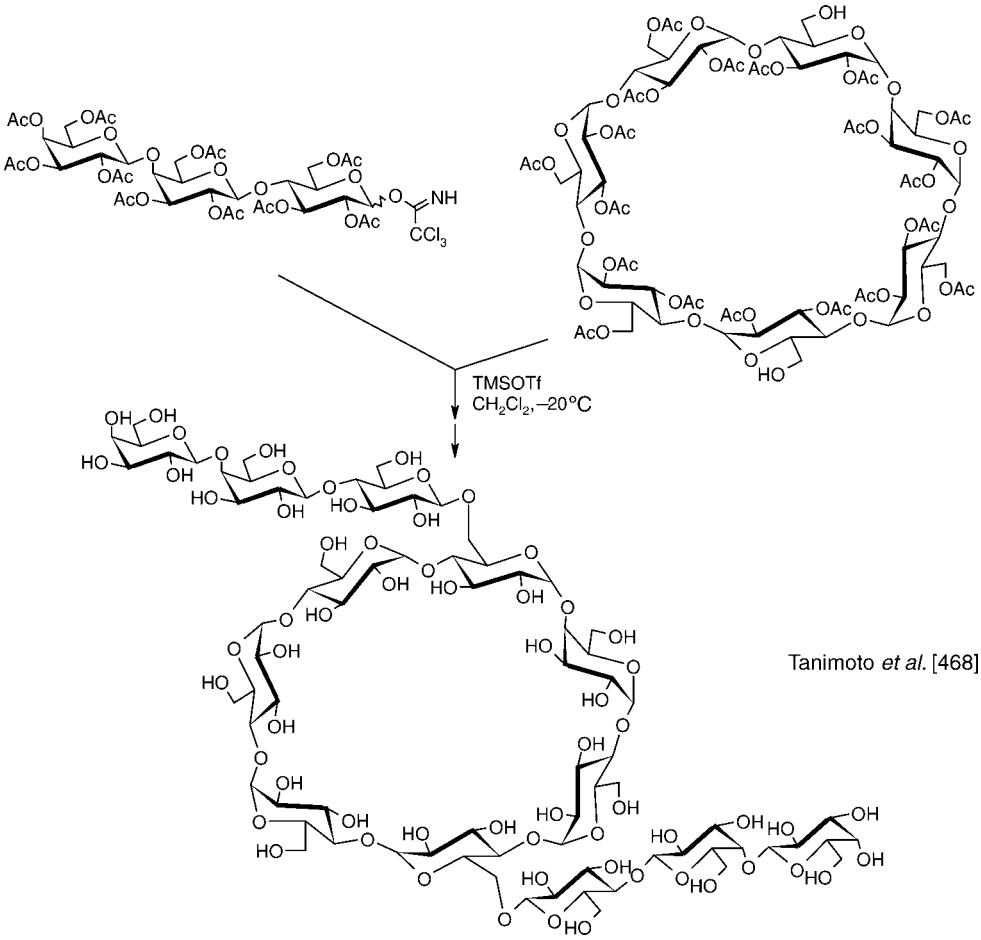
flexneri 2a, was synthesized using trichloroacetimidates as glycosylating agents [466], as shown in Scheme 3.39. The convergent route was established by the condensation of two key pentasaccharide building blocks, which were synthesized in a linear fashion. The first glycosylation in the synthesis was conducted in diethyl ether to obtain high α-selectivity, and the β-GlcNAc residue was introduced with *N*-trichloroacetyl-protected glucosaminyl trichloroacetimidate. The whole synthesis reflected the high efficiency and great power of the Schmidt protocol.



Scheme 3.39

Also, the key step in the synthesis of a mucin oligosaccharide derived from *Trypanosoma cruzi*, the causative agent of Chagas' disease, adopted trichloroacetimidate method in which the solvent effect of acetonitrile was exploited to build up the 1,2-*trans* glycosidic bond in the absence of the neighboring-group participation [467]. A series of branched β-cyclodextrins possessing β-galactose residues at the nonreducing terminal end of the sugar side chains were also prepared using trichloroacetimidate method [468], as enumerated in Scheme 3.40. These types of structures could be useful drug carriers in targeted drug delivery systems, considering the fact that galactose plays important roles in the recognition of receptors on the cell surface.

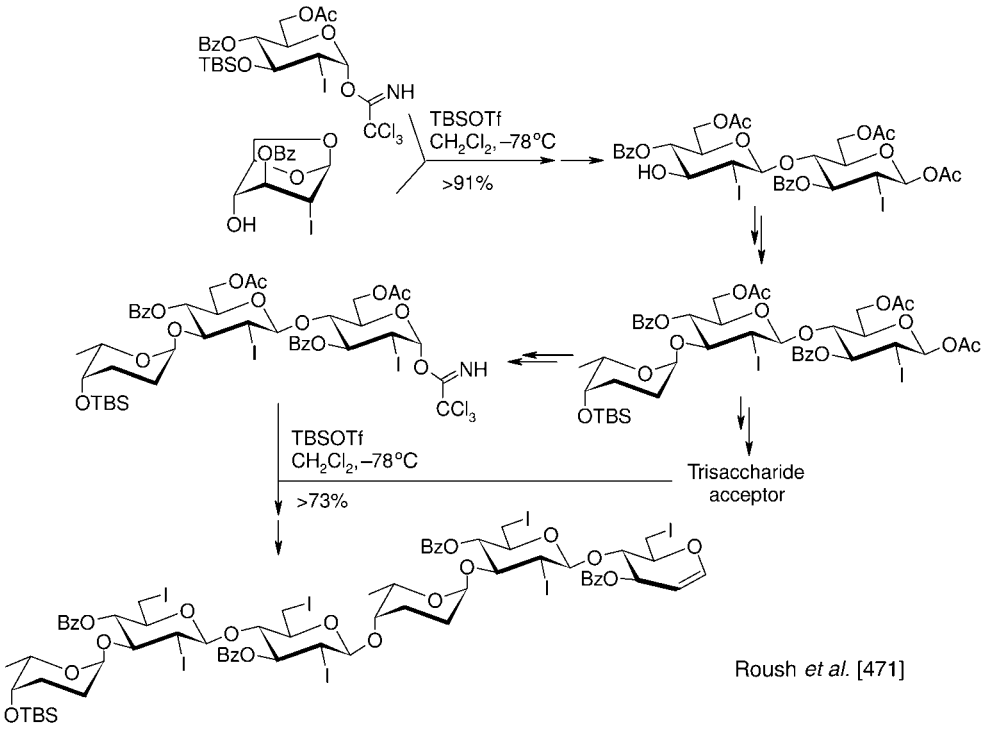
2-Deoxy-β-glycosides are important structural components of many natural products. Recently, 2-deoxy-2-iodoglycosyl trichloroacetimidates [469] have proved to be



Scheme 3.40

highly reactive glycosyl donors and could undergo highly β-stereoselective glycosylation reactions with various acceptors to form 2-deoxy-2-iodo-β-glycosides, precursors of 2-deoxy-β-glycosides. Investigations have been subsequently carried out on the possible intermediates generated in the reactions using conformationally constrained glycosyl imidates [470], and on the application of this methodology to the synthesis of a complex deoxyhexasaccharide derived from landomycin A, a member of the angucycline antibiotic family (Scheme 3.41) [471].

In the past years, some oligosaccharides containing relatively rare monosaccharides have also been synthesized with glycosyl trichloroacetimidates as donors. For instance, an L-*glycero*-D-*manno*-heptose-containing tetrasaccharide derived from Neisserial lipooligosaccharides was synthesized recently by regioselective glycosylation of mannose derivative with a heptosyl trichloroacetimidate [472]. Also, glycosylations with D-rhamnosyl trichloroacetimidates were performed to construct a branched D-rhamnotetraose [473], a repeating unit of the *O*-chain from bacterial lipopolysaccharides. In addition, nonnative oligosaccharides containing 5-thiosugars have also been prepared as molecular probes for biological and medicinal studies using the trichloroacetimidate method [474–476]. All the glycosylations proceeded smoothly and gave the desired products in high yields and stereoselectivities.

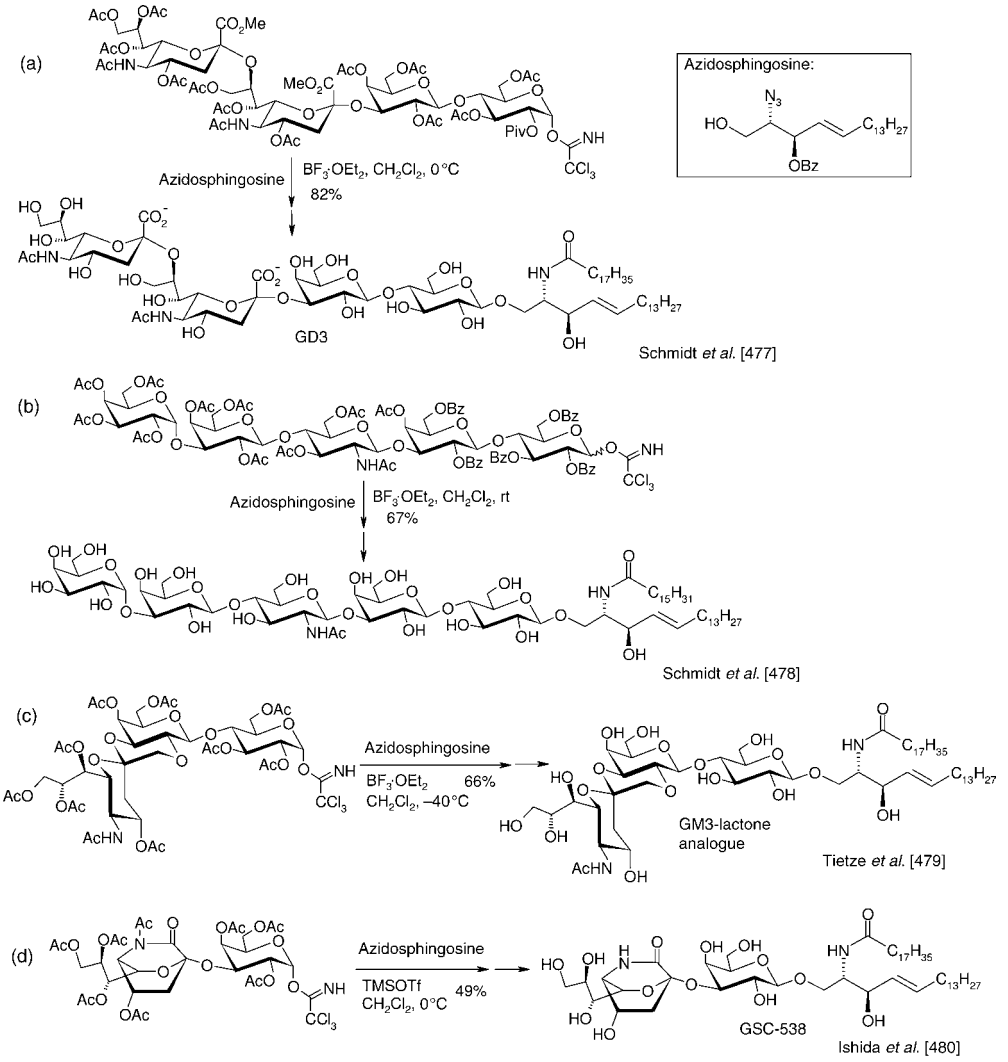


Scheme 3.41

3.2.4
Synthesis of Glycoconjugates

3.2.4.1 Glycosphingolipids and Mimics

Several syntheses of glycosphingolipids (GSLs) based on azidosphingosine glycosylation strategy have been reported in the last few years. Among these, disialoganglioside GD3, a human-melanoma-associated antigen, was synthesized in overall high yield by glycosylation of an azidosphingosine derivative with a tetrasaccharide trichloroacetimidate [477] (Scheme 3.42a). The same strategy was also applied to



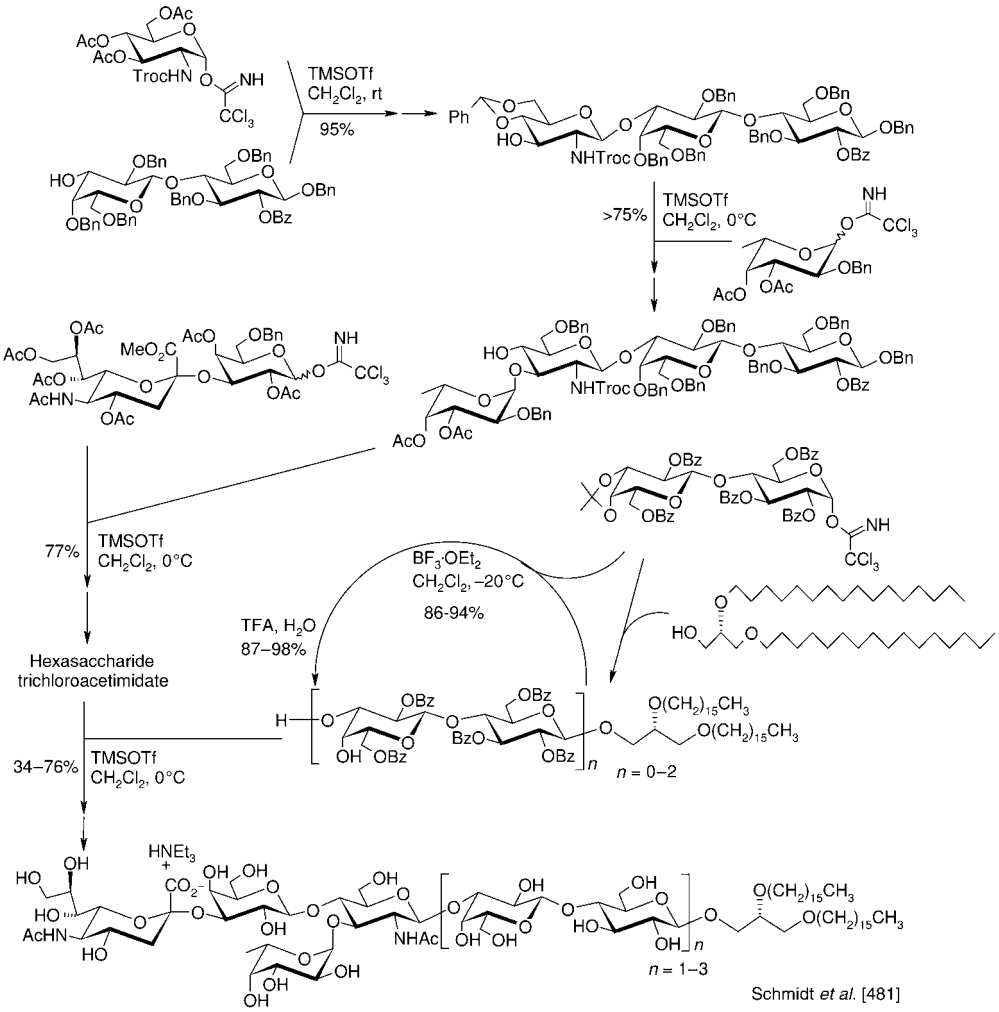
Scheme 3.42

synthesize the natural antigen involved in the hyperacute rejection response to xenotransplants, which consists of a pentasaccharide and a ceramide moiety (Scheme 3.42b). The pentasaccharide itself was also prepared by the Schmidt glycosylation protocol [478]. In view of the low hydrolytic stability of ganglioside lactones, an ether-bridged analog of ganglioside GM3-lactone has been constructed recently as a target for an antibody-based cancer therapy, in which the final ligation between the sugar and azidosphingosine was also achieved using the trichloroacetimidate method [479] (Scheme 3.42c). Also, systematic syntheses of novel lactamized gangliosides, such as GSC-538 in Scheme 3.42d, have been reported recently, in which the key steps were also glycosylations of azidosphingosine with trichloroacetimidates [480].

The sialyl Lewis X (sLe^X) epitope has become a prominent target for biological studies because of its participation in the inflammation process that takes place through binding to selectins. This epitope is located at the terminal end in GSLs, and the lactose unit serves as a spacer to the ceramide moiety. Recently, the influence of the spacer structure and length in regard to the mobility of sLe^X epitope has been investigated with synthetic neoglycolipids [481]. Successive glycosylations of a dialkylglycerol with a lactosyl trichloroacetimidate followed by the attachment of an sLe^X oligosaccharide provided a series of neoglycolipids with one to three lactose units as spacer. The sLe^X oligosaccharide itself was also assembled from the corresponding sugar building blocks using trichloroacetimidate method (Scheme 3.43), wherein the fucosylation of the *N*-Troc-protected glucosamine trisaccharide exclusively afforded the desired α-linked tetrasaccharide.

Another series of GSL mimics with oligo-ethylene glycol as spacer have also been obtained successfully using trichloroacetimidate method [482]. In addition, fluorescence-labeled sLe^X glycosphingolipids have also been chemically synthesized as targets for investigating microdomain formation in membranes [483].

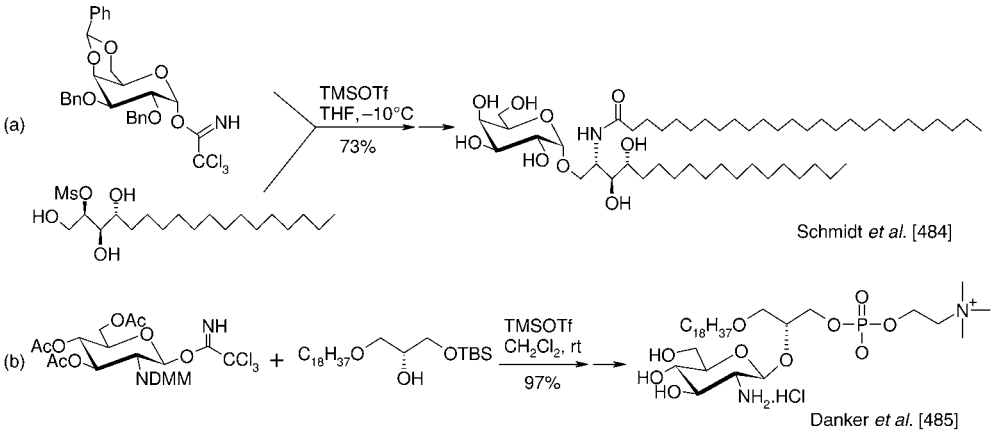
α-Galactosphingolipids have been found to have interesting immunomodulating activities. They can specifically activate CD1d-restricted natural killer T cells, which are primed to produce and release an array of cytokines such as interferon IFN-γ and interleukin IL-4. These cytokines are recognized subsequently by other cells of the immune system and may have a widespread influence on immune responses, including protection against autoimmune diseases, the host responses to parasites and bacteria and antitumor responses. Many efforts have thus been devoted in the past decade to synthesize this type of compounds to explore further structure–function relationship of individual α-galactosylceramides (α-GalCers). Recently, the total synthesis of α-GalCer was successfully achieved in which the key step was the highly regio- and stereoselective galactosylation of phytosphingosine acceptor with the galactosyl trichloroacetimidate donor [484] (Scheme 3.44a). Also, glucosamine–glycerophospholipid conjugates have been prepared for the investigation of their structure–function relationships (Scheme 3.44b), wherein *N*-DMM-protected glucosamine trichloroacetimidate was used as the glycosylating agent [485].



Scheme 3.43

3.2.4.2 Glycosyl Phosphatidyl Inositol Anchors

Glycosyl phosphatidyl inositol (GPI) anchors are a class of naturally occurring glycolipids that serve as anchors for proteins and glycoproteins in membranes. They consist of many variants in both the carbohydrate and the lipid moieties. On the basis of versatile building blocks, a highly variable concept for the synthesis of branched GPI anchors has been established recently, and the building blocks were readily accessible and could be transformed into products in high regio- and stereoselectivity in all reaction steps [486]. The efficiency of this concept was demonstrated through the synthesis of the 4,6-branched GPI anchor of *rat brain* Thy-1 and *scrapie* prion protein in which a group of trichloroacetimidates were used as glycosylating

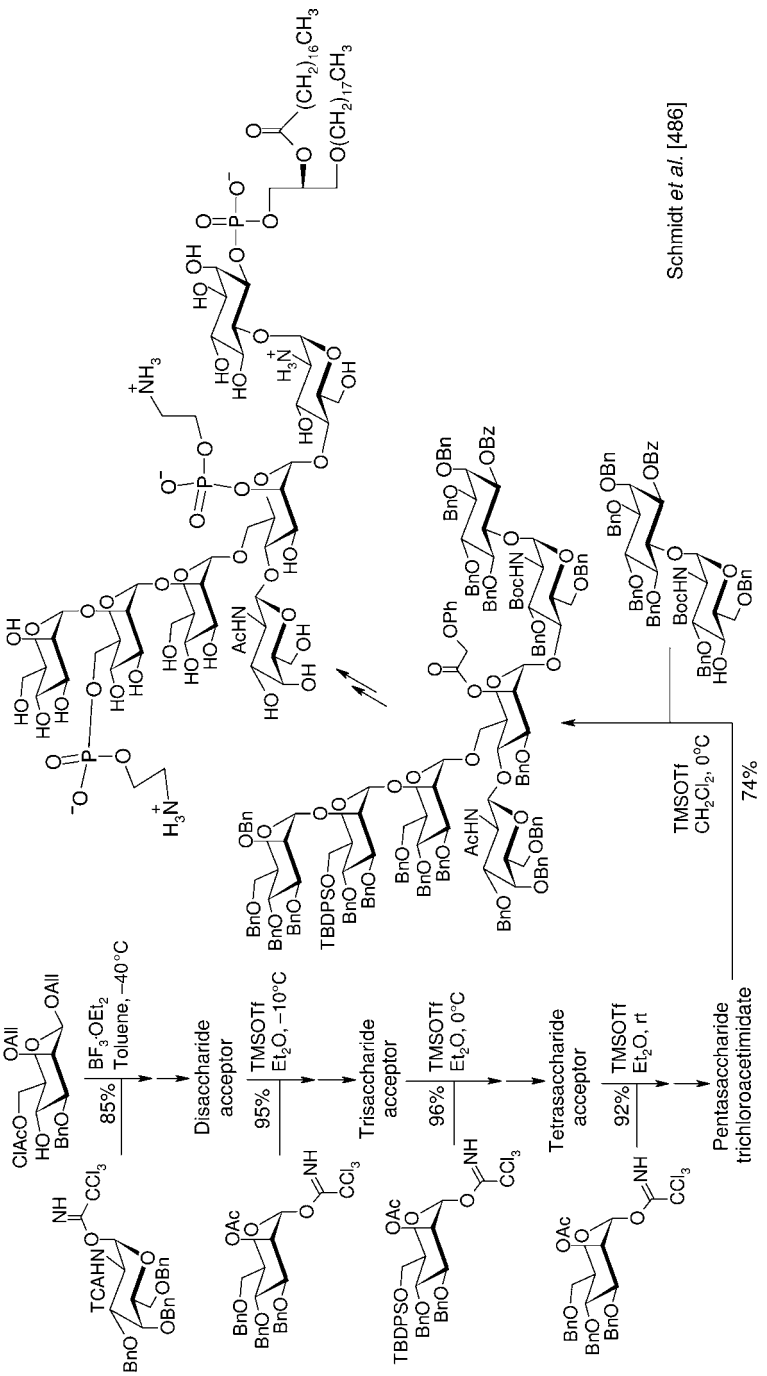


Scheme 3.44

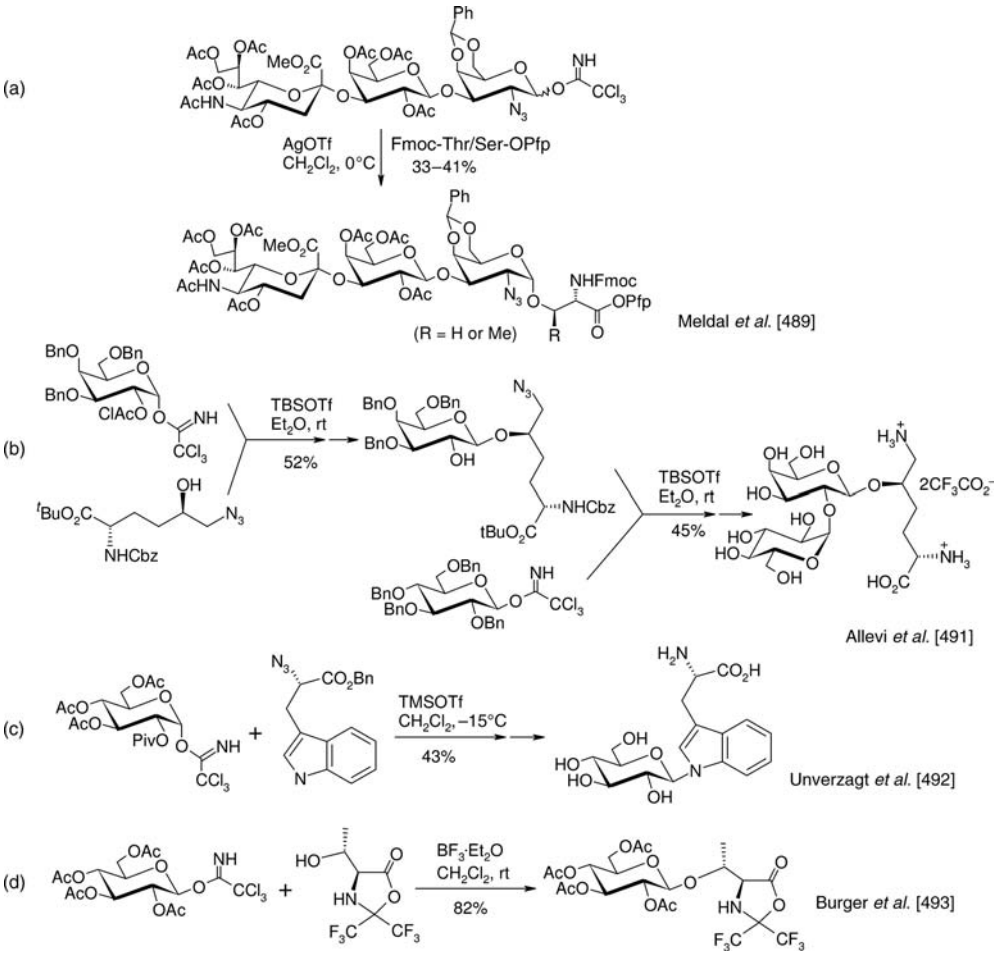
agents (Scheme 3.45). The key intermediate, pentasaccharide trichloroacetimidate, was first built up by a consecutive glycosylation of the mannose acceptor with three suitably protected monosaccharide trichloroacetimidates. With the pentasaccharide donor in hand, the carbohydrate backbone was then assembled by glycosylation of the pseudodisaccharide acceptor. All the glycosylations proceeded stereoselectively and gave the products in high yields. The total synthesis was finally completed by attaching various phosphate residues at the proper positions. Another fully phosphorylated pseudohexasaccharide has also been synthesized efficiently using the trichloroacetimidate method [487]. In addition, synthesis of an inositol-containing pseudohexasaccharide derived from Type A inositolphosphoglycans (IPGs), structurally related to GPIs, has been described [488].

3.2.4.3 Glycosyl Amino Acids and Glycopeptides

The trichloroacetimidate method has been used frequently in the synthesis of glycosyl amino acids and glycopeptides. Glycosyl amino acids carrying tumor-associated antigens were prepared recently by glycosylation of Fmoc-Thr/Ser-OPfp with sialyl-T antigen trisaccharide trichloroacetimidate [489], which gave mainly α-product because of the neighboring nonparticipating azido group (Scheme 3.46a).T-Antigen-containing glycosyl amino acid was also prepared in a similar manner and α-selectivity was obtained again with 2-azidogalactosyl trichloroacetimidate [490]. Both the glycosyl amino acids obtained could be used directly in automated solid-phase glycopeptide synthesis. Glucogalactosyl hydroxylysine, an important biological indicator of collagen turnover, was synthesized relying on the trichloroacetimidate method [491], as shown in Scheme 3.46b. The glucosylation was performed in Et_2O as the solvent, and its participation from β-face ensured excellent α-selectivity. A strategy to obtain *N*-linked glucosyl tryptophan has also been developed recently on the basis of Schmidt glycosylation protocol (Scheme 3.46c). The key steps involved the introduction of a 2-pivaloyl group to the donor to suppress the formation of a tryptophan-1-yl amide acetal by-product. The use of an


Schmidt et al. [486]
85%
BF3·OEt2
Toluene, –40 °C
Disaccharide acceptor
95%
TMSOTf
Et2O, –10 °C
Trisaccharide acceptor
96%
TMSOTf
Et2O, 0 °C
Tetrasaccharide acceptor
92%
TMSOTf
Et2O, rt
Pentasaccharide trichloroacetimidate
TMSOTf
CH2Cl2, 0 °C
74%

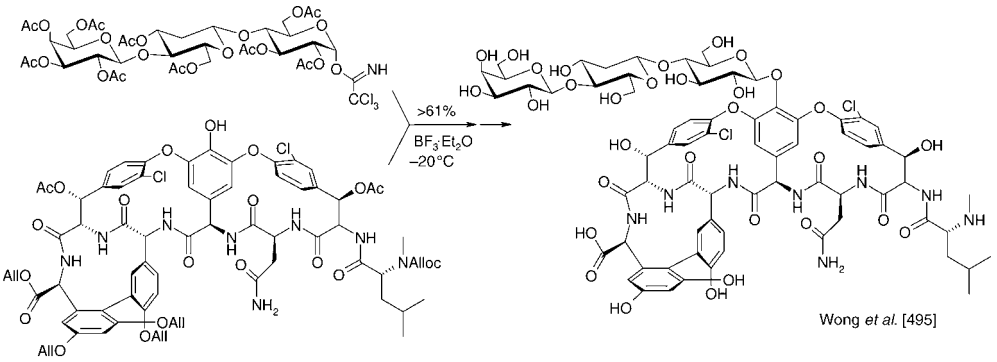
Scheme 3.45



Scheme 3.46

α-azido tryptophan derivative was beneficial to improve the yield [492]. The orthogonal protection of α-amino and carboxylic groups is usually required in the conventional synthesis of glycosyl amino acids to ensure that the amino or carboxylic group can be selectively deprotected and used in subsequent glycopeptide synthesis. Recently, a new protecting-group/activation concept has been developed so that the glycosyl amino acids prepared therein could be directly used to synthesize glycopeptides, and glycodipeptide and tripeptide fragments could be prepared from hydroxyl amino acids by this concept in only three or four synthetic steps [493]. The trichloroacetimidate method exhibited advantages over other glycosylation procedures in the preparation of this type of glycosyl amino acids (Scheme 3.46d).

In general, a convergent coupling between a sugar and a peptide to form an *O*-glycopeptide is problematic because of the generally poor solubility of peptides under glycosylation conditions and also because of regio- and stereochemical



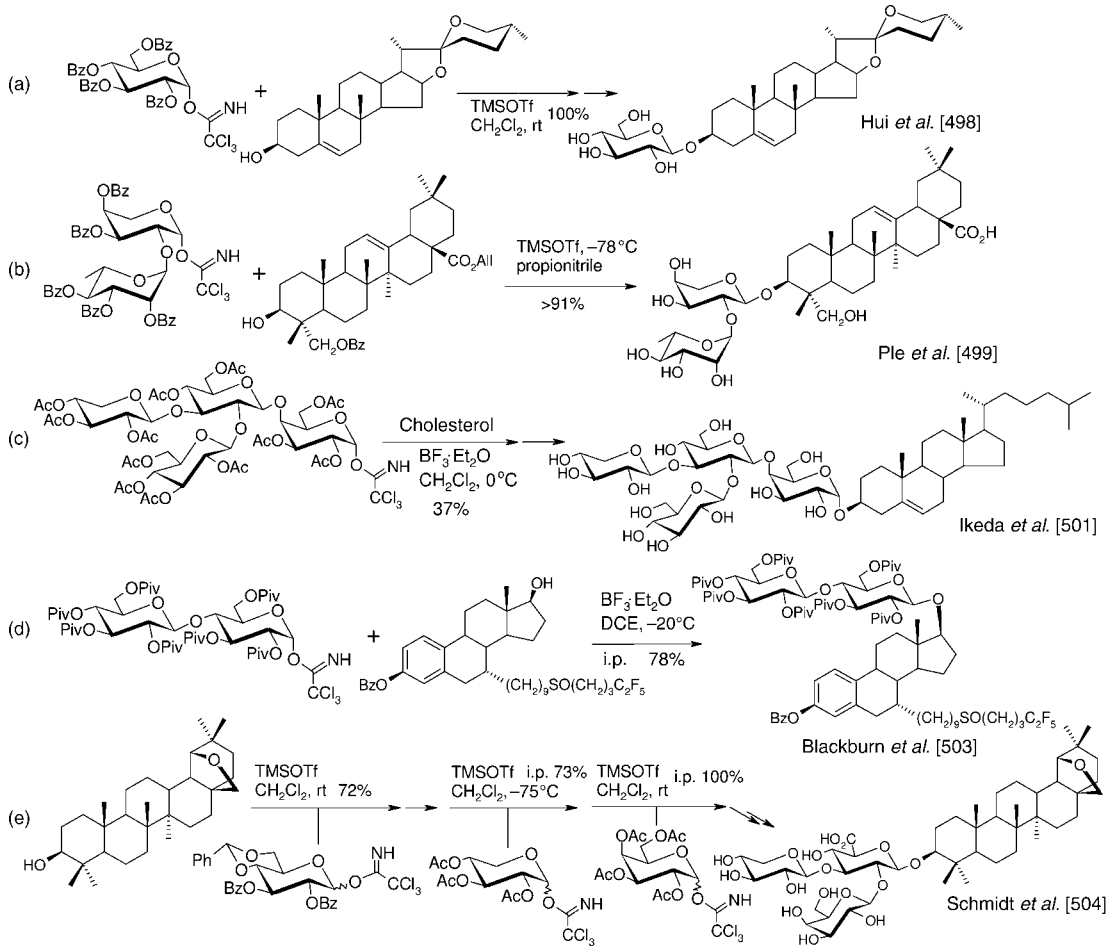
Scheme 3.47

aspects. However, the efficient solid-phase glycosylation of amino acid side chains (Ser, Thr and Tyr) in peptides was accomplished recently with a variety of glycosyl trichloroacetimidates in high yields and purities [494]. Also, as enumerated in Scheme 3.47, direct glycosylations of vancomycin aglycone with different glycosyl trichloroacetimidates were also achieved [495–497], allowing rapid creation of libraries of vancomycin derivatives bearing unnatural sugar substituents.

3.2.4.4 **Saponins**

Saponins are steroid or triterpenoid glycosides possessing various biological and pharmacological activities. A highly efficient procedure has been reported recently for the glycosylation of sapogenins [498] in which TMSOTf-catalyzed glycosylation with benzoylated glycosyl trichloroacetimidates is the key to success (Scheme 3.48a). The solvent effect of propionitrile has been exploited to control the stereochemistry in the glycosylation of hederagenin derivatives with a $(1 \rightarrow 2)$-linked disaccharide trichloroacetimidate to synthesize kalopanaxsaponin A [499], as shown in Scheme 3.48b. Other hederagenin saponins have also been synthesized using a series of disaccharide trichloroacetimidates as donors to investigate the structure–activity relationship between triterpenoid saponins and hemolytic activity [500]. Lycotetraose, one of the major oligosaccharides in steroid saponins, has been installed onto cholesterol via its trichloroacetimidate intermediate to verify its antitumor property (Scheme 3.48c). Unexpectedly, α-lycotetraosyl cholesterol was formed instead of the β-isomer in a stereoselective manner despite the presence of neighboring participating group [501]. To verify the biological role of chacotriose, several chacotriosides of cholesterol, diosgenin and glycyrrhetic acid were also synthesized by a similar *trans*-glycosylation strategy [502].

In addition, the fulvestrant could be glycosylated effectively at its 17-OH position with pivaloylated glycosyl trichloroacetimidates, which suppressed the competing transacylation side reaction and led to improved yields of the desired glycosides (Scheme 3.48d) [503]. In this synthesis, the inverse procedure (i.e. addition of a trichloroacetimidate donor to a mixture of an acceptor and a promoter) was found to be superior for glycosylations. Very recently, a stepwise synthesis of branched


(a)
TMSOTf
CH2Cl2, rt 100%
Hui et al. [498]
(b)
TMSOTf, –78 °C
propionitrile
>91%
Ple et al. [499]
(c)
Cholesterol
BF3·Et2O
CH2Cl2, 0 °C
37%
Ikeda et al. [501]
(d)
BF3·Et2O
DCE, –20°C
i.p. 78%
Blackburn et al. [503]
(e)
TMSOTf
CH2Cl2, rt 72%
TMSOTf i.p. 73%
CH2Cl2, –75°C
TMSOTf i.p. 100%
CH2Cl2, rt
Schmidt et al. [504]

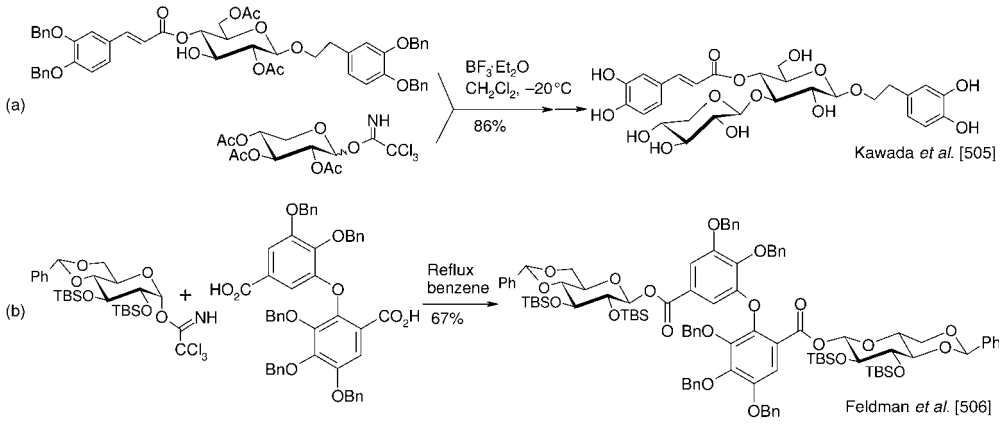
Scheme 3.48

glucuronic-acid-containing trisaccharides of allobetulin and glycyrrhetic acid has been described (Scheme 3.48e). All the glycosylations proceeded smoothly either under normal conditions or by an inverse procedure and gave the corresponding products in high yields [504].

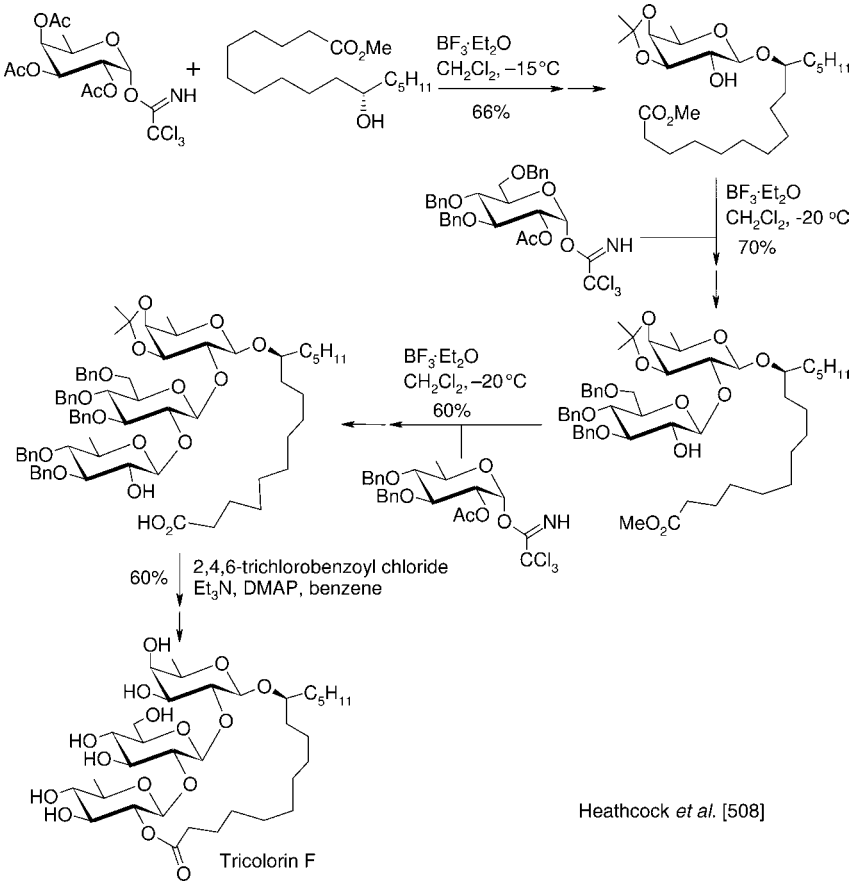
3.2.4.5 Other Natural Products and Derivatives

Glycosyl trichloroacetimidates have also been widely used in the synthesis of many other classes of natural products and their derivatives. Conandroside, a 'bitter glycoside' isolated from Conandron ramoidioides, was synthesized using trichloroacetimidates as building blocks [505] (Scheme 3.49a). The first total synthesis of the naturally occurring dimeric ellagitannin, Coriariin A, has also been achieved recently [506], wherein the critical bis-glucosylation step was performed with a trichloroacetimidate donor in the absence of a Lewis acid activator. Strictly speaking, the glycosylation in the synthesis is not a glycosidation process, but we list it in this chapter as an interesting application of trichloroacetimidate donors. As shown in Scheme 3.49b, simply refluxing the glycosyl donor and the acidic acceptor in benzene provided the requisite anomerically pure diglucosyl dehydrodigalloyl diester in good yield, which indicated the excellent reactivity and high stability of the trichloroacetimidate donor.

Resin glycoside has a very widespread occurrence in the plant kingdom and possesses various biological activities, such as cytotoxicity against human cancer cell lines, antibacterial activity, purgative properties and plant-growth-regulating capacity. Structurally, resin glycoside often contains (11*S*)-hydroxyhexadecanoic acid (jalapinolic acid) as a common aglycone, which is usually tied back to form a characteristic macrolide ring that spans two or more sugar units of its oligosaccharide backbone. Following the previous work on resin glycoside synthesis [507], Tricolorin F has been synthesized efficiently using the Schmidt glycosylation protocol [508], as shown in Scheme 3.50. Consecutive glycosylations with three trichloroacetimidate donors, followed by Yamaguchi lactonization, furnished the resin glycoside in an overall good yield after deprotection.



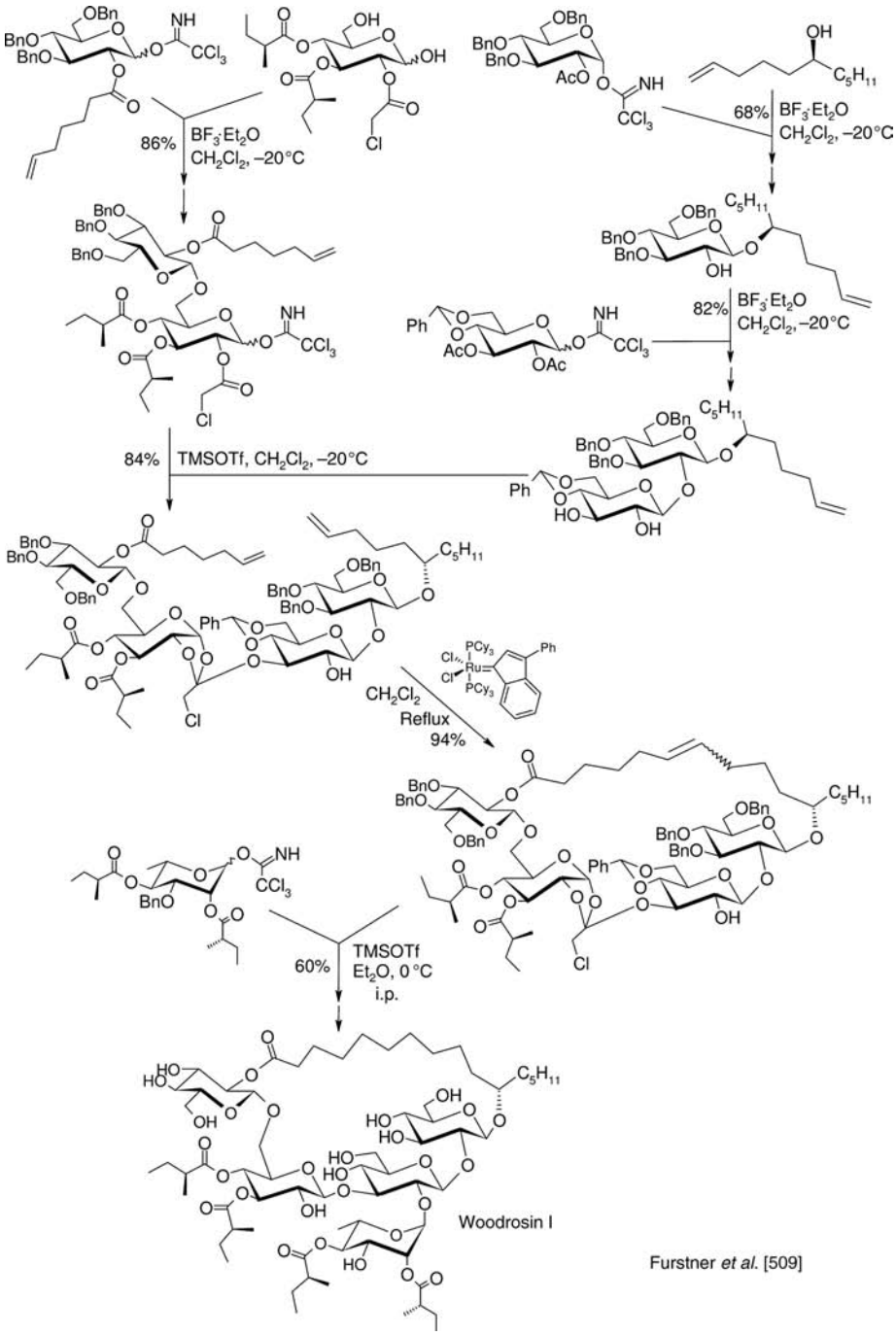
Scheme 3.49



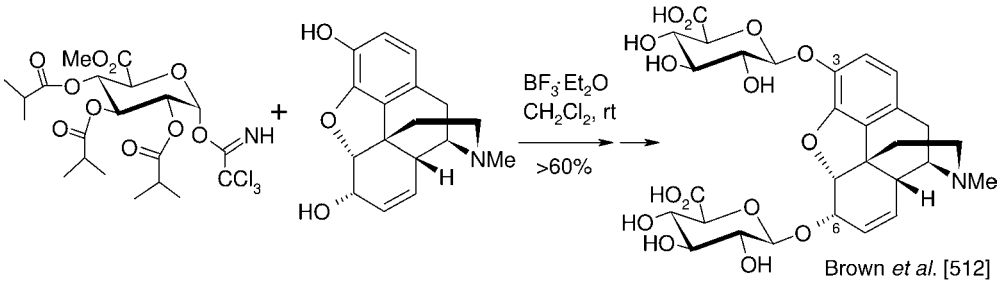
Scheme 3.50

The total synthesis of Woodrosin I, one of the most complex resin glycosides, was also reported recently [509]. The executed approach clearly demonstrated again the great power of the trichloroacetimidate method. The whole synthesis was graced with two regioselectiveglycosylations and the final inverse addition procedure, which dramatically simplified the synthetic route (Scheme 3.51). In addition, cycloviracin B [510] and glucolipsin A [511] have also been synthesized successfully by the same laboratories, taking advantage of the trichloroacetimidate method.

As a drug candidate advances through clinical development, the synthesis of its glucuronide often becomes necessary to provide an analytical standard for use in quantification of metabolite levels in clinical samples and to provide material for further pharmacological evaluation. In the past years, several glucuronides have been prepared by the Schmidt glycosylation protocol [512–516]. For example, morphine-3,6-di-glucuronide could be prepared in a very good yield by direct glycosylation of morphine with isobutyryl-protected glucuronic acid trichloroacetimidates


86%
BF3·Et2O
CH2Cl2, –20°C
68%
BF3·Et2O
CH2Cl2, –20°C
82%
BF3·Et2O
CH2Cl2, –20°C
84%
TMSOTf, CH2Cl2, –20°C
CH2Cl2
Reflux
94%
60%
TMSOTf
Et2O, 0 °C
i.p.
Woodrosin I
Furstner et al. [509]

Scheme 3.51



Scheme 3.52

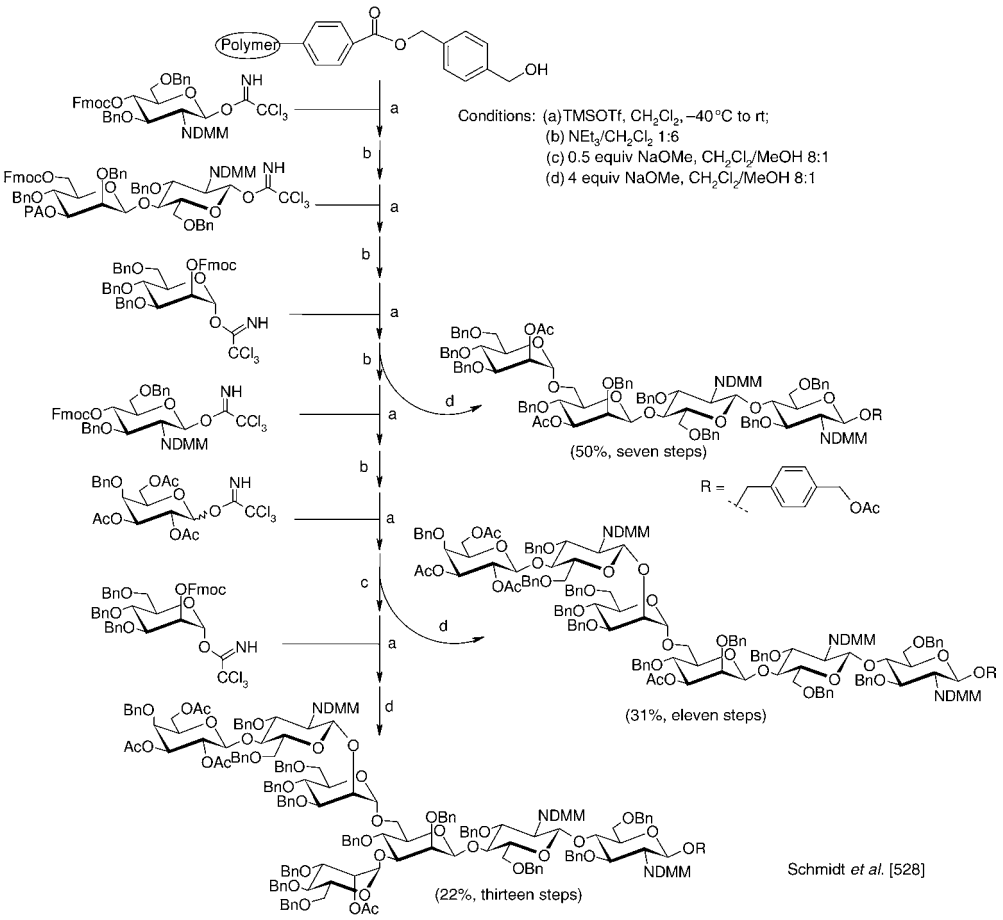
(Scheme 3.52), whereas the corresponding acetyl-protected donor gave little product under the same reaction conditions [512]. Additionally, the trichloroacetimidate method has also been applied to synthesize other natural products, such as buprestin A and B [517], macrophylloside D [518] and neomycin mimetics [519].

3.2.4.6 **Miscellaneous Glycoconjugates**

The simultaneous presentation of sugars on a macromolecular scaffold can create a multivalent display that amplifies the affinity of glycoside-mediated receptor targeting. Dendrimer-like poly(ethylene oxide) glycopolymers bearing sulfated β-lactose have been prepared recently as potential L-selectin inhibitors, in which protecting-group manipulations were minimized by the use of lactose trichloroacetimidate donors [520]. Glycosyl trichloroacetimidate has also been used to prepare a modified nucleoside, which was then incorporated into oligonucleotides of biological interest by automated solid-phase synthesis [521]. Also, a direct glycosylation of oligonucleotides with trichloroacetimidate donors has been reported recently [522,523]. Glycosyl trichloroacetimidates are also suitable donors for the synthesis of *C*-/*N*-glycosides [524–526].

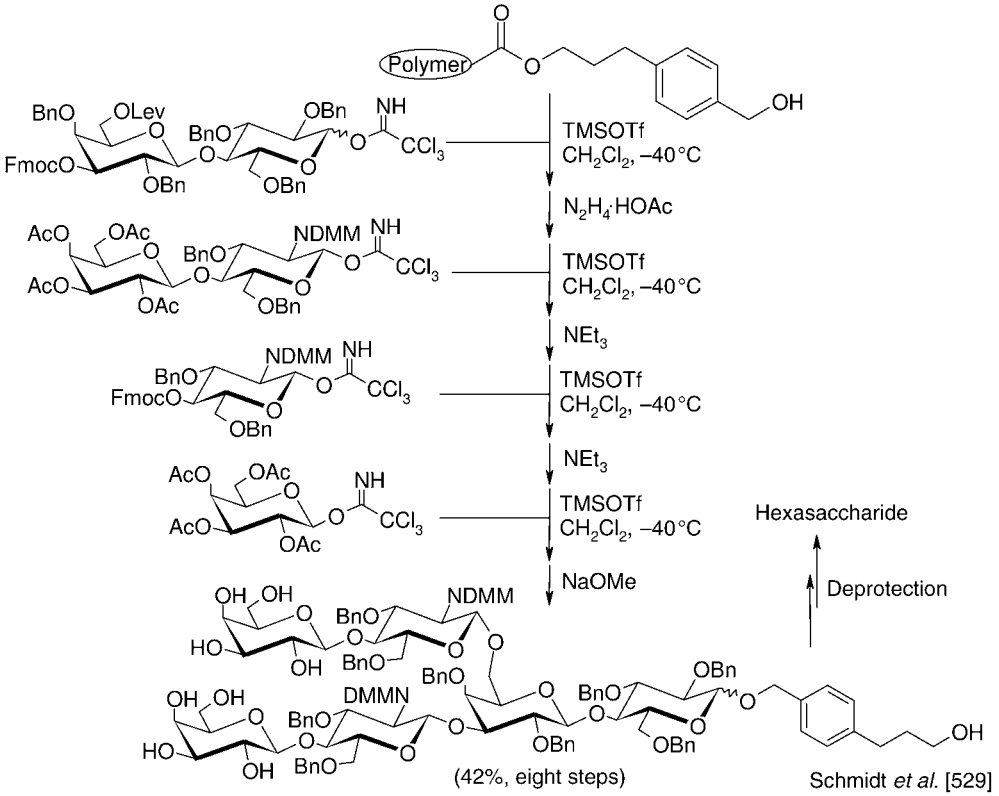
3.2.5 **Solid-Phase Oligosaccharide Synthesis**

In recent years, a notable progress has been made on solid-phase oligosaccharide synthesis based on the trichloroacetimidate method [527–538]. One important advance is that glycosyl trichloroacetimidates, bearing the *O*-Fmoc protecting group, have been successfully prepared and proved to be suitable for oligosaccharide synthesis on solid support [527]. Very recently, a series of *N*-glycan oligosaccharides have been synthesized on Merrifield resin with a hydroxymethyl-benzyl benzoate spacer–linker system [528]. As enumerated in Scheme 3.53, the glycosylations were stereospecifically performed with three types of trichloroacetimidate donors, which allowed chain extension, branching and chain termination, respectively. For chain-branching donors, Fmoc and phenoxyacetyl (PA) were used as temporary protecting groups with Ac, Bz, Bn and/or *N*-DMM as permanent protecting groups. The crude products released from the resin were of high purity after all glycosylation and



Scheme 3.53

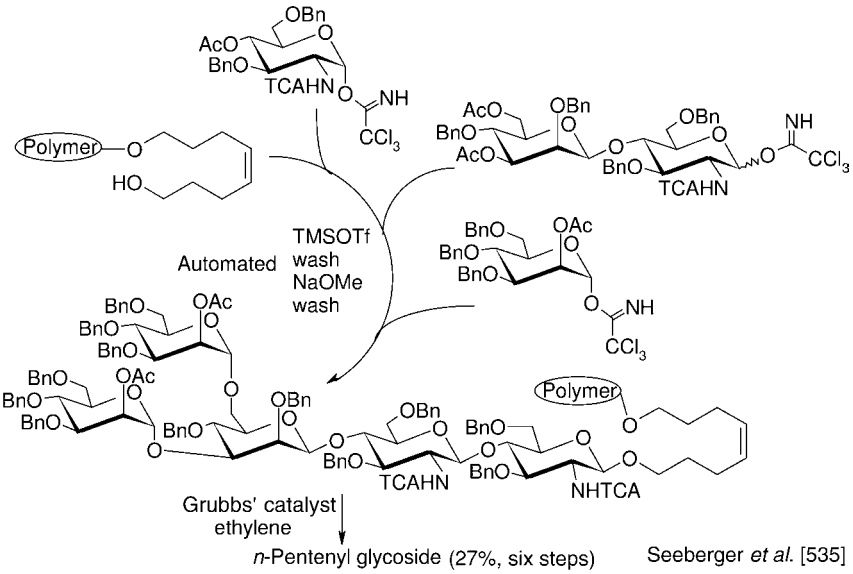
protecting-group manipulation steps. The simplicity and efficiency of the whole synthesis provided a basis for the development of a general approach to the synthesis of oligosaccharides having different glycosidic linkages. For example, a similar strategy has been applied to synthesize a branched lacto-*N*-neohexasaccharide occurring in human milk (Scheme 3.54) [529], and the product was also released from the resin as a benzylic glycoside, which made further deprotection easy. The key building block, lactose trichloroacetimidate, was protected orthogonally with Fmoc and Lev groups, allowing for selective derivatization at both positions. All glycosylations on the solid support were highly stereoselective and high yielding, and the hexasaccharide was furnished in an excellent overall yield of 42%. The great utility of Fmoc-protected glycosyl trichloroacetimidates has also been demonstrated in the synthesis of other oligosaccharides, such as oligomannosides [530], lactosamine- and lactose-containing oligosaccharides [531].



Scheme 3.54

In addition, some other techniques have been developed for solid-phase oligosaccharide synthesis in combination with the Schmidt glycosylation protocol in the past years, including real-time reaction-monitoring method [532] and novel capping reagents [533]. Recently, the automated synthesis of oligosaccharides has been achieved by using a solid-phase synthesizer with trichloroacetimiates as glycosylating agents [534], and *N*-glycan core pentasaccharide was successfully assembled within 3 days after three consecutive glycosylation reactions (Scheme 3.55) [535]. The final release of the pentasaccharide as its *n*-pentenyl glycoside from the octenediol-functionalized Merrifield resin was performed with Grubbs catalyst. A rapid synthesis of a tetrasaccharide fragment of malarial toxin has also been accomplished on this synthesizer using trichloroacetimidate method [536].

Heparin-like oligosaccharides have been synthesized on soluble polymer support, polyethylene glycol monomethyl ether, in which the acceptor was bound to the polymer through the carboxylic group of the uronic acid unit by a glycol–succinic ester linkage [539,540]. By this protocol, an octasaccharide fragment, containing the structural motif of the regular region of heparins, has been synthesized using



Scheme 3.55

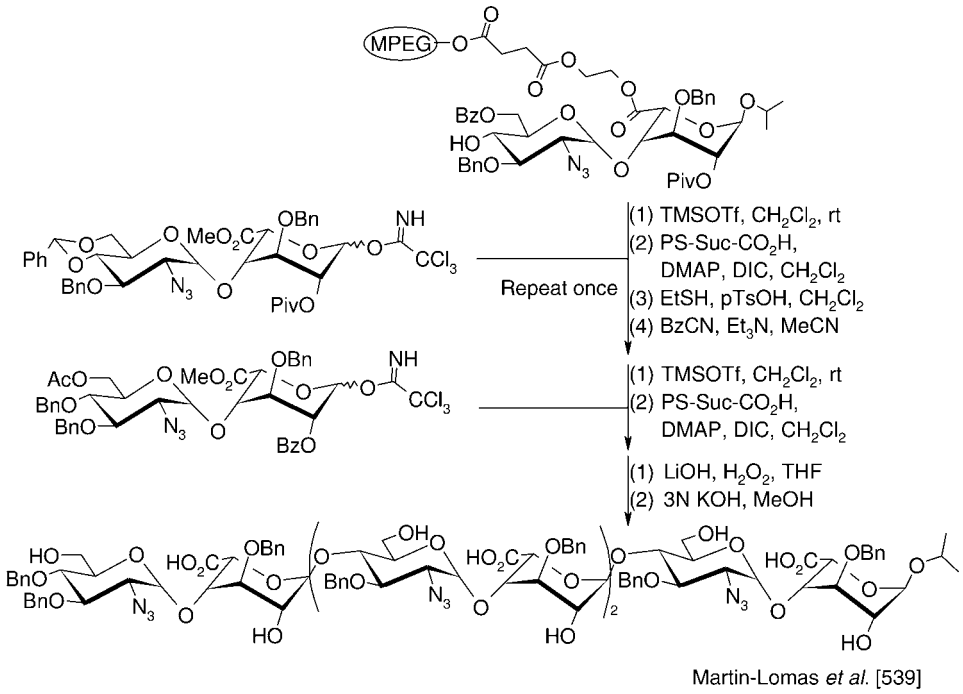
trichloroacetimidates as glycosylating agents and a functionalized Merrifield resin as capping agent, as shown in Scheme 3.56 [539].

In addition, a novel fluorous support has been developed recently as an alternative to traditional polymer supports and applied successfully to oligosaccharide synthesis in combination with the trichloroacetimidate method [541]. Each intermediate in the fluorous oligosaccharide synthesis [542,543] could be obtained by simple fluorous-organic solvent extraction, and the reactions could be monitored by TLC, NMR and MS, in contrast to solid-phase reactions. Moreover, the new liquid-phase technique is anticipated to be easily applicable to the large-scale synthesis.

3.2.6 Trifluoroacetimidates

3.2.6.1 Preparation and Activation

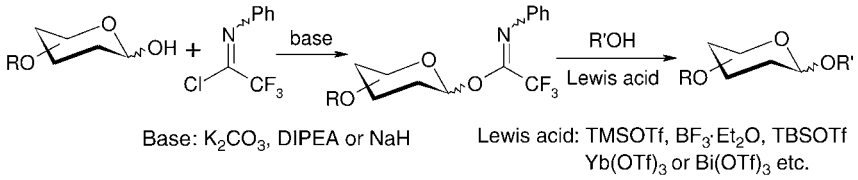
As trichloroacetimidate analogs, glycosyl trifluoroacetimidates have received interest many years ago [383]. However, unlike trichloroacetimidates, the *N*-unsubstituted trifluoroacetimidates are difficult to prepare because the corresponding trifluoroacetonitrile is gaseous (bp $-64\,^{\circ}C$) and toxic. Nakajima reported a one-pot preparation of glycosyl trifluoroacetimidates [544], wherein volatile trifluoroacetonitrile was generated from trifluoroacetamide with an 'activated' DMSO species at low temperature. In this section, emphasis is placed on glycosyl *N*-phenyl trifluoroacetimidates (PTFA), the most common and widely investigated trifluoroacetimidates [384,385]. PTFA donors are usually prepared from anomeric hemiacetals by



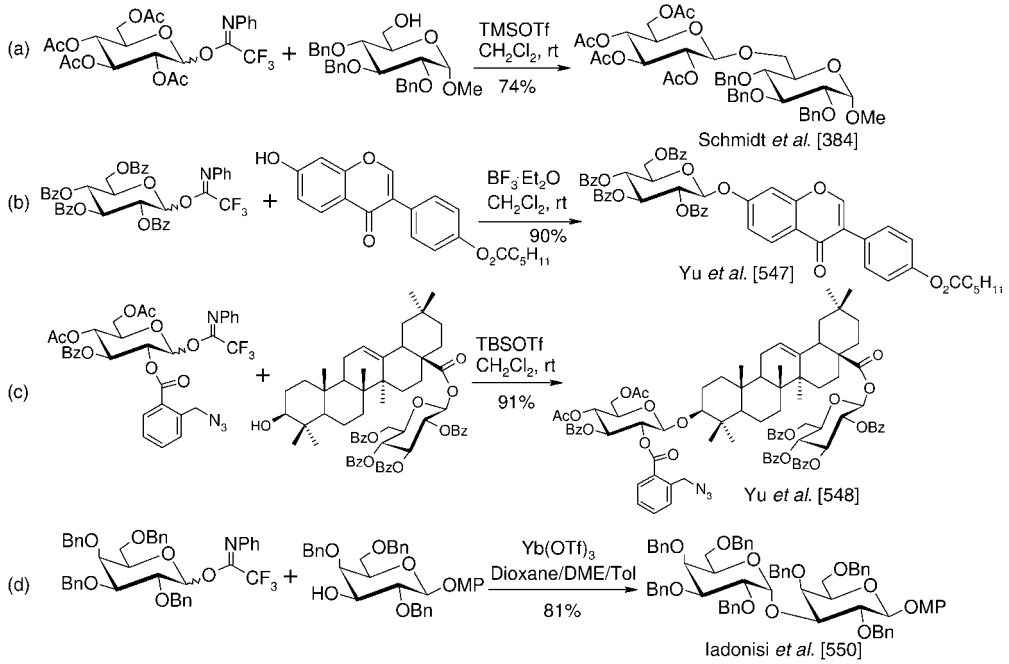
Scheme 3.56

treatment with *N*-phenyl trifluoroacetimidoyl chloride in the presence of a stoichiometric amount of base (Scheme 3.57). In contrast to the trichloroacetimidate formation, the use of K_2CO_3 as the base generally favors α-PTFA [545], whereas the use of NaH [384] or DIPEA [546] mainly yields β-products; more commonly, α-/β-mixtures are produced.

PTFAs are generally less reactive than the corresponding trichloroacetimidate donors presumably because of the lower *N*-basicity or the presence of an *N*-substituent. Although most trichloroacetimidate activators could also be used to promote PTFA glycosidations, such as TMSOTf [384], $BF_3{\cdot}Et_2O$ [384,547], TBSOTf [548], $Yb(OTf)_3$ [549,550] and acid-washed molecular sieves [551], the activation of PTFA usually requires more forceful conditions. Several representative Lewis-acid-catalyzed PTFA glycosidation reactions are listed in Scheme 3.58. It is worth



Scheme 3.57

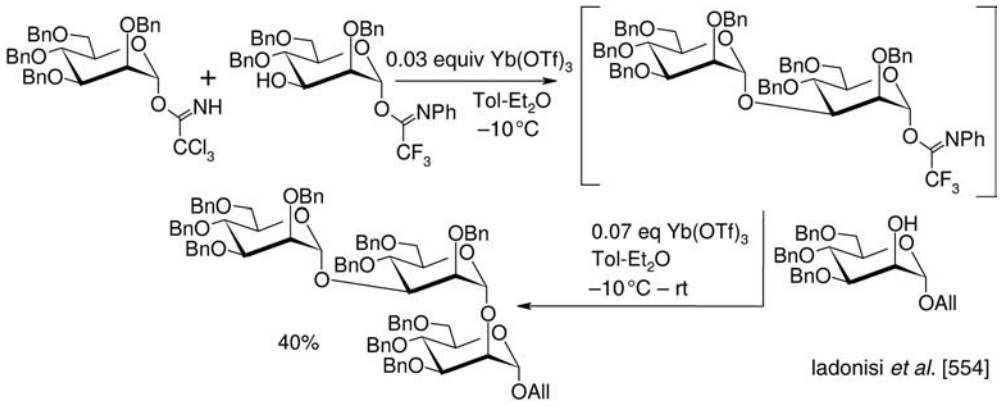


Scheme 3.58

mentioning that glycosyl trifluoroacetimidates bearing 2-(azidomethyl)benzoyl (AZMB) group at O-2 position have been used as efficient glycosylating agents in the synthesis of triterpenoid saponins [548], as enumerated in Scheme 3.58c. The AZMB group ensured 1,2-*trans*-glycosylation, but more importantly, it could be removed selectively in the presence of other acyl protecting groups. Also, some other activation systems such as I_2–Et_3SiH [386], $Bi(OTf)_3$ [552] and $TMSB(C_6F_5)_4$ [553] have been used to promote PTFA glycosidations. The different reactivities of PTFA and trichloroacetimidate donors have been exploited to develop a one-pot multistep procedure featuring selective activation of a trichloroacetimidate donor in the presence of a PTFA moiety [554], in which the PTFA derivative was partially protected to serve as a glycosyl acceptor in the first glycosidation step (Scheme 3.59).

3.2.6.2 Application to Target Synthesis

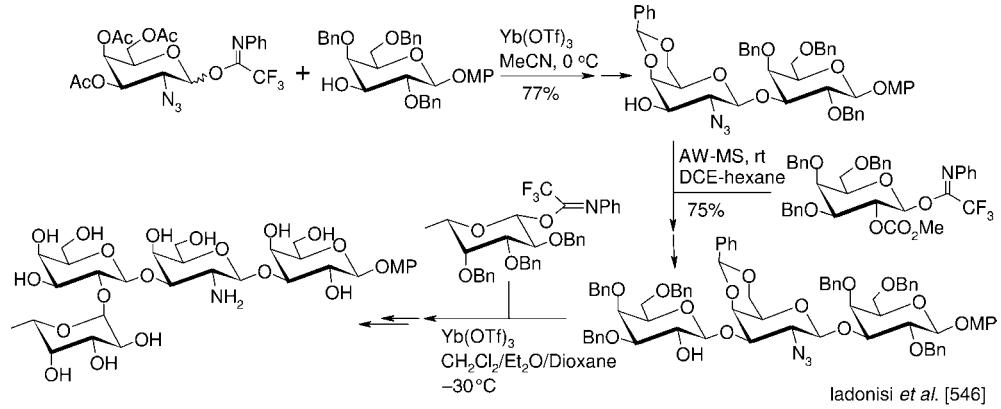
Trifluoroacetimidate donors have shown advantages over trichloroacetimidates in the synthesis of β-mannosides [553] because of their lower propensity to undergo side reactions during glycosidations. In the course of trichloroacetimidate glycosidation, a certain amount of an *N*-glycoside by-product is occasionally produced by the glycosylation of trichloroacetamide liberated from the donor. Particularly, this side reaction takes place when the acceptor is of low nucleophilicity or sterically hindered, whereas it is diminished in PTFA glycosidation because of the increased steric hindrance of the *N*-phenyl group. PTFA donors have thus gained some applications in oligosaccharide and glycoconjugate synthesis. Also, direct sialylation



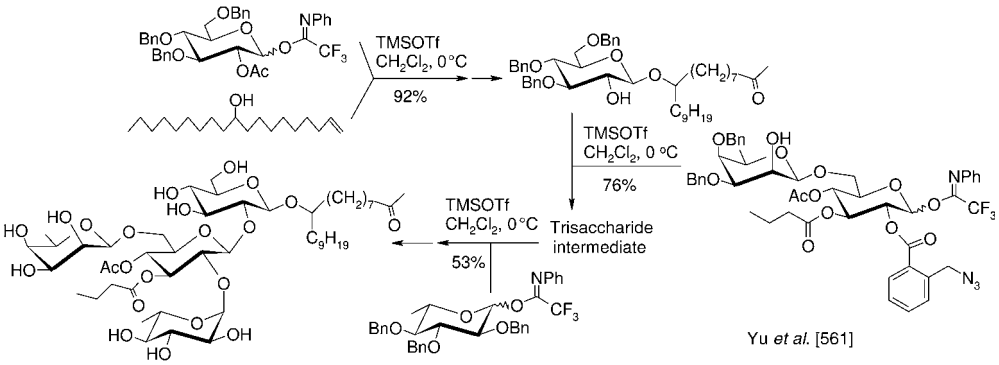
Scheme 3.59

has been achieved with PTFA as the glycosyl donor [555], whereas the corresponding trichloroacetimidate donors are not suitable for sialylation. A linear synthesis of a biologically relevant tetrasaccharide fragment of Globo H antigen has been described recently using PTFA as glycosylating agents (Scheme 3.60) [546]. Neighboring-group participation and solvent effect were exploited to stereoselectively introduce the three glycosidic bonds. The trifluoroacetimidate method has also been used in the synthesis of Fuc*p*3NAc-containing oligosaccharides [556], found exclusively in phytopathogenic bacterial *O*-antigens, and a tetrasaccharide fragment of clarhamnoside [557], a GSL isolated from marine sponge. A few other applications of PTFA donors in oligosaccharide synthesis have been reported [558–560].

The total synthesis of caminoside A, an antimicrobial glycolipid from the marine sponge, has been achieved with PTFA as the key building blocks (Scheme 3.61) [561]. In this synthesis, the disaccharide trifluoroacetimidate donor was formed



Scheme 3.60



Scheme 3.61

regioselectively in the presence of a nonanomeric hydroxyl group. Toralactone tetraglucoside possessing strong antiallergic activity has also been synthesized using PTFA as glycosyl donors [562]. In addition, trifluoroacetimidate donors have been employed to synthesize glycoconjugates of (*E*)-resveratrol [563], saponins [564], isoflavone glucuronide [565], *C*-glycosides [566] and β-lactam glycoconjugates [567].

3.2.7
Conclusions and Outlook

In this review, some important efforts made in the past 8 years in the synthesis of oligosaccharides and glycoconjugates by glycosyl trichloro- and trifluoroimidates have been summarized. It is needless to mention that it is a difficult task to cover all aspects within this brief review. On the whole, the glycosyl trichloroacetimidate protocol has again proven to be an extremely powerful method for carbohydrate synthesis, which has often been featured as the key step in the synthesis of complex sugar-containing natural products. Undoubtedly, this method will continue to contribute tremendously to the future development of the glycoscience. On the contrary, in the recent years some applications of the related glycosyl trifluoroacetimidate method in the carbohydrate synthesis have been observed, and continued advances in this area can surely be expected.

3.2.8
Experimental Procedures

3.2.8.1 Typical Procedure for the Preparation of *O*-Glycosyl Trichloroacetimidates

Successively excess Cl_3CCN (generally 6.0 mmol) and a catalytic amount of DBU (<0.1 mmol) are added to a solution of an anomeric *O*-unprotected sugar (1.0 mmol) in dry CH_2Cl_2 (5 ml), and the resulting mixture is stirred at room temperature for 30 min and then concentrated *in vacuo*. The residue is purified by short-column chromatography on silica gel (gradient petroleum ether–EtOAc) to afford the corresponding trichloroacetimidate.

3.2.8.2 Typical Procedure for the Glycosylation with *O*-Glycosyl Trichloroacetimidates

A solution of a glycosyl trichloroacetimidate (1.2 mmol) and a glycosyl acceptor (1.0 mmol) in dry CH_2Cl_2 (10 ml) is treated at about −40 to −50 °C with a solution of TMSOTf in CH_2Cl_2 (0.01–0.05 equiv). When TLC analysis indicates completion of the reaction (typically 10–30 min), the reaction is quenched with $NaHCO_3$ or Et_3N. The mixture is filtered and/or directly concentrated *in vacuo* to give a residue, which is purified by flash column chromatography (gradient petroleum ether/EtOAc) to furnish the glycosidation product.

3.2.8.3 Typical Procedure for the Preparation of *O*-Glycosyl *N*-Phenyl Trifluoroacetimidates

N-phenyl trifluoroacetimidoyl chloride (1.2 mmol) is added to a stirred mixture of an anomeric *O*-unprotected sugar (1.0 mmol) and K_2CO_3 (3.0 mmol) in acetone (20 ml) at room temperature. After being stirred overnight, the mixture is filtered and concentrated. The residue is purified by flash column chromatography (gradient petroleum ether/EtOAc) to produce the corresponding trifluoroacetimidate.

3.2.8.4 Typical Procedure for the Glycosylation with *O*-Glycosyl *N*-Phenyl Trifluoroacetimidates

a solution of TMSOTf in CH_2Cl_2 (0.1 equiv) is slowly added to a mixture of a glycosyl trifluoroacetimidate (1.2–2.0 mmol), a glycosyl acceptor (1.0 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (10–20 ml) at room temperature. Upon completion, as indicated by TLC (typically >3 h), the reaction is quenched with $NaHCO_3$ or Et_3N and then filtered and concentrated. The residue is purified by flash column chromatography (gradient petroleum ether/EtOAc) to afford the glycosidation product.

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3.3
Anomeric Transglycosylation

Kwan-Soo Kim, Heung-Bae Jeon

3.3.1
Introduction

Enzymatic transglycosylation has often been successfully applied to the synthesis of simple oligosaccharides generally in short reaction steps without or with the minimal use of conventional protecting groups [568]. Construction of complex structures is, however, not easy by the enzymatic procedure. Therefore, chemical transglycosylation is attracting growing interest and has been studied very extensively during the past two decades [569].

4
Glycoside Synthesis from 1-Sulfur/Selenium-Substituted Derivatives

4.1
Thioglycosides in Oligosaccharide Synthesis

Wei Zhong, Geert-Jan Boons

4.1.1
Preparation and *O*-Glycosidation of Thioglycosides

Alkyl and aryl thioglycosides are versatile building blocks for oligosaccharide synthesis [1]. Owing to their excellent chemical stability, anomeric thio groups offer efficient protection of the anomeric center. However, in the presence of soft electrophiles, thioglycosides can be activated and used in direct glycosylations. Other attractive features of thioglycosides include their ability to be transformed into a range of other glycosyl donors and act as acceptors in glycosylation reactions, which make thioglycosides particularly suitable for use in chemoselective, orthogonal and iterative glycosylations [2]. This chapter reviews these properties of thioglycosides in detail.

4.1.2
Preparation of Thioglycosides

Many methods exist for the efficient preparation of thioalkyl and aryl glycosides (Table 4.1). Among these approaches, (Lewis) acid-mediated thiolysis of peracetylated sugars is the most commonly employed route. Lemieux and coworkers [3,4] were the first to demonstrate the efficiency of this reaction by preparing several 1,2-*trans* ethyl 1-thioglycopyranosides using ethanethiol as a solvent and zinc chloride as a nonprotic acid catalyst. A number of other catalysts have been reported, such as trimethylsilyl triflate (TMSOTf) [5], boron trifluoride diethyl etherate [5–10], tin(IV) chloride [11], titanium tetrachloride [12–14], iron(III) chloride [15], MoO_2Cl_2 [16] and *p*-toluenesulfonic acid [6]. The use of phosphorus oxychloride for the thioglycosidation of β-per-*O*-acetates has also been described [17], however, this procedure

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Table 4.1 Methods for the preparation of thioglycosides.

Starting material	Reagents	References
Peracetylated hexapyranoside	Thiol, (Lewis) acid	[3–20]
Acylated glycosyl halide	Thiolate anion	[24–34]
Acylated glycosyl halide	(i) (a) Thiourea (b) H_2O, K_2CO_3, (ii) alkylation	[36–40]
Acylated glycosyl halide	(i) Thioacetamide, (ii) RBr, phase transfer catalyst	[41,42]
Unprotected sugar	Ac_2O, acid, arene thiols	[21–23]
Dithioacetal	(i) Partial hydrolysis, (ii) alkylation	[37,45]
Acylated 1-thioaldose	Alkyl halides	[35]
Acylated 1-thioaldose	(i) Diazonium salt, (ii) ¦	[46]
Acylated glycosyl xanthates	Sodium iodide	[48]
Acylated glycosyl thiocyanates	Grignard reagent	[49]
Acylated 1-thioaldoses	Alkene, AIBN	[47]
1-*O*-Alkyl glycosides	$PhSSiMe_3$, ZnI_2, Bu_4NI	[43,44]

gave poor selectivities and yields. Zirconium(IV) chloride [18,19] is an efficient catalyst in thioglycosylations leading mainly to the formation of peracetylated 1,2-*trans* 1-thioglycosides starting from the corresponding 1,2-*trans* acetylated saccharides. However, the preparation of peracetylated 1,2-*trans* 1-thiomannosides proceeded in a disappointing yield.

Treatment of *p*-methoxyphenyl (*pMP*) glycosides prepared from the corresponding 1-*O*-acetyl sugars using boron trifluoride etherate as promoter in combination with thiophenol gave the corresponding thioglycosides in high yield and high 1,2-*trans* selectivity [20]. The sequential per-*O*-acetylation and thioglycosidation of unprotected reducing sugars using a stoichiometric quantity of acetic anhydride and alkyl or aryl thiols have been reported. These reactions that are catalyzed by BF_3 etherate [21,22] or $HClO_4$ [23] constitute an efficient one-pot method for the synthesis of acetylated 1-thioglycosides.

1,2-*trans* Alkyl and aryl 1-thioglycosides have also been prepared by reaction of acylated glycosyl halides with thiols [24–33], disulfides [34] or, alternatively, by *S*-alkylation of tetra-*O*-acetyl-1-thiosugars [35]. A convenient and simple approach for the stereoselective synthesis of 1,2-*trans* 1-thioglycosides is based on the utilization of glycosyl isothiourea derivatives as precursors [36]. Conversion of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-hexapyranoses into their pseudothiourea derivatives [37] followed by treatment with alkyl iodides (bromides) under basic conditions provides an efficient method for the synthesis of alkyl 1-thio-β-D-glucosides [38]. Recently, this procedure was successfully used for the synthesis of thio-linked oligosaccharides [39]. A simple and efficient procedure for the synthesis of thioglycosides has been achieved by the reaction of glycosylisothiouronium salts with alkyl or heteroaryl halides under microwave irradiation, which allows short reaction times. The yields of the products were comparable to conventional methods [40]. Mild and stereoselective aryl thioglycoside syntheses have also been accomplished by displacement of glycosyl halides under phase-transfer-catalyzed conditions [41,42]. Hanessian and Guindon reported a direct conversion of alkyl *O*-glycosides to their corresponding

thioglycosides [43]. This reaction was applied recently by Liu *et al.* for the synthesis of various thioglycosyl building blocks [44].

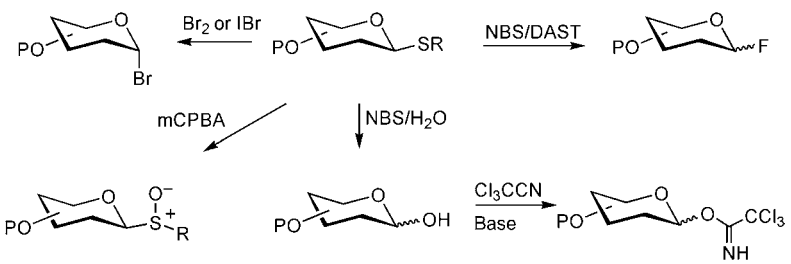
Partial hydrolysis of dithioacetals has been found useful for the preparation of anomers, not obtained by the methods discussed above, and furanosidic thioglycosides [37,45].

Aryl thioglycosides can be obtained by the reaction of 1-thioglycopyranosides with diazonium salts, followed by thermal decomposition of the intermediate diazo-product [46]. Acylated 1-thio-aldoses react with alkenes in the presence of azobis (isobutyronitrile) (*AIBN*) to give acylated alkyl 1-thio-glycopyranosides [47]. Thermal decomposition of glycosyl xanthates, which can be prepared by treating acylated glycopyranosyl halides with potassium alkyl or benzyl xanthate, gives the corresponding 1-thioglycosides [48]. Acylated glycopyranosyl thiocyanates can be prepared by reaction of acylated glycopyranosyl halides with potassium thiocyanate [49]. Treatment of the resulting product with Grignard reagents led to the formation of alkyl and acyl thioglycosides.

4.1.3
Indirect Use of Thioglycosides in Glycosidations

Thioglycosides can be transformed into a range of other glycosyl donors (Scheme 4.1). For example, treatment of a thioglycoside with bromine gives a glycosyl bromide, which after work up can be used in a Hg(II), Ag(I) [50] or phosphine oxide [51] promoted glycosylations. Iodine monobromide, an efficient reagent for the conversion of both activated and deactivated thioglycosides into glycosyl bromides, also permits the glycosylation via a bromide intermediate [52].

A glycosyl bromide can also be prepared *in situ* followed by glycosylation by reaction with $(Bu_4N)_2CuBr_4$ and AgOTf [8,53] or Et_4NBr and *N,N,N′,N′*-tetramethylurea [54]. In an alternative approach, $AgOTf/Br_2$ was used as the activation reagent. A thioglycoside can also be converted into a glycosyl fluoride by treatment with *N*-bromosuccinimide/(diethylamino)sulfur trifluoride (NBS/DAST) [55–57], or hydrolyzed to give the corresponding aldose using a number of reagents such as NBS or *N*-iodosuccinimide (*NIS*) in wet acetone [58–60], $AgNO_3$ in wet acetone [61,62], $NBS/NaHCO_3$ (aq) or $CaCO_3$ (aq) in THF [63], NBS/HCl [64], $n Bu_4NIO_4/TrB(C_6H_5)_4$, $n Bu_4NIO_4$/trifluoromethanesulfonic acid (TfOH), $n Bu_4NIO_4/HClO_4$



Scheme 4.1 Leaving-group interconversions of thioglycosides.

[65], $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O-H_2O_2$ with $HClO_4/NH_4Br$ [66], $V_2O_5-H_2O_2/NH_4Br$ [67], chloramine T [68], NIS/TfOH [69] and NIS/TFA [70]. The resulting hemiacetals are suitable substrates for the preparation of anomeric trichloroacetimidates [71–73]. Finally, another approach involves the oxidation of a thioglycoside to the corresponding sulfoxide using *m*CPBA [74–78], hydrogen peroxide–acetic anhydride–SiO_2 [76], oxone [79,80], selectfluor [81], magnesium monoperoxyphthalate (*MMPP*) [82] or *tert*-butyl hydroperoxide [83]. The resulting compound can then be activated with triflic anhydride at low temperature to give glycosides [74,76,84–88].

4.1.4 Direct Use of Thioglycosides in Glycosidations

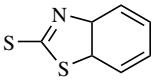
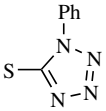
Ferrier *et al*. reported, for the first time, the use of thioglycosides in direct glycosylations [89]. A number of phenyl 1-thioglucopyranosides were solvolyzed in methanol in the presence of $Hg(OAc)_2$ to give the corresponding methyl glycosides. These reactions proceeded with inversion of anomeric configuration and gave only acceptable yields when reactive sugar alcohols were employed. For example, the reaction of phenyl 1-thioglucopyranosides with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose gave an α-linked disaccharide in a yield of 54%. Several other heavy-metal-salt promoters (Table 4.2) have been proposed for the activation of thioglycosides: a notable example being $Pd(ClO_4)_2$, which was used by Woodward *et al*. [90] for the synthesis of Erythromycin A and by Wuts and Bigelow [91] for the preparation of Avermectin.

Despite these important achievements, heavy-metal-salt-mediated activation of thioglycosides did not give high yields consistently and consequently did not find wide application in glycosidic bond chemistry. Lönn demonstrated [12] that methyl triflate is an efficient thiophilic promoter and glycosylations mediated by this reagent usually gave good yields of glycosides. For example, thioglycosides activated with MeOTf were applied for the preparation of a saccharide component of a glycoprotein isolated from fucosidosis patients and for the preparation of phytoelicitor oligosaccharides involved in the recognition and defense of soybean plants against infections by *Phytophthora megasperma*.

Methyl triflate is highly toxic and can methylate hydroxyls when glycosyl acceptors of low reactivity are used. Intensive research has focused on finding alternative reagents with more favorable properties, and today the most commonly used reagents include dimethyl(methylthio) sulfonium triflate (*DMTST*) [92], *N*-iodosuccinimide-triflic acid (NIS-TfOH) or NIS/TMSOTf [93,94], iodonium dicollidine perchlorate (*IDCP*) [95,96] and phenylselenyl triflate (PhSeOTf) [97,98]. The activation of thioglycosides involves the reaction of an electrophilic species with the sulfur lone pair, resulting in the formation of a sulfonium intermediate. The latter intermediate is an excellent leaving group and can be displaced by a sugar hydroxyl.

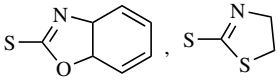
Recently, a number of thiophilic activators that can activate thioglycosides of low reactivity at low temperature have been described. For example, thiophilic promoter systems, such as diphenylsulfoxide [87,99], *S*-(4-methoxyphenyl) benzenethiosulfinate

Table 4.2 Glycosidation of thioglycosides.

Activator	SR	References
$HgSO_4$	SPh	[89]
$HgCl_2$	SEt, SPh	[89,251]
PdHgOTf	SPh	[252]
$Hg(OBz)_2$	SPh	[253]
$Hg(NO_3)_2$	SPh	[254]
$Cu(OTf)_2$		[255]
$Pd(ClO_4)_2$	SPy	[90,91]
$CuBr_2/Bu_4NBr/AgOTf$	SMe, SEt	[8,53]
PhSeOTf	SMe	[97,98]
N-(Phenylseleno) phthalimide/TMSOTf	SMe, SPh	[256]
$AgOTf/Br_2$	SEt	[8]
NBS	SPh	[257]
NIS/TfOH	SMe, SEt, SPh	[93,94]
IDCP	SEt	[95,96]
IDCT	SEt	[258]
I_2	SMe	[259]
$PhIO/Tf_2O$	SMe	[260]
NOBF4	SMe	[261,262]
MeI	SPy	[263]
MeOTf	SEt	[12]
PhSOTf	SMe, SEt, SPh	[264]
DMTST	SMe, SEt, SPh	[92]
$TrClO_4$	SCN Ph	[154–156]
AgOTf		[265]
TBPA	SEt, SPh	[102,103]
e	SPh	[104–106]
$TrB(C_6F_5)_4/I_2/DDQ$	SEt	[107]
$TrB(C_6F_5)_4/NaIO_4$	SMe, SEt, SPh	[108,110]
$TrB(C_6F_5)_4/PhthNSEt$	SEt	[109]
NBS/TfOH	SPh	[266]
NBS/Me_3SiOTf	SEt, SPh	[267]
1-Fluoropyridinium triflates	SEt	[268]
$NIS/HClO_4$–Silica	STol	[269]
NBS/strong acid salts	SMe, SPh	[270]
IX/AgOTf (X = Cl, Br)	SMe, SEt, SPh	[271,272,111]
I_2/hexamethyldisilane (HMDS) or IX (X = Cl, Br)	SMe	[112,113]
$NISorNBS/TrB(C_6F_5)_4$	SEt	[273]
Ph_2SO/Tf_2O	SPh	[87,99]

(*continued*)

Table 4.2 (*Continued*)

Activator	SR	References
N-(Phenylthio)-¦Å-caprolactam	STol	[274]
Benzenesulfinyl morpholine /triflic anhydride (BSM/Tf_2O)	STol	[101]
N-Phenylselenophthalimide–$Mg(ClO_4)_2$/PhIO–$Mg(ClO_4)_2$	SMe, SPh	[275]
S-(4-Methoxyphenyl) benzenethiosulfinate/triflic anhydride (MPBT/Tf_2O)	SPh	[100]
1-Benzenesulfinyl piperidine /2,4,6-tri-tertbutylpyrimidine /triflic anhydride (BSP/TTBP/Tf_2O)	SEt, SPh	[85]
AgOTf		[114–118]

(MPBT) [100], benzenesulfinyl morpholine (*BSM*) [101] or 1-benzenesulfinyl piperidine/2,4,6-tri-*tert*-butylpyrimidine (*BSP/TTBP*) [85], in combination with triflic anhydride (Tf_2O) provide high yields of products for difficult glycosylations.

Thioglycosides can also be activated by a one-electron transfer reaction from sulfur to the activating reagent tris-(4-bromophenyl)ammoniumyl hexachloroantimonate ($TBPA^+$) [102,103]. The use of this promoter was inspired by an earlier report where activation was achieved under electrochemical conditions to give an intermediate *S*-glycosyl radical cation intermediate [104], and the reactivity and mechanism have also been explored [105,106].

A combined use of trityl tetrakis(pentafluorophenyl) borate [$TrB(C_6F_5)_4$], iodine (I_2) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) effectively activates thioglycosides of low reactivity, whereas a combined use of trityl tetrakis(pentafluorophenyl) borate and *N*-(ethylthio)phthalimide (PhthNSEt) activates highly reactive thioglycosides. The use of trityl tetrakis(pentafluorophenyl) borate and $NaIO_4$ as co-oxidant can activate thioglycosides as well. A selective use of trityl salts to activate thioglycosides has been applied in a one-pot glycosylation [107–110]. ICl/AgOTf works well for glycosylations with thioglycosyl donors having a participating group at C-2 of the glycosyl donor, whereas IBr/AgOTf is superior for glycosyl donors having a nonparticipating group at this position. The interhalogens in combination with silver triflate have been applied in the synthesis of bislactam analogs of Ganglioside GD3. IX promoter systems offer convenient handling of reagents and do not produce by-products such as *N*-succinimide, which is released in the popular NIS/TMSOTf-promoted glycosylations [111–113].

S-Benzoxazolyl (*SBox*) and, especially, *S*-thiazolinyl (*STaz*) moieties are sufficiently stable for use in anomeric protection. These derivatives can, however, be activated under mild conditions using silver triflate [114–118].

4.1.5
Anomeric Control in Glycosidations of Thioglycosides

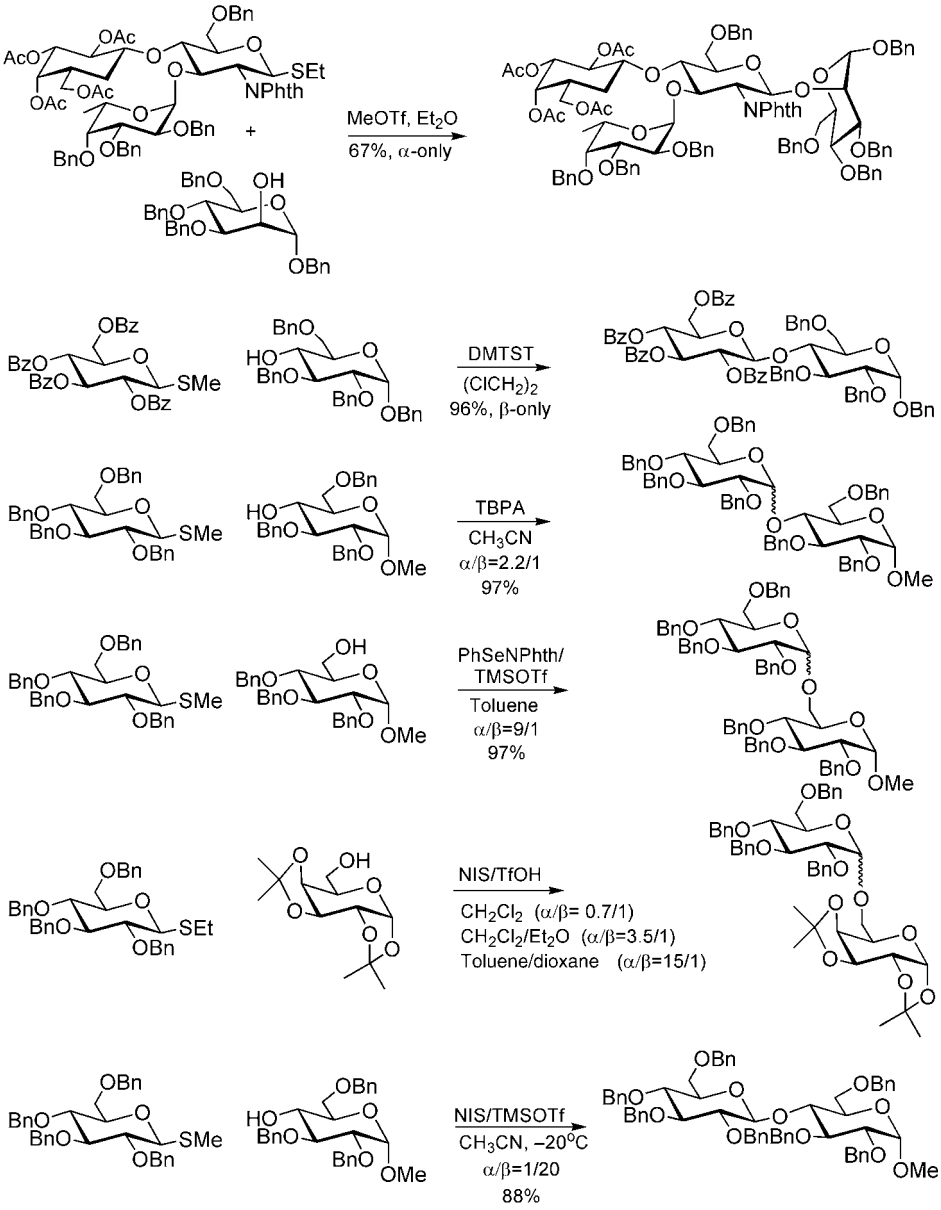
The protecting group at C-2 of a glycosyl donor is an important determinant of the stereochemical outcome of a glycosylation [119–121]. In general, participating groups at C-2, such as *O*-acetyl, *O*-benzoyl and *N*-phthaloyl, lead to the formation of 1,2-*trans* glycosides, whereas nonparticipating groups, such as benzyl ethers, give mixtures of anomers (Scheme 4.2). The anomeric outcome of glycosylations with glycosyl donors having a nonparticipating group at C-2 is markedly influenced by the nature of the solvent [122]. In general, solvents of low polarity are thought to increase α-selectivity by suppressing the formation of oxacarbenium ions. Solvents of moderate polarity, such as mixtures of toluene and nitromethane, are highly beneficial when the glycosyl donors have participating C-2 substituents. It is likely that these solvents stabilize the positively charged intermediates.

Mechanistic studies [123] have shown that thioglycosides can undergo *in situ* anomerization in the presence of iodonium ion catalysts. It has been demonstrated that this anomerization proceeds by intermolecular exchange of alkyl thio groups. An increase in the steric bulk of the leaving group resulted in incomplete or no anomerization. It has been proposed that this anomerization process is important for the stereochemical outcome of glycosylations [123].

Some solvents form complexes with the oxacarbenium ion intermediates, thereby affecting the stereoselectivity of glycosylations. For example, diethyl ether is known to increase α-anomeric selectivity, presumably by formation of a diethyl oxonium-ion intermediate. The β-configuration of this intermediate is probably favored due to steric reasons. Nucleophilic displacement with inversion of configuration will then give an α-glycoside. Boons and coworkers showed that iodonium-ion-mediated glycosidations of thioglycosides in toluene/1,4-dioxane give much higher α-selectivities than when conventional glycosylation solvents are employed [124]. Furthermore, it was shown that the iodonium-ion source, glycosyl donor/acceptor ratio and presence of molecular sieves also have major impacts on the stereochemical outcome of a glycosylation.

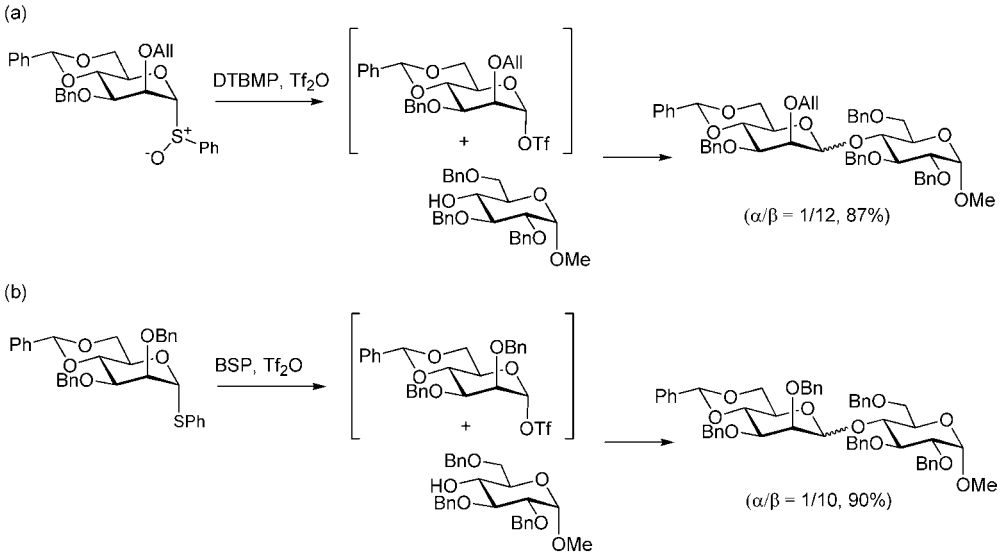
Acetonitrile is another participating solvent, which in many cases leads to the formation of an equatorially linked glycoside [125–131]. It has been proposed that these reactions proceed via an α-nitrilium ion intermediate. It is not well understood why the nitrilium ion adopts an axial orientation; however, spectroscopic studies support the proposed anomeric configuration [130,131]. It is known that nucleophilic substitution of the α-nitrilium ion by an alcohol leads to β-glycosidic bonds and the best β-selectivities are obtained when reactive alcohols at low reaction temperatures are employed. Unfortunately, mannosides give poor anomeric selectivities under these conditions.

β-Mannosides are difficult to introduce because the axial C-2 substituent of a mannosyl donor sterically and electronically disfavors nucleophilic attack from the β-face. β-Mannosides have been obtained by the direct substitution of α-glycosyl triflates, which are conveniently prepared by the treatment of an anomeric sulfoxide with triflic anhydride (Tf_2O) or thioglycosides with NIS (Scheme 4.3a)



Scheme 4.2 Stereoselective glycosidations of thioglycosides.

[128,132–134]. An α-triflate is formed because this anomer is stabilized by a strong *endo*-anomeric effect. Upon addition of an alcohol, the triflate is displaced in an S_N2 fashion resulting in the formation of a α-mannoside. A mixture of anomers is obtained when triflic anhydride is added to a mixture of sulfoxide and alcohol. In



Scheme 4.3 Glycosidation of intermediate α-triflates.

this case, it is very likely that the glycosylation proceeds through an oxacarbenium ion because triflate formation is less likely owing to the greater nucleophilicity of an alcohol.

Another prerequisite of β-mannoside formation is the protection of the mannosyl donor as a 4,6-*O*-benzylidene acetal. Although this observation is difficult to rationalize, it has been suggested that oxacarbenium ion formation is disfavored because of the torsional strain engendered on going to the half-chair conformation of this intermediate. Crich and Chandrasekera employed α-deuterium kinetic isotope effects to unravel the mechanism of 4,6-*O*-benzylidene-directed β-mannosylation. It was found that a torsionally disarming benzylidene acetal opposed rehybridization at the anomeric carbon, thereby shifting the complete set of equilibria toward the covalent triflate and away from the solvent-separated ion pair (*SSIP*), resulting in minimization of α-glycoside formation [135].

Recently, powerful and metal-free thiophilic reagents have been shown to readily activate thioglycosides via glycosyl triflates leading to β-mannosides. For example, a combination of BSP and Tf_2O in the presence of TTBP [85] or MPBT and Tf_2O in the presence of DTBMP [100] at low temperature has been used to prepare β-mannosides in good yield and high β-anomeric selectivity. It was also found that 2-*O*-propargyl ethers were advantageous in the 4,6-*O*-benzylidene acetal-directed β-mannosylations (Scheme 4.3b) [136,137]. This approach has been applied to the synthesis of β-mannans from *Rhodotorula glutinis*, *Rhodotorula mucilaginosa* and *Leptospira biflexa* [138]. van Boom and coworkers developed the very potent thiophilic glycosylation promoter system, diphenylsulfoxide in combination with triflic anhydride, to activate thioglycosides for β-mannosylation [87,99,139]. Furthermore, Demchenko and coworkers

found that the stereoselectivity of β-mannosylation could be improved when a participating moiety at C-4 (*O*-anisoyl, *O*-thiocarbamoyl) is employed. This improvement was achieved in glycosidations of *S*-ethyl and, especially, SBox mannosides [140].

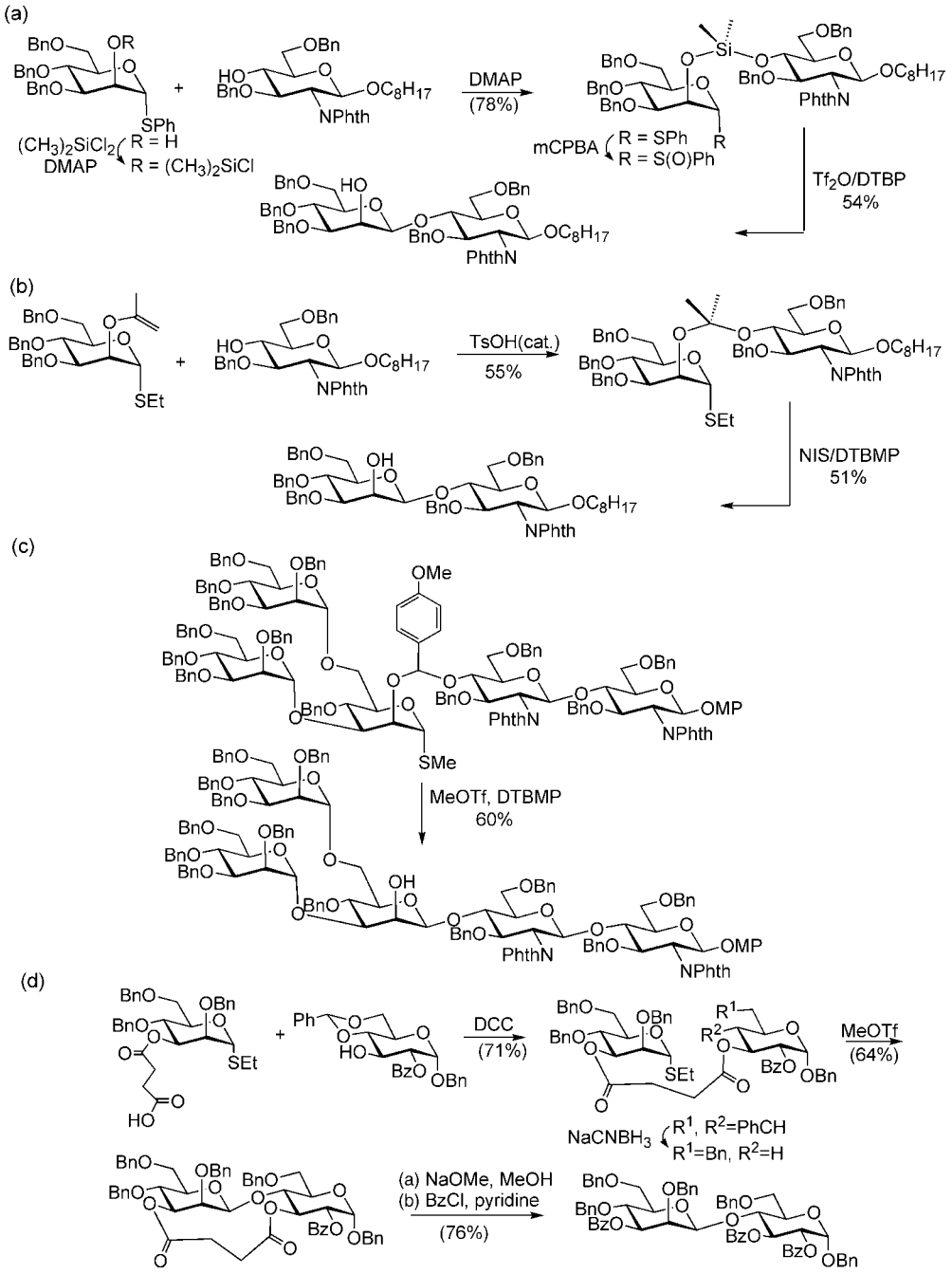
Stork and coworkers [141,142] and Hindsgaul and coworkers [143–145] reported independently the preparation of β-mannosides in a highly stereoselective manner by intramolecular aglycon delivery (*IAD*). In this approach, a sugar alcohol (ROH) is first linked via an acetal or silicon tether to the C-2 position of a mannosyl donor and the subsequent activation of the anomeric center of this adduct forces aglycon delivery from the β-face of the glycosyl donor. The remnant of the tether hydrolyses during the work-up procedure (Scheme 4.4a). A silicon tether was easily introduced by the conversion of a glycosyl acceptor into a corresponding chlorodimethyl silyl ether and the subsequent reaction with the C-2 hydroxyl of a donor to give the silicon-tethered compound [141,142]. Oxidation of the phenylthio group yielded a phenylsulfoxide, which upon activation with Tf_2O resulted in the selective formation of a β-mannoside in a 61% overall yield. Alternatively, the direct activation of thioglycosides also resulted in the formation of β-mannosides. Acetal tethers could easily be prepared by the treatment of equimolar amounts of a 2-propenyl ether derivative of a saccharide with a sugar hydroxyl in the presence of a catalytic amount of acid (Scheme 4.4b) [143–145]. Activation of the anomeric thio moiety of the tethered compound with NIS in dichloromethane resulted in the formation of β-linked disaccharides. In this reaction, no α-linked disaccharide could be detected. It is of interest to note that when this reaction was performed in the presence of methanol, no methyl glycosides were obtained. This experiment indicates that the glycosylation proceeds through a concerted reaction and not by addition to an anomeric oxacarbenium ion.

Fairbanks modified the intramolecular aglycon delivery to achieve stereospecific 1,2-*cis* glycosylation via 2-*O*-vinyl thioglycosides, which were synthesized from the corresponding alcohols by Ir-catalyzed transvinylation with vinyl acetate, followed by iodine-mediated tethering of a range of primary and secondary carbohydrate acceptors and finally intramolecular aglycon delivery [146–150]. The use of such an intramolecular glycosylation strategy furnished the desired α-gluco and β-manno disaccharides in a stereoselective manner [146–149]. The methodology has been applied for the synthesis of a tetrasaccharide derived from *N*-linked glycans [150].

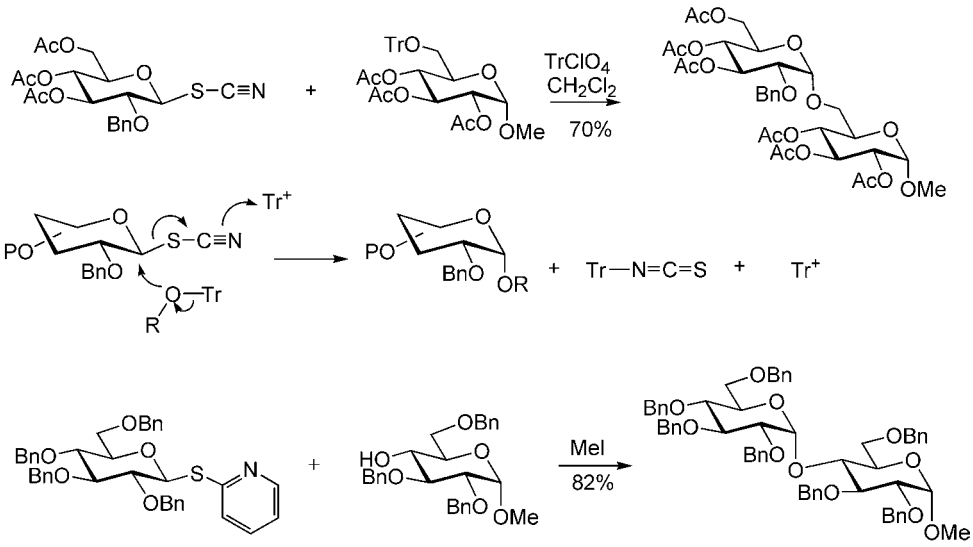
An intramolecular acetal has also been introduced by the treatment of a mixture of a 1-thio-mannoside, having a methoxybenzyl protecting group at C-2 and an alcohol with DDQ [71] (Scheme 4.4c). Activation of the thioglycoside with methyl triflate gave a β-mannoside as the only anomer. This approach was employed for the synthesis of the core pentasaccharide of *N*-linked glycoproteins.

Ziegler and coworkers prearranged a glycoside by employing a succinyl tether between C-6 of a mannosyl donor and C-3 of glucosyl acceptor [151,152]. They found that the nature of the glycosyl acceptor and the length of the tether affected the anomeric selectivity of the intramolecular mannosylation (Scheme 4.4d) [153].

Kochetkov and coworkers have reported [154–156] an efficient approach for the synthesis of 1,2-*cis* pyranosides employing 1,2-*trans*-glycosyl thiocyanates as glycosyl donors and tritylated sugar derivatives as glycosyl acceptors (Scheme 4.5). This



Scheme 4.4 Synthesis of β-mannosides by intramolecular aglycon delivery.

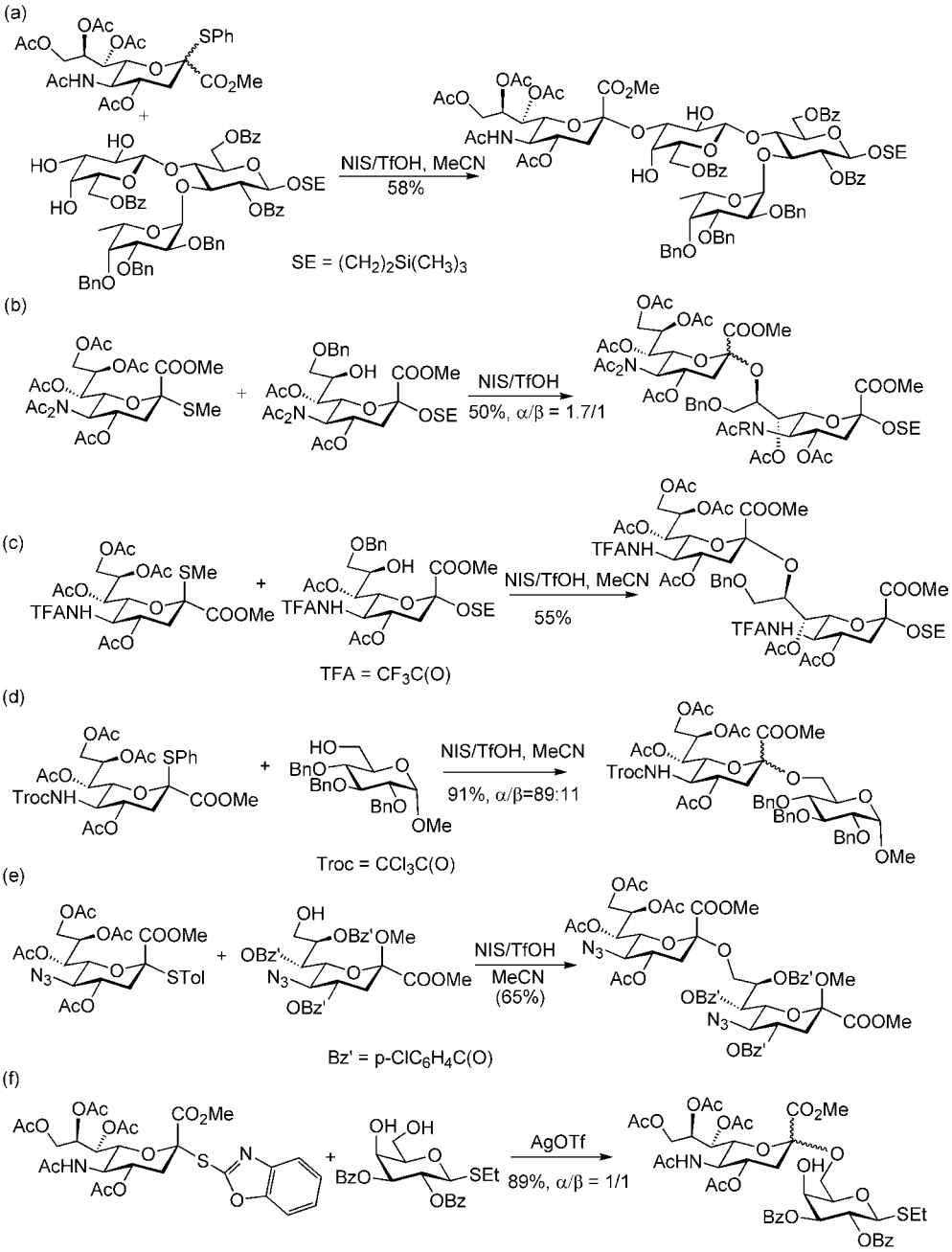


Scheme 4.5 Glycosidations of thioglycosides by inversion of configuration.

coupling is initiated by the reaction of the nitrogen of the thiocyanate with trityl cation from $TrClO_4$. This results in leaving-group departure accompanied by simultaneous nucleophilic attack by a trityl-protected sugar alcohol to give an α-glycoside. It appears that this reaction proceeds by clean S_N2 inversion of configuration at the anomeric center. Mereyala and coworkers [157–159] used 2-pyridyl 1-thioglycosides having a nonparticipating C2-substituent as glycosyl donors and methyl iodide as an activator to achieve stereoselective α-glycosylations in the D-gluco and D-galacto series. The reaction is proposed to proceed via the electrophilic activation of the glycosyl donor by methyl iodide, followed by the formation of sulfenium salt. An alcohol displaces the latter intermediate via an S_N2 mechanism.

2-Thio-sialyl glycosides (Scheme 4.6a) are commonly used for the preparation of α-sialyl glycosides [97,98,160–163]. The best yields and anomeric selectivities have been obtained when partially protected galactosyl acceptors are employed. Furthermore, it has been found that the reactivity of sialyl thioglycosyl donors can be significantly increased by acetylation of the acetamido group [164] (Scheme 4.6b). This modification enables the efficient synthesis of α-(2 → 8)-dimers of Neu5Ac [165].

Boons and coworkers [165,166] modified the C-5 amino group of 2-methyl and 2-thiophenyl sialosides into *N*-TFA derivatives, which provided a glycosyl donor that gives good yields and high α-anomeric selectivities in direct sialylations with a wide range of glycosyl acceptors of differing reactivities (Scheme 4.6c). Sialyl acceptor, protected as an *N*-TFA derivative, gave the best yields and it was postulated that lower nucleophilicity of the TFA-protected amino functionalities and enhanced reactivity affect the efficiency of the glycosylations.



Scheme 4.6 Glycosidations of thioglycosides of Neu5Ac.

Takahashi and coworkers described an effective sialylation method utilizing the *N*-Fmoc, *N*-Troc and *N*-trichloroacetyl-β-thiophenyl sialosides (Scheme 4.6d) [167]. It was found that the *N*-Troc derivative of *N*-acetylneuraminic acid performed better than the corresponding *N*-Fmoc derivative. An *N*-Troc β-thiosialoside was applied for the synthesis of glycosyl amino acids by one-pot glycosylation [167]. Importantly, it was found that the *N*-Troc protecting group could be converted into an acetamido moiety without causing racemization of the peptide.

Another effective α-selective sialylation involves the use of a 5-*N*,4-*O*-carbonyl-protected sialyl donor, which could efficiently be used for the preparation of an α(2,8)-tetrasialoside. It was found that the 5-*N*,4-*O*-carbonyl protecting group improves the reactivity of the C-8 hydroxyl group of the sialyl acceptor [168].

Wong and coworkers showed that 5-azido sialyl donors protected with *O*-acetyl ester are useful for α-selective glycosylations of primary hydroxyls (Scheme 4.6e) [169]. It was proposed that the linear and electron-withdrawing nature of the C-5 azido moiety stabilizes the reactive axial acetonitrile adduct to allow the incoming nucleophile to approach the α-face in an S_N2-like fashion. In addition, a chemoselective glycosylation method has been developed for the synthesis of NeuAcα-(2 → 9) NeuAc as thioglycoside donor for use in the subsequent glycosylations [169].

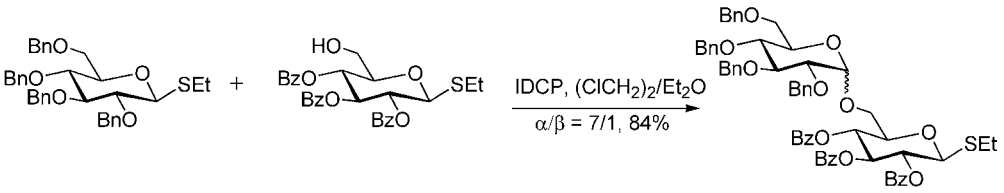
Recently, De Meo and Parker described two novel sialyl donors bearing a thioimidoyl moiety as leaving group (Scheme 4.6f) [170]. The SBox and STaz sialosides proved to be excellent glycosyl donors when activated with MeOTf or AgOTf. In general, good yields and stereoselectivities were observed with a number of glycosyl acceptors ranging from highly reactive primary hydroxyls to less reactive secondary hydroxyls. The most attractive feature of thiomidoyl moieties is that they can be selectively activated in the presence of thioglycosides using AgOTf as promoter.

In brief, the use of acetonitrile as solvent and the selection of an appropriate C-5 amino protecting group and reactive promoter system are critical for achieving high α-selectivities and yields in the synthesis of sialosides.

4.1.6
Glycosylation Strategies Using Thioglycosides

4.1.6.1 Chemoselective Glycosylations

van Boom and coworkers showed that the reactivity of thioglycosides can be controlled by the selection of appropriate protecting groups. It was found that a C-2 ether protecting group activates and a C-2 ester deactivates the anomeric center [96]. This difference in reactivity was exploited for attractive chemoslective glycosylations. For example, iodonium-ion-mediated coupling of a fully benzylated thioglycoside with a partially benzoylated thioglycosyl acceptor gave a disaccharide mainly as the α-anomer in a yield of 84% (Scheme 4.7). It has been established that the resulting disarmed thioglycosyl disaccharide can be readily activated using the strong thiophilic promoter NIS/TfOH. The subsequent coupling with a glycosyl acceptor gives a trisaccharide [93,171–175]. The chemoselective glycosylation approach was rationalized as follows: the electron density of the anomeric sulfur atom in a 2-*O*-acyl ethylthio glycoside is decreased because of the inductive effects by the

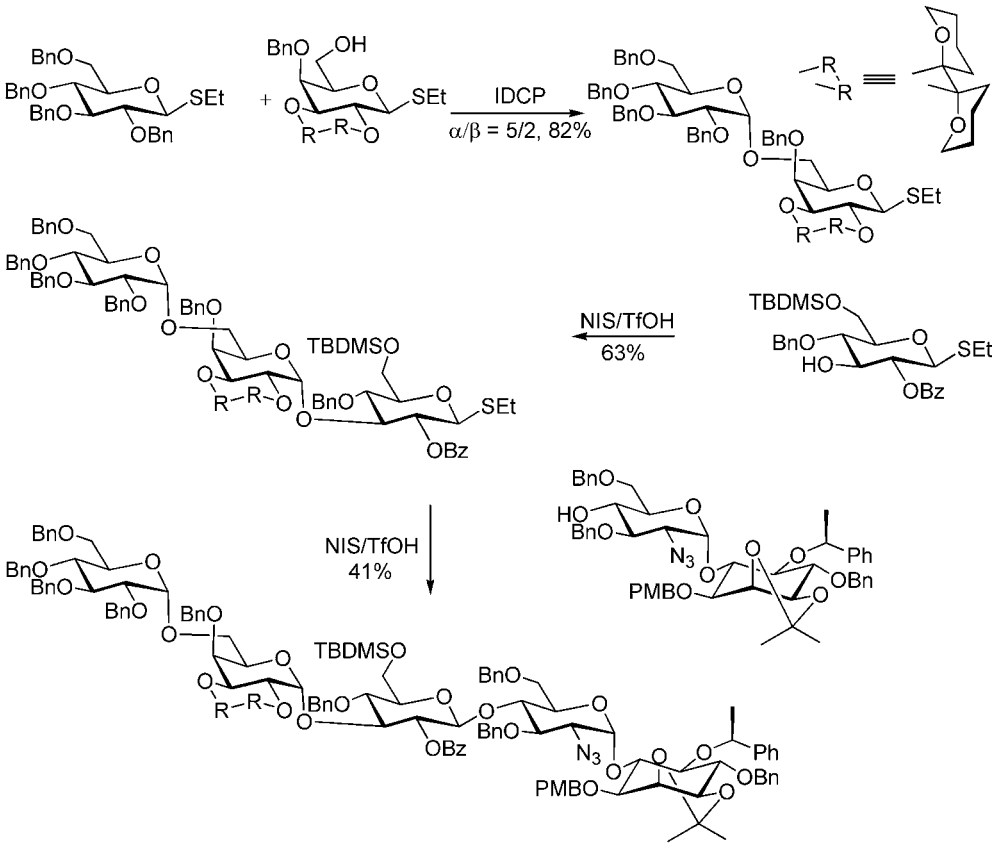


Scheme 4.7 Armed–disarmed glycosylations of thioglycosides.

electron-withdrawing ester functionality at C-2. As a result, nucleophilic complexation of the anomeric thio group with iodonium ions decreases and the thioglycoside can be regarded as disarmed with respect to an armed 2-*O*-alkyl thioglycoside. It is important to note that Fraser-Reid and coworkers introduced the armed–disarmed glycosylation protocol using *n*-pentenyl glycosides as glycosyl donors and acceptors [94,176,177].

Ley and coworkers proposed [178–186] that the armed–disarmed glycosylation strategy could gain versatility by further tuning of glycosyl donor leaving-group ability. In this respect, a dispiroketal or a butane-2,3-diacetal (*BDA*) protecting group has a marked effect on the reactivity of the anomeric center. It was found that thioglycosides protected with these functionalities have reactivities between an armed C-2-alkylated thioglycoside and a disarmed C-2-acylated thioglycoside (Scheme 4.8). For example, the three levels of anomeric reactivity were exploited for the preparation of a protected pseudopentasaccharide unit common to the variant surface glycoprotein of *Trypanosoma brucei* [178]. Thus, iodonium dicollidine perchlorate (*IDCP*)-mediated chemoselective glycosylation of benzylated-thioglycosyl donor with dispiroketal-protected acceptor gave a disaccharide in excellent yield (82%, $\alpha/\beta = 5/2$). Further chemoselective glycosylation of the torsionally deactivated glycosyl donor with an electronically deactivated acceptor in the presence of the more powerful activator NIS/TfOH gave a 63% yield of trisaccharide as one isomer. The pseudopentasaccharide was obtained by NIS/TfOH-mediated condensation of the trisaccharide donor with a pseudodisaccharide acceptor.

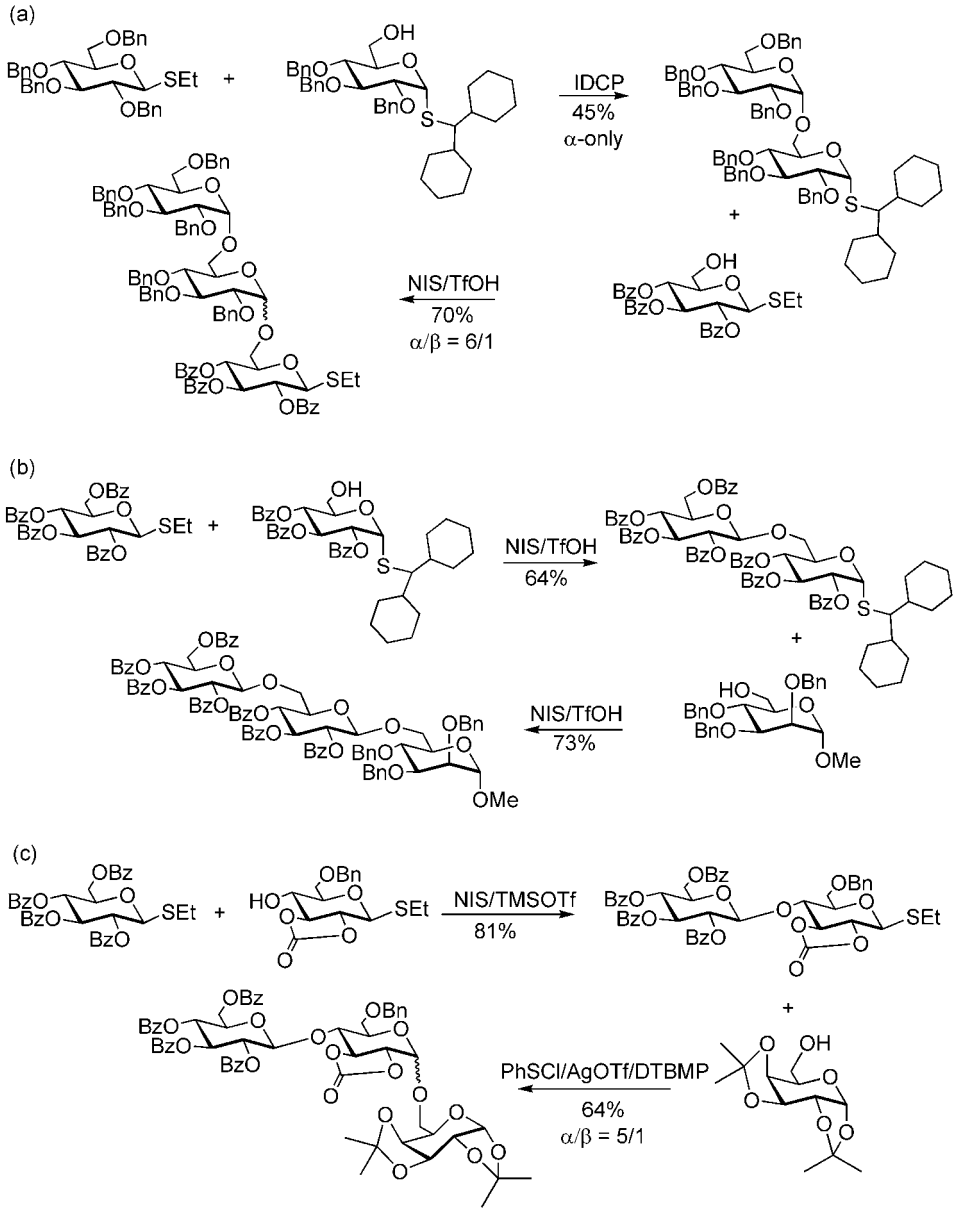
In the armed–disarmed glycosylation approach, the leaving-group ability is controlled by protecting groups (ether/dispiroketal/ester). It may, however, be advantageous to control the anomeric reactivity by means of modifying the leaving group. Boons and coworkers [187,188] showed that the bulkiness of the anomeric thio group has a marked effect on the glycosyl donor reactivity and provides an opportunity to produce a new range of differentially reactive coupling substrates. For example, IDCP-mediated chemoselective glycosylation of a fully benzylated ethyl thioglycosyl donor with a partially benzylated dicyclohexylmethyl thioglycosyl acceptor gave a disaccharide in a yield of 45% as one anomer (Scheme 4.9). Further chemoselective coupling of the resulting sterically deactivated donor with an electronically deactivated glycosyl acceptor in the presence of the more powerful promoter system NIS/TfOH gave a trisaccharide in a yield of 70%. In both glycosylations, no self-condensed or polymeric products were detected (Scheme 4.9a). These experiments show that the reactivity of a C2-benzylated dicyclohexylmethyl thioglycoside is



Scheme 4.8 Chemoselective glycosidations of thioglycosides.

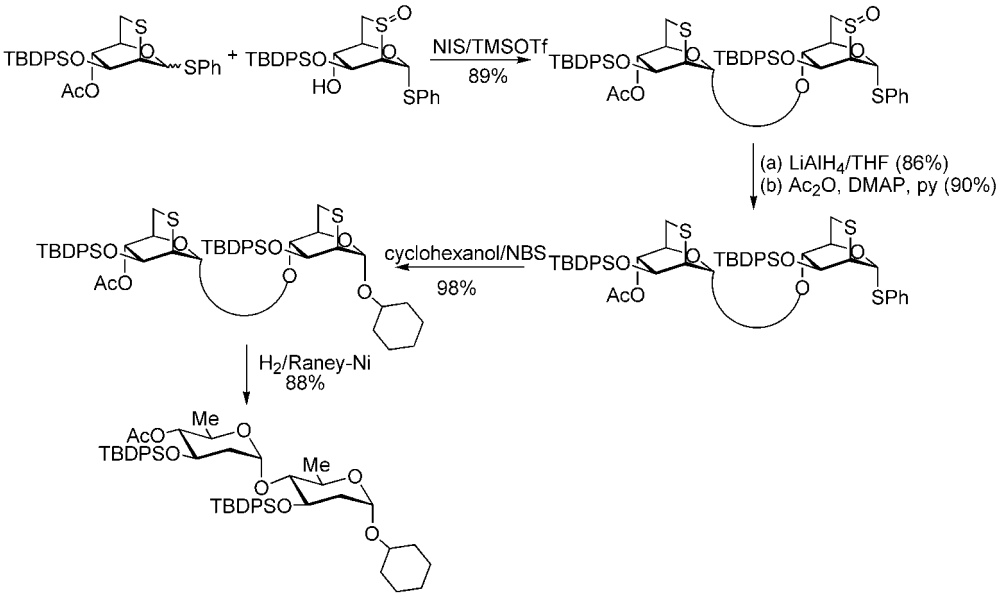
between ethyl thioglycosides having a fully armed ether and disarmed ester protecting group on C-2. This new approach to tuning thioglycoside reactivity was employed for the preparation of a phytoalexin-elicitor active oligosaccharide and its photoreactive derivatives (Scheme 4.9b) [189].

The *trans*-2,3-cyclic carbonate function was introduced as a nonparticipating thioglycoside, which deactivates the anomeric center of thioglycosides by both electronic and conformational effects. These thioglycosides are significantly less reactive than corresponding ones having ester-protecting groups at C-2 [190]. Thioglycosides protected as a *trans*-2,3-cyclic carbonate remain intact upon treatment with thiophilic promoters such as NIS/TMSOTf, NIS/AgOTf and MeOTf. However, the activator PhSOTf, generated *in situ* by the reaction of PhSCl with AgOTf, can activate these thioglycosides. It was concluded that thioglycosides protected as *trans*-2,3-cyclic carbonates have significantly lower anomeric reactivities compared to the fully acylated and the *N*-acyl protected thioglycosides. As a result, these derivatives can be used as acceptors in chemoselective glycosylations



Scheme 4.9 Chemoselective glycosidations with sterically deactivated thioglycosides.

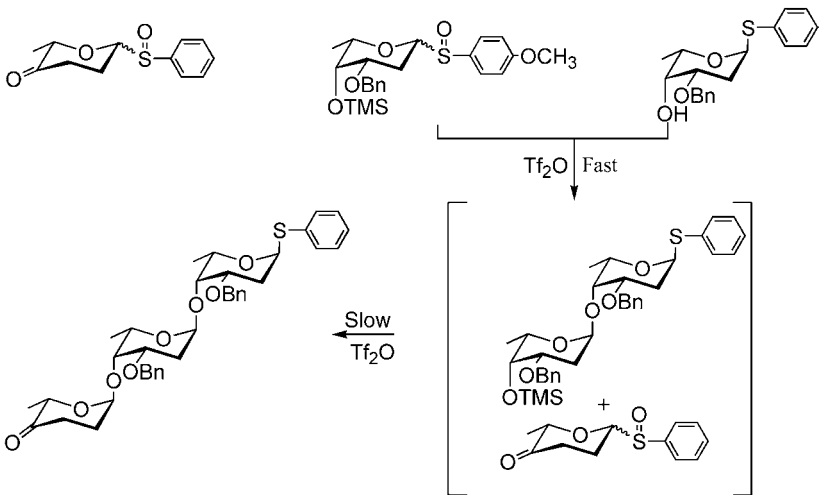
with a wide range of C2-alkylated or -acylated thioglycosyl donors (Scheme 4.9c). An interesting feature of these disarmed donors is that they permit the introduction of a 1,2-*cis* glycosides, whereas this is not possible with classical 2-acyl-disarming derivatives.



Scheme 4.10 Thioglycosides for the preparation of 2,6-di-deoxy-glycosides.

Toshima and coworkers developed a strategy for the chemoselective activation of thioglycosides for the preparation of 2,6-dideoxy glycosides [191–195]. Thus, the activated 2,6-anhydro-2-thioglycoside was coupled with the deactivated 2,6-anhydro-2-sulfinyl substrate to afford a disaccharide (Scheme 4.10). The resulting compound was converted into its active 2-thio-analog by reduction of the sulfinyl moiety and condensation with cyclohexanol. Reductive removal of the thio bridge afforded a 2,2′,6,6′-tetra-deoxy-disaccharide, which corresponds to the saccharide moiety of the biologically important Avermectin antibiotic.

Several methods for chemoselective glycosylations by one-pot procedures have been reported. For example, Kahne *et al.* [74] described a glycosylation method, which is based on selective activation of anomeric sulfoxides with triflic anhydride (Tf_2O) or triflic acid (TfOH). Mechanistic studies have revealed that the rate-limiting step in this reaction is triflation of the phenyl sulfoxide. Therefore, the reactivity of the glycosyl donor can be influenced by the nature of the substituent of the *para* position of the phenyl ring and the following reactivity order was established OMe $H > NO_2$. Interestingly, the reactivity difference between a *p*-methoxyphenylsulfenyl glycoside and an unsubstituted phenylsulfenyl glycoside is sufficient to permit selective activation. In addition, silyl ethers are appropriate glycosyl acceptors when catalytic triflic acid is used as the activating reagent but these compounds react more slowly than the corresponding alcohols. These observations allowed for a one-pot synthesis of a trisaccharide from a mixture of three monosaccharides (Scheme 4.11) [84]. Thus, the treatment of the mixture with triflic acid resulted in the formation of



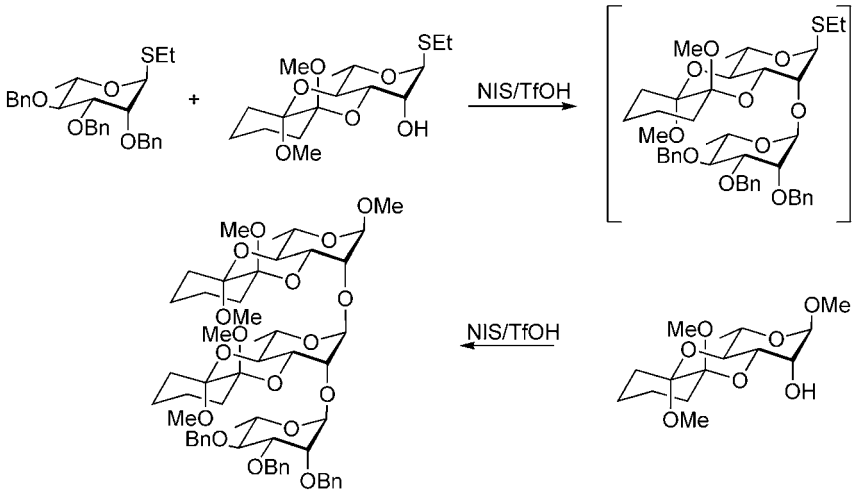
Scheme 4.11 Chemoselective glycosidations of anomeric sulfoxides by a one-pot procedure.

the expected trisaccharide in a 25% yield. No other trisaccharides were isolated and the only other coupling product was a disaccharide.

The products of the reaction indicate that the glycosylation takes place in a sequential manner. First, the most reactive *p*-methoxyphenylsulfenyl glycoside was activated and reacted with the sugar alcohol and not with the silyl ether. In the second stage of the reaction, the less reactive silyl ether of the disaccharide reacted with the less reactive sulfoxide to give the trisaccharide. The phenylthio group of the trisaccharide could be oxidized to a sulfoxide, which could be used in a subsequent glycosylation to give a part structure of the natural product Ciclumycin. Despite the relatively low yield of the coupling reactions, this methodology provides an efficient route to this compound.

Several variations of the one-pot multistep glycosylation concept have been reported. For example, Ley and coworkers [179,196] prepared a trisaccharide derived from the common polysaccharide antigen of group B *Streptococcus* by a facile one-pot two-step synthesis (Scheme 4.12). In this strategy, a benzylated activated thioglycosyl donor was chemoselectively coupled with the less reactive cyclohexane-1,2-diacetal (*CDA*)-protected thioglycosyl acceptor to give a disaccharide. Next, a second acceptor and additional activator were added to the reaction mixture, which resulted in the clean formation of a trisaccharide. The lower reactivity of the CDA-protected thioglycoside reflects the torsional strain inflicted upon the developing cyclic oxacarbenium ion, the planarity of which is opposed by the cyclic protecting group.

The one-pot two-step glycosylation strategy allows the construction of several glycosidic bonds without time-consuming work up and purification steps. It should, however, be realized that this type of reaction will only give satisfactory results when all the glycosylations are high yielding and highly stereoselective. For example, by exploiting neighboring-group participation, it is relatively easy to selectively install

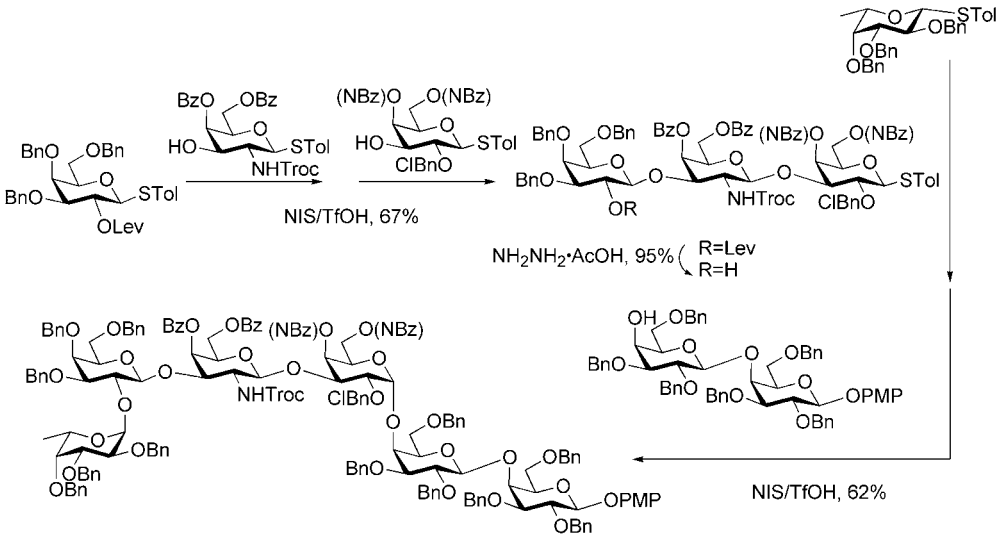


Scheme 4.12 One-pot multistep glycosidations of thioglycosides.

1,2-*trans* glycosides. Also, in general, mannosides give very high α-selectivities. Other types of glycosidic linkages may, however, pose problems.

Wong and coworkers have pursued an approach using HPLC for the rapid and precise measurement of relative reactivities of thioglycosyl donors. It was found that the nature of the saccharide, the position and the type of protecting groups contribute to anomeric reactivity. This information was employed to create a database of thioglycosyl reactivities, which can be used to select glycosyl donors and acceptors for easy and rapid one-pot assemblies of various linear and branched oligosaccharide structures [197]. The database has been successfully employed for one-pot multistep preparations of oligosaccharide libraries [198,199] and complex oligosaccharides such as Globo-H [200], fucosyl GM1 [201], sialyl Lewis X [202], oligolactosmine [203], α-Gal pentasaccharide [204], oligomannan [205] and Lewis Y [206]. The 'OptiMer' computer program was developed to guide the selection of appropriate thioglycosyl building blocks that have sufficiently different reactivities for one-pot multistep glycosylations. For example, the program aided in the selection of appropriate building blocks for the convenient synthesis of the tumor-associated hexasaccharide Globo-H. The reactivity of the building blocks was tuned by using electron-donating groups, such as benzyl ether and 2,2,2-trichloroethylcarbamate, and electron-withdrawing protecting groups, such as benzoyl, *p*-nitrobenzoyl (NBz) and *o*-chlorobenzyl ethers (ClBn) (Scheme 4.13).

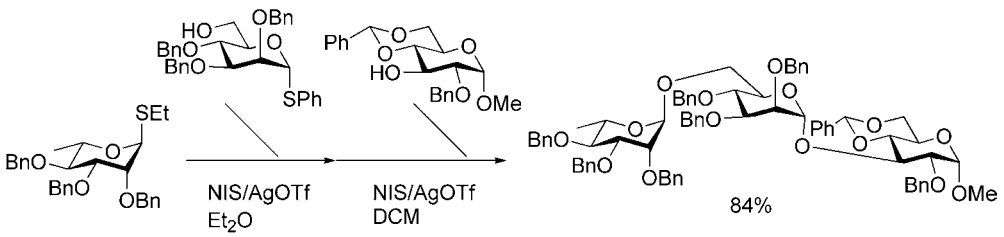
A one-pot two-step glycosylation to give a trisaccharide was accomplished by simply changing the solvent system [207]. In this approach, the solvent controls the anomeric selectivity and also the rate of glycosylation. Thus, when a reactive ethyl thiorhamnoside and a less reactive thiophenyl mannoside were dissolved in diethyl ether, only the rhamnosyl donor was activated by promoter system NIS/AgOTf to give the corresponding thiophenyl disaccharides in an almost quantitative yield. After adding a



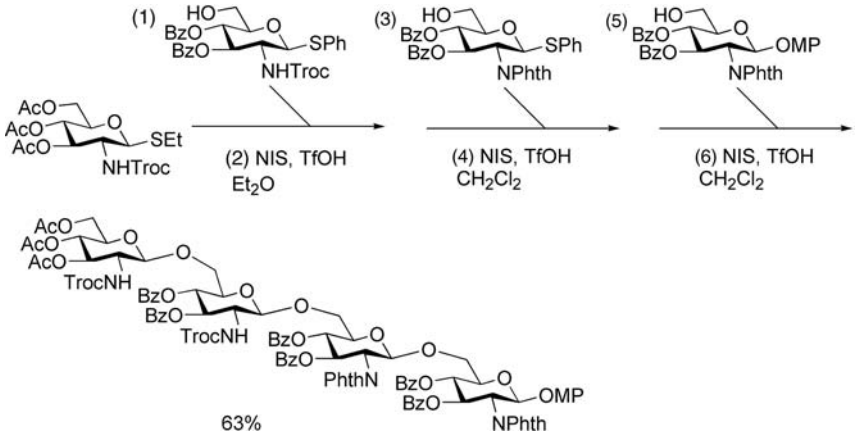
Scheme 4.13 One-pot synthesis of the Globo-H hexasaccharide.

glucosyl acceptor and an additional promoter dissolved in CH_2Cl_2, the intermediate thiophenyl disaccharide donor was activated by NIS/TMSOTf leading to the formation of a trisaccharide in high yield and stereoselectivity. Thus, by tuning the reactivity of acceptors and donors and performing the first glycosylation in diethyl ether (low glycosylation rate) and the second in CH_2Cl_2/Et_2O (higher glycosylation rate), a trisaccharide could be prepared by a one-pot two-step procedure (Scheme 4.14).

Baasov and coworkers achieved an efficient synthesis of an oligosaccharide using a one-pot procedure whereby the reactivity of glycosyl donors and acceptors were tuned by a combination of the nature of the C-2 amino protecting group (Troc, Phth) and anomeric leaving group (ethylthio and phenylthio) [208]. In addition, by exploiting solvent reactivity effects, an ethyl 1-thioglycoside could be activated in the presence of a phenyl 1-thioglucosyl acceptor. Thus, the synthesis exploited the observation that NTroc-protected thioglycosides are significantly more reactive than their NPhth-protected counterparts. Furthermore, successful synthesis of the target tetrasaccharide



Scheme 4.14 Solvent reactivity effects in one-pot oligosaccharide synthesis.



Scheme 4.15 One-pot synthesis of glucosamine oligosaccharide.

exploited the higher reactivity of thioethyl glucosides compared to similar thiophenyl glycosides. As a result, the desired tetraglucosamine could be prepared in an overall yield of 63% by a one-pot three-step glycosylation (Scheme 4.15).

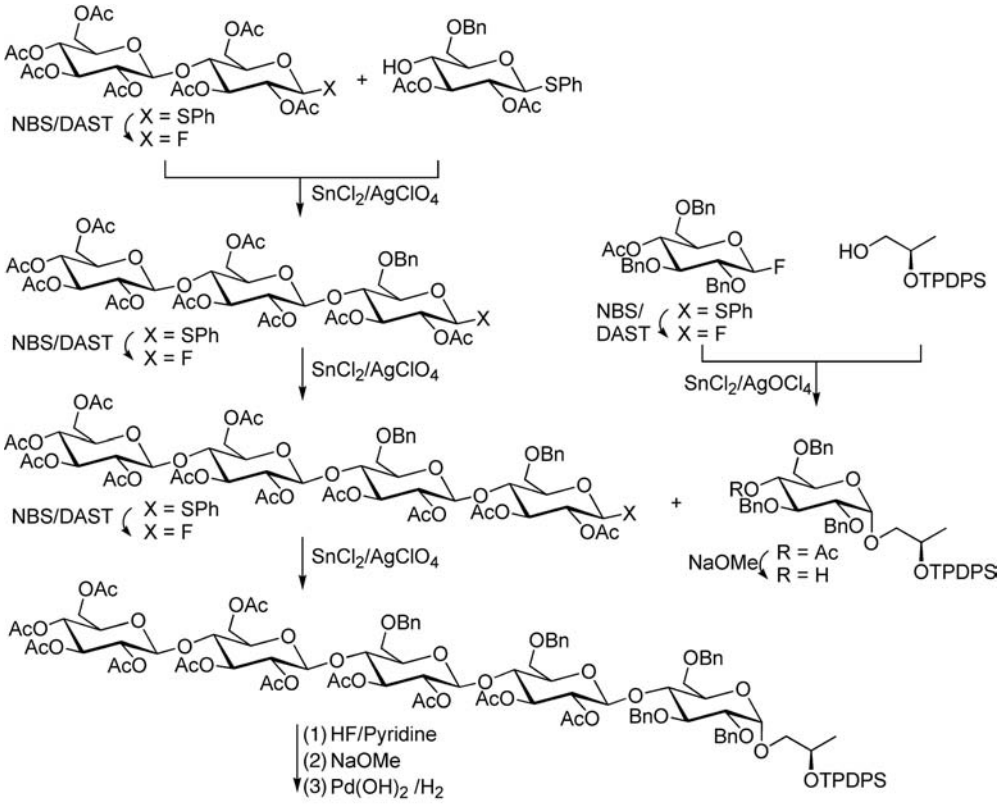
4.1.6.2 **Orthogonal and Semiorthogonal Glycosylations**

Orthogonal glycosylations use glycosyl donors and acceptors that have different anomeric groups (e.g. X = F and Y = SR), which can be activated without affecting the other one. These synthetic approaches are attractive as no or very few protecting-group manipulations are involved during the assembly of a complex oligosaccharide.

Nicolaou and coworkers [209–214] have described a two-stage glycosylation strategy whereby a thioglycoside is converted into a glycosyl fluoride donor, which is then employed as a glycosyl donor for coupling with a thioglycosyl acceptor. The procedure can be repeated by the conversion of the anomeric thio group of the oligosaccharide into an anomeric fluoride that can be used in a further coupling reaction. This glycosylation strategy was exploited for the preparation of *Rhynchosporides* and key reactions are depicted in Scheme 4.16.

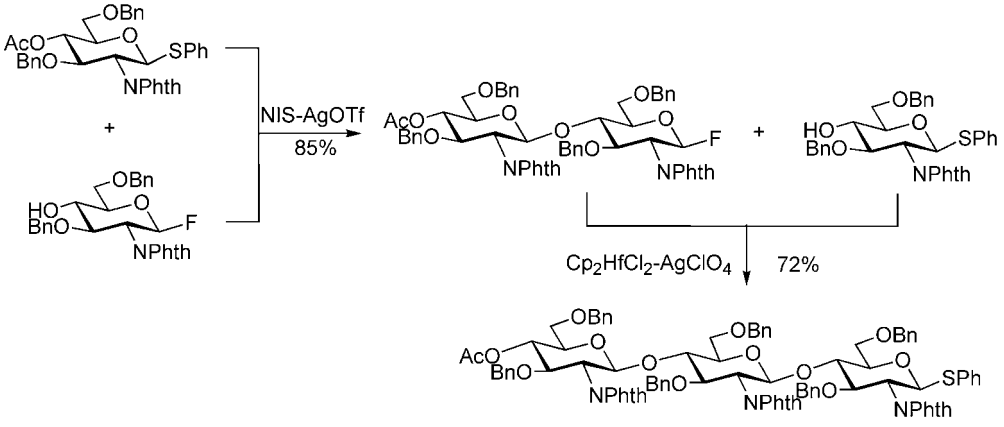
In a further improved orthogonal glycosylation strategy [215], thioglycosides and glycosyl fluorides act as glycosyl donors and acceptors and are coupled with each other in a chemoselective manner [215]. An example of this strategy is depicted in Scheme 4.17, in which the synthesis of β(1 → 4)-2-acetamido-2-deoxy-D-glucose-linked oligosaccharides is described. Thus, a thioglycosyl donor was coupled with a glycosyl fluoride acceptor using a thiophilic promoter. Next, the resulting glycosyl fluoride acted as a glycosyl donor and coupled with a thioglycosyl acceptor. Reiteration of the process leads to the rapid buildup of long-chain oligosaccharides.

Several other examples have been reported in which thioglycosides were used as glycosyl acceptors. Thus, thioglycosides containing free hydroxyls can be coupled chemoselectively with glycosyl bromides and chlorides in the presence of silver triflate or tin(II) chloride-silver perchlorate as the promoter system [12,53,56,162,218–221].



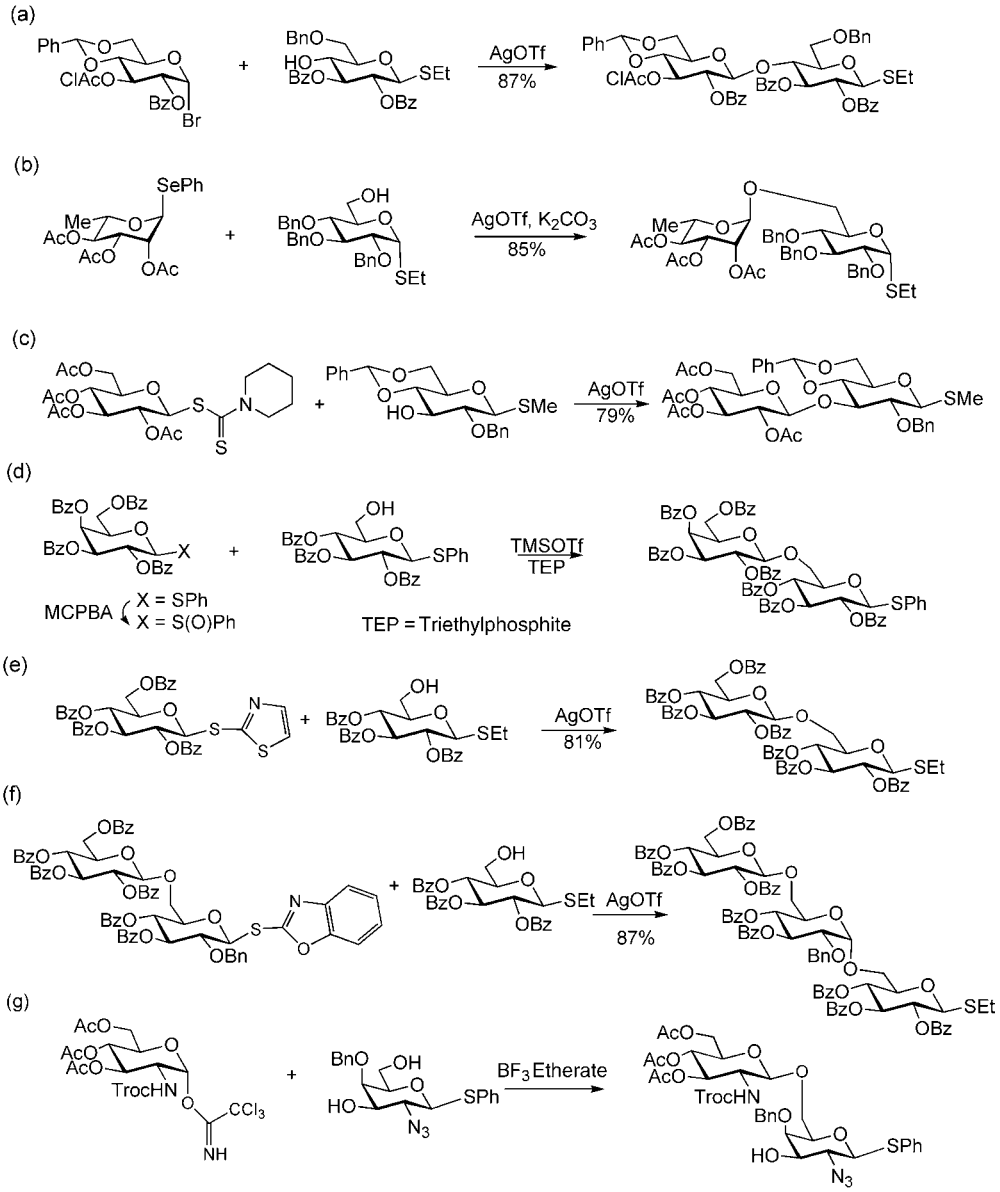
β-D-Glcp-(1-4)-β-D-Glcp-(1-4)-β-D-Glcp-(1-4)-β-D-Glcp-(1-4)-α-D-Glcp-(1-1)-1,2-propane diol

Scheme 4.16 Two-stage activation of thioglycosides.



Scheme 4.17 Orthogonal glycosylations of thioglycosides and glycosyl fluorides.

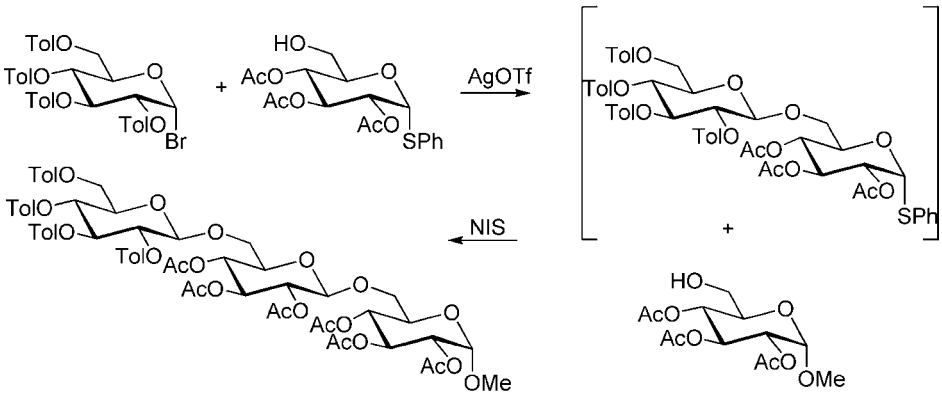
Such a synthesis is shown in Scheme 4.18a, in which a glycosyl bromide is coupled with the thioglycosyl acceptor to afford a thioglycosyl disaccharide. The glycosyl bromide was obtained from the corresponding 1-thioglycoside by treatment with Br_2. It was shown [222–224] that phenyl selenoglycosides can be selectively activated in the



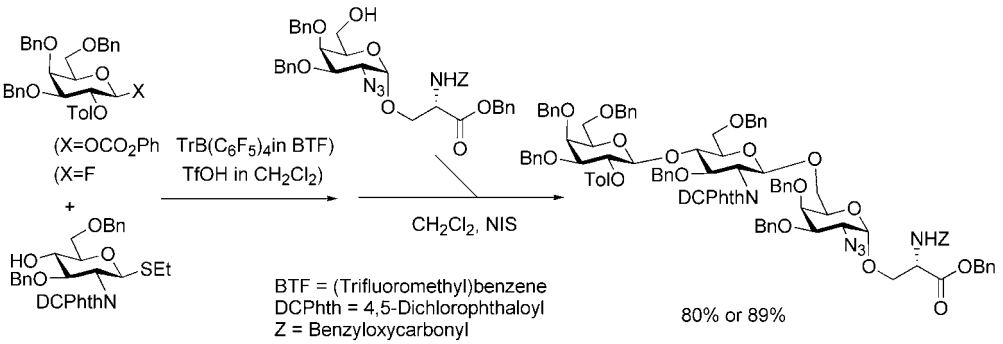
Scheme 4.18 Glycosylations with thioglycosyl acceptors.

presence of ethyl thioglycosides using silver triflate/potassium carbonate (or silver carbonate) as the promoter system (Scheme 4.18b). Garegg and coworkers reported the use of glycosyl 1-piperidinecarbodithioates in combination with thioglycosides (Scheme 4.18c) [225]. Peracetylated piperidinecarbodithioate donor could be selectively activated in the presence of the thioglycosyl acceptor by using silver triflate as the promoter to afford a thioglycosyl disaccharide. Kahne and coworkers reported a glycosylation approach in which glucosyl sulfoxides are activated in the presence of thioglycosides (Scheme 4.18d) [276–278]. Next, the resulting thioglycosyl disaccharides could be activated using a thiophilic promoter or converted into the corresponding sulfoxides. The reaction of thioglycosyl acceptors with trichloroacetimidates has also been described (Scheme 4.18g) [216,226]. Demchenko and coworkers have studied a series of thioimidate-based glycosyl donors, such as *S*-Benzoxazolyl and *S*-thiazolinyl (*STaz*) glycosides, which can be activated by AgOTf or $Cu(OTf)_2$ in the presence of ethyl 1-thioglycosides (Scheme 4.18e and f) [115,116]. In addition, a strategy was developed whereby anomeric reactivities were reduced by metal complexation with the anomeric group [227]. Furthermore, STaz glycosides can selectively be activated over conventional 1-thioglycosides and *O*-pentenyl glycosides, whereas bromides, trichloroacetimidates and 1-thioglycosides can be activated over the STaz moiety [228].

Orthogonol and semiorthogonal glycosylations have also been performed in one-pot multistep fashion. For example, Takahashi and coworkers [216] reported a one-pot two-step glycosylation in which the difference in reactivity between glycosyl donors and acceptors was accomplished through the use of two types of anomeric leaving groups with different reactivities (Scheme 4.19). Thus, a glycosyl bromide was coupled with a thioglycosyl acceptor in the presence of silver triflate to give a disaccharide. Although the anomeric thiophenyl groups are stable to silver triflate (AgOTf), an addition of both the second activator (NIS) and the glycosyl acceptor promoted selective activation of the glycosyl donor, resulting in the formation of a trisaccharide (84% overall yield). In this example, the stereochemical outcome of the glycosylations was controlled by the neighboring-group participation of the 2-*O*-



Scheme 4.19 One-pot multistep glycosylations with thioglycosides and glycosyl bromides.

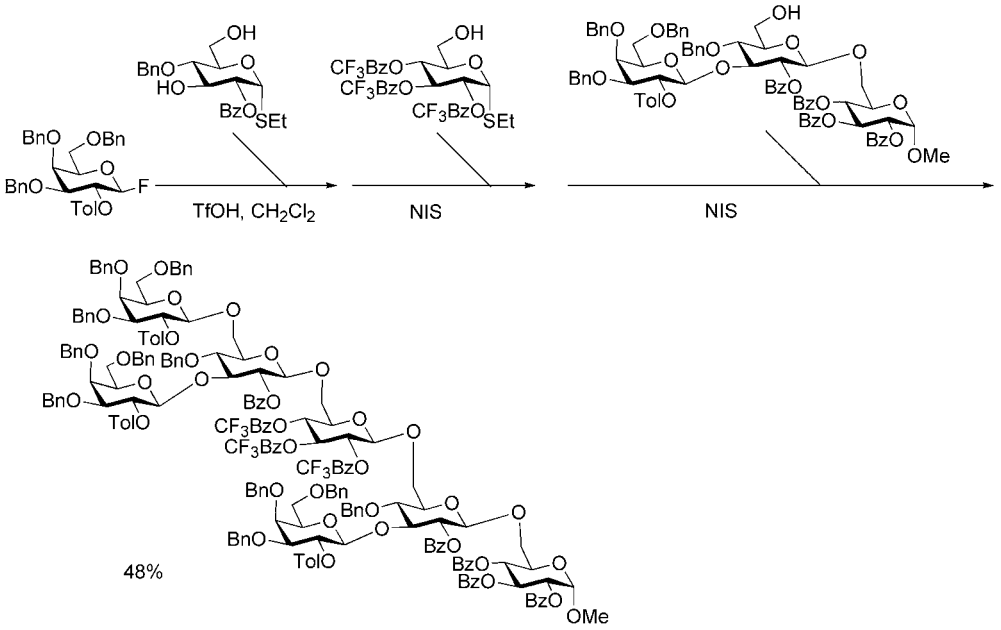


Scheme 4.20 One-pot synthesis of mucin-related F1α antigen.

toluoyl (Tol) and acetyl protecting groups. A similar one-pot two-step glycosylation procedure was employed for the preparation of an elicitor-active hexaglycoside.

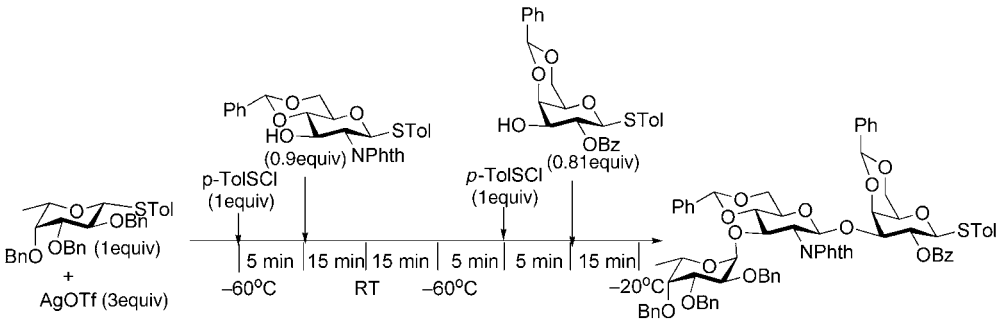
Mukaiyama and Kobashi have reported a one-pot assembly of a mucin-related F1α antigen using anomeric fluorides and carbonates [51]. After a careful evaluation of solvent systems, promoters and reaction temperatures, a fully protected F1α antigen was synthesized by a one-pot sequential glycosylation using a galactosyl phenyl carbonate or fluoride, a thioglycoside and a glycosyl amino acid (Scheme 4.20). In the first step, the phenylcarbonate or fluoride donor was coupled with the ethyl thioglucoside in the presence of $TrB(C_6F_5)_4$ or TfOH, respectively. After TLC analysis indicated complete consumption of the glycosyl donor, consecutive addition of the terminal glycosyl amino acid and NIS provided the target trisaccharide in high yield (80 and 89%, respectively). In a similar manner, an anomeric fluoride donor and two different thioglycosides were employed for the preparation of a phytoalexin elicitor heptasaccharide (Scheme 4.21) [217]. Thus, TfOH-catalyzed double glycosylation of the fluoride with the ethyl thioglycosyl acceptor gave a trisaccharide, which was coupled with the highly deactivated *p*-(trifluoromethyl)benzoyl (CF_3Bz)-protected thioglycoside to afford a tetraglucoside intermediate as the major product. Next, the consecutive addition of a trisaccharide acceptor and NIS led to the formation of a heptasaccharide in an overall yield of 48%. Thus, four glycosidic linkages were stereoselectively introduced in a one-pot manner.

Huang *et al.* designed a general one-pot multistep glycosylation approach independent of differential glycosyl donor and acceptor reactivities. The new and elegant method is based on the preactivation of a thioglycosyl donor to give a reactive intermediate in the absence of the acceptor. Subsequently, a thioglycosyl acceptor can be added to the activated donor leading to the formation of a coupling product [229]. The resulting thioglycoside can be activated and employed in a subsequent glycosylation with a thioglycosyl acceptor. For example, a trisaccharide was assembled that contains the biologically relevant Fuc-α1,3-GlcNAc and GlcNAc-β1,3-Gal moieties. Thus, preactivation of the toluyl thiofucoside by *p*-TolSOTf at −60 °C was followed by the addition of a phthaloyl-protected thioglycosyl acceptor. The reaction

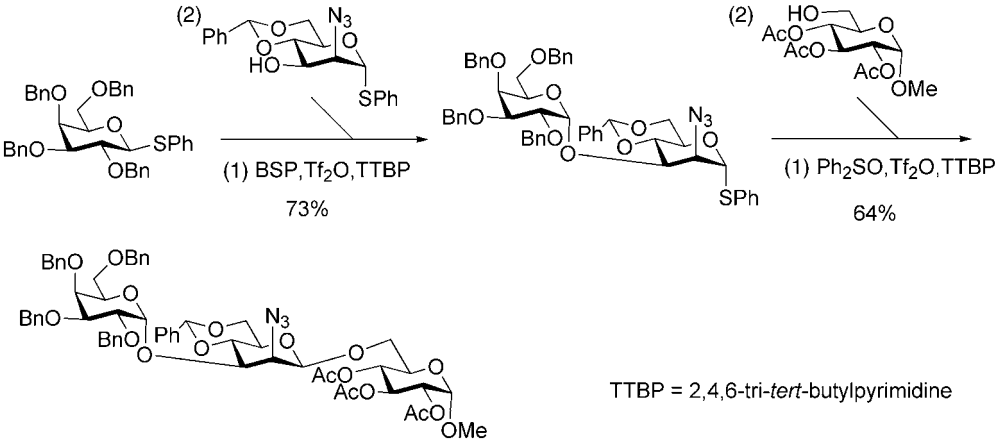


Scheme 4.21 Mukaiyama's one-pot synthesis of phytoalexin-elicitor active heptasaccharide.

mixture was allowed to warm to room temperature for over a period of 15 min, during which time a disaccharide was formed. After cooling the reaction mixture to −60 °C, the disaccharide was preactivated with *p*-TolSOTf, followed by the addition of the thiogalactosyl acceptor, producing a trisaccharide in 59% overall yield within a period of 1 h (Scheme 4.22). The trisaccharide carrying an anomeric *p*-thiotolyl moiety could be utilized as glycosyl donor for the synthesis of Le^x containing oligosaccharides. Excellent anomeric stereoselectivities were obtained in each glycosylation.



Scheme 4.22 Preactivation of *p*-tolyl thioglycoside in one-pot oligosaccharide synthesis.



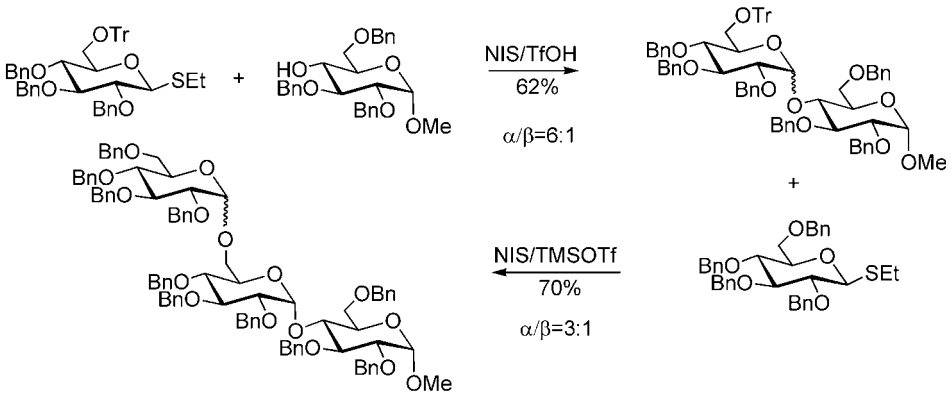
Scheme 4.23 Chemoselective glycosylation by preactivation strategy using Ph_2SO/Tf_2O promoter.

van Boom and coworkers described a similar preactivation strategy for thioglycosides. It was found that diphenylsulfoxide in combination with triflic anhydride provides a very potent thiophilic reagent capable of activating deactivated thioglycosides [87,99]. A novel chemoselective condensation sequence was developed, in which a benzylated reactive thioglycosyl donor was selectively activated by a mild thiophilic promoter and chemoselectively condensed with a relatively unreactive thioglycosyl donor (Scheme 4.23). Addition of the acceptor and the more reactive promoter system Ph_2SO/Tf_2O led to the formation of a trisaccharide. The side products formed from the BSP/Tf_2O activation system were quenched by the addition of triethyl phosphite after each glycosylation to avoid activation of the acceptor and glycosylation product [87].

Finally, a novel sequential glycosylation procedure has been reported using 1-hydroxyl and thioglycosyl donors [230]. Yamago *et al.* reported a broad substrate scope utilizing the BSP/Tf_2O promoter system to preactivate thioglycosyl donors [231].

4.1.6.3 Two-Directional Glycosylation Strategies

The overall efficiency of chemoselective and orthogonal glycosylations is compromised by the linear nature of the glycosylation sequence and the fact that the growing oligosaccharide chain acts in each reaction as glycosyl donor. These problems can be addressed by two-directional glycosylation strategies. In such an approach, a thiosaccharide building block can act as glycosyl donor as well as glycosyl acceptor. These properties enable oligosaccharide assembly in a very flexible and highly convergent manner. For example, the coupling of a tritylated thioglycosyl donor with an acceptor having a 4-hydroxyl afforded a disaccharide in a yield of 62% ($\alpha/\beta = 6/1$) (Scheme 4.24) [232]. In this case, the 6-*O*-trityl group improved the α-selectivity of the glycosylation because of the steric effects. The trityl ether of the resulting product can act as an acceptor when it is glycosylated with a fully benzylated thioglycosyl donor using NIS

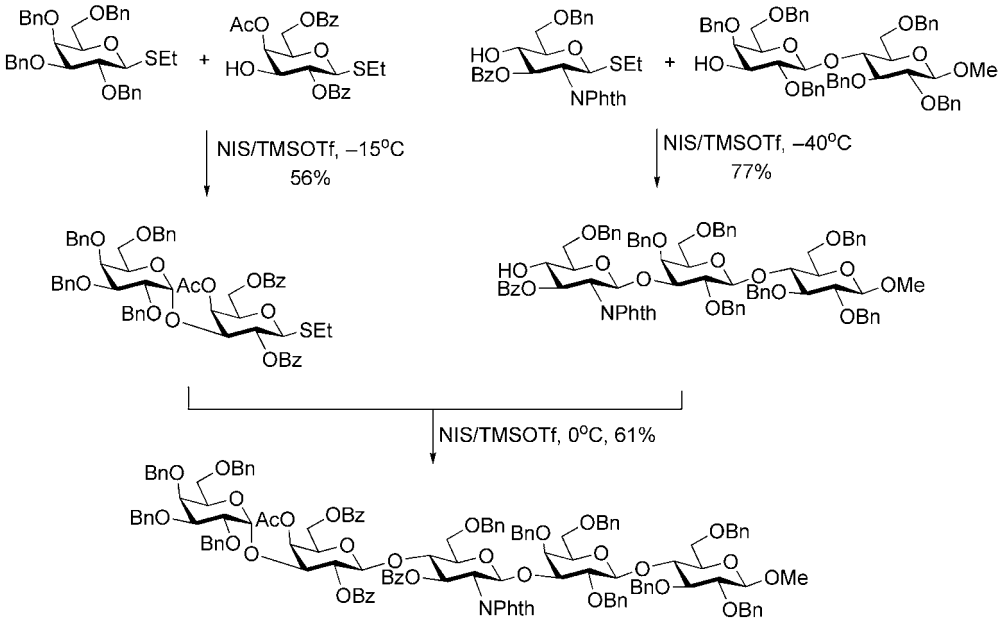


Scheme 4.24 Two-directional glycosylations with tritylated thioglycosides.

and a stochiometric amount of TMSOTf as the activator to give a trisaccharide in excellent yield as a mixture of anomers ($\alpha/\beta = 3/1$).

A two-direction glycosylation strategy can also be performed by regioselective glycosylation between glycosyl donors and acceptors, both of which contain a free hydroxyl group to give di- and trisaccharides [233]. The products of these glycosylations can immediately be employed as glycosyl acceptors in subsequent glycosylations without the need to perform protecting-group manipulations. In combination with the previously reported chemoselective glycosylations, this methodology provides a powerful method to assemble oligosaccharides in a highly convergent manner, avoiding protecting-group manipulations at the oligosaccharide stage. A prerequisite of regioselective glycosylation is that the acceptor's hydroxyl functionality must be substantially more reactive than the hydroxyl group of the glycosyl donor. Differences in reactivity may be achieved by primary versus secondary or equatorial versus axial disposition of hydroxyl groups. The new methodology was employed for the preparation of a pentasaccharide involved in the hyper-acute rejection response in xenotransplantation (Scheme 4.25) [234]. Thus, the α-linked Gal($1 \rightarrow 3$)Gal dimer was obtained by an armed–disarmed chemoselective glycosylation using NIS/TMSOTf as promoter and toluene/1,4-dioxane as reaction solvent. The right-hand trisaccharide was obtained in a good yield of 77% by a NIS/TMSOTf-mediated glycosylation between a lactoside acceptor and partially protected 2-deoxy-phthalimido-glucosyl acceptor. No self-condensation of the glycosyl donor was observed owing to the deactivation of the 4-OH by the neighboring benzoyl group. The pentasaccharide was obtained by coupling of the thiodisaccharide and trisaccharide acceptor in the presence of NIS/TMSOTf. Two-directional glycosylations using thioglycosides have also been performed on solid support [235].

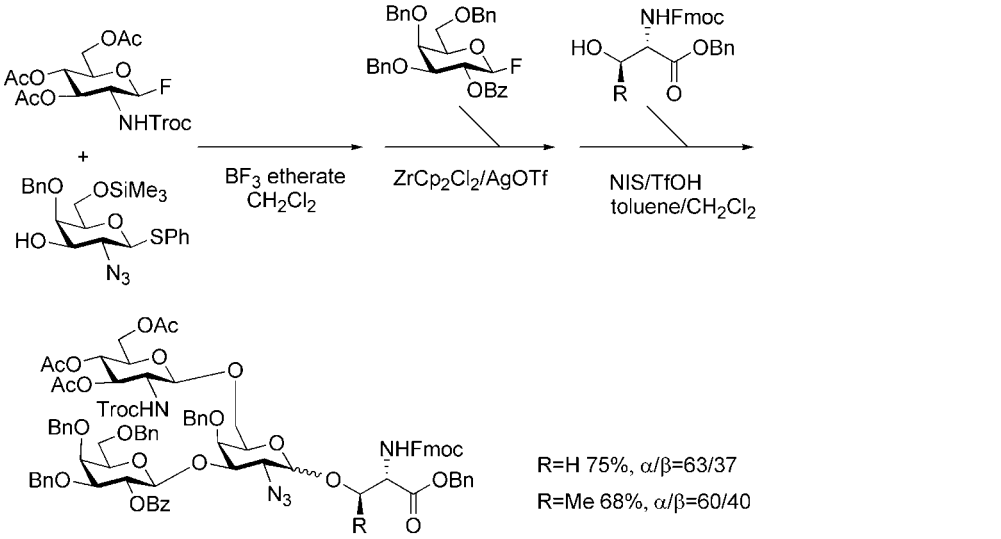
Takahashi and coworkers described the one-pot synthesis of core 2 branched oligosaccharides [236]. It was found that boron trifluoride complexed with a trimethylsilyl ether would enhance the nucleophilicity of the silyl ether. As a result, glycosylations of the 6-*O*-TMS modified acceptor with a glycosyl fluoride provided



Scheme 4.25 The preparation of the Galili pentasaccharide using thioglycosyl donors and acceptors in a two-directional glycosylation strategy.

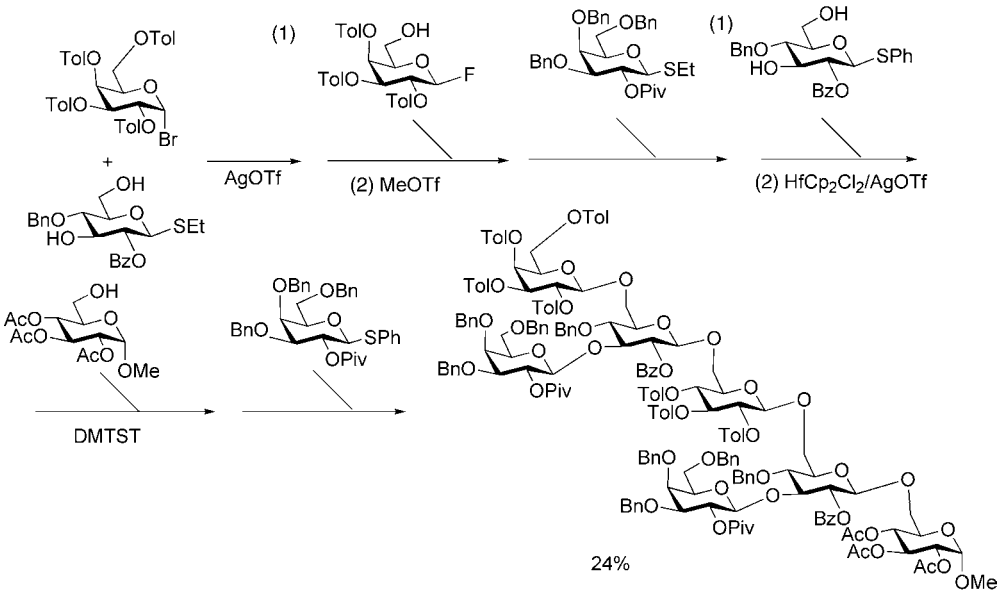
selectively glycosylation at C-6 of the thioglycosyl acceptor without the glycosylation of the C-3 hydroxyl. Therefore, a chemoselective glycosylation was performed between 6-*O*-silyl-4-benzyl-2-azido-thiogalactoside and a glycosyl fluoride in the presence of BF_3 etherate, followed by sequential coupling of the remaining secondary hydroxyl group with galactosyl fluoride in the presence of $ZrCp_2Cl_2$/AgOTf to provide the desired trisaccharide. Subsequent NIS/TfOH-promoted glycosidation of the thioglycoside with amino acids provided products in good yield (Scheme 4.26).

The same group also prepared a phytoalexin elicitor heptamer by a one-pot six-step glycosylation protocol, providing the most impressive example of the potential of chemoselective glycosylation technology [216,237]. The sequential addition of seven reaction components with six appropriate activators resulted in the one-pot six-step glycosylation. First, a toluoyl-protected galactosyl bromide, in combination with AgOTf, ensured the regioselective glycosylation of the primary alcohol of thioglucoside diol. Second, the resulting 1-thioglycoside acted as a glycosyl donor in a coupling with a galactosyl fluoride acceptor using large excess of MeOTf to avoid self-condensation. Third, the glycosylation of the C3-hydroxyl was achieved using thioglucoside. Fourth, $HfCp_2Cl_2$–AgOTf-mediated coupling of the branched tetraglucoside to the third thioglycosidic building block was performed regioselectively. Fifth, the terminal glucose acceptor was condensed with the resulting pentasaccharide thiophenyl donor using a large excess of dimethyl(methylthio)

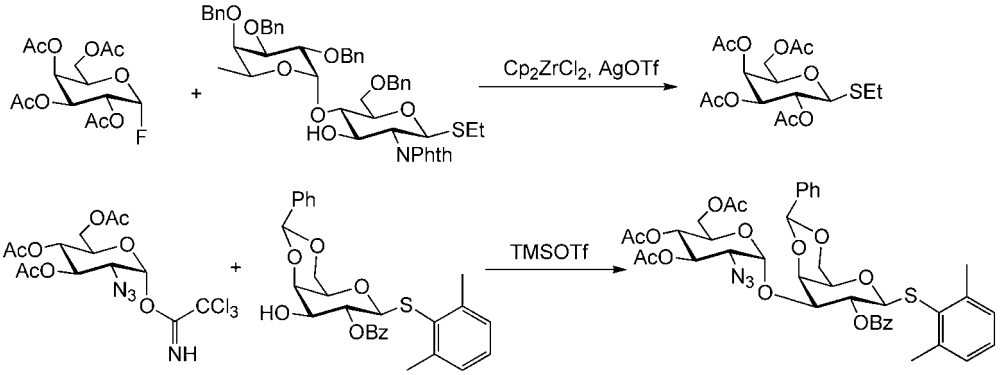


Scheme 4.26 One-pot synthesis of core 2 class amino acids.

sulfonium triflate. Finally, the heptasaccharide, the largest oligosaccharide amongst the reaction products, was formed via the second β-glucosidic linkage. The final compound was purified by size exclusion chromatography in a good yield of 24% (Scheme 4.27).



Scheme 4.27 Takahashi's one-pot synthesis of phytoalexin elicitor active heptasaccharide.



Scheme 4.28 Aglycon transfer of thioglycosides.

4.1.7
Aglycon Transfer

Although thioglycosides have been successfully employed as glycosyl acceptors, at times this type of glycosylation is plagued by aglycon transfer [2,236,238–249]. The aglycon transfer process is shown to affect both armed and disarmed thioglycosides, it causes anomerization of the carbon-sulfur bond of a thioglycoside and destroys the product of a glycosylation reaction. This side reaction is especially important to consider when carrying out complex reactions, such as solid-phase glycosylations, one-pot or orthogonal multicomponent glycosylations and construction of carbohydrate libraries. For example, an intermolecular aglycon transfer reaction was observed in a Cp_2ZrCl_2/AgOTf-mediated coupling of a glycosyl fluoride donor and a 1-thiodisaccharide acceptor (Scheme 4.28) [244]. It was rationalized as follows: the acyloxonium ion generated after activation of the glycosyl fluoride attacked the sulfur instead of the sterically hindered alcohol, leading to the formation of β-thioglycoside. Aglycon transfer could be avoided by employing a less reactive 1-thioglycosyl acceptor. Li and Gildersleeve examined a number of modified aglycons to prevent aglycon transfer [250]. It was found that the 2,6-dimethylphenyl 1-thio moiety was effectively blocking the transfer in a variety of model studies and glycosylation reactions. The DMP group can be installed in one step from a commercially available 2,6-dimethylthiophenol and is usable as a glycosyl donor.

4.1.8
General Procedure for Synthesis of Thioglycosides from Peracetylated Hexapyranosides Promoted by BF_3-Etherate [5–10]

To a solution of peracetylated hexapyranoside (1.0 equiv), ethanethiol (1.2 equiv) and freshly activated 4 Å powdered molecular sieves in dichloromethane (4.0 ml $mmol^{-1}$) was added BF_3-Et_2O (2.0 equiv) dropwise at 0 °C under an argon atmosphere.

The reaction mixture was stirred for 2 h at room temperature until TLC analysis indicated that the reaction was complete. The solution was filtered through Celite and washed with dichloromethane. The filtrate was washed with saturated aqueous $NaHCO_3$ and H_2O. The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded the target compound.

4.1.9
General Procedure for Synthesis of Thioglycosides by Displacement of Acylated Glycosyl Bromide with Thiolate Anion [34]

To a solution of diaryl or diaralkyldisulfide (1.0 equiv) in CH_3CN (5.0 ml $mmol^{-1}$) was added zinc dust (1.0 equiv) followed by fused $ZnCl_2$ (0.2 equiv). The reaction mixture was placed in a preheated oil bath at 70 °C for 45 min, during that time the reaction mixture became turbid indicating the formation of zinc thiolate. A solution of acylated glycosyl bromide (2.0 equiv) in CH_3CN (2.5 ml $mmol^{-1}$) was added to the turbid reaction mixture that was then stirred at 70 °C until TLC analysis indicated that the reaction was complete. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded the target compound.

4.1.10
General Procedure for Synthesis of Sialyl Thioglycosides Using TMSSMe and TMSOTf [165]

To a solution of methyl 2,4,7,8,9-penta-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-glycero-α,β-D-*galacto*-non-2-ulopyranosonate (1.0 equiv) and freshly activated 4 Å powdered molecular sieves in 1,2-dichloroethane (2.0 ml $mmol^{-1}$) was added TMSSMe (1.4 equiv) and TMSOTf (0.75 equiv). The reaction mixture was stirred for 4.5 h at 50 °C and a further 16 h at room temperature. The solution was filtered through Celite and washed with dichloromethane. The filtrate was washed with saturated aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded methyl [methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-2-thiol-D-glycero-α,β-D-*galacto*-non-2-ulopyranosid]onate as α/β mixture (1 : 1).

4.1.11
General Procedure for Activation of Thioglycosides with Ph_2SO/Tf_2O [87,99]

To a solution of thioglycoside (1.0 equiv), Ph_2SO (2.8 equiv) and TTBP (3.0 equiv) in dichloromethane (4.0 ml $mmol^{-1}$) was added trifluoromethanesulfonic anhydride (1.4 equiv) at −60 °C under an argon atmosphere. The reaction mixture was

stirred for 5 min, after which a solution of the glycosyl acceptor (1.5 equiv) in dichloromethane (2.0 ml $mmol^{-1}$) was added. The mixture was stirred at −60 °C for 1 h, after which it was slowly warmed to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded the product.

4.1.12
General Procedure for Activation of Thioglycosides with BSP/TTBP/Tf_2O [85]

To a solution of thioglycoside (1.0 equiv), 1-benzenesulfinyl piperidine (1.0 equiv), TTBP (2.0 equiv), and freshly activated 3 Å powdered molecular sieves in dichloromethane (25.0 ml $mmol^{-1}$) was added trifluoromethanesulfonic anhydride (1.1 equiv) at −60 °C under an argon atmosphere. The reaction mixture was stirred for 5 min, after that a solution of the glycosyl acceptor (1.5 equiv) in dichloromethane (4.0 ml $mmol^{-1}$) was added. The reaction mixture was stirred at −60 °C for 2 min, after that it was slowly warmed to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded the product.

4.1.13
General Procedure for Activation of Sialyl Thioglycosides with NIS/TfOH [165,166]

To a solution of sialyl thioglycoside (3.0 equiv), glycosyl acceptor (1.0 equiv) and freshly activated 3 Å powdered molecular sieves in MeCN (30.0 ml $mmol^{-1}$) was added NIS (6.0 equiv) and TfOH (0.6 equiv) at −35 °C under an argon atmosphere. The reaction mixture was stirred for 5 min until TLC analysis indicated that the reaction was complete. The solution was filtered through Celite and washed with dichloromethane. The filtrate was washed with aqueous $Na_2S_2O_3$ (20%) and H_2O. The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated to dryness. Purification of the crude product by column chromatography over silica gel afforded the product.

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4.2
Sulfoxides, Sulfimides and Sulfones

David Crich, Albert A. Bowers

4.2.1
Introduction

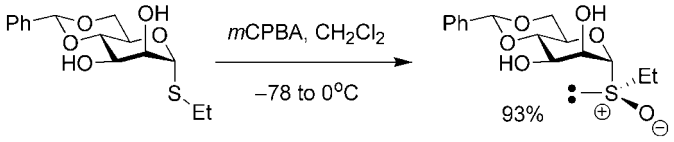
The combination of high reactivity and mildness of the reaction conditions renders the sulfoxide method one of the most powerful glycosylation procedures, and it is surprising that it has not been more widely adopted since its introduction in 1989 [279]. However, despite the fact that this method is a relative newcomer in the glycosylation arena, it has been more closely scrutinized than any other protocol in terms of its mechanism, and so is one of the better understood reactions [135,280,281]. All major classes of glycosidic bond have been successfully prepared by the sulfoxide method with the single exception of sialic acid glycosides. The related glycosyl sulfimides, sulfones and cyclic sulfites have been much less extensively studied compared to glycosyl sulfoxides.

The field has been reviewed [282,283] most recently and comprehensively in 2004 when extensive tables of examples and numerous experimental parts were provided [86].

4.2.2
Donor Preparation

4.2.2.1 Sulfoxides

Glycosyl sulfoxides are generally shelf-stable entities that are readily prepared by the oxidation of the parent thioglycosides (discussed in Section 4.1) [284]. It may be that the additional step required to convert a thioglycoside into a sulfoxide deters some in the field, but in reality this is no more than is needed to convert typical anomeric esters or silyl ethers into the corresponding hemiacetals and then to imidate esters. Historically, Micheel and Schmitz were the first to prepare a glycosyl sulfoxide by the oxidation of ethyl α-D-thioglucopyranoside with wet hydrogen peroxide. This reaction resulted in high yields of a single diastereomer at the sulfur center, the

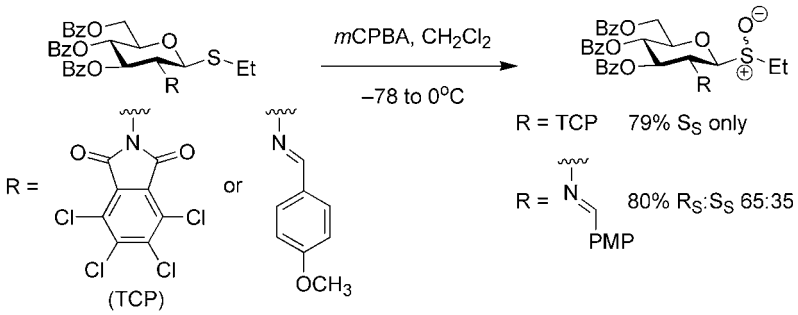


Scheme 4.29 Diastereoselective sulfoxide formation in the axial series.

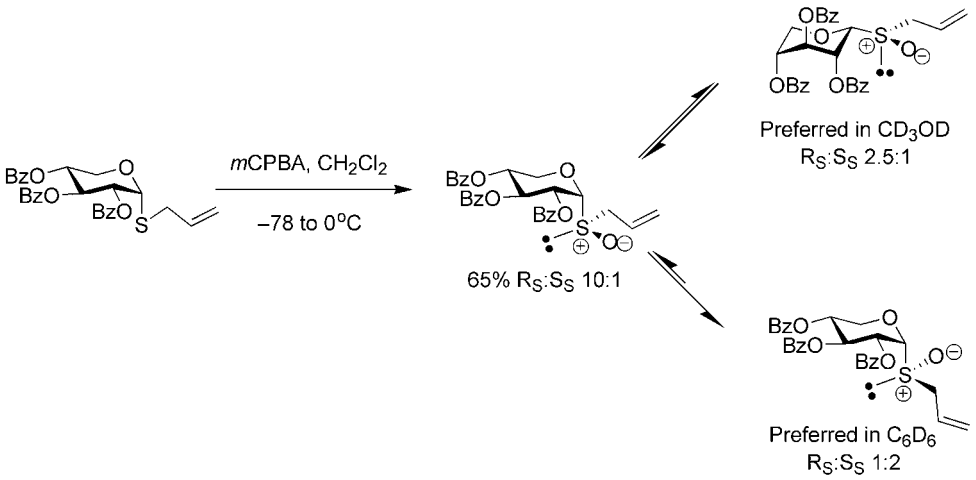
stereochemical sense and rationale for which were not determined at that time. Subsequently, it was found that high selectivity is the norm in the oxidation of axial thioglycosides to the corresponding sulfoxides, and it has been suggested that this is a consequence of the differential shielding of the two lone pairs imposed by the *exo*-anomeric effect, compounded by the steric contributions of the C-2 substituent (Scheme 4.29) [285–289]. In the equatorial series, where both lone pairs are exposed, selectivities are much lower, not withstanding the *exo*-anomeric effect, and depend to a greater extent on the configuration and the nature of the substituent at C-2 (Scheme 4.30) [75,288,290,291].

In contrast to the kinetic selectivities obtained by the oxidation of thioglycosides, thermodynamic selectivities were obtained in a series of *S*-allyl glycosyl sulfoxides by taking advantage of the allyl sulfoxide–allyl sulfenate equilibrium. Occasionally, the pyranose ring conformation is seen to be dependent on the configuration at sulfur. For example, the oxidation of allyl tri-*O*-benzoyl-thio-α-D-xylopyranoside with *m*CPBA in dichloromethane selectively gave (*R*)-sulfoxide, which was crystallographically and spectroscopically shown to adopt the inverted $^1C_4$ conformation. On heating in benzene, the inversion of stereochemistry at sulfur was observed along with a return to the $^4C_1$ conformation. In methanolic solution, the (*R*)-configuration and the $^1C_4$ conformation were preferred thermodynamically, reflecting the increased steric bulk of the solvated sulfoxide (Scheme 4.31). In the more commonly studied hexose sugars, the $^4C_1$ conformation is typically retained regardless of the configuration at sulfur [288].

In addition to the standard *m*CPBA, many oxidants have been applied in the conversion of thioglycosides into glycosyl sulfoxides, including sodium metaperio-



Scheme 4.30 Protecting-group-dependent stereoselectivity in the equatorial series.

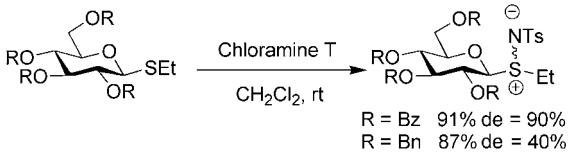


Scheme 4.31 Sulfoxide equilibration and pyranose ring inversion.

date [287], perbenzoic acid [292], OXONE® [287,293], urea/H_2O_2 complex [76], H_2O_2/acetic acid [294] and magnesium monoperoxyphthalate (MMPP)/wet THF [285,295]. All of these provide varying degrees of improvement over the common problems of the *m*CPBA oxidation: (1) need for low temperatures (−78 to −30 °C), (2) removal of the by-product *m*-chlorobenzoic acid and (3) overoxidation to the sulfone [75,279,296]. In this regard, it is noteworthy that *t*-butyl hydrogen peroxide, OXONE® and H_2O_2/HOAc achieve rapid oxidations at room temperature with little observance of sulfone by-products when employed with SiO_2 as a solid support [76,297]. The H_2O_2/HOAc/SiO_2 protocol has been applied effectively on the kilogram scale [298]. Protic, perfluorinated solvents, such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), have also been shown to suppress the formation of sulfone by-products when used in conjunction with 30% H_2O_2 [299,300]. Quantum mechanical calculations have been used to rationalize this effect in terms of the acidity of HFIP, which appears appropriately tuned to activate the oxidant while simultaneously deactivating the sulfoxide products, both through hydrogen bonding [299]. Recent work has demonstrated that MMPP is an effective reagent for the rapid conversion of thioglycosides into sulfoxides in dichloromethane when used in conjunction with microwave irradiation [301].

Methods for indirect oxidation have also been developed. The combination of KF/*m*CPBA in acetonitrile and water has been used to generate KOF·CH_3CN reagent, a mild and selective oxidant that reacts at 0 °C with no overoxidation [78]. This reagent functions by providing a fluorosulfonium ion intermediate, which is hydrolyzed in the presence of water to the desired sulfoxides. As a result of the indirect oxidation method, the typical stereoselectivity of *m*CPBA-type oxidations is not observed here. The KOF·CH_3CN oxidant is similar in scope and mechanism to 1-fluoropyridinium triflates, Selectfluor® [302] and the more classical *t*-butyl hypochlorite [288].

Typically, armed thioglycosides are more rapidly converted into sulfoxides than their disarmed congeners, irrespective of the oxidant used.



Scheme 4.32 Preparation of sulfimides with chloramine T.

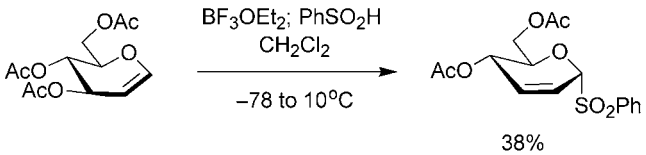
4.2.2.2 **Sulfimides**

The glycosyl sulfimides are prepared by the oxidation of thioglycosides with chloramine T (Scheme 4.32) [303,304]. This method can be plagued by side formation of sulfoxides, possibly resulting from the hydrolysis of intermediates by adventitious water. This tends to be more problematic with armed thioglycosides than with disarmed ones, and the *S*-ethyl moiety is more readily oxidized than the *S*-phenyl moiety. Similar to the preparation of sulfoxides, the oxidation to sulfimides results in high diastereoselectivities at the stereogenic sulfur, but the configuration of the major isomer is yet to be determined [304]. As with the sulfoxides [291], diastereoselectivity in the equatorial series is strongly dependent on the protecting group at O-2 [304]. Because of their intrinsic instability, sulfimides are generally prepared and glycosidated without intervening purification.

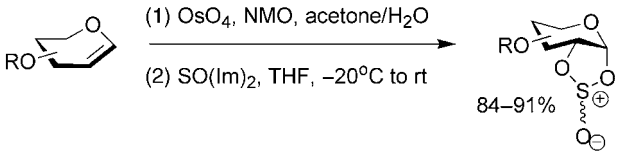
4.2.2.3 **Sulfones**

Although the exhaustive oxidation of thioglycosides with peracids is the standard entry into the glycosyl sulfones [305–308], they have also been produced from glycals and lactols [307]. From the glycal, the Ferrier reaction with benzenesulfinic acid proceeds readily at room temperature for standard armed protecting-group patterns. The disarmed glycals require activation with a Lewis acid such as BF_3OEt_2 (Scheme 4.33) [307,309].

Alternatively, lactols react with benzenesulfinic acid in the presence of $CaCl_2$ to yield the sulfones, again at room temperature [307,309]. In the axial series, the bulk of the sulfone group is such that the $^4C_1$ chair is not always the preferred conformation, and it has been shown that a twist-boat conformer is adopted in at least one instance [305]. Nevertheless, equilibration studies have shown that the sulfonyl group has a small anomeric effect and that the 'axial' anomer is preferred [310].



Scheme 4.33 Formation of sulfones by Ferrier reaction.



Scheme 4.34 Preparation of cyclic sulfites from glycols.

4.2.2.4 **Other Oxidized Derivatives of Thioglycosides**

A range of other sulfur(IV) and (VI) derivatives formally obtained by the oxidation of thioglycosides have been prepared, but they are apparently not employed to date in *O*-glycosylation reactions. These include glycosyl sulfenamides and sulfonamides, as well as sulfinates and sulfonates [289]. *S*-Glycosyl sulfenic acids have been prepared as transients by the *syn*-elimination of *S*-(2-cyanoethyl) glycosyl sulfoxides [311].

4.2.2.5 **1,2-Cyclic Sulfites**

The 1,2-cyclic sulfites are readily obtained from anomeric mixtures of 1,2-diols by reaction with sulfinyl diimidazolide as mixtures of *exo*- and *endo*-isomers at sulfur (Scheme 4.34) [312–314].

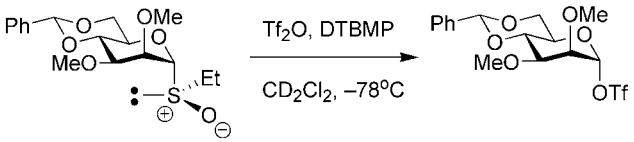
4.2.3 **Glycosylation**

4.2.3.1 **Sulfoxides**

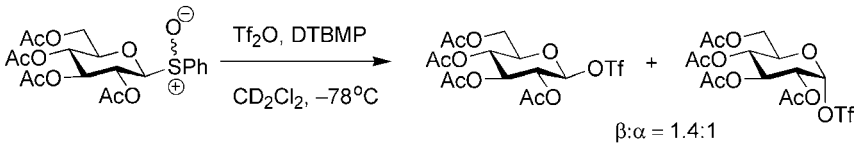
The most common activator for the glycosyl sulfoxides is trifluoromethanesulfonic anhydride (triflic anhydride), which, in the absence of nucleophiles, rapidly and cleanly converts most sulfoxides into the corresponding glycosyl triflates in a matter of minutes at −78 °C in dichloromethane solution [86,280,315,316]. In the more extensively studied mannopyranose series, only the α-mannosyl triflate is observed by low-temperature NMR spectroscopy (Scheme 4.35) [280]. In the glucopyranose series, mixtures of α- and β-triflates are observed, in which the α-anomer nevertheless predominates (Scheme 4.36) [280].

After the formation of glycosyl triflate, addition of an acceptor alcohol, still at low temperature, results in the rapid formation of the desired glycosidic bond.

In the critical area of β-mannoside synthesis [317–321], the evidence strongly suggests that α-mannosyl triflate serves as a reservoir for a transient contact ion pair (CIP), which is the glycosylating species (Scheme 4.37), although the possibility of an S_N2-like mechanism with an exploded transition state cannot be completely excluded [135]. In view of the probable operation of the contact ion-pair mechanism



Scheme 4.35 Glycosyl triflate formation in the mannose series.

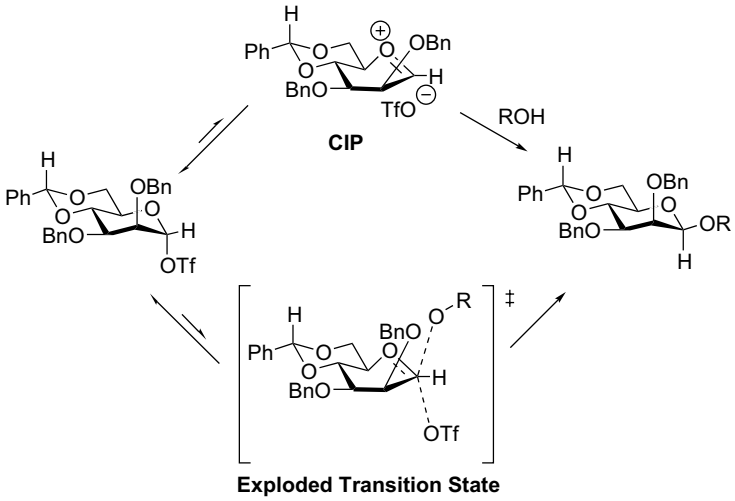


Scheme 4.36 Formation of an anomeric mixture of glucosyl triflates.

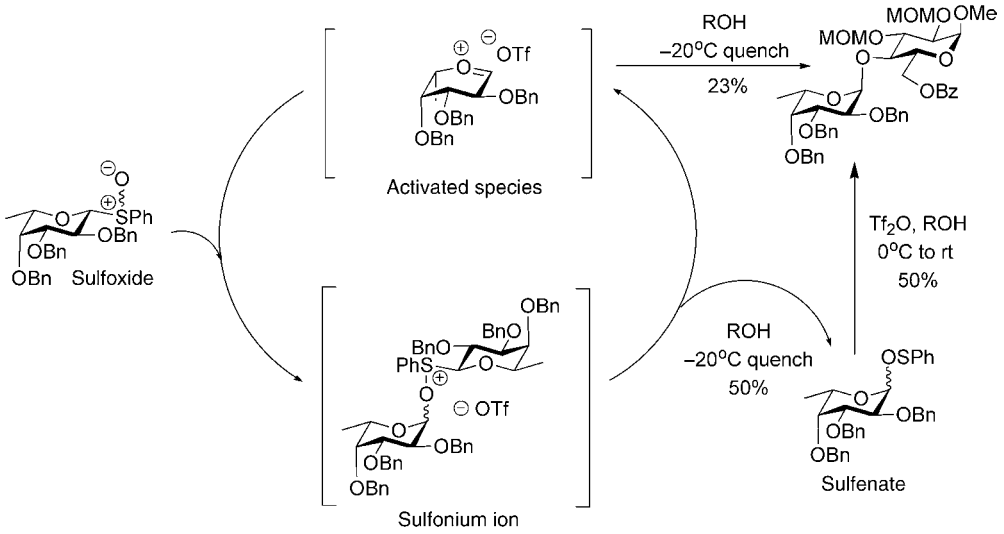
for the highly β-selective 4,6-*O*-benzylidene-protected mannose series, it is highly likely that closely related mechanisms are the rule in this type of glycosylation reaction. Differences in the selectivity likely arise from variations in the tightness of the contact ion pair and in the extent of equilibration with the solvent system.

When substoichiometric triflic anhydride is employed, an alternative mechanism comes into play, at least for the highly armed 2,3,4-tri-*O*-benzyl-fucose system [281]. Under these conditions, the oxacarbenium formed in the initial activation step of the sulfoxide is trapped not by the triflate anion but by another molecule of sulfoxide. Overall, this process results in the isomerization of the glycosyl sulfoxide to the corresponding *O*-glycosyl sulfenate, which is much less reactive as a donor and can be isolated (Scheme 4.38) [281]. *O*-Glycosyl sulfoxonium ions have subsequently been detected spectroscopically in the activation of hemiacetals with triflic anhydride and excess diphenyl sulfoxide, and are likely the intermediates in the activation of thioglycosides by the same combination [322]. The triflic-anhydride-catalyzed isomerization of glycosyl sulfoxides to *O*-glycosyl sulfenates can be suppressed by the inverse addition of the glycosyl sulfoxide to triflic anhydride [281].

When triflic anhydride is added to a preformed mixture of glycosyl sulfoxide and acceptor alcohol, it seems apparent that the first formed oxacarbenium ion is directly trapped by the alcohol, without the need for the implication of glycosyl triflates [75,280,323].

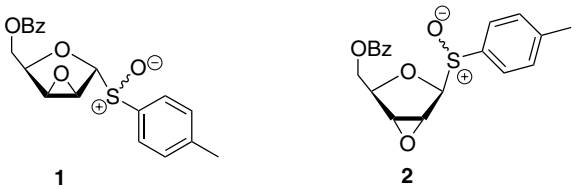


Scheme 4.37 Mechanism of β-mannosylation.



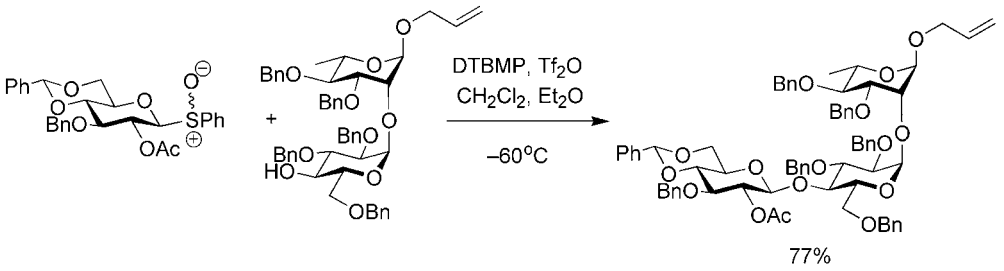
Scheme 4.38 Alternative mechanism for sulfoxide glycosylation.

Although most glycosyl sulfoxides are cleanly and rapidly activated by triflic anhydride at −78 °C, occasional exceptions are found. Examples include the 2,3-anhydro lyxo- and ribo-pentofuranosyl sulfoxides **1** and **2** that were demonstrated by NMR spectroscopy to not proceed to completion below −40 °C [324].

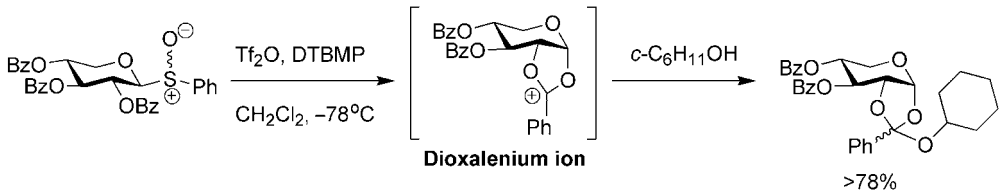


1 **2**

Although glycosyl triflates have been demonstrated to be intermediates with a number of armed donors, and even with disarmed donors not capable of neighboring-group participation, such as the sulfonate esters, typical disarmed donors with esters in the 2-position function in the anticipated manner through anchimeric



Scheme 4.39 Glycosylation with neighboring-group participation.



Scheme 4.40 Orthoester formation from a 2-*O*-benzoate.

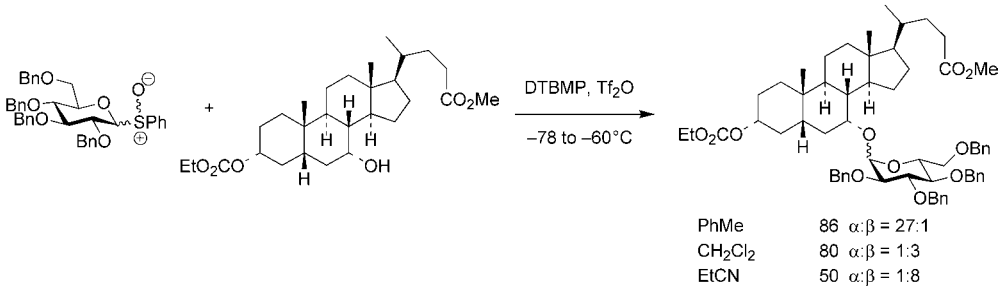
assistance (Scheme 4.39) [75,86,279,325]. Moreover, low-temperature ^{13}C NMR experiments enabled the clear identification of an intermediate dioxalenium ion and a subsequent orthoester in the activation of a benzoylated sulfoxide with triflic anhydride (Scheme 4.40) [326].

The stereodirecting nitrile effect [131,327–330] is also applicable to sulfoxide glycosylations with activation by triflic anhydride (Scheme 4.41) [279], even if selectivities remain modest for the formation of the 1,2-*cis*-equatorial class of glycosidic bond [329,331].

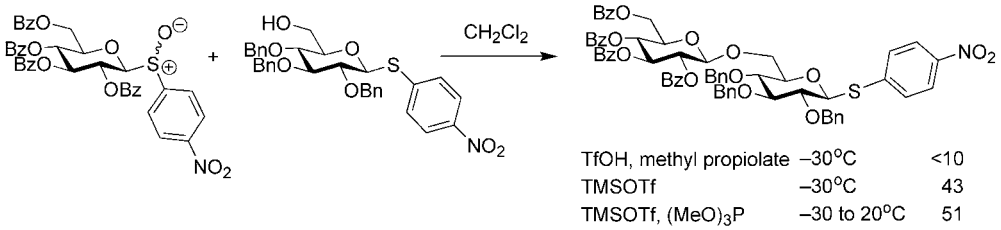
A variety of other activating systems have been employed for the promotion of sulfoxide-based glycosylation reactions, but none have been studied to the same extent as the triflic-anhydride-mediated reaction [86]. One of the most potent activators, benzenesulfenyl triflate, a by-product of the activation with triflic anhydride, has been shown to bring about rapid conversion of sulfoxides into glycosyl triflates [280]. Unfortunately, this reagent is unstable and has to be prepared *in situ* from silver triflate and benzenesulfenyl chloride.

Although the existence of glycosyl triflates has only been demonstrated for the triflic anhydride and benzenesulfenyl triflate promoter systems, presumably the same intermediates may be invoked on preactivation with other triflate-incorporating systems such as TMSOTf (Scheme 4.42) [332] and triflic acid (Scheme 4.43) [84,333].

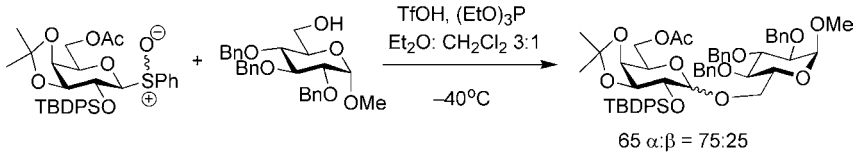
Molecular iodine has also been demonstrated to activate certain mannosyl sulfoxides albeit over extended periods of time and at higher temperatures. Mannosyl iodides may be involved as intermediates here, but *O*-iodyl mannosyl sulfonium salts have also been discussed [334]. The yield and selectivity of these reactions vary with respect to the potency of the iodonium ion source, IBr yielding much less



Scheme 4.41 Influence of solvent with an armed donor.



Scheme 4.42 Activation with triflic acid, TMS triflate.

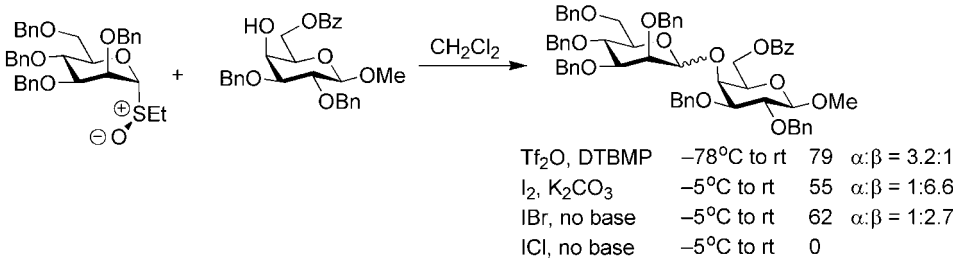


Scheme 4.43 Activation by means of triflic acid.

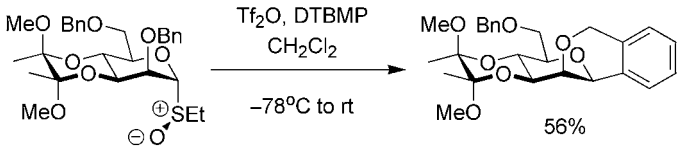
pronounced β-mannoside selectivity relative to molecular iodine and ICl affording somewhat unreactive mannosyl chloride (Scheme 4.44).

The combination of dicyclopentadienylzirconium dichloride and silver perchlorate activates armed glycosyl sulfoxides in dichloromethane between −20 °C and room temperature, but only very simple acceptors were studied [335]. Other Lewis and Brønsted acids studied include the environmentally benign europium, lanthanum and ytterbium triflates [336], certain polyoxometallates [337], sulfated zirconia [338] and Nafion H [338].

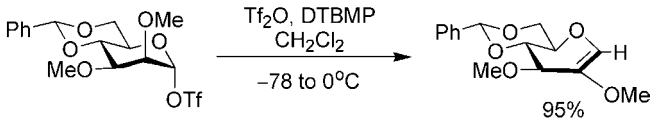
It has been demonstrated that the warming of glycosyl triflates above the decomposition temperature (which varies according to structure) results in the formation of two types of products, both of which appear to arise from the oxacarbenium ion. One pathway involves cyclization onto the O-2 protecting group, as in the example shown in Scheme 4.45 [339], whereas the other is deprotonation resulting in the formation of a glycal-type derivative, as shown in Scheme 4.46 [280]. As the temperature at which such by-products form for any given substrate can be readily



Scheme 4.44 Activation with iodine and interhalogen compounds.



Scheme 4.45 Trapping of the oxacarbenium ion by a 2-*O*-benzyl ether.

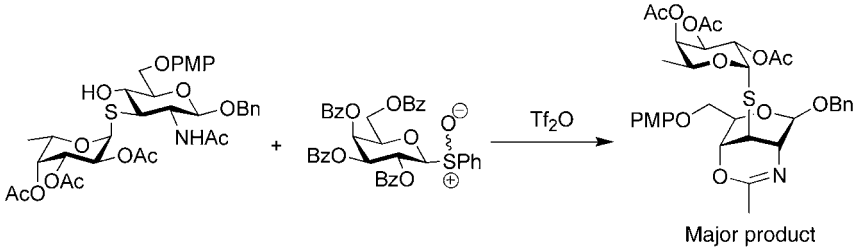


Scheme 4.46 Decomposition with glycal formation.

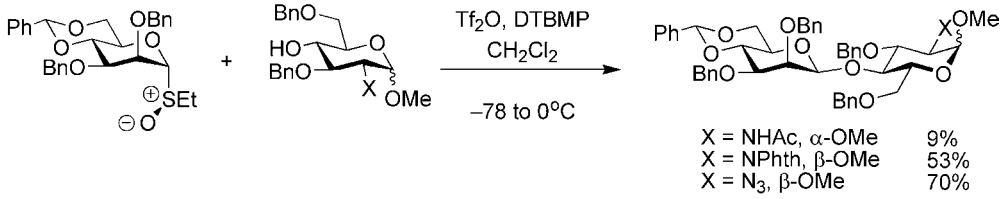
ascertained by a simple variable temperature NMR experiment, these side reactions are easily avoided in practice.

The presence of strongly nucleophilic groups in either the donor or the acceptor can be problematic in sulfoxide-type glycosylations when activation is conducted with triflic anhydride. The most common culprit is the amide group [340,341], which is illustrated by the formation of a dihydrooxazine when a 3-acetamido alcohol was employed as acceptor (Scheme 4.47) [342]. Self-evidently, acceptor-based problems of this type could be avoided by the preactivation of the sulfoxide with triflic anhydride.

In comparative studies, it has been shown that the azide group is a better surrogate for the acetamido moiety than the phthalimido system (Scheme 4.48) in sulfoxide-type couplings [340]. Subsequent work with trichloroacetimidates, however, suggests that the *N*-trichloroethoxycarbamate group should also function well [343].



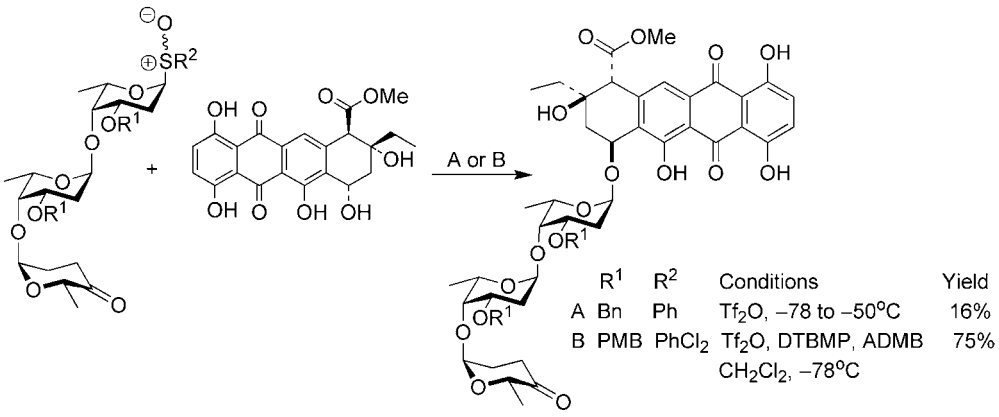
Scheme 4.47 Activation of an amide with triflic anhydride.



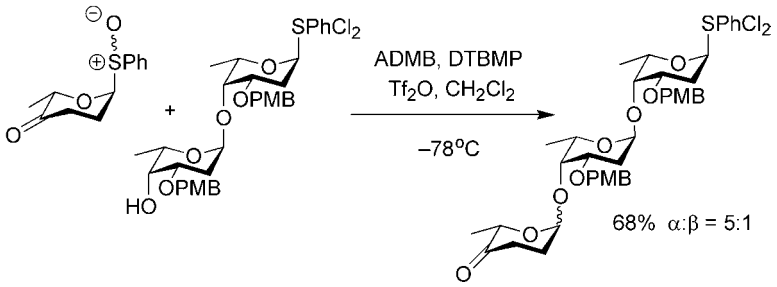
Scheme 4.48 Comparative study of nitrogen protecting groups.

The problem of the nucleophilicity of amides in glycosylation reactions is not limited to the sulfoxide method and has been shown to result in the formation of glycosyl imidates from intermolecular reaction with activated donors. It appears that this problem may be suppressed by the prior silylation of the amide [348,349]. Accordingly, it may be sufficient to operate the sulfoxide method with an excess of triflic anhydride when amides are present so as to convert all amides into *O*-triflyl imidates, which are then hydrolyzed on work-up. Despite these problems, several examples have been published of successful sulfoxide glycosylation reactions with acceptors carrying remote peptide bonds [344,345] and with donors coupled to resins via amide-based linkages [346,347], with no apparent problems reported. Sulfonamides and tertiary amides appear to be well tolerated by the sulfoxide method [340,350].

Further sources of potential problems in sulfoxide glycosylations are the electrophilic by-products generated on activation. These include the sulfenyl triflates and the products of their own reaction with glycosyl sulfoxides [280]. Unavoidable electrophiles of this type may result in the prior activation of acceptor-based sulfoxides, thioglycosides [351] and some [352], but not all [353], pentenyl glycosides. A number of scavengers have been developed to circumvent problems of this kind. Thus, methyl propiolate was first employed to this end in a one-pot synthesis of ciclamycin 0 trisaccharide [84], with the alkyne acting as an effective trap for sulfenic acid. Alkynes can also serve to capture electrophiles generated on activation of sulfoxides with triflic acid, and so prevent them from reacting prematurely with acceptor-based sulfoxides. However, it was shown that the dehydration of two molecules of sulfenic acid to the anhydride competes effectively with trapping by the alkyne and that the molecule of water generated in this process reacts effectively with the activated glycosylating species and lowers the overall yield (Scheme 4.49) [333]. The use of *tert*-butyl mercaptan as a nucleophile for the removal of sulfenic acid by-products presumably also suffers from the formation of a molecule of water [337]. More recent applications of the sulfoxide method have seen alkynes replaced by double bonds, particularly 4-allyl-1,2-dimethoxybenzene (ADMB), as effective scavengers of



Scheme 4.49 Influence of a sulfenate scavenger.



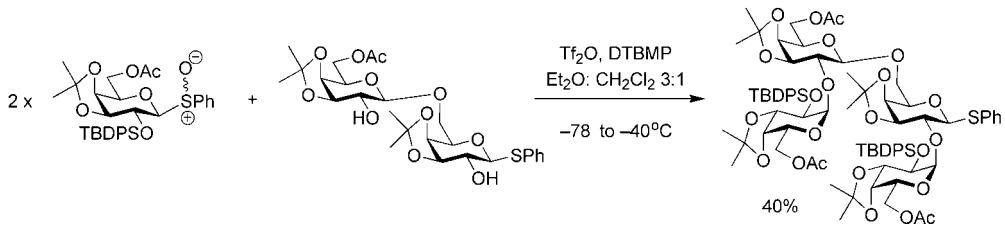
Scheme 4.50 Synthesis of the ciclamycin 0 trisaccharide assisted by a sulfenate scavenger.

electrophilic by-products (Scheme 4.49) [354]. Triethyl phosphite and trimethyl phosphite have also been employed as effective scavengers of electrophilic by-products generated in sulfoxide glycosylation reactions (Schemes 4.42 and 4.43) [332,333].

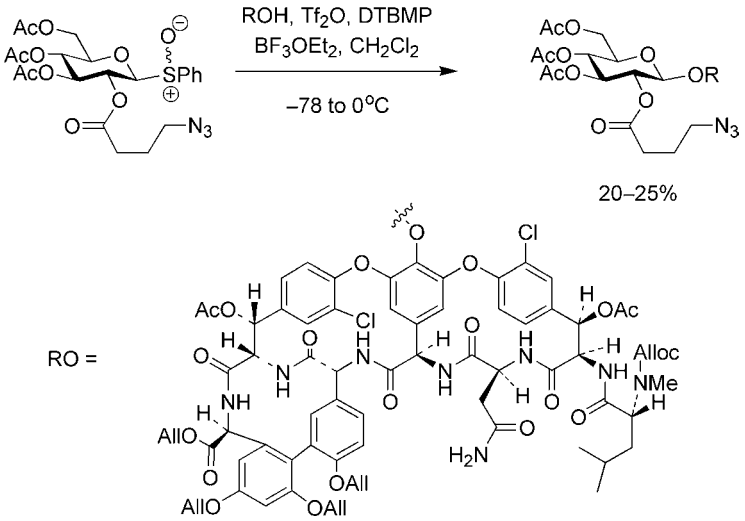
Problems with the reactivity of highly armed thioglycosides in the acceptor toward by-products from the sulfoxide activation may also be suppressed by the introduction of steric bulk in the *ortho*-positions of the thioglycoside. For example, a synthesis of the ciclamycin 0 trisaccharide was carried out with the assistance of ADMB as scavenger, leaving the 2,6-dichlorophenyl thioglycoside intact (Scheme 4.50) [354]. However, it should be noted that with less armed thioglycosides such precautions are not always necessary, and there are numerous sulfoxide glycosylations in which thioglycosides have been successfully carried [86], excellent examples of which are provided in Schemes 4.42 and 4.51 [355].

Hindered nonnucleophilic bases are typically added to sulfoxide glycosylations to buffer the acidic by-products. Classically, the 2,6-di-*tert*-butylpyridines have been employed for this purpose [86], but the more highly crystalline and easily handled 2,4,6-tri-*tert*-butylpyrimidine is finding increasing favor in this regard [356].

When neighboring-group participation is a feature of the glycosylation reaction, the use of a base in this manner frequently results in the isolation of orthoesters rather than the desired glycosides. In the case of activation by triflic anhydride, it is possible to avoid this problem by simply omitting the base. Alternatively, with more sensitive substrates, the hindered base may be retained and boron trifluoride etherate be added to promote the rearrangement of the orthoester to the glycoside, as in



Scheme 4.51 Multiple glycosylation in the presence of a thioglycoside.

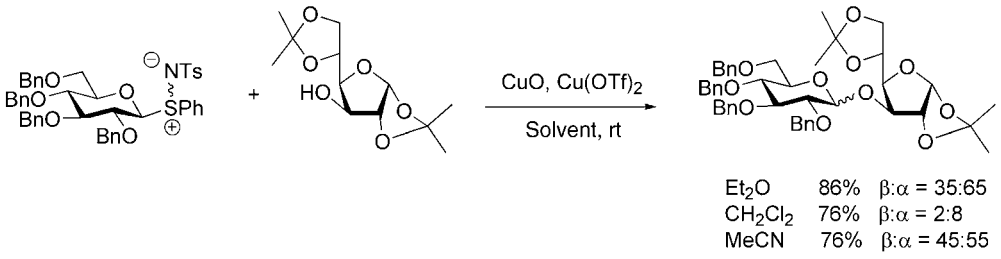


Scheme 4.52 Overcoming orthoester formation in the presence of a base.

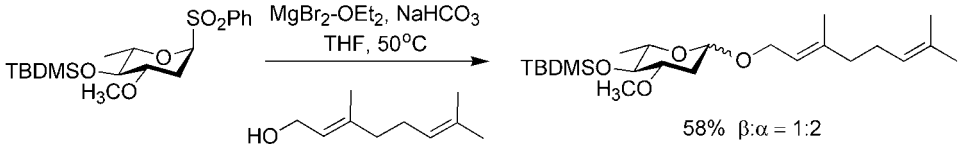
the example of Scheme 4.52. This example also illustrates the use of a hindered phenol as glycosyl acceptor and the ability to function in the presence of remote amide bonds [344]. The success of this protocol derives from the inability of the highly hindered bases to form amine–borane adducts. The 4-azido butanoyl protecting group could be selectively removed with triphenylphosphine.

4.2.3.2 **Sulfimides**

This class of donor is activated by soft Lewis acids, such as copper triflate at room temperature, and despite their hydrolytic instability, they appear inert to conditions of sulfoxide activation, TMSOTf or Tf_2O (Scheme 4.53). Activation is achieved with stoichiometric promoter in the presence of the acceptor alcohol, and although the mechanism has not been investigated, presumably it proceeds via coordination followed by collapse to a stabilized oxacarbenium ion. The method is compatible with standard glycosidation solvents such as dichloromethane, acetonitrile and diethyl ether, and ester-directed couplings do not lead to orthoesters, perhaps as a result of the presence of the Lewis acid promoter [303,304].



Scheme 4.53 Glycosylation with a sulfimide.



Scheme 4.54 Glycosylation with a phenyl sulfone.

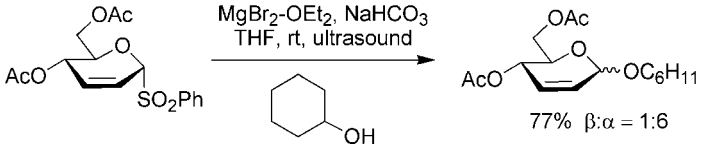
4.2.3.3 **Sulfones**

Both glycosyl phenyl sulfones and glycosyl 2-pyridyl sulfones have been employed as donors in glycosylation reactions. The phenyl sulfones are activated with $MgBr_2$ etherate in THF at room temperature (Schemes 4.54 and 4.55) [307,309]. Considerable rate enhancement has been reported either by heating at reflux or by the use of ultrasonication.

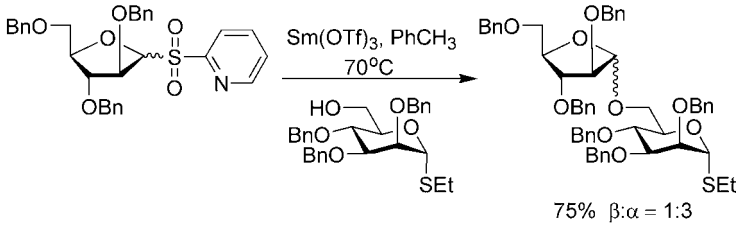
The 2-pyridyl sulfones have been activated with $Sm(OTf)_3$ in toluene at 70 °C. The reaction also proceeds in refluxing methylene chloride, albeit with slightly diminished yields (Scheme 4.56) [308]. The mechanism has not been studied in either case, but activation has been suggested to involve the complexation of the metal ion with the pyridyl nitrogen and one of the sulfur oxygens, followed by the cleavage of the C1−S bond leading to an oxacarbenium ion, for the pyridyl sulfones.

4.2.3.4 **Cyclic Sulfites**

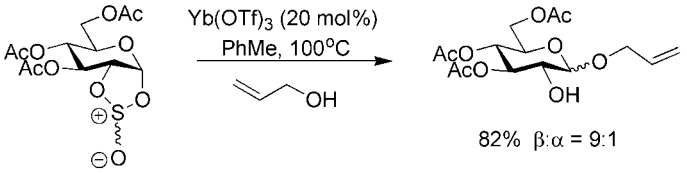
The cyclic sulfites were first found to react with lithium phenoxides as nucleophiles in DMF in a one-pot procedure commencing from the unprotected diol [357]. Subsequent work opened up this class of donor to alcohol nucleophiles in conjunction with the use of a Lewis acid, such as $Yb(OTf)_3$ or $Ho(OTf)_3$, to activate the donor in refluxing toluene (Scheme 4.57) [314,358,359]. The very high degree of β-selectivity observed in these reactions is consistent with an S_N2-like displacement of the sulfite oxygen.



Scheme 4.55 Glycosylation with a 2,3-unsaturated glycosyl sulfone.



Scheme 4.56 Stability of a thioglycoside toward sulfone activation.



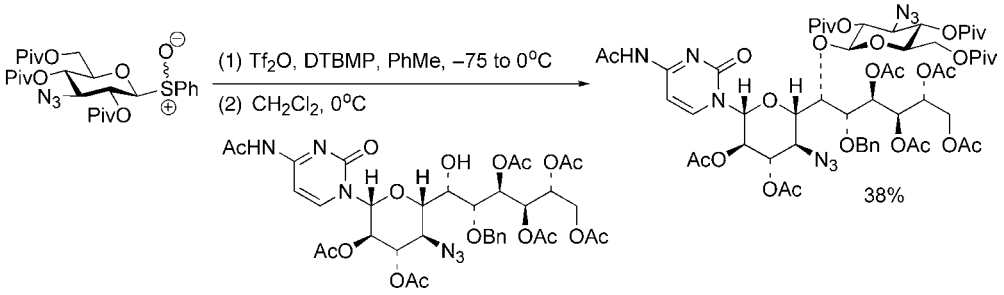
Scheme 4.57 Glycosylation with a cyclic sulfite.

4.2.4
Applications in Total Synthesis

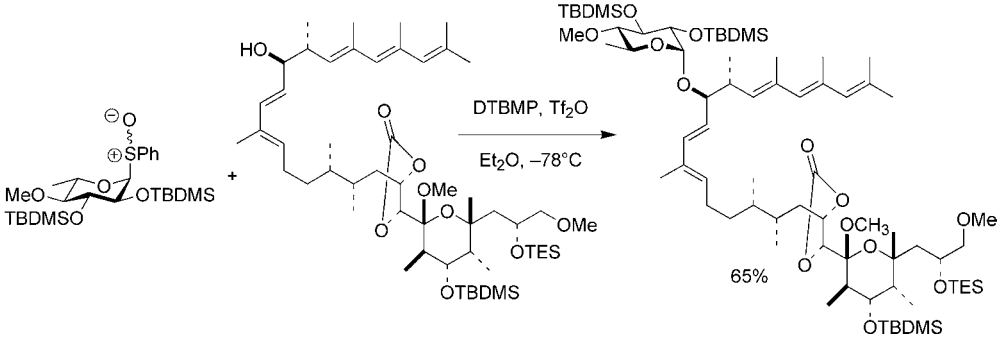
In addition to the examples laid out in the above schemes, the sulfoxide method has been employed in the synthesis of numerous natural products. The examples presented below are chosen to illustrate the power of the method and the broad functional group compatibility.

The glycosylation of an unreactive alcohol, for which several other methods were reported to have failed, constituted a key step in the synthesis of hikizimycin (Scheme 4.58) [360].

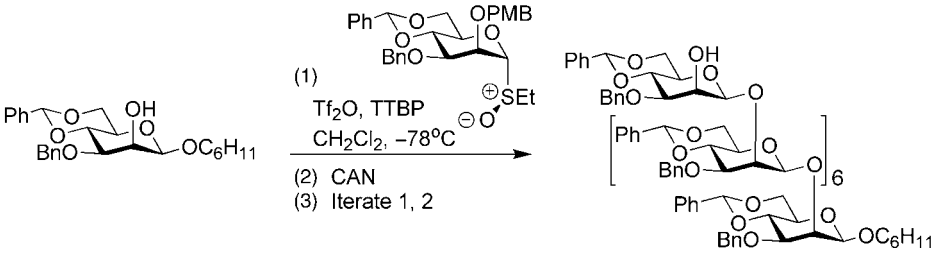
A remarkable example of the compatibility of the sulfoxide method with polyene functionality is taken from a key step in the synthesis of apoptolidin (Scheme 4.59) [361].



Scheme 4.58 Glycosylation of hindered substrate in a hikizimycin synthesis.



Scheme 4.59 Tolerance of polyene functionality *en route* to apoptolidin.



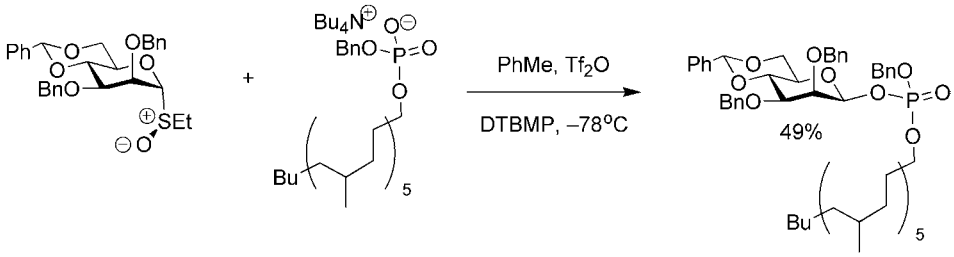
Scheme 4.60 Synthesis of a β-mannan.

The sulfoxide method was employed in the direct synthesis of a β-1,2-mannooctaose (Scheme 4.60) [362–364]. The synthesis of a β-mannosyl phosphoisoprenoid illustrates the possibility of employing even such weak nucleophiles as phosphates (Scheme 4.61) [365]. Both syntheses rely on the presence of 4,6-*O*-benzylidene acetal, and its effect on the covalent triflate–contact ion-pair equilibrium [366,367], to influence the stereochemistry of the glycosylation process [295,323].

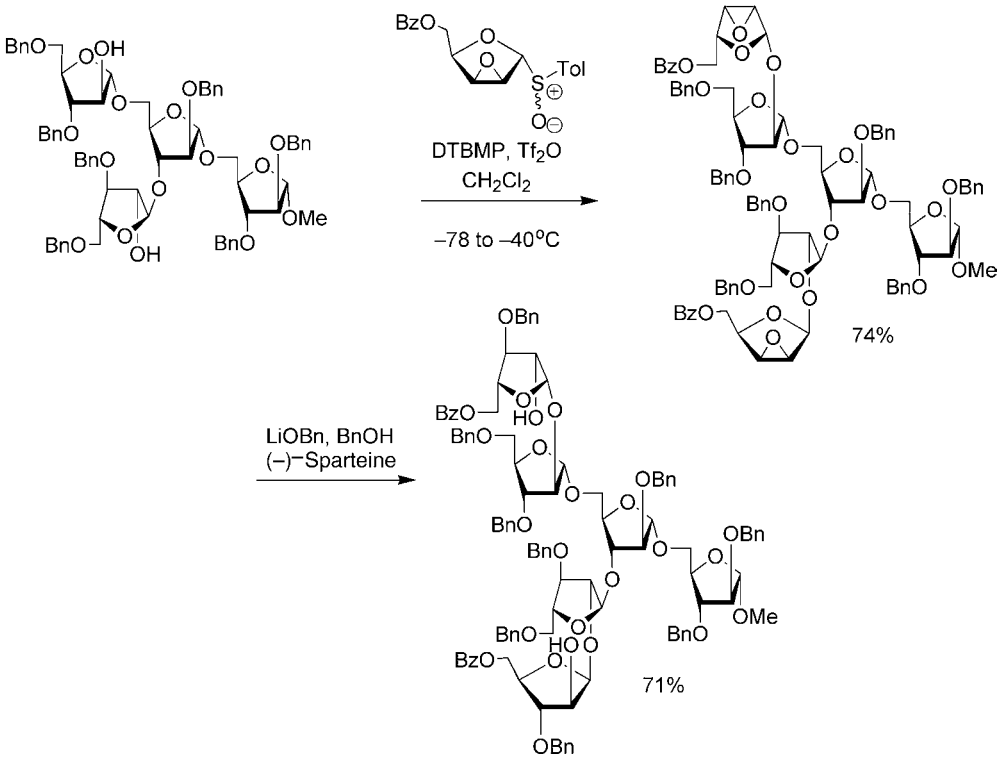
In the furanoside field, the introduction of the last two β-arabino units of a hexasaccharide motif from a bacterial cell wall arabinogalactan was achieved by the sulfoxide method with stereocontrol achieved because of the presence of the 2,3-anhydro group (Scheme 4.62) [368]. More recently, the direct stereocontrolled synthesis of arabinofuranosides has been achieved by the sulfoxide method with the aid of a 3,5-*O*-(di-*tert*-butylsilylene)-protected donor [369].

Related 2,3-anhydrogulofuranosyl sulfoxides have been employed in the stereocontrolled synthesis of β-arabinofuranosides [370]. The epimeric α-arabinofuranosides have also been synthesized by the sulfoxide method, with the aid of the neighboring-group participation [371,372].

The crown jewel in the application of the sulfoxide method to the assembly of natural products is the synthesis of a pentasaccharide from the antibiotic moenomycin A, wherein each glycosidic bond was formed in a stereocontrolled manner by one variant or another by the sulfoxide method (Scheme 4.63) [373].



Scheme 4.61 Synthesis of a β-mannosyl phosphoisoprenoid.



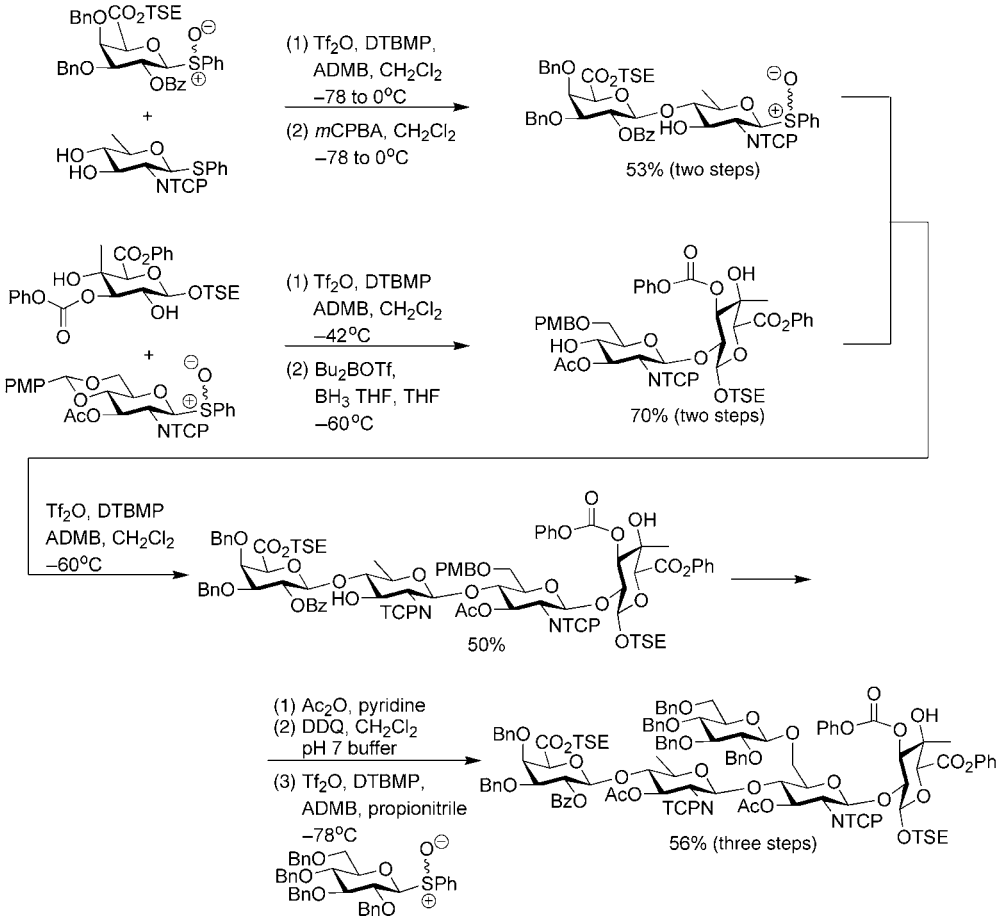
Scheme 4.62 Stereocontrolled β-arabinofuranoside formation in an arabinogalactan synthesis.

4.2.5 Special Topics

4.2.5.1 Intramolecular Aglycone Delivery (IAD)

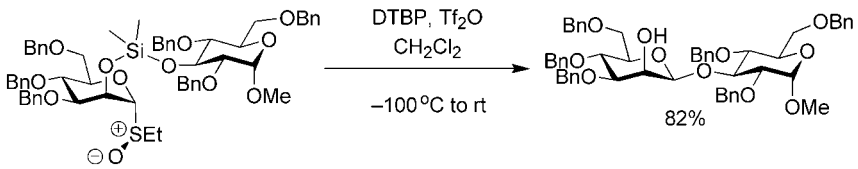
The sulfoxide method has been applied to the concept [319,374] of intramolecular aglycone delivery for the formation of β-mannosides by means of a silylene linker. In the original work, the acceptor and a thioglycoside donor were joined by means of a silylene group before the oxidation to the sulfoxide [141]. However, it was later found that the preformed sulfoxide was tolerated by the chemistry for the introduction of the linker [286,375]. The intramolecular aglycone delivery step was shown to function effectively for the transfer of the donor to the 2-, 3- and 6-position of glucopyranosides, as exemplified in Scheme 4.64.

Problems were encountered, however, when the transfer to the 4-position of glucopyranosides was investigated. In these cases, the major product was that of trapping of the activated donor by the benzyloxy group at the 6-position, via a nine-membered cyclic transition state, with concomitant loss of the benzyl group (Scheme 4.65). Interestingly, no such problems were described for closely related intramolecular delivery of the glucose and glucosamine 4-OH groups with other linkers and methods of donor activation [319,374,376].

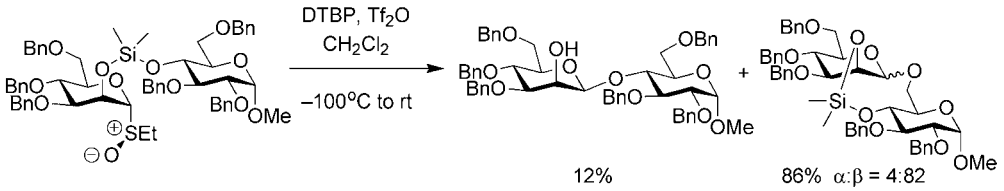


Scheme 4.63 Multiple use of the sulfoxide glycosylation in the synthesis of the moenomycin A pentasaccharide.

Sulfoxide-mediated intramolecular aglycone delivery has been conducted with a temporary linker formed *in situ* by the reaction of lanthanide triflates with the donor and acceptor-based alcohols (Scheme 4.66) [336]. However, as the selectivities recorded were modest, it has to be assumed that intermolecular glycosylation was an important side reaction in this chemistry.



Scheme 4.64 Sulfoxide-mediated intramolecular aglycone delivery.



Scheme 4.65 Diverted intramolecular aglycone delivery.

Additional aspects of intramolecular aglycone delivery are discussed in Section 5.4.

4.2.5.2 Polymer-Supported Synthesis

Sulfoxide donors have been employed in the glycosylation of soluble and insoluble polymer-supported glycosyl acceptors, and the area has been reviewed [86,283].

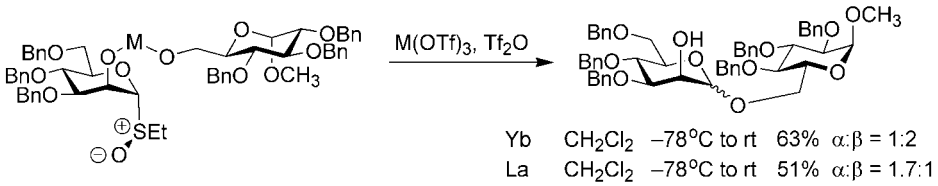
In the original report, which employed a thioglycoside linker to an insoluble cross-linked polystyrene resin, the donor carried a labile 6-*O*-triphenylmethyl ether protecting group such that after the treatment with acid the coupling could be iteratively operated (Scheme 4.67) [377]. In addition to the example given, a range of axial and equatorial glycosidic linkages to typical carbohydrate acceptors were formed in this manner [377]. This general method was also applied to the parallel synthesis of an approximately 1300-member combinatorial library of disaccharides using a split-and-pool technique, a tentagel resin and the thioglycoside-type linker [346].

In a later study, an insoluble Rink amide resin was employed with the linkage of the glucuronic-acid-based acceptor through an amide bond (Scheme 4.68) [347,378].

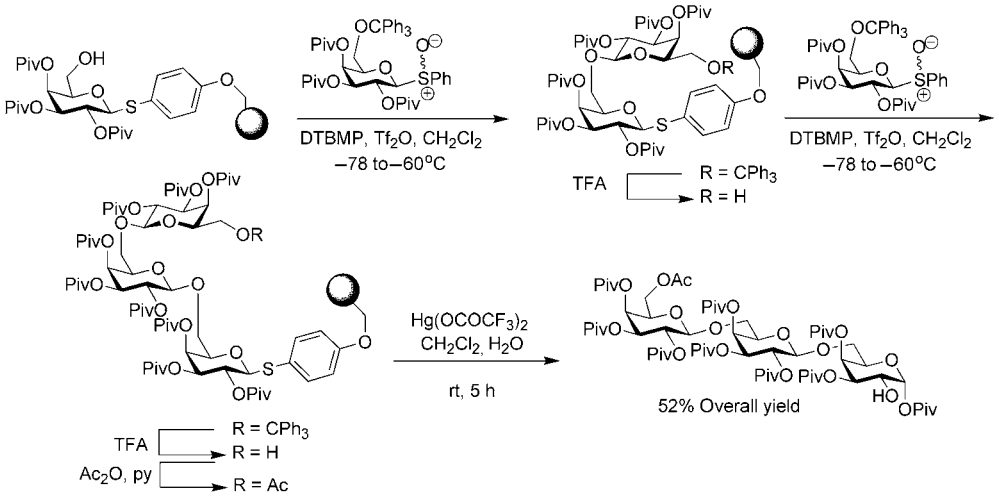
A soluble aminomethylated polyethylene glycol and a succinoyl linker were used to support a 9-fluorenylmethyl group for solution-phase glycosylation by the sulfoxide method. With the help of temporary protection by a 6-*O*-triphenylmethyl ether, the method could be carried out iteratively to form disaccharides (Scheme 4.69) [379].

4.2.5.3 Ring Closing and Glycosylation

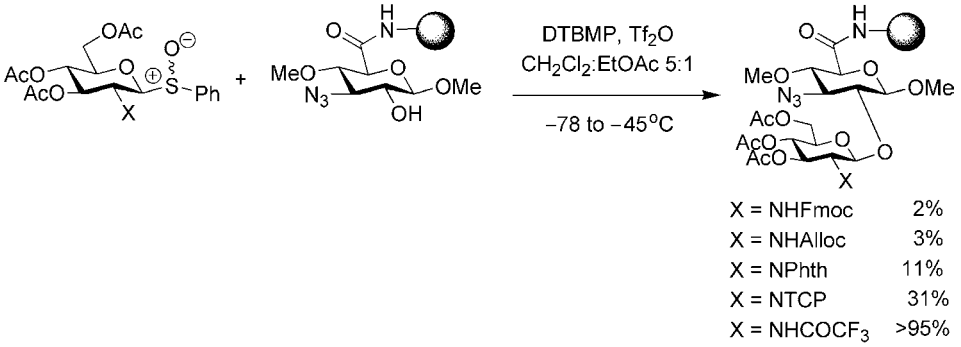
An elegant method for the formation of glycosidic bonds from acyclic dithioacetal monosulfoxides and glycosyl acceptors with triflic anhydride has been developed. This method takes advantage of the sulfenyl triflate generated from the reaction of



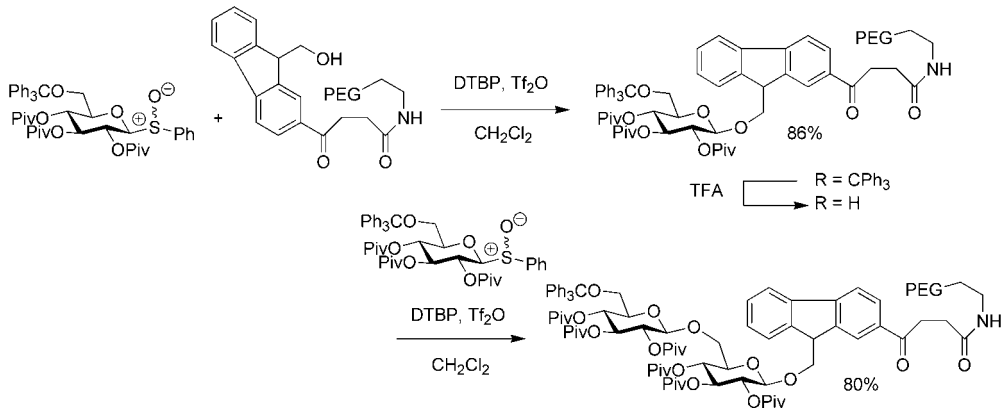
Scheme 4.66 Intramolecular aglycone delivery via metal complexes.



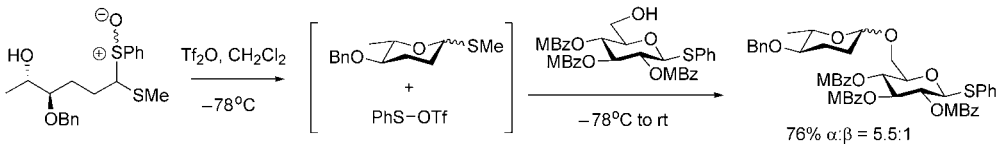
Scheme 4.67 Solid-phase oligosaccharide synthesis on a Merrifield resin.



Scheme 4.68 Solid-phase synthesis on a Rink resin.



Scheme 4.69 Disaccharide synthesis on a soluble polyethylene glycol support.



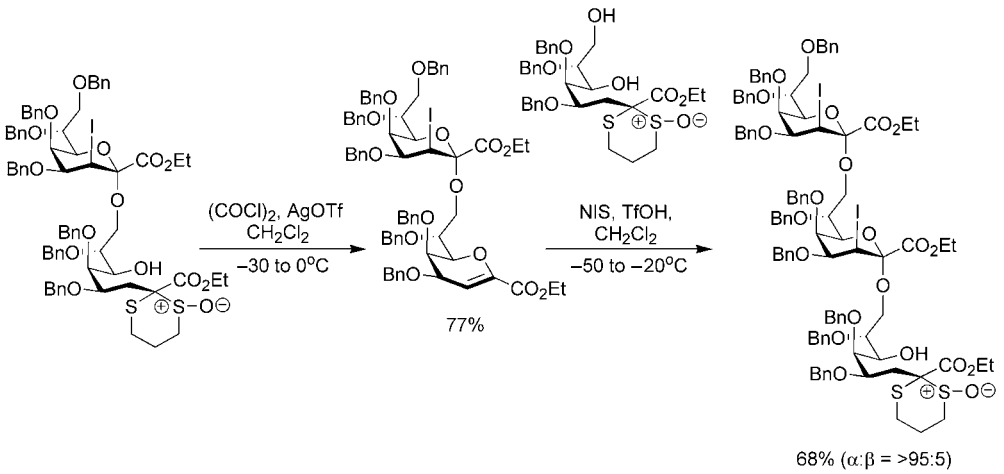
Scheme 4.70 Disaccharide synthesis by ring-closing glycosylation.

sulfoxide and triflic anhydride in the initial ring-closing step to bring about the activation of the intermediate thioglycoside for the coupling reaction (Scheme 4.70) [380].

A variation on this theme was applied to the synthesis of oligo-α-(2,8)-3-deoxy-D-manno-2-octulosonic acid derivatives. In this sequence, the monosulfoxide of α-keto ester-derived dithianes is activated with triflic anhydride resulting in the ring closure onto an adjacent alcohol and the elimination of the final sulfur residue. The glycal-like 2,3-unsaturated octulosonate ester generated in this manner subsequently serves as electrophile in an iodoalkoxylation reaction with a second molecule of the dithiane sulfoxide, thereby setting the stage for iteration of the entire sequence and synthesis of oligomeric derivatives (Scheme 4.71) [381].

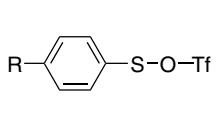
4.2.5.4 **Activation of Thioglycosides by Sulfoxides and Related Reagents**

The power of the sulfoxide method and the mildness of the conditions have stimulated the development of a number of reagents capable of activating simple thioglycosides under comparable circumstances. Benzenesulfenyl triflate **3** and the analogous *p*-toluenesulfenyl triflate **4** perform admirably in this respect [295,351,382,383], but the need to generate these unstable reagents *in situ* from the corresponding sulfenyl chlorides and silver triflate drove the search for more

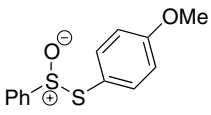


Scheme 4.71 Iterative ring-closing glycosylation approach to mannooctulsonic acid derivatives.

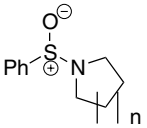
convenient reagents. The first among these was *S*-(methoxyphenyl)benzenethiosulfenate **5**, which in conjunction with triflic anhydride was capable of rapidly activating armed thioglycosides at −78 °C [384]. 1-Benzenesulfinylpiperidine **6** was subsequently developed [85] as a readily prepared [385] crystalline substance capable, together with triflic anhydride, of activating all but the most highly disarmed thioglycosides at −60 °C in dichloromethane. This reagent has been applied successfully in the stereocontrolled synthesis of a number of complex oligosaccharides [386,387] and in the polymer-supported synthesis of β-mannosides with the aid of a 4,6-*O*-polystyrylboronate-supported thiomannoside donor [388]. The success of the BSP method has spawned the development of a number of alternatives, all of which work in conjunction with triflic anhydride, including the liquid 1-benzenesulfinyl pyrrolidine **7**, which has a higher solubility at lower temperatures [385], a sulfenamide version **8** [389] and the apparently still more potent 1-benzenesulfinyl morpholine **9** [390]. The combination of diphenyl sulfoxide **10** with triflic anhydride also activates both thioglycosides [391,392] and 1-hydroxy sugars (hemiacetals) [393] under conditions comparable to the sulfoxide glycosylation method and is somewhat more potent than **6** and its variants toward strongly disarmed donors. Most recently, the combination of dimethyl disulfide **11** and triflic anhydride has been demonstrated to rapidly activate both armed and disarmed thioglycosides toward glycosylation at low temperatures [394].



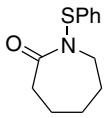
3: R = H
4: R = Me



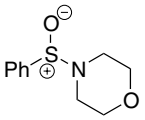
5



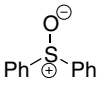
6: n = 2
7: n = 1



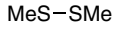
8



9



10



11

4.2.6 Experimental Procedures

4.2.6.1 General Procedure for the Preparation of Glycosyl Sulfoxides

The thioglycoside donor is dissolved in CH_2Cl_2 (~0.1 M) and cooled to −78 °C under an inert atmosphere. *m*CPBA (70 wt%, 1.2 equiv) is then added portionwise with minimal exposure to the atmosphere. The reaction mixture is warmed to room temperature over 1 h, at which time TLC shows the dissappearance of starting material and the formation of more polar compounds. The sulfoxides are purified by column chromatography over silica.

4.2.6.2 General Procedure for Sulfoxide Glycosidation

The sulfoxide donor (1.0 equiv) and 2,4,6-tri-*tert*-butylpyrimidine (2.0 equiv) are dissolved in dry CH_2Cl_2 (0.04 M) together with crushed 4-Å molecular sieves under argon and cooled to −78 °C. Tf_2O (1.2 equiv) is added and the solution is allowed to stir for ∼30 min. The acceptor (1.0 equiv) in CH_2Cl_2 (0.1 M) is then added dropwise. The reaction mixture is allowed to warm to −30 °C, when it is quenched by the addition of Et_3N and filtered through Celite. The solvent is removed and the crude mixture is directly purified by column chromatography on silica gel.

4.2.7 Conclusion

The sulfoxide method has been successfully applied to the formation of most common classes of glycosidic bond with the exception of the sialosides. The high yields and relative lack of sensitivity to steric hindrance in the acceptor evident from the examples presented more than outweigh the minor inconvenience of the extra step required to convert thioglycoside into sulfoxide. Mechanistically, the sulfoxide method is one of the easiest glycosylation reactions to study, making it one of the better understood methods and, therefore, one of the better candidates for rationale improvement. Taking all of these factors into consideration, it is to be expected that this method will continue to develop into one of the most widely applied and reliable glycosylation protocols.

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4.3
Xanthates, Thioimidates and Other Thio Derivatives

Wiesław Szeja, Grzegorz Grynkiewicz

4.3.1
Introduction

Carbohydrate derivatives, in which one or more of the oxygen atoms bonded directly to the carbon skeleton have been replaced by sulfur, are termed *thiosugars*. The placement of the sulfur atom at the anomeric position constitutes a special case, because thioglycosides, alkyl, aryl and heterocyclic, occupy a very important place as versatile glycosyl donors in glycosidation methodology. Anomeric thiocarbonyl compounds, on the contrary, have been less explored, although their potential and scope is likely to be similar.

The versatility of thiosugars in carbohydrate chemistry derives from the fact that the sulfur atom is a 'soft base' and is therefore able to react selectively with soft acids such as heavy-metal cations, halogens, alkylating reagents and carbonium ions. The oxygen-bearing groups, in relation to the former, are 'hard bases', which can be functionalized with 'hard acids', usually without affecting the thiofunction. The sulfur-bearing substituents at the anomeric center can be selectively activated with soft electrophilic promoters to form reactive glycosylating species. Thus, the thiosugars are useful building blocks for differentiating selected steps in the glycoside synthesis. The compounds, which constitute the scope of this chapter (Figure 4.1), add to this versatility because their activation conditions and reactivity differ from conventional alkyl and aryl glycosides, discussed in Section 4.1. Methods for their

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4.3
Xanthates, Thioimidates and Other Thio Derivatives

Wiesław Szeja, Grzegorz Grynkiewicz

4.3.1
Introduction

Carbohydrate derivatives, in which one or more of the oxygen atoms bonded directly to the carbon skeleton have been replaced by sulfur, are termed *thiosugars*. The placement of the sulfur atom at the anomeric position constitutes a special case, because thioglycosides, alkyl, aryl and heterocyclic, occupy a very important place as versatile glycosyl donors in glycosidation methodology. Anomeric thiocarbonyl compounds, on the contrary, have been less explored, although their potential and scope is likely to be similar.

The versatility of thiosugars in carbohydrate chemistry derives from the fact that the sulfur atom is a 'soft base' and is therefore able to react selectively with soft acids such as heavy-metal cations, halogens, alkylating reagents and carbonium ions. The oxygen-bearing groups, in relation to the former, are 'hard bases', which can be functionalized with 'hard acids', usually without affecting the thiofunction. The sulfur-bearing substituents at the anomeric center can be selectively activated with soft electrophilic promoters to form reactive glycosylating species. Thus, the thiosugars are useful building blocks for differentiating selected steps in the glycoside synthesis. The compounds, which constitute the scope of this chapter (Figure 4.1), add to this versatility because their activation conditions and reactivity differ from conventional alkyl and aryl glycosides, discussed in Section 4.1. Methods for their

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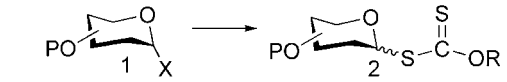
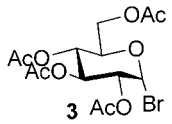
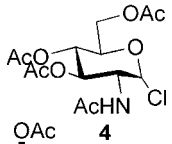
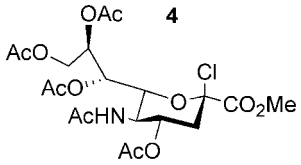




$EtOCS_2K$, EtOH, 90%, only-β [396]

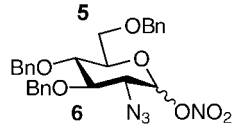


PTC: $EtOCS_2K$, AcOEt, Bu_4NHSO_4 (cat), 87–95%, only β [400]

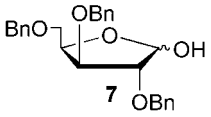


$EtOCS_2K$, EtOH, 71%, only α [397]

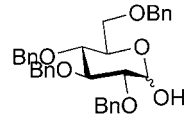
PTC: $EtOCS_2K$ [4], Bu_4NHSO_4 (cat), AcOEt, aq Na_2CO_3, 91%, only-α [400]



$EtOCS_2K$, EtOH, 43%, α:β, 1:6 [399]



PTC: TsCl, $EtOCS_2K$, Bu_4NBr(cat), aq NaOH [402]



$(iPrOCS_2)_2$, Bu_3P, toluene; 80%, α:β, 80:1 [403]

Scheme 4.72 Synthesis of *S*-glycosyl dithiocarbonates (glycosyl xanthates).

preparation and reactivity characteristics of particular thiocarbonyl systems that follow general rules have been previously reviewed [395].

4.3.2
Dithiocarbonates – Preparation and Application as Glycosyl Donors

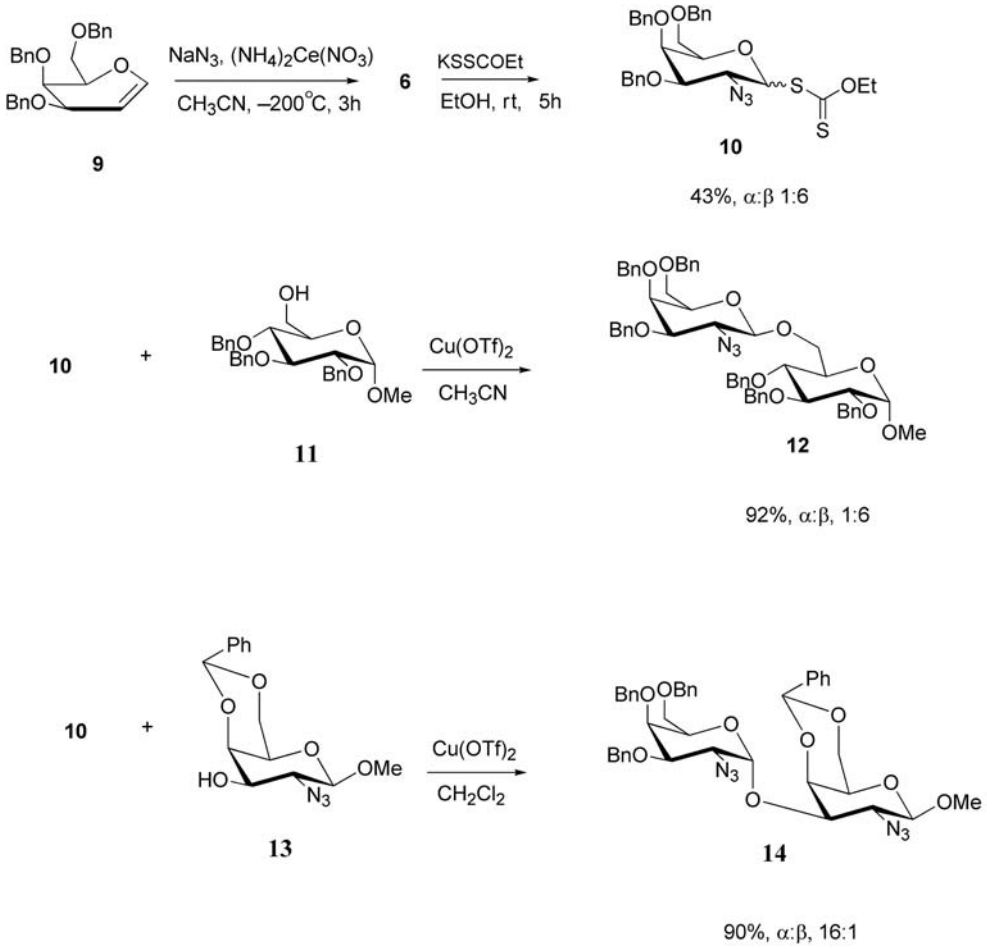
Glycosyl dithiocarbonates (xanthates) are attractive glycosyl donors because of their high reactivity in glycosylation reactions. Most procedures for the synthesis of dithiocarbonates involve reaction of per-*O*-acetylglycosyl halide **3** or **4** with

potassium ethoxydithiocarbonate or related thio reagent [396] as illustrated on Scheme 4.72. The synthesis of glycosyl xanthates and their application as glycosyl donors were done by Sinay and coworkers [397–399]. 2-(Ethoxy)dithiocarbonate (2-xantho) derivative of Neu5Ac had been synthesized from the 2-chloride **5** by the reaction with potassium ethoxydithiocarbonate in EtOH [397]. Sialyl xanthate is a stable crystalline material that has a long shelf life. Roy and coworkers demonstrated [400] that phase-transfer-catalyzed (*PTC*) nucleophilic displacement of a wide range of glycosyl halides could secure the entry into *S*-glycosyl xanthates. Per-*O*-acetylated glycosyl bromides or chlorides were selectively transformed into their corresponding *S*-glycosyl xanthates in high yield (91–98%) using tetrabutyl ammonium hydrogen sulfate (*TBAHS*) as the catalyst and ethyl acetate as the solvent with aqueous sodium carbonate as the counter phase. The substitution proceeded with complete inversion of the configuration. Substituents other than anomeric halides have also been employed for such syntheses. The azidonitration of tri-*O*-benzyl-D-galactal gave a mixture of anomeric nitrates of 2-azido-2-deoxy-D-galactopyranose **6** (Scheme 4.72). Treatment of the reaction mixture with *O*-ethyl-*S*-potassium dithiocarbonate led to the mixture of *O*-ethyl-*S*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranosyl) dithiocarbonates [399]. The common method for the synthesis of dithiocarbonates by displacement of an anomeric substituent is ineffective when applied to reactive glycosyl bromides, derivatives of 2-deoxysugars, because of the competing elimination reaction.

Transformation of 2-deoxysugar derivatives into glycosyl xanthates can be performed by the treatment of *O*-benzyl-protected hemiacetal derivative with diphenylphosphoryl chloride, followed by the reaction with *O*-ethyl potassium xanthate in the presence of a base (NaOH, PTC reaction or NaH in appropriate organic solvent). High yields and selectivities in such reactions were observed when using sodium hydride in anhydrous THF [401].

S-(Glycofuranosyl)-*O*-ethyl dithiocarbonates derivatives of L-arabinose, D-xylose **7** and D-ribose were conveniently prepared by treatment of *O*-benzyl-protected 1-OH pentoses with diphenylphosphoryl chloride and potassium *O*-alkyl dithiocarbonate under PTC conditions [402]. In these reactions, the initially formed glycosyl 1-*O*-diphenylphosphate reacts with sulfur nucleophile present in the organic phase in the form of ion pair with tetrabutylammonium ion. An efficient, simple 'one-pot' procedure to obtain glycosyl xanthate was reported by Rollin and coworkers [403]. Treatment of a solution of tetra-*O*-benzyl-D-glucose **8** in toluene with tri-*n*-butyl phosphine and diisopropyl dithiocarbonate disulfide gave a mixture of glycosyl xanthates in good yields (82–87%).

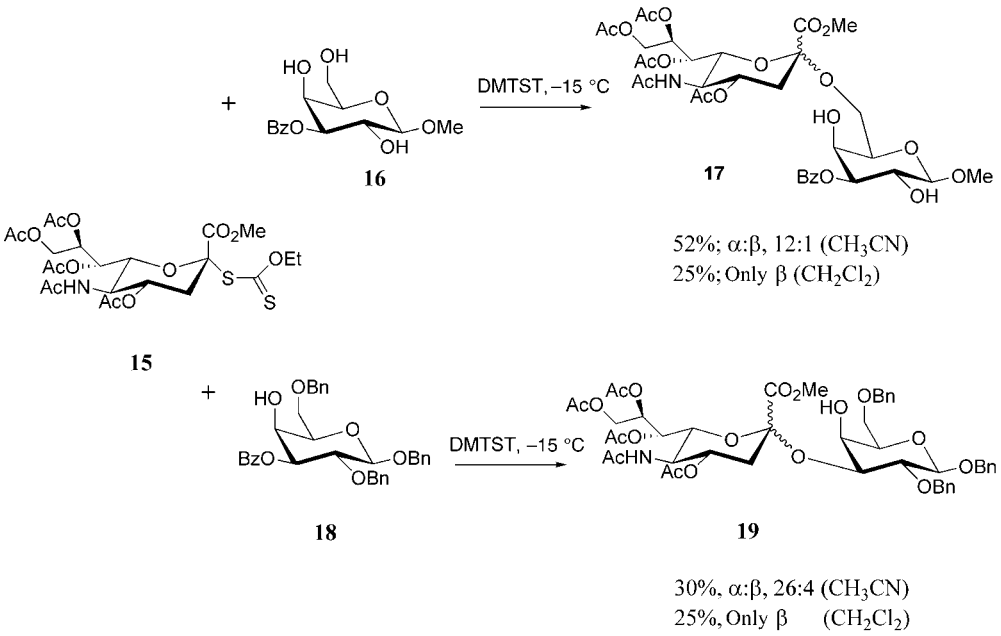
The use of glycosyl xanthate as a glycosyl donor in the presence of $BF_3{\cdot}Et_2O$ was first reported by Pougny [404]. Sinay and coworkers used *S*-glycosyl xanthates for the stereoselective synthesis of biologically important galactosamine-containing oligosaccharides [399]. The xanthate prepared was reacted with methyl 2,3.4-tri-*O*-benzyl-α-D-glucopyranoside **11** in acetonitrile in the presence of copper(II) triflate to give a mixture of disaccharides **12** ($\alpha/\beta = 1/6$). The β-selectivity observed is because of the formation of the α-nitrilium intermediate in the rate-determining step that upon substitution leads to the β-anomer. In contrast, excellent α-stereoselectivity was



Scheme 4.73 Glycosyl xanthates in stereoselective synthesis of galactosamine-containing oligosaccharides [399].

observed ($\alpha/\beta = 16/1$) for the reaction of **10** with acceptor **13** carried out in dichloromethane (Scheme 4.73) .

The application of sialyl xanthate **15** as glycosyl donor was done by Marra and Sinay [397,398]. Dimethyl(methylthio)sulfonium triflate (*DMTST*)-promoted reaction of **15** with 6-hydroxyl of a galactosyl acceptor **16** (Scheme 4.74) afforded α-(2,6)-linked disaccharide **17** in 48% yield, contaminated with β-isomer (4%). A 2-thioalkyl glycosyl donor gave a lower yield (32%) of the disaccharide **17** ($\alpha : \beta = 3 : 1$) when reacted under similar conditions, illustrating the advantageous properties of 2-xanthates. When glycosylation was performed in dichloromethane, β-isomer was the only product that was isolated (25% yield). Regioselective glycosylation of **18** led to (2,3)-linked disaccharide **19**. In dichloromethane, the glycosylation probably

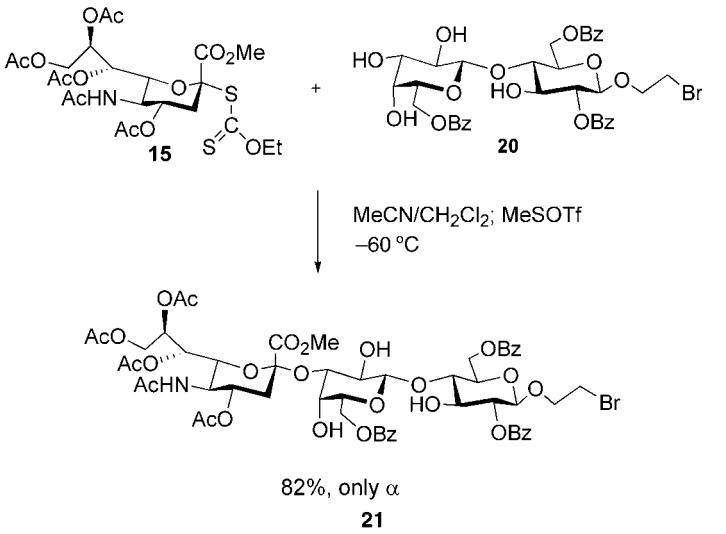


Scheme 4.74 Sialyl xanthate in regioselective and stereoselective glycosylations [398].

involves a reactive anomeric oxocarbenium ion, which is subject to axial attack, to give β-isomer. In acetonitrile, the reaction may involve the β-nitrilium ion, which is more reactive than the α-isomer as a consequence of the reverse anomeric effect displayed by a positively charged leaving group [405,406,410].

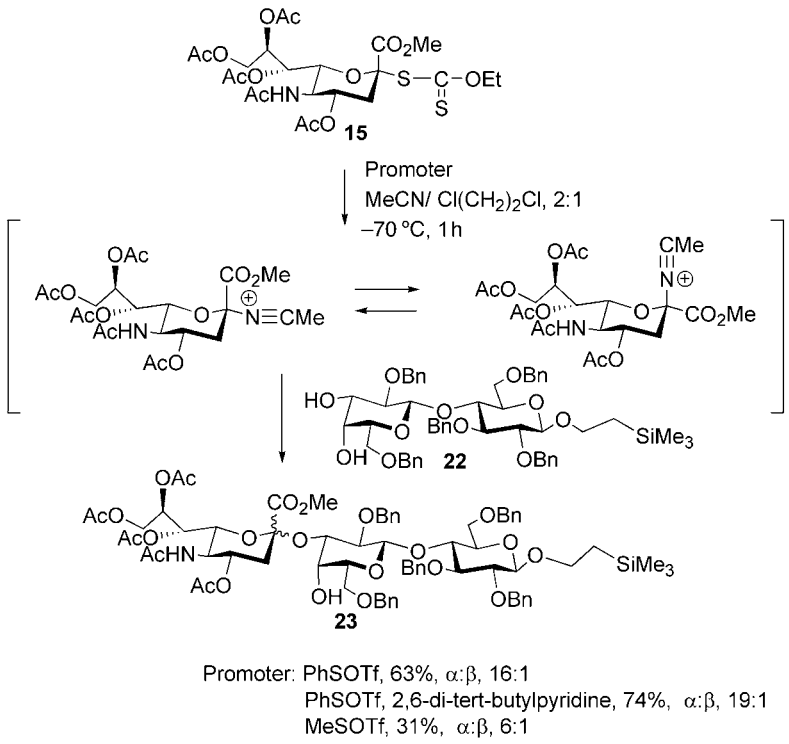
The application of highly reactive thiophilic reagents, such as methylsulfenyl triflate (MeSOTf) [407–409], as the promoter greatly improved the synthesis of sialyl glycosides. The reactive thiophilic reagent can be generated *in situ* by the reaction of methylsulfenyl bromide (MeSBr) with AgOTf. MeSOTf activates 2-xanthate **15** at low temperature (−70 °C), and the best results of glycosylation were obtained when a mixture of MeCN/CH_2Cl_2 (3/2 vol/vol) was used as the reaction solvent [407]. The reaction mechanism of xanthate activation is similar to that of thioglycosides [410]. The oxonium cation formed in the first step of reaction of xanthate with PhSOTf is stabilized by interaction with acetonitrile. In the next step, nucleophile reacts with more reactive, less hindered cation to mainly give α-product. This approach was used in the synthesis of ganglioside GM_3 analog **21** as shown in Scheme 4.75 [409]. An attractive feature of this glycosylation protocol is that sialyl xanthate **15** can be selectively activated in the presence of thioglycosides [407].

It was found that PhSOTf is superior to MeSOTf in terms of both yield and stereoselectivity of sialylation, especially when applied in combination with the hindered base 2,6-di(*tert*-butyl)-pyridine (*DTBP*) at low temperatures (−70 °C) [410]. Promoter was generated by the reaction of phenylsulfenyl chloride (PhSCl)



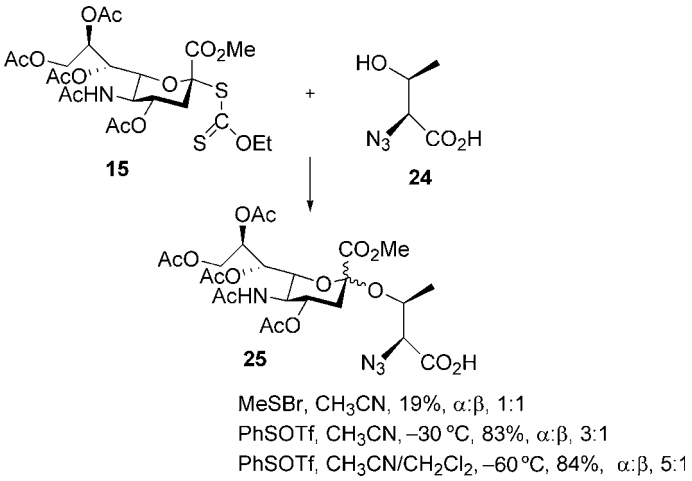
15 **20** **21**

Scheme 4.75 Sialyl xanthate in the synthesis of GM_3 ganglioside [409].



15 **22** **23**

Scheme 4.76 Sialyl xanthate in stereoselective glycosylation [410].



Scheme 4.77 Preparation of solid-phase glycopeptide library [411,412].

with AgOTf. A relevant example is shown in Scheme 4.76: thus, protected GM_3 trisaccharide **23** was obtained on a gram scale in an excellent yield of 74%, mainly as the α-anomer.

One of the disadvantages of this method is a reduced yield because of the formation of sialyl glycal during both the preparation of sialyl xanthates and their glycosidation. Also, some amount of the β-sialoside is often formed, especially when reaction is performed with more reactive alcohols. Separation of the anomeric mixture is usually difficult and requires careful chromatography [410]. Salic-acid-containing amino acid building blocks were used for the preparation of glycopeptide libraries on the solid phase [411,412]. It was concluded that PhSOTf is the promoter of choice for the sialylation of amino acid acceptors. Thus, the coupling of the sialyl donor **15** with an easily available acceptor **24** in acetonitrile/methylene chloride gave compound **25** in a high yield (Scheme 4.77).

Several other examples of successful application of sialyl xanthates for oligosaccharide synthesis have been reported [411,413–427].

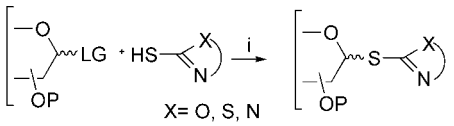
4.3.3
Glycosyl Thioimidates – Preparation and Application as Glycosyl Donors

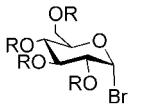
Glycosyl thioimidates (heteroaryl thioglycosides) were proposed as a new class of glycosyl donors [428,429]. Similar to the thioglycosides, glycosyl thioimidates are easily accessible. General approach to the synthesis of these compounds may proceed through the nucleophilic displacement of a leaving group of the glycosyl donor by a thioimidate anion. The convenient method of synthesis consists of the reaction between a per-*O*-acetyl **3**, per-*O*-benzoyl **26**, per-*O*-benzyl glycosyl halide **27** and appropriate thiolate anion. Owing to the high nucleophilicity of thioimidate anion, it is

possible to perform the reaction in polar solvents such as acetone, acetonitrile, alcohol or even acetone–water. The reaction is performed in the presence of inorganic bases such as sodium or potassium hydroxide, sodium hydride or potassium carbonate, and usually 1,2-*trans* glycoside is obtained [430]. By this procedure, Bertram and coworkers prepared peracetylated *N*,*N*-diethyl and *N*,*N*-diallyl *S*-glycosyl dithiocarbamate derivatives of D-glucose, lactose and cellobiose [431,432].

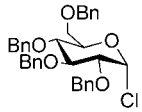
Zinner used sodium as a base [433,434] for the exchange reaction. Demchenko performed reaction of glycosyl bromide **26** with potassium *S*-benzoxazolyl (SBox) in the presence of 18-crown-6 [435]. Similarly, benzoylated *S*-thiazolinyl (STaz) glycosides were obtained when NaSTaz or KSTaz reacted in the presence of a crown ether with per-*O*-benzoyl glycosyl bromide **26** or chloride **27**. The latter reaction mixture containing the desired *S*-glycosyl derivative was contaminated with the products of *N*-glycosylation and β-elimination. Alternatively, glycosyl bromides were reacted directly with HSBox in the presence of K_2CO_3 in acetone [435]. Similarly, benzoylated *S*-thiazolinyl glycosides were obtained when NaSTaz or KSTaz reacted in the presence of a crown ether with per-*O*-benzoyl glycosyl bromide or chloride. Again, formation of some *N*-glycosylation and β-elimination products [437] was observed. Per-*O*-benzylated *S*-benzothiazolyl glycoside (SBtaz) was prepared from the anomeric chloride **27** and mercaptobenzothiazole **32** in the presence of 1,8-bis(dimethylamino)naphthalene [438], indicating significant influence of the base on the reaction outcome. A new approach to the preparation of these types of compounds was developed by Szeja and Bogusiak [439]. It is especially suited for acetal- and benzyl-protected sugars and involves generating glycosyl tosylates under phase-transfer conditions *in situ*, followed by substitution with thioimidate ion. Under the PTC conditions, a mixture of thioimidates was obtained when 2-mercaptobenzothiazole was reacted with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **8** with tosyl chloride in a two-phase system (50% aqueous sodium hydroxide/benzene) in the presence of catalytic amounts of tetrabutyl ammonium chloride. Another method for the synthesis of glycosyl thioimidates involves the treatment of protected hemiacetal precursors with disulfide in the presence of trialkyl phosphines to give a mixture of heteroaryl thioglycosides [157,440,441]. Thus, the reaction of **8** with piridinium disulfide in the presence of tributyl phosphine afforded the pyridyl 1-thio-D-glucopyranosides [440]. Benzylated β-D-mannopyranose orthoacetate **29** was coupled with 2-mercaptopyridine **36**, 2-mercaptopyrimidine **35**, 2-mercaptobenzoxazole **33** and 2-mercaptobenzothiazole **32** to give the 1-thio-α-D-mannopyranosides in excellent yields (89–93%) [442]. Easily available per-*O*-acetylated sugars are convenient substrates for the synthesis of glycosyl thioimidates [435,437,443]. The standard procedure involves the reaction of such sugar derivative with a slight excess of mercapto imidate derivative using Lewis acid as the promoter, and usually, 1,2-*trans* product predominates [435,437,443]. For example, D-glucose pentaacetate **28** reacted with 2-mercaptobenzoxazole (HSBox) **33** in the presence of BF_3–Et_2O to afford the corresponding thioglycopyranoside as an anomeric mixture [435].

Similarly, the reaction of per-*O*-acetyl D-ribofuranose **38** with 2-mercaptopyridine **36** afforded the corresponding thioglycoside in a good yield (Scheme 4.79) [446]. Ferrieres



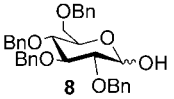


R= Bz; **26** HSBox, K_2CO_3, acetone — Only β [436]
KSBox, 18-c-6 — Only β [435]
NaSTaz, 15-c-5 — 60%, Only β [437]
KSTaz, 15-c-5 — Only β [437]
R=Ac; **3** HSPyrm, Bu_4NHSO_4 — 95%, Only β [491]
CH_2Cl_2, water



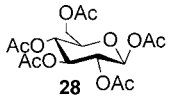
27

NaSTaz, 15-c-5 — [437]
HSBtaz, 1,8-bis(dimethylamino)naphtalene — 80%, only β [438]



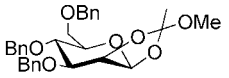
8

HSBtaz, TsCl, Bu_4NCl, C_6H_6/50% aq NaOH — 95%, α:β, 1:3 [439]
$(SPyr)_2$, Bu_3P, CH_2Cl_2 — Anomeric mixture [440]



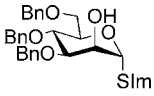
28

HSBox, BF_3-Et_2O, CH_2Cl_2 — 79%, α:β, 1:3 [435]
HSTaz, BF_3-Et_2O, CH_2Cl_2 — 69%, Anomeric mixture [443]
HSTaz, BF_3-Et_2O, CH_2Cl_2 — 91% [437]

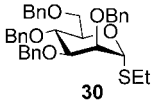


29

HSPyr, (a)$HgBr_2$, (b)MeONa
HSPyrm, (a) $HgBr_2$, (b)MeONa
HSBtaz, (a) $HgBr_2$, (b)MeONa
HSBox, (a) $HgBr_2$, (b)MeONa



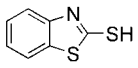
SPyr 93% [442]
SPyrm 93%
SBox 89%, only α
SBtaz 89%, only α



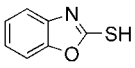
30

(a) Br_2, MS3A (b)KSBox, 18-c-6 — only α [446,447]

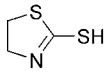
ImSH:



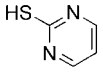
2-Mercaptobenzothiazole
HSBtaz **32**



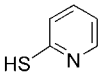
2-Mercaptobenzoxazole
HSBox **33**



2-Mercaptothiazole
HSTaz **34**

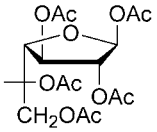


2-Mercaptopyrimidine
HSPyrm **35**



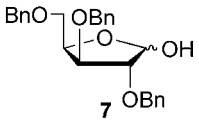
2-Mercaptopyridine
HSPyr **36**

Scheme 4.78 Synthesis of *S*-glycopyranosyl imidates.



37

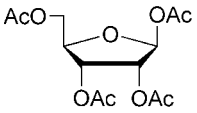
HSPyrm, BF_3-Et_2O, CH_2Cl_2 99%, Only α [444]
HSBtaz, BF_3-Et_2O, CH_2Cl_2 83%, α:β, 1:6.7 [444]



7

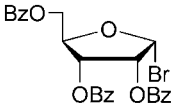
HSBtaz, $(PhO)_2P(=O)Cl$
Bu_4NBr, CH_2Cl_2 /aq NaOH

Anomeric mixture [445]



38

HS Pyr, BF_3-Et_2O, $ClCH_2CH_2Cl$ 85%, β-only [446]



39

HSPyr, K_2CO_3, Toluene–acetone 88%, β-only [440]

Scheme 4.79 Synthesis of *S*-glycofuranosyl imidates.

and coworkers described the synthesis of per-*O*-acetylated *S*-benzothiazolyl galactofuranosides by the treatment of acetylated galactofuranose **37** with 2-mercaptobenzothiazole **32** in the presence of BF_3–Et_2O [444]. Bogusiak reported the synthesis of *S*-benzothiazolyl furanosides of the L-arabino, D-ribo and D-xylo series from the reducing sugars **7** and **32** in the presence of diphenyl phosphoryl chloride [$(PhO)_2P(=O)Cl$] under phase-transfer conditions [445]. A number of acetylated *S*-benzothiazolyl D-gluco and D-galactofuranosides have been synthesized from per-*O*-acetylated glycofuranosyl bromides and sodium thiolates in MeCN [443]. 2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl bromide **39** was reacted with **36** in the presence of K_2CO_3 in hot toluene–acetone as the solvent to give the expected thioglycoside in a high yield [440].

The main efforts in the field of synthetic carbohydrate chemistry have been focusing on the development of new glycosylation methodologies and convergent strategies for

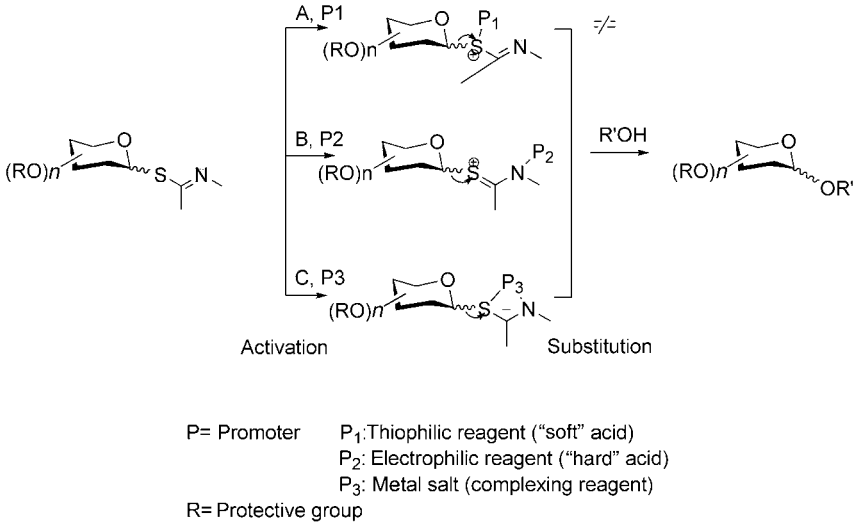
oligosaccharide synthesis [1,63,447–453]. The development of new and efficient strategies for the assembly of oligosaccharides and glycoconjugates is an intensive field of research. The synthesis of oligosaccharides is traditionally a time-consuming process, mainly because of the extensive need for protective-group manipulations. Most of the contemporary researches in this field are therefore focused on the development of glycosylation approaches in which the number of synthetic and purification steps is reduced. Recent solution-phase methodologies that omit the need for the intermediate installation of suitable anomeric leaving-group and/or protecting-group manipulations include chemoselective [454–208,459,460], orthogonal [237,436,450], iterative [461–463] and one-pot glycosylations [464–466]. The majority of these approaches are based on selective activation of one leaving group over another. Among these, one-pot strategies perhaps offer the shortest pathway to oligosaccharides, as the sequential glycosylation reactions are performed in a single flask and do not require isolation and purification of the intermediates.

Although it is difficult to imagine realization of such strategies with the use of classic glycosyl donors such as acetylated glycosyl halides, glycosyl imidates, efforts are underway to design appropriate procedures on the basis of diversified thioglycosyl synthons. Garegg and coworkers have examined the potential of glycosyl 1-piperidinecarbothioates as glycosyl donors in oligosaccharide synthesis. Thiophilic promoters such as methyl triflate (MeOTf) and silver triflate, as well as metal salts such as tin(IV) chloride and iron(III) chloride gave good yields of the desired disaccharides. In their approach, activation of carbothioate over ethyl thioglycosides exemplifies the principle of selective activation of anomeric thio substituents [467].

Demchenko and coworkers have demonstrated that glycosyl thioimidates, a class of glycosyl donors, with the generic leaving group $SCR^1 = NR^2$ fulfill the requirements for modern building blocks and are suitable for a variety of convergent synthetic strategies for oligosaccharide synthesis [118,227,428,435,436,446,447,468,469]. Considering the multifunctional character of the thioimidoyl moiety, three major activation pathways (a–c, Scheme 4.80) for their glycosidation have been postulated.

In the first pathway, thiophilic reagents (NIS/TMSOTf) activate the anomeric leaving group via complexation to the sulfur atom (pathway a). In the second approach, electrophilic promoters such as MeOTf target the thioimidoyl nitrogen (pathway b). Finally, metal-salt-based promoters (AgOTf or $Cu(OTf)_2$) can complex to both the sulfur and nitrogen atoms intra- or intermolecularly (pathway c) and stimulate the anomeric activation. Some of these promoters are already commonly used for thioglycoside activation [1]. However, there is a possibility of using metal-salt-based activation that distinguishes the thioimidates from their *S*-alkyl/aryl counterpart. Examples of practical and highly stereoselective glycosylations [435,436] are presented in Scheme 4.81. Thus, when per-*O*-benzoylated SBox derivatives of the D-gluco **39**, D-galacto and D-manno series were reacted with glycosyl acceptor **40** in the presence of AgOTf, the corresponding disaccharides such as **41** were obtained [435]. Glucosyl donor **42** and its galactosyl counterpart bearing a nonparticipating group at C-2 were used in stereoselective synthesis of 1,2-*cis* disaccharides, for example **44** [436].

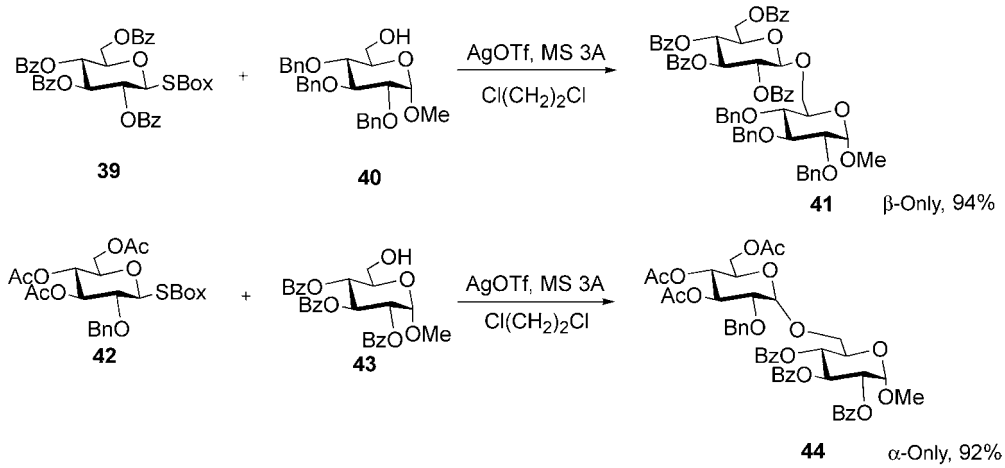
It was reported that selective activation of the SBox glycosyl donors over SEt and *O*-pentenyl glycoside acceptors can also be achieved in the presence of AgOTf



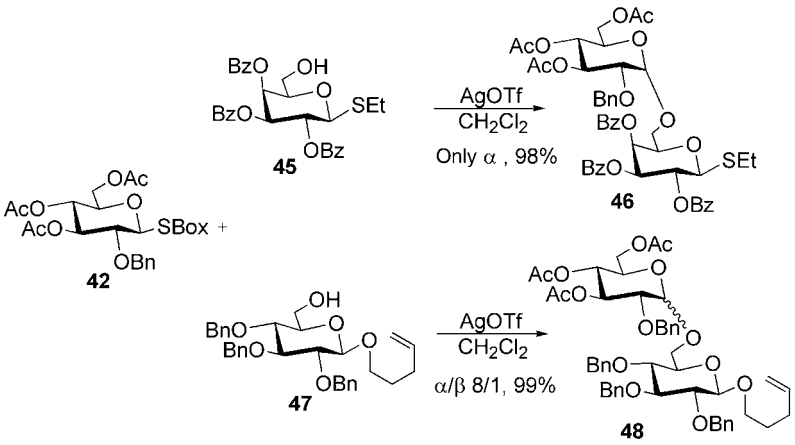
Scheme 4.80 Activation pathways for thioimidate glycosidation [227].

[435,436]. Thus, the reaction of glycosyl acceptors **45** and **47** with SBox glycosyl donor **42** provided a complete stereoselectivity in 1,2-*cis* glycosidations of **45** and high stereoselectivity was achieved in the reaction with **47** [435,436] (Scheme 4.82).

It has been found that 2-*O*-benzyl-3,4,6-tri-*O*-acyl SBox glycosides are significantly less reactive than 'disarmed' peracylated derivatives. Taking into account this observation, a convergent synthesis of oligosaccharides was developed. Activation of the *armed* **49** SBox glycoside over *moderately disarmed* **50** provided disaccharide **52** in a good yield (Scheme 4.83). Disaccharide **52** was then activated over the disarmed glycosyl acceptor **53** to afford the trisaccharide **54**.

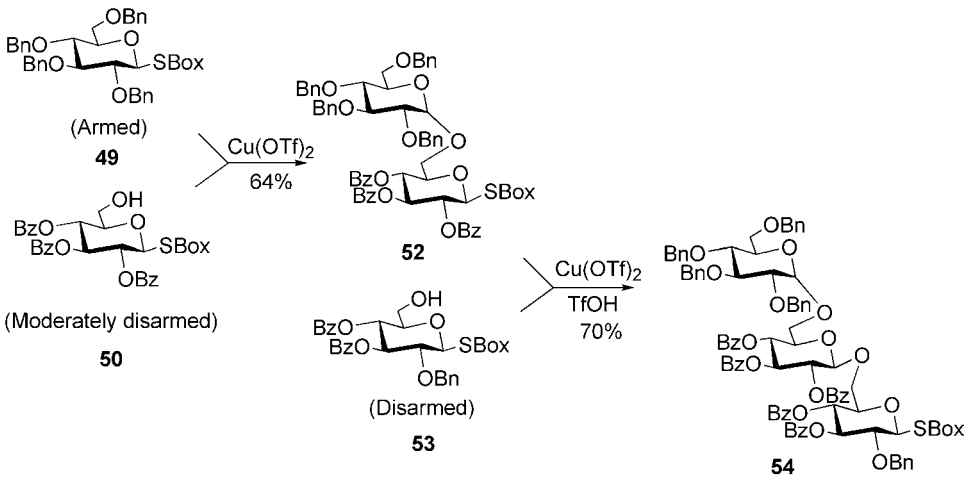


Scheme 4.81 SBox glycosides in the stereoselective glycoside synthesis [436].

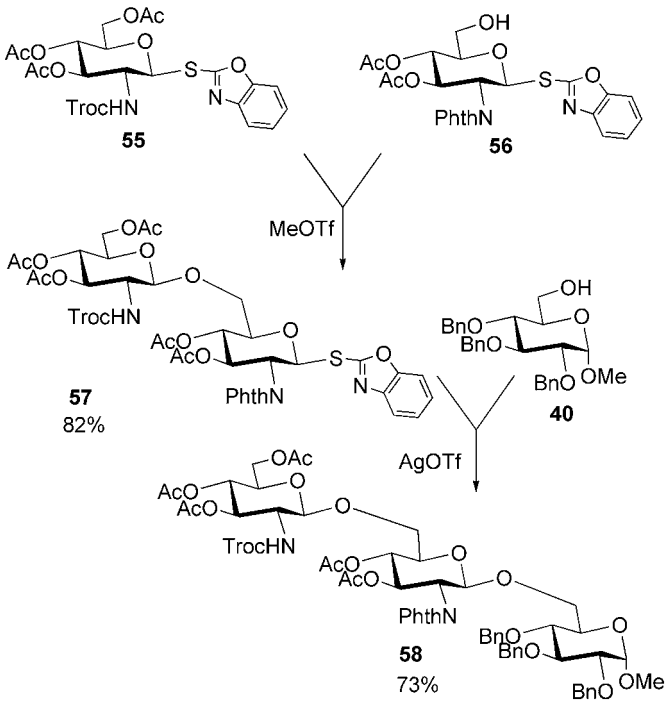


Scheme 4.82 Orthogonality of the SBox glycosides [435,436].

Continuing this work, Demchenko *et al.* reported the application of the SBox glycosides to the high-yielding synthesis of disaccharides of the 2-amino-2-deoxy series [469]. The *N*-substituted SBox glycosides, 2-NPth, 2-NHTFA, 2-*N*-trichloroethoxy carbonyl (NHTroc) and NHAc, were activated with AgOTf or MeOTf, affording the disaccharide derivatives in high yields and with complete stereoselectivity. The reactivity of glycosyl donors strongly depends on the *N*-protecting groups and promoters. It was found that in MeOTf-promoted glycosylation NPth derivative is less reactive than NHTroc glycosyl donor. This observation gave rise to a complementary glycosylation approach for chemoselective glycosidation of 2-aminosugars. Glycosyl acceptor **56** was glycosylated with glycosyl donor **55**, as illustrated in Scheme 4.84. This coupling is best accomplished at a reduced temperature (5°C); under these reaction conditions, the disaccharide **57** was obtained with complete



Scheme 4.83 Chemoselective activation of the SBox glycoside [428].

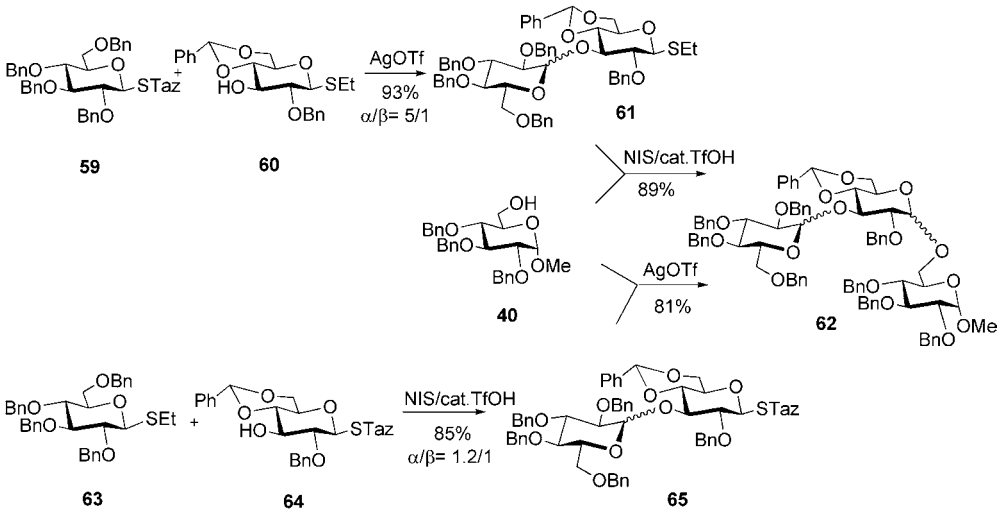


Scheme 4.84 Synthesis of oligosaccharides of 2-deoxy-2-aminosugars [469].

1,2-*trans* stereoselectivity and a high yield of 82%. Subsequent AgOTf-promoted glycosidation of disaccharide **57** with glycosyl acceptor **40** at room temperature gave trisaccharide **58** in 73% yield and with complete β-selectivity. This two-step sequential activation leads to the *trans–trans*-linked oligosaccharides.

Investigation of the glycosyl donor properties of STaz glycosides resulted in the development of another general approach to 1,2-*cis* and 1,2-*trans* glycosylation [437]. Thiophilic reagents, AgOTf, MeOTf, NIS/TfOH and $Cu(OTf)_2$, were found to be effective as the promoters in glycosylation reactions. Perbenzoylated STaz derivatives of the D-glucose and D-galactose were selected to probe 1,2-*trans*-glycosidation experiments with *S*-ethyl glycosyl acceptors. These glycosylations proceeded smoothly and afforded good results consistently. Perbenzylated STaz glycosides were employed in 1,2-*cis* glycosylations of the SEt-moiety-containing glycosyl acceptors. In all the cases high yields were achieved, and desired disaccharides were obtained as anomeric mixtures in 86–99% yield.

As the activation of STaz glycoside is observed in the presence of NIS and stoichiometric amount of TfOH, it has been reasoned that it might be also possible to activate SEt or SPh glycosyl donors over STaz glycosides [437]. Indeed, glycosidation of the *S*-ethyl glycosyl donor **63** over STaz glycosyl acceptor **64** was activated with NIS in the presence of catalytic amounts of TfOH. This allowed the use of STaz glycosides **59** and **64** in orthogonal glycosylations in combination with *S*-ethyl thioglycosides **60** and **63** (Scheme 4.85). The activation of **59** over SEt glycosyl acceptor **60** with

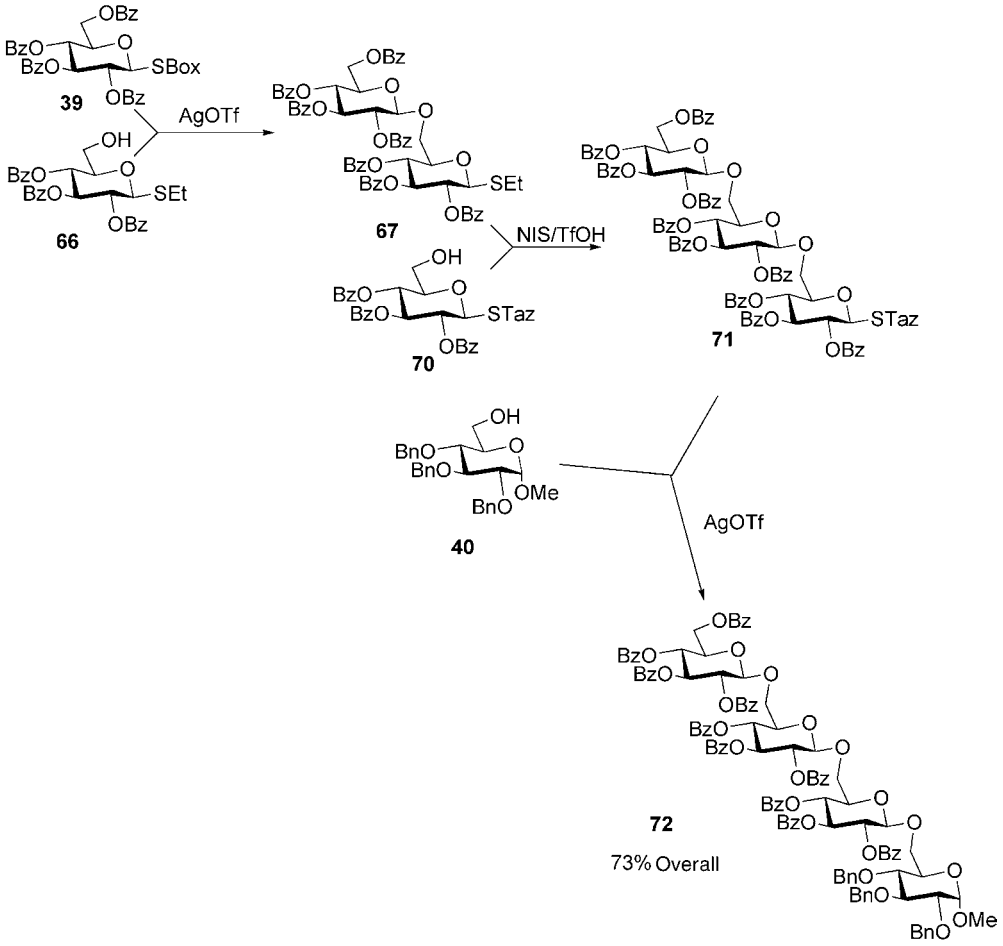


Scheme 4.85 Orthogonality of the STaz and SEt glycosides [437].

AgOTf gave disaccharide **61**. Under these reaction conditions, ethylthio glucoside was stable. In the next step, the activation of the SEt glycosyl donor **61** with NIS and catalytic amount of TfOH gave trisaccharide **62** in a good yield. The second pathway involved glycosidation of the SEt glycosyl donor **63** with STaz glycosyl acceptor **64** in the presence of NIS and a catalytic amount of TfOH. The disaccharide **65** formed was then activated with AgOTf to afford trisaccharide **62**. These results imply a fully orthogonal character of the two classes of leaving groups, STaz and SEt.

On the basis of the results of selective activations, Demchenko and coworkers performed a one-pot synthesis of tetrasaccharides [468]. This was achieved by the stepwise activation of SBox over *S*-ethyl, *S*-ethyl over STaz and, finally, STaz over stable glycosyl acceptor (OMe). To execute this one-pot sequence, authors chose the following building blocks: SBox glycosyl donor **39** was glycosidated at the first step with *S*-ethyl glycosyl acceptor **66**. This resulted in the formation of a disaccharide derivative **67**, the SEt moiety of which was further activated over the STaz moiety of the second step (Scheme 4.86). The resulting trisaccharide **71** could then be glycosidated with 6-OH glycosyl acceptor **40**, bearing a stable *O*-methyl moiety at the anomeric center to afford a linear tetrasaccharide **72**. The promoters of choice were AgOTf for the activation of the SBox and NIS/catalytic TfOH for the activation of *S*-ethyl and, finally, more AgOTf should be added for the activation of STaz moiety of the trisaccharide **71**.

Demchenko and coworkers demonstrated that some glycosyl imidates (STaz) can serve as both the glycosyl donor and glycosyl acceptor in accordance with the so-called temporary deactivation concept [227]. It was found that the STaz moiety forms a stable, nonionizing metal complex with palladium bromide. This allows chemoselective activation of a 'free' STaz leaving group (glycosyl donor) over a deactivated (complexed) STaz moiety (glycosyl acceptor). It was demonstrated that either benzoylated or benzylated STaz glycosyl donors could be activated over temporarily deactivated benzoy-

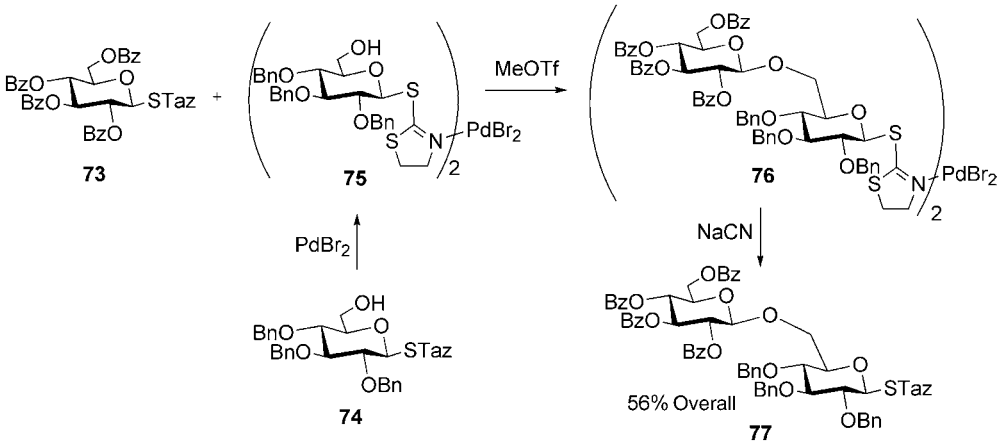


Scheme 4.86 Orthogonal thioimidate-based, one-pot oligosaccharide synthesis [468].

lated or benzylated glycosyl acceptors. The concept is illustrated in Scheme 4.87. An attractive feature of this strategy is that it does not rely on protecting groups to control the leaving-group ability and, thus, glycosyl donor reactivity.

Upon glycosylation of the complex **75** with STaz glycosyl donor **73**, the obtained disaccharide **76** was decomplexed by the treatment with NaCN in acetone. As a result, the β-linked disaccharide **77** was isolated in good yield. These results provide encouraging support for the idea of the temporary deactivation that allows for the preferential activation of one leaving group over another without the requirement for altering the protecting-group pattern. As protecting groups also control the anomeric stereoselectivity of glycosylation, the new approach offers more flexibility in this respect.

Novel sialosyl donors, *S*-benzoxazolyl and *S*-thiazolyl sialosides, have been synthesized [170]. Both SBox and STaz sialosides proved to be excellent glycosyl donors

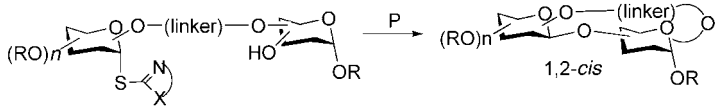


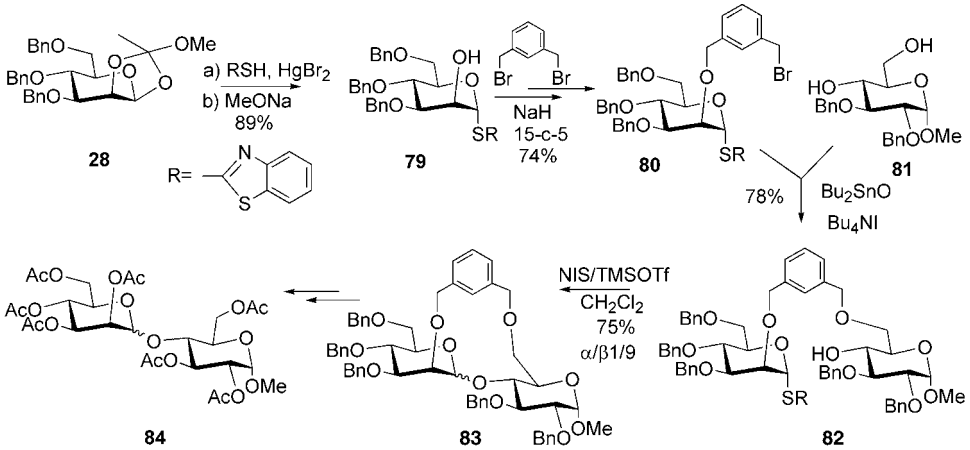
Scheme 4.87 Temporary deactivation method [227].

when activated with MeOTf and AgOTf. In general, good yields and stereoselectivities were observed with a number of glycosyl acceptors, ranging from highly reactive primary to less reactive secondary alcohols. The most attractive feature of the thiomidoyl moieties is that they can be selectively activated over thioglycosides in the presence of AgOTf as the promoter. It was demonstrated that the selective activation of the SBox sialyl donor over ethyl thioglycoside allows the synthesis of disaccharides that can be used in subsequent glycosylations without further manipulations [170].

Recently, various studies of anomeric stereocontrol have been reported using the intramolecular reaction between a glycosyl donor and a glycosyl acceptor, which are connected via a suitable linker (Scheme 4.88) [470]. The intramolecular glycosylation approach by 'linking the accepting atom to the donor via a bifunctional group' (intramolecular aglycon delivery, *IAD*) was originally developed for the synthesis of β-mannopyranosides and later extended to the synthesis of other glycosides. The synthesis of the β-mannosidic linkage is a difficult task [472–475] because both anomeric effect and participating neighboring groups at 2-O favors the formation of α-mannosides (1,2-*trans* configuration). To obtain the desired proximity between the glycosyl donor and acceptor moiety, the rigid spacer concept was designed [476–478]. As a powerful example for a rigid spacer, the *m*-xylylene moiety and derivatives were chosen. Taking this into account, Schmidt and coworkers have developed an efficient and highly regio- and stereoselective protocol for the intramolecular β-mannopyranoside synthesis by using glycosyl thioimidates as glycosyl donors and *m*-xylylene moieties as rigid spacers linked to the 2-hydroxy group of the mannose residue [442].

Reaction of glycosyl thioimidate **79** with αα′-dibromo-*m*-xylene in the presence of NaH as a base and 15-crown-5 as a supporting reagent allowed the intermediate **80** (Scheme 4.88). Treatment of the diol **81** with dibutyltin oxide in dry toluene and then reaction with **80** in the presence of tetrabutylammonium iodide afforded the desired *O*-linked intermediate **82**. Activation of this compound with NIS–TMSOTf afforded **83** in a good yield. Hydrogenolysis followed by acetylation gave the desired disac-

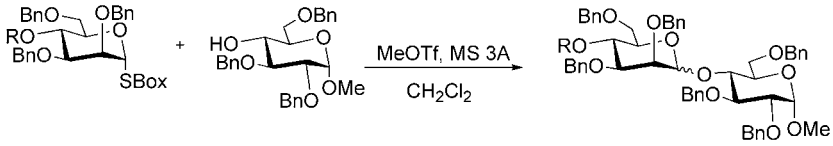




Scheme 4.88 Intramolecular β-mannosylation [158].

charide **84** with good stereoselectivity. The method developed permits the synthesis of a variety of differently functionalized β-mannopyranoside derivatives.

Application of the SBox glycosides to β-mannosylations was also investigated [140]. It was determined that the use of the SBox glycosyl donors protected with either *p*-methoxybenzoyl or *N,N*-diethylthiocarbamoyl moieties at C-4 improve the stereoselectivity. Thus, coupling of the SBox glycoside **86** with glycosyl acceptor **87** afforded disaccharide **89** in good yield and stereoselectivity. It has been postulated that the improved stereoselectivity is because of the long-range participation of a substituent at C-4 and the formation of cyclic carboxonium ion followed by the nucleophilic attack from the β-face of the sugar ring. In contrast, when perbenzylated glycosyl donor **85** was used, disaccharide **88** was obtained with low stereoselectivity [140] (Scheme 4.89) .



85 R= Bn
86 R= *p*-MeOPhCO

88 R= Bn, 83%, α:β, 1:2.5
89 R= *p*-MeOPhCO, 76%, α:β, 1:7

Scheme 4.89 SBox glycoside in the remote-assisted β-mannosylation [146].

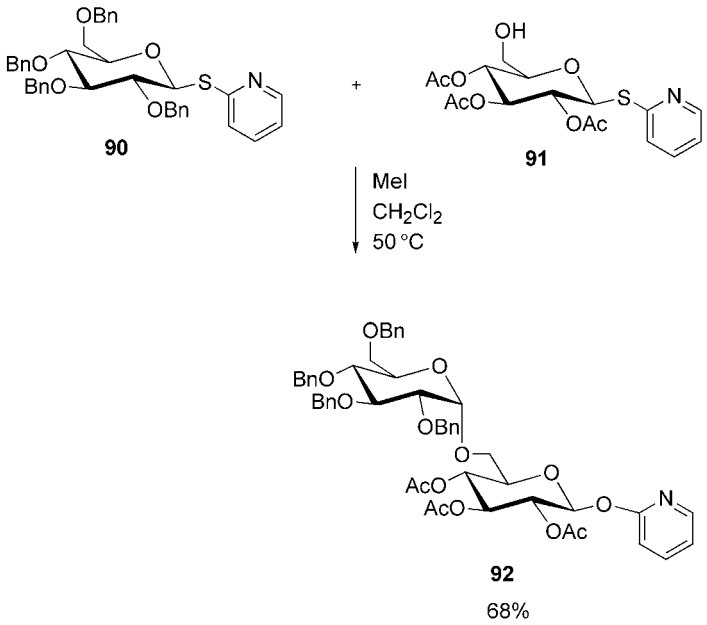
Hanessian explored the scope of 2-thiopyridyl (SPyr) and 2-thiopyrimidinyl (SPyrm) compounds as glycosyl donors by developing a 'remote activation' concept [254,479]. It was assumed that a suitable substituent at the anomeric center such as sulfur (soft base) in combination with a nitrogen (hard base) could satisfy the requirements for the remote activation. Bidendate activation through a chelation of nitrogen and sulfur with the metal cation and formation of an oxocarbenium intermediate were postulated. Subsequent nucleophilic attack by an alcohol would form the glycoside bond. Treatment of *O*-unprotected glycosyl donors, SPyrm and SPyr-β-D-glucopyranoside, with a variety of alcohols in the presence of mercuric nitrate in acetonitrile solution, led to the anomeric mixture of glycosides within a few minutes [254]. However, the necessity to use an excess of acceptor, the formation of anomeric mixture of glycosides, and the use of mercuric salts limited the generality of this method of glycoside synthesis. The glycosyl-donating properties of protected thiopirydyl and thiopyrimidinyl glycosides activated with other thiophilic salts such as silver triflate [480] and lead perchlorate [481] were also studied.

The most impressive application of 2-thiopyridyl and 2-thiopyrimidinyl donors is in the area of antibiotics. Thus, Woodward *et al.* [481] successfully completed the total synthesis of erythromycin by using SPyrm glycoside of D-desosamine and SPyr-glycoside of L-cladinose as glycosyl donors to the subsequent glycosylation with erythronalide A. This methodology was also successfully used in the synthesis of oleandomycin [482,483], erythromycin A [484] and erythromycin B [485].

A thorough investigation of the glycosyl donor properties of the 2-thiopyridyl glycosides was performed by Mereyala and coworkers using MeI as the activator [159,486,158,487–490]. Although in some cases the reaction was rather sluggish and required prolonged reaction times at elevated temperatures, the benefit of high yield and excellent to complete stereoselectivities was apparent. One of the most valuable applications of the SPyr and SPyrm glycosides is for chemoselective oligosaccharide synthesis in accordance with 'armed–disarmed' strategy [457,458]. Thus, the benzylated *S*-pyridyl glycoside **90** (armed donor) can be chemoselectively activated with MeI over the partially acetylated **91** (disarmed) acceptor to afford the α-linked oligosaccharide **92** in complete stereoselectivity [158] (Scheme 4.90) .

The application of per-*O*-benzylated SPyrm-D-gluco, D-galacto, D-xylo and D-arabinopyranosides to stereoselective glycosylation was reported by Kong and coworkers [491,492]. The results are qualitatively similar to those obtained with thiopyridyl derivatives. Thus, glycosylation of methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside with benzylated SPyr–β-D-glucopyranoside in the presence of TMSOTf afforded disaccharide in good yields with complete 1,2-*cis* stereoselectivity. The SPyr glycosides were successfully applied for the synthesis of 2-deoxyglycosides [486,158,487], aminosugars [490], furanosides [440] and α-fucosides [490].

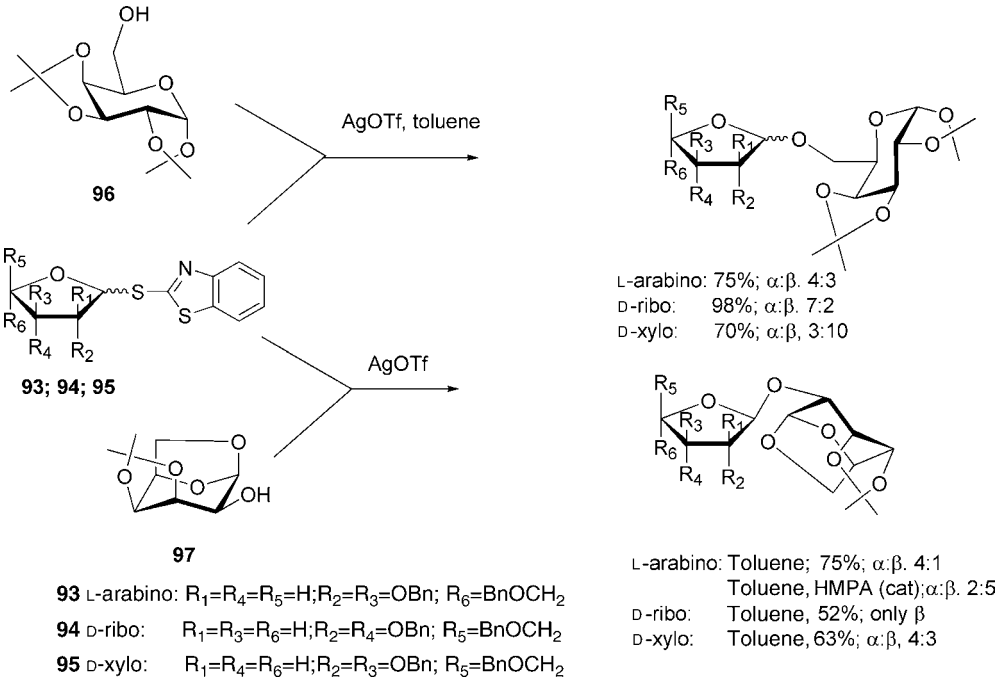
It was reported that 5-nitro-2-thiopyridyl group can be used for the anomeric protection of the glycosyl acceptor unit [493]. As this anomeric group was found to be stable in the presence of AgOTf, NIS/TfOH or TMSOTf, a variety of glycosyl donors such as bromides, dithiocarbamates and even *S*-alkyl glycosides could be selectively activated in the presence of 5-nitropyridyl moiety. Recently, Lowary reported the use of this class of glycosyl donors for the *O*-glycosidation of furanoses and pyranoses.



Scheme 4.90 Arming–disarming properties of the SPyr glycosides [158].

Thus, samarium(III)-triflate-promoted reactions provided *O*-linked disaccharides in moderate to excellent yields [308]. Szeja and Niemiec reported the use of 5-nitro-*S*-pirydyl glucoside as glycosyl donors in β-glucosidase-catalyzed glycosylation of alcohols [494].

Glycofuranosyl thioimidates have attracted attention as versatile and flexible building blocks for the synthesis of simple as well as complex oligosaccharides. These compounds can be activated with a number of thiophilic reagents to act as glycosyl donors [1]. The use of *S*-pyridyl thioglycosides in the synthesis of oligofuranosides was introduced by Mereyala *et al.* [488]. Direct coupling of *S*-pyridiyl ribofuranoside and *S*-pyridyl 2-deoxy-ribofuranoside derivatives with a variety of protected sugars promoted by methyl iodide in methylene chloride exclusively gives 1,2-*cis* glycosidic linkages. However, small amounts of 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol are formed along with 2-deoxy-ribofuranosido disaccharides. The properties of glycofuranosyl *S*-xanthates, *N,N*-diethyldithiocarbamate and *O,O*-diethyldithiophosphate derivatives of benzylated D-ribo, D-xylo and L-arabinofuranoses as glycosyl donors have been studied by Bogusiak and Szeja [495–497]. These functional groups can be effectively activated by silver triflate. Independent of the anomeric ratio of the glycosyl donors, the 1,2-*trans* glycofuranosides were formed with moderate to high stereoselectivity. These donors can also be converted into 1,2-*cis* glycofuranosides using a combination of silver triflate and stoichiometric amount of polar organic reactants such as DMSO, tetramethylurea (*TMU*) or hexamethylphosphoric triamide (*HMPA*). Glycosylation has been found to proceed most stereoselectively with HMPA [497]. It was found that NIS/TfOH-mediated coupling of



Scheme 4.91 Glycosidation of *S*-benzothiazolyl glycofuranosides [445].

S-glycofuranosyl dithiocarbamates with 5-nitro-2-pyridyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside as an acceptor gives access to valuable 1,2-*cis*-linked furanosyl-1-thiopyranosides [498]. Recently, Bogusiak reported that perbenzylated *S*-benzothiazolyl glycosides of L-arabino, D-ribo and D-xylofuranose can be used as glycosyl donors (Scheme 4.91) .

A satisfactory result was obtained in AgOTf- or NIS/TfOH-activated condensation of *S*-benzothiazolyl pentofuranosides **93**, **94** and **95** with 1,2:3,4-di-isopropylidene-α-D-galactopyranose **96** and 1,6-anhydro-3,4-isopropylidene-β-D-galactopyranose **97** as the acceptor to afford the corresponding disaccharides in moderate to good yields and stereoselectivity [445].

4.3.4
Glycosyl Thiocyanates as Glycosyl Donors

Kochetkov and coworkers have reported the use of 1,2-*trans*-glycosyl thiocyanates, having a nonparticipating group (methyl, benzyl) at C-2, for highly stereoselective 1,2-*cis* glycosylation [499–501]. The synthesis of 1,2-*trans* thiocyanates, accomplished by the reaction of α-D-glucopyranosyl, α-D-galactopyranosyl (**98**), α-D-mannopyranosyl and β-L-arabinopyranosyl bromides with KSCN in the presence of crown ether, was typically accompanied by the formation of the corresponding isothiocyanates (8–18%) [499]. Acetylated glycosyl thiocyanates kept at low temperature remain stable for at least 1 month.

The glycosylations were carried out in dry dichloromethane in the presence of 0.1 equiv of triphenylmethylium perchlorate. It was assumed that the triphenylmethylium cation attacks the nitrogen of the thiocyanate group whereas the oxygen of the trityl ether attacks the anomeric carbon in a 'push–pull' fashion. The trityl isothiocyanate formed was found to be unreactive under the reaction conditions. The disaccharide derivatives with (1–6), (1–4), (1–3) and (1–2) linkages have been obtained in good yields.

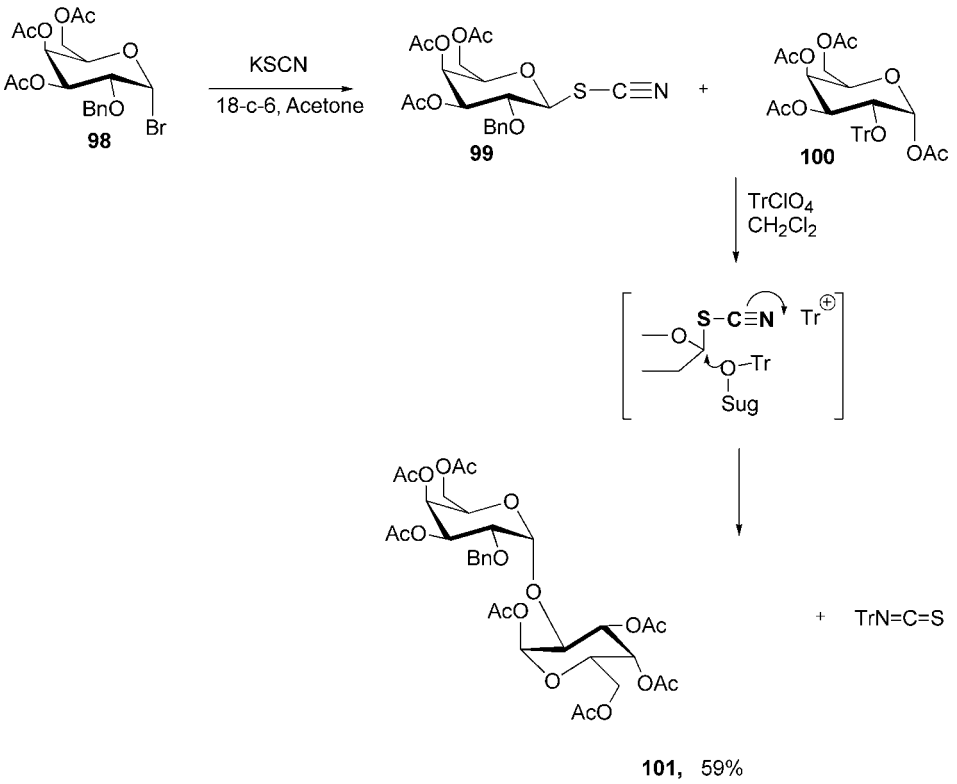
The method was also applied in the stereoselective synthesis of 1,2-*cis* glycosidic linkage of 2-aminosugars. The 1,2-*trans*-2-azido-2-deoxyglycosyl thiocyanate was used as the glycosyl donor with subsequent reduction of the azido group. The α-D-glucosaminyl-D-glucoses with (1–6), (1–3) and (1–2) glycosidic linkages were obtained [499].

4.3.5
Glycosyl Dithiophosphates as Glycosyl Donors

Glycosyl dithiophosphates are useful intermediates in the synthesis of various classes of sugar derivatives. The breaking of the C−S bond in the presence of suitable nucleophiles results in glycosides. The methods for the synthesis of glycosyl dithiophosphates are shown in Scheme 4.92. The phosphorothioate anion is a very active nuclephile, and the displacement of an anomeric leaving group is a convenient method for the synthesis of *S*-glycosyl phosphorothioates. Reaction of per-*O*-acetylglycosyl halides with *O,O*-dialkyl phosphorothioates led to a mixture of anomeric phosphate esters [502].

This method is very efficient when applied to hexopyranose series. Some difficulties have been experienced in attempted syntheses of glycosyl dithiophosphates of pentofuranoses. Michalska *et al*. [503,504] have found that the reaction of peracetylated mono- and disaccharides with *O,O*-dialkylphosphorothioates, its trimethylsilil esters or trialkylammonium salts in the presence of boron trifluoride etherate allows the synthesis of *S*-glycosyl phosphorothioates with high yield. Stereochemical course of nucleophilic substitution was influenced by the anomeric configuration, the kind of substituent used at C-2 and the molar ratio of reagents. In the case of D-glucose pentaacetate, the β-anomer was significantly more reactive than the α-anomer. In the presence of a participating acetyl group, the 1,2-*trans* products were formed stereoselectivity.

The synthetic route proposed by Szeja and Bogusiak [505,506] involves a one-pot conversion of reducing sugar derivatives into 1-thiosugar by intermolecular nucleophilic substitution of the intermediate glycosyl 1-*O*-sulfonates. Generation of a good leaving group from the free anomeric hydroxyl was achieved by the treatment with tosyl chloride under phase-transfer conditions (aqueous sodium hydroxide/organic solvent and tetrabutylammonium bromide as a catalyst). The treatment of the glycal derivatives with an equimolar amount of *O,O*-dialkyl *S*-hydrogen phosphorothioates in benzene for 24 h quantitatively afforded an anomeric mixture of *S*-(2-deoxyglycosyl)phosphorothioates [507–509]. Glycosyl dithiophosphates can also be synthesized from glycals in a two-step procedure. Epoxidation of the glycals with



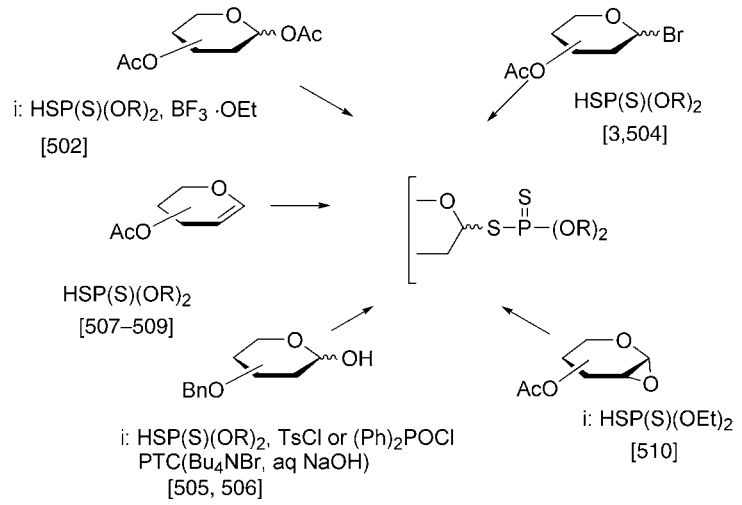
Scheme 4.92 Stereoselective glycosylation via glycosyl thiocynate [155].

dimethoxydioxirane (*DMDO*) afforded the 1,2-anhydro sugar that underwent oxirane ring opening with commercially available *O,O*-diethyldithiophosphate to afford glycosyl dithiophosphate in good yields (82–88%) [510] (Scheme 4.93) .

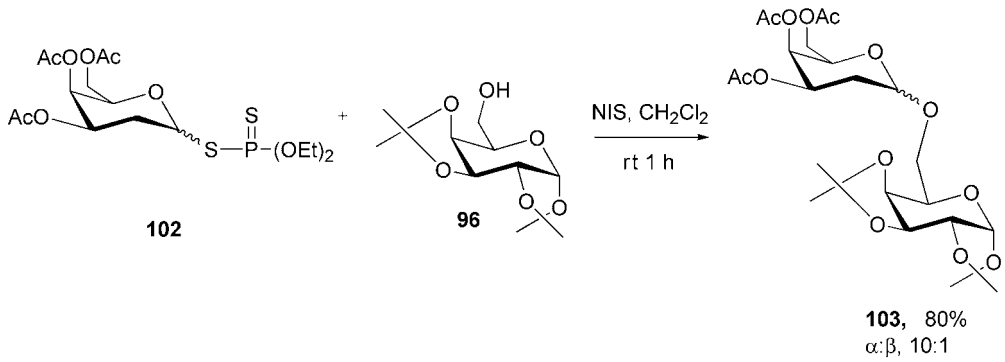
Bielawska and Michalska [511] have introduced *S*-(2-deoxyglycosyl)phosphorothioates as glycosyl donors. Activation of these compounds for glycosidation with silver salts (AgF, $AgClO_4$ or AgOTf) resulted in the formation of 2′-deoxydisaccharides as anomeric mixtures. Thiem and coworkers reported [507] an efficient activation method for *S*-(2-deoxyglycosyl)phosphorothioate donors **102** by using *N*-iodosuccinimide (*NIS*) or iodonium bis(2,4,6-trimethylpyridine) perchlorate (*IDCP*) (Scheme 4.94).

This improvement allowed achieving the synthesis of 2-deoxy disaccharide **103** with high stereoselectivity and good yield in short reaction times. The composition of the reaction mixture was found to be practically independent of the configuration of the *S*-(2-deoxy-D-glucopyranosyl)phosphorothioate. These results seem to provide an evidence that this glycosylation procedure proceeds via the S_N1 displacement reaction mechanism.

In the search for more efficient promoters for β-selective glycosylation, Seeberger and coworkers [510] explored coupling conditions used for thioglycoside donors.



Scheme 4.93 Synthesis of glycosyl dithiophosphates.



Scheme 4.94 Stereoselective synthesis of 2-deoxy-α-glycosides [507].

Although the coupling of glycosyl dithiophosphates using an excess methyl triflate as an activator in the presence of 2,6-di-tertbutylpyridine proceeded in a satisfactory yield (70%), the application of dimethylsulfonium triflate resulted in the formation of disaccharides in a considerably more effective way (94% yield).

4.3.6 Conclusions

Chemical entities discussed in this chapter as glycosyl donors share the principal structural feature: C(anomeric)–sulfur atom bond with thioglycosides, discussed earlier. However, the electron density on the sulfur atom is diminished, and consequently its chemical reactivity differs considerably, because of substitution with electron-withdrawing groups such as carboxylic or phosphoric acid residues. This

marked difference in the reactivity of *m*-alkyl (or some aryl) glycosides can be taken as an advantage in the design of procedures for one-pot, armed–disarmed or orthogonal glycosylations. Moreover, apart from chemoselective activation, some of the *S*-glycosidic compounds described herein are also prone to selective deactivation through metal complexation (e.g. heteroaryl thioglycosides).

Xanthates, thioimidates and other anomeric thio derivatives discussed in this chapter constitute convenient glycosyl donors because they are easy to prepare, reasonably stable, as well as afford excellent yields and stereoselectivities of *O*-glycosides upon activation with a variety of mildly acidic or thiophilic activators, such as Lewis acids and heavy-metal salts (particularly triflates). These glycosyl donors, in combination with more traditional glycosylating reagents, allow for the fine tune-up of an anomeric leaving-group reactivity, which in turn makes possible to design the synthesis of challenging glycosidic linkages and complex oligosaccharides needed as molecular probes for biological studies and new chemical entities for drug discovery.

4.3.7 Typical Experimental Procedures

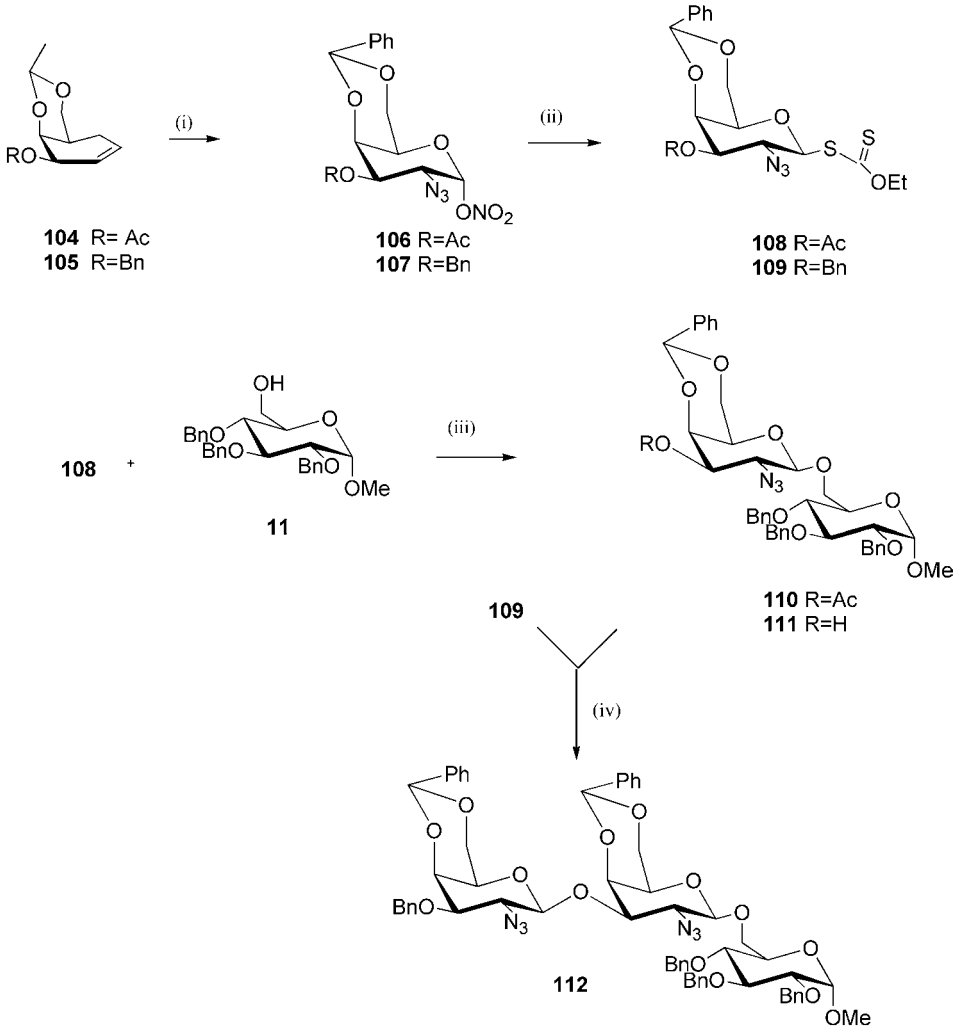
4.3.7.1 Preparation of Xanthates

O-Ethyl S-(2-Azido-3,4,6-Tri-O-Benzyl-2-Deoxy-β-D-Galactopyranosyl) Dithiocarbonate A solution of 2-azido glycosyl nitrate 6 (2.5 mmol) and *O*-ethyl *S*-potassium dithiocarbonate 5 mmol) in acetonitrile (20 ml) was kept for 5 h at room temperature, diluted with dichloromethane (200 ml), washed with water (30 ml), dried ($MgSO_4$) and concentrated. Column chromatography of the residue (4 : 1 hexane–ethyl acetate, 0.3% triethylamine) gave the title compound in 97% yield.

O-Ethyl S-[Methyl (5-Acetamido-4,7,8,9-Tetra-O-Acetyl-3,5-Dideoxy-α-D-Glycero-D-Galacto-2-Nonulopyranosyl)onate] Dithiocarbonate (15) To a solution of sialyl chloride (1 mmol), tetrabutylammonium hydrogen sulfate (1 mmol) and *S*-potassium *O*-ethyldithiocarbonate in ethyl acetate (5 ml) was added 2 M sodium carbonate (5 ml). The two-phase mixture was vigorously stirred at room temperature until TLC showed disappearance of the halide. Ethyl acetate (50 ml) was then added, the organic phase was separated and successively washed with saturated sodium hydrogen carbonate, water and brine. The combined organic extracts were dried (sodium sulfate), filtered and concentrated to afford *S*-glycosyl dithiocarbonate. The oily residue obtained was purified by column chromatography over silica gel (toluene–ethyl acetate, 1 : 2) as eluant to provide pure product **15** as foam in 91% yield. Crystallization from benzene–pentane afforded **15** (72%).

4.3.7.2 Glycosidation of Xanthates (Scheme 4.95)

Methyl 6-O-(3-O-Acetyl-2-Azido-4,6-O-Benzylidene-2-Deoxy-α- and β-D-Galactopyranosyl)-2,3,4-Tri-O-Benzyl-α-D-Galactopyranoside (110) A solution of xanthate **108** (1.2 mmol), glycosyl acceptor **11** (372 mg, 0.8 mmol) and activated 4-A powdered



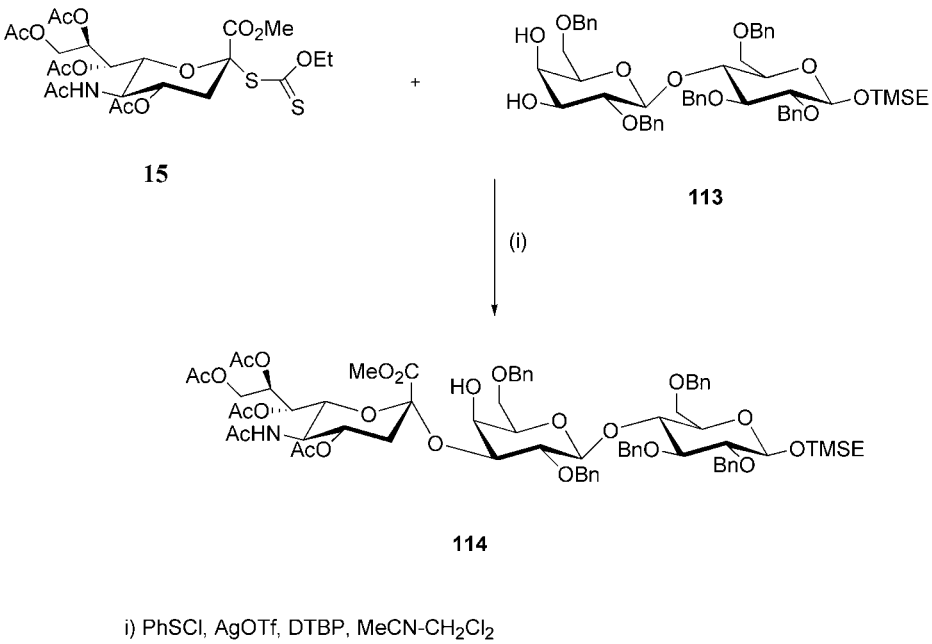
Scheme 4.95 Stereoselective synthesis of oligosaccharides via glycosyl xanthate [399].

molecular sieves (0.60 g) in anhydrous acetonitrile (10 ml) was stirred for 15 min at room temperature. Dimethyl(methylthio)sulfonium triflate was added and the stirring was continued for 1 h at room temperature. The suspension was treated with an excess of diisopropylamine, diluted with dichloromethane, filtered (Celite) and concentrated. Column chromatography of the residue (10 : 1 → 5 : 1 toluene–ethyl acetate) gave the title oligosaccharides **110** as separate anomers in 13 (α) and 73% (β) yield.

Methyl *O*-(2-Azido-3-*O*-Benzyl-4,6-*O*-Benzylidene-2-Deoxy-α-D-Galactopyranosyl)-(1–3)-*O*-(2-Azido-4,6-*O*-Benzylidene-2-Deoxy-β-D-Galactopyranosyl)-(1–6)-2,3,4-Tri-*O*-Benzyl-α-D-Glucopyranoside (112) A mixture of the disaccharide acceptor **111** (0.1 mmol),

xanthate donor **109** (0.15 mmol), activated 4-A powdered molecular sieves (0.20 g) and anhydrous dichloromethane (2 ml) was stirred for 15 min at room temperature. Copper(II) triflate (0.43 g, 1.2 mmol) was then added and stirring was continued for 6 h at room temperature. The mixture was diluted with dichloromethane (200 ml), washed with water (30 ml), dried ($MgSO_4$) and concentrated. Column chromatography of the residue (2 : 1 toluene–ethyl acetate, containing 0.3% triethylamine) gave the title α-trisaccharide **112** in 80% yield.

2-(Trimethylsilyl)-Ethyl-[Methyl (5-Acetamido-4,7,8,9-Tetra-*O*-Acetyl-3,5-Dideoxy-α-D-Glycero-D-Galacto-2-Nonulopyranosyl)onate] (2–3)-(2,6-Di-*O*-benzyl-β-D-Galactopyranosyl)-(1–4)-2,3,6-Tri-*O*-Benzyl-β-D-Glucopyranoside (114) (Scheme 4.96) A solution of dithiocarbonate **15** (1.44 mmol) and disaccharide acceptor **113** (0.96 mmol) in a mixture of dry acetonitrile (20 ml)/methylene chloride (10 ml) and powdered molecular sieves (3 g, 4A) was stirred under nitrogen for 1 h. AgOTf (1.58 mmol) and 2,6-di-*tert*-butylpyridine (1.70 mmol) were added and the mixture was cooled to −70 °C and kept protected from light. Benzenesulfenyl chloride (1.55 mmol) was then added, and stirring was continued for 2 h at −70 °C. The mixture was diluted with a suspension of silica gel (5 g) in ethyl acetate (30 ml), filtered (Celite), washed with saturated aqueous sodium hydrogen carbonate and water, dried (sodium sulfate) and concentrated. The residue was chromatographed (chloroform–acetone, 9 : 1, 4 : 1) to give trisaccharide **114** as foam (74%).



Scheme 4.96 Stereoselective sialylation with sialyl xanthate [410].

4.3.7.3 Preparation of Thioimidates

2-Thiazolinyl 2,3,4,6-Tetra-*O*-Benzoyl-1-thio-β-D-Glucopyranoside (3) Crown ether [15]-crown-5 and salt NaSTaz (6 mmol), prepared from NaOMe and 2-mercaptothiazoline in methanol, were added to a stirred solution of a tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (3.0 mmol) in a dry acetonitrile (24 ml) under argon. The reaction mixture was stirred for 1 h at room temperature. Upon completion, the mixture was diluted with toluene (30 ml) and washed with 1% aq NaOH (15 ml) and water (3 × 10 ml), and the organic phase was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the STaz glycoside (53%).

2-Benzoxazolinyl 2,3,4,6-Tetra-*O*-Benzoyl-1-thio-β-D-Glucopyranoside (39) 18-Crown-6 (0.6 mmol) and KSBox (3.45 mmol, prepared from HSBox and K_2CO_3) were added to a stirred solution of a glycosyl bromide (3.0 mmol) in dry acetone (4 ml) under an atmosphere of argon. The reaction mixture was stirred for 1 h at 55 °C. Upon completion, the mixture was diluted with CH_2Cl_2 (30 ml) and washed with 1% aq NaOH (15 ml) and water (3 × 10 ml). The organic phase was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford the title SBox glycoside (87%).

One-Pot Synthesis of Methyl *O*-(2,3,4,6-Tetra-*O*-Benzoyl-β-D-Glucopyranosyl)-(1–6)-*O*-(2,3,4-Tri-*O*-Benzoyl-β-D-Galactopyranosyl)-(1–6)-*O*-(2,3,4-Tri-*O*-Benzoyl-β-D-Glucopyranosyl)-(1–6)-2,3,4-Tri-*O*-Benzyl-β-D-Glucopyranoside (72) (Scheme 4.86) A mixture of SBox donor **39** (0.0274 mmol), *S*-ethyl acceptor **66** (0.0249 mmol) and freshly activated molecular sieves (3 A, 60 mg) in $(ClCH_2)_2$ (0.5 ml) was stirred under argon for 1 h. AgOTf (0.0603 mmol) was added. The reaction mixture was then stirred for 10 min at room temperature. Upon completion, the reaction mixture was cooled to −20 °C, and STaz acceptor **70** (0.0224 mmol), NIS (0.05 mmol) and TfOH (0.005 mmol) were added to it. The reaction mixture was stirred for 30 min. Upon completion, the reaction mixture was warmed up to room temperature, and then glycosyl acceptor **40** (0.0249 mmol) and AgOTf (0.05 mmol) were added. Upon completion (2 h), the solid was filtered and washed with CH_2Cl_2. The combined filtrate (30 ml) was washed with 20% aq $Na_2S_2O_3$ (15 ml) and water (3 × 10 ml). The organic phase was then separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (acetone/toluene gradient elution) to allow the title tetrasaccharide **72** in 73% yield.

4.3.7.4 Synthesis of Glycosyl Thiocyanates (Scheme 4.92)

3,4,6-Tri-*O*-Acetyl-2-*O*-Benzyl-β-D-Galactopyranosyl Thiocyanate (99) 2-*O*-Benzyl-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl bromide (**98**) (4.0 mmol), potassium thiocyanate (12.0 mmol), dried *in vacuo* at 110 °C, and 18-crown-6 (0.4 mmol), dried *in vacuo*

for 24 h at 20 °C, were dissolved in dry acetone (10 ml). The reaction was monitored by TLC and when complete, the reaction mixture was concentrated, and traces of acetone was removed by coevaporation with benzene, filtered and concentrated. Residue was subjected to column chromatography (elution with benzene–ether) to allow the title compound in 54% yield.

4.3.7.5 Glycosidation of Thiocyanates

1,3,4,6-Tetra-*O*-Acetyl-2-*O*-(3,4,6-Tri-*O*-Acetyl-2-*O*-Benzyl-α-D-Galactopyranosyl)-α-D-Galactopyranose (101) (Scheme 4.92) Thiocyanate **99** (0.20 mmol), tritylated acceptor derivative **100** (0.20 mmol) and triphenylmethylium perchlorate (0.02 mmol) were dissolved in dry methylene chloride (2.5 ml). The reaction was monitored by TLC and when completed, a few drops of pyridine were added to quench the reaction. Reaction mixture was diluted with chloroform (30 ml), washed with water and concentrated to dryness. The residue was then dissolved in dry pyridine (2 ml), Ac_2O (1 ml) was added and the mixture was stored overnight at room temperature. Thereafter, methanol was added, the mixture was coconcentrated several times with toluene and the residue was subjected to column chromatography. Elution with benzene–ether gave disaccharide **101** as syrup in 59% yield.

4.3.7.6 Synthesis of *S*-(2-Deoxyglycosyl) Phosphorodithioates (Scheme 4.93)

Treatment of a 1,2-dehydro derivative (1 mmol) with an equimolar amount of *O*,*O*-diethyl *S*-hydrogen phosphorodithioate (1 mmol) in benzene (3 ml) for 24 h quantitatively yielded a crude anomeric mixture of the title compounds after evaporation *in vacuo*.

4.3.7.7 Glycosidation of Glycosyl Phosphorodithioates

1,2:3,4-Di-*O*-Isopropylidene-6-*O*-(2-Deoxy-3,4,6-Tri-*O*-Acetyl-α,β-D-Galactopyranosyl)-α-D-Galactopyranose 103 (Scheme 4.94) Glycosyl donor **102** (1 mmol) and the acceptor **96** (1.2 mmol) in CH_2Cl_2 (2 ml) were allowed to react in the presence of 4A molecular sieves and NIS (1.1 mmol) at room temperature in a dry N_2 atmosphere. After 1 h the mixture was diluted with $CHCl_3$, washed with 10% $Na_2S_2O_3$ solution and water, dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (silica gel, flash technique). This afforded the disaccharide **103** in 80% yield as anomeric mixture.

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4.4
Selenoglycosides

Robert A. Field

4.4.1
Background

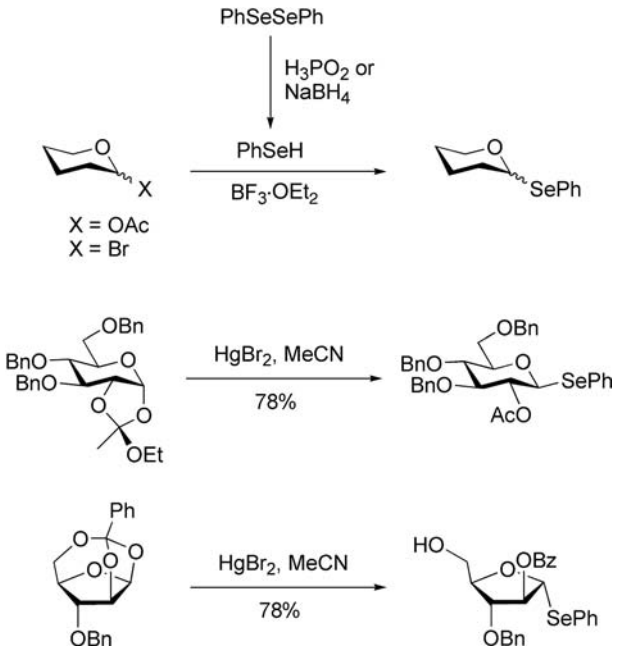
Interest in the use of selenoglycosides as donors for *O*-glycosylation mainly emanates from Pinto's work in the early 1990s, which introduced this versatile class of compound to the armory of donor molecules for glycosylation chemistry [222,223,512]. Earlier studies on selenium-containing sugars have been comprehensively reviewed by Witczak and Czernecki [513]. As with the difference in chemistry and reactivity of oxygen versus sulfur, migration down the periodic table to selenium, and indeed beyond to tellurium, results in increased reactivity per se and a greater propensity for homolysis of the anomeric carbon–chalcogen bond. The latter provides ready access to anomeric radical chemistry *en route* to *C*-glycosides [513,514]. The former has attracted attention in relation to expanding the repertoire of tunable sugar donor functionalities (protecting groups; nature and substitution of the anomeric leaving group) in relation to *O*-glycosylation. Specifically, O versus S versus Se reactivity differences have received attention for the exploitation of armed–disarmed [515,474] approaches to one-pot, multiple-glycosylation reaction sequences. This chapter outlines common methods for the preparation of selenoglycosides and their activation for *O*-glycoside synthesis using either the conventional or single-electron transfer (SET) process. The application and integration of selenoglycosides in multistep oligosaccharide syntheses is also highlighted.

4.4.2
Selenoglycoside Preparation

Selenoglycosides are typically prepared by treating a glycosyl acetate with phenylselenol, derived from the hypophosphorus acid reduction of PhSeSePh in the presence of $BF_3{\cdot}OEt_2$ [222] or by treating glycosyl halides with $NaBH_4$-reduced PhSeSePh (Scheme 4.97) [516]. The latter chemistry is also effective for the preparation of the related telluroglycosides [517]. Selenoglycosides can also be prepared from orthoesters by treatment with phenylselenol in the presence of $HgBr_2$ [147,518] or $SnCl_4$ (Scheme 4.97) [518].

Selenoglycosides of sialic acid have been successfully prepared in excellent yields from the corresponding peracetylated glycosyl chloride with phenylselenol in the presence of *N,N*-di-isopropylethylamine [519]. This reagent combination succeeded where others were less effective or failed (Scheme 4.98; [520].

The exposure of selenostannane to glycosyl acetates in the presence of catalytic $Bu_2Sn(OTf)_2$ also provides selenoglycosides in good yield and with reasonable stereocontrol (Scheme 4.99) [520]. Thioglycosidation can be achieved in a similar manner by the use of thiostannane; this reaction is also reported to be effective for the conversion of methyl glycosides into thioglycosides. A recent alternative to this approach employs indium(I)-iodide-mediated cleavage of diselenides for reaction with glycosyl bromides. This convenient and odorless methodology gives selenoglyco-



Scheme 4.97 Selenoglycoside synthesis.

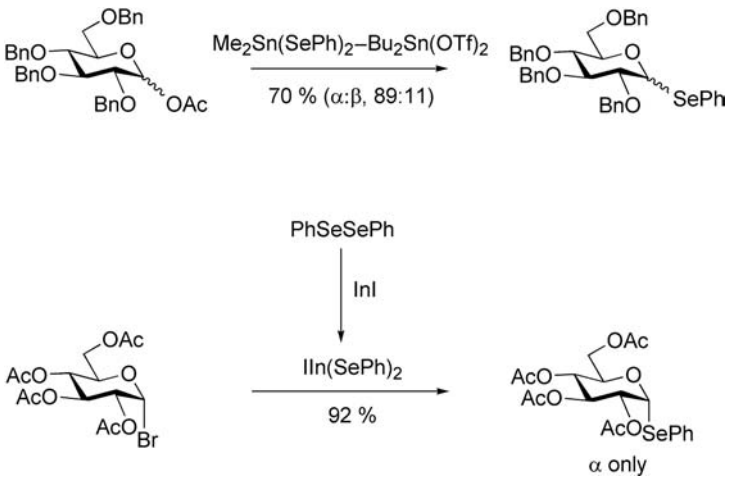
X	Conditions	Yield
OAc	PhSeH, $BF_3{\cdot}OEt_2$	0 %
Cl	PhSeSePh, NaH	20 %
Cl	PhSeH, $BnEt_3N^+Cl^-$	60 %
Cl	PhSeH, iPr_2NEt	97 %

Scheme 4.98 α-Selenosialoside synthesis.

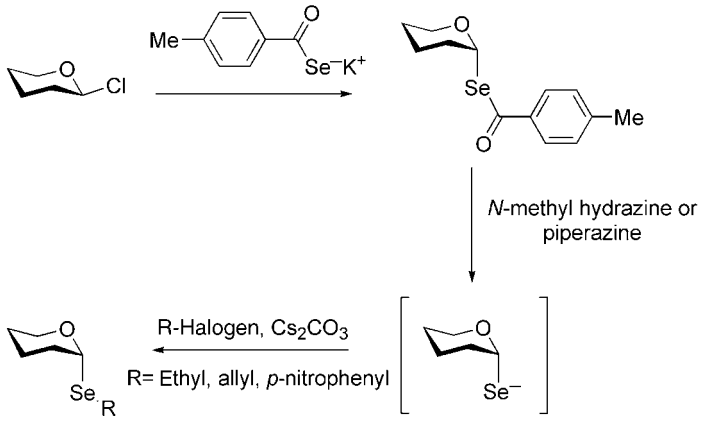
sides in excellent yield. The method is successful across a range of sugars, including sialic acid (Scheme 4.99) [521].

The stereoselective synthesis of α-selenoglycosides can also be achieved through recently described reactions of selenocarboxylates [522]. Reaction of β-glycosyl chlorides with potassium *p*-methylselenobenzoate gives the selenoglycosyl *p*-methylbenzoate, which upon reaction with an amine nucleophile gives the α-anomeric selenolate anion. Subsequent *in situ* reaction with various electrophiles in the presence of Cs_2CO_3 gives α-selenoglycosides, including alkyl and aryl selenoglycosides, selenoglycosyl amino acid and selenodisaccharides (Scheme 4.100) [523].

For the synthesis of glycans containing 2-amino-2-deoxysugars, the regioselective azidophenylselenation of glycals is popular [524–528]. This methodology follows on from the classic azidonitration work of Lemieux and Ratcliffe, first reported in the



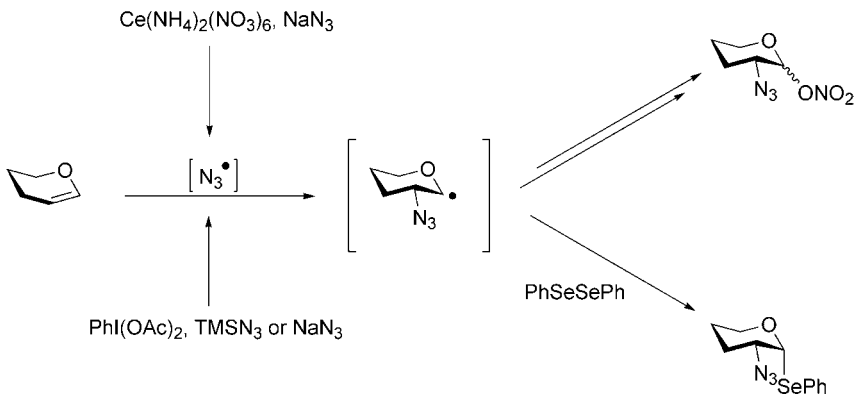
Scheme 4.99 Tin and indium in selenoglycosides synthesis.



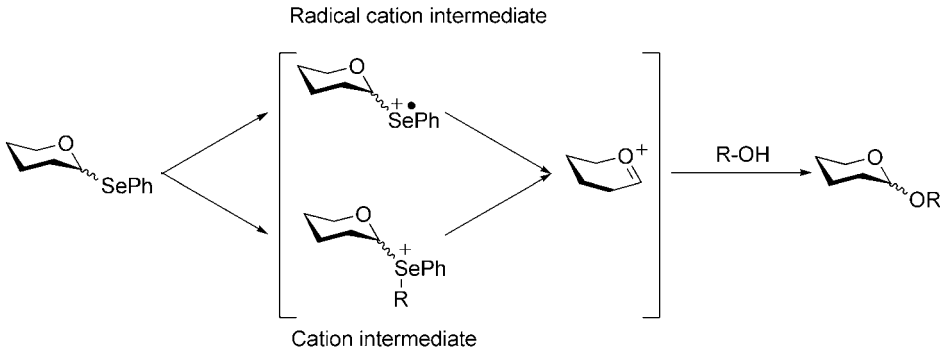
Scheme 4.100 Selenoglycosides from selenobenzoates.

late 1970s [529]. Radical-mediated, anti-Markovnikov azidophenylselenylation of variously protected glycals affords phenyl 2-azido-2-deoxy-α-selenoglycopyranosides (Scheme 4.101).

A mixture of the *manno* and *gluco* isomers was obtained from D-glucal, albeit in very high yield (> 80%). In contrast, azidophenylselenylation of D-galactal gave complete stereocontrol, affording exclusively the α-*galacto* isomer in 70–80% yield. More recent work by Nifantiev and colleagues [530] reports an improved preparative method for homogeneous azidophenylselenylation of glycals, consisting of the reaction with $TMSN_3$ and $(PhSe)_2$ in the presence of $PhI(OAc)_2$. The use of $TMSN_3$ instead of NaN_3, as in the earlier heterogeneous procedure [524–528], allowed both a reduced reaction time and scale-up that was not previously achievable on a reliable basis.



Scheme 4.101 Azidonitration and azidophenylselenation.



Scheme 4.102 Cation and radical-cation pathways for selenoglycoside glycosylation.

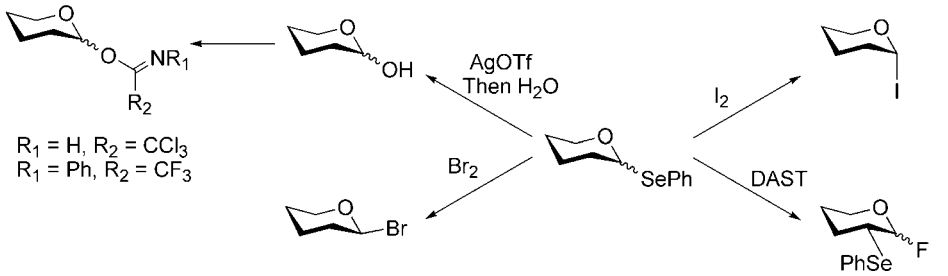
4.4.3 Selenides as Donors

Selenoglycosides are attractive donor species owing to the wide range of reagents that can promote cation- and radical-cation-based processes for their activation and subsequent *O*-glycosylation (Scheme 4.102) [223,512].

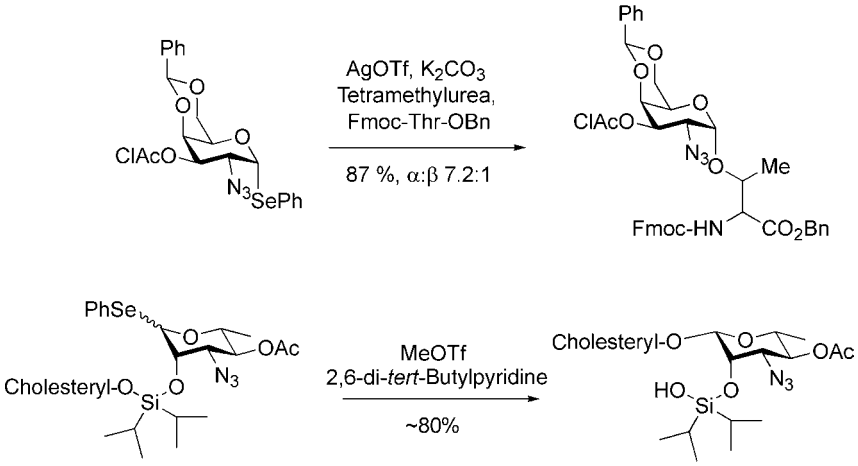
In addition to their direct activation for glycosylation, selenoglycosides are versatile building blocks that can easily be converted into other glycosyl donor species (Scheme 4.103). For instance, hydrolysis to hemiacetal [223] provides access to glycosyl *N*-phenyltrifluoroacetimidates [531]. Treatment with molecular iodine gives rise to the thermodynamically favored glycosyl iodides [532], whereas treatment with bromine kinetically favored β-bromides [533]. Reaction of 2-hydroxy phenyl selenoglycosides with diethylaminosulfur trifluoride (DAST) leads to the corresponding 2-phenylselenoglycosyl fluorides, which react stereoselectively with carbohydrate accepters to afford 2-phenylselenoglycosides *en route* to 2-deoxy glycosides (by reduction) or orthoesters (by oxidative elimination and rearrangement) [534].

4.4.3.1 Promoters for Selenoglycoside Activation

Cation-Based Activation Pinto's works not only described $AgOTf/K_2CO_3$ as the promoter of choice for the activation of phenyl selenoglycosides but also indicated



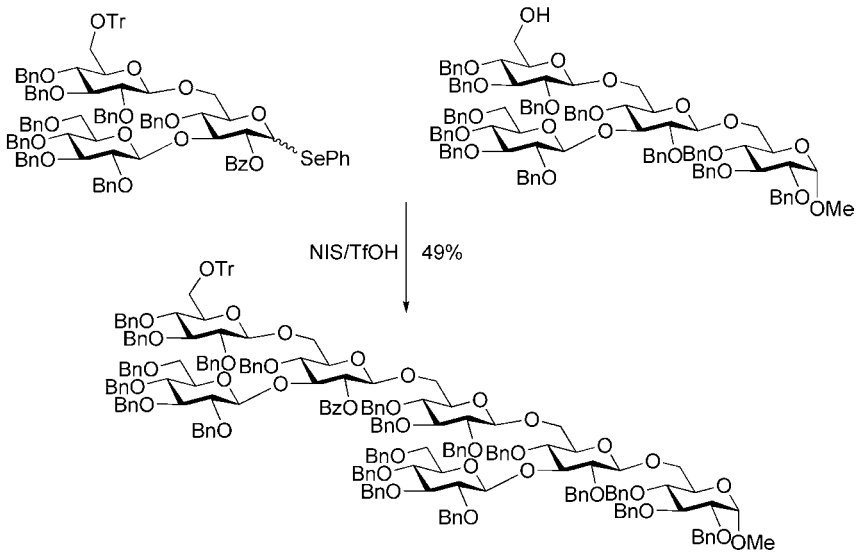
Scheme 4.103 Transformation of selenoglycosides to other potential donor species.



Scheme 4.104 AgOTf/K_2CO_3 and MeOTf promoters for selenoglycoside glycosylation.

that donors of this type can be activated by other promoters such as MeOTf, PhSeOTf or $CuBr_2$–Bu_4NBr–AgOTf [223,512]. It is also to be noted that AgOTf in the presence of an organic base, such as collidine or 1,1,3,3,-tetramethylurea, is *not* capable of activating phenyl selenoglycosides. This offers an additional opportunity for glycosylation of acceptors based on partially protected phenyl selenoglycosides (see Sections 4.4.4 and 4.4.5).

Although AgOTf/K_2CO_3 had proved to be a suitable promoter in connection with the synthesis of the *O*-glycosylated amino acid building blocks related to TF antigen



Scheme 4.105 NIS/TfOH-promoted heptaglucan synthesis.

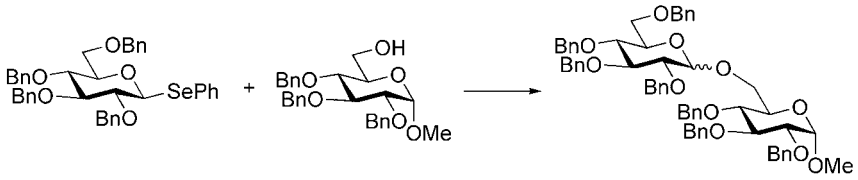
[535], it proved ineffective in selenoglycoside-based glycosylation using an intramolecular aglycone delivery approach (Scheme 4.104). However, MeOTf was successfully employed in this latter study [386], which aimed to develop generic methods for the stereoselective coupling of D-mycosamine, a common sugar often found attached to macrolide antibiotics.

As noted by Pinto, electrophilic selenylating agents, and in particular PhSeOTf, are useful promoters for the activation of the phenylseleno group in glycosylation reactions, including those of 2-azido-2-deoxysugar donors [536]. However, $NO{\cdot}BF_4$ proved only moderately effective when used in conjunction with the phenyl selenoglycoside of a 5-deoxy-5-thioglucose-based donor. An extensive transfer of acetate from the donor to the acceptor alcohol was noted, in addition to modest yields of disaccharides [537].

Extending the application of glycosylation chemistry initially developed for thioglycosides [541,538,539], the van Boom group have shown the potential of iodonium-ion-mediated glycosidations of phenyl selenoglycosides in the chemoselective synthesis of 1,2-*cis*- or 1,2-*trans*-linked disaccharides. Specifically, fully benzylated or benzoylated phenyl selenoglycosides can be activated by the promoters NIS/TfOH and IDCP [540,541]. The former reagent has been employed in several selenoglycoside-based syntheses, including the bis-*O*-glycosylation of 4,4′-dihydroxybiphenyl that was achieved in moderate yield [542]. NIS/TfOH has also been used in the sialylation of phenolic and sugar alcohols, in moderate yields; dimethyl methylthiosulfonium triflate (DMTST) gave similar modest results with phenols [519]. The NIS/TfOH promoter combination is also used for the preparation of a tetrasaccharide fragment of the cell wall from a *Proteus vulgaris* strain [543] and the blockwise coupling of a trisaccharide phenyl selenoglucosyl donor with a tetrasaccharide to furnish a heptaglucan phytoalexin elicitor (Scheme 4.105; see also Section 4.4.5) [544].

Molecular iodine has also been investigated as a promoter iodonium ion equivalent. It has been shown to be an effective general promoter for the activation of armed glycosyl donors based on thio-orthoesters, glycosyl-sulfoxides, -selenides and -phosphites, trichloroacetimidates and pentenyl glycosides [545]. *N*-iodosuccinimide (NIS) alone is also capable of activating armed thioglycosides and selenoglycosides, but glycosylation yields are somewhat erratic [546]. The stereochemical outcome of glycosylation reactions with model thioglycosides and selenoglycosides has been shown to be dependent on the solvent and the source of promoter iodonium ion, with iodine giving different results to NIS alone and to NIS/TMSOTf (Scheme 4.106).

Further investigation of donor activation with iodine in the absence of alcohol nucleophile showed that, in contrast to armed thioglycosides that anomerize and disarmed thioglycosides that do not react [547], both armed and disarmed selenoglycosides give rise to the corresponding glycosyl iodides [546]. This may point to the involvement of glycosyl iodides as intermediates in iodine-promoted glycosylation with armed thio- and seleno-glycosides, which potentially has an impact on the stereochemical outcome of the glycosylation process. Although this may be an issue when solvent-assisted stereocontrol with acetonitrile is being used [548,549], it can be overcome by *in situ* oxidation of iodide to iodine by the use of iodine in

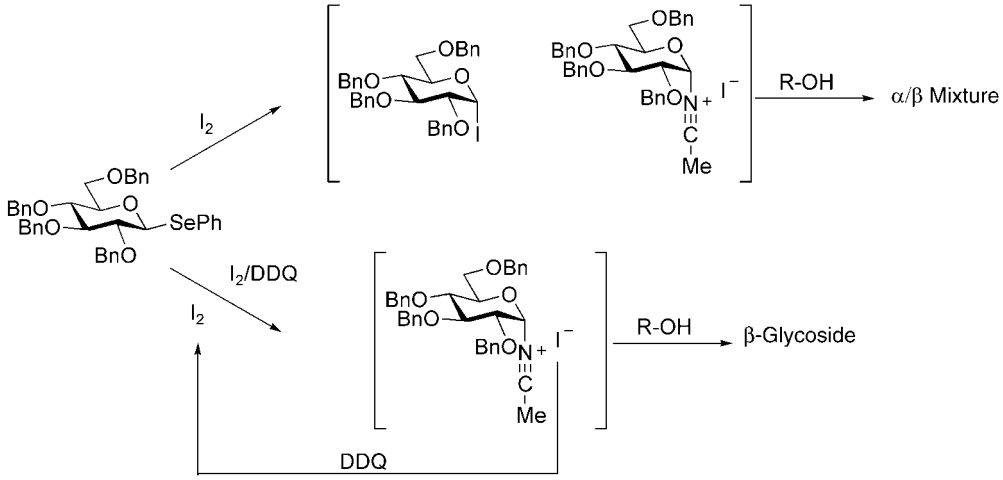


Conditions	Yield	α:β
NIS, MeCN	64%	1/5
NIS, CH_2Cl_2	32%	1/1.2
NIS, TMSOTf, MeCN	83%	1/5
NIS, TMSOTf, CH_2Cl_2	92%	1/1.4
I_2 (2 equiv), MeCN	91%	1/1.5
I_2 (2 equiv), CH_2Cl_2	52%	2/1

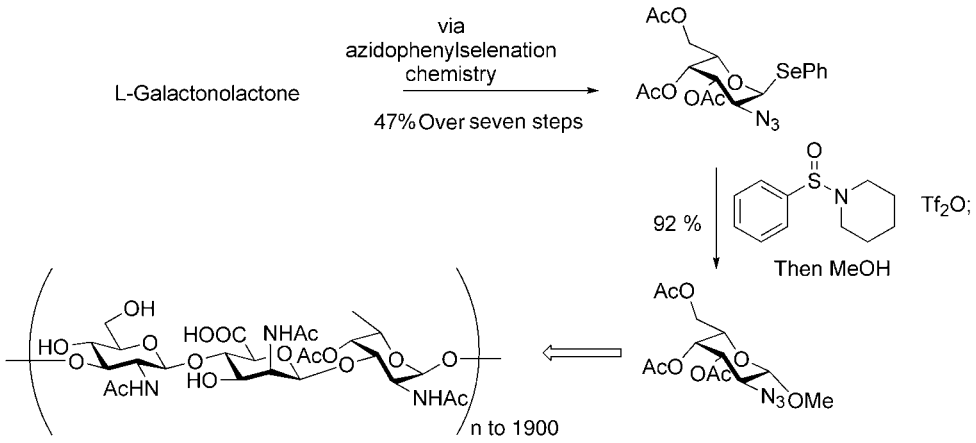
Scheme 4.106 Promoter- and solvent-dependent selenoglycosylation.

combination with DDQ as the glycosylation promoter (DDQ itself is not an effective activator of thio- and seleno-glycosides, Scheme 4.107).

Synthesis of the trisaccharide repeating unit of the acidic polysaccharide of the bacteriolytic complex of lysoamidase provided a vehicle for the identification of a new single set of activation conditions for use with both thio- and selenoglycosides [550]. The powerful 1-benzenesulfinyl piperidine (BSP)/Tf_2O sulfonium-activator system developed by Crich and Smith [85] enabled the construction process to be based on a linear glycosylation strategy starting from the reducing end (Scheme 4.108).



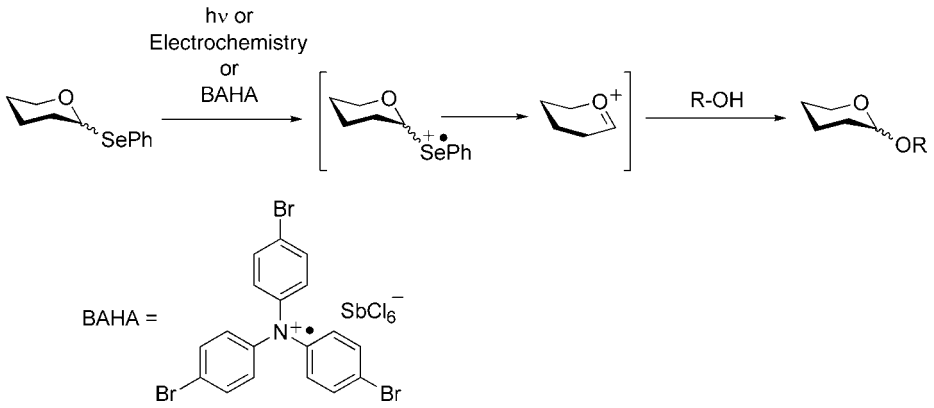
Scheme 4.107 Iodine/DDQ-enhanced β-glycosylation with selenoglycoside donor.



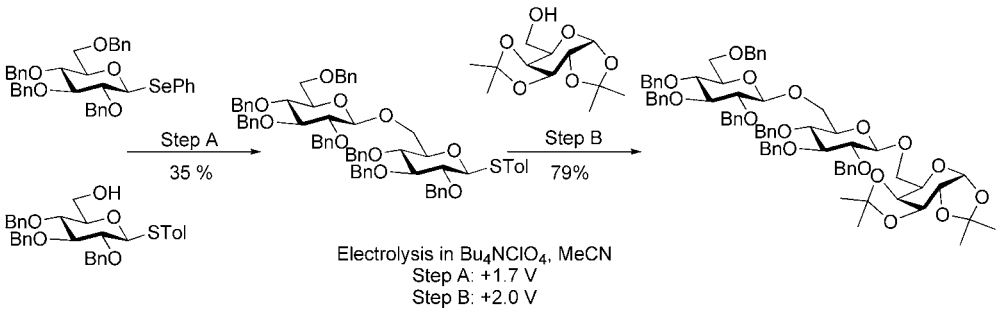
Scheme 4.108 *En route* to the lysoamidase trisaccharide repeat unit.

The selective activation of phenyl selenoglycosides over ethyl thioglycosides with AgOTf and anhydrous K_2CO_3 gives an efficient synthesis of disaccharides from selenoglycoside donors and thioglycoside acceptors [222,223]. In addition, the selective activation of telluro- over selenoglucoside donors identifies a clear reactivity scale for various telluro-, seleno- and thiosugars [551], although this is yet to be fully exploited in oligosaccharide synthesis.

Radical-Cation-Based Activation As for thioglycosides and also telluroglycosides, phenyl selenoglycosides are amenable to single-electron transfer activation. This can lead to photochemical oxidation, electrochemical activation or the use of organic single-electron transfer agents, such as tris(4-bromophenyl)ammoniumyl hexachloroantimonate (*BAHA*, Scheme 4.109).



Scheme 4.109 Single-electron transfer activation of selenoglycosides.

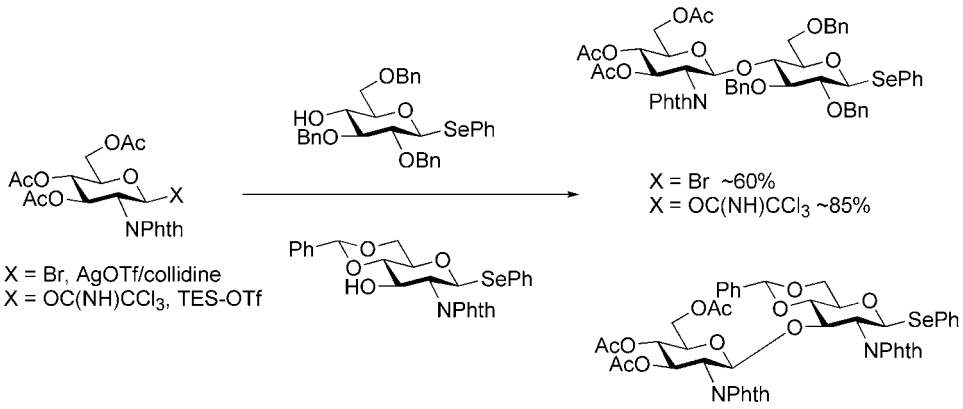


Scheme 4.110 Electrochemical synthesis employing *O*-, *S*- and *Se*-glycosides.

Photochemical oxidation has been employed for the activation of *O*-glycosides [552], thioglycosides [553] and telluroglycosides [554]. It is also effective for *O*-glycosylation with the phenyl selenoglycoside donors [555], although this approach has not been widely taken up for preparative use.

Similarly, the electrochemical glycosylation methods developed for use with aryl *O*-glycosides [103] and thioglycosides [556–558] can also be applied to the phenyl selenoglycosides and telluroglycosides [559] . The lower oxidation potentials of the phenyl *Se*-glycosides compared to phenyl *S*-glycosides, which in turn are lower than that for phenyl *O*-glycosides, offers compatibility with a wider range of protecting groups [106,560]. Ionization potentials (kJ mol^{-1}) for a series of typical glycosides are O (314) > S (239) > Se (225) > Te (208) [561]. The selection of selenoglycosides with ionization potentials that are dependent on aglycone and/or sugar protecting groups is attractive in the context of iterative electrochemical glycosylation. However, application of this information is not entirely straightforward. Although disaccharide syntheses have been achieved in good yield, the relative reactivity of selenoglycosides in preparative glycosylation has proved rather insensitive to oxidation potential values [561]. Furthermore, despite reporting the first electrochemical trisaccharide synthesis (Scheme 4.110) and that a variety of disaccharides are readily synthesized in high yield, Fairbanks and coworkers have also noted limitations in the use of selenoglycosides for the selective electrochemical glycosylation of thioglycoside acceptors [562].

Chemically induced glycosylation reactions with phenyl selenoglycosides promoted by BAHA [548], as previously described for thioglycosides [563–565], are thought to proceed via a single-electron transfer mechanism. Studies have provided support for the SET mechanism, but an alternative involving electrophilic activation cannot be discounted [106]. BAHA-promoted glycosylation with per-*O*-benzylated phenyl β-selenoglucoside gives α-1,6-linked glucosides in moderate to good yield but with poor stereocontrol in either dichloromethane or acetonitrile. In contrast, the same reaction promoted by iodine in combination with DDQ gave better acetonitrile-assisted β-stereoselectivity and higher yields with both thioglycoside and selenoglycoside donors than by reactions promoted by BAHA in acetonitrile [546].

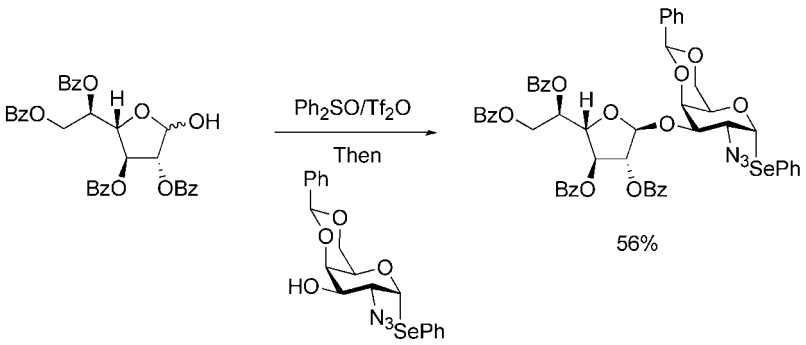


Scheme 4.111 Selenide acceptors with bromide and trichloroacetimidate donors.

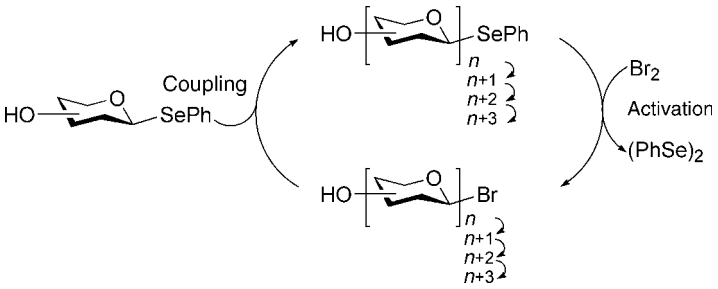
4.4.4
Selenoglycosides as Acceptors

The fact that phenyl selenoglycosides are rendered unreactive toward AgOTf in the presence of an organic base, such as collidine, suggested that the preferential coordination of silver cation to the base left it unavailable for coordination to and activation of the selenoglycoside. This, in turn, highlighted the possibility of selective activation of another donor over a selenoglycoside, leaving the latter to serve as a glycosyl acceptor [223]. Indeed, reaction of selenoglycoside acceptors with a glycosyl bromide donor gave disaccharides in good yield (Scheme 4.111). The selective activation of glycosyl trichloroacetimidate over selenoglycoside has also been demonstrated: in the presence of a catalytic amount of TESOTf, disaccharides were obtained in excellent yield (Scheme 4.111) [223].

Dehydrative glycosylation of 1-hydroxy donors with Ph_2SO/Tf_2O in conjunction with thioglycoside acceptors opens the way for sequential double glycosylation, one-pot procedures for trisaccharide synthesis, as exemplified by the efficient one-pot synthesis of the α-Gal epitope and a hyaluronan trisaccharide [566]. This study also shows the potential of selenoglycoside as acceptors in dehydrative glycosylation (Scheme 4.112).



Scheme 4.112 Selenide acceptors for dehydrative glycosylation.



Scheme 4.113 Iterative glycosylation based on a glycosylselenide acceptor and its facile conversion into reactive β-glycosyl bromide donor.

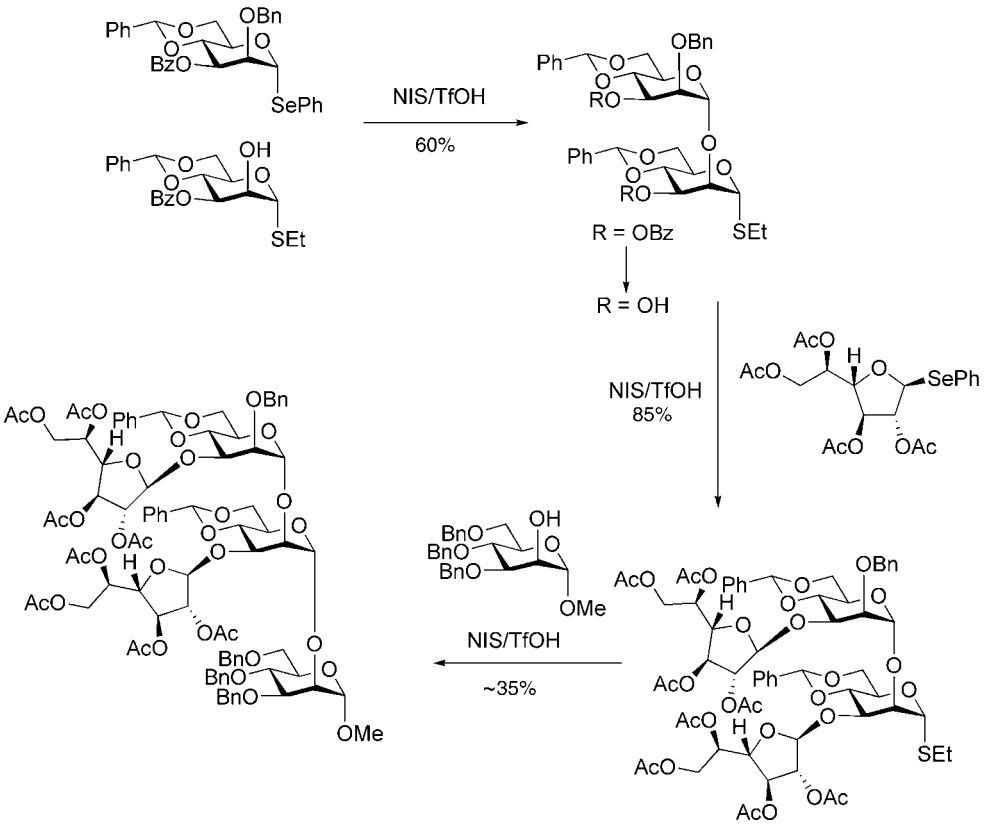
The use of selenoglycosides as acceptors in iterative glycosylation with reactive β-glycosyl bromides, themselves derived from selenoglycosides, has also been investigated recently (Scheme 4.113; see also Section 4.4.5) [533,567].

4.4.5
Exploiting Selenoglycoside Relative Reactivity in Oligosaccharide Synthesis

The versatility of selenoglycosides in oligosaccharide synthesis is illustrated by the synthesis of galactofuranosyl-containing oligosaccharides corresponding to the glycosylinositolphospholipid of the protozoan parasite *Trypanosoma cruzi*, the causative agent of Chagas' disease [568]. The synthesis employs the NIS/TfOH-mediated selective activation of a phenyl selenogalactofuranoside or a phenyl selenomannopyranoside donor over ethyl thioglycoside acceptors. The need for careful control of reaction conditions and reagent stoichiometry to achieve such selectivity is crucial; NIS/TfOH is also capable of thioglycoside activation, as exploited later in the same synthesis (Scheme 4.114).

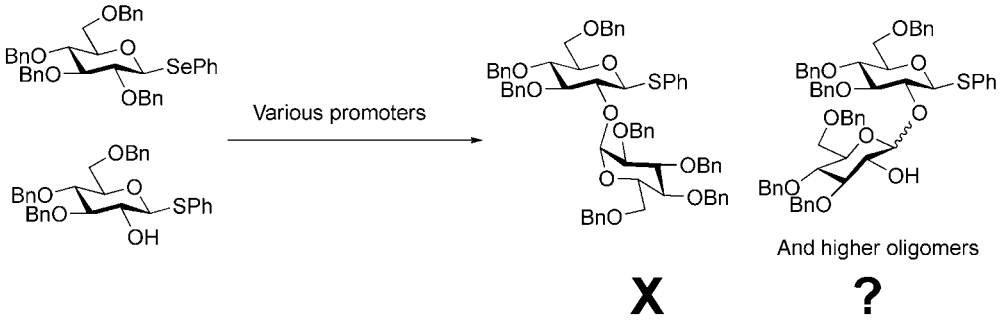
Although selective activation of selenoglycosides in the presence of thioglycosides is well precedented, it cannot always be relied on. In studies on the preparation of 2-*O*-ribofuranosyl-ribofuranosides from selenoglycoside donors and various thioglycoside acceptors, the formation of the desired disaccharide thioglycoside was accompanied by side products arising from *trans*-glycosylation and the formation of 1,1′-linked donor-derived disaccharides ([513] [569]. Furthermore, in the synthesis of a tetrasaccharide portion of the glucose-terminated arm of the *N*-glycan tetradecasaccharide, several attempted glycosylation reactions of prospective selenoglyside donor and thioglycoside acceptor met with failure [570]. Despite assessing a range of promoters (IDCP, AgOTf/K_2CO_3 and NIS/TfOH), TLC analysis indicated the formation of many reaction products, presumably because of the competitive activation of the thioglycoside and subsequent self-condensation (Scheme 4.115).

On a positive note, tuning the reactivity of glycosyl donors by selective introduction of different protecting and leaving groups has enabled highly efficient

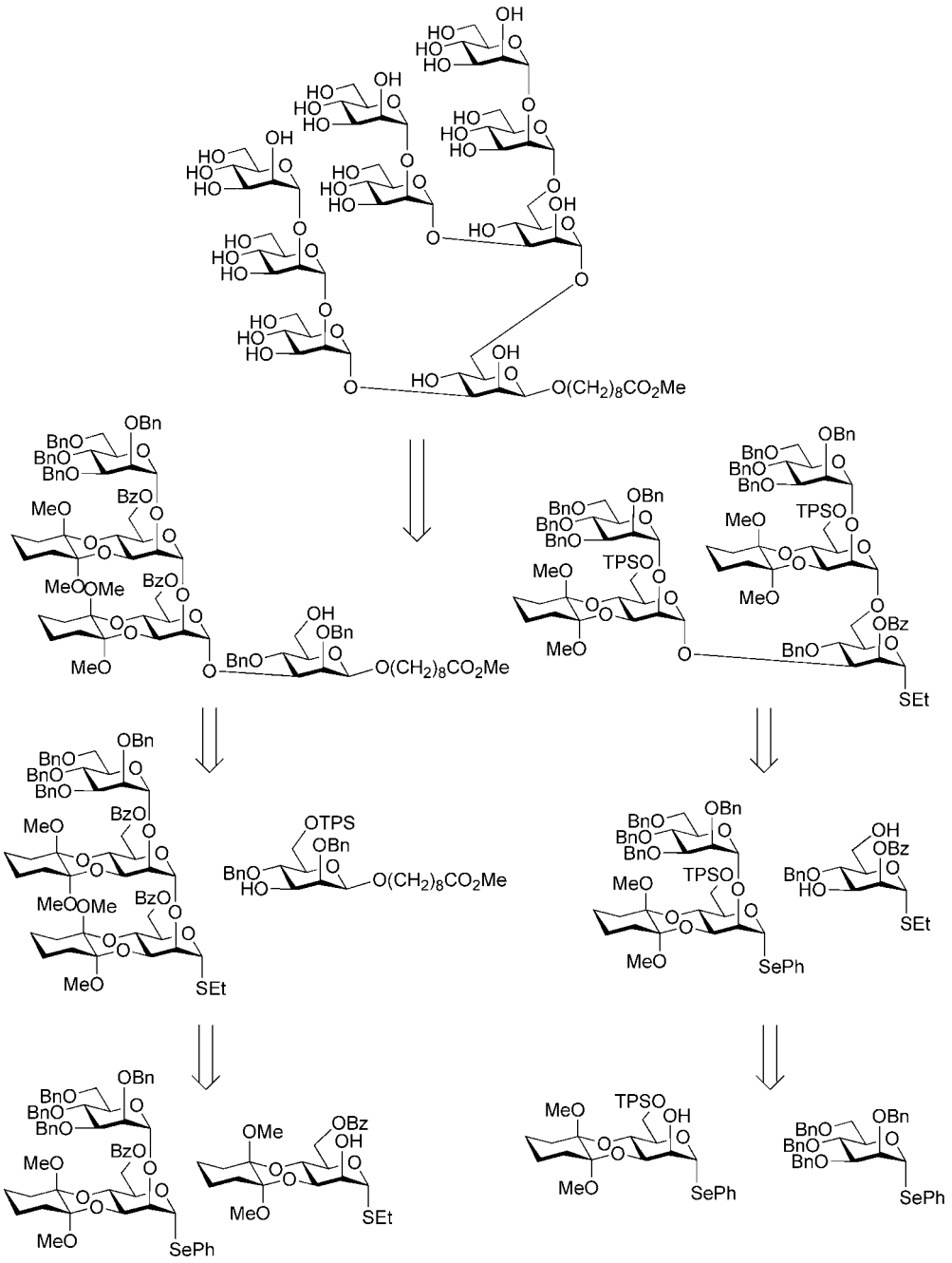


Scheme 4.114 Selenide donors and acceptors for multistep oligosaccharide synthesis.

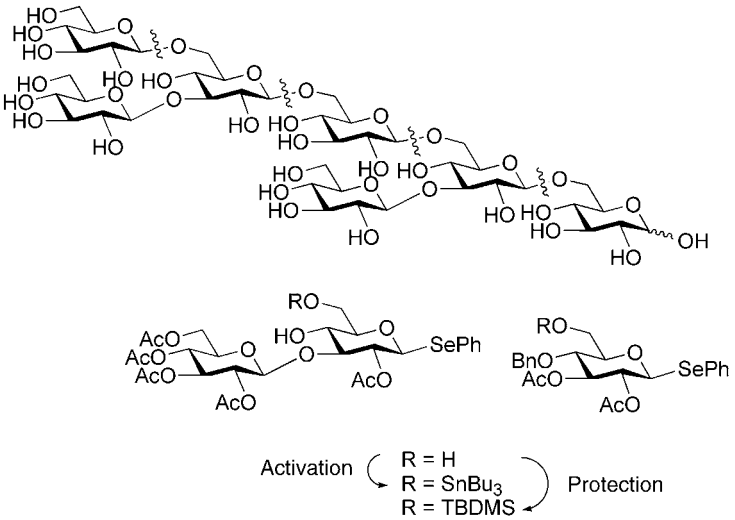
oligosaccharide synthesis. Utilizing both phenylseleno and ethylthio glycosides in combination with the cyclohexane-1,2-diacetal (*CDA*) protecting group provided four different levels of reactivity. One-pot sequential glycosidation of three components gave trisaccharides and tetrasaccharides, whereas the further extension



Scheme 4.115 Selenoglycoside donors and thioglycoside acceptors do not always behave similarly.



Scheme 4.116 Tuning building block reactivity for stream-lined high-mannose nonasaccharide synthesis.



Scheme 4.117 Retrosynthetic analysis of heptaglucan phytoalexin synthesis achieved using an iterative approach.

of the approach reduced the number of steps from the monosaccharide building blocks to a nonasaccharide, triantennary mannan to only five (Scheme 4.116) [571,182,572].

On a similar grand scale, the ease of conversion of selenoglycosides into β-glycosyl bromides enables the iterative glycosylation of selenoglycosides [533,567]. Treatment of 2-*O*-acyl-protected selenoglycosides with bromine selectively generates β-glycosyl bromides for use as glycosyl donors. Coupling the β-glycosyl bromide with another selenoglycoside then affords the corresponding glycosylated selenoglycoside, which can be directly used in the next round of glycosylation. The iteration of this sequence allows the synthesis of a variety of oligosaccharides, including a set of nested oligoglucoside fragments of a heptasaccharide phytoalexin (Scheme 4.117). A feature of the iterative approach is that glycosyl donors and acceptors with the same anomeric reactivity can be selectively coupled by the activation of the glycosyl donor prior to the introduction of the glycosyl acceptor. The same selenoglycosides can, therefore, in practice be used as both glycosyl donors and acceptors. This approach exemplifies the structural diversity that can be constructed solely from selenoglycoside building blocks.

4.4.6 Summary

In conclusion, the phenyl selenoglycosides are versatile building blocks for oligosaccharide synthesis. Through judicious choice of protecting groups, and particularly promoters, they can be exploited as either donors or acceptors in glycosylation

reactions. Although a number of syntheses have exploited the differential reactivity of selenoglycosides over thioglycosides, it is evident that, using either cation-based or electrochemical activation, the expected difference in reactivity of such building blocks cannot always be relied upon. Nonetheless, examples of selenoglycoside-based oligosaccharide syntheses continue to appear in the literature. Thus, further investigation of selenoglycosides is justified and is necessary, to realize their full potential.

4.4.7 Examples of Experimental Procedures

4.4.7.1 Typical Procedure for the Preparation of Selenoglycosides from Glycosyl Bromides

A solution of diphenyldiselenide (20 mmol) in dry ethanol (100 ml) was cooled by an ice bath. To this solution was 'carefully' added a preformed, cold solution of sodium borohydride (40 mmol) in dry ethanol (20 ml). As the mixture was stirred over 30 min, the yellow diselenide solution became colorless, reflecting selenol formation. To this mixture was added a solution of glycosyl bromide (30 mmol) in CH_2Cl_2 (20 ml) and the stirring was continued for 2 h at room temperature. After aspirating the solution to oxidize the remaining selenol, the solvent was evaporated *in vacuo* and the resulting material was dissolved in CH_2Cl_2 (200 ml) and washed with water (2×100 ml), and the organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The desired selenoglycoside product was obtained by column chromatography (EtOAc/hexane, 1/10 to 1/2, vol/vol) in high yield (typically more than 90%)

4.4.7.2 Typical Procedure for the Preparation of Selenoglycosides from Glycals

Sodium azide (10.0 mmol), diphenyldiselenide (3.0 mmol) and (diacetoxyiodo)benzene (5.6 mmol) were added to a solution of acetylated glycal (4.0 mmol) in CH_2Cl_2 (60 ml) under nitrogen. The reaction mixture was stirred at room temperature for 48 h and washed with water (50 ml), and the aqueous layer was back-extracted with CH_2Cl_2 (3×50 ml). The combined organic extracts were then dried over $MgSO_4$ and concentrated to dryness. The resulting oil was purified by column chromatography (EtOAc/hexane, 1/10 to 1/2, vol/vol) to give the phenyl 2-azido-2-deoxy-selenoglycoside in good yield (typically $\sim$80%).

4.4.7.3 Typical Procedure for NIS/TfOH-Promoted Glycosylation with Selenoglycosides

Powdered 4-Å molecular sieves (100 mg) were added to a solution of glycosyl donor (0.2 mmol) and glycosyl acceptor (0.16 mmol, 0.8 equiv) in dry CH_2Cl_2 (5.0 ml). The resulting mixture was stirred at room temperature under nitrogen for 30 min and then NIS (1.1 mmol, 5 equiv) and TMSOTf (0.02 mmol) were added to it. When TLC analysis indicated the completion of the reaction (typically $\sim$30 min), the mixture was diluted with EtOAc (10 ml) and washed with 10% aq $Na_2S_2O_3$ (2×5 ml) and brine (5 ml). The organic phase was then separated, dried over $MgSO_4$ and concentrated to dryness. The resulting residue was purified by column chromatography on

silica gel (EtOAc/hexane, 0/1 to 1/4, vol/vol) to provide the desired disaccharide (typical range 60–85%).

4.4.7.4 Typical Procedure for BAHA-Promoted Glycosylation with Selenoglycosides

Powdered 4-Å molecular sieves (100 mg) were added to a solution of glycosyl donor (0.2 mmol) and glycosyl acceptor (0.16 mmol, 0.8 equiv) in dry CH_2Cl_2 (5.0 ml). The resulting mixture was stirred at room temperature under nitrogen for 30 min and then BAHA (0.6 mmol, 3 equiv) was added. When TLC analysis indicated the completion of the reaction (typically ~30–60 min), the reaction mixture was cooled by an ice bath and neutralized with Et_3N, filtered through Celite with the help of CH_2Cl_2 and concentrated to dryness. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 0/1 to 1/4, vol/vol) to provide the desired disaccharide (typical range 60–85%).

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5
Other Methods for Glycoside Synthesis

5.1
Orthoesters and Related Derivatives

BertFraser-Reid, J.Cristóbal López

5.1.1
Introduction

The difficulties in the preparation of complex oligosaccharides, compared to other biopolymers such as peptides or nucleic acids, are the result of a greater number of possibilities for the combination of monomeric units. For instance, the hypothetical 'simple' glycosidation shown in Scheme 5.1 entails three of the four modes of selectivity: stereo, chemo and regio. These modes, according to Trost [1], confront organic synthesis in general and any reliable glycosylation is expected to comply with them. The fourth one, enantioselectivity, is usually not encountered in oligosaccharide synthesis because the chiralities of donor and acceptor are usually specified by nature.

Contributions in twentieth-century chemical syntheses of oligosaccharides have been aimed at stereoselective, chemoselective and regioselective saccharide couplings. In fact, the search for stereoselective couplings occupied most of the last century, and it was only in the early 1990s that the relevance of chemoselective couplings was addressed. The advent of regioselective coupling processes can be considered an even more recent development.

As a result of the explosion of interest in oligosaccharide synthesis, a plethora of different glycosylation methods is now available, and yet chemical oligosaccharide synthesis still remains a formidable problem at the beginning of the twenty-first century. Clearly, the preparation of large oligosaccharides demands the use of more than one reliable method for the construction of glycosidic linkages.

From a historic perspective glycosyl chlorides and bromides introduced, respectively, by Michael [2] and Koenigs and Knorr [3] were the most widely used donors in the saccharide synthesis for a very long time. The introduction of 1,2-orthoesters in 1964 [4] was the first important attempt to find an alternative to the Koenigs–Knorr method. However, Paulsen in his 1990 review of reliable donors for glycosyl

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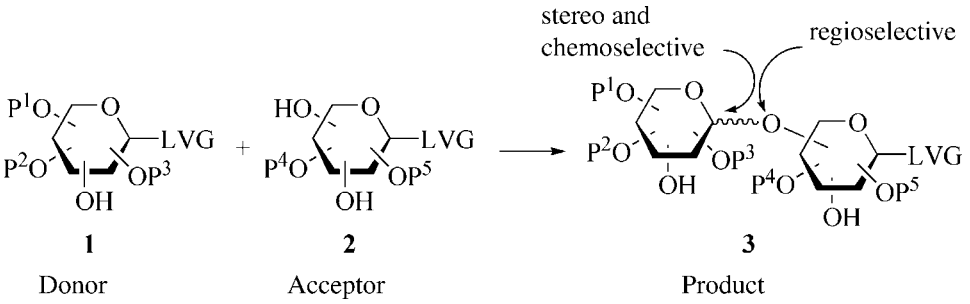


Scheme 5.1 Glycosyl coupling and selectivity.

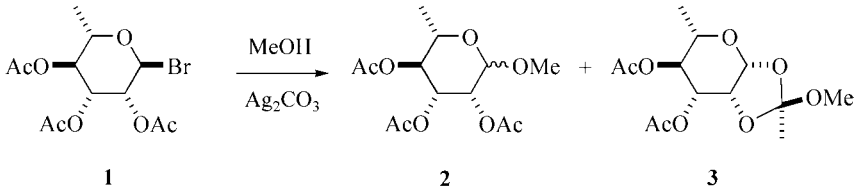
couplings cited only halogenides, imidates and thioglycosides. [5] The aim of this chapter is to provide some insight into recent developments in 1,2-orthoester chemistry that recognize the trustworthiness of these donors for stereoselective, chemoselective and regioselective glycosyl couplings.

The concept of neighboring-group participation and the formation and isolation of 1,2-orthoesters are intimately linked, as evident from the title of Isbell's monumental 1941 paper 'Sugar acetates, acetylglycosyl halides and orthoacetates in relation to the Walden inversion' [6]. Indeed, in today's terminology it could be said that 1,2-orthoesters benefit from the 1,2-*trans* stereodirecting properties of 2-*O*-acyl donors without being disarmed. Thus, they can be regarded as 'glycosyl donors with a nondisarming participating group at C-2'. Their high reactivity makes them amenable to *chemoselective* activation in the presence of different glycosyl donors, and they have recently proved themselves as privileged donors for *regioselective* couplings [7].

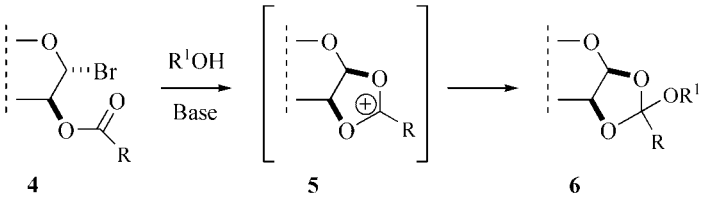
5.1.2
Sugar 1,2-Orthoesters

Carbohydrate orthoesters, first reviewed by Pacsu more than 60 years ago [8], were reported by Fischer *et al.* [9] as by-products of the Koenigs–Knorr reaction [3] of acetobromo-L-rhamnose (**1**) with methanol. Orthoacetate **3** was isolated along with the expected α- and β-methyl rhamnosides **2** (Scheme 5.2). However, its 'true structure' was assigned only 10 years later by several research groups [10–12].

In this connection, early syntheses of 1,2-orthoesters employed 1,2-*trans* acylhalogenoses as the starting materials in the presence of alcohols and a base (Scheme 5.3) [13].



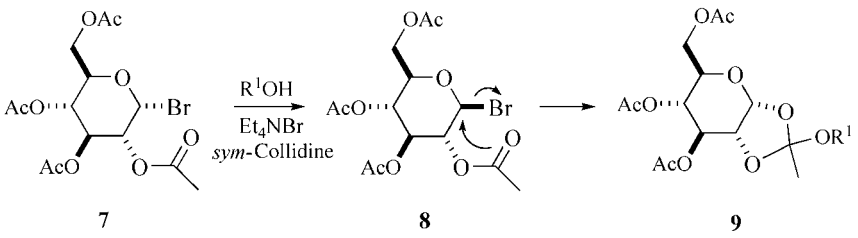
Scheme 5.2 First preparation of a sugar 1,2-orthoester.



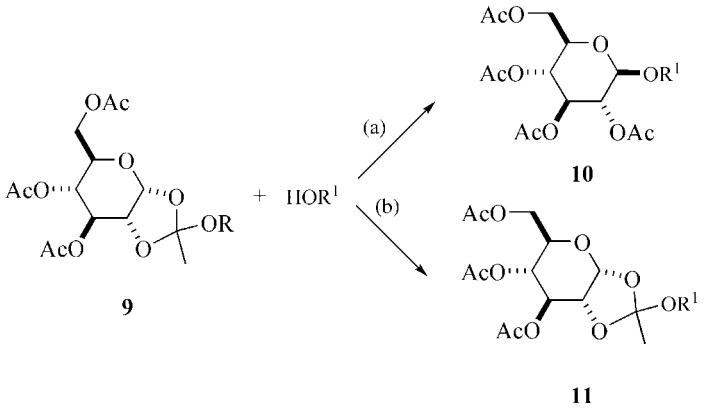
Scheme 5.3 Othoesters formation from 1,2-*trans* acylhalogenoses.

It is also possible to prepare 1,2-orthoesters from 1,2-*cis*-glycosyl halides, as reported by Lemieux and Morgan, using alcohols in the presence of tetraalkylammonium halides and *sym*-collidine [14]. This reaction is believed to occur with double inversion at C-1, the initial step being the anomerization of α-bromide (Lemieux's halide ion-catalyzed method) [15], and the orthoester is then produced by the attack at C-1 of the participating *trans*-ester group at C-2 with subsequent reaction of the alcohol at the acyloxonium center (as in Scheme 5.2). The formation of the substituted ethylidene derivative is accompanied by the appearance of a new chiral center at the dioxolane ring with the possible formation of *exo*- and *endo*-orthoesters. However, normally the *exo*- isomer is preferred owing to the greater accessibility of the *exo*- side in the dioxolenium cation to attack by nucleophile (alcohol) (Scheme 5.4).

Additional methods for the synthesis of 1,2-orthoesters from acetohalogeno sugars include the treatment with lead carbonate and calcium sulfate in ethyl acetate [16], silver nitrate and 2,4,6-trimethylpyridine [17], *N,N*-dimethylformamide dialkylacetals–AgOTf [18], silver triflate–2,4,6-collidine [19], trialkylstannyl methoxide–Et_4NBr [20], silver salicilate [21], silver nitrate–2,4,6-collidine [22], mercury(II) bromide–2,4,6-collidine [23], *N,N*-dimethylformamide dialkylacetals–Et_4NBr [24], potassium fluoride [25] and 2,6-lutidine in ionic liquid [bmin]PF_6 [26]. Other starting materials have also been used to prepare orthoesters: (a) pyranose hemiacetals have been converted into 1,2-orthoesters by the treatment with 1-chloro-2,*N,N*-trimethylpropenylamine followed by alcohol in the presence of triethylamine [27], (b) peracetylated sugars can be changed into 1,2-orthoesters via the *in situ* generation of glycosyl iodides promoted by I_2/Et_3SiH followed by the treatment with lutidine and Bu_4NBr [28] and (c) 1,2-*O*-vinylidene acetals can yield 1,2-orthoesters on treatment with alcohols in the presence of *p*-toluenesulfonic or camphorsulfonic acids [29].



Scheme 5.4 Orthoester formation from 1,2-*cis* acylhalogenoses.



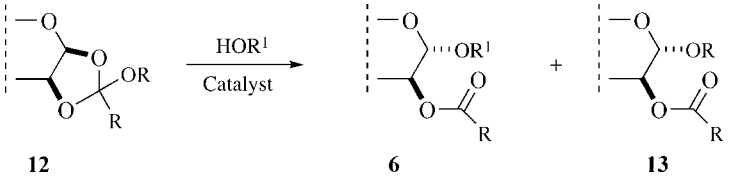
Scheme 5.5 1,2-*O*-Alkyl orthoesters in glycosylation: (a) polar or nonpolar solvents, high amount of acid; (b) low polarity solvents, minor amounts of acid catalyst.

5.1.2.1 1,2-*O*-Alkyl Orthoesters as Glycosyl Donors – Early Developments

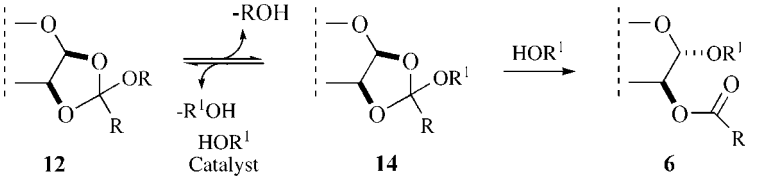
In 1964, Kochetkov, Khorlin and Bochkov reported that the reaction of 1,2-alkylorthoacetates with alcohols in the presence of catalytic amounts of $HgBr_2$ and *p*TsOH furnished acetylated 1,2-*trans* glycosides or isomeric orthoesters depending on the reaction conditions [4]. Polar solvents (nitromethane, acetonitrile) and large amounts of catalyst promoted glycosylation (a, Scheme 5.5), whereas solvents of low polarity (dichloroethane) and the use of small amounts of catalyst favored *trans*-orthoesterification (b, Scheme 5.5) [16].

The application of these optimized conditions permitted Kochetkov *et al.* to prepare, among others, β-cholesteryl glucoside in 45% yield. However, with low reactive aglycons (R^1OH) the yield was poor (10–20%) owing to the competing glycosylation of the extruded alcohol (ROH) from the initial orthoesters (Scheme 5.6).

To address this problem, the authors devised two modifications. [30] The first one, two-stage glycosylation (Scheme 5.7), employed an initial, reversible *trans*-orthoesterification step (**12** → **14**, Scheme 5.7) in which the departing alcohol was removed either azeotropically or by molecular sieves [31]. The new orthoester **14** was then processed to give the glycoside (**6**) under the conditions developed in their previous work. The second variation consisted of the use of orthoacetates of hindered alcohols (isopropyl and *tert*-butyl) that minimize the return of the alcohol that is split off.



Scheme 5.6 The competing glycosylation issue with orthoesters.



Scheme 5.7 The two-stage modification for glycosylation with orthoesters.

These modifications met with only limited success; however, they set the basis for the future applications of orthoesters as glycosyl donors.

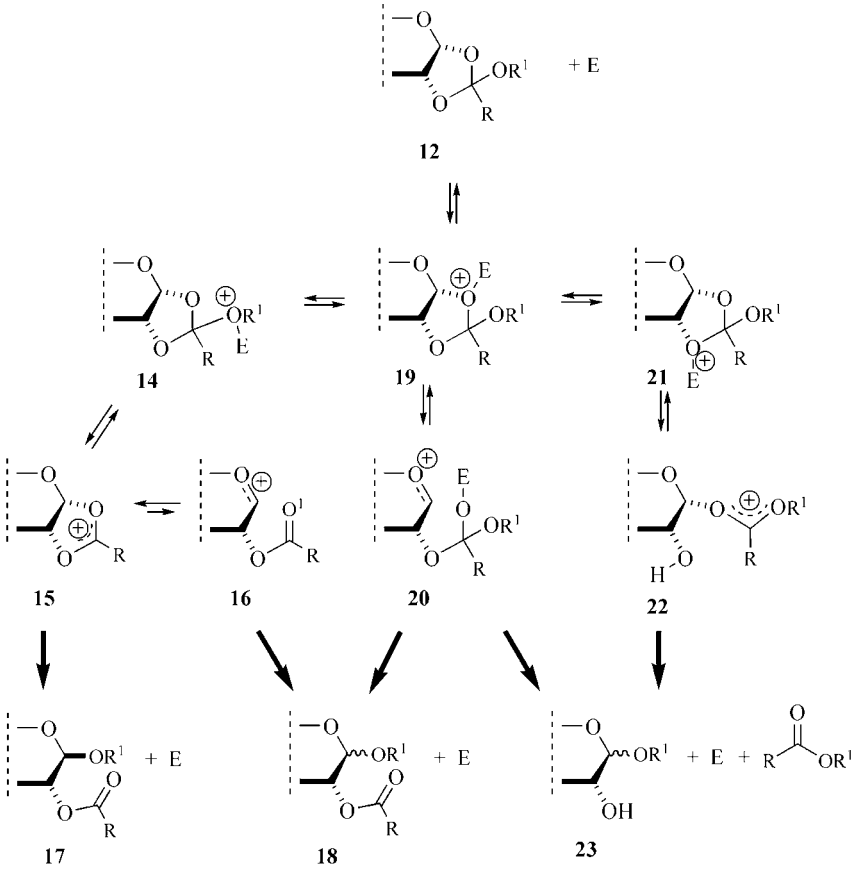
Another drawback, soon noted by Kochetkov's school, was the presence of a variety of other side products [32]. These included 1,2-*cis* counterparts of the expected 1,2-*trans* glycosides, appreciable amounts of acylated aglycons, glycosides (*cis* and *trans*) with a free hydroxyl group at C-2 and compounds arising from the latter after further glycosylation of the 2-OH group. All of these side products can be assembled under a unified mechanistic interpretation, resulting from the efforts of several groups that cataloged some of the perils of working with 1,2-orthoester glycosyl donors [19,33–35]. The nature of the side products was rationalized by reference to the different possible pathways depicted in Scheme 5.8. The majority of the oxonium and acyloxonium ion intermediates are connected with starting orthoester by fast reversible equilibria. The main reaction pathway is the one arising from the equilibrating intermediates **14** and **15**, and the rate-determining steps are the ones shown by bold arrows. The product composition has been shown to be dependant on parameters such as the promoter (E), the solvent and the structure of the alcohol.

5.1.2.2 1,2-*O*-Cyanoethylidene Derivatives

Further modifications of the original orthoester glycosylation method were developed to eliminate these disadvantages. Among them the use of 1,2-*O*-(1-cyanoethylidene) derivatives **24** [36,37] was particularly noteworthy. Cyanoethylidene derivatives could be chemoselectively activated by trityl ion, thereby allowing chemoselective entry to bridging cation **15**, and thus minimizing the side products arising from intermediates **19** and **21** (see Scheme 5.8). The implementation of this method, however, requires the use of trityl ethers of alcohols as the glycosyl acceptors.

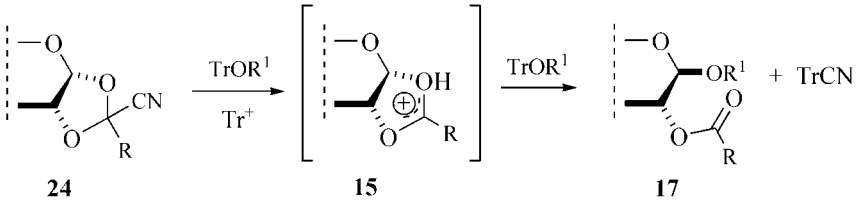
Cyanoethylidene derivatives can be prepared from the corresponding glycosyl halides by the treatment with KCN and *n*-Bu_4NBr in CH_3CN or from the corresponding peracetates and TMSCN in the presence of stannous chloride (Scheme 5.9).

A recent synthesis of mannodendrimers by Backinowsky *et al.* illustrates the state of the art of this methodology (Scheme 5.10) [38]. Acetobromomannose (**25**) could be chemoselectively activated in the presence of cyanoethylidene-derived triol **26** to afford trimannan **27a** in a regioselective manner. The acetylation of the latter led to **27b**, which could regioselectively glycosylate di-trityl derivative **28** at the secondary trityl group to yield tetramannan **29**, in keeping with the greater reactivity of secondary versus primary trityl groups with various glycosyl donors [39,40]. Alternatively, **28** could be bis-glycosylated with 2 equiv of **26b** to furnish heptamannan **30**.

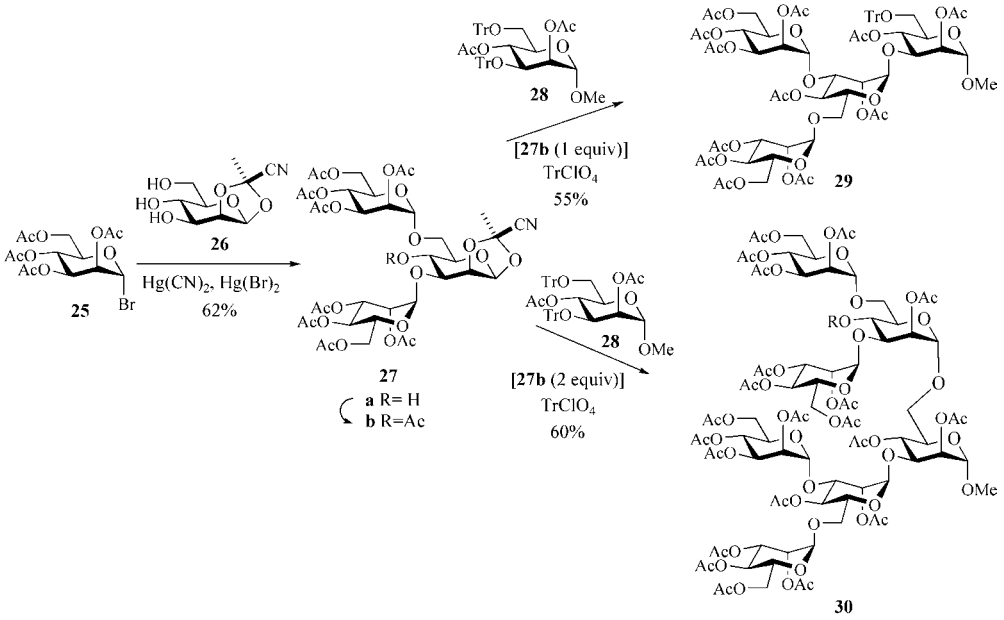


Scheme 5.8 Proposed reaction pathways for the reaction of orthoester **12**.

The 1,2-*O*-cyanoethylidene method also became the basis for a polycondensation reaction, which allowed the synthesis of many polysaccharides [37]. When both the *O*-trityl and cyanoethylidene groups are present in the same molecule as in **31**, polycondensation takes place under glycosidation conditions giving a polysaccharide chain, for example **32** (Scheme 5.11).



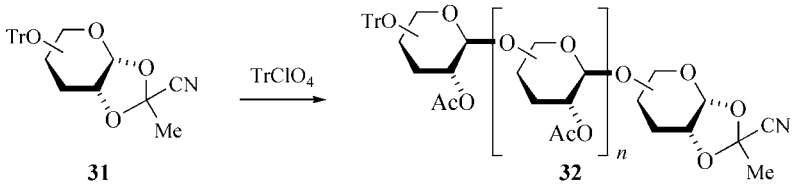
Scheme 5.9 1,2-*O*-Cyanoethylidene derivatives in glycosyl couplings.



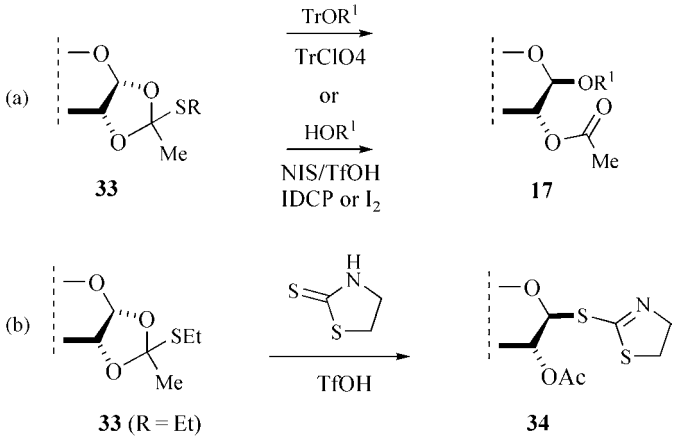
Scheme 5.10 Synthesis of tetra- and heptamannan derivatives.

5.1.2.3 **1,2-Thioorthoester Derivatives**

Related to the above cyanoethylidene derivatives, 1,2-thioorthoesters, for example **33**, obtained by the reaction of peracetylglycosyl bromides with thiols in the presence of 2,6-lutidine or 2,4,6-collidine, were also introduced by Kochetkov *et al.* as glycosyl donors [41]. Primary and secondary trityl ethers of monosaccharides could be coupled under the agency of triphenylmethylium perchlorate (Scheme 5.12a) [42]. However, some 4-*O*-trityl ether derivatives failed to undergo glycosyl coupling, and anomeric mixtures of acetylated thioglycosides were isolated instead. More recently, iodonium-based promoters iodonium dicollidine perchlorate (IDCP) [43], NIS/TfOH [44–46] and I_2 [47] have been assayed for the activation of 1,2-thioorthoesters. Although these promoters allowed the use of hydroxyl groups (rather than trityl ethers) as acceptors, the glycosyl coupling proved successful only with primary OH (Scheme 5.12a) [46,47]. Thioorthoesters have recently been used as starting materials for the preparation of *S*-thiazolinyl (STaz) glycosides, for example **34** (Scheme 5.12b) [48].



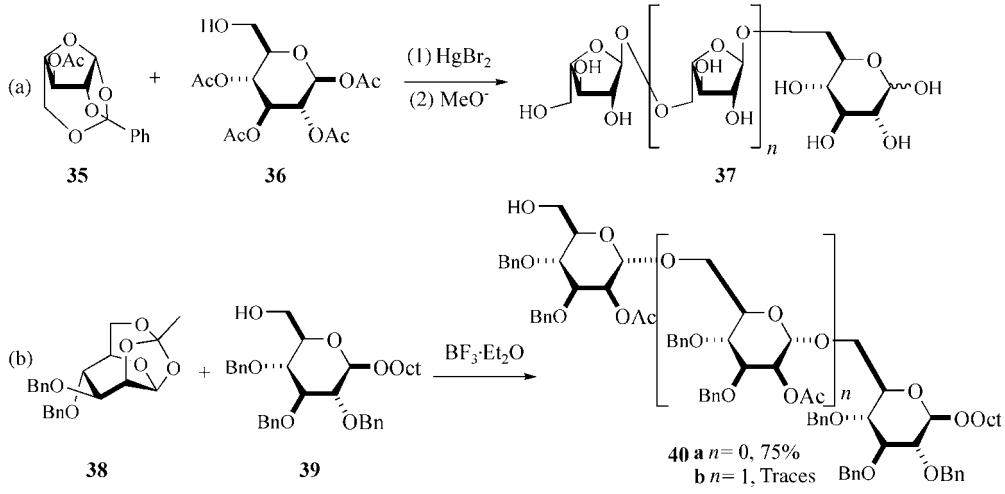
Scheme 5.11 Polycondensation of a monosaccharide unit leading to a homopolysaccharide.



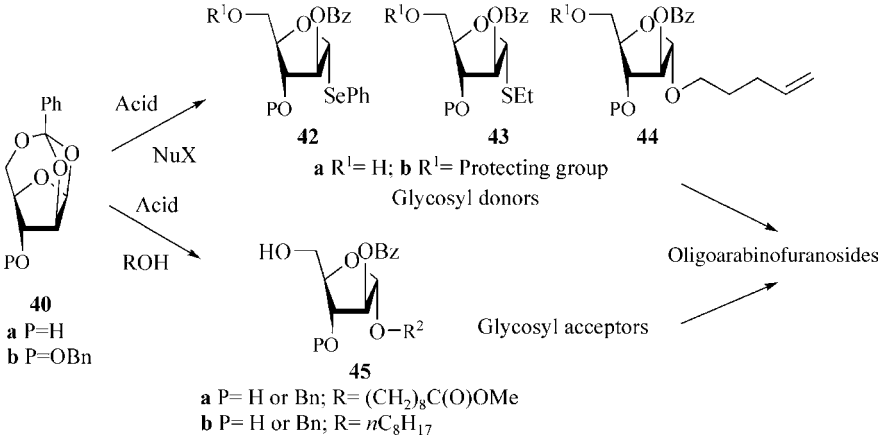
Scheme 5.12 Thioorthoesters in glycosylation and in the synthesis of (STaz)-glycosyl donors.

5.1.2.4 Internal Orthoesters

Arabinofuranose 1,2,5-orthoesters and mannopyranose 1,2,6-orthoesters have been evaluated as glycosyl donors with limited success. Kochetkov *et al.* used β-L-arabinofuranose 1,2,5-orthobenzoate **35** as a monomer unit in a polymerization strategy (Scheme 5.13a), the implementation of which demanded the use of an alcohol initiator, **36** [49]. Wong and coworkers described the preparation of mannose 1,2,6-orthoester **38** and its glycosylation with primary hydroxyl acceptors. Glycosylation of **38** with $BF_3{\cdot}Et_2O$ yielded disaccharide **40a** (Scheme 5.13b) [50], whereas other catalysts gave variable amounts (4–14%) of trisaccharide **40b** arising from further glycosyl coupling of the liberated 6-OH group.



Scheme 5.13 Internal orthoesters in polymerization strategies.

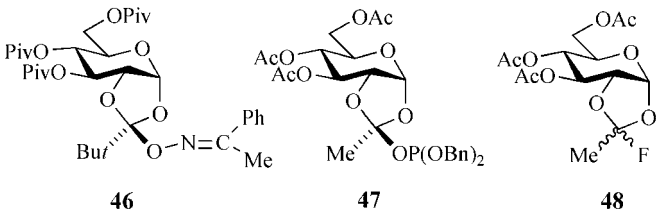


Scheme 5.14 Prandi's strategy to oligoarabinofuranosides from internal orthoester **41**.

Finally, Prandi and coworkers have described the use of D-arabinose 1,2,5-orthoesters, for example **41**, in a convergent–divergent strategy to oligoarabinofuranosides (Scheme 5.14) [51]. Acid-catalyzed opening of orthoesters **41** in the presence of selenophenol, thioethanol, 4-pentenol, followed by the protection of their 6-OH, gave raise to the corresponding selenyl- [52], thio- [53] and *n*-pentenyl- glycosyl donors [54] (**42b–44b**), whereas ring opening in the presence of alcohols furnished glycosyl acceptors **45**. Protecting-group manipulation and glycosyl assembly of these building blocks thus permitted the synthesis of oligoarabinofuranosides.

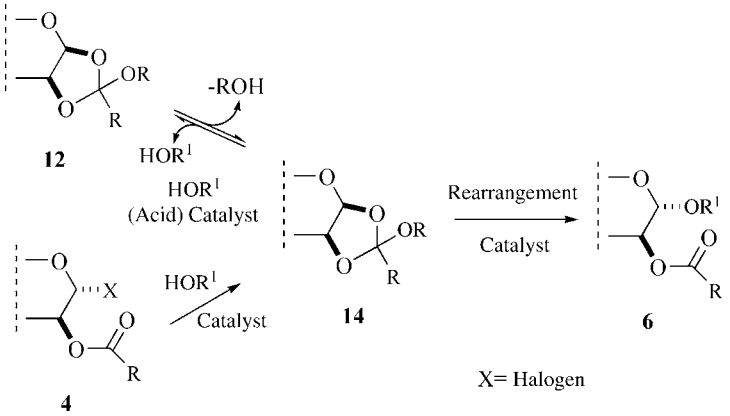
5.1.2.5 Miscellaneous Orthoesters

Kunz and Pfrengle reported the use of an oximate orthoester (**46**) in the $BF_3{\cdot}Et_2O$-catalyzed glycosylation of some primary and secondary hydroxyl groups and phenols (70–80% yield) (Figure 5.1) [55]. A phosphite orthoester (**47**), isolated by Wong and coworkers as a side product in the attempted conversion of a glycosyl phosphite into a thioglycosyl derivative, reacted with thiocresol in the presence of TMSOTf to give the corresponding *p*-methylphenyl-1-thio-glycoside [56]. Griffith and Hindsgaul reported the formation of stable fluoro-orthoesters (**48**) in the reaction of 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranose with DAST. They could be rearranged to glycosyl fluorides in the presence of $BF_3{\cdot}Et_2O$ [57].



46 47 48

Figure 5.1 Miscellaneous orthoesters.



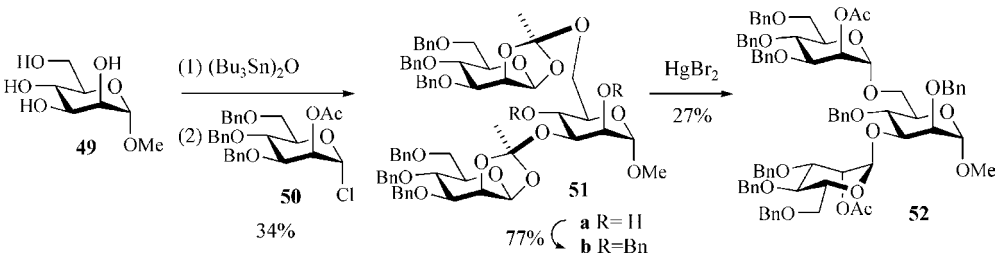
Scheme 5.15 Alternative strategies for efficient glycosylation with orthoesters.

5.1.3
Orthoester to Glycoside Rearrangement – The Two-Stage Glycosylation Method Revisited

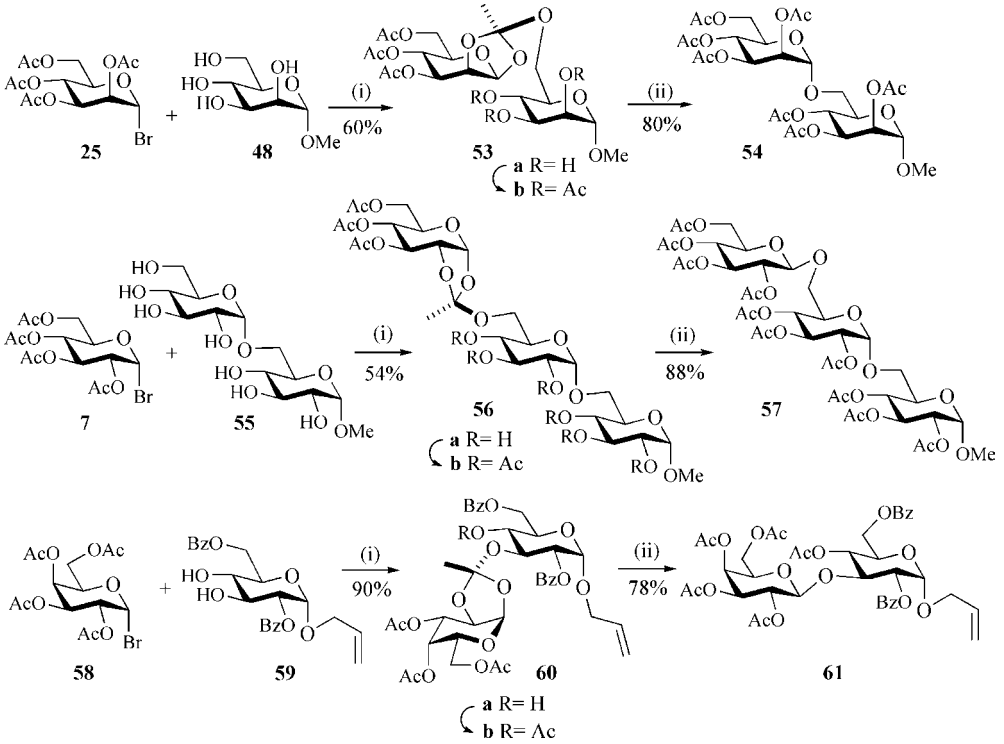
The *two-stage glycosylation method* (**12** → **14** → **6**, Scheme 5.15) had been introduced to avoid problems related to the competitive incorporation of the acceptor (R^1OH) and the extruded alcohol (ROH) from **12**. In this context, more efficient glycosylation strategies (**4** → **14** → **6**, Scheme 5.15), which circumvent the competitive aspect, have been studied [58].

A remarkable example of this strategy came from Ogawa *et al.* [59]. They reported the regioselective preparation of bis-orthoester **51a** by the reaction of glycosyl chloride **55** with a partially stannylated [20] mannoside arising from **49** (Scheme 5.16). Rearrangement, after benzylation, of bis-orthoester **51b** took place in the presence of $HgBr_2$ at 120 °C to give trimannan **52** in 27% yield. Shortly after this work appeared, Ogawa *et al.* reported the value of TMSOTf, in replacing $HgBr_2$ as the reagent of choice for effecting orthoester to glycoside rearrangements [60].

Very recently, Kong has incorporated refinements to this approach and illustrated its potential with the regioselective synthesis of a large variety of oligosaccharides



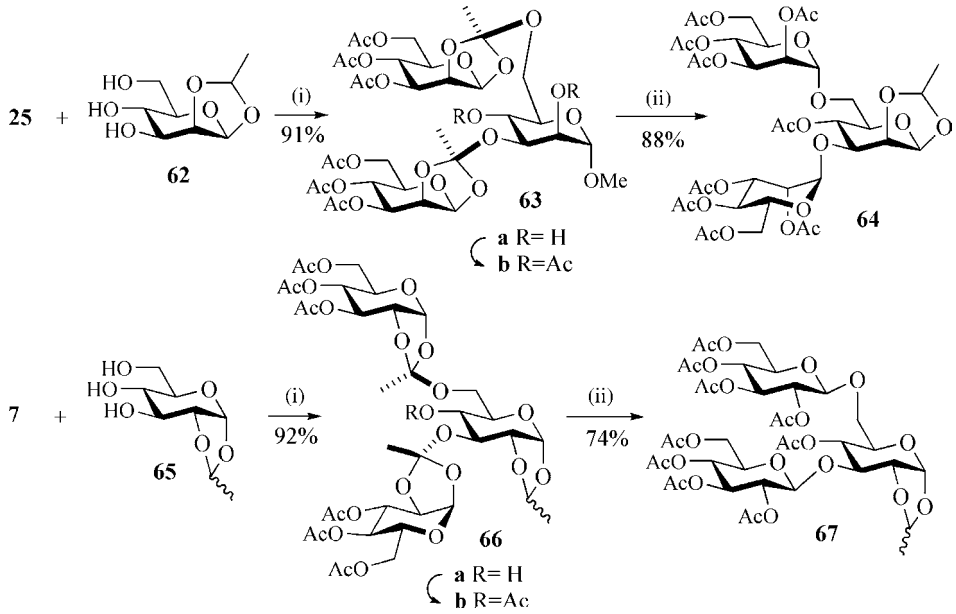
Scheme 5.16 Ogawa's synthesis of trisaccharide **52**.



Scheme 5.17 Kong and coworkers approach to oligosaccharide synthesis. Reaction conditions: (i) 2,4-lutidine, AgOTf and molecular sieves; (ii) TMSOTf, 0 °C.

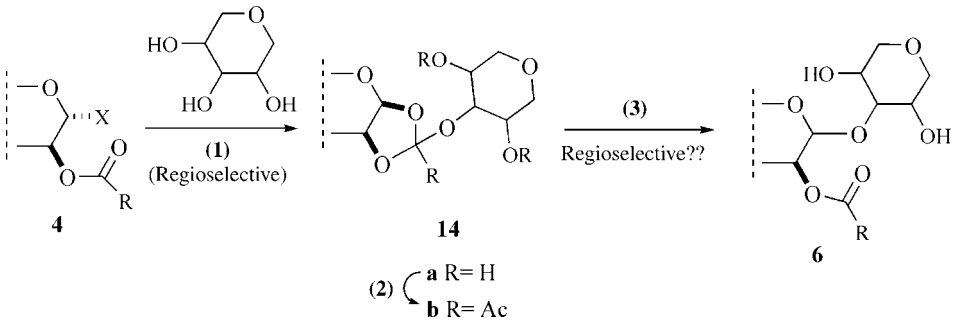
[61]. In his initial studies, he found that prior stannylation of the polyol acceptor was not a requisite for regioselective orthoester formation [62]. Indeed, a remarkable, see below, regioselectivity was found in the reaction of acetobromosugars and pyranosidic polyols leading to the formation of orthoesters (Scheme 5.17). Reaction of acetobromomannose (**25**), glucose (**7**) and galactose (**58**) with unprotected acceptors **48**, **55** and **59** in the presence of AgOTf and 2,6-lutidine [19] yielded mono-orthoesters **53a**, **56a** and **60a**, respectively, with complete regioselectivity. After the acetylation, the resulting orthoesters (**53b**, **56b**, **60b**) were transformed into the corresponding saccharides (**54**, **57**, **61**) by treatment with TMSOTf in CH_2Cl_2 at 0 °C.

Further application of this protocol, by Wang and Kong [63], led to the high-yielding synthesis of double glycosylated gluco- and mannoderivatives **64** and **67** by the reaction of bromoaldoses **25** and **7** with triols **62** and **65** (Scheme 5.18). Regioselective preference was found for the formation 1 → 6- (with acceptors containing unprotected 3,4,6-hydroxy groups) and 1 → 3- (with acceptors containing unprotected 2,3,4-hydroxy groups)-linked saccharides. This strategy was used to provide access to a series of 1 → 6- and 1 → 3-linked and 3,6-branched oligosaccharides such as **54**, **57**, **61**, **64** and **67** [64].

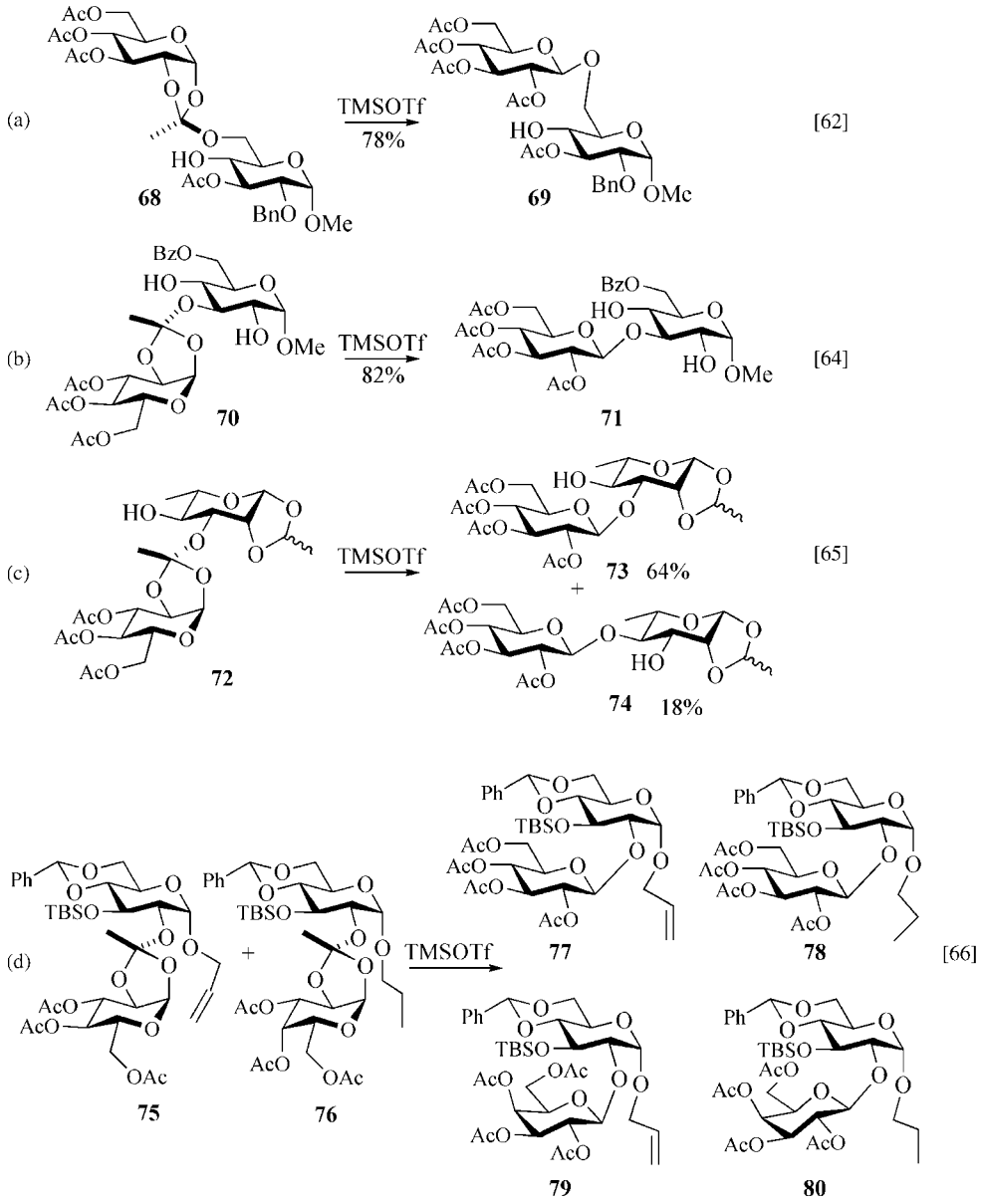


Scheme 5.18 Kong and coworkers one-pot method for saccharide synthesis. Reaction conditions: (i) 2,4-lutidine, AgOTf, molecular sieves; (ii)TMSOTf, 0 °C.

As the final regioselective outcome of the two-stage glycosylation has been ascribed to regioselection in orthoester formation (step 1, Scheme 5.19), one additional protection step (**14a** → **14b**, Scheme 5.20) was required to prevent hydroxyl scrambling during the final rearrangement step (**14b** → **6**, R = Ac), Scheme 5.19. Thus, the once two-stage method had to be converted into a three-step procedure if high regioselectivity was to be ensured. To avoid this, Kong and coworkers subjected hydroxylated orthoesters (e.g. **14a**, Scheme 5.19) to the action of TMSOTf and



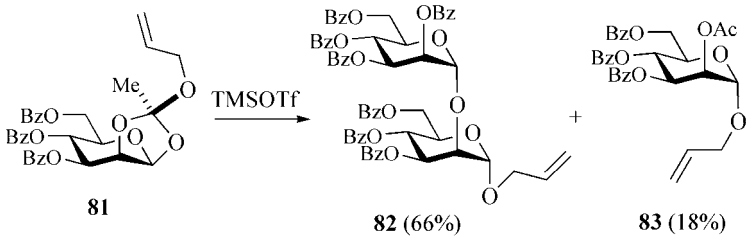
Scheme 5.19 Regioselectivity issue in the rearrangement of mixed orthoesters.



Scheme 5.20 Regioselectivity issue in the rearrangement of mixed orthoesters.

found that the rearrangement could sometimes be completely regioselective (Scheme 5.20a, b versus c) [62,64,65].

In an elegant experiment, Yu and coworkers showed that intermolecular *crossover* is also possible. Thus, the TMSOTf-catalyzed rearrangement of two structurally similar orthoesters **75** and **76** led to crossover products **77**/**78** and **79**/**80** (Scheme 5.20d) [66].



Scheme 5.21 Kong' approach to (1–2)-linked mannose oligosaccharides.

5.1.3.1 Self-Condensation of Mannose 1,2-Orthoesters: Ready Access to (1 → 2)-Linked Mannose Oligosaccharides

Although, as shown in Scheme 5.8, several reaction pathways are possible for a given orthoester (e.g. **12**), the transformation **12** → **17** is generally observed. Therefore, the presence of (usually minor) compounds such as **18** or **23**, arising from alternative reaction pathways (Scheme 5.8), is normally considered as the result of an undesired side reaction. However, recent studies by Kong and Zhu have revealed that the transformation **12** → **23** can be the main reaction course under appropriate conditions, and they have shown its usefulness for the synthesis of α-(1 → 2)-linked mannose disaccharides (Scheme 5.21) [67,68]. Thus, the treatment of allyl orthoester **81** with TMSOTf permitted the synthesis of α-(1 → 2)-linked disaccharide **82** in 66% yield, with the 'normal' rearranged allyl glycoside **83** also being obtained in 18% yield.

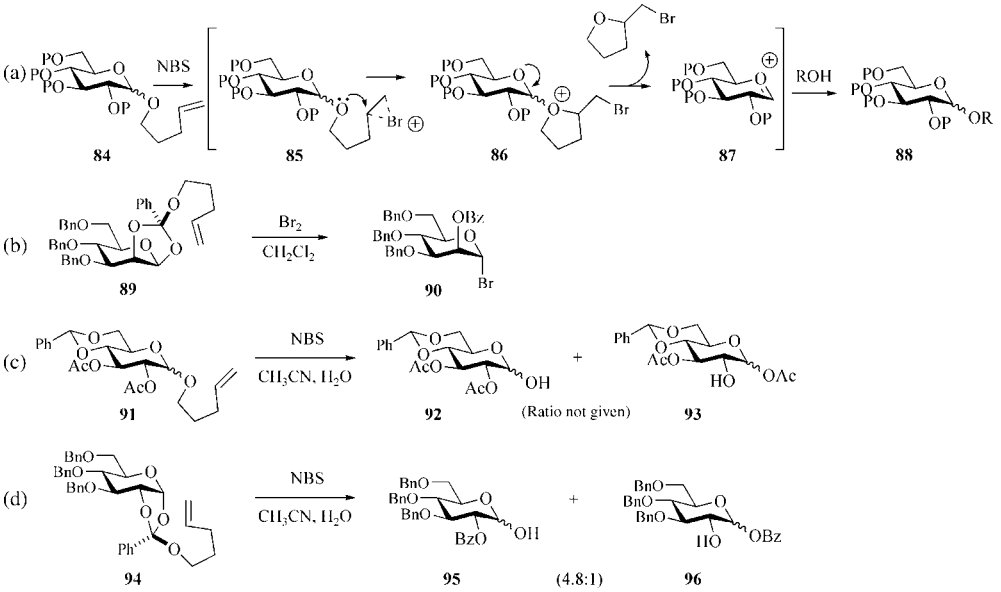
5.1.3.2 Rearrangement of Sugar–Sugar Orthoesters Leading to 1,2-*cis*-Glycosidic Linkages

The rearrangement of sugar–sugar orthoesters, as shown in Scheme 5.20, usually gives 1,2-*trans*-linked oligosaccharides. However, recent studies by Kong and Zhu have revealed that pure α-linked saccharides can be obtained by the glycosylation with glucosyl trichloroacetimidate donors with a C-2 ester capable of neighboring-group participation [69,70]. The authors assumed that the presence of 3-linked glucooligosaccharide–glucooligosaccharide orthoester intermediates, which might rearrange, gives rise to 1,2-*cis*-linked oligosaccharides.

5.1.4 *n*-Pentenyl-1,2-Orthoesters: Glycosyl Donors with Novel Implications

In 1988, a report from Fraser-Reid's laboratories drew attention to a novel anomeric leaving group [71]. *n*-Pentenyl glycosides (NPGs) were introduced as new derivatives that facilitated the chemospecific liberation of the anomeric center under *non*acidic conditions. The postulated mechanism for this transformation involved the participation of the exocyclic anomeric oxygen in the formation of a bromofuranylium ion (**86**), which triggered the formation of oxocarbenium ion **87** (Scheme 5.22a).

Although the first published *n*-pentenyl orthoester (NPOE) **89** appeared shortly after (Scheme 5.22b) [72], the initial link between NPGs and 1,2-orthoesters could be

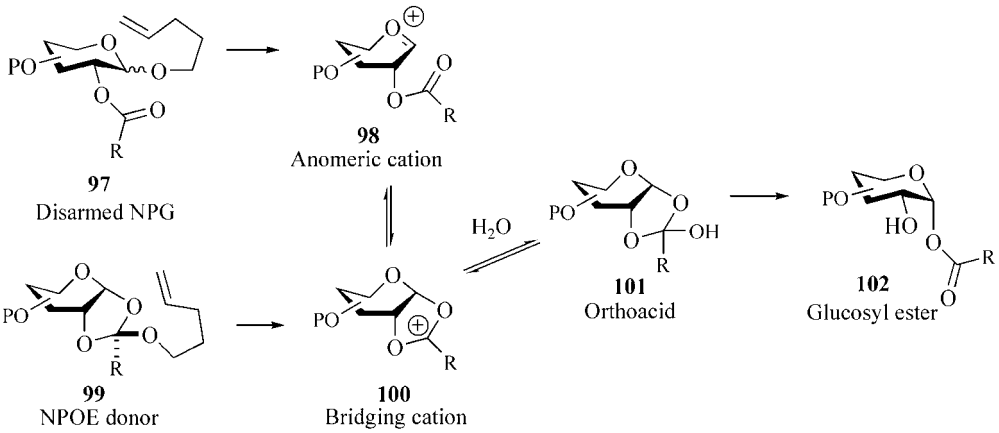


Scheme 5.22 *n*-Pentenyl glycosides and *n*-pentenyl orthoesters.

inferred from the formation of anomeric acetate **93** in the earlier contribution [71]. Thus, the formation of **93** as a side product in the oxidative hydrolysis (NBS, CH_3CN, H_2O) of **91** (Scheme 5.22c) could be rationalized through the rearrangement of either an orthoacid or an acyloxonium ion intermediate (see below). Indeed, a similar result (formation of **96**, Scheme 5.22d) was recently observed when *gluco*-NPOE **94** was treated under similar reaction conditions [73].

A rationale for the formation of **93** and **96** emerges from the seminal investigations of King [74], who established that bridging cations such as **100** (Scheme 5.23) scavenge water to generate unstable orthoacid intermediates (e.g. **101**). The latter undergo stereoelectronically driven [75] rearrangements favoring axially oriented esters on cyclohexyl scaffolds.

Disarmed glycosyl donors and orthoester analogs such as **97**and **99** (Scheme 5.23), upon appropriate treatment, give (potentially) equilibrating cations **98** and **100** and then products **101** and **102**. For substrates with alkoxy leaving groups (i.e. **97** and **99**, **LVG = OAlkyl**), this can be achieved by treatment with acidic reagents. However, for *n*-pentenyl analogs, activation can be carried out under nonacidic conditions, which brings about new possibilities. For example, it is possible to effect 'irreversible' *trans*-orthoesterification reactions that would be impossible under acidic conditions, as the work of the Kochetkov's school clearly shows [37]. Thus, the treatment of the *manno* and *gluco* NPOEs **89** and **105** with isopropanol under the agency of iodonium *sym*-collidinium triflate (IDCT) (Scheme 5.24) [73] led to the exchange of the alkoxy moieties in **104** and **107**, respectively.

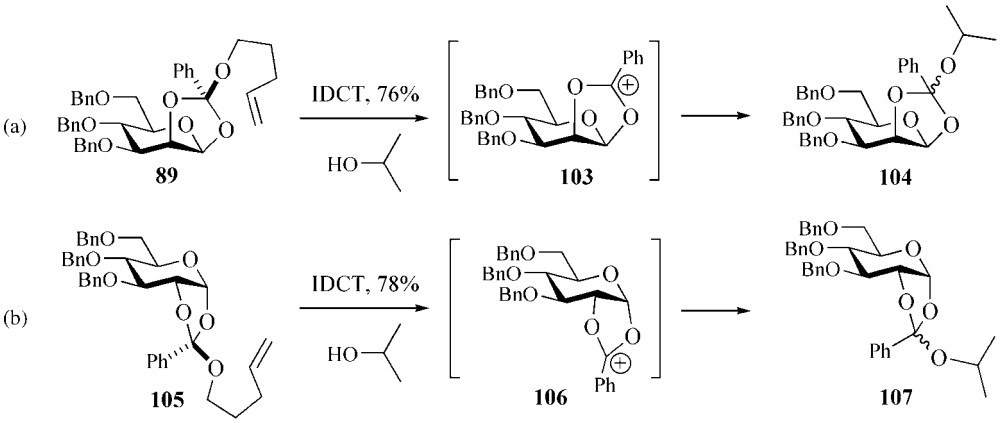


Scheme 5.23 Analogies between disarmed NPGs and NPOEs.

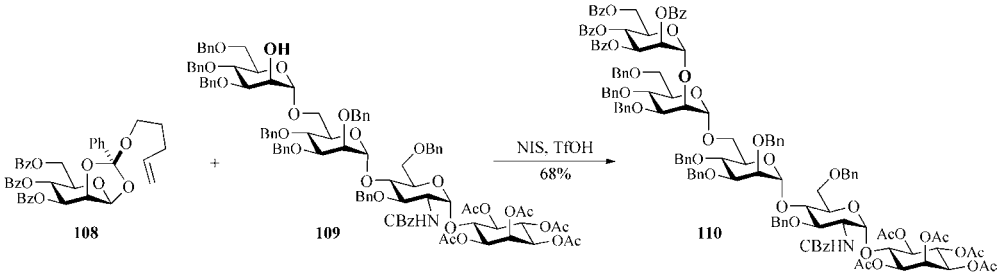
The first synthetic task assigned to an NPOE was the demanding glycosylation of an axial 2-OH group in the *pseudo*tetrasaccharide **109**, *en route* to the pseudopentasaccharide core of the protein membrane anchor found in *Trypanosoma brucei* that was obtained in 68% yield (Scheme 5.25) [76].

5.1.4.1 Divergent–Convergent Synthesis of Glycosylaminoglycan 120 from Glycosyl Donors and Acceptors Ensuing from NPOEs

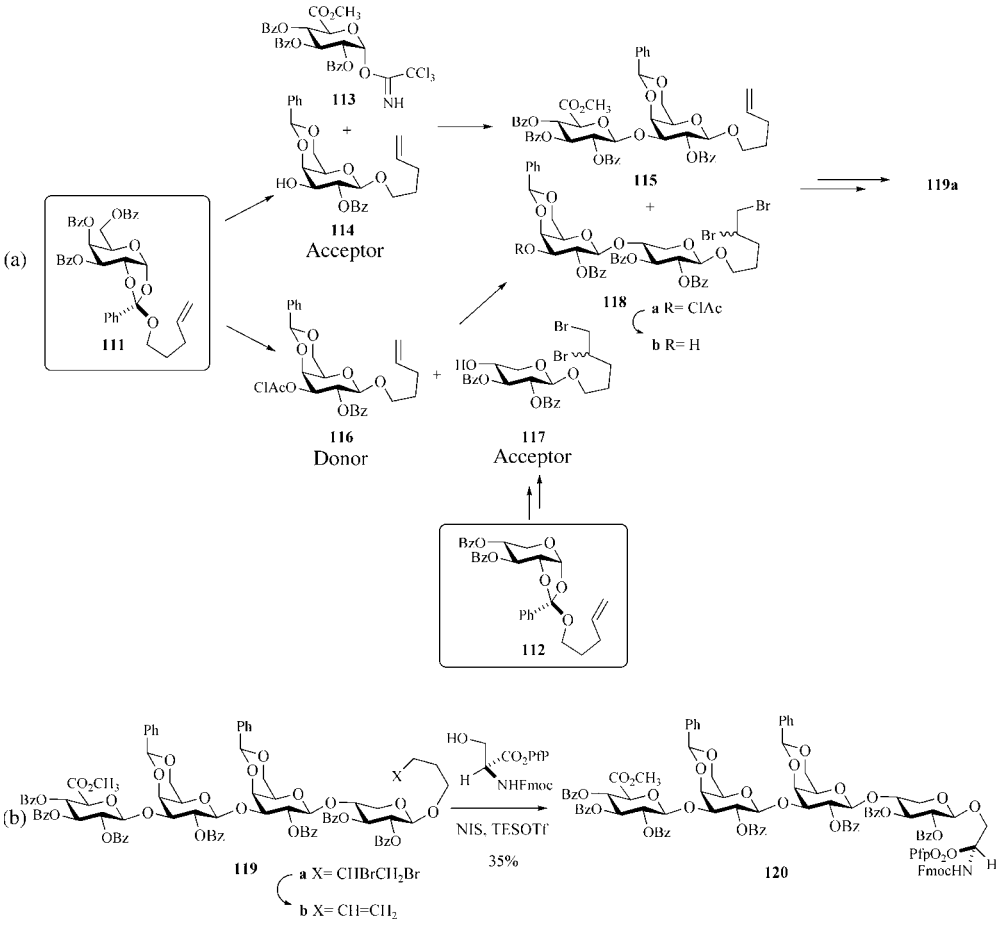
The first extensive use of NPOEs as key intermediates in oligosaccharide synthesis was undertaken by Allen and Fraser-Reid with the synthesis of glycosylaminoglycan **120** (Scheme 5.26) [77]. Their approach benefited from the uniqueness of the NPOE → NPG transformation in combination with the sidetracking of NPGs [78]. In the synthetic strategy, NPOEs of D-galactose and D-xylose **111** and **112**, respectively, furnished all the required glycosyl donors and acceptors (Scheme 5.26a).



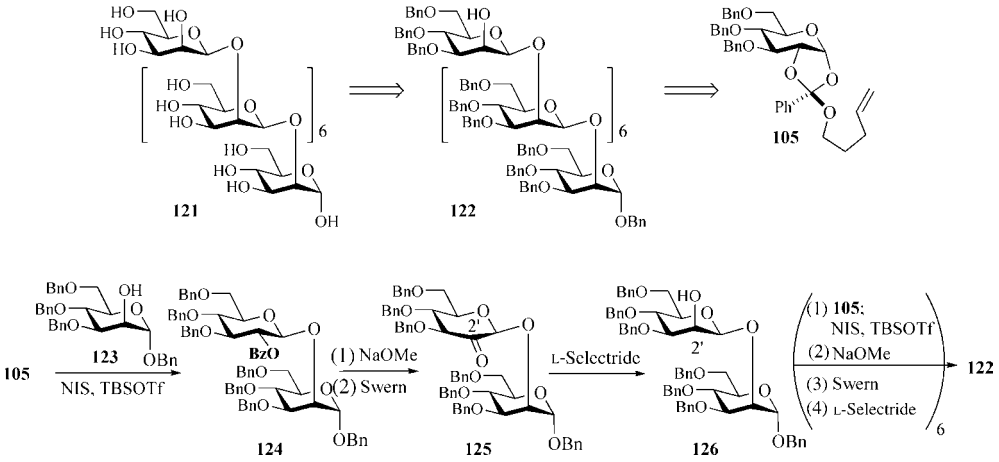
Scheme 5.24 Reaction of NPOEs promoted by IDCT.



Scheme 5.25 First utilization of an NPOE in oligosaccharide synthesis.



Scheme 5.26 Divergent–convergent use of NOPEs in oligosaccharide synthesis.



Scheme 5.27 NPOE-based strategy for preparation of β-mannosides.

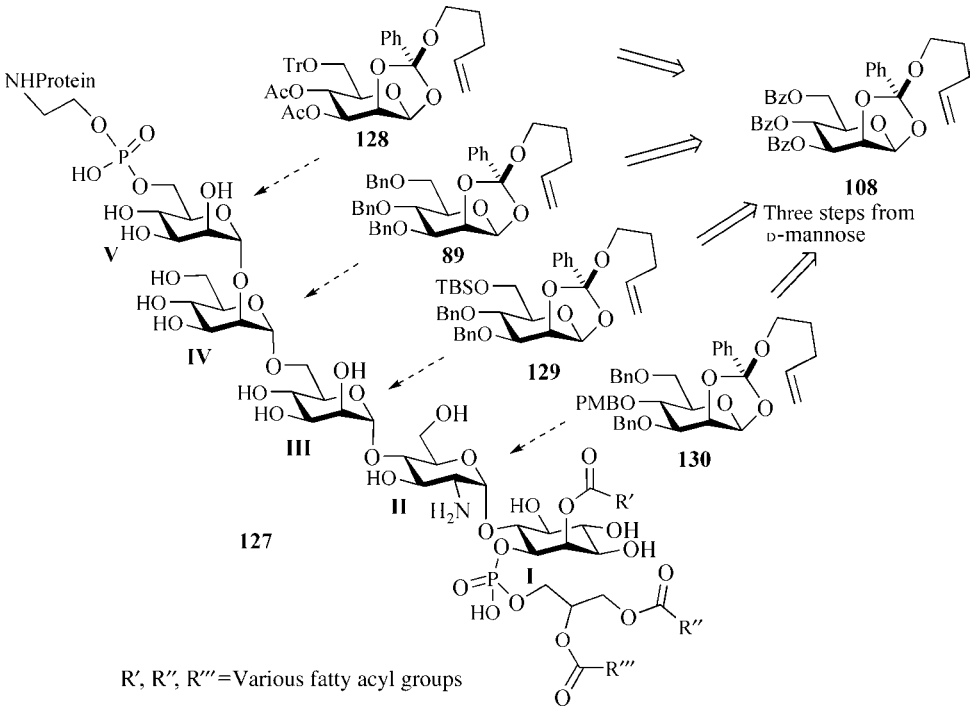
Accordingly, orthoester **111** was transformed into NPGs **114** and **116**. The former functioned as an acceptor to the trichloroacetimidate **113** to yield **115**. The latter was then used as a donor to glycosylate sidetracked xylosyl acceptor **117**, prepared in turn from xylose orthoester **112**, to yield dibromopentanyl derivative **118**. The final glycosylation of **118** with donor **115** provided the sought tetrasaccharide **119a**, which was used in the final transformations: **119a** → **119b** → **120** (Scheme 5.26b).

5.1.4.2 From NPOEs to the 1,2-β-Linked Oligomannans of *Candida albicans*

Fraser-Reid and coworkers described an entirely NPOE-based protocol for the synthesis of the β-1,2-linked oligomannan components of *C. albicans*, **121** (Scheme 5.27) [79], using glucosyl orthoester **105** as the key building unit. The strategy benefited from two characteristics inherent to orthoesters: (a) the 1,2-*trans* selectivity in their glycosyl coupling and (b) the protecting-group differentiation at O-2 that takes place after glycosidation. Accordingly, the reaction of **105** with **123**, under the agency of NIS/TBSOTf exclusively furnished disaccharide **124**, bearing a strategically important 2′-*O*-benzoyl group. The manipulation of the latter through a sequence involving saponification, oxidation and stereoselective reduction yielded *manno*-disaccharide **126** via ulose **125**. The iteration of the process, up to six times, produced protected octasaccharide **122**, in yields ranging from 82 to 93% per cycle. Final deprotection of **122** (HCOOH, Pd/C, MeOH, room temperature) led to **121**.

5.1.4.3 From NPOEs to the Synthesis of a Malaria Candidate Glycosylphosphatidylinositol (GPI)

A congener of the GPI membrane anchor, present on the cell surface of the malaria pathogen *Plasmodium falciparum* **127**, was also tackled. The molecule is composed of one inositol moiety (**I**) and four monosaccharide units (**II–V**) [80]. The retrosynthesis identified a single NPOE retron **108** as the precursor for all glycan units (Scheme 5.28). Transformations of the latter afforded NPOE analogs **128**, **89**,



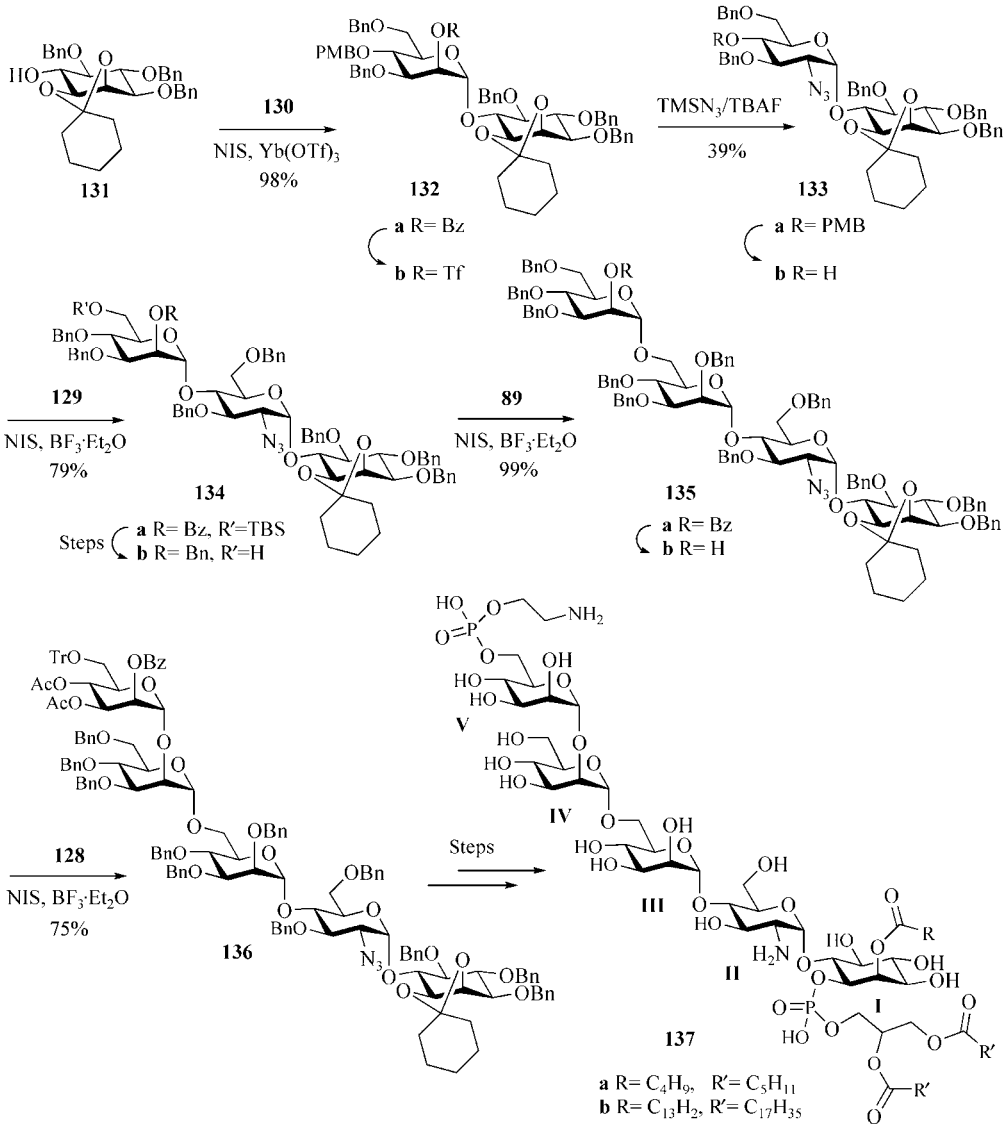
Scheme 5.28 Retrosynthesis of **127** from a single NPOE, **108**.

129 and **130**, which are correlated with glycan units **V–II**, respectively, as indicated in Scheme 5.28.

The synthetic protocol (Scheme 5.29) followed the guidelines shown in Scheme 5.28. Thus each NPOE **89**, **128–130** was specifically designed to allow the liberation of the required OH-group for further coupling or processing. The GPIs α-glucosaminide component (unit **II** in **127**, Scheme 5.28) requires special comment [81,82]. The glycosylation of inositol derivative **131** with NPOE **130** gave pseudodisaccharide **132a** in 98% yield, and the convenient 2-*O*-acyl group, after being replaced by a triflate, underwent azide displacement [83] to yield 2-azido-pseudodisaccharide **133**. Saccharide growth was then effected by sequential glycosylation with NPOEs **130**, **89** and **128**. All NPOE-mediated glycosyl couplings took place with excellent yields and paved the way to key intermediate **136**. Finally, the elaboration of **136** into **137** required the following: (1) attachment of the phosphoethanolamine complex [84] at unit **V**, (2) regioselective incorporation of the glyceryl chains [81] at the inositol moiety (**I**, Scheme 5.28) and (3) global debenzylation and azide reduction to isomeric **137a** and **137b** that differ by the acyl chains.

5.1.4.4 From NPOEs to the Preparation of Glycolipids for Multivalent Presentation

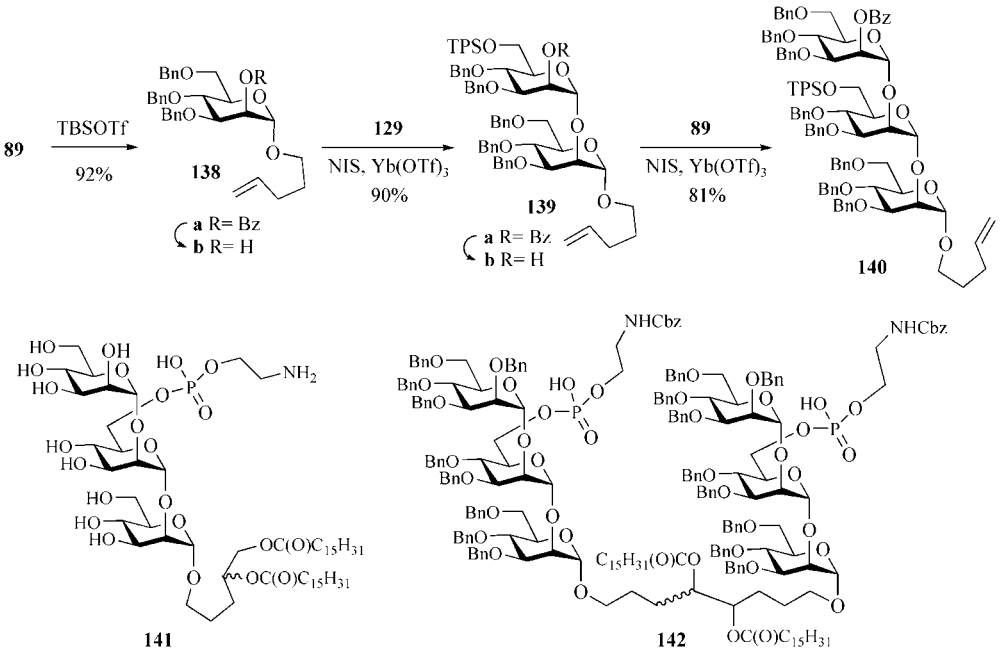
NPOEs have been employed in a straightforward route for the preparation of multivalent presentations of the trimannan array present at the distal end of



Scheme 5.29 Preparation of GPI **137** from NPOEs.

membrane-anchored GPIs (Scheme 5.30) [85]. The strategy for the preparation of mono- and divalent neoglycolipids relied on the unique characteristics of NPOEs for ensuring the following: (a) high-yielding glycosyl couplings, (b) rearrangement to NPGs, (c) chemoselective activation of NPOEs and (d) the potential of the *n*-pentenyl chain to be utilized itself in tethering processes [86].

The sole source progenitor was NPOE **108** by way of counterparts **89** and **129**. The synthesis started with the rearrangement of NPOE **89** to NPG **138** (TBSOTf, 92%) that



Scheme 5.30 Use of NPOEs for multivalent presentations.

was homologated to **139** and **140** by sequential de-*O*-benzoylation followed by the glycosylation with NPOE donors **129** and **89**, respectively. The exquisite chemoselective activation of NPOEs by NIS/$Yb(OTf)_3$ in the presence of NPGs [87] allowed the olefinic residue, in trisaccharide **140**, to remain unaltered for further processing. Notably, this chemoselective feature dispenses with the earlier 'sidetracking' strategy [77], where dibromination was required to neuter one of the pentenyl residues (e.g. Scheme 5.26a).

Hydroxylation of the terminal double bond in **140** followed by the esterification paved the way to phosphodiester **141**, whereas Grubbs' olefin metathesis followed by hydroxylation and esterification led to divalent phosphodiester **142**.

5.1.4.5 The Lipoarabinomannan Components of the Cell Wall Complex of *Mycobacterium tuberculosis*: NPOEs in Chemoselective, Regioselective and Three-Component Double Differential Glycosidations

The lipoarabinomannan (LAM) capsule is the major virulence factor of *M. tuberculosis* [88]. The multifaceted architecture, shown as **143** (Figure 5.2) by Turnbull *et al.* [89], anticipates the complexity of any synthetic scheme aimed to its conquest. However, a simple analysis of the molecule shows that the *mannan* and *arabino* segments possess 1,2-*trans* glycosidic linkages, which point toward a retrosynthesis in which NPOEs could be the donors of choice.

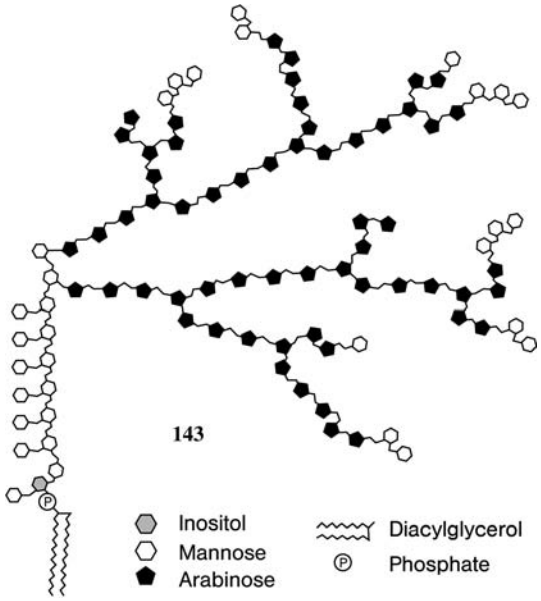
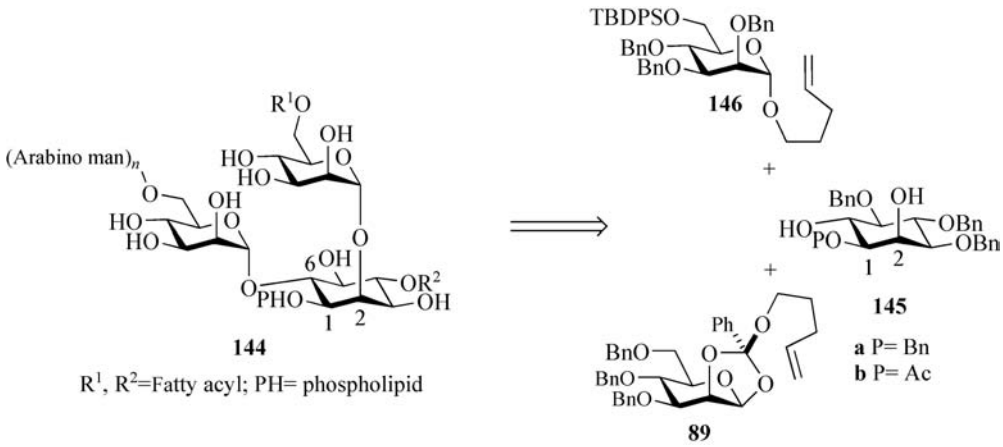
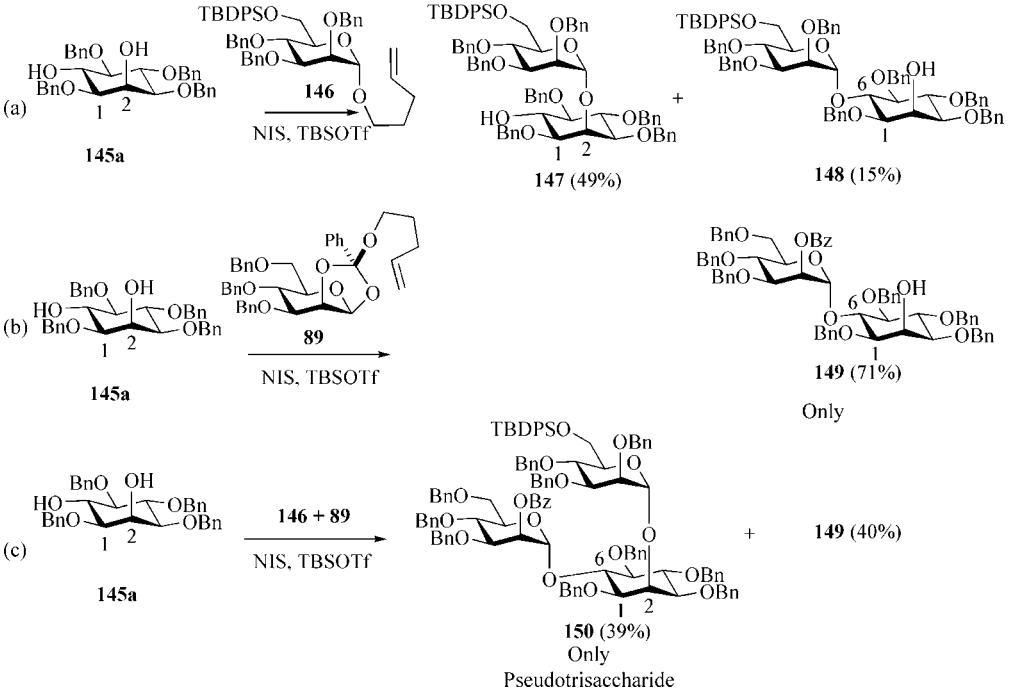


Figure 5.2 Lipoarabinomannan **143**.

The Inositol Core of Lipoarabinomannans: NPOE Donors in Chemo- and Regioselective Three-Component Double Differential Glycosidations Initial independent studies, by van Boom's [90] and Fraser-Reid's [91] groups, on the preparation of the pseudo-trisaccharide core of LAM **144**, by mannosylation of inositol diol **145**, had made it clear that the choice of the glycosyl donor and/or the protecting group at O-1 was crucial for optimal results (Scheme 5.31). This observation is in keeping with the concept of matching/mismatching phenomena in glycosyl couplings [92,93].



Scheme 5.31 Retrosynthesis of **144**.

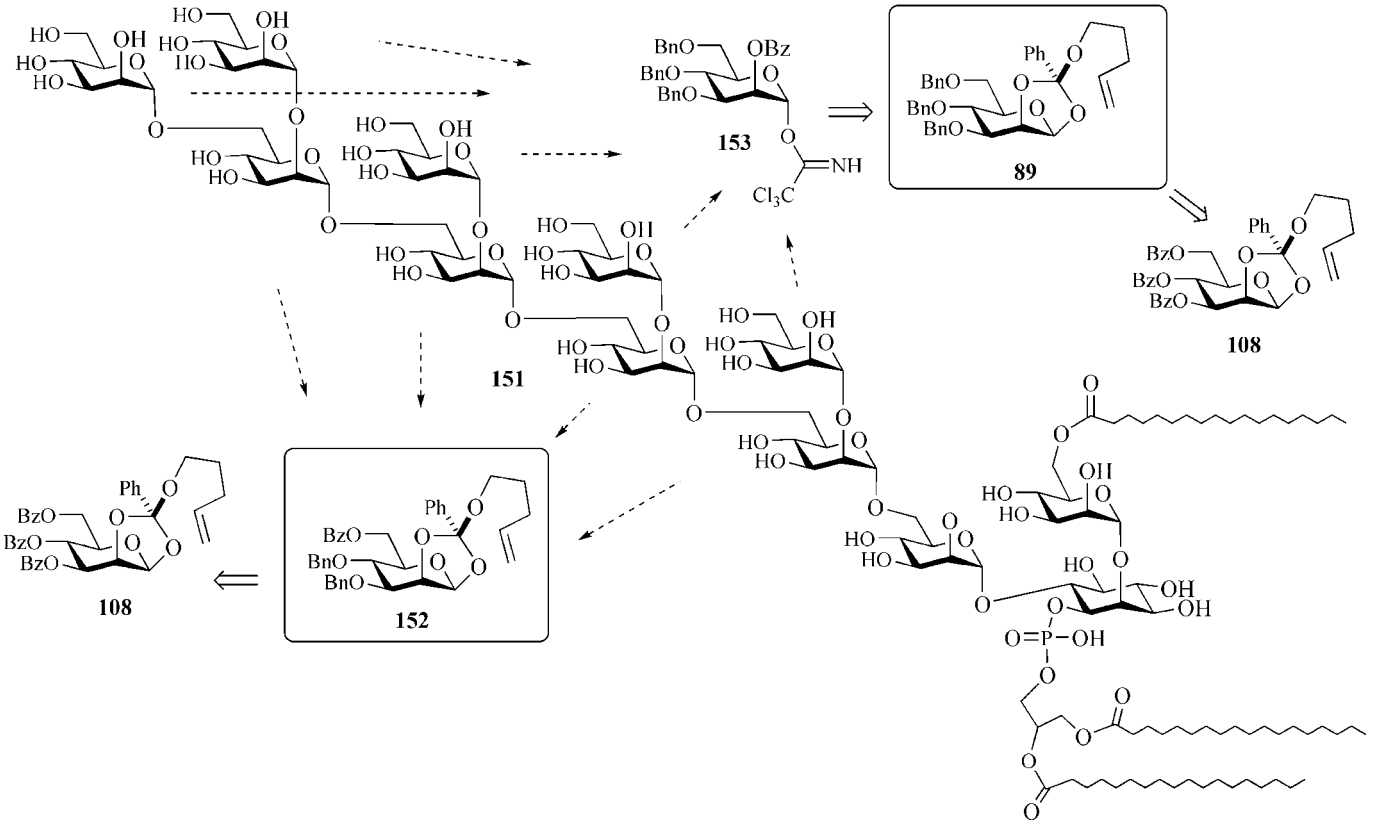


Scheme 5.32 Regioselective *in situ* three-component synthesis of **150**.

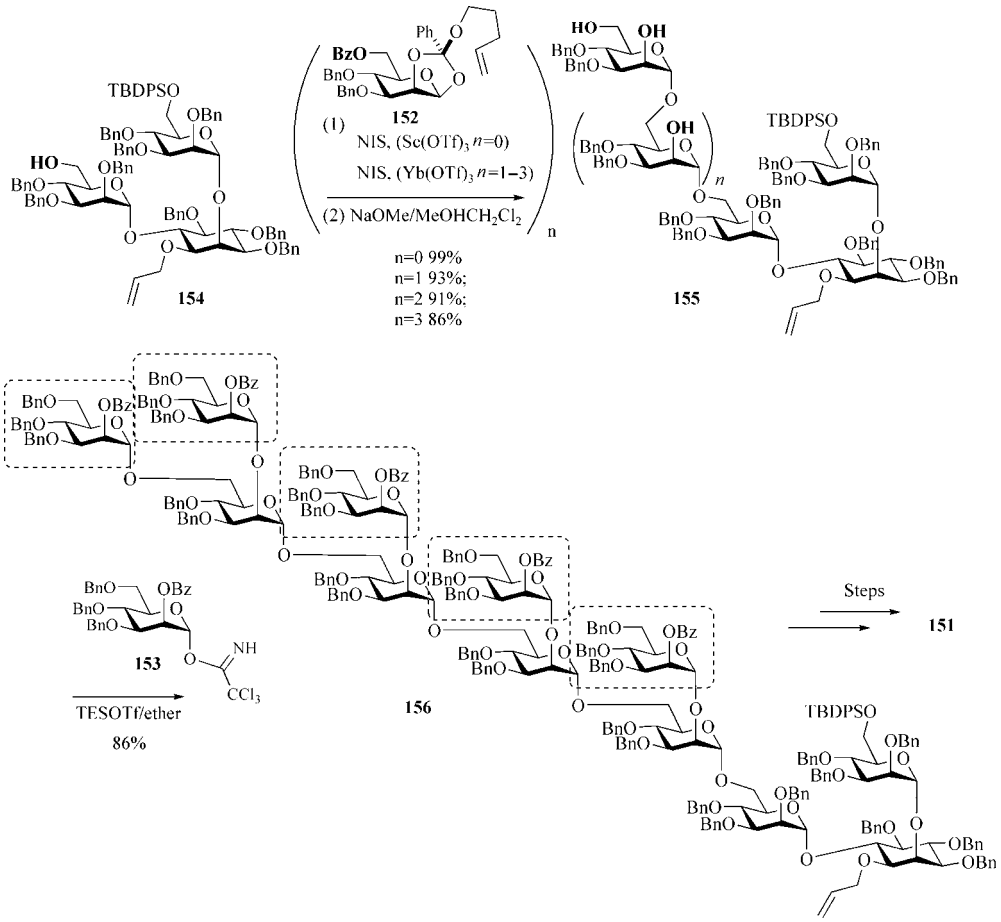
Subsequent studies by Anilkumar *et al.* [94] revealed that the glycosylation of a diol **145a** with NPG **146** was weakly regioselective, giving rise to a 3 : 1 mixture of pseudodisaccharides **147** and **148** arising from glycosylation at O-2 and O-6, respectively (Scheme 5.32a). By contrast, the glycosylation of **145a** with NPOE **89** furnished exclusively pseudodisaccharide **149** from glycosidation at O-6 (Scheme 5.32b). This different behavior, although not yet completely understood, permitted the authors to devise an *in situ*, site-selective protocol for double glycosidation of the inositol core of the LAM antigen **150** (Scheme 5.32c). The successful implementation of this strategy benefits not only from the exquisite regioselectivity of NPOE **89** but also from the possibility to chemoselectively activate NPOEs in the presence of armed NPGs. Notably, the more reactive NPOEs also display higher regioselectivity in glycosyl couplings than that achieved with NPGs.

The Lipomannan Component of LAM: Regioselective Couplings with NPOEs The architecture of compound **143** (Figure 5.2) indicated that the inositol phospholipids moiety is linked to the oligomannan portion of LAM. The retrosynthetic route to structure **163** again used NPOE **119** as the sole source for the *manno* components [95]. The glycosyl unit correlation in this approach is outlined in Scheme 5.33.

The synthesis was carried out by four successive glycosylations with NPOE **89**, which yielded a linear, α-linked 1,6-mannan chain, with benzoate esters strategically



Scheme 5.33 Retrosynthesis of LAM **151** from two NPOE precursors.



Scheme 5.34 Synthesis of **151**.

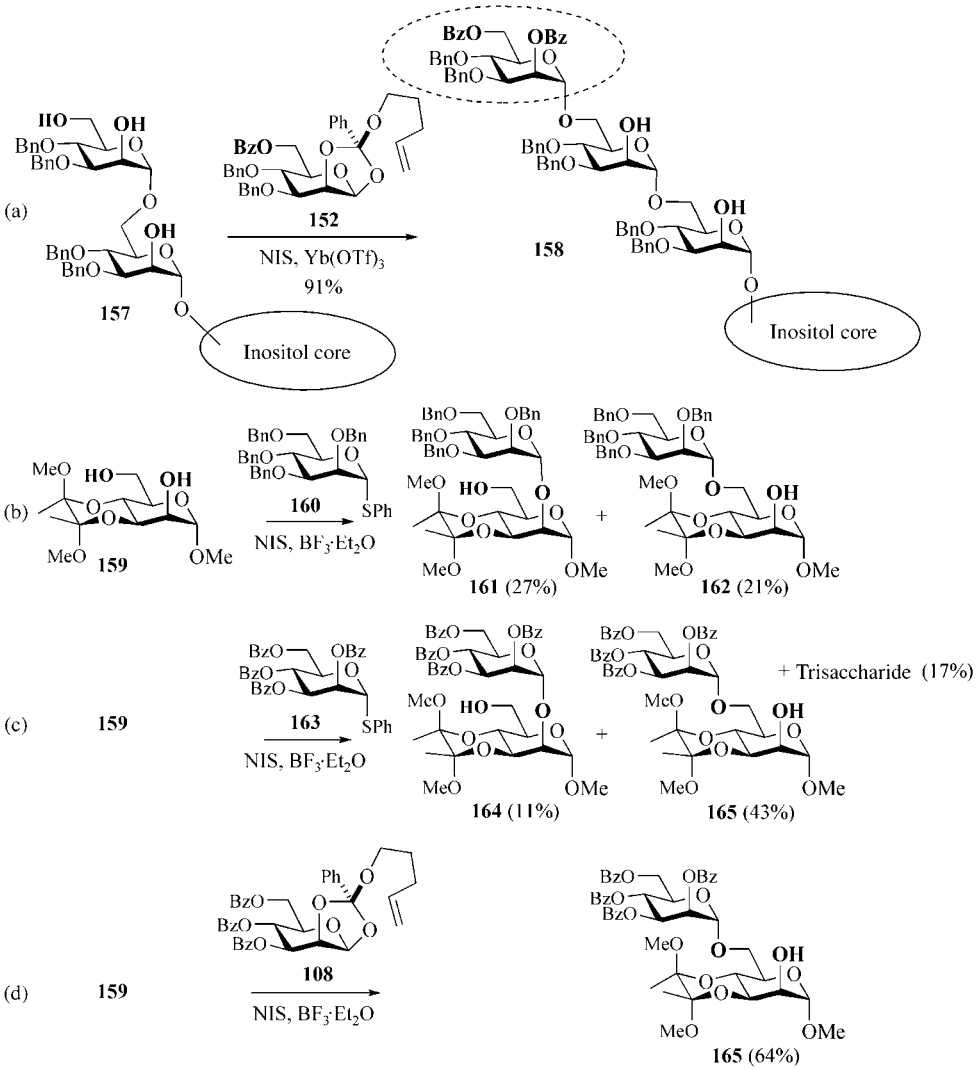
located at all O-2 sites (Scheme 5.34). Saponification of these, followed by exhaustive glycosylation with trichloroacetimidate **153**, readily prepared from NPOE **89**, achieved the one-pot incorporation of all five mannose branches. The synthesis was completed by the protecting-group manipulations that allowed the incorporation of stearoyl ester and phosphoglycerolipidation, using the previously credited procedure [81,82]. Finally, exhaustive debenzylation and purification led to **151**.

5.1.4.6 Relevance of NPOEs to the Regioselectivity in the Glycosylation of Primary Versus Secondary Hydroxyls

The conventional thinking in organic synthesis indicates that primary hydroxyls are more reactive than secondary hydroxyls [96]. Under this assumption, the glycosylation of triol **157** to furnish diol **158** by exclusive glycosylation at the

primary-OH might seem to be routine laboratory experience (Scheme 5.35a). However, recent studies by López and coworkers have shown that the 'primary versus secondary' issue in regioselective glycosylation is not that simple and that the choice of the glycosyl donor plays a determinant role in eliciting regioselectivity [97].

Diol **159** was chosen as a model for probing regioselective glycosylation with armed and disarmed thioglycosides **160** and **163**, and NPOE **108**. The results obtained were not anticipated (Scheme 5.35b–d).



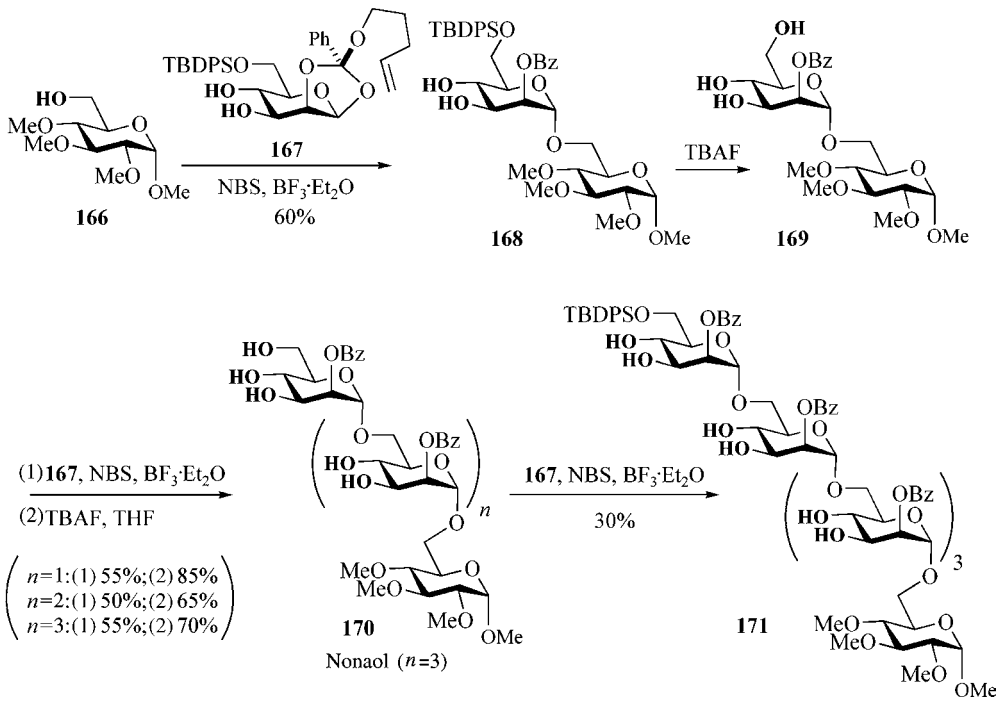
Scheme 5.35 The issue of regioselectivity in the glycosylation of primary versus secondary hydrosyls.

Remarkably, armed glycosyl donor **160** preferred the secondary-OH of **159** (Scheme 5.37b). Disarmed donor **163** and NPOE **108** both 'preferred' the primary-OH, but the NPOE furnished a single regioisomer **176** (Scheme 5.35c and d).

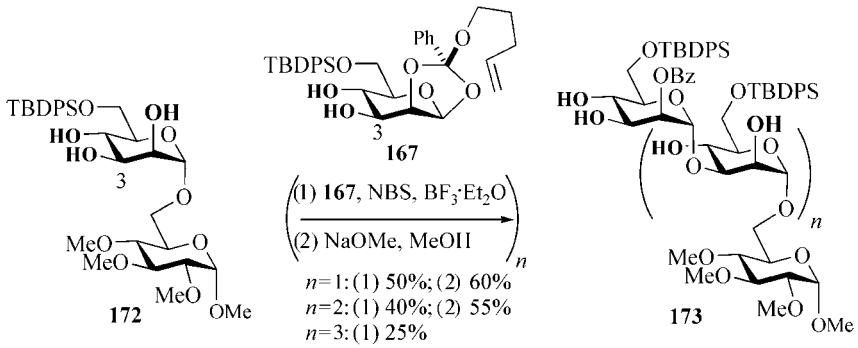
These results clearly demonstrate that (a) it is relevant (and importance) to match glycosyl donors and glycosyl acceptors to achieve regioselective couplings, (b) an absolute reactivity order cannot be ascribed to the glycosyl acceptor's hydroxyl groups and by corollary (c) NPOE regioselectivities (e.g. **157** → **158**, Scheme 5.35a and **154** → **155**, Scheme 5.34) cannot be regarded as 'trivial' or routine.

5.1.4.7 Iterative Regioselective Glycosylations of Unprotected Glycosyl Donors and Acceptors

In Scheme 5.35, the issue of regioselectivity is focused on polyol glycosyl acceptors. By contrast, examples in which the glycosyl donor itself has one or more free hydroxyl groups are rarely seen [98–100]. Encouraged by the regioselectivity displayed by NPOE donors, López *et al.* studied the regioselective couplings of NPOE diol **167** with polyol acceptors (Scheme 5.36) [101]. Reaction with methyl glucoside **166** furnished a single compound **168**, thus showing that self-coupling of **167** was not a competing reaction. Triol **169**, obtained by the deprotection of silyl ether **168** with TBAF, was next tested as a glycosyl acceptor. Again only one compound, **170** ($n = 1$), was obtained in the reaction of the NPOE donor diol **167** with triol **169**. The iteration of the process, up to three times, permitted the synthesis of pentasaccharide **170** ($n = 3$) with nine free-OH



Scheme 5.36 Iterative glycosylation of polyol acceptors with unprotected glycosyl donors.



Scheme 5.37 Iterative glycosylation of secondary triols with NPOE diol **167**.

groups, resulting from the glycosylation of a heptaol acceptor with diol **167**. Glycosidation of **170** with **167** then gave hexasaccharide **171** with 10 free-OH groups.

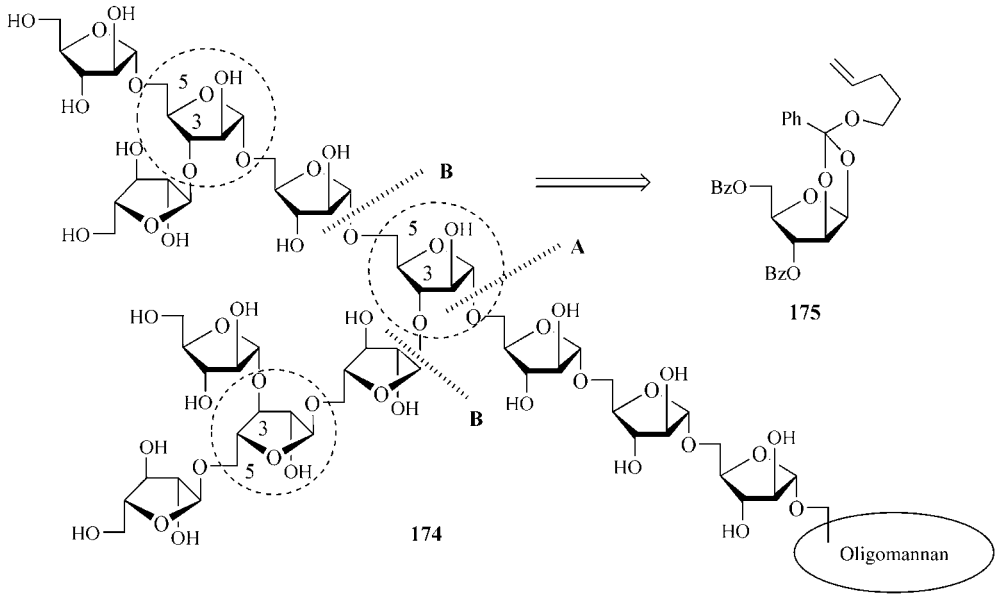
In none of the above cases were significant amounts of products from self-condensation of **167** seen.

The synthesis of a hexasaccharide by successful differentiation between one primary OH group and up to 10 secondary OH groups (eight in the acceptor plus two in the donor) prompted the authors to explore the feasibility of oligosaccharide synthesis through secondary versus secondary hydroxyl group selectivity. Accordingly, the glycosylation of triol **172** with NPOE **167** resulted in the formation of one single trisaccharide **173** ($n = 1$) in 50% yield by selective glycosylation at O-3, thus showing that discrimination was also possible among secondary OH groups (Scheme 5.37). The iteration of the protocol two more times resulted in the preparation of octaol pentasaccharide **173** ($n = 3$).

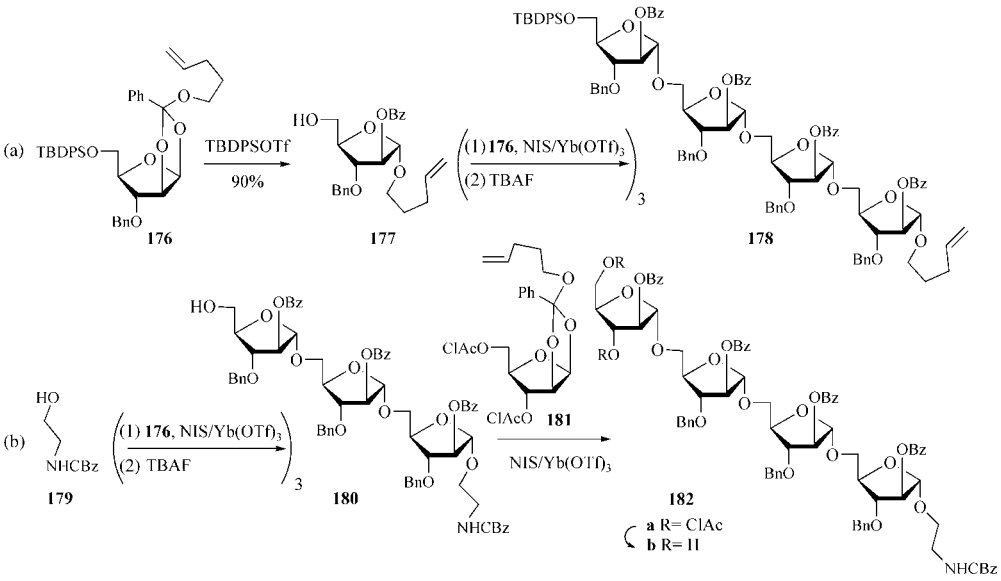
5.1.4.8 NPOEs of Furanoses: Key Intermediates in the Elaboration of the Arabino Fragment of LAM

The multibranched dodeca-arabinosaccharide **174** (Scheme 5.38) is a relevant part of the of LAM glycolipid of *M. tuberculosis*, illustrated in Figure 5.2. The structure features a repeated 3,5-branched motif, represented by the encircled units, along with linear catenated *arabino*-1 → 5 units. Lu and Fraser-Reid proposed two retrosynthetic plans (based on dissections **A** and **B**, Scheme 5.38), which employ as the sole source NPOE **175** [102,103]. In option **A**, a nona-arabinan donor would be delivered to the primary hydroxyl of a tri-arabinan acceptor, whereas in option **B** two identical tetra-arabinan donors would be delivered to the tetra-arabino acceptor.

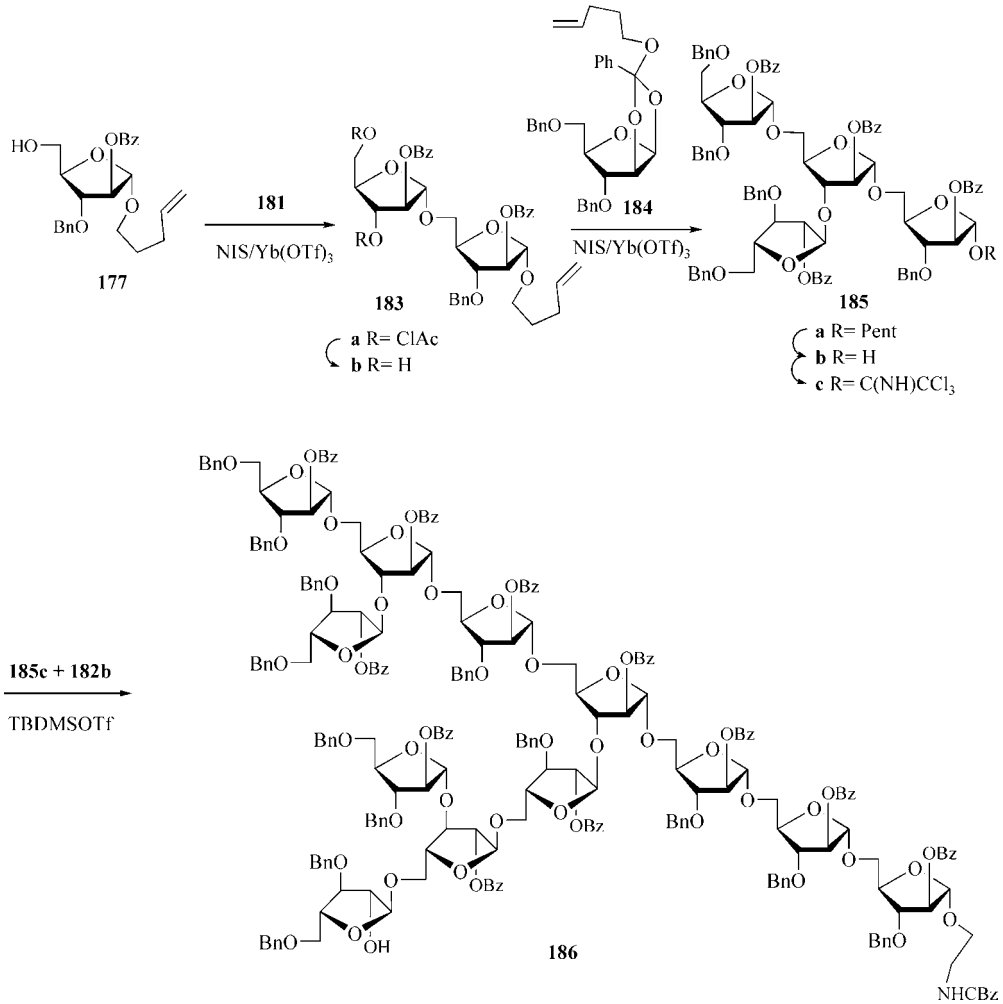
In preliminary studies, Lu and Fraser-Reid had reported the efficient assembly of tetra-arabino derivative **178** by iterative couplings of donor **176** with NPG **177**, also accessible by TBDPSOTf-catalyzed rearrangement of **176** (Scheme 5.39a) [104]. They applied a similar protocol to the preparation of tetra-arabinan diol acceptor **182b** (Scheme 5.39b). In this case, the protected ethanolamine **179** [84] was used as the first acceptor for the iterative sequence with NPOE donors **176** to obtain **180**, and then with **181** to obtain **182a**, which on treatment with thiourea furnished 3,5-diol **182b**.



Scheme 5.38 Retrosynthesis of oligoarabinan **174** from NPOE **175**.



Scheme 5.39 Synthesis of linear oligosaccharide **182**.



Scheme 5.40 Final assembly of arabinnan **186**.

The synthesis of the branched donor unit **185a** was carried out by using NPOE **184** to bis-glycosylate diol **183b** (Scheme 5.40), the latter having been easily prepared by the glycosylation of **177** with NPOE donor **181** followed by thiourea deprotection. The final step of the convergent synthesis (**B**, Scheme 5.38) was the glycosyl coupling of trichloroacetimidate **185c** with the tetrasaccharide acceptor **182b**.

5.1.5
Conclusions and Future Directions

In conclusion, NPOEs, which can be prepared and manipulated routinely, have excellent shelf life, but can yet be readily activated by the action of mild reagents.

Their value is enhanced by the facility with which they serve as progenitors to other donors, some of which are too reactive for prolonged storage, and also to other less readily prepared counterparts, such as NPGs, thioglycosides and glycosyl fluorides. These properties mean that NPOEs can be selectively, and even chemospecifically, targeted, thereby enabling one-pot sequences as well as *in situ* glycosylation(s). The recent extension to furanose systems is propitious in view of the generally greater reactivity *vis-a-vis* pyranoses. In this connection, the masked O-2 benzoate is extremely valuable, as it provides a nascent disarming device that confers stability on reactive species such as the trichloroacetimidate **185c**.

5.1.6 Typical Experimental Procedures

5.1.6.1 General Procedure for the Preparation of Orthoesters

The corresponding bromide (0.111 mol) was dissolved in dry CH_2Cl_2 (250 ml), and 2,6-lutidine (20 ml, 0.172 mmol), 4-pentenyl alcohol (14 ml, 0.14 mol) and tetra-*n*-butylammonium iodide (2.0 g, 5.4 mmol) were added. The resulting mixture was refluxed under argon for 24 h, during which TLC (hexane/ethyl acetate) showed complete disappearance of the starting material. After cooling to room temperature, water and diethyl ether were added, and the organic layer was washed with water and with brine and dried. After evaporation the residue was filtered through silica gel using hexanes/ethyl acetate (from 9 : 1 to 4 : 1) to effect partial purification of polar impurities.

5.1.6.2 General Procedure for Glycosidation with *n*-Pentenyl Orthoesters

General Glycosylation Procedure with NIS/$BF_3{\cdot}OEt_2$ To a solution of glycosyl acceptor and NPOE (1.1 equiv) in dry CH_2Cl_2 were added 5 Å molecular sieves (1 mg mg^{-1} donor) and *N*-iodosuccinimide (1.5 equiv) at $-30\,^{\circ}C$. After stirring the mixture for 5 min, $BF_3{\cdot}OEt_2$ (0.045 mmol) was added. The reaction was monitored by TLC and after acceptor disappearance was observed, it was quenched with 10% aqueous sodium thiosulfate and saturated aqueous bicarbonate solutions. The reaction mixture was extracted with CH_2Cl_2 and dried over anhydrous sodium sulfate. The solvents were removed and the residue was purified by flash chromatography.

General Glycosylation Procedure with NIS/TBDMSOTf The glycosyl acceptor and the NPOE (1.1 equiv) were dissolved in a small quantity of toluene, azeotroped to dryness and then dissolved in dry CH_2Cl_2 at $0\,^{\circ}C$ under argon atmosphere. *N*-Iodosuccinimide (1.2 equiv) was added to the solution, and after stirring for 3 min, TBDMSOTf (0.25 equiv) was added. The reaction was quenched with 10% aqueous sodium thiosulfate and saturated sodium bicarbonate, extracted with CH_2Cl_2 and worked up as above. After work-up the mixture was purified by flash chromatography.

General Glycosylation Procedure with NIS/$Yb(OTf)_3$ The glycosyl acceptor and the NPOE (2.2 equiv) were dissolved separately in small amounts of toluene, and

the solutions were evaporated to dryness and kept overnight under vacuum. The acceptor was dissolved in CH_2Cl_2, the solution cooled to 0 °C, NIS (2.5 equiv) was added, followed by the addition of $Yb(OTf)_3$ (0.3 equiv). After stirring for a few minutes, a methylene chloride solution of the NPOE was then added dropwise over 15 min. The reaction was quenched with 10% aqueous sodium thiosulfate and saturated aqueous bicarbonate, extracted with CH_2Cl_2 and dried. The resulting mixture was purified by flash chromatography.

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5.2
Other Methods for Glycoside Synthesis: Dehydro and Anhydro Derivatives

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5.2.1
Introduction

Sugar derivatives containing a double bond, 'dehydro sugars', and those that feature an intramolecular anhydride, 'anhydro sugars', are versatile building blocks for the synthesis of glycosides and other natural products. Both classes of sugars have been utilized in the construction of an impressive range of complex carbohydrates and found application in emerging fields of solid phase and combinatorial synthesis of glycosides and sequential one-pot glycosylation strategies.

Of the unsaturated sugars, it is those with the double bond between C-1 and C-2 that can be utilized in glycosidic bond formation. These pyranoid or furanoid vinyl ethers (**I**, **II**, **IV** and **V**, Figure 5.3) are referred to as 'glycals' or more specifically *endo*-glycals to distinguish them from the *exo*-glycals bearing an exocyclic C-1–C-2 double bond (**III**, Figure 5.3). Their utility lies in the unique reactivity of the cyclic enol ether, with the ring oxygen influencing the regioselectivity of addition and rearrangement reactions, and the nature and orientation of ring substituents contributing to the overall reactivity and the stereochemical outcomes of reactions. They are glycosyl donors in their own right and are precursors to several other glycosyl donors, thereby serving as building blocks for the construction of a wide range of *O*-, *N*-, *S*- and *C*-glycosides. Their reactivity has been particularly exploited in the construction of

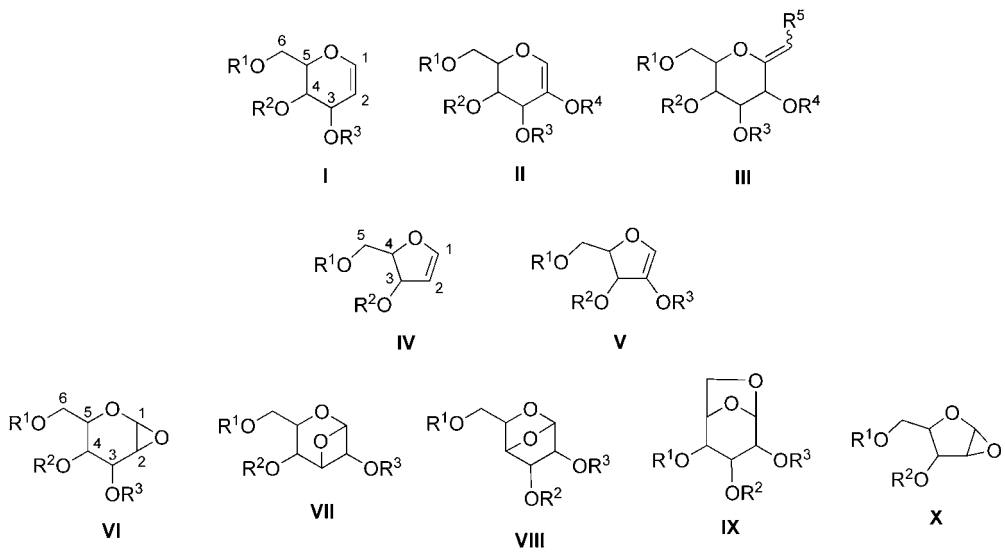


Figure 5.3 Generalized structures of dehydro and anhydro sugars.

2-deoxyglycosides, 2-amino-glycosides and in glycosidic bond formation where subsequent elaboration at C-2 in the glycosyl donor component is required.

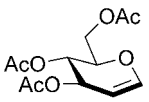
Of the various anhydro sugar glycopyranoses (**VI–IX**, Figure 5.3), the 1,2-anhydro sugars (**VI**) and the 1,6-anhydro sugars (**IX**) are of most use in glycosidation reactions, the 1,3- and 1,4-anhydro sugars (**VII** and **VIII**) being more difficult to prepare and of insufficient stability to facilitate practical use. Similarly, the 1,2-anhydrofuranoses (**X**) are the most useful of the anhydrofuranoses. The 1,2-anhydro sugars are, indeed, derivable from the glycals, and their ease of preparation and excellent reactivity in glycosidation protocols contribute to the utility and versatility of this class of dehydro and anhydro sugars.

Comprehensive reviews of the chemistry of both the glycals [105–107] and anhydro sugars [108,109] have appeared in the recent literature. This chapter will attempt to summarize what is known about their preparation and reactivity in the formation of the glycosidic linkage and highlight recent examples to emphasize practical and strategic considerations in the choice of glycosyl donors.

5.2.2
Glycals in Glycoside Synthesis

5.2.2.1 Preparation of Glycals

Several protected glycals are available commercially, including the simple but important glycals 3,4,6-tri-*O*-acetyl-D-glucal (**1**) and 3,4,6-tri-*O*-acetyl-D-galactal (**2**), and these as well as others serve as precursors to a wide range of selectively protected glucals and galactals via strategies common in carbohydrate chemistry. The synthetic value of acetylated glucals has been enhanced by the availability of simple, one-pot procedures for the conversion of acyl- into alkyl-protected glucals [110].



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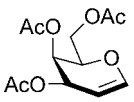

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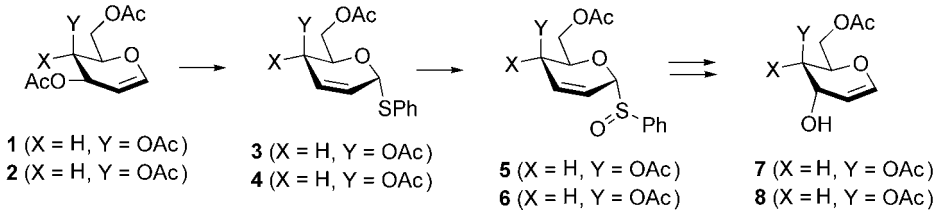
Most of the common *O*-acetylated pyranoid glycals can be obtained using variations of the traditional Fischer–Zach method [111] of zinc-promoted elimination of glycosyl halides in acetic acid. The scope of this method has been extended with the development of efficient aprotic, nonacidic conditions for this reaction using zinc dust and 1-methyl imidazole in ethyl acetate [112] and other methods where the acetylated glycosyl halide is treated with catalytic amounts of Vitamin B_{12} (as source of Co(III)) together with zinc and ammonium chloride [113] or with THF solutions of the Ti(III) dimer $(Cp_2TiCl)_2$ [114]. These elimination methods are, however, limited to the readily available glucosyl and galactosyl halide precursors, and therefore are primary sources of D-glucal and D-galactal derivatives. The most attractive route to D-allal and D-gulal derivatives **7** and **8** (Scheme 5.41) is via oxidation and rearrangement of *S*-phenyl-2,3-dideoxy derivatives **3** and **4**, derived



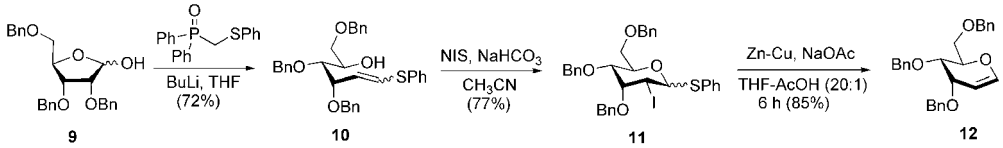
Scheme 5.41 Synthetic route to D-allal and D-gulal derivatives.

from acetylated D-glucal and D-galactal, respectively, using the Ferrier reaction on glycals [115].

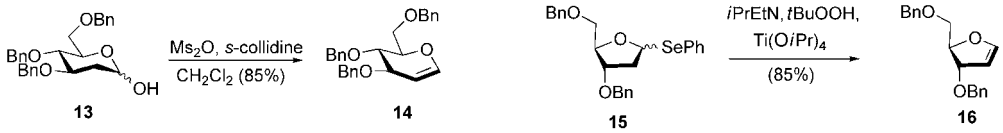
A useful and promising addition to the methodologies for the synthesis of the whole range of glycals, including D-allal and D-gulal derivatives, is illustrated (Scheme 5.42) for the conversion of benzylated D-ribose into benzylated D-allal through an olefination–cyclization–elimination sequence [116]. Wittig–Horner olefination of protected ribose **9** gave alkenylated derivative **10**, which could be readily converted using NIS-activation of the olefin into 2-iodo-thioglycoside **11**, and this underwent smooth elimination to give benzylated allal **12**. The efficiencies of the individual steps in this sequence vary with the nature and orientation of the substituents, but it represents a useful route to rare glycals.

Glycals are also available from 2-deoxy sugars by acid- or base-induced eliminations of anomeric substituents. These methods are limited by the availability of the 2-deoxy sugars, for which the glycals themselves are the most obvious synthetic precursors. However, examples of these methods (Scheme 5.43) are in the direct preparation of tri-*O*-benzyl-D-glucal (**14**) from 2-deoxy-tri-*O*-benzyl-D-glucopyranose (**13**) via its 1-*O*-mesylate [117], and di-*O*-benzyl-D-ribal (**16**) from the phenylselenide **15** via oxidation to the selenoxide followed by elimination [118].

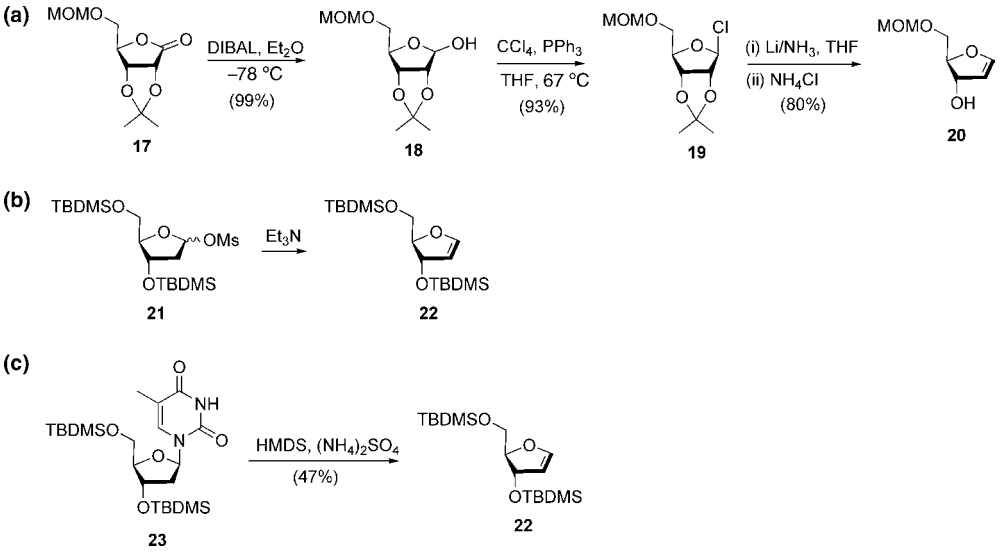
The latter elimination route to D-ribal is illustrative of the approach necessary for the preparation of the sensitive furanoid glycals, which are not accessible via the



Scheme 5.42 Alternative synthesis of a D-allal derivative.



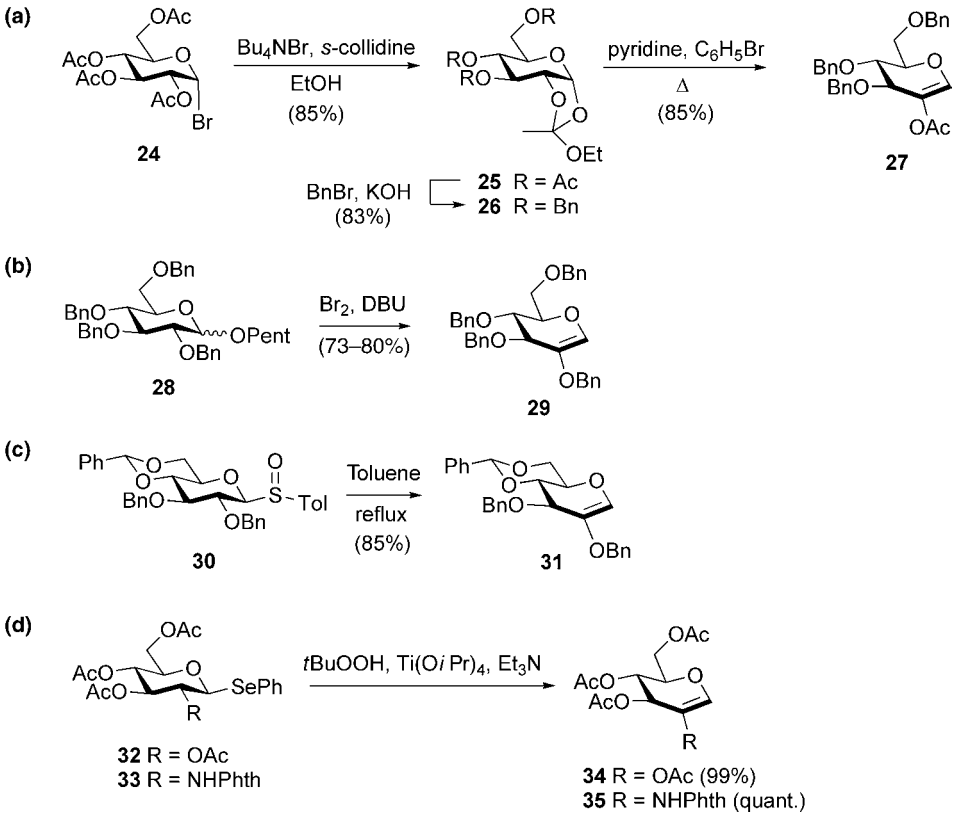
Scheme 5.43 Preparation of glycals via base-induced eliminations.



Scheme 5.44 Preparations of D-ribal.

zinc-mediated reductive elimination routes to pyranoid glycals noted above. The first efficient preparation of a D-ribal [119] proceeded via DIBAL (diisobutyl aluminium hydride) reduction of ribonolactone **17** (pathway a, Scheme 5.44) to give ribose derivative **18**, followed by the formation of the ribosyl chloride **19** and then treatment of this with Li–NH_3 followed by careful quenching using NH_4Cl to give partially protected D-ribal **20**. A more practical preparation of D-ribal derivatives (pathway b, Scheme 5.44) involves treatment of 2-deoxyribosyl mesylate **21** with triethylamine, giving the silylated D-ribal **22** in good yield [120]. This can also be obtained by heating *O*-protected thymidine **23** in refluxing HMDS (hexamethyl disilazane) in the presence of ammonium sulfate under inert atmosphere [121].

The 2-substituted glycals, such as the 2-oxyglycals **II** and **V** in Figure 5.3, have traditionally enjoyed less attention than their 2-unsubstituted counterparts, presumably because of their limitations as glycosyl donors in glycosidation reactions. Earlier methods [122,123] for the preparation of the 2-oxyglycals involved acid- or base-induced eliminations of protected glycosyl halides, as illustrated more recently [124] in the preparation of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucal **27** (reaction a, Scheme 5.45). This was achieved by the conversion of tetra-*O*-acetyl glucosyl bromide **24** into orthoester **25**, exchange of acetyl for benzyl protecting groups to give **26**, and then heating in bromobenzene and pyridine to give **27** in good yield. A robust procedure of this kind, suitable for large-scale preparation of tetra-*O*-benzyl-D-glucal **29** (reaction b, Scheme 5.45), involves a sequential treatment of pentenyl glycoside **28** with bromine and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). These approaches are somewhat limited in terms of the range of protecting groups that are tolerated, but this is overcome by an attractive alternative that utilizes highly efficient *syn* elimination of 1,2-*trans* glycosyl sulfoxides [125] or glycosyl selenoxides



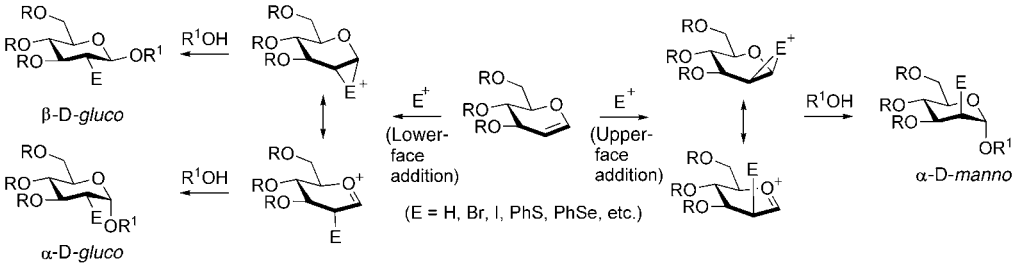
Scheme 5.45 Methods for preparing 2-substituted glycals.

[126], the latter generated *in situ* by the oxidation of the corresponding phenylselenides. Selected examples are shown in Scheme 5.45 (reactions c and d), illustrating that both 2-oxypyranoid glycals (**32** and **34**) as well as 2-amidoglycals (**35**) are available in this way.

5.2.2.2 Glycals as Glycosyl Donors

Glycals can be glycosylated not only directly via electrophilic addition, cyclo addition, nucleophilic addition and rearrangement reactions but also indirectly by conversion into a range of other glycosyl donors. One of the most important classes of these glycal-derived donors, the 1,2-anhydro sugars, is discussed in detail in Section 1.3.

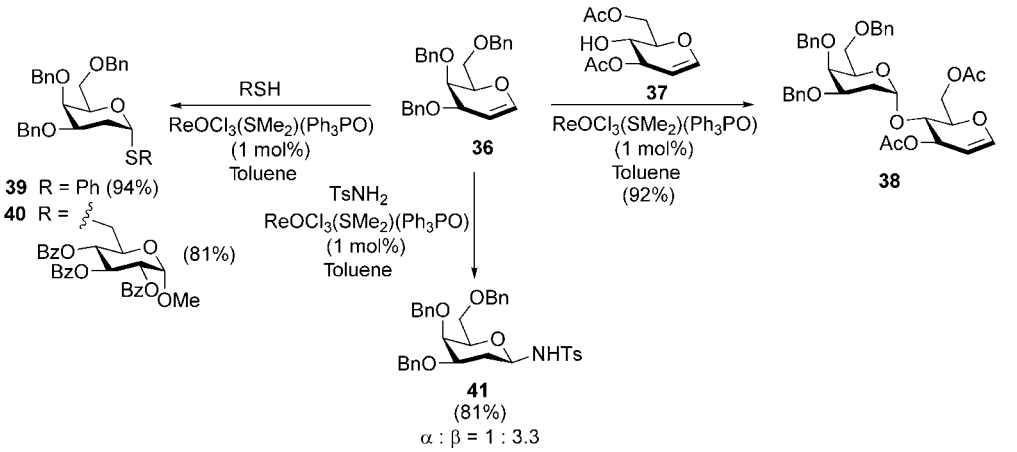
Direct Synthesis of 2-Deoxyglcosides from Glycals Glycals are important donors in the preparation of glycosides of 2-deoxy sugars [106]. In polar addition reactions to the double bond, the regiochemical outcome is governed by the intermediacy of an oxocarbenium ion, which may be in equilibrium with a cyclic onium species across C-1–C-2, thus directing the incoming nucleophile to C-1. The stereochemistry is



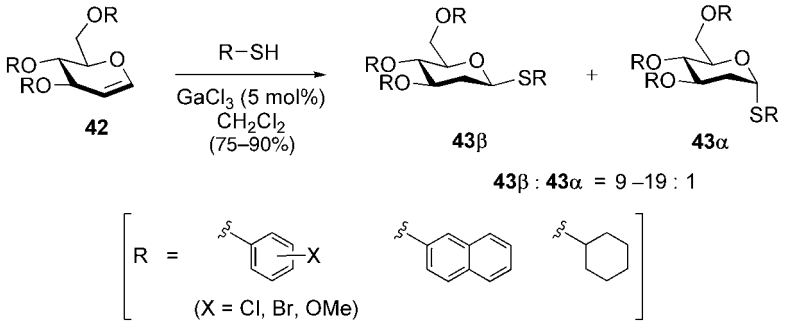
Scheme 5.46 General mechanisms for polar additions to glycols.

influenced by a complex interplay of stereochemical and stereoelectronic factors including, *inter alia*, the nature and orientation of ring substituents, the nature of the electrophilic species, the solvent and the kinetic anomeric effect. These mechanisms and outcomes are summarized in Scheme 5.46 and have been comprehensively evaluated [127–129]. Representative examples of the synthetically useful addition protocols are discussed below.

The most direct route to 2-deoxyglycosides is by acid-promoted addition of alcohols to the glycals, although care must be taken to prevent acid-catalyzed rearrangements or deprotection. For example, treatment of *O*-acylated glycals in dichloromethane with alcohols and triphenylphosphine-hydrogen bromide [130], or with acid resins in acetonitrile containing anhydrous lithium bromide [131], mainly gives the thermodynamically more stable 2-deoxy-α-glycosides. This kind of direct glycosidation has found somewhat limited application because of the difficulties associated with the stereocontrol and acid sensitivity of glycals. However, the scope has been expanded by the recent report [132], wherein a Re(V)-oxo complex is used in catalytic amounts to activate a nucleophile for addition to glycals to give α-linked 2-deoxyglycosides in very high yields and selectivities (Scheme 5.47). For example,



Scheme 5.47 Synthesis of 2-deoxy-α- and β-glycosides using Re(V)-oxo complex.



Scheme 5.48 $GaCl_3$-promoted formation of 2-deoxy-β-thioglycosides.

deactivated ('disarmed') glycal alcohol **37** could be coupled to benzylated galactal **36** to give α-linked disaccharide **38** in excellent yield. The methodology could also be applied to the preparation of 2-deoxythioglycosides such as **39** and **40** or *N*-glycosides **41**, although in the latter case the β-glycoside predominated.

In contrast to the α-selectivity in 2-deoxythioglycoside formation in the preceding example, excellent β-selectivity has been achieved [133] on treatment of protected glycals **42** with a range of thiophenols in the presence of $GaCl_3$ (Scheme 5.48).

Preparation of 2-deoxyglycosyl azides represents a useful alternative method for the construction of 2-deoxy-*N*-glycosides. Reddy [134] has recently described a method for direct conversion of glycals into 2-deoxyglycosyl azides using a TMS nitrate–TMS azide combination. Protected galactals gave only the α-galactosyl azides, whereas benzylated glucal (**14**) or its 3-deoxy analog gave mixtures of the α- and β-glucosyl azides.

An alternative and more stereocontrolled approach to 2-deoxyglycosides and C2-modified glycosides is the simultaneous introduction of glycosyl acceptor and a removable substituent at C-2. In this category, bromo- and iodoalkoxylation have emerged as the most useful reactions based on the early work of Lemieux [135,136] in which he introduced iodonium dicollidine perchlorate (IDCP) as the promoter, and subsequent reports on the use of *N*-bromo-succinimide [137] and *N*-iodo-succinimide (NIS) [138] as useful sources of the halonium species. These methods predominantly give the product of 1,2-*trans* addition, and subsequently the bromo- or iodo-substituents are reductively removed using reagent combinations such as Bu_3SnH and catalytic azobis(isobutyronitrile) (AIBN). The stereochemical outcome of the reactions is influenced by a range of factors, including the preferred conformation of the glycal ($^5H_4$ versus $^4H_5$, as illustrated in Figure 5.4), steric factors in both the glycal and nucleophile, the solvent and temperature.

With most protected D-glucals, the sequence is highly selective toward formation of α-2-deoxyglucosides because haloalkoxylation of glucals gives predominantly, and often exclusively, the 2-halo-2-deoxy-α-mannosides as a result of upper-face addition of the iodonium species and *trans*-1,2-addition. The two representative examples in Scheme 5.49 illustrate the utility of this methodology. In reaction (a), glucal **1** reacted cleanly with primary sugar alcohol **44** to give the α-linked disaccharide **45** in good yield [139], whereas reaction (b) illustrates the exploitation of the influence of

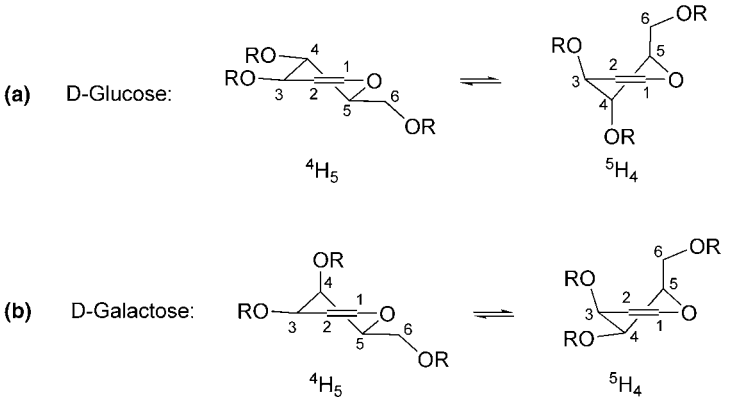
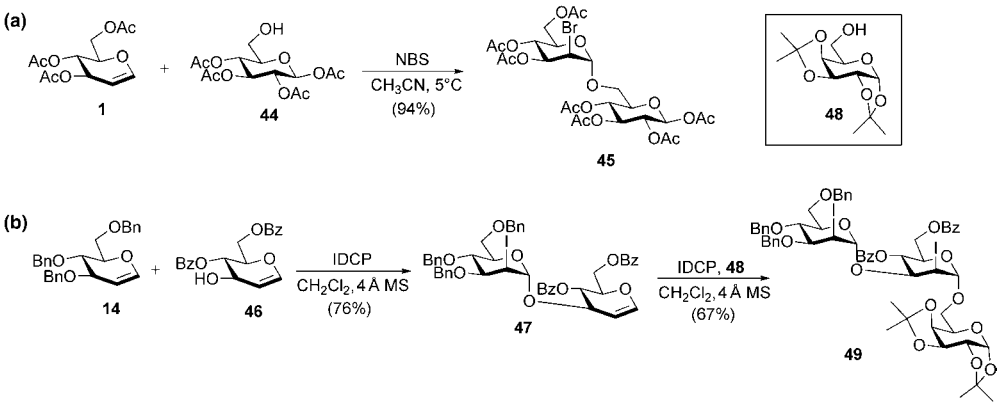


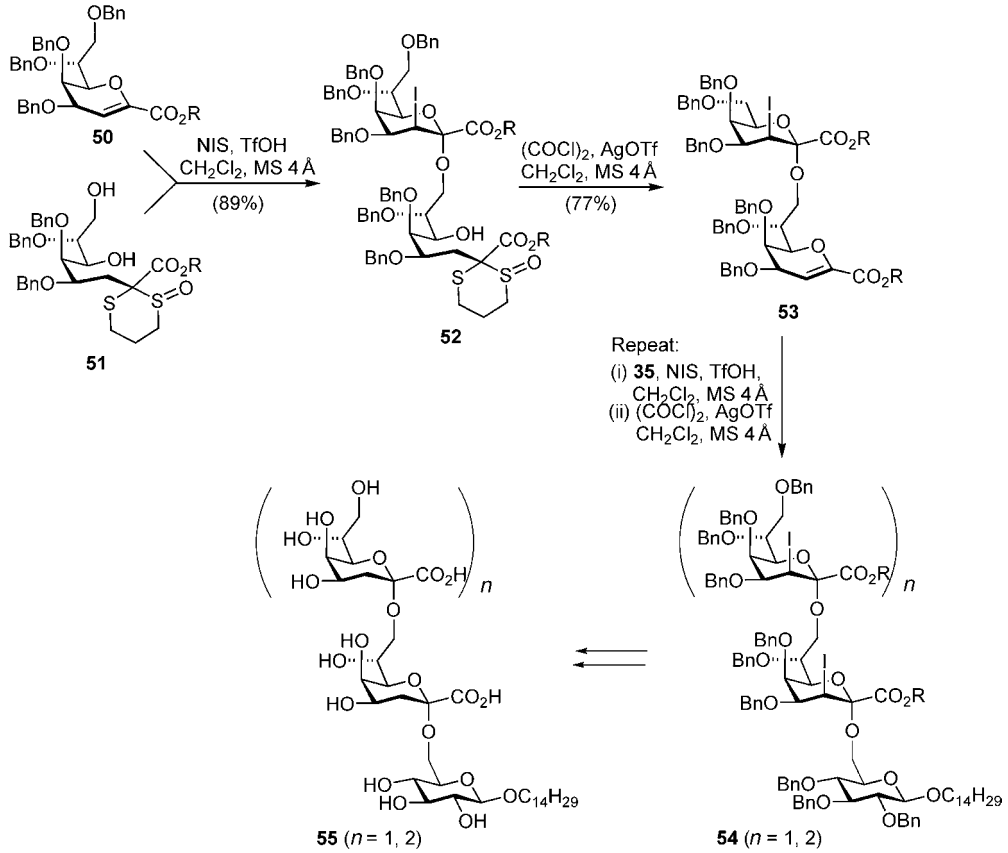
Figure 5.4 Conformational options in derivatives of D-glucose and D-galactose.

protecting groups in controlled, iterative assembly of oligosaccharides [140]. 'Armed' benzylated glucal **14** was combined with 'disarmed' benzoylated glucal **46** in the presence of the promoter IDCP to selectively give disaccharide **47**, which was in turn used in subsequent glycosylation of protected galactoside **48** to give trisaccharide **49**.



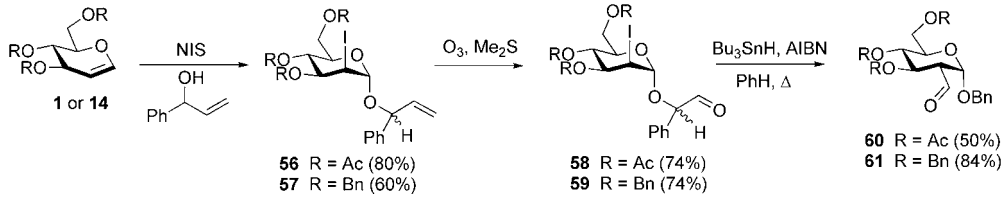
Scheme 5.49 Formation of 2-deoxyglycosides via haloalkoxylation of glycals.

An unusual application of the iterative iodoalkoxylation sequence was recently described in a synthetic route to oligo-(2,8)-3-deoxy-α-D-*manno*-2-octulosonic acid derivatives (Scheme 5.50) [141]. The C-1-substituted glycal **50** was treated with acyclic D-*manno*-2-octulosonic acid diol **51**, bearing alkyl sulfanyl and alkyl sulfoxide groups at C-2, in the presence of NIS and TfOH to give dimer **52**. The sequential activation with $(COCl)_2$ and AgOTf removed the sulfoxide and alkyl sulfanyl groups and regenerated the glycal ester **53**. The repetition of the sequence afforded an oligomer **54**, which upon deprotection and reductive removal of iodine gave the KDO oligomer **55**.



Scheme 5.50 Synthetic route to oligo-(2,8)-3-deoxy-α-D-*manno*-2-octulosonic acid derivatives via iterative iodoalkoxylation sequence.

Unusually-substituted deoxy sugars are found in a number of biologically important natural products, and an application of iodoglycosylation for the preparation of these compounds is shown in Scheme 5.51 [142]. Protected glucals **1** or **14** were selectively converted into 2-deoxy-2-iodo-α-mannopyranosyl glycosides **56** or **57**. The



Scheme 5.51 Method for preparation of 2-deoxy-2-*C*-alkylated glucosides.

allyl group was then transformed by reductive ozonolysis to the aldehydes **58** or **59** and these underwent intramolecular radical cyclization on treatment with Bu_3SnH and AIBN to eventually give the C-2 branched glucosides **60** and **61**.

In brief, a wide range of 2-deoxyglycosides are available from glucals, either directly using proton or Lewis acids together with nucleophiles, or by haloalkoxylation with subsequent reductive removal of the halide at C-2.

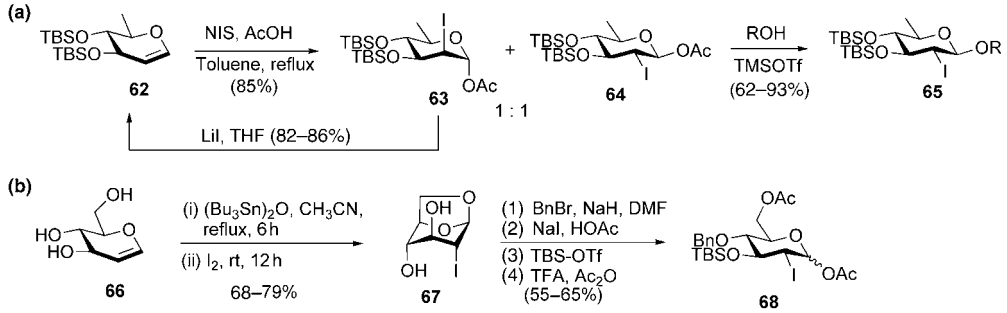
Conversion of Glycals into Other Glycosyl Donors The versatility of glycals in glycoside synthesis lies not only in their direct use as glycosyl donors but also in the ease with which they can be converted into a wide range of other glycosyl donors. Apart from the available variation in the anomeric substituent, there is also a potential for installing new substituents at C-2, which can be selected according to stereodirecting requirements in the subsequent glycosylation steps, or the need to elaborate the structures further at this key position in the newly formed glycoside. These considerations are particularly important in addressing the problem of stereoselective synthesis of 2-deoxy-β-glycosides.

The methods can be divided into three categories: those directly leading to glycosyl acetates, halides or other glycosyl donors, mostly with simultaneous introduction of a removable substituent at C-2; a second similar category resulting in glycosyl donors bearing a protected amino function at C-2; finally, those methods involving conversion of glycals into 1,2-anhydro sugars.

The glycals are easily converted into the 1,2-dihalo-derivatives, which in principle can act as glycosyl donors. However, these derivatives have not found wide application in glycoside synthesis, mainly because of the low facial selectivity in the initial addition of the electrophilic species [143–145]. In an example of a successful application, 2-deoxy-2-bromo-α-D-glucopyranosyl bromide [146] has been shown to give predominantly the 2-deoxy-β-D-glucopyranosides in silver-triflate-promoted reactions with alcohols.

However, the 2-bromo- and 2-iodo glycosyl acetates are more synthetically useful glycosyl donors. These are available either through formation of halohydrins from glycals using a source of halonium ions in the presence of water [147], followed by acetylation, or by direct haloacetoxylation of the glycals [148]. The halohydrin route has been the subject of renewed interest in the exploration of alternative catalytic routes to generating the required bromonium or iodonium species [149,150]. Although the generation of these species is efficient, the diastereoselectivity in the subsequent halohydrin formation is somewhat limited, with the 2-halo-α-mannopyranoses predominating.

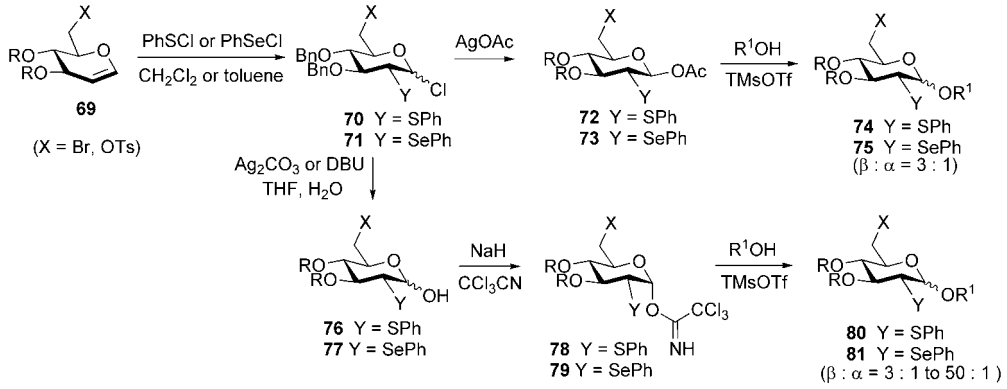
The direct route from glycals to 2-halo-glycosyl acetates using a halonium ion source in the presence of acetic acid is more useful. A number of variations have been described, notably that of Roush [148] in which 2-deoxy-2-iodo-α-mannoanosyl acetates are formed with high α-selectivity using cerium(IV) ammonium nitrate and sodium iodide in acetonitrile. Comparable results [151,152] were obtained using a reagent mix of NH_4I/50% H_2O_2/AcOH/Ac_2O, wherein the iodonium species is generated by oxidation of the simple iodide, with reactions proceeding at low temperatures and in short reaction times with high yields and stereoselectivities.



Scheme 5.52 Preparation of 2-deoxy-2-iodo-β-glycosyl acetates and their use in formation of 2-deoxy-β-glycosides.

As glycosyl donors, 2-deoxy-2-iodo-α-mannopyranosyl acetates lead predominantly to the formation of 2-deoxy-α-glycosides, whereas 2-deoxy-2-iodo-β-glucopyranosyl acetates lead to 2-deoxy-β-glycosides [153,154]. Thus, for example the 2-iodoglucosyl acetate **64** (pathway a, Scheme 5.52) was treated with a range of alcohols in the presence of TMSOTf or TBSOTf as the promoter to give the 2-deoxy-β-glycosides **65** after the reductive removal of 2-iodo substituent [153]. The required 2-deoxy-2-iodo-glucosyl acetates can be prepared by iodoacetoxylation of TBS-protected glucal **62**, where the undesired mannosyl acetate **63** is separated from **62** and recycled to the starting glucal. Alternatively (pathway b, Scheme 5.52), they can be selectively obtained from 1,6-anhydro-2-deoxy-2-iodo-D-glucose **67**, itself prepared from the D-glucal **66** using stannylene chemistry [155], in a sequence involving initial simultaneous benzylation at O-4 and formation of the β-2,3-epoxide, followed by reintroduction of the iodine at C-2, protection of O-4 and finally acetolysis to give 2-iodo-β-glucoside **68**.

The addition of phenyl sulfenyl choride and phenyl selenenyl chloride to glycals has been investigated, which provides another entry to the 2-deoxy-β-glucosides. As summarized by Roush *et al.* [156] (Scheme 5.53), the method gives the best selectiv-

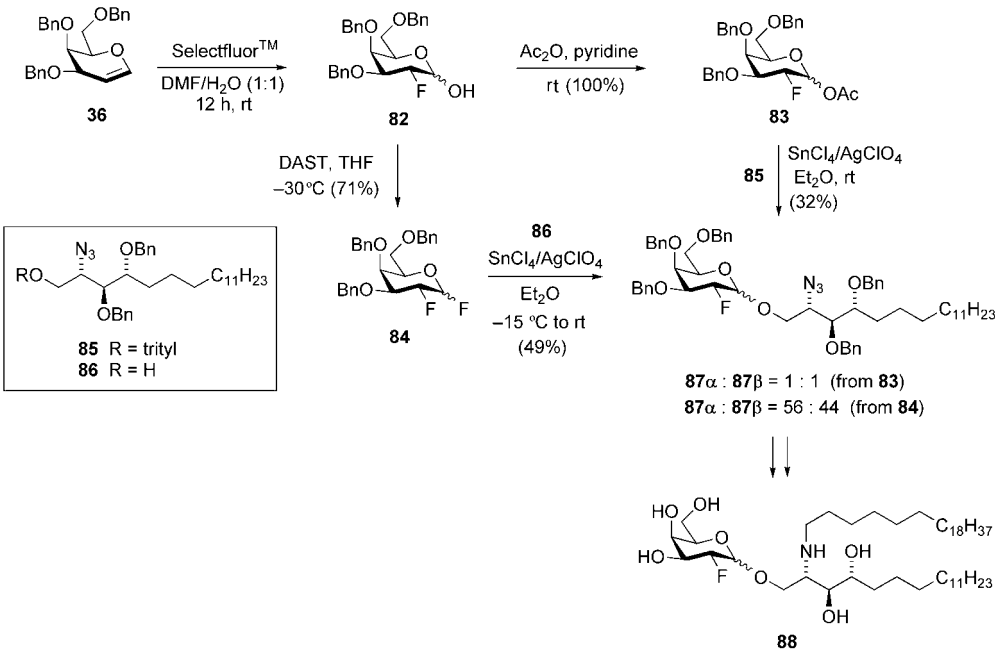


Scheme 5.53 Preparation of glycosyl donors from glycals using PhSCl and PhSeCl.

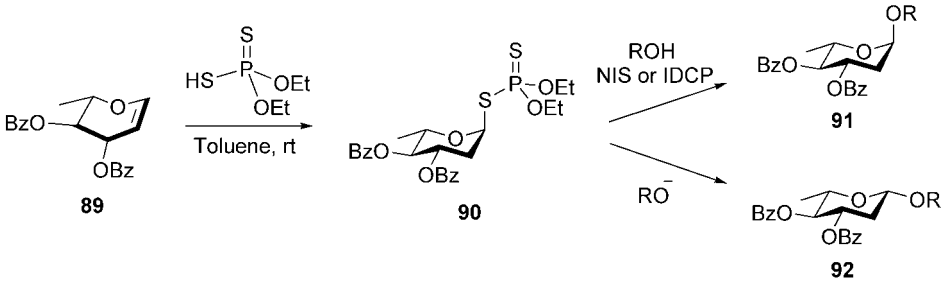
ities with glucals bearing an electron-withdrawing substituent at C-6 (X = Br or OTs in Scheme 5.53). In these cases, the 2-sulfenyl- or 2-selenenyl glucosyl chlorides **70** and **71** are formed selectively from glucals **69** on treatment with phenyl sulfenyl chloride or phenyl selenenyl chloride, respectively, and these can be transformed to glycosyl acetates (**72** and **73**) or trichloroacetimidates (**78** and **79**) via the corresponding hemiacetals **76** and **77**. Subsequently, β-selective glycosidation is achieved in glycosylations of a range of alcohols, with highest selectivity being achieved with the least sterically demanding alcohols.

Novel entry to the biologically important 2-fluoro derivatives has been recently described (Scheme 5.54) [157] in the context of a synthesis of 2′-fluoro-2′-deoxy-α-D-galactopyranosylceramide **88**, an immunomodulatory galactoglycosphingolipid. Selectfluor® was used to convert benzylated D-galactal (**36**) into 2-fluorogalactose **82**. This was followed either by acetylation to give the 2-fluorogalactosyl acetate **83** or treatment with diethylaminosulfur trifluoride (DAST) to give 2-fluorogalactosyl fluoride **84**. Both were then used as glycosyl donors in the preparation of glycoside **87αβ**, albeit with modest yields and selectivities, *en route* to the desired compound **88**.

Finally, *S*-(2,6-dideoxyglycosyl)phosphorodithioates **90** were prepared from 6-deoxy-L-glycals **89** [158] and transformed to either α- or β-2-deoxyglycosides **91** and **92** depending on the conditions used in adding the alcohol (Scheme 5.55).



Scheme 5.54 Preparation and use of 2-deoxy-2-fluoro-glycosyl donors from glycals.



Scheme 5.55 Conversion of glycals to phosphorodithioates as glycosyl donors.

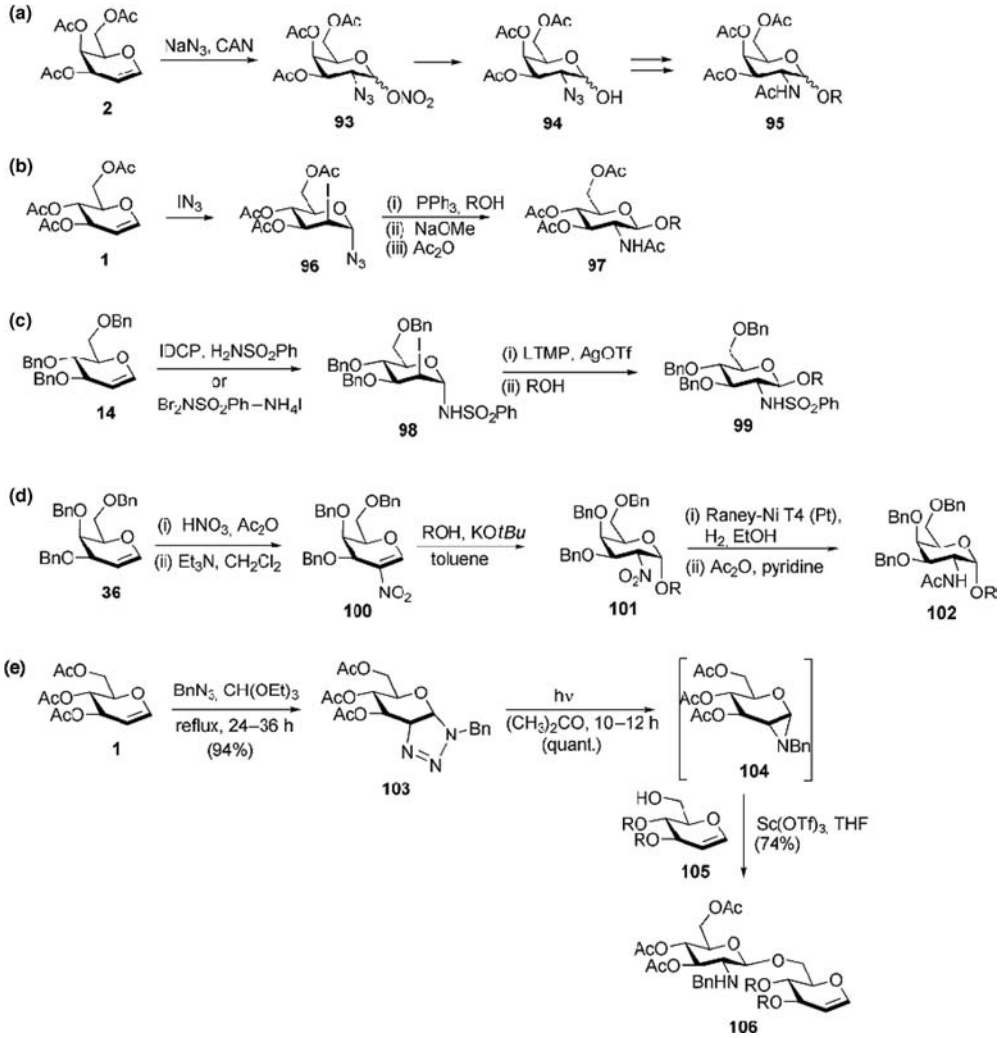
A wide range of glycosyl donors is, thus, directly available from glycals, allowing for careful tuning of reactivity depending on requirements for the synthesis of target 2-deoxyglycosides.

Synthesis of 2-Amino-2-Deoxyglycosides from Glycals Glycals are a useful source for preparation of 2-amino-2-deoxyglycosides as summarized in Scheme 5.56, with selectivity dependent on the structure and substituents in the starting glycals. A useful comparison of the glycal approach to this important class of sugars is provided in a recent review [159].

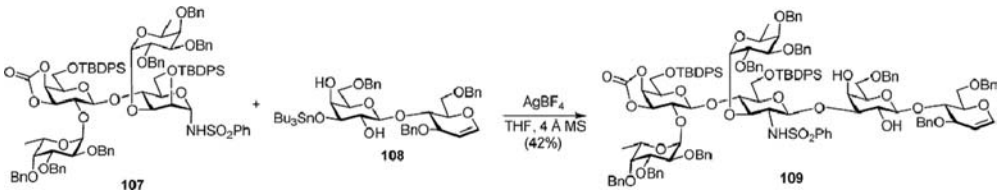
In the first of these approaches from glycals (pathway a), an azidonitration reaction using sodium azide and cerium(IV) ammonium nitrate is used to convert galactals and glucals into 2-azido-2-deoxyglycosyl nitrates [160,161]. The best regioselectivity is obtained in the case of D-galactals **2** that predominantly give the 2-azido-D-galactosyl nitrates **93**, whereas the D-glucals give mixtures of 2-azido-*gluco*- and *manno*-adducts. Hydrolysis of **93** gives 2-azido-D-galactose **94** that can be converted into other donors to form acetamido glycosides **95** after the reduction of the azide and acetylation.

A second approach (pathway b) involves the addition of iodoazide to glucal **1** to give 2-iodoglycosyl azides **96**, predominantly in the α-*manno*-configuration [162]. These can be converted into 2-deoxy-2-acetamido-β-glucosides **97** by treatment with PPh_3 and an alcohol, followed by subsequent protection of the amino moiety.

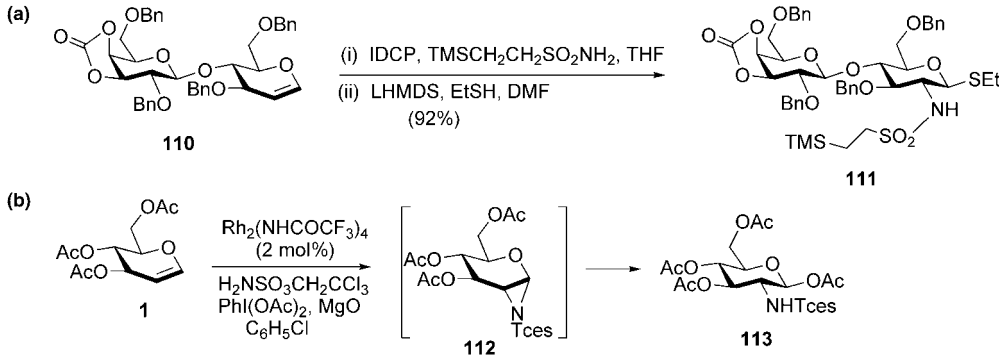
Pathway (c) illustrates the third approach, the 'azaglycosidation' route pioneered and developed by Danishefsky and coworkers [163,164]. Thus, for example treatment of benzylated glucal **14** with IDCP and benzenesulfonamide leads to the formation of 2-iodo-1-benzenesulfonamido-α-mannoside **98**, which can be induced to rearrange via aziridinium intermediates in the presence of alcohols and bases such as lithium tetramethylpiperidide (LTMP) to give 2-deoxy-2-sulfonamido-β-glucoside **99**. The iodobenzenesulfonamido derivatives can also be converted into the alternative thioethyl glycosyl donors by substituting ethane thiol for the alcohol. An example of the efficiency and versatility of this method is its use in the preparation of complex oligosaccharide fragments of Lewis-Y and KH-1 tumor-associated carbohydrate antigens (Scheme 5.57) [165]. 2-Iodo-sulfonamido glycoside **107**, derived from the corresponding glycal-terminated tetrasaccharide, was treated with tributylstannyl ether **108** in the presence of $AgBF_4$ in a stereoselective coupling to give protected hexasaccharide fragment **109** in an acceptable yield.



Scheme 5.56 Routes to 2-amino-2-deoxy-glycosides from glycals.

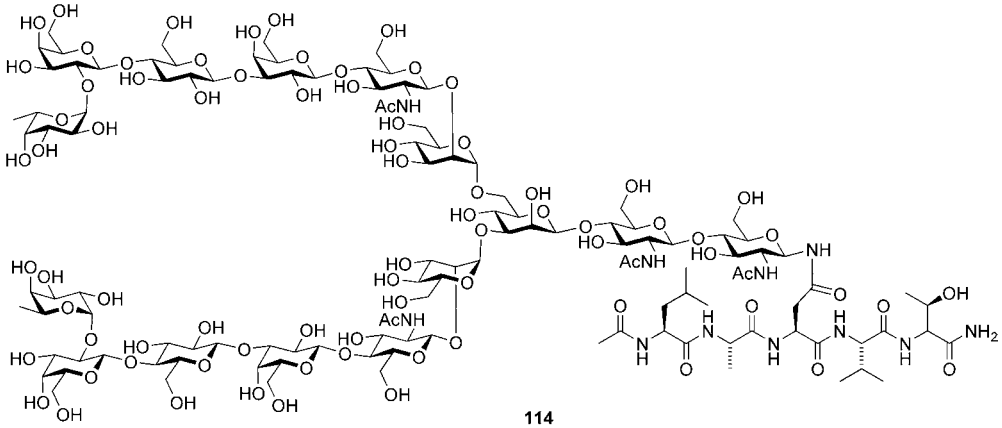


Scheme 5.57 Example of azaglycosidation route to complex oligosaccharides.



Scheme 5.58 Variations on azaglycosidation.

Two variations of this method are shown in Scheme 5.58. In reaction (a), the benzenesulfonamide is replaced by (2-trimethylsilyl)ethylsulfonamide, which is subsequently removed using cesium fluoride in DMF. The key thioglycoside building block **111**, required in the synthesis of the fucosylated biantennary *N*-glycan of erythropoietin, [166] was prepared from glycal **110** by a sequence involving the formation of the 2-iodo-1-(2-trimethylsilyl)ethylsulfonamide followed by rearrangement induced by ethanethiolate formed by the treatment of ethane thiol with lithium hexamethyldisilazide (LHMDS). In a more recent variant (reaction b) [167], tri-*O*-acetyl-D-glucal **1** is treated with a catalytic amount of $Rh_2(COCF_3)_4$, together with 2,2,2-trichloroethylsulfamate, $PhI(OAc)_2$ and MgO, to give the 2-trichloroethylsulfonamido-β-glucosyl acetate **113** via the aziridine **112**, with the trichloroethylsulfonamide (Tces) protecting group removable with Zn under relatively mild reducing conditions. The impressive scope of this methodology was recently illustrated in the synthesis of β-2-acetamidoglucosyl linkages in a complex β-*N*-linked glycopeptide **114** containing the H-type 2 blood group determinants [168].



114

The fourth method (pathway d, Scheme 5.56) is particularly efficient in accessing 2-acetamido-2-deoxy-α-galactosides via 2-nitrogalactals, with lower selectivities observed using the corresponding 2-nitroglucals [169–175]. For example, 2-nitrogalactal **100** is formed from benzylated galactal **36** on treatment with nitric acid and acetic anhydride, and this is followed by Michael-type addition of alkoxide to form 2-nitro-α-galactosides **101** with subsequent reduction of the nitro group and acetylation giving 2-acetamido-2-deoxy-α-galactoside **102**.

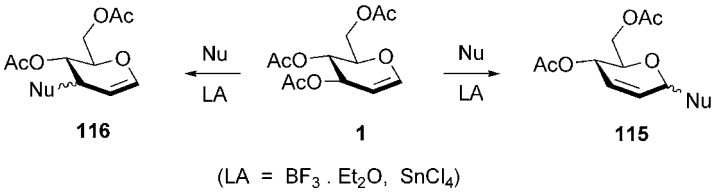
Finally (pathway e, Scheme 5.56), triazoline **103** formed by cyclo addition of azide to glycal **1** can be photolytically converted into a 1,2-aziridine intermediate **104**, from which 2-benzylamino-2-deoxy-β-glucosides can be formed on addition of an alcohol and catalytic scandium triflate [176].

These methods complement other approaches [159] to the preparation of 2-deoxy-2-aminoglycosides and serve to further emphasize the rich diversity of products available from the glycals.

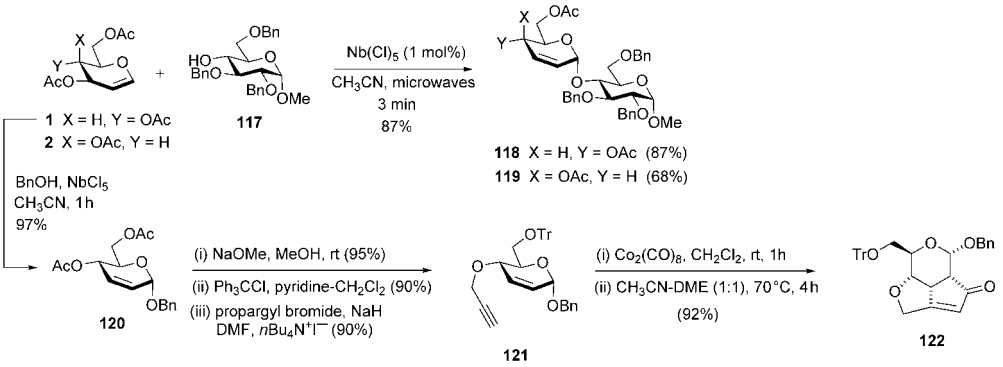
2,3-Dehydro-Glycosides via Ferrier Reactions of Glycals As noted earlier, glycals react with protic acids in the presence of nucleophiles to give 2-deoxyglycosides. However, the reaction with Lewis acids generally induces loss of the allylic substituent to give 2,3-dehydroglycosides. This reaction, fully investigated and described by Ferrier and others [105,177,178], has continued to attract attention for the stereoselective formation of *O*-, *N*-,*S*- and *C*-glycosides of interest in the synthesis of a variety of complex natural products. The general reaction is illustrated in Scheme 5.59, where acetylated glucal **1** reacts with nucleophiles in the presence of Lewis acids such as BF_3 to give 2,3-dehydroglycosides **115**, predominantly with anomeric α-configuration, and glycal **116**, a possible alternative product, given the fact that the intermediate in this reaction is an allylic carbenium ion.

Priebe and coworkers [107,178] have attempted to rationalize the product distribution in terms of Pearson's theory of hard and soft acids and bases (HSAB) [179], concluding as a broad generalization that soft bases (*S*-, *N*- and *C*-nucleophiles) form bonds at the softer C-3 electrophilic center, whereas hard bases (*O*-based nucleophiles) react preferentially at the harder C-1 center to give glycosides. They acknowledge that other factors may overrule this interpretation, such as when *C*-nucleophiles give kinetic C-1-alkylated products whose formation is not reversible.

The 2,3-dehydroglycosides continue to be of interest in view of the potential for further functionalization of the double bond toward unusual sugars or other natural products. The efficiency and selectivity depends on the catalyst and the conditions



Scheme 5.59 Ferrier reaction of glycals.

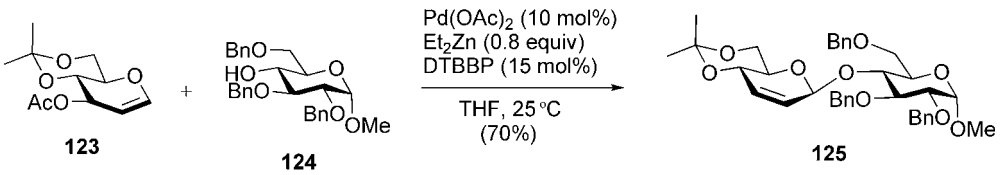


Scheme 5.60 Use of catalytic $NbCl_5$ in microwave-assisted glycosylations of glycals.

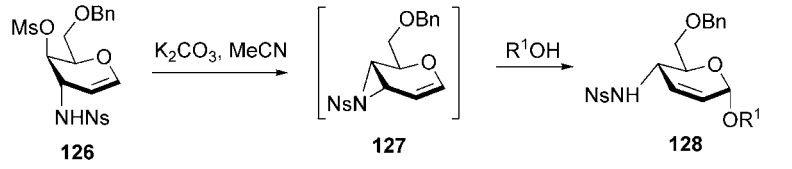
for the reaction, and considerable effort has been expended recently on the evaluation of a range of homogeneous and heterogeneous catalysts. This is summarized in a recent publication of Hotha and Tripathi [180] in which the potential of these investigations is exemplified by the use of catalytic $NbCl_5$ under microwave irradiation in acetonitrile to achieve remarkably quick and efficient glycosylation of glycals using a range of alcohols. Thus, for example when acetylated glucal **1** or galactal **2** were treated with sugar alcohol **117** under these conditions (Scheme 5.60), the 2,3-dehydro-α-glycosides **118** and **119** were produced cleanly within 3 min. The usefulness of unsaturated glycosides like these as substrates for 'diversity oriented synthesis' of tricyclic molecules was then demonstrated by preparing benzyl-2,3-dehydro-α-glucoside **120**, converting this into the 4-*O*-propargyl derivative **121** and carrying out an intramolecular Pauson–Khand reaction on this enyne system to give tricyclic product **122** [181].

The Ferrier reaction of glucals proceeds in most cases with high α-selectivity, but a recent example involving Pd-catalyzed glycosylation of glycals (Scheme 5.61) [182] illustrates that under appropriate conditions high β-selectivity can be achieved. Addition of acceptor **124** to glycal **123** in the presence of catalytic $Pd(OAc)_2$ and other additives gave a good yield of β-linked 2,3-dehydroglycoside **125**, with the finding that α-/β-selectivity was dependent on the choice of ligand. Thus, di(*tert*-butyl)-2-biphenylphosphine (DTBBP) gave almost exclusively β-selectivity, whereas the use of $P(OMe)_3$ gave variable outcomes.

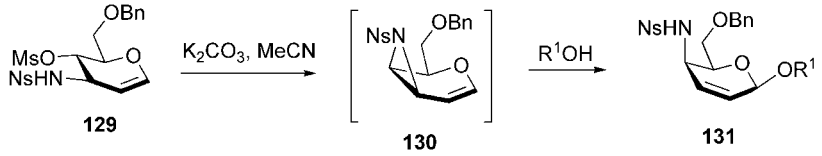
A concluding example illustrates an interesting reaction whose outcome is analogous to the Ferrier rearrangement but involves a conjugate addition of alcohols to



Scheme 5.61 Pd-catalyzed β-selective glycosylation of glycals.



(Ns = *o*-nitrobenzenesulphonyl)

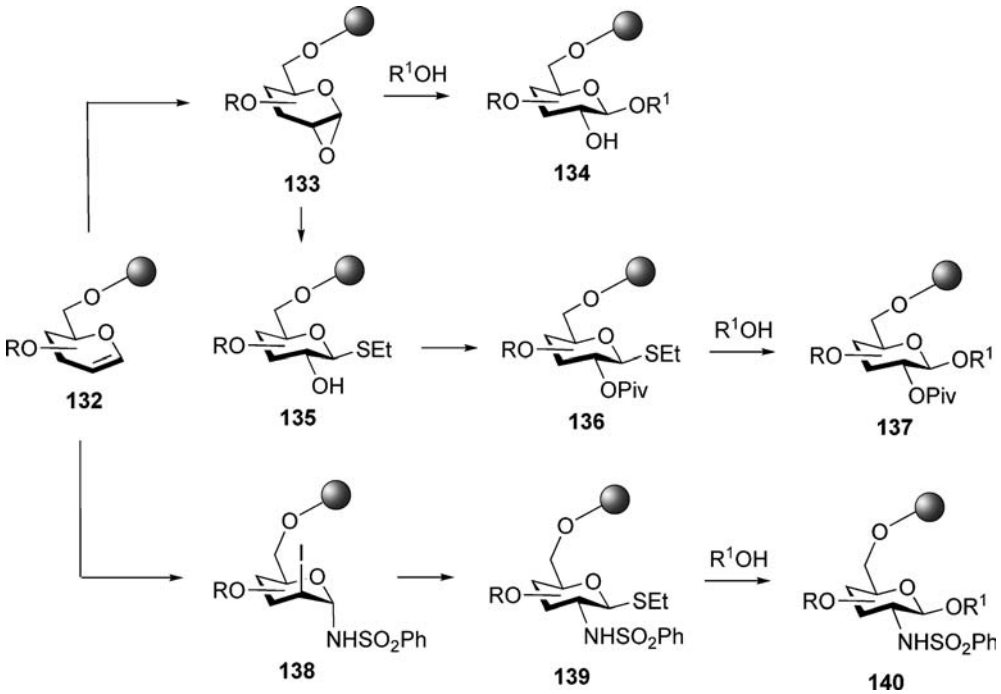


Scheme 5.62 Conjugate addition to allylic aziridines in glycals.

allyl aziridines [183]. Glycals **126** and **129** (Scheme 5.62), having vicinal *trans*-oriented mesyloxy and nosylamino groups, were treated with base to form the allyl aziridines **127** and **130**, respectively, and these then reacted smoothly with a range of alcohols in highly regio- and stereoselective manner to give 2,3-dehydro-4-nosylamino-α-glycoside **128** or 2,3-dehydro-4-nosylamino-β-glycoside **131**. The authors rationalize the observed regio- and stereoselectivities as arising from the hydrogen bonding of the alcohols with the nitrogen in the aziridine intermediates **127** and **128**, with the resultant face-selective attack at the anomeric carbon, migration of the double bond and opening of the C(3)-N bond. The nosyl (*o*-nitrobenzensulfonyl) group is easily removed by treatment with thiophenol and potassium carbonate to give the corresponding amines, and this, thus, appears to provide an excellent route to 4-aminoglycosides.

These examples and many others illustrate the ongoing fascination with the Ferrier rearrangement. The growing catalog of catalysts and subtle variations in outcomes that are associated with these serve to enhance the practical utility of this reaction in glycoside and natural product synthesis.

Glycals in Solid-Phase Synthesis of Glycosides The role of glycals in solid-phase synthesis of oligosaccharides has been recently reviewed [184–186], and the broad strategy of this application of glycals is briefly highlighted here. Bearing in mind the precautions and limitations associated with resin-bound saccharides, the glycals have found particularly effective use in 'donor-bound' strategies and 'bidirectional' strategies [186]. In the donor-bound strategy, the partially protected glycals are linked via a free hydroxyl group to a resin (compound **132**, Scheme 5.63) and then efficiently converted using standard glycal chemistry into a range of polymer-supported glycosyl donors, including 1,2-anhydro glycoses (**133**), thioethyl glycosides (**135**, **136**) and 2-phenlysulfonylamido-thioglycosides (**139**), to mention a few. These are then efficiently converted into resin-linked glycosides such as **134**, **137** and **140**, utilizing the high efficiency and stereoselectivity of the coupling reactions. The assembled oligosaccharide is then cleaved from the resin using selective reactions that are

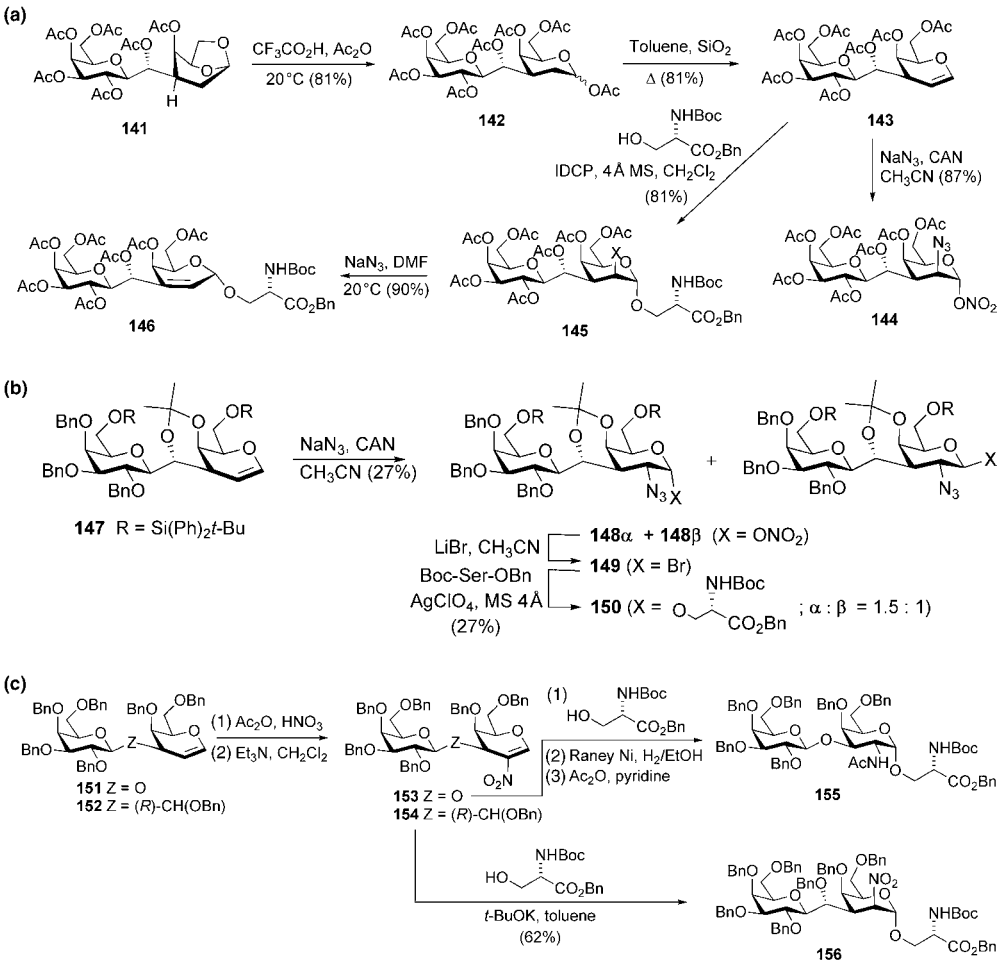


Scheme 5.63 Use of glycals in solid-phase synthesis of glycosides.

compatible with sugar functionalities. The bidirectional strategy arises when polymer-bound glycals can act as either donors or acceptors in glycoside synthesis, by virtue of selectively removable protecting groups, with the potential to assemble branched glycans. Despite some shortcomings of these approaches, they have been used to good effect in the preparation of a range of complex oligosaccharides.

Conclusion and Outlook The foregoing discussion has illustrated the impressive range of structures available from glycals. Current challenges in oligosaccharide chemistry include not only the synthesis of naturally occurring compounds in all their complexity but also the assembly of analogs of these as probes of their biological activity. It is thus pertinent to conclude this section with a selected recent example in which many facets of glycal chemistry were incorporated into the assembly of analogs of a complex oligosaccharide.

Awad *et al.* have recently described the synthesis of *C*-disaccharide analogs of the T-epitope (β-D-Gal*p*(1–3)-α-D-Gal*p*Nac). Their approach to these structures features formation of glycals and manipulation of glycals toward glycosides and 2-aminoglycosides and illustrates the scope and some limitations of the use of glycals in synthesis. As shown in Scheme 5.64, *C*-disaccharide **141**, with the 1,6-anhydro unit arising from levoglucosenone, was converted into the anomeric acetate of 2-deoxy-D-galactose containing *C*-disaccharide **142**, which underwent efficient elimination to glycal **143** upon



Scheme 5.64 Use of glycal methodology in the synthesis of complex *C*-glycosides.

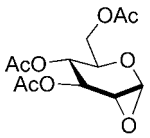
heating in toluene over silica. Iodoalkoxylation using IDCP and a serine derivative gave the glycopeptide **145**. However, on treatment of **145** with sodium azide, in an attempt to generate the equatorial 2-azide, an elimination took place to give the 2,3-dehydro derivative **146**. In contrast to the earlier results on analagous *O*-linked disaccharides and with expectations from the original Lemieux work, the attempted Lemieux azidonitration of **143** unexpectedly gave the *talo*-2-azido pseudodisaccharide **144**, thus emphasizing the dependence of the stereochemical outcome on substituents and conformational mobility. Azidonitration from the α-face was then engineered by preparing the conformationally restrained derivative **147** that was then shown to give azidonitrates **148**α and **148**β, bearing the equatorial azido group, in moderate yield. Conversion into the glycosyl bromide **149** and Königs–Knorr glycosidation gave the desired glycosides **150** in an α : β ratio of 1.5 : 1.

The importance of substituent and conformational effects in glycal additions was also demonstrated in attempting Michael addition of an alkoxide to the *O*-linked 2-nitrogalactal **153** and its *C*-linked analog **154**. The α-*talo*-isomer **156** was obtained from **154** in contrast to the result of Michael addition to the analogous *O*-linked disaccharide **153**, which eventually gave the 2-acetamido-α-galactoside-terminated disaccharide **155**.

5.2.3 Anhydro Sugars as Glycosyl Donors

5.2.3.1 1,2-Anhydro Sugars

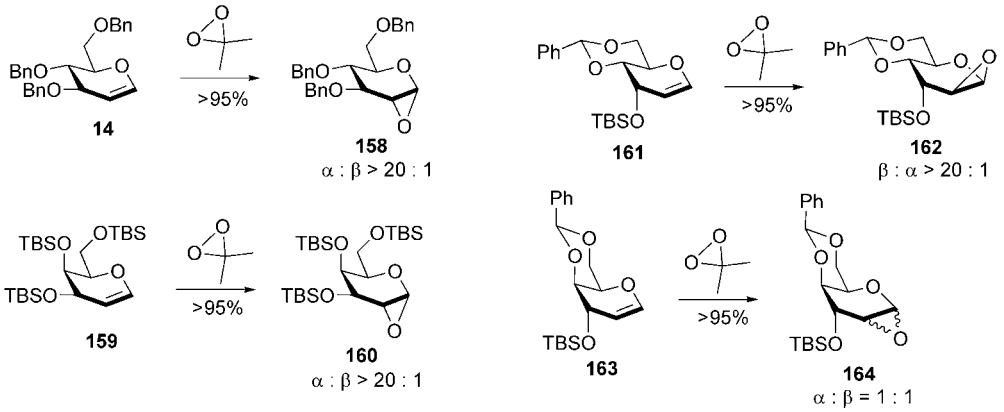
Since the first description of 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glycopyranose, 'Brigl's anhydride' **157** [187,188], compounds of this type have gained prominence [109] as glycosyl donors, particularly through the contribution of Danishefsky and coworkers [189–192]. Attention will be focused here on the most widely applicable methods for preparation of these derivatives, as well as on promising new methodologies and the scope for efficient and stereoselective glycoside formation using the 1,2-anhydro sugars.



157

Synthetic Routes to 1,2-Anhydro Sugars from Glycals Involving a Single-Step Oxirane Formation The potential for the use of 1,2-anhydro sugars as glycosyl donors was only fully realized in the late 1980s and early 1990s with the development by Danishefsky's group of efficient procedures for the formation of these from glycals using Murray's reagent dimethyldioxirane (DMDO) [193], and their use in controlled glycosidations with appropriate Lewis acids. As a reflection of this method of preparation, the 1,2-anhydro sugars are often referred to as 'glycal epoxides'. These developments and applications thereof are elegantly summarized in the literature [194], and Scheme 5.65 summarizes the efficiencies and stereochemical outcomes of dioxirane-mediated glycal epoxide formation. Protected glucal **14** and galactal **159** predominantly give α-1,2-anhydroglycopyranoses **158** and **160**, whereas oxidation of D-allal derivative **161** predominantly gives β-epoxide **162**, and stereoselectivity is lost in the oxidation of D-gulal derivative **163**, presumably because of the competing steric influences on either face.

The oxidation is carried out with DMDO solutions prepared from Oxone and acetone [193], and the epoxide products are obtained in virtually quantitative yields and often used in subsequent steps after simple work-up and little or no further purification. A simplified procedure for high-yielding multigram-scale epoxidation of glucal and galactal has been recently described [195], where DMDO is generated *in situ* using Oxone and acetone in a biphasic system (CH_2Cl_2–aqueous $NaHCO_3$).

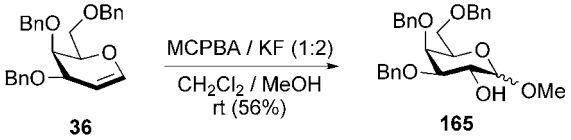


Scheme 5.65 Summary of reaction outcomes in DMDO epoxidation of glycals.

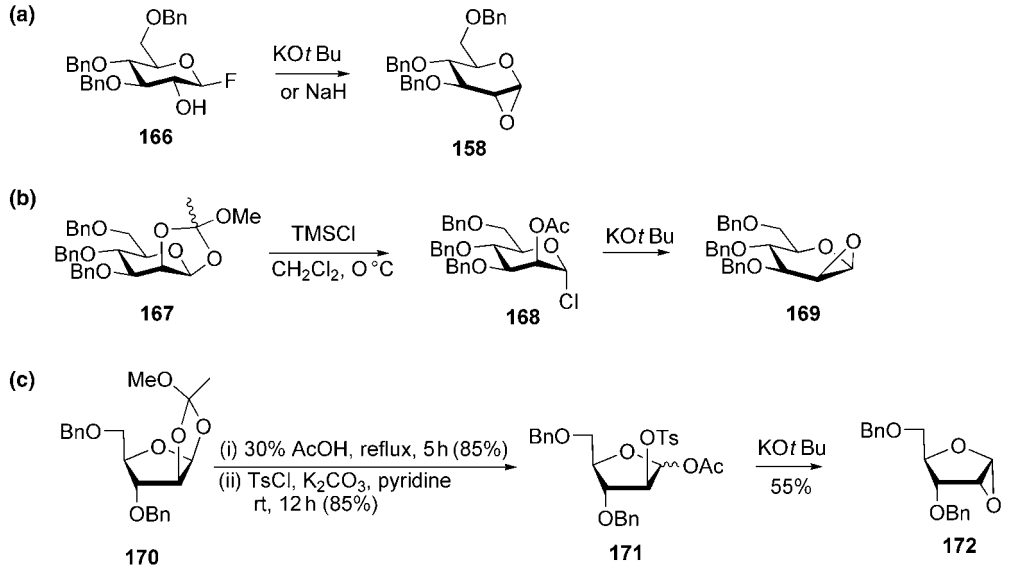
Several alternative methods for converting glycals into epoxides have been described. For example, Di Bussolo *et al.* [196] have described a one-pot method for oxidative glycosylation using the combination of triflic anhydride and diphenylsulfoxide to effect the formation of 1,2-anhydro-α-glucose from protected glucals. Subsequent addition of zinc chloride and an acceptor alcohol leads to the formation of β-glucosides in acceptable yields. In one interesting exception to the observed β-selectivity, glycosylation of the hindered 3-OH of an otherwise protected glycosyl acceptor using zinc chloride was not successful, but yielded the α-linked disaccharide when the stronger Lewis acid, $Sc(OTf)_3$, was used.

The use of other peroxides in the epoxidation of glycals is limited by selectivities that are often inferior to those achieved with DMDO. One notable exception is the use of the *m*CPBA (*m*-chloroperbenzoic acid)/KF combination and its recent successful application in one-pot epoxidation alcoholysis (Scheme 5.66) [197]. This involved treatment of benzylated D-galactal **36** in dichloromethane/methanol with a mixture of *m*CPBA and KF (2 : 1) in anhydrous dichloromethane to give methyl-2-hydroxygalactoside **165**.

Other Synthetic Routes to 1,2-Anhydro Sugars The most common alternative preparation of 1,2-anhydro sugars proceeds via 1,2-*trans*-glycosyl halides having the 2-OH free or latent, such that on treatment with a base an intramolecular displacement of the halide takes place to give the 1,2-oxiranes [198]. Examples (Scheme 5.67) include the formation of 1,2-anhydro-tri-*O*-benzyl-D-glucose **158** from β-glucosyl fluoride **166** (pathway a). The corresponding β-epoxide **169**, not readily available



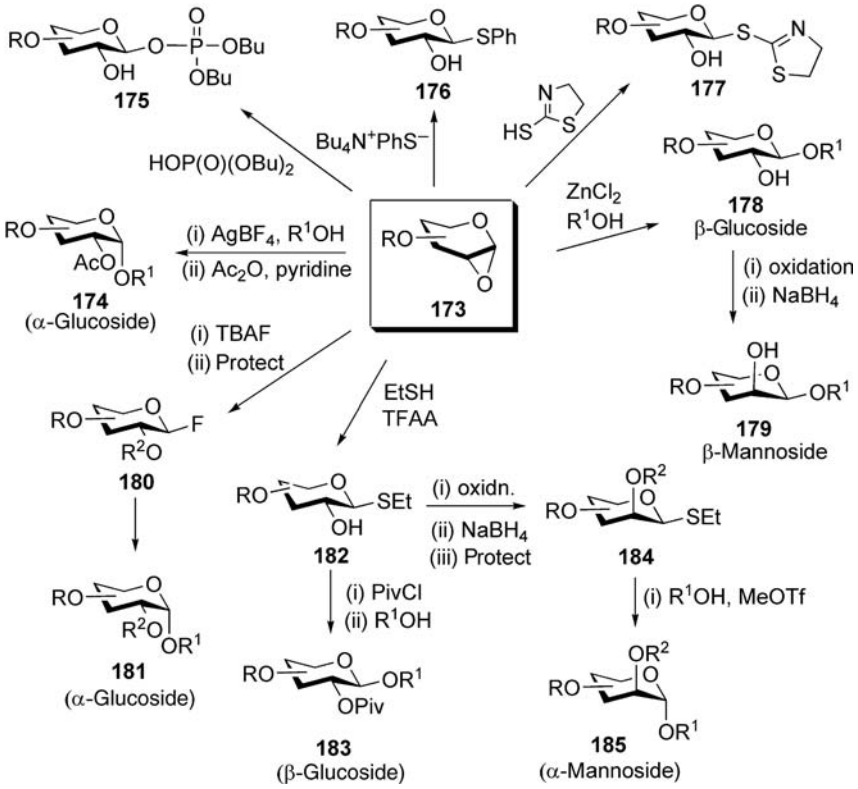
Scheme 5.66 Use of *m*CPBA/KF in the preparation of 1,2-anhydro sugars.



Scheme 5.67 Alternative routes to 1,2-anhydro sugars.

by DMDO oxidation, has been prepared [199–201] by treating the precursor 2-*O*-acetyl-α-D-mannosyl chloride **168** with potassium *tert*-butoxide in THF (pathway b). In a related approach [202], the sensitive D-ribofuranosyl epoxide **172** [203] could be prepared from 2-*O*-tosyl-D-ribofuranosyl acetate **171**, obtained in turn from the orthoester **170** (pathway c). This and similar methods for preparing 1,2-anhydropyranose sugars [204] proceed via prior installation of a leaving group such as a tosylate at C-2, and subsequent intramolecular attack by an alkoxide generated at C-1. Interestingly, the more direct approach to preparing 2-bromoglycoses from glycals, followed by sequential base-mediated 1,2-epoxide formation and trapping with thiolates or alkoxides, suffers from poor yields and selectivities in the final steps and has not found practical application [147].

1,2-Anhydro Sugars in the Synthesis of *O*-, *N*- and *S*-Glycosides The tremendous versatility of 1,2-anhydro sugars in the synthesis of glycosides is illustrated in Scheme 5.68, and there are now numerous examples of their use in the preparation of a wide array of complex oligosaccharides, glycoconjugates and other glycosides [190,194]. Glycal epoxides such as **173** can be used directly as glycosyl donors, with dual advantages of stereocontrol in glycoside formation and the simultaneous generation of glycosides with a free 2-OH, for further modification or use as a glycosyl acceptor in iterative glycosylation processes. Perhaps, the most frequent use of this methodology is in glycosylation reactions to generate β-*O*-glucosides [192,205] such as **175** and **178** and the corresponding β-thioglucosides [205–208] **176**, **177** and **182**, using conditions that ensure controlled, concerted opening of the epoxide. However, α-glucosides are also accessible [191] in a direct manner using alternative Lewis acids



Scheme 5.68 1,2-Anhydro sugars as glycosyl donors.

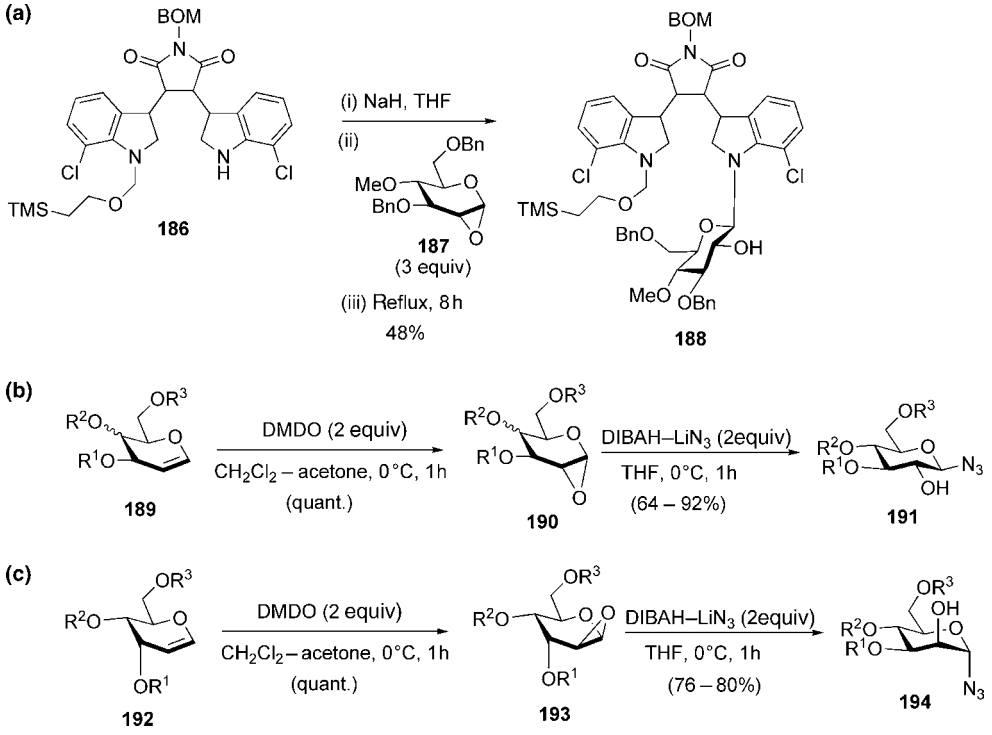
such as $AgBF_4$ in the formation of **174**, or indirectly via β-glycosyl fluoride **180**, which after introduction of a suitable nonparticipating protecting group can be stereoselectively glycosylated to give **181**.

Access to β-mannosides [209] is illustrated by the preparation of **179** from β-glucoside **178** by oxidation of the equatorial 2-OH followed by stereoselective reduction to give the axial alcohol an efficient indirect route to the α-mannosides [206] utilizes the β-thioglucoside **182**, readily obtained from epoxide **173**, proceeding via an oxidation–reduction protection sequence to give β-thiomannoside glycosyl donor **184**, from which α-mannoside **185** can be stereoselectively prepared.

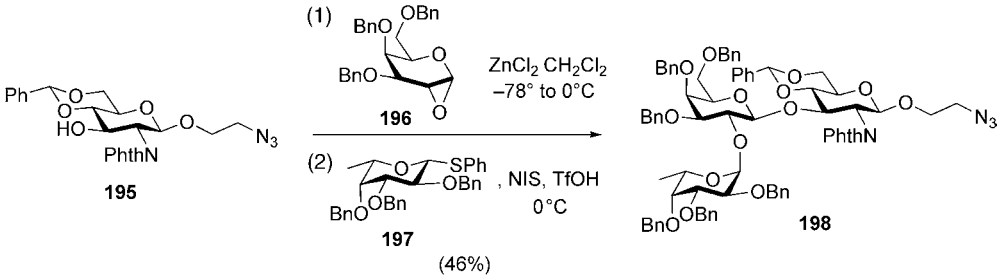
As noted above, the possibility of converting 1,2-anhydro sugars into a range of glycosyl donors significantly enhances their scope in glycosidation reactions. For example, thiazolinyl glycosides **177** represent a recently introduced attractive alternative [208], as these thioglycosides are easily activated by AgOTf in the presence of alcohols to form *O*-glycosides. In addition, the formation and use of glycosylphosphates [210] such as **175** continues to be explored, as illustrated in recent investigations [211,212] of an alternative approach to their preparation involving treatment of benzylated glucal **14** with catalytic methyltrioxorhenium (MTO) and urea-hydroper-

oxide (UHP) in the presence of dibutylphosphate to give mixtures of gluco- and mannosylphosphates, with the *gluco*-isomers favored. The efficiency of this process was found to be crucially dependent on addition of the ionic liquid dimethylimidazolium tetrafluoroborate and the accelerating ligand imidazole in dichloromethane or toluene. This example highlights the fact that the search for efficient catalytic routes to the sugar epoxides and other derivatives may well drive further efforts in this arena.

The use of 1,2-anhydro sugars in the preparation of *N*-glycosides is illustrated (pathway a, Scheme 5.69) by the glycosylation of protected bisindole **186** by deprotonation using NaH, then addition of 3 equiv of epoxide **187** to give glycoside **188**, a precursor of the anticancer compound rebeccamycin [213]. The scope is widened to provide routes to glycosyl amines and glycosyl amides by the development of methodology for the formation of glycosyl azides from 1,2-anhydro sugars. Lee *et al.* [214] have shown (pathway b, Scheme 5.69) that the treatment of α-1,2-anhydrides **190** of D-glucose and D-galactose, bearing a variety of protecting groups, with lithium azidohydridodiisobutylaluminate (DIBAH–LiN_3) in THF, exclusively gives the β-azidoglycosides **191**. The corresponding β-1,2-anhydrides **193** derived from the protected D-allal **192** were shown to give α-altrosyl azides **194** as the major products (pathway c, Scheme 5.69).



Scheme 5.69 Synthesis of *N*-glycosides from 1,2-anhydro sugars.



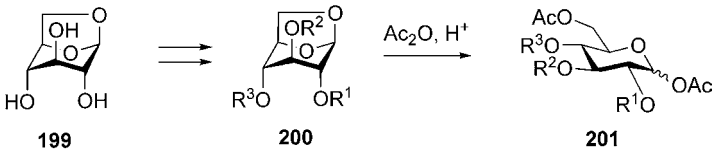
Scheme 5.70 Sequential, one-pot glycosylation using 1,2-anhydro sugars.

Examples and Future Outlook From the foregoing discussion, it is evident that 1,2-anhydro sugars are readily prepared and are highly versatile glycosyl donors. Further developments in their *in situ* generation and in the management and control of glycosylation sequences will enhance their usefulness in rapid generation of complex, diverse structures. A concluding example that illustrates their potential is the account of a sequential one-pot glycosylation (Scheme 5.70) in which benzylated galactal epoxide **196** was combined with acceptor **195** in the presence of the promoter zinc chloride, followed immediately by the addition of NIS and the thioglycoside donor **197** to give the trisaccharide **198** in 46% yield based on epoxide donor **196**.

5.2.3.2 1,6-Anhydro Sugars as Glycosyl Donors

The 1,6-anhydro sugars are another member of the class of anhydro sugars that are of significant use in the preparation of glycosyl donors and in glycoside bond formation. The chemistry of these derivatives has recently been comprehensively reviewed [109], and it will only be necessary here to summarize the key features of these sugars and highlight their role in glycoside synthesis.

The significance of these bicyclic 1,6-anhydro sugars is illustrated by considering a common member of this family, 1,6-anhydro-β-D-glucopyranose **199** (levoglucosan). It exists predominantly in the $^1C_4$ conformation, and the availability of O-2, O-3 and O-4 in inverted orientations relative to glucopyranose itself allows for unique manipulations and generation of a range of selectively protected or substituted derivatives **200** (Scheme 5.71). A range of methods is available for the synthesis of **199**, including pyrolysis of cellulose, which is practical for large-scale

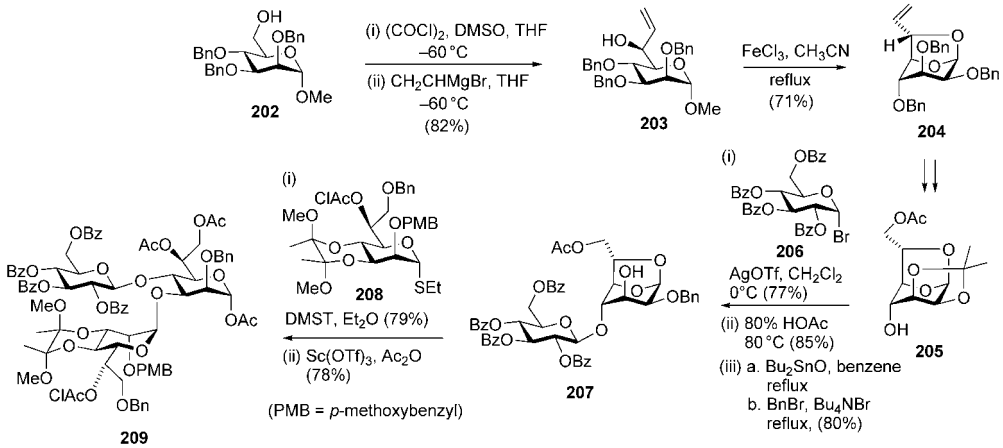


Scheme 5.71 Structure of 1,6-anhydro glucose, and its use in the synthesis of selectively protected glycosyl donors.

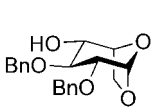
preparations. In addition to this *gluco* version, the *allo, altro, manno, gulo, ido, galacto* and *talo* anhydropyranoses are also known. Differentially protected glucosyl acetate **201** is easily regenerated by a number of methods, of which the most common and efficient is acetolysis using acetic anhydride with catalysts such as trifluoroacetic acid, triethylsilyl trifluoromethanesulfonate or scandium triflate, and 1,6-anhydrosugar derivatives can also be directly *S*-glycosylated [215] by treatment with trimethylsilyl phenlysulfide (TMSSPh) and ZnI_2. The fact that the 1,6-anhydro sugars are readily converted into glycosyl donors thus enhances their utility as building blocks for the synthesis of oligosaccharides.

A few selected examples from the recent literature illustrate the strategic importance of these sugar derivatives. In a recent synthesis of a key trisaccharide intermediate for the preparation of inner core structures of *Haemophilus* and *Neisseria* lipopolysaccharides [216], heptoses donors were assembled via 1,6-anhydro derivatives. Mannoside **202** (Scheme 5.72) was oxidized at C-6 and then reacted with vinyl magnesium bromide to give the chain-extended sugar **203**. This was converted into 1,6-anhydro sugar **204** on treatment with ferric chloride, and the heptose derivative **205** was then obtained by the oxidation of the olefin followed by further manipulation of protecting groups. Glycosylation with glycosyl bromide **206**, followed by the hydrolysis of the isopropylidene group and selective benzylation, gave glycosyl acceptor **207**, which could be glycosylated with donor **208** to give, after acetolysis, the protected heptose-containing trisaccharide **209** in a form in which it can be readily converted into other suitable glycosyl donors.

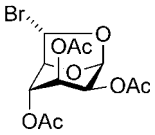
As a further illustration of the scope for use of 1,6-anhydro sugars in the preparation of uncommon sugars, the rare L-idose derivative **210** has been prepared recently and used in the preparation of oligosaccharides containing iduronic acid



Scheme 5.72 Preparation of modified 1,6-anhydromannosides and their use in the synthesis of heptose-containing oligosaccharide.

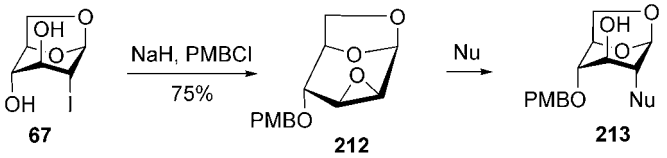


210



211

derivatives [217]. The 6-*exo*-bromo-derivatives such as **211** are also readily prepared [218,219] in a highly regio- and stereoselective radical bromination of acetylated 1,6-anhydroglycoses, providing a template for stereoselective preparation of C-6 alkylated sugars [220].



67 **212** **213**

(PMB = *p*-methoxybenzyl) (Nu = N_3^-, $PhthN^-$, $AllO^-$, BzO^-)

Scheme 5.73 Selective preparation of 2-substituted glucosides via 1,6-anhydro-D-glucose derivatives.

The final example (Scheme 5.73) illustrates the efficient preparation of epoxide **212** from 2-iodo-1,6-anhydro-D-glucose **67** (see Scheme 5.5) [221,222]. This "Černý epoxide" [109] is a useful and versatile precursor to a range of 2-substituted glucose derivatives **213**, which can be elaborated further to suitable glycosyl donors.

In the 1970s and 1980s considerable effort was directed at establishing the application of the 1,6-anhydro sugars in the preparation of stereoregular polysaccharides. Although this effort appears to have dissipated, a recent report [223] described the ring-opening polymerization and copolymerization of a benzylated 1,6-anhydro-3-azido-3-deoxy-β-D-allopyranose in the preparation of aminopolysaccharides containing 1,6-α-allopyranosidic linkages.

5.2.4 Conclusion

This overview has served to emphasize the versatility of dehydro and anhydro sugars in the preparation of a wide range of glycosidic linkages. They are, in general, easily accessible from readily available starting materials, and the principles governing their reactivities are now sufficiently understood to enable rational planning of synthetic strategies toward complex targets. They have also been well adapted to the rigorous requirements of modern-day synthetic chemistry, with its renewed emphasis on atom efficiency and low environmental impact without sacrificing stereo- and regiocontrol. The need for methodologies that permit rapid assembly of complex arrays of well-defined structures for biological evaluation, coupled with the search for new and better chemical technologies such as

development of new catalytic synthetic routes, will continue to dominate the investigations in this area.

5.2.5 General Experimental Procedures

5.2.5.1 General Method for the Preparation of 2-Deoxy-2-Iodoglycosides from Glycals

Powdered 4-Å molecular sieves (200 mg) was added to a solution of glycal (0.5 mmol) and glycosyl acceptor (0.55 mmol, 1.1 equiv) in dry CH_2Cl_2 (0.04 M in glycal). The resulting mixture was stirred at room temperature for 30 min and then IDCP was added as a solid. When TLC analysis indicated the completion of the reaction (typically, 1–2 h), the mixture was filtered and the solid washed with CH_2Cl_2. The combined filtrate was washed with 10% aqueous $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel (gradient hexanes-ethyl acetate) provided the coupled product (60–85%).

5.2.5.2 Preparation of 1,2-Anhydro-tri-*O*-Benzyl-α-D-Glucose and General Method for Its Use as a Glycosyl Donor in the Formation of β-Glycosides

Benzylated glucal (0.5 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and cooled to 0 °C in a nitrogen atmosphere. DMDO (20 ml of a 0.03 M solution in acetone, 0.6 mmol) was added dropwise and the solution was stirred at 0 °C for 15 min. The α-1,2-anhydro sugar was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 1 h. A solution of the glycosyl acceptor (0.75 mmol, 1.5 equiv) in dry THF (1.5 ml) was then added to the 1,2-anhydro sugar and the temperature reduced to −78 °C. $ZnCl_2$ (1.5 equiv of a 1 M solution in diethyl ether) was added dropwise to the reaction mixture and the reaction allowed to slowly warm to 25 °C with stirring overnight. The reaction was quenched by the evaporation of the solvent and the resulting residue purified by chromatography on silica (gradient hexanes-ethyl acetate) to give the β-glycosides (42–80%).

5.2.5.3 General Method for the Preparation of 2-Deoxy-2-Iodoglycosylbenzenesulfonamides from Glycals and Its Use as Glycosyl Donors in the Synthesis of 2-Benzenesulfonamido-2-Deoxy-β-Glycosides

(i) Glycal (0.5 mmol), benzene sulfonamide (1.25 mmol, 2.5 equiv) and 4-Å molecular sieves (0.6 g) were suspended in dry CH_2Cl_2 (10 ml), and the resulting suspension was stirred at room temperature for 10 min. The suspension was then cooled to 0 °C and treated with IDCP (1 mmol, 2 equiv). The reaction mixture was stirred in the absence of light at 0 °C for 1 h, then the reaction mixture was diluted with EtOAc (25 ml) and filtered through a pad of silica gel. The clear yellow filtrate was washed successively with saturated $Na_2S_2O_3$ (aq) (3 × 70 ml), saturated $CuSO_4$ (aq) (3 × 70 ml) and brine (3 × 70 ml), and dried over Na_2SO_4. The resulting crude product was purified by column chromatography (gradient ethyl acetate–hexanes) to yield the iodosulfonamide (90–99%). (ii) A solution of the iodosulfonamide

(0.5 mmol) and glycosyl acceptor (0.65 mmol, 1.3 equiv) in THF (0.15 M in iodosulfonamide) was cooled to −78 °C and a solution of lithium tetramethylpiperidide(LTMP) (1 M in THF, 1.1 ml, 2.2 equiv) was added dropwise, followed by dropwise addition of silver trifluoromethanesulfonate (1 M in THF, 0.7 ml, 1.4 equiv) after 10 min. Ensuring the exclusion of light, the reaction was allowed to slowly warm to room temperature. The reaction was monitored by TLC, and after several hours (5–15 h) solid NH_4Cl (several equiv) was added with stirring. Thereafter, the suspension was filtered and the filtrate concentrated to dryness. Flash chromatography of the resulting residue on silica (gradient hexanes-ethyl acetate) provided the coupled product (23–64%).

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5.3
Miscellaneous Glycosyl Donors

Kazunobu Toshima

5.3.1
Introduction

This chapter describes the preparations and chemical glycosylation reactions of miscellaneous glycosyl donors and some of their applications to the synthesis of natural products. For a survey on the general current methodological advances, miscellaneous glycosyl donors are classified into 18 groups on the basis of the type of anomeric functional group and their activating methods: (1) 1-*O*-silyl glycoside, (2) diazirine, (3) telluroglycoside, (4) carbamate, (5) 2-iodosulfonamide, (6) *N*-glycosyl triazole, (7) *N*-glycosyl tetrazole, (8) *N*-glycosyl amide, (9) DNA and RNA nucleosides, (10) oxazoline, (11) oxathiine, (12) 1,6-lactone, (13) sulfate, (14) 1,2-cyclic sulfite, (15) 1,2-cyclopropane, (16) 1,2-*O*-stannylene acetal, (17) 6-acetyl-2*H*-pyran-3(6*H*)-one and (18) *exo*-methylene. Furthermore, the stereochemical aspects of the glycosidic bonds formed by the glycosylations are also discussed in this chapter.

5.3.2
1-*O*-Silyl Glycoside

In the use of 1-*O*-silyl glycoside as a glycosyl donor, trimethylsilyl (TMS) and *t*-butyldimethylsilyl (TBS) groups were more commonly used (Table 5.1). These donors were prepared from the corresponding hemiacetals using an appropriate silylating agent such as a chlorotrialkylsilane and a base. Tietze *et al.* [224] introduced the glycosylation reaction of 1-*O*-trimethylsilyl glycoside with aryltrimethylsilyl ethers in the presence of a catalytic amount of TMSOTf as a Lewis acid. In a similar manner, Nashed and Glaudemans [225] used a 6-*O*-*t*-butyldiphenylsilyl-protected sugar as a glycosyl acceptor (Scheme 5.74). Cai and coworkers applied the method for the synthesis of alkyl glycosides from 1-*O*-trimethylsilyl glycoside using $BF_3{\cdot}Et_2O$ instead of TMSOTf as an activator [226]. On the contrary, Mukaiyama and his coworkers developed stereoselective glycosylation reactions using 1-*O*-trimethylsilyl furanosides and pyranosides. According to this method, 1,2-*trans* ribofuranosides were predominantly synthesized by the glycosylation of 1-*O*-trimethylsilyl ribofuranose and trimethylsilyl ethers as glycosyl acceptors in the presence of a catalytic amount of TMSOTf and $Ph_2Sn{=}S$ as an additive. Interestingly, predominantly 1,2-*cis* ribofuranosides and 1,2-*cis* glucopyranosides were stereoselectively prepared by using $LiClO_4$ additive to the above reaction conditions (Scheme 5.75) [227]. Furthermore, Mukaiyama *et al.* introduced the glycosylation of 1-*O*-trimethylsilyl arabinofuranose and trimethylsilyl ethers using the combined catalyst, TMSOTf-[1,2-benzenediolato(2−)-*O*,*O*′]oxotitanium, to furnish the corresponding 1,2-*cis* arabinofuranosides (Scheme 5.76) [228]. On the contrary, the 1-*O*-*t*-butyldimethylsilyl glycosyl donor was used for the synthesis of 2-deoxy glycosides by Priebe *et al.* [229], and it

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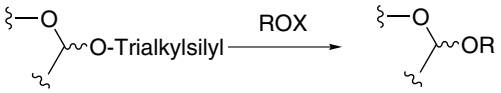
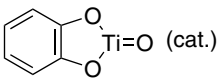
Table 5.1 Glycosylation of 1-*O*-silylglycoside.



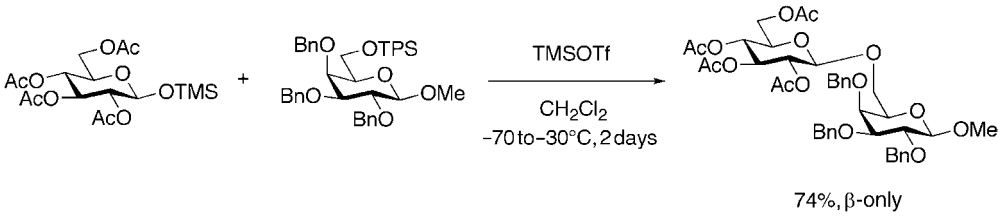
R=aryl, alkyl, sugar residue

Trialkylsilyl	Activator	X	References
TMS	TMSOTf (cat.)	TMS or TBS	[224,225]
	$BF_3{\cdot}Et_2O$	H	[226]
	TMSOTf (cat.)−$Ph_2Sn{=}S$	TMS	[227]
	TMSOTf (cat.)−$Ph_2Sn{=}S-LiClO_4$	TMS	[228]
	TMSOTf (cat.)	TMS	[228]
			
TBS	TMSOTf (cat.)	H	[229,230]

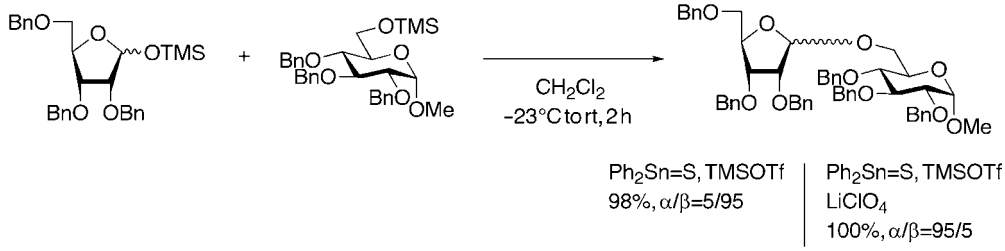
was employed in the anthracycline oligosaccharide synthesis by Kolar and Kneissl (Scheme 5.77) [230].

5.3.3 Diazirine

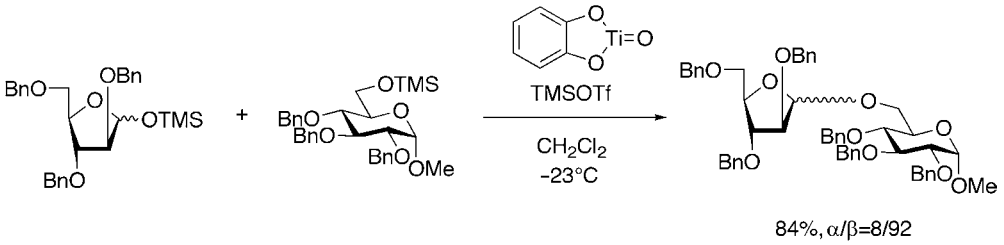
Vasella *et al*. introduced an approach to glycoside synthesis using the glycosylidene carbene generated from the diazirine sugar as a novel type of glycosyl donor. The



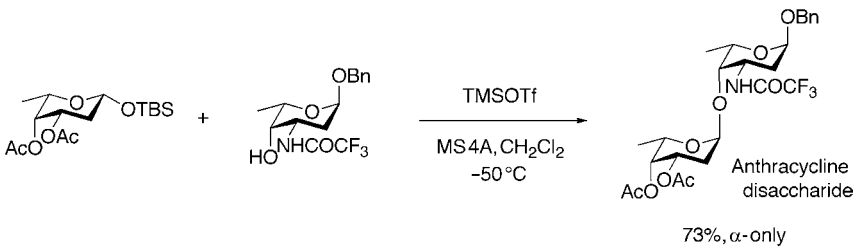
Scheme 5.74 Ref. [225].



Scheme 5.75 Ref. [227].

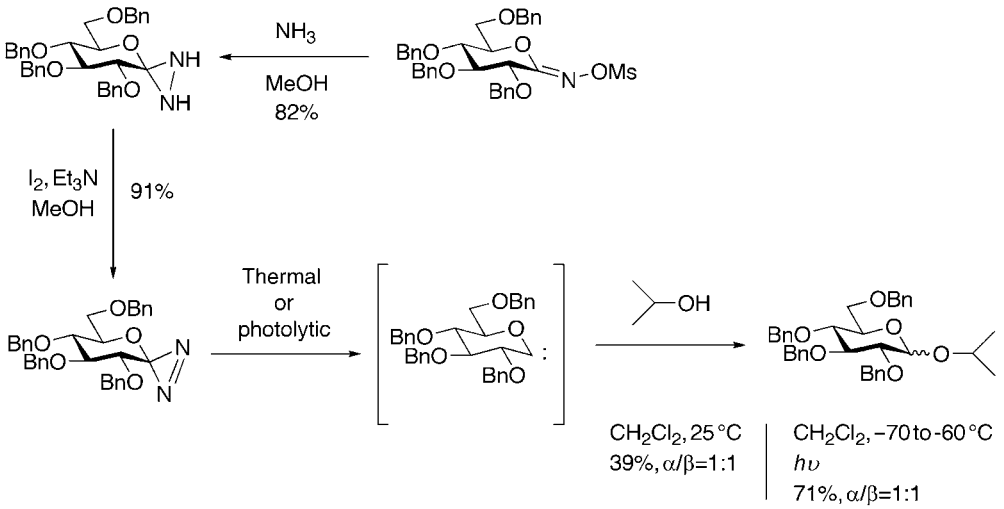


Scheme 5.76 Ref. [228].



Scheme 5.77 Ref. 230a.

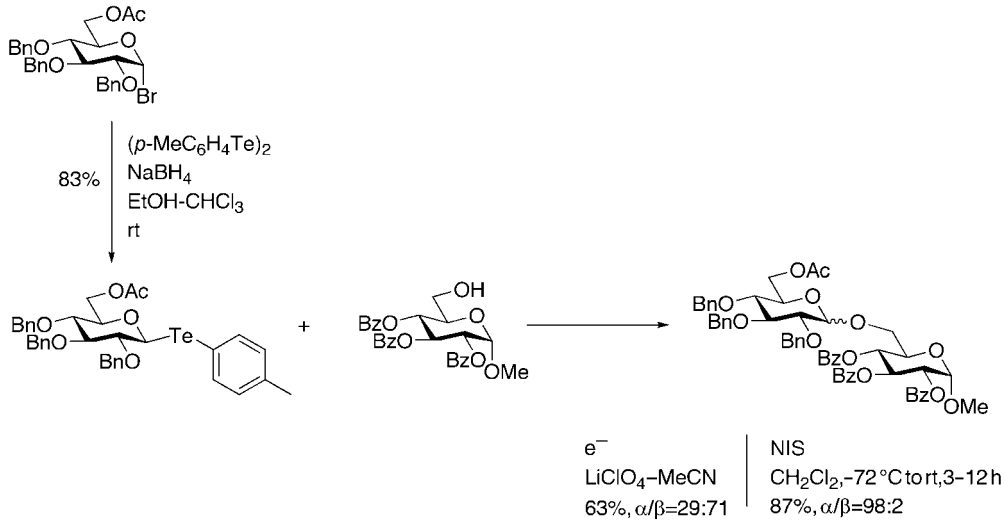
glycosylidene diazirines were prepared by I_2-mediated oxidation of the corresponding diaziridines, which were in turn formed from [(glycosylidene)amino]methanesulfonates with a saturated solution of NH_3 in MeOH (Scheme 5.78) [231]. The glycosylidene diazirine reacted with alcohols via the glycosylidene carbene in the absence of any additives under thermal and/or photolytic conditions to give the corresponding glycosides.



Scheme 5.78 Ref. [231].

5.3.4
Telluroglycoside

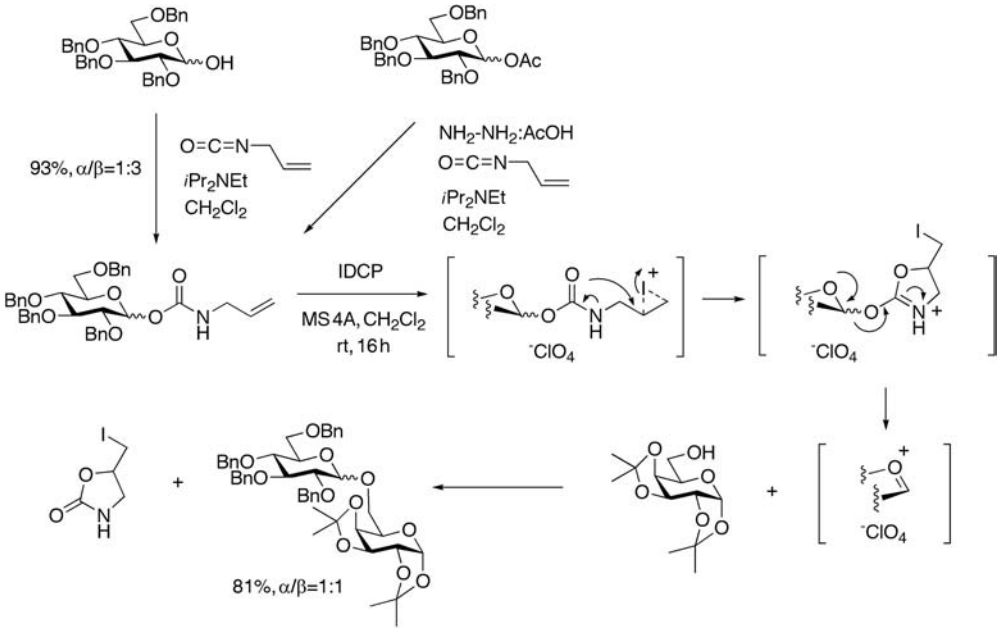
Barton and Ramesh first introduced the telluroglycoside as a glycosyl donor for *C*-glycosylation by means of a radical reaction [232]. Later, Yamago and Yoshida and coworkers reported *O*-glycosylations using aryl telluroglycosides [233]. Aryl telluroglycosides were prepared by the reaction of the corresponding bromoglycosides with diaryl ditelluride in the presence of $NaBH_4$. The activation methods including NBS, NIS, NIS-TMSOTf or by electrochemical activation, all of which were also used for the activation of thio- and selenoglycosides, were demonstrated for telluroglycosides (Scheme 5.79).



Scheme 5.79 Ref. [233].

5.3.5
Carbamate

Kunz and Zimmer introduced glycosyl *N*-allyl carbamates as glycosyl donors [234]. The glycosyl donors were prepared from the corresponding hemiacetals by the reaction with allyl isocyanate in the presence of $^{i}Pr_2NEt$ or their 1-*O*-acyl derivatives after treatment with hydrazine acetate. The glycosylation of glycosyl *N*-allyl carbamates is based on an electrophile-induced lactonization of anomeric alkenoic esters, and is somewhat similar to the Fraser-Reid method [235] for the activation of pentenyl glycosides. Thus, soft electrophiles such as dimethyl methylthiosulfonium trifluoromethansulfonate (DMTST), di-(*sym*-collidine) iodonium perchlorate (IDCP) or methyl bis-methylthiosulfonium hexachloroantimonate (TMTSB) were used as the activator (Scheme 5.80). Along similar lines, Kiessling introduced glycosyl *N*-sulfonylcarbamates as new glycosyl donors with tunable reactivity [236]. The donors were synthesized by the reaction of



Scheme 5.80 Ref. [234].

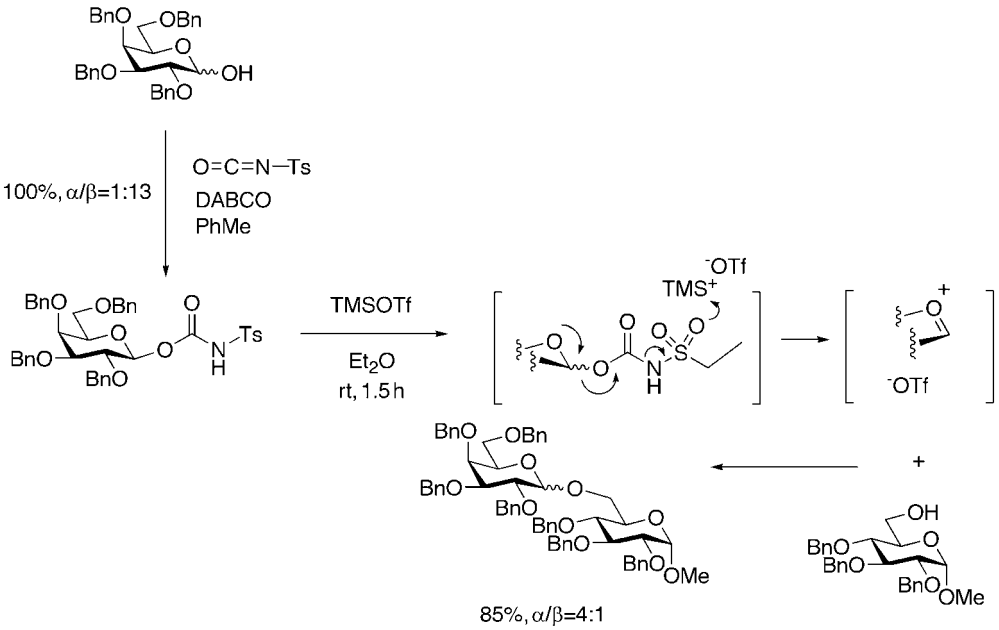
the corresponding aldoses and *N*-sulfonyl isocyanates with 1,4-diazabicyclo[2.2.2] octane (DABCO), and activated by several protic and Lewis acids such as TfOH, $BF_3{\cdot}Et_2O$, $Yb(OTf)_3$ or TMSOTf (Scheme 5.81). Furthermore, it was found that the reactivity of glycosyl *N*-sulfonylcarbamates toward TMSOTf could be tuned with the variation of the alkyl substituent on the nitrogen as shown in Table 5.2.

5.3.6
2-Iodosulfonamide

2-Iodosulfonamides were employed as glycosyl donors by Danishefsky *et al.* for the construction of 2-aminoglycosides [237]. Reaction of 2-(trimethylsilyl)ethanesulfonamide ($SESNH_2$) and glycal with IDCP provided *trans*-2-iodosulfonamide, which was activated by silver catalyst (AgOTf, $AgBF_4$) and then coupled with alcohols to furnish 1,2-*trans*-2-aminoglycosides. This method was successfully applied to the syntheses of sialyl-Lewis X antigen oligosaccharides and chitinase inhibitors (Scheme 5.82).

5.3.7
N-Glycosyl Triazole

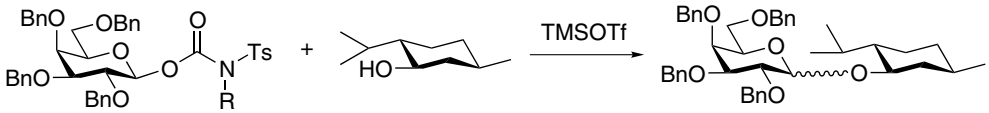
Kunz *et al.* demonstrated the glycosylation using *N*-glycosyl triazoles as glycosyl donors [238]. These glycosyl donors were prepared from the corresponding glycosyl



Scheme 5.81 Ref. [236].

azides by the reaction with alkynes. The glycosylation of *N*-glycosyl triazoles with alcohols in the presence of TMSOTf produced the corresponding glycosides (Scheme 5.83).

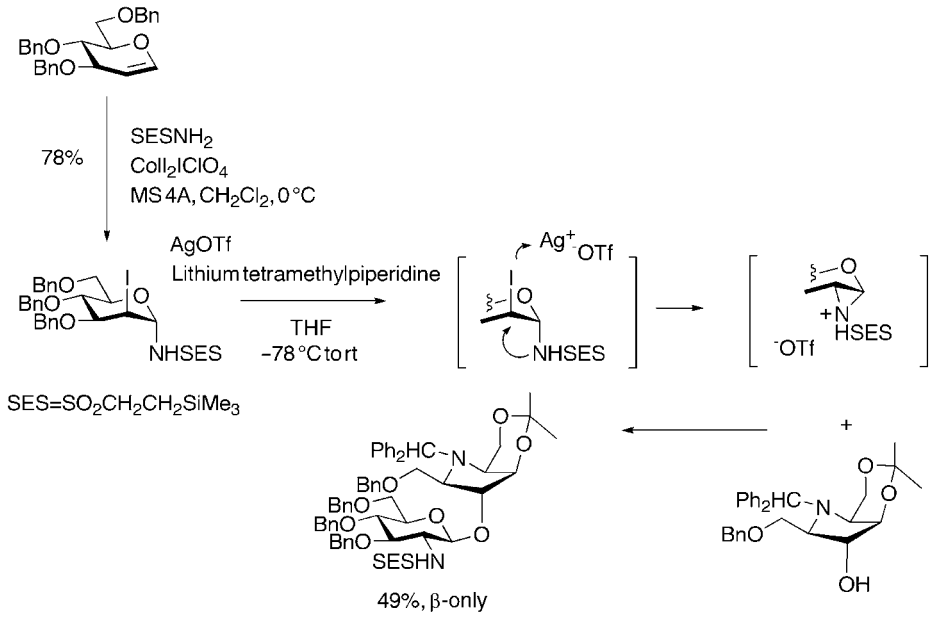
Table 5.2 Glycosylation using different glycosyl sulfonylcarbamates [236].



R	Equiv. of TMSOTf	Yield	α/β ratio
H	1.1	82	6/1
Me	0.1	84	1.7/1
CH_2CN	0.1	89	1.3/1
	0.1	0	—

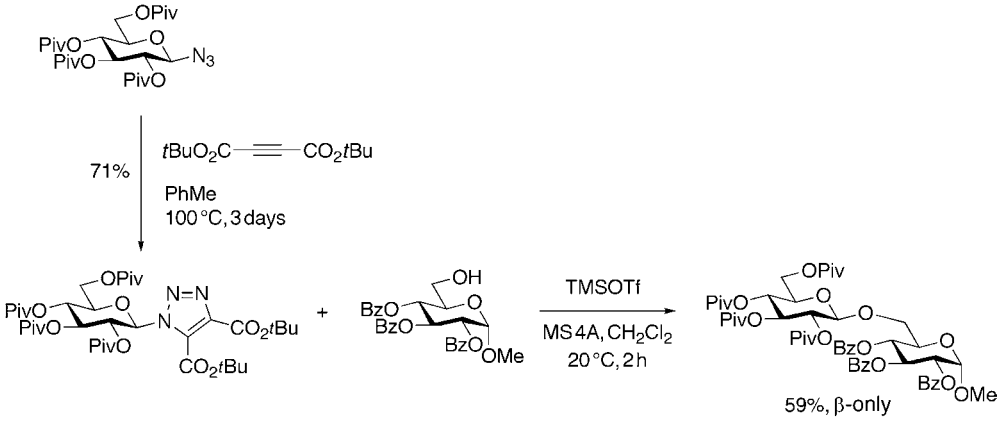
5.3.8
N-Glycosyl Tetrazole

Besides *N*-glycosyl triazoles, *N*-glycosyl tetrazoles were introduced by Sulikowski and coworkers [239]. *N*-Glycosyl tetrazoles were formed via phosphitylation of

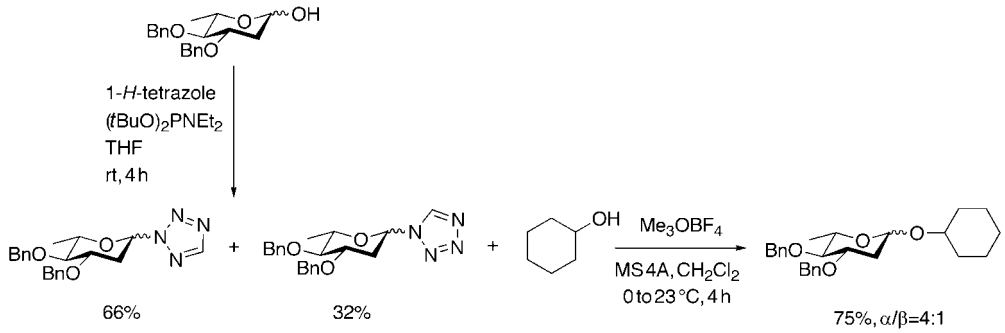


Scheme 5.82 Ref. [237].

2-deoxy sugars, and these worked as glycosyl donors when activated by $ZnCl_2$ or Me_3OBF_4 furnishing α-glycosides selectively (Scheme 5.84). The method was successfully employed in the syntheses of the deoxyoligosaccharides of the antibiotics PI-080 and landomycin A (Scheme 5.85) [239b,c].



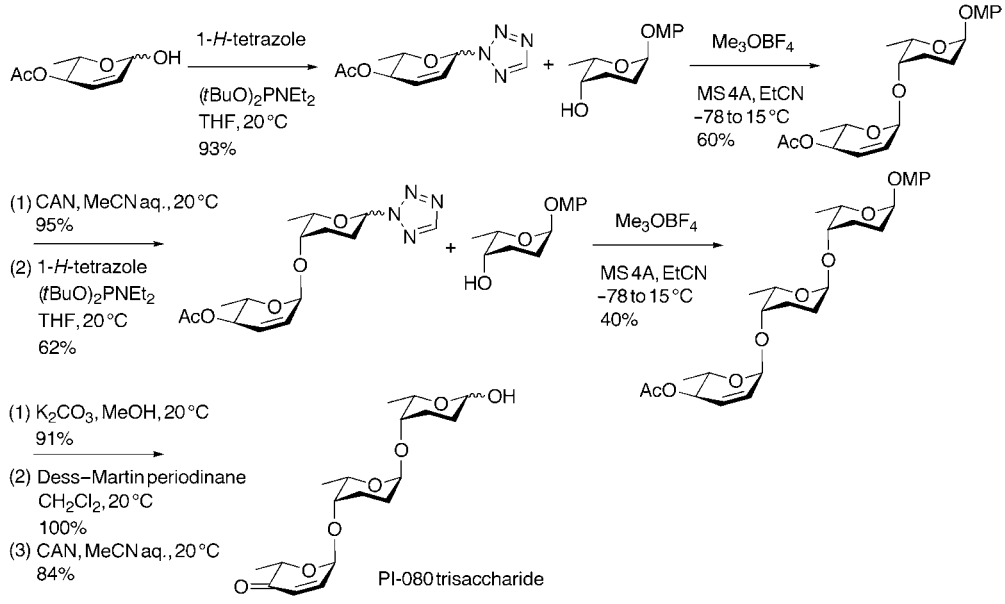
Scheme 5.83 Ref. [238].



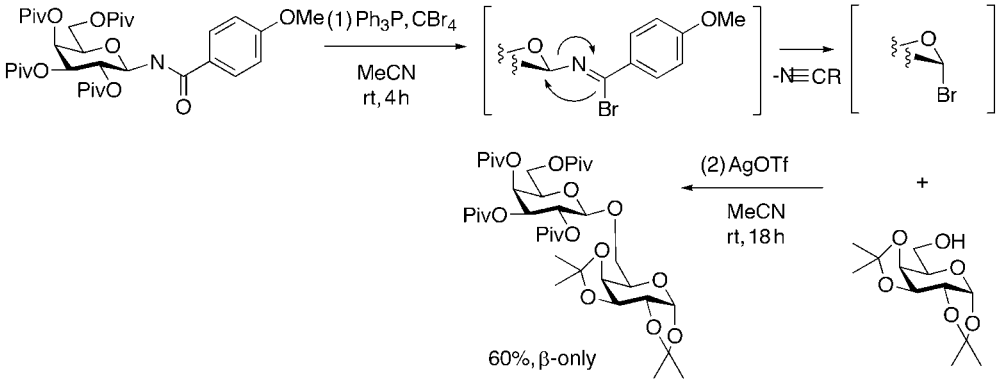
Scheme 5.84 Ref. [239].

5.3.9
N-Glycosyl Amide

The use of *N*-glycosyl amides as glycosyl donors was reported by Pleuss and Kunz [240]. These amides were activated by Ph_3P and CBr_4 to produce bromo-*N*-imidates, which were spontaneously converted into the corresponding bromide concomitant with releasing nitrile, and then coupled with alcohols by activation with AgOTf (Scheme 5.86).



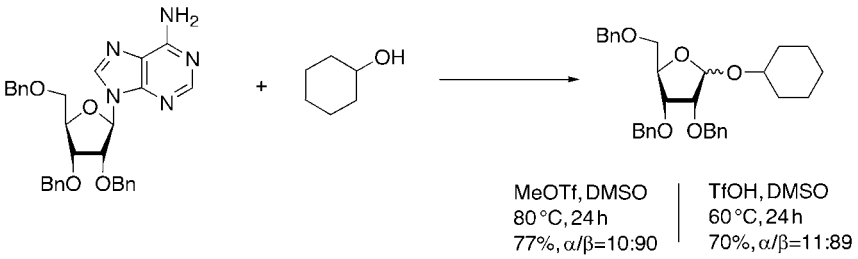
Scheme 5.85 Ref. [239b].



Scheme 5.86 Ref. [240].

5.3.10
DNA and RNA Nucleosides

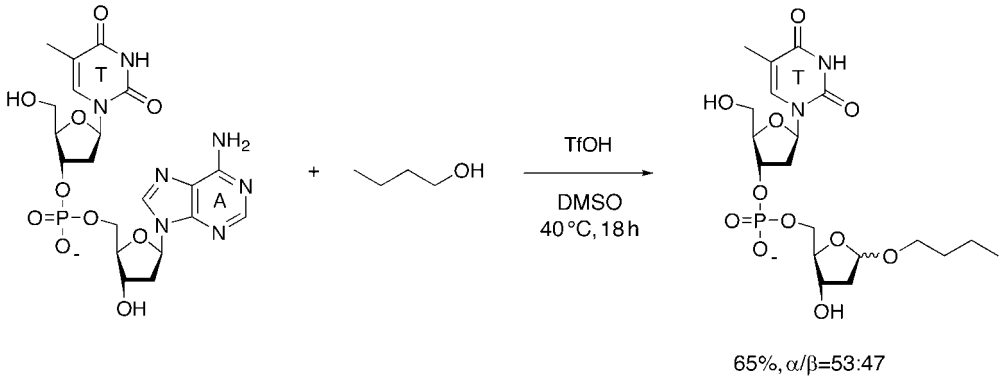
Toshima and coworkers developed a novel glycosylation method using DNA bases as leaving groups based on one of the most typical DNA sequence protocols, Maxam–Gilbert method [241]. Thus, the simple and practical synthesis of alkyl glycosides by protic and alkylative glycosylations using natural starting compounds, DNA and RNA nucleosides, was realized (Scheme 5.87). In this study, it was found that purine bases (adenine and guanine) worked as good leaving groups, whereas the pyrimidine bases (cytosine and thymine) had no such ability under MeOTf- or TfOH-promoted glycosylation conditions. Importantly, the chemoselectivity of this glycosylation method was exploited for the preparation of modified DNA oligomers from naturally occurring DNA fragments (Scheme 5.88).



Scheme 5.87 Ref. [241].

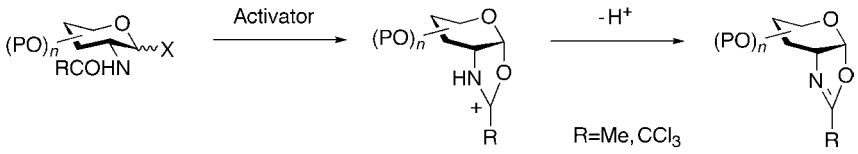
5.3.11
Oxazoline

Oxazoline glycosyl donors are generally prepared from the corresponding 2-acylamido-2-deoxyglycosides by the activation of the C-1 leaving group using an

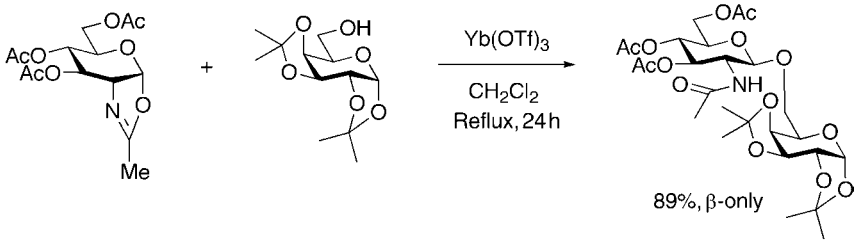


Scheme 5.88 Ref. [241].

appropriate activator (Scheme 5.89). Oxazolines can then be activated for glycosylation with $Yb(OTf)_3$ [247] (Scheme 5.90), *p*-TsOH [242], $FeCl_3$ [243], TMSOTf [60], camphorsulfonic acid (CSA) [244], $CuCl_2$ [245], pyridinium triflate with microwave irradiation [246] and PPTS [246]. Instead of the most commonly used methyl-oxazolines, trichloro-oxazolines, which could be activated under milder conditions with TMSOTf, were also introduced [248]. The advantage of using oxazolines as glycosyl donors in glycosylation reactions is the direct and stereoselective access to the *trans*-2-aminoglycosides.



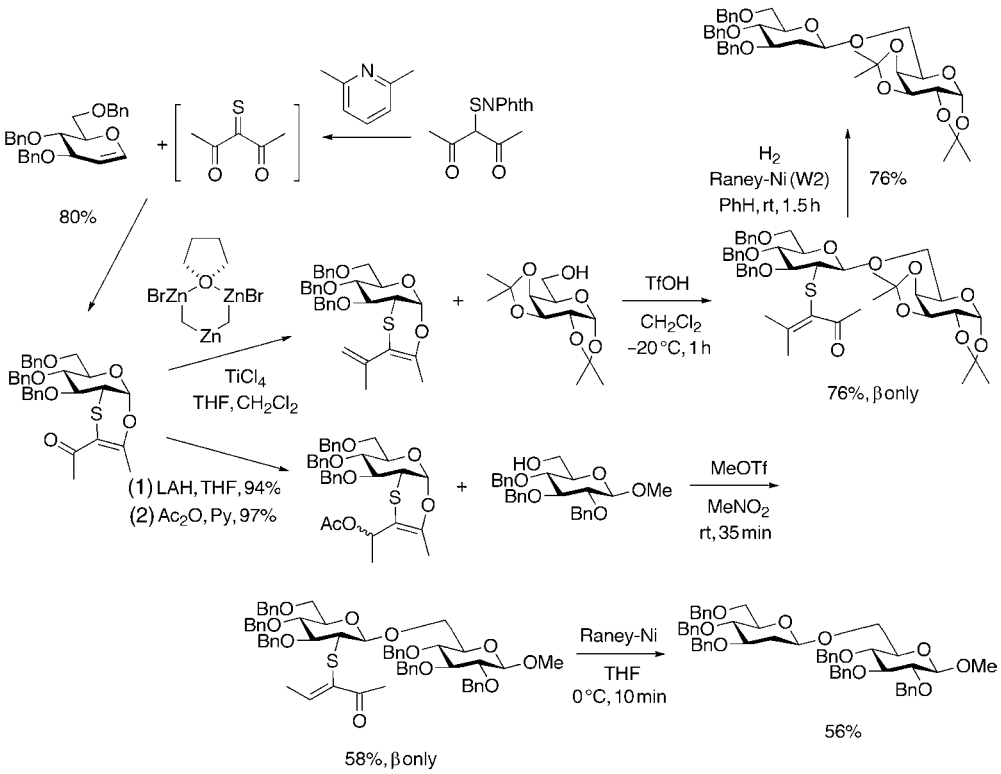
Scheme 5.89



Scheme 5.90 Ref. [247].

5.3.12
Oxathiine

Franck, Marzabadi, Capozzi and Nativi introduced bicyclic glycosyl donors, oxathiines [249]. These glycosyl donors were prepared via Diels–Alder cycloaddition

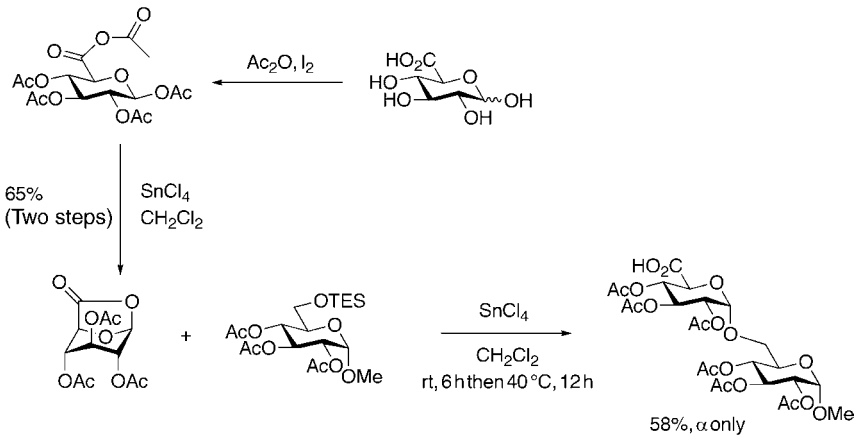


Scheme 5.91 Ref. [249].

reactions between glycals and 3-thioxopentane-2,4-dione (Scheme 5.91). Treatment of the cycloadducts with Nysted reagent in the presence of $TiCl_4$ gave the vinyl glycosides as glycosyl donors, which could be activated by TfOH and then coupled with alcohols to furnish β-glycosides. These products were converted into the corresponding 2-deoxy-β-glycosides by desulfurization using Raney-Ni. On the contrary, the allyl acetates as glycosyl donors were prepared from the cycloadducts by reduction using lithium aluminum hydride (LAH) followed by acetylation. The glycosylations of alcohols with the allyl acetates using MeOTf proceeded to afford β-glycosides, which were also converted into the corresponding 2-deoxy-β-glycosides by hydrogenolysis using Raney-Ni. It was also found that the obtained β-glycosides could be transformed into the corresponding α-anomer by anomerization in the same reaction medium; the isomerization was presumably induced by acid catalysis.

5.3.13
1,6-Lactone

1,6-Lactone derivatives derived from glucuronic acid were used as glycosyl donors by Murphy and coworkers [250]. These glycosyl donors were found to react with silyl

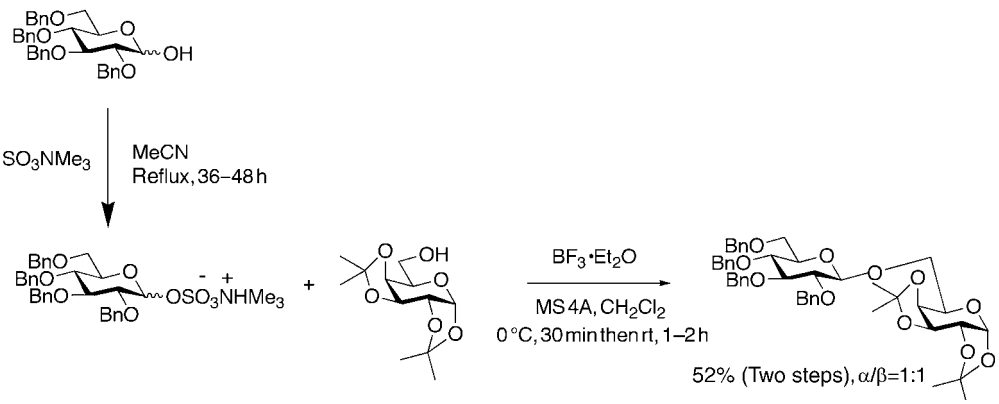


Scheme 5.92 Ref. [250].

ethers in the presence of $SnCl_4$ to stereoselectively give the corresponding α-glucuronides (Scheme 5.92). In contrast, the donor possessing an iodo-substituent at the C-2 position afforded the corresponding β-glucuronides through the iodonium intermediate.

5.3.14
Sulfate

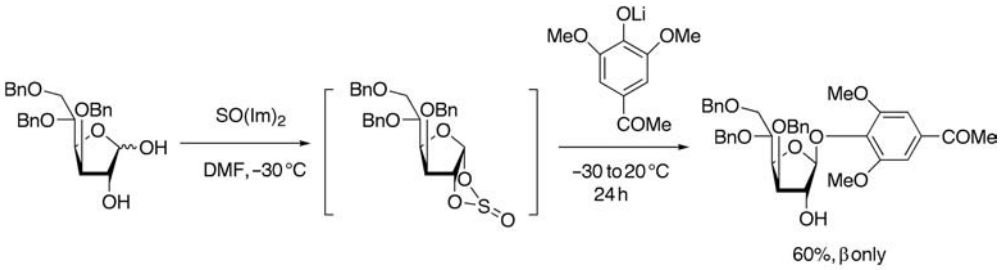
Russo and coworkers introduced glycosyl sulfates as glycosyl donors [251]. These glycosyl donors were synthesized by the treatment of the corresponding aldoses with $SO_3 \cdot NMe_3$ complex and could be stored for several weeks as the triethylammonium salts. The glycosylations using $BF_3 \cdot Et_2O$ or TMSOTf gave glycosides in fair to good yields (Scheme 5.93).



Scheme 5.93 Ref. [251].

5.3.15
1,2-Cyclic Sulfite

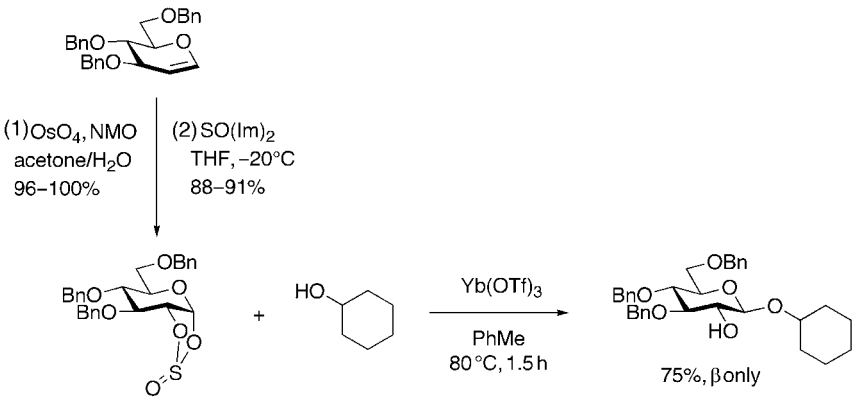
Beaupere and coworkers [252] and Sanders and Kiessling [253] independently reported the glycosylations of 1,2-cyclic sulfites as glycosyl donors, which were prepared from 1,2-dihydroxy sugars by the reaction using thionyldiimidazole ($SO(Im)_2$). These glycosyl donors reacted with phenoxide ions to yield the corresponding β-aryl glycosides (Scheme 5.94), and also coupled with alcohols by the activation using $Yb(OTf)_3$ or $Ho(OTf)_3$ to afford the corresponding β-glycosides (Scheme 5.95).



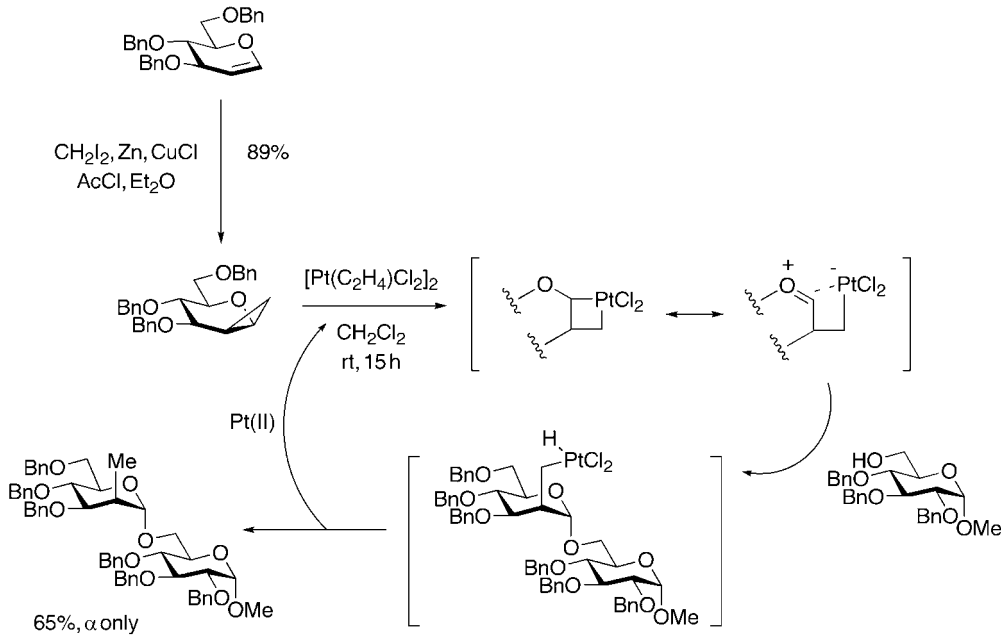
Scheme 5.94 Ref. [252].

5.3.16
1,2-Cyclopropane

Madsen *et al.* reported platinum(II)-mediated ring-opening glycosylation of 1,2-cyclopropanated sugars, which were prepared from the corresponding glycals by Simmons–Smith cyclopropanation reaction using CH_2I_2, Zn and CuCl. These glycosyl donors were found to react with alcohols by activation using Zeise's dimer [$Pt(C_2H_4)Cl_2$] to yield the corresponding 2-*C*-methyl glycosides [254] (Scheme 5.96).



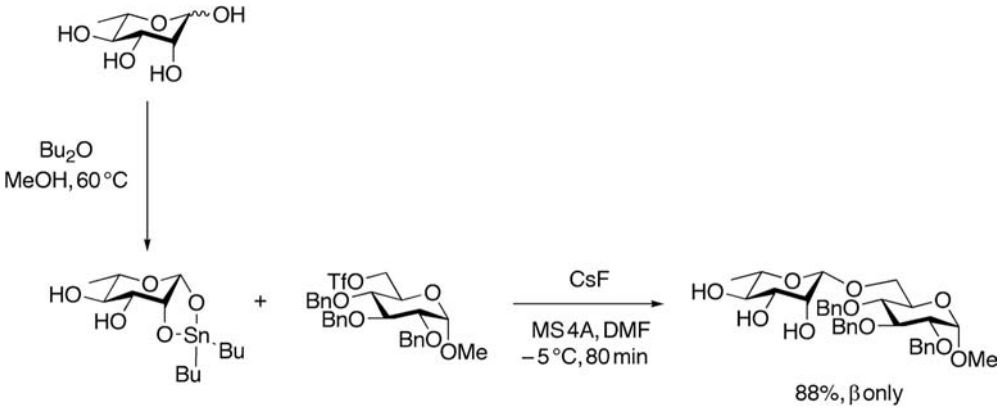
Scheme 5.95 Ref. [253].



Scheme 5.96 Ref. [254].

5.3.17
1,2-*O*-Stannylene Acetal

Srivastava and Schuerch [255] and Desinges *et al.* [256] demonstrated the potential utility of glycosyl 1,2-*O*-stannylene acetals, and Hodosi and Kovác [257] established this method involving alkylation of a 1,2-*O*-stannylene acetal with a triflate derivative as an aglycon (Scheme 5.97). This glycosyl donor was prepared by the

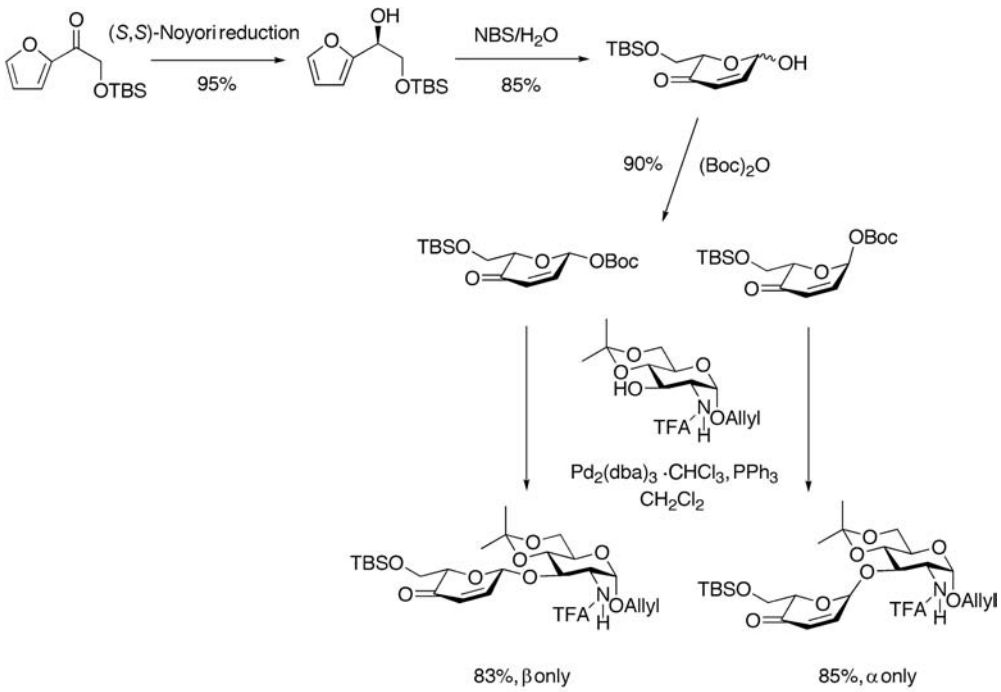


Scheme 5.97 Ref. [257].

reaction of the corresponding 1,2-dihydroxy sugar with dibutyltin oxide, and the glycosylation was shown to be useful for constructing 1,2-*cis*-glycosidic linkages such as β-mannopyranosyl or β-rhamnopyranosyl linkages. Importantly, the glycosylation proceeded with the retention of anomeric configuration in the glycosyl donor.

5.3.18
6-Acyl-2*H*-Pyran-3(6*H*)-One

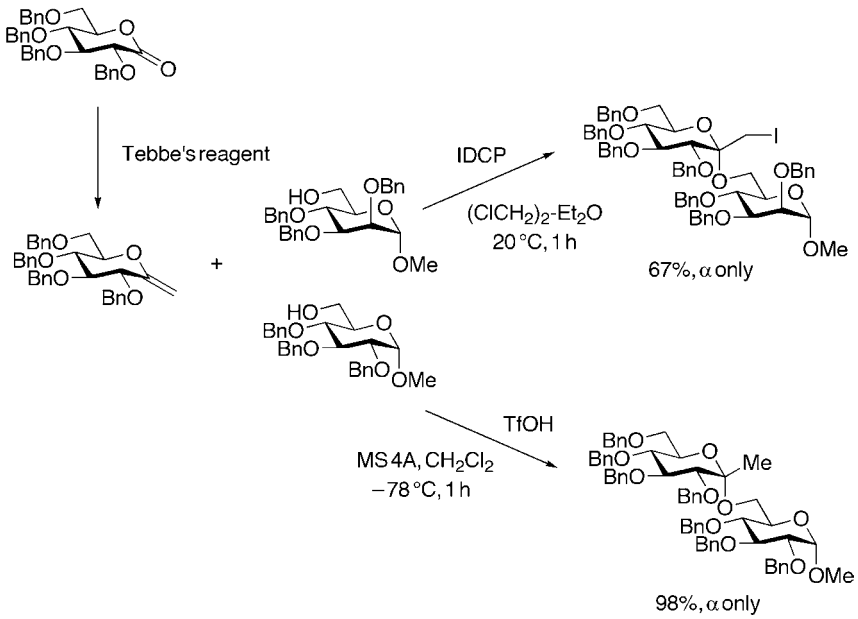
Feringa and coworkers [258] and O'Doherty *et al.* [259] independently reported palladium-catalyzed glycosylations of 2-substituted 6-acyl-2*H*-pyran-3(6*H*)-one derivatives and alcohols (Scheme 5.98). This reaction presumably involves electrophilic Pd π-allyl complex intermediate, which was generated by the reaction of 2-substituted 6-acyl-2*H*-pyran-3(6*H*)-one and Pd(0)/PPh_3. It is noteworthy that 2-substituted 6-acyl-2*H*-pyran-3(6*H*)-one derivatives were stereoselectively converted into 2-substituted 6-alkoxy-2*H*-pyran-3(6*H*)-one derivatives with complete retention of configuration by this reaction. A two-step reduction/oxidation manipulation after the glycosylation can install new stereocenters in the obtained glycosides.



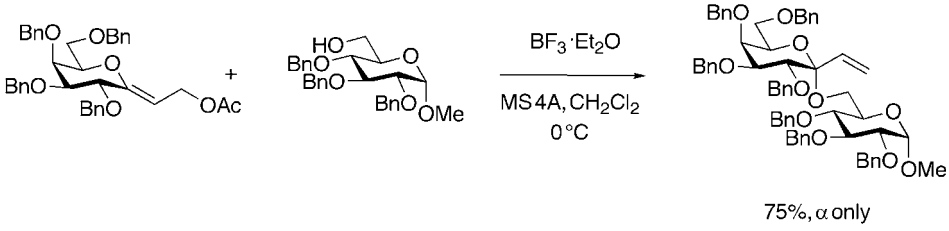
Scheme 5.98 Ref. [259].

5.3.19
exo-Methylene

The use of 1-methylene sugars as glycosyl donors was first demonstrated by van Boom *et al.* [260]. These glycosyl donors were prepared from the corresponding sugar lactones with Tebbe's reagent, and could be converted into α-linked ketopyranosides by the reactions with alcohols in the presence of IDCP (Scheme 5.99). Similar strategies using protic and Lewis acids, such as TfOH, TMSOTf, MsOH, 10-CSA, BCl_3 and $HBr{\cdot}PPh_3$, were also reported by Ikegami *et al.* [261] and Bravo *et al.* [262]. On the contrary, Lin *et al.* reported a glycosylation of 1-methylene sugars using $BF_3{\cdot}Et_2O$, which was promoted by Ferrier-type rearrangement [263] (Scheme 5.100).



Scheme 5.99 Refs. [260,261].



Scheme 5.100 Ref. [263].

5.3.20 Concluding Remarks

The glycosylation methodology has made tremendous progress in the past three decades and has been successfully applied to the synthesis of glycomolecules. However, a universal method for chemical glycosylation has not yet appeared from the point of view of chemical yield and stereoselectivity. Therefore, we always ask as to which method is the most suitable for the synthesis. Does a single powerful method in the glycosylation area really exist? In the future, two alternative ways may be determined to be efficient for glycosylation reactions: one is the development of a more general method, and another is the creation of a special method that is peculiar to each type of sugar or linkage, considering the features of each sugar structure. Furthermore, a major breakthrough may be needed for synthesizing any given glycomolecule by fully controlled chemistry. Because carbohydrates are indispensable substances in our life activities, the study of carbohydrate chemistry will continue for a long time.

5.3.21 Typical Experimental Procedure

5.3.21.1 General Procedure for the Preparation of Diazirines from Glycosyl Sulfonates

After the treatment of a sulfonate (16.0 mmol) with a saturated NH_3 solution in MeOH (180 ml) for 36 h, until the starting material had disappeared, according to TLC, half of the solvent was distilled. Keeping the remaining solution at −25 °C afforded the corresponding crystalline diaziridine. The solution of the oily diaziridine was evaporated, the residue was taken up in diethyl ether and the precipitated NH_4OSO_2Me was filtered to give the crude diaziridine. A solution of I_2 (1.81 mmol) in dry MeOH (9 ml) at −25 °C was added dropwise over 15 min to a mixture of diaziridine (1.81 mmol) and triethylamine (28.7 mmol) in dry MeOH (50 ml). The precipitated crystalline glycosyl diazirine was filtered. A second crop of crystals was obtained by the concentration of the mother liquor and crystallization at −25 °C.

5.3.21.2 General Procedure for the Glycosylation of Diazirines

Under thermal conditions, reaction of glycosyl diazirine (0.18 mmol) and glycosyl acceptor (0.19 mmol) in dry dichloromethane (1.5 ml) for 3 h at 25 °C yielded, after column chromatography, the corresponding glycoside. Under photolytic conditions, irradiation of a solution of glycosyl diazirine (0.087 mmol) and glycosyl acceptor (0.13 mmol) in dry dichloromethane (0.75 ml) with an HPK-125-Philips high-pressure Hg lamp (Solidex filter) at −65 °C for 20 min gave, after column chromatography, the corresponding glycoside.

5.3.21.3 General Procedure for the Preparation of Glycosyl Sulfonylcarbamates from Hemiacetals

A hemiacetal (1.0 mmol) and DABCO (10 mmol) were azeotroped thrice with dry benzene. The resultant residue was dissolved in dry toluene (10 ml) and cooled to

0 °C, and freshly distilled TsNCO (1.1 mmol) dissolved in dry toluene (5 ml) was added dropwise over 2 h. Upon completion, the reaction was warmed to room temperature and quenched by pouring 10% citric acid into it (50 ml). The resulting mixture was extracted with Et_2O (50 ml) and washed with sat. $NaHCO_3$ (aq) (25 ml) and brine (25 ml). The organic phase was dried over $MgSO_4$ and concentrated. The purification of the residue by column chromatography on silica gel gave the corresponding glycosyl sulfonylcarbamate.

5.3.21.4 General Procedure for the Glycosylation of Glycosyl Sulfonylcarbamates

Glycosyl sulfonylcarbamate (0.10 mmol) and glycosyl acceptor (0.15 mmol) were azeotroped thrice with dry toluene, and the resulting residue was dissolved in dry Et_2O (1.0 ml) under nitrogen atmosphere. TMSOTf (0.11 mmol) was then added dropwise and the reaction was stirred for 1.5 h. The reaction was quenched by the addition of solid $NaHCO_3$, and the Et_2O was removed under reduced pressure. Purification of the residue by column chromatography on silica gel gave the corresponding glycoside.

5.3.21.5 General Procedure for the Preparation of 1,2-*O*-Stannyl Acetals from Hemiacetals and the Glycosylation

A mixture of a hemiacetal (3.92 mmol) and dibutyltin oxide (3.52 mmol) in dry MeOH (25 ml) was stirred at 60 °C until a clear solution was obtained (~1.5 h). CsF (4.7 mmol) and toluene (5 ml) were added, and the mixture was concentrated. After having been kept at 50 °C and 0.2 Torr for 2 h to assure dryness, the residue was dissolved in DMF (5 ml), 4-Å molecular sieves (0.5 g) were added and the solution was cooled to −5 °C. After the addition of a triflated glycosyl donor (0.79 mmol), the mixture was stirred vigorously at −5 °C for 80 min and concentrated. The residue was triturated with acetonitrile, the resulting suspension was filtered through a pad of Celite, solids were washed with acetonitrile and the combined filtrate was concentrated. Purification of the residue by column chromatography on silica gel gave the corresponding glycoside.

5.3.21.6 General Procedure for the Preparation of 6-Acyl-2*H*-Pyran-3(6*H*)-Ones from1-(2′-Furyl)-2-*tert*-Butyldimethylsilanyloxyethan-1-Ols

1-(2′-Furyl)-2-*tert*-butyldimethylsilanyloxyethan-1-ol (6.97 mmol), THF (12 ml), and H_2O (3 ml) were added to a round-bottom flask and cooled to 0 °C. Solid $NaHCO_3$ (13.9 mmol), $NaOAc{\cdot}3H_2O$ (6.98 mmol) and NBS (6.97 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (aq) (15 ml), extracted with Et_2O (25 ml × 3), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel gave 6-hydroxy-2-*tert*-butyldimethylsilanyloxymethyl-2*H*-pyran-3-(6*H*)-one. This compound (10 mmol) was dissolved in CH_2Cl_2 (8 ml), and the solution was cooled to −78 °C. A CH_2Cl_2 (2 ml) solution of $(Boc)_2O$ (12 mmol) and a catalytic amount of DMAP (1 μmol) was added to the reaction mixture. After stirring for 1 h at −78 °C, the reaction was quenched with saturated $NaHCO_3$ (aq) (50 ml), extracted with Et_2O (50 ml × 3), dried over Na_2SO_4 and

concentrated under reduced pressure. The purification of the residue by column chromatography on silica gel gave carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethylsilanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester.

5.3.21.7 **General Procedure for the Glycosylation of 6-Acyl-2*H*-Pyran-3(6*H*)-Ones**

A CH_2Cl_2 (0.3 ml) solution of carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethylsilanyloxymethyl)-5-oxo-5,6-dihydro-*2H*-pyran-2-yl ester (0.279 mmol) and glycosyl acceptor (0.558 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.3 ml) solution of $Pd_2(DBA)_3{\cdot}CHCl_3$ (2.5 mol%) and PPh_3 (10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ (aq) (5 ml), extracted with Et_2O (5 ml × 3), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel gave the corresponding glycoside.

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262 (a) Colinas, P.A., Lieberknecht, A. and Bravo, R.D. (2002) *Tetrahedron Letters*, **43**, 9065–9068. (b) Colinas, P.A., Ponzinibbio, A., Lieberknecht, A. and Bravo, R.D. (2003) *Tetrahedron Letters*, **44**, 7985–7988.

263 (a) Lin, H.-C., Yang, W.-B., Gu, Y.-F., Chen, C.-Y., Wu, C.-Y. and Lin, C.-H. (2003) *Organic Letters*, **5**, 1087–1089. (b) Lin, H.-C., Du, W.-P., Chang, C.-C. and Lin, C.-H. (2005) *Tetrahedron Letters*, **46**, 5071–5076.

5.4
The Twenty First Century View of Chemical *O*-Glycosylation

Thomas Ziegler

5.4.1
Indirect and Special Methods

Indirect and special methods for *O*-glycosidic bond formation are usually only applied to special cases where common glycosylation methods via glycosyl donors or anomeric *O*-alkylation, as outlined in the previous chapters, fail or appear to be impractical. Nevertheless, some of these indirect and rather special methods provide for the efficient preparation of glycosides and saccharides that are otherwise difficult to obtain. Special methods for glycoside synthesis also give more insight into the intriguing and sometimes puzzling effects reigning stereo- and regioselectivity and reactivity of glycosylation reactions. This chapter summarizes some of these indirect and special methods and discusses their applicability for glycoside and oligosaccharide synthesis.

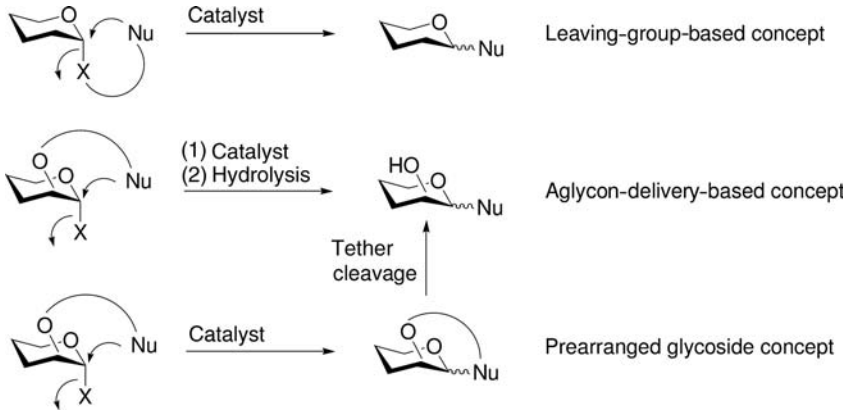
5.4.1.1 Intramolecular *O*-Glycosylation

Intramolecular glycosylations can be regarded as a biomimetic variant of *O*-glycosidic bond formation as they resemble enzymatic glycoside synthesis where glycosyl donor and acceptor are bound to the active site of an enzyme, and thus the *O*-glycosidic bond forms intramolecularly. Three different approaches or concepts to achieve the intramolecularization of *O*-glycosidic bond formation can be envisaged and had been studied over the past years (Scheme 5.101) [264,265].

In the following chapters, these three concepts will be discussed and the currently available literature will be summarized.

5.4.1.2 Leaving-Group-Based Concept

In the 'leaving-group-based concept', the glycosyl acceptor (nucleophile) is attached to the leaving group of the glycosyl donor. Upon activation, the leaving group is



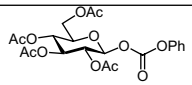
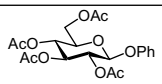
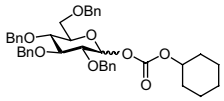
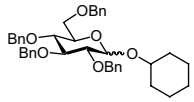
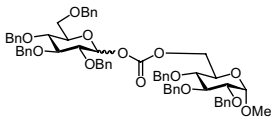
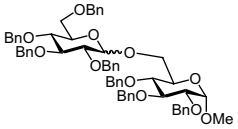
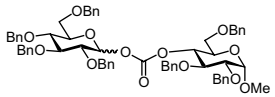
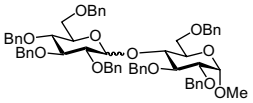
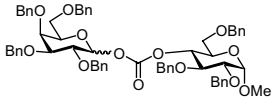
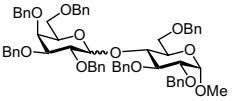
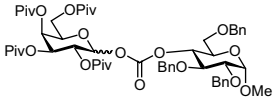
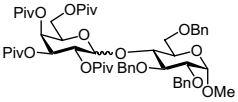
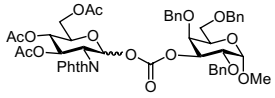
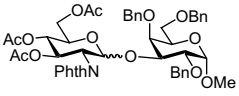
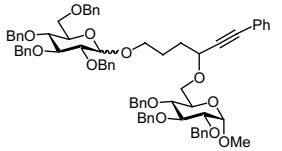
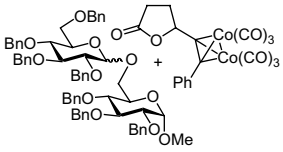
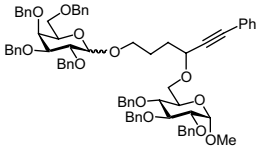
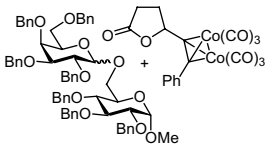
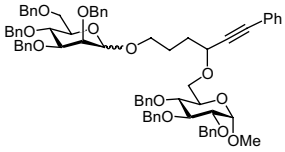
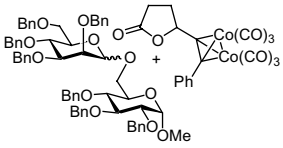
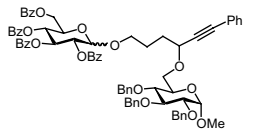
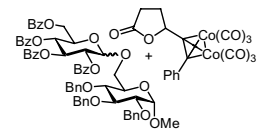
Scheme 5.101 Concepts for intramolecular glycosylation. X = leaving group, Nu = glycosyl acceptor.

released and the glycosidic bond forms. Glycosyl carbonates have been used for this purpose (Table 5.3, entries 1–8) [266–269]. Activation can be induced either by simple heating or, preferentially, by Lewis acid catalysis. Stereoselectivities for these leaving-group-based glycosylations were similar to those obtained for the corresponding intermolecular glycosylations, suggesting that glycosylations via anomeric carbonates rather proceed intermolecularly. Indeed, it could be shown from competitive experiments that such glycosylations proceed, at least in part, intermolecularly as well [266]. Other examples for leaving-group-based concept glycosylations are glycosyl hexynoates that can get activated by converting the alkyne moiety into a dicobalthexacarbonyl complex (Table 5.3, entries 9–13) [270]. Stereoselectivities are high, provided a participating neighboring group is present in the donor moiety. Yet another approach for leaving-group-based concept glycosylations uses benzo-annelated pentenyl-type tethers that, however, were also shown by competitive experiments to proceed intermolecularly (Table 5.3, entries 14–15) [271]. Similarly, several thio-linked glycosides have been used as well (Table 5.3, entries 16–18) [272]. However, stereoselectivities were similarly unsatisfactory here. To this point, it remains unclear as to which extend this concept can be regarded as a truly intramolecular glycosylation and whether further experiments are necessary.

Recently, Jensen and coworkers presented yet another protocol for leaving-group-based glycosylation using an intramolecular S_N2 reaction without the need of any activation of the leaving group [273] (Scheme 5.102). Glycosyl donor and acceptor are first tethered via dinitrofluorobenzoic acid. Next, glycosylation is effected either by simple heating of the tethered glycoside in nitromethane or, in the alternative, by activation with a Lewis acid. The anomeric selectivity is usually low in this approach.

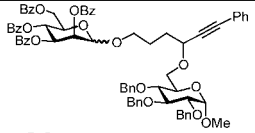
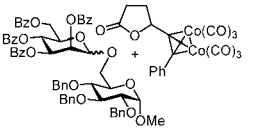
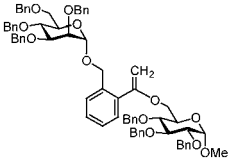
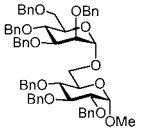
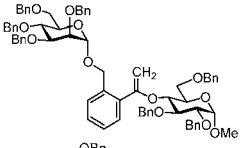
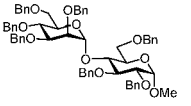
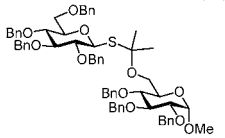
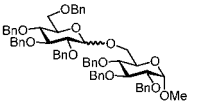
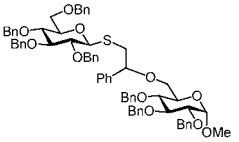
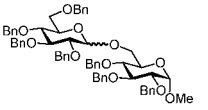
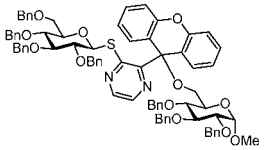
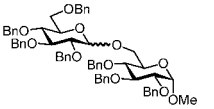
Intramolecular Aglycon Delivery (IAD) Concept The 'intramolecular aglycon-delivery concept' for intramolecular glycosylations has gained significant applications for oligosaccharide synthesis. Originally developed for the highly stereoselective synthesis of β-mannosidic linkages, still an imminent problem in saccharide synthesis

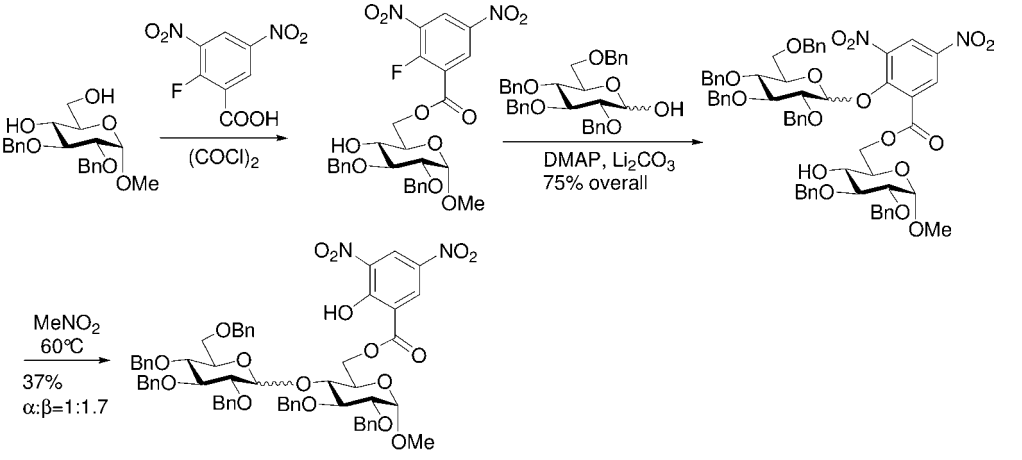
Table 5.3 Leaving-group-based concept glycosylations.

Entry	Starting material	Product	Activation	Yield %	α : β	References
1			170 °C	46	β only	[267]
2			TMSOTf, CH_2Cl_2 TMSOTf, toluene TBDMSOTf, CH_2Cl_2 TBDMSOTf, toluene	81 85 75 73	41:59 32:68 32:68 19:81	[268]
4			TMSOTf, toluene TBDMSOTf, toluene	79 85	32:68 28:72	[268]
5			TMSOTf, toluene TBDMSOTf, toluene	67 67	42:58 36:64	[268]
6			TMSOTf, toluene TBDMSOTf, toluene	69 72	42:58 34:66	[268]
7			TMSOTf, CH_2Cl_2	63	1:99	[269]
8			TMSOTf, CH_2Cl_2	72	1:99	[269]
9			(1) $Co_2(CO)_8$, Et_2O (2) TMSOTf, CH_2Cl_2	60	46:54	[270]
10			(1) $Co_2(CO)_8$, Et_2O (2) TMSOTf, CH_2Cl_2	77	42:58	[270]
11			(1) $Co_2(CO)_8$, Et_2O (2) TMSOTf, CH_2Cl_2	65	94:4	[270]
12			(1) $Co_2(CO)_8$, Et_2O (2) TMSOTf, CH_2Cl_2	37	1:99	[270]

(*continued*)

Table 5.3 (*Continued*)

Entry	Starting material	Product	Activation	Yield %	α : β	References
13			(1) $Co_2(CO)_8$, Et_2O (2) TMSOTf, CH_2Cl_2	43	99:1	[270]
14			PhSeCl, AgOTf, toluene	80	α only	[271]
15			PhSeCl, AgOTf, toluene	80	α only	[271]
16			DMTST, CH_2Cl_2	27	50:50	[272]
17			DMTST, CH_2Cl_2	51	40:60	[272]
18			AgOTf, CH_2Cl_2	75	60:40	[272]

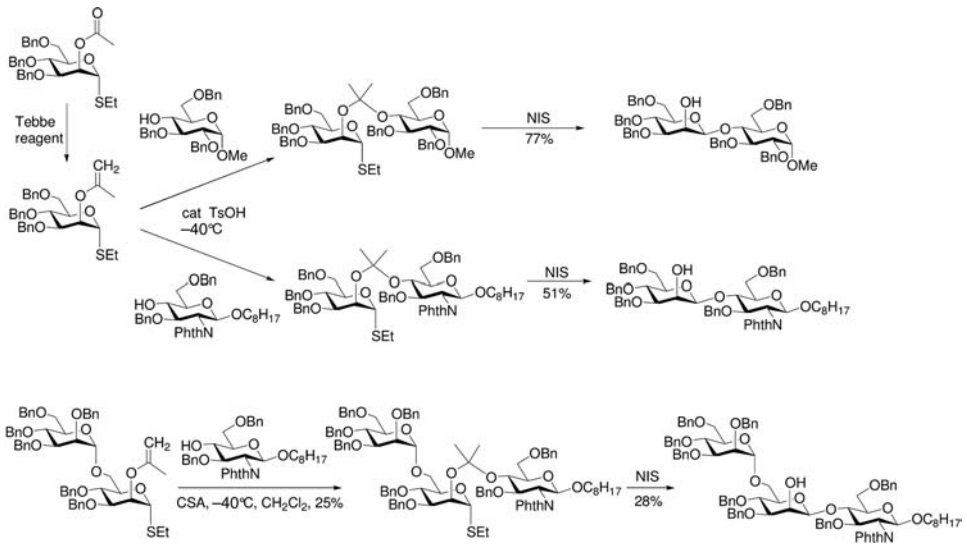


Scheme 5.102

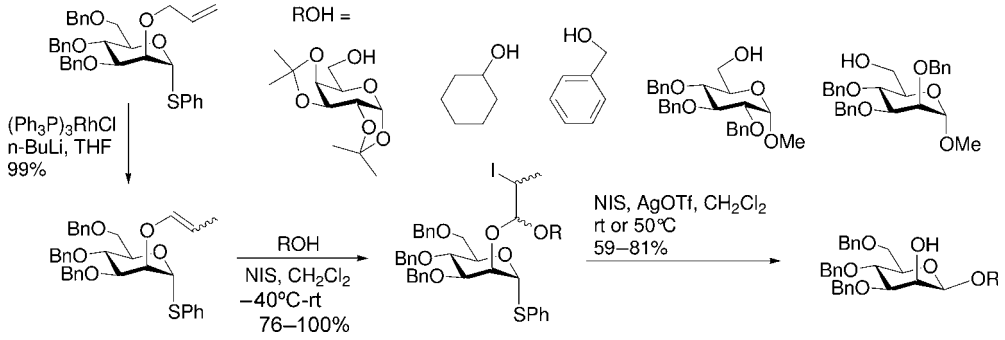
and later extended to other glycoside syntheses, two approaches via acetal tethers and silylene tethers have been grown into useful methods for the efficient construction of oligosaccharides.

IAD via Acetal Tethering The first example for this concept was presented by Barresi and Hindsgaul in 1991 and later extended to other examples [274,275]. Starting from ethyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-propenyl)-1-thio-α-D-mannopyranoside, which is easily accessible from the corresponding 2-*O*-acetyl derivative with Tebbe reagent, acid-catalyzed acetalization with suitable glycosyl acceptors affords the tethered glycosides in medium yield. Next, activation of the donor with NIS exclusively gives the corresponding β-linked disaccharides [275]. A major drawback, however, are rather low yields when this concept is applied to the synthesis of more complex oligosaccharides, where both the acetalization step and the IAD glycosylation proceed in less than 30% yield owing to side reactions [276] (Scheme 5.103).

Recently, Fairbanks and coworkers published a highly efficient protocol that circumvents the above-mentioned problems and allows for the efficient preparation of complex oligosaccharides using the IAD concept [277–279]. For example, the acetal tether is efficiently established by the reaction of a 2-*O*-(1-propenyl)-mannoside, which is generated from the corresponding 2-*O*-allyl-mannoside, with the glycosyl acceptor and *N*-iodosuccinimide (NIS), affording the tethered glycosides in high yield. NIS-induced activation of the tethered glycosides then results in a clean intramolecular glycosylation to give the β-mannosides in high yield as well [278] (Scheme 5.104). Another advantage of this protocol is that acetalization and intramolecular glycosylation can be performed with the same reagents. The solvent



Scheme 5.103 Disaccharide synthesis via IAD.



Scheme 5.104 Disaccharide synthesis via Fairbanks' IAD concept.

solely needs to be changed [280]. Table 5.4 summarizes the examples of this promising approach published so far [280–283].

Yet another improvement of the IAD concept was presented by Ito and Ogawa [284]. Substituting the aliphatic tether used by Hindsgaul and Fairbanks by an aromatic tether circumvents the difficulties encountered during acetal formation. Ogawa's *p*-methoxyphenylmethyl tether can be generated from a *p*-methoxyphenyl group (PMP) by oxidation with DDQ in the presence of the respective glycosyl acceptor. Thus, tethered glycosides are very conveniently accessible in high yield. Another significant improvement is the fact that the intermediate tethered glycosides do not need to get isolated but, instead, can directly get converted into the corresponding saccharides (Scheme 5.105) [284].

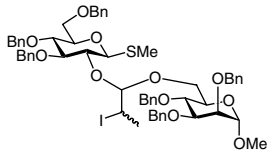
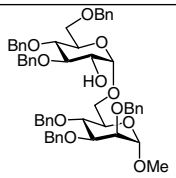
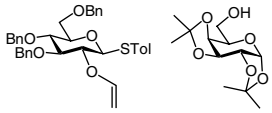
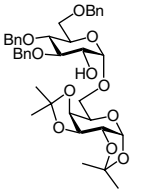
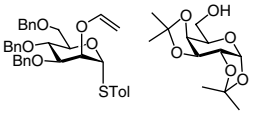
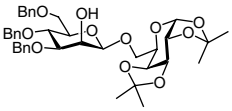
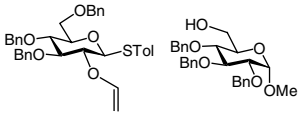
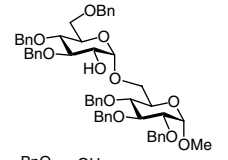
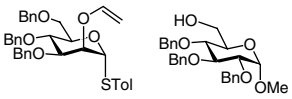
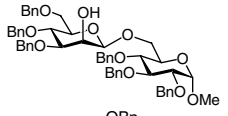
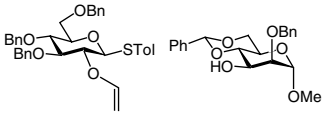
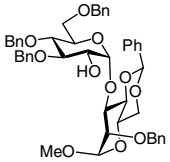
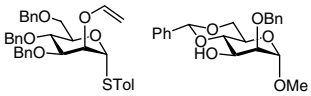
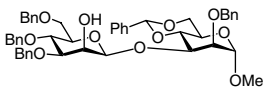
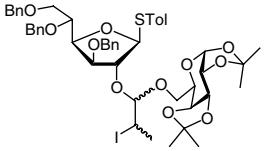
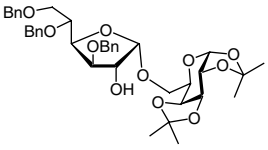
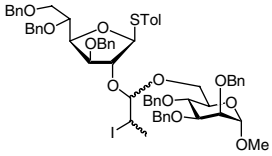
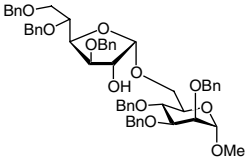
Another advantage of the IAD concept via *p*-methoxybenzylidene acetals lies in the compatibility of the oxidative tethering procedure with 1-thio-glycosyl donors [285,286]. Thus, highly flexible strategies for oligosaccharide synthesis can be realized [287–289]. For example, fragments related to the core region of Asn-linked glycans have been prepared efficiently this way [285–291] (Scheme 5.106).

The IAD concept via *p*-methoxybenzylidene acetals was also shown to be suitable for polymer-supported syntheses of disaccharides (Scheme 5.107) [292]. A suitable *p*-allyloxybenzyl group at position 2 of a 1-thio-mannosyl donor is first converted into a PEG-modified benzyl group that allows for the convenient isolation of the intermediate tethered glycosides.

The synthesis of β-D-fructofuranosides is yet another useful application of this concept [293–295]. The latter 1,2-*cis*-glycosidic linkage is as difficult to establish as in the case of β-mannosides. In an elegant synthesis of α-D-fucofuranose-containing disaccharides, Plusquellec and coworkers used the IAD concept via *p*-methoxybenzylidene acetals in combination with a glycosylation protocol via pentenyl glycosides. Here, the intermediate NIS-adduct could be isolated (Scheme 5.108) [295].

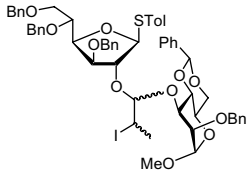
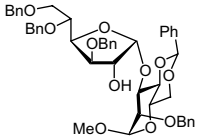
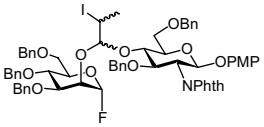
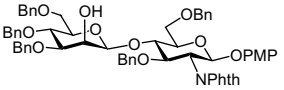
IAD via Silylene Tethering IAD through silylene-tethered glycosides was introduced by Bols [296–301] and Stork [302,303]. The silylene tether is usually established by

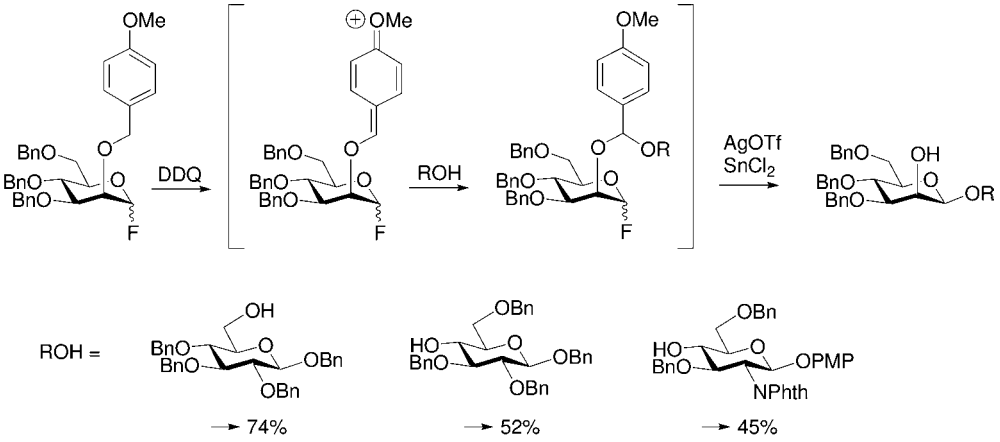
Table 5.4 Examples applying the IAD concept.

Entry	Starting materials	Product	Conditions	Yield[a] %	References
1			NIS, AgOTf, CH_2Cl_2	72	[278]
2			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 90% Then I_2, AgOTf, MeCN −20°C–rt	51	[280]
4			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 86% then I_2, AgOTf, MeCN −20°C–rt	65	[280]
5			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 81% then I_2, AgOTf, MeCN −20°C–rt	78	[280]
6			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 79% then I_2, AgOTf, MeCN −20°C–rt	79	[280]
7			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 71% then I_2, AgOTf, MeCN −20°C–rt	55	[280]
8			I_2, AgOTf, CH_2Cl_2 −78°C–rt, 75% then I_2, AgOTf, MeCN −20°C–rt	63	[280]
9			NIS, AgOTf, CH_2Cl_2, rt	70	[281]
10			NIS, AgOTf, CH_2Cl_2, rt	39	[281]

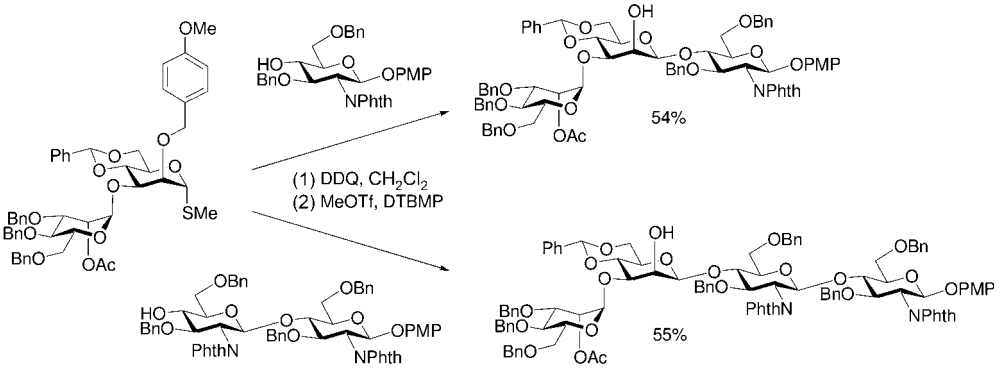
(*continued*)

Table 5.4 (*Continued*)

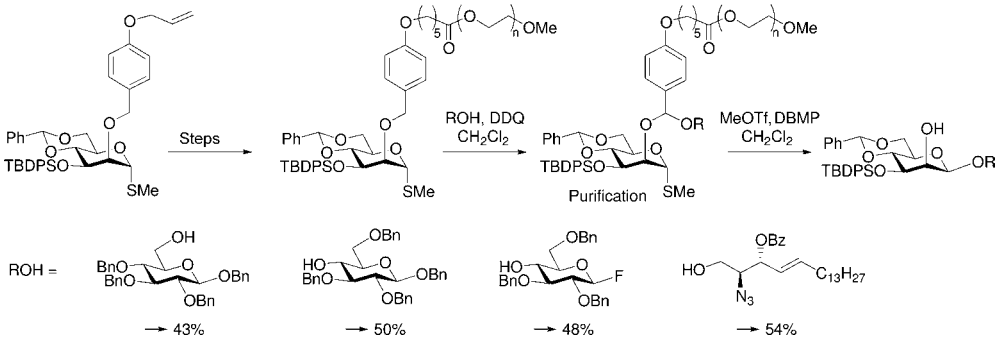
Entry	Starting materials	Product	Conditions	Yield[a] %	References
11			MeOTf, Me_2S_2, CH_2Cl_2,	32	[281]
12			SnCl2, AgOTf, CH_2Cl_2, 50 °C	54	[282]



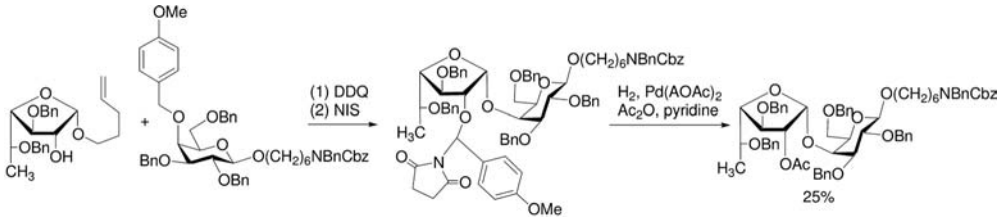
Scheme 5.105 IAD via *p*-methoxybenzylidene acetals.



Scheme 5.106

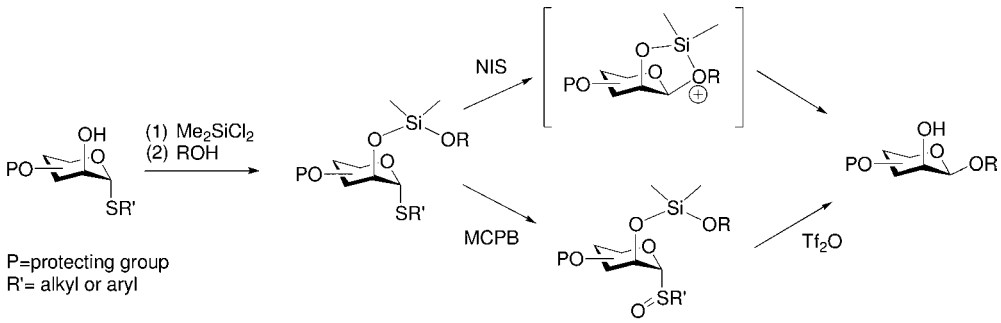


Scheme 5.107 Polymer-supported synthesis via IAD.



Scheme 5.108 Synthesis of furanosides via IAD concept.

reacting a suitable 1-thio-glycoside with dichlorodimethyl silane, followed by the corresponding glycosyl acceptor. Next, glycosylation can be effected either by NIS, resulting in intramolecular glycosylation with concomitant removal of the silylene tether, or by first converting the thio group into a sulfoxide and initiating glycosylation with triflic anhydride (Scheme 5.109) [303]. The literature up to 1995 was reviewed [304,305], and Table 5.5 summarizes the glycosylations using this approach.



Scheme 5.109 IAD concept via silylene tethers.

Table 5.5 IAD concept via silylene tethers.

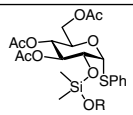
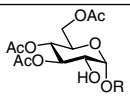
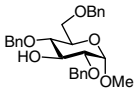
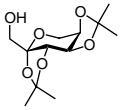
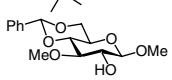
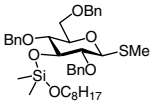
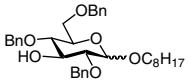
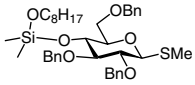
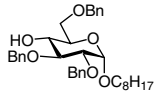
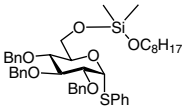
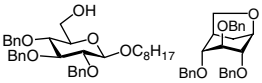
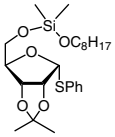
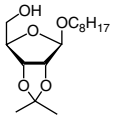
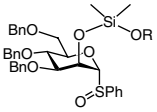
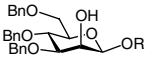
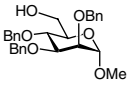
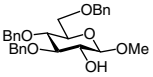
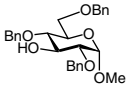
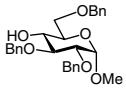
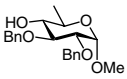
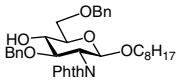
Entry	Starting materials	Product	Conditions	Yield[a] %	References
1	 R= n-octyl cyclohexyl t-butyl phenyl		NIS, TfOH, CH_2Cl_2, rt	59 62 61 72	[296]
2			NIS, $MeNO_2$, 100 °C	74	[297]
3			NIS, $MeNO_2$, 100 °C	85	[297]
4			NIS, $MeNO_2$, 100 °C	39	[297]
5			NIS, $MeNO_2$, 25 °C	22	[297]
6			NIS, $MeNO_2$, 25 °C	45	[300]
7			NIS, $MeNO_2$, 25 °C glycoside:anhydro glycose = 2:7	70	[300]
8			NIS, $MeNO_2$, 25 °C	63	[300]
9	 ROH = MeOH		Tf_2O, DTBP, CH_2Cl_2, 78 °C–25 °C	—[a]	[302]
10			Tf_2O, DTBP, CH_2Cl_2, 100 °C–25 °C	92	[303]
11			Tf_2O, DTBP, CH_2Cl_2, 100 °C–25 °C	65	[303]
12			Tf_2O, DTBP, CH_2Cl_2, 100 °C–25 °C	82	[303]
13			Tf_2O, DTBP, CH_2Cl_2, 100 °C –25 °C	12	[303]

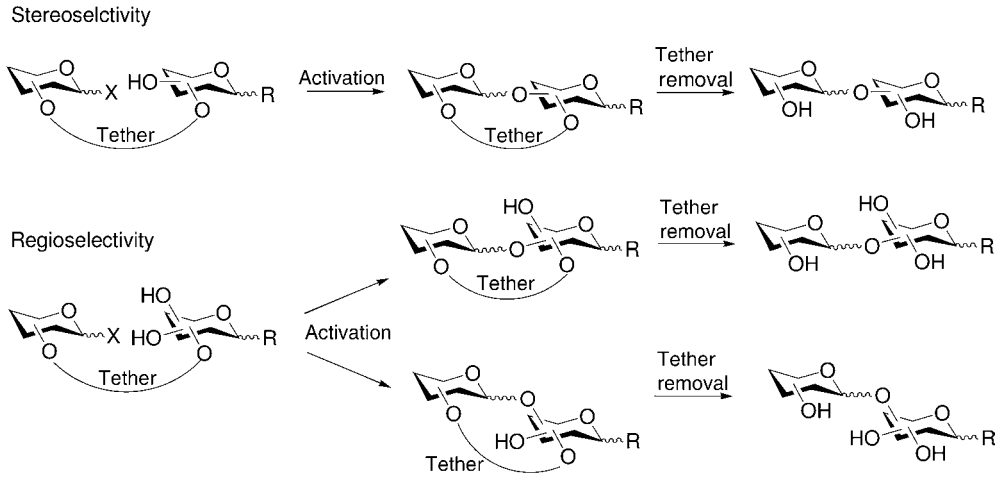
Table 5.5 (*Continued*)

Entry	Starting materials	Product	Conditions	Yield[a] %	References
14			Tf_2O, DTBP, CH_2Cl_2, 100 °C–25 °C	48	[303]
15			Tf_2O, DTBP, CH_2Cl_2, 100 °C–25 °C	54	[303]
					

5.4.1.3 **Prearranged Glycoside Concept**

This concept uses stable tethers that link glycosyl donor and acceptor at positions that are not involved in the glycosylation step. This concept is sometimes referred to as 'remote glycosylation'. To this extend, this concept for intramolecular glycosylation resembles best enzymatic glycosylations, where glycosyl donor and acceptor are also bound to the active site of an enzyme through hydroxyls that are not primarily involved in the formation of the glycosidic bond. In general, the concept of *O*-glycosidic bond formation via prearranged glycosides allows for both stereoselective and regioselective glycosylations depending on the nature of the tether and the positions through which glycosyl donor and acceptor are linked (Scheme 5.110).

As various parameters concerning the nature of the tether (length, torsional rigidity, etc.) and the positions in the glycosyl donor and acceptor to which it is attached govern the outcome of intramolecular glycosylations applying this concept, a vast number of examples have been investigated so far. Tables 5.6A–5.6C



Scheme 5.110 Prearranged glycoside concept.

Table 5.6A Intramolecular glycosylations via prearranged glycosides – glucose donors.

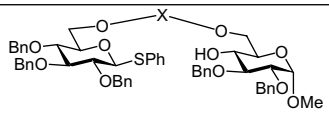
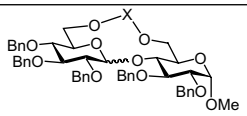
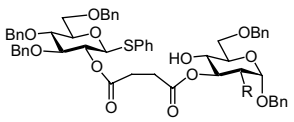
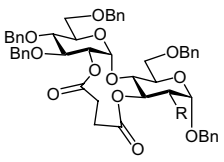
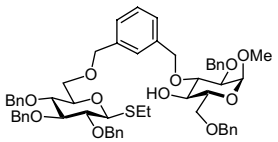
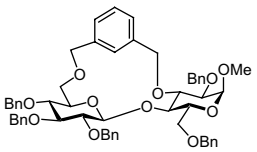
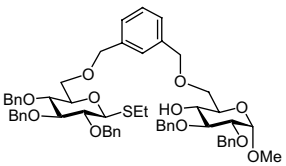
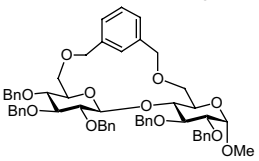
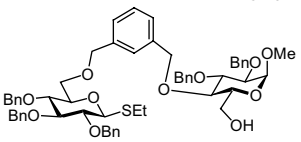
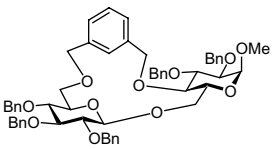
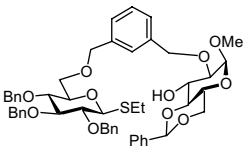
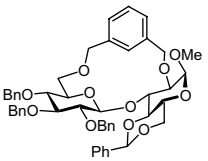
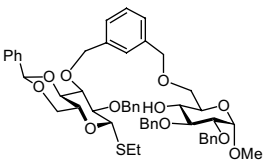
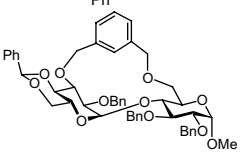
Entry	Starting material	Product	Activation	Yield %	α:β	References
1	 X = -CO-$(CH_2)_3$-CO-	 X = -CO-$(CH_2)_3$-CO-	PhIO, TMSOTf	37	89:11	[306]
	-CO-$(CH_2)_2$-CO-	-CO-$(CH_2)_2$-CO-	PhIO, TMSOTf	67	93:7	[306]
	phthaloyl	phthaloyl	PhIO, TMSOTf	86	99:1	[306]
	-Si(t-Bu)$_2$-	-Si(t-Bu)$_2$-	PhIO, TMSOTf	77	3:97	[306]
2	 R = OBz		NIS, TMSOTf	80	α only	[307]
	NPhth		NIS, TMSOTf	75	α only	[307]
4			NIS, TMSOTf	84	β only	[308]
5			NIS, TMSOTf	65	β only	[309]
6			NIS, TMSOTf	72	β only	[309]
7			NIS, TMSOTf	81	β only	[309]
8			NIS, TMSOTf	9	α only	[309]

Table 5.6A (*Continued*)

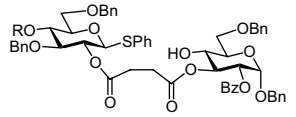
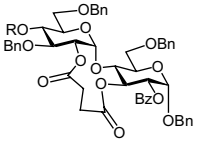
Entry	Starting material	Product	Activation	Yield %	α : β	References
9						
	R = 2,3,4,6-tetra-O-benzyl-α-D-glucosyl		NIS, TMSOTf	64	α only	[310]
	2,3,4,6-tetra-O-benzyl-β-D-glucosyl		NIS, TMSOTf	65	α only	[310]
	2,3,4,6-tetra-O-benzyl-β-D-galactosyl		NIS, TMSOTf	65	α only	[310]

Table 5.6B Intramolecular glycosylations via prearranged glycosides – glucose donors.

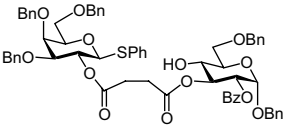
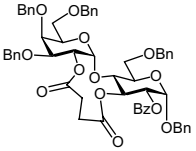
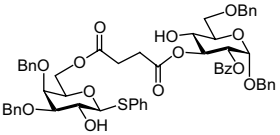
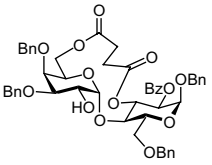
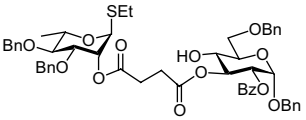
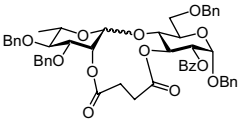
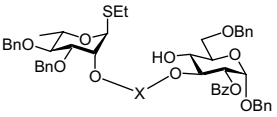
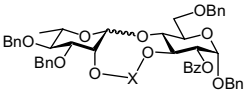
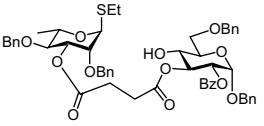
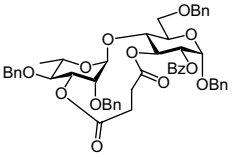
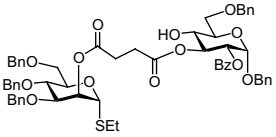
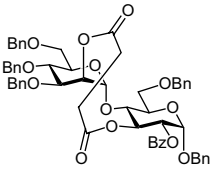
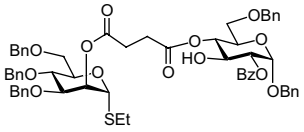
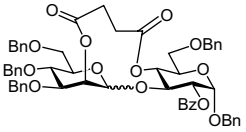
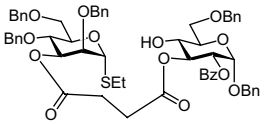
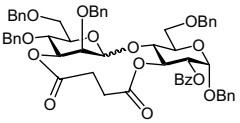
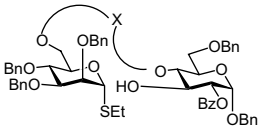
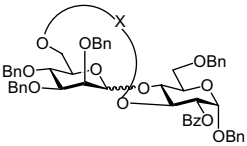
10			NIS, MeCN	51	α only	[311]
11			NIS, MeCN	69	α only	[311]

Table 5.6C Intramolecular glycosylations via prearranged glycosides – glucose donors.

12			NIS, TMSOTf, MeCN	74	18:82	[312]
			NIS, TMSOTf, CH_2Cl_2	75	71:29	[313]
13						
	X = phthaloyl	X = phthaloyl	NIS, TMSOTf, MeCN	68	50:50	[313]
	malonyl	malonyl	NIS, TMSOTf, MeCN	64	46:54	[313]
14			NIS, TMSOTf, MeCN	48	α only	[313]
15			NIS, TMSOTf, MeCN	54	α only	[314]

(*continued*)

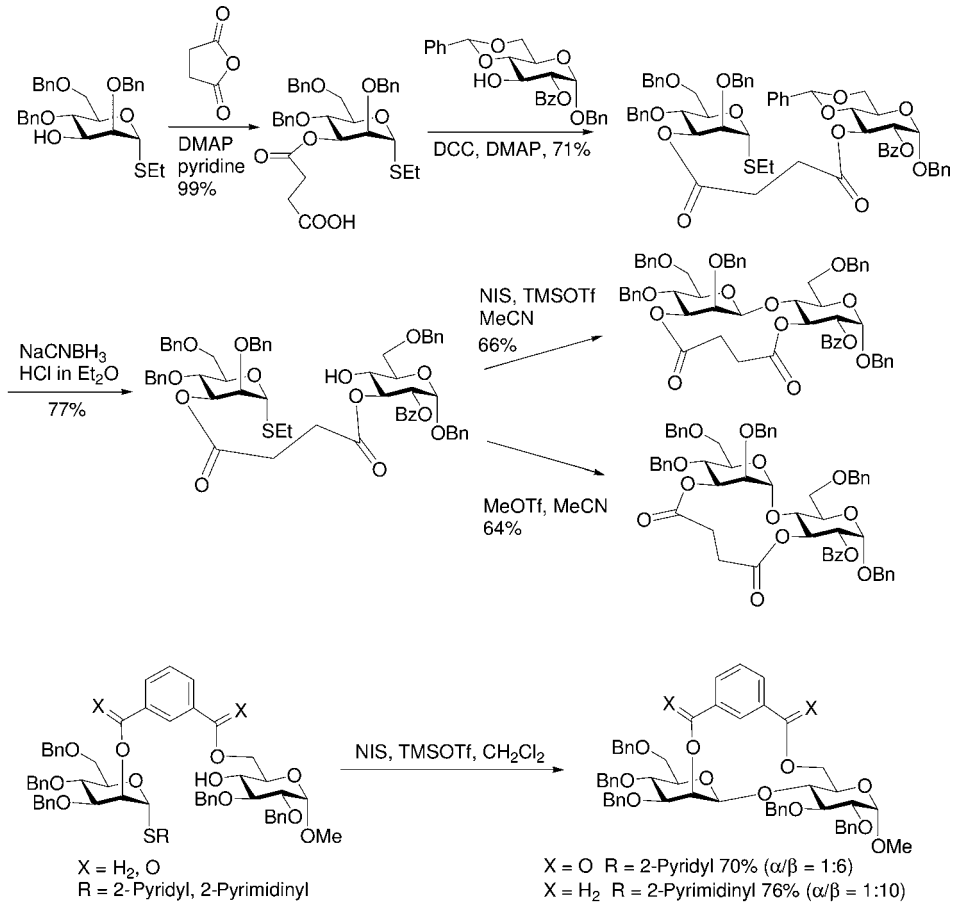
Table 5.6C (*Continued*)

Entry	Starting material	Product	Activation	Yield %	α : β	References
16			NIS, TMSOTf, MeCN	72	23:77	[314]
17			NIS, TMSOTf, MeCN MeOTf, MeCN	66 64	β only α only	[315] [316]
						
18	X = Carbonyl		NIS MeOTf (1) MCPBA (2) Tf_2O	— — 79%	— — α only	[317]
	Oxalyl		NIS MeOTf	— —	— —	[317] [317]
			(1) MCPBA (2) Tf_2O	75%	α only	[317]
	Malonyl		NIS MeOTf	51% 52%	β only β only	[317]
			NIS	70%		[317]
	Succinyl		MeOTF	70%	61:39 39:61	
	Phthaloyl		NIS MeOTf	69% 63%	89:11 86:11	[317]

summarizes the most significant examples with respect to anomeric selectivity and yield of the glycosylation step. It must be noted that it is still rather difficult to predict the outcome of such intramolecular glycosylations via prearranged glycosides though.Tables 5.6A–5.6C.

As can be seen from the data in Tables 5.6A–5.6C, the outcome of the intramolecular glycosylations via prearranged glycosides is somehow confusing. Especially in the manno series, the stereoselectivity of the glycosylation is governed not only by the tether and the position to which it is linked but also by the activation procedure of the donor moiety (Tables 5.6A–5.6C, entries 15–18). In one case, the anomeric selectivity was even inverted depending on the activation procedure [315,317]. Another efficient β-mannosylation uses more rigid *m*-xylylene tethers [318] (Scheme 5.111).

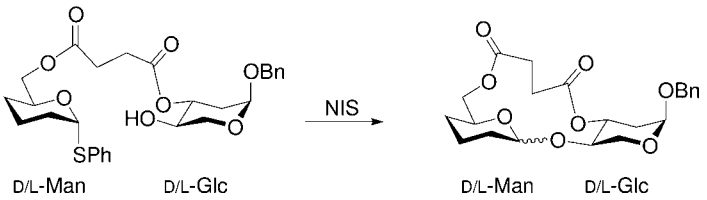
One aspect, besides the size of the ring that forms upon intramolecular glycosylation, governing the stereoselective outcome using this concept has been shown to be



Scheme 5.111 Mannosylation via prearranged glycosides.

the site where the tether is attached to the donor and the configuration of the positions in the acceptor where the tether is bound and where the glycosylation occurs (1,2- versus 1,3-diols, and D/L-*threo* or D/L-*erythro*) [308,309]. It was also shown that a double asymmetric induction influences the anomeric selectivity of the intramolecular glycosylation. For example, this was shown for the pair D/L-mannose donor and D/L-glucose acceptor prearranged by a succinyl tether via positions 6 of the mannose and position 3 of the glucose moieties for a 1,4-glycosylation (Scheme 5.112). Here, no significant change in the stereoselectivity of the intramolecular glycosylation step was observed upon changing the topographic properties of the pairs whereas an inversion was found upon changing the geometric properties [319].

The regioselectivity of glycosylations via prearranged glycosides is even more intriguing. Valverde *et al.* have reported several examples that are summarized in Table 5.7 [320–324]. Although it has been shown that the tethering has a dramatic influence on the regioselectivity compared to the corresponding intermolecular



Donor	Acceptor	Yield%	α/β Ratio
L-Man	L-Man	76	65:35
D-Man	D-Man	70	68:32
L-Man	L-Man	75	44:56
D-Man	D-Man	78	30:70

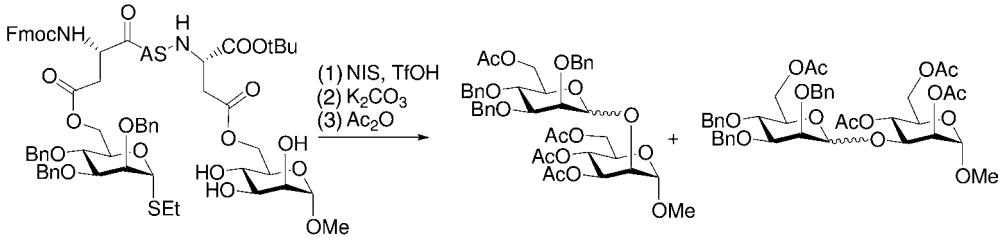
Scheme 5.112 Double asymmetric induction.

glycosylations [324], more examples are still needed to deduct more general rules for predicting selectivity.

Yet another approach uses peptides as tethers for intramolecular glycosylations via prearranged glycosides (Scheme 5.113) [326,327]. The regio- and anomeric selectivity of the intramolecular glycosylation depends on the amino acid sequence of the peptide, which links glycosyl donor and acceptor.

Despite the still virulent difficulties for predicting the outcome of intramolecular glycosylations via prearranged glycosides, several examples of complex oligosaccharide syntheses using this approach had been published. Müller and Schmidt demonstrated the usefulness of the 'rigid spacer concept' via *m*-xylylene tethers with a stepwise synthesis of maltotriose by applying two consecutive intramolecular glycosylation steps [328] (Scheme 5.114).

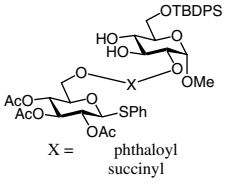
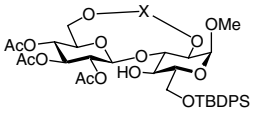
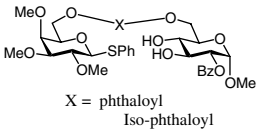
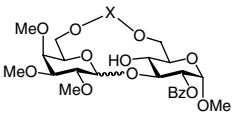
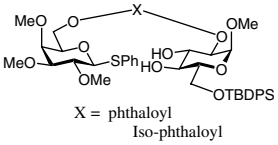
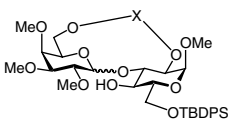
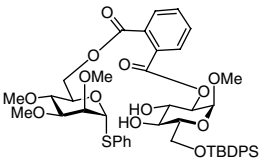
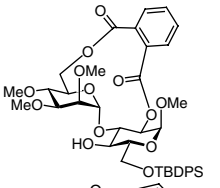
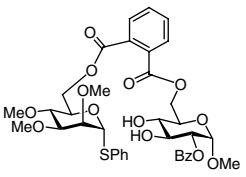
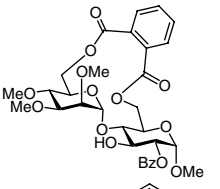
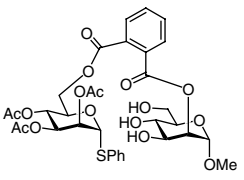
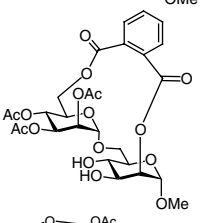
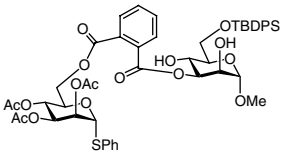
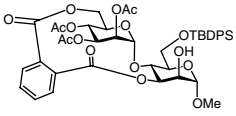
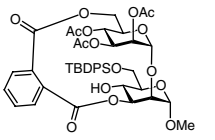
An efficient synthesis of the pyruvated repeating unit of the *exo*-polysaccharide of *Streptococcus pneumoniae* containing a β-linked L-rhamnosyl moiety was also



AS	α(1,2)%	β(1,2)%	α(1,3)%	β(1,3)%
—	—	13%	11	23
Gly	—	—	21	20
Phe	—	—	13	18
Pro	14%	16%	—	19
GlyGly	—	—	—	56

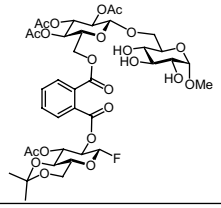
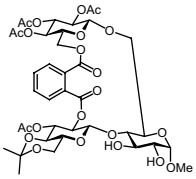
Scheme 5.113

Table 5.7 Regioselectivity in intramolecular glycosylations via prearranged glycosides.

Entry	Starting material	Product	Activation	Yield %	Linkage	α:β	References
1	 X = phthaloyl, succinyl		NIS, TfOH, 0°C–25°C	80 65	1,3 1,3	— —	[320] [320]
2	 X = phthaloyl, Iso-phthaloyl		NIS, TfOH, CH_2Cl_2, 0°C	72 47	1,3 1,3	58:42 α only	[323] [323]
3	 X = phthaloyl, Iso-phthaloyl		NIS, TfOH, CH_2Cl_2, 0°C	72 47	1,3 1,3	72:28 α only	[323] [323]
4			NIS, TfOH, CH_2Cl_2, 0°C	76	1,3	α only	[323]
5			NIS, TfOH, CH_2Cl_2, 0°C	72	1,4	α only	[323]
6			NIS, AgOTf, CH_2Cl_2	48	1,6	α only	[322]
7		 	NIS 25°C	25 75	1,3 1,2	α only α only	[324] [324]

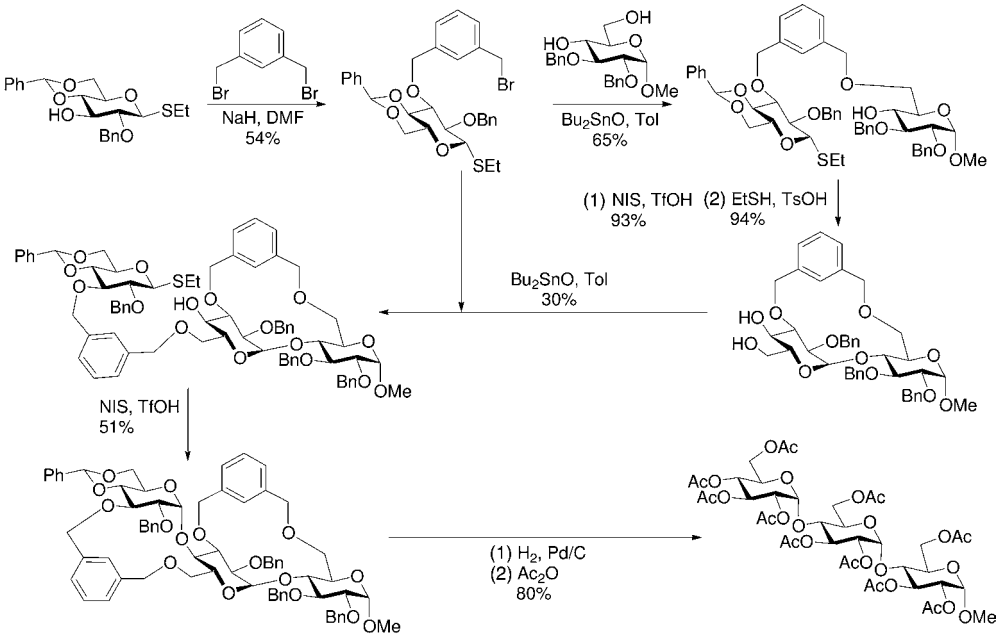
(*continued*)

Table 5.7 (*Continued*)

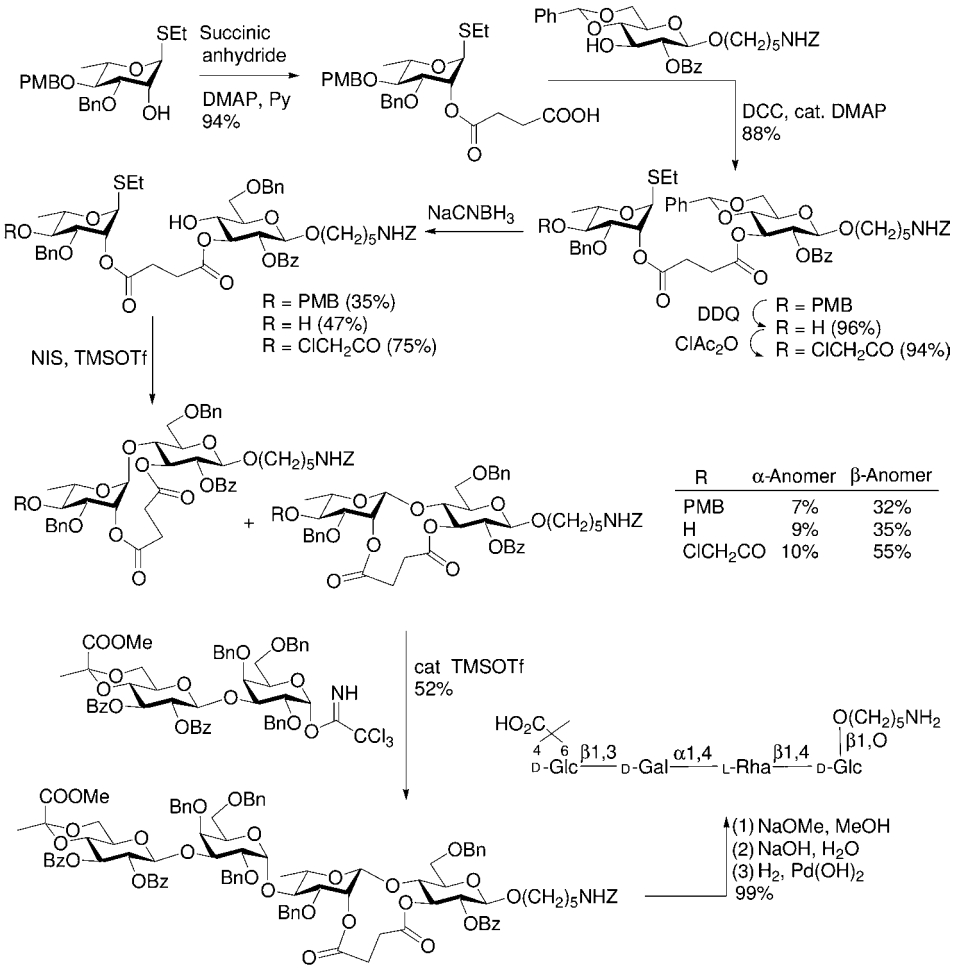
Entry	Starting material	Product	Activation	Yield %	Linkage	α:β	References
8			Cp_2HfCl_2, AgOTf	37	1,4	β only	[325]

established through intramolecular glycosylation (Scheme 5.115) [329] Here, starting from monosaccharide precursors, prearranged succinyl-tethered L-Rha-Glc-glycosides were first prepared by a standard condensation/reduction sequence, and their intramolecular rhamnosylation was studied. Next, the β-linked disaccharide building block obtained in 55% yield was converted into the desired tetrasaccharide 5-aminopentyl glycoside in one step. The latter may serve as an antigen for synthetic vaccines against *S. pneumoniae* infection.

Intramolecular glycosylations via prearranged glycosides can also be combined with common strategies usually applied for the synthesis of complex oligosaccharides. For example, prearranged glycosides can be combined with the strategy of armed and disarmed glycosyl donors as outlined in Scheme 5.116 [330]. Once again, in a standard condensation/reduction sequence, an armed ethyl 1-thio-mannosyl



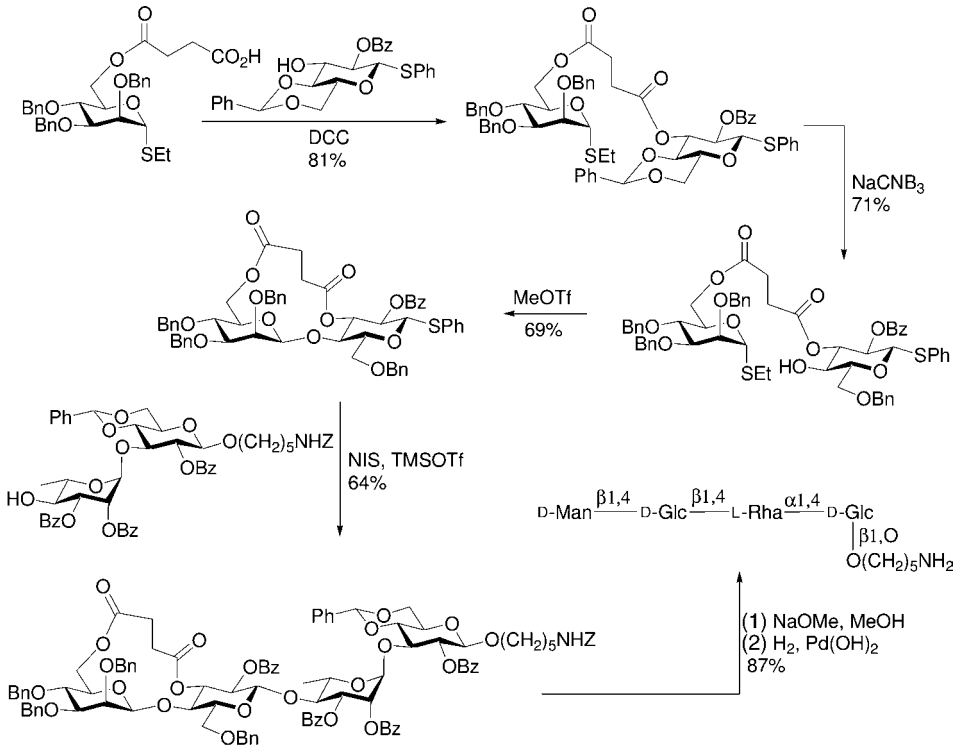
Scheme 5.114



Scheme 5.115

donor was succinyl tethered with a disarmed phenyl 1-thio-glucosyl donor that also functions as an acceptor for the intramolecular glycosylation step. Activation of the mannose donor in the prearranged glycoside with methyl triflate gave the β-linked disaccharide in 69% yield, which upon activation with *N*-iodosuccinimide was coupled to disaccharide acceptor in 64% yield. Thus, a tetrasaccharide 5-aminopentyl glycoside related to the exopolysaccharide of *Arthrobacter sp.* could be prepared in just a few steps.

Another significant improvement of the prearranged glycoside concept are non-symmetric tethers that allow flexible oligosaccharide syntheses [331]. As shown in Scheme 5.117, brommethyl benzoates are well suited for that purpose. Alkylation of either the glycosyl donor or the glycosyl acceptor followed by condensation with the respective counterpart donor or acceptor results in tethered glycosides that after intramolecular glycosylation and saponification of the tether afford disaccharides



Scheme 5.116

suitable for further chain elongation at different positions. Nonsymmetric tethers have also been applied for iterative intramolecular glycosylations [332].

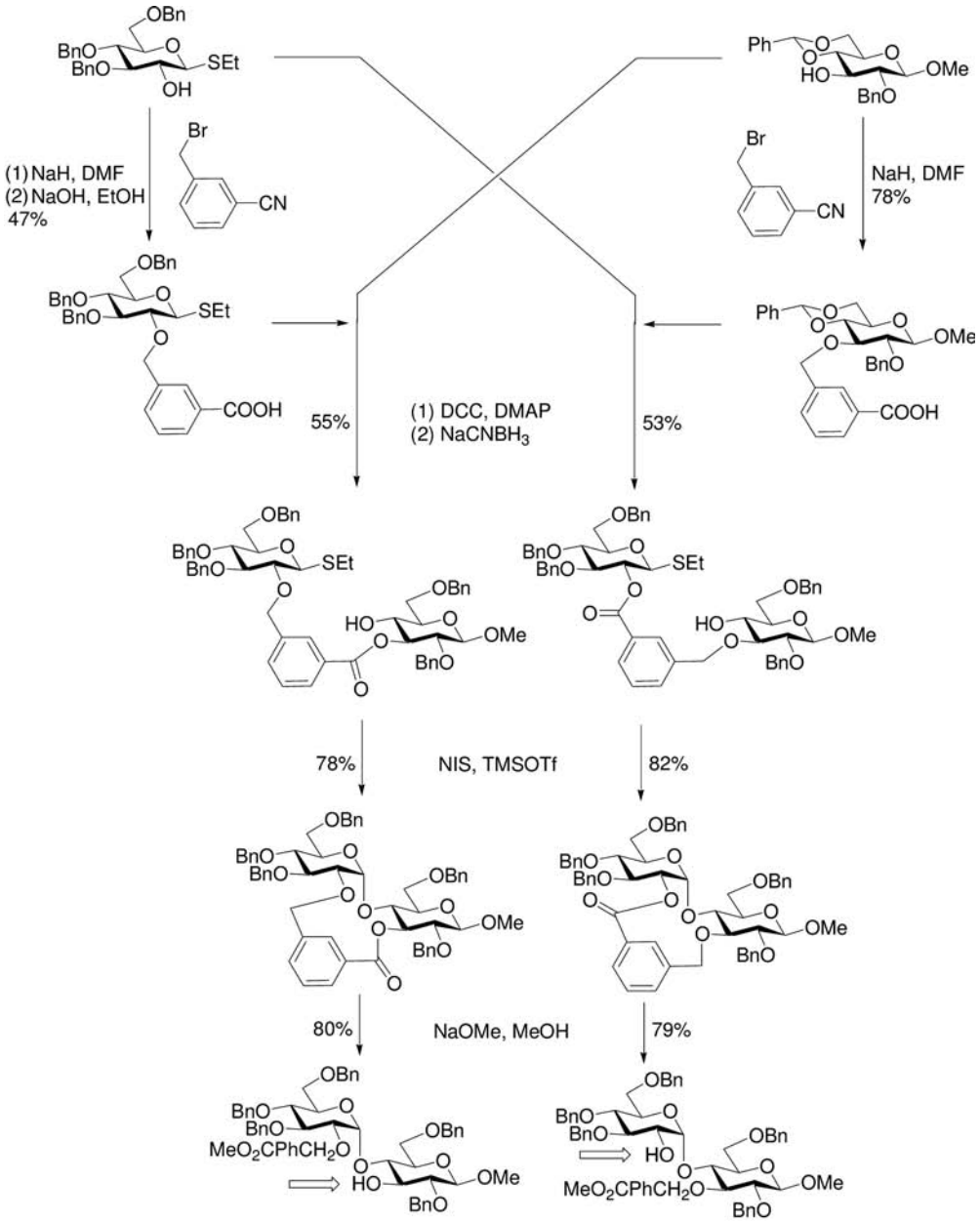
The strategy via nonsymmetrical tethers has also been applied to the synthesis of pentasaccharides related to the repeating unit of *Shigella sp.* (Scheme 5.118) [333]. Here, *o*-brommethyl benzoate was used as nonsymmetrical tether for the synthesis of a Glcα(1,4)GlcNAc disaccharide donor that was used for the preparation of the pentasaccharides either directly or after regioselective opening of the tether with concomitant chain extension at position 3 of the GlcNAc moiety.

5.4.2 Other Indirect and Special Methods

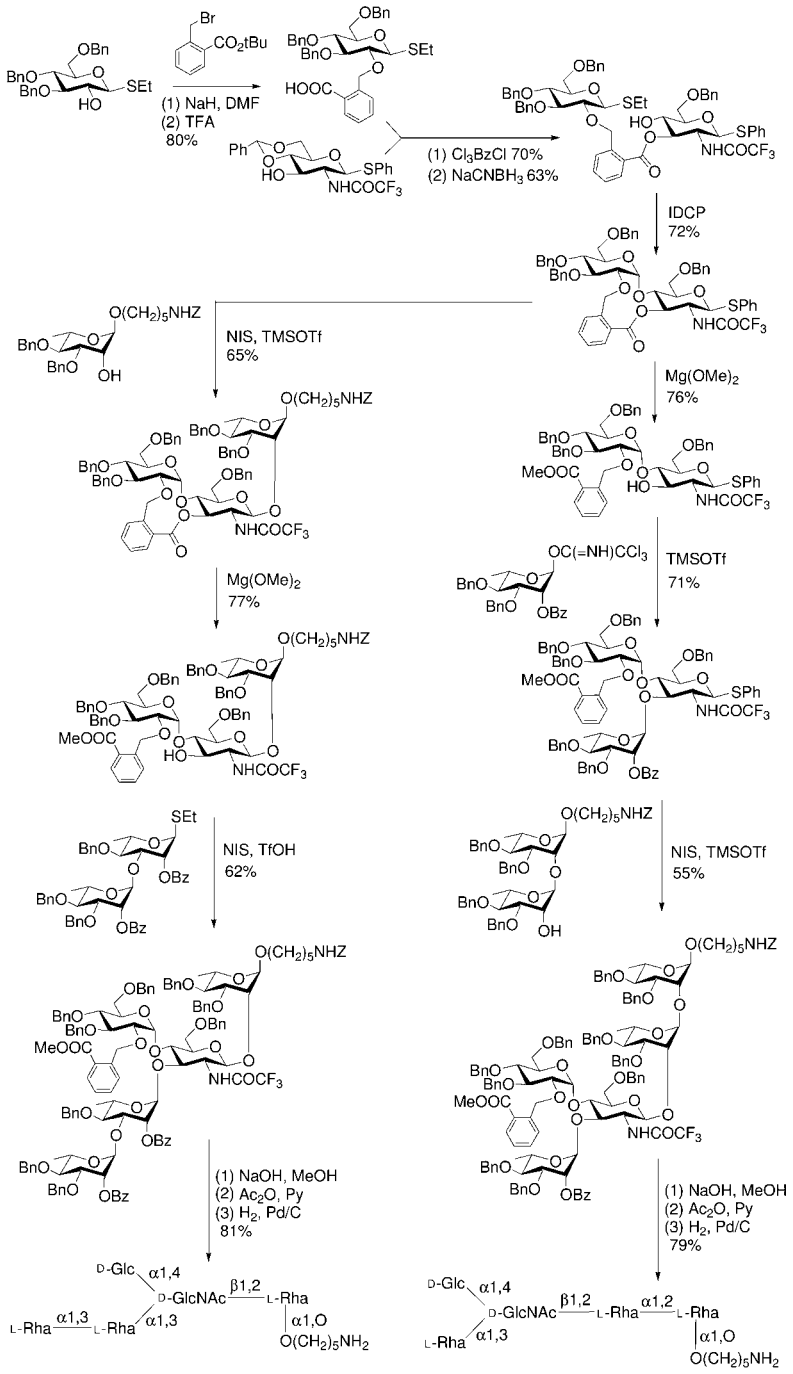
There are several other indirect and special methods that have not found any broader application for glycoside and saccharide synthesis yet but that might be useful for certain cases or might develop into more common procedures in the future. Such other indirect and special methods are discussed in this chapter.

5.4.2.1 [4 + 2] Cycloadditions of Glycals

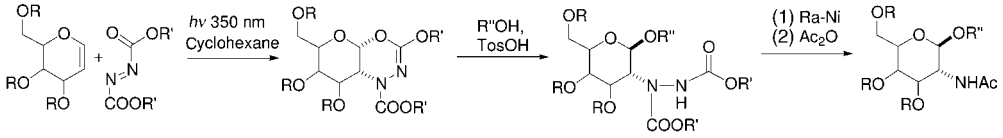
When irradiated with light, azidodicarboxylates react with glycals as dienophiles to give Diels–Alder adducts via formal [4 + 2] cycloadditions [334]. Upon treatment of


(1) NaH, DMF
(2) NaOH, EtOH
47%
NaH, DMF
78%
55%
(1) DCC, DMAP
(2) NaCNBH3
53%
78%
NIS, TMSOTf
82%
80%
NaOMe, MeOH
79%

Scheme 5.117


(1) NaH, DMF
(2) TFA
80%
(1) Cl3BzCl 70%
(2) NaCNBH3 63%
IDCP
72%
NIS, TMSOTf
65%
Mg(OMe)2
76%
Mg(OMe)2
77%
TMSOTf
71%
NIS, TfOH
62%
NIS, TMSOTf
55%
(1) NaOH, MeOH
(2) Ac2O, Py
(3) H2, Pd/C
81%
(1) NaOH, MeOH
(2) Ac2O, Py
(3) H2, Pd/C
79%
D-Glc
D-GlcNAc
L-Rha
α1,4
β1,2
α1,3
α1,2
α1,O
O(CH2)5NH2

Scheme 5.118

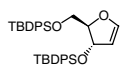
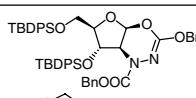
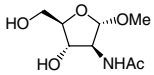
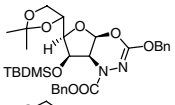
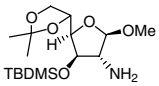
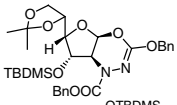
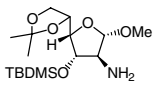
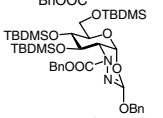
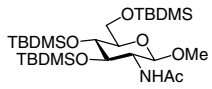
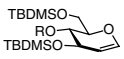
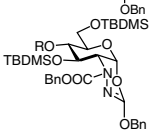
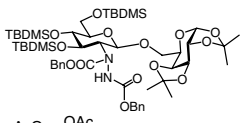
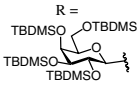
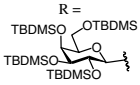
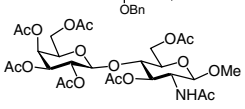


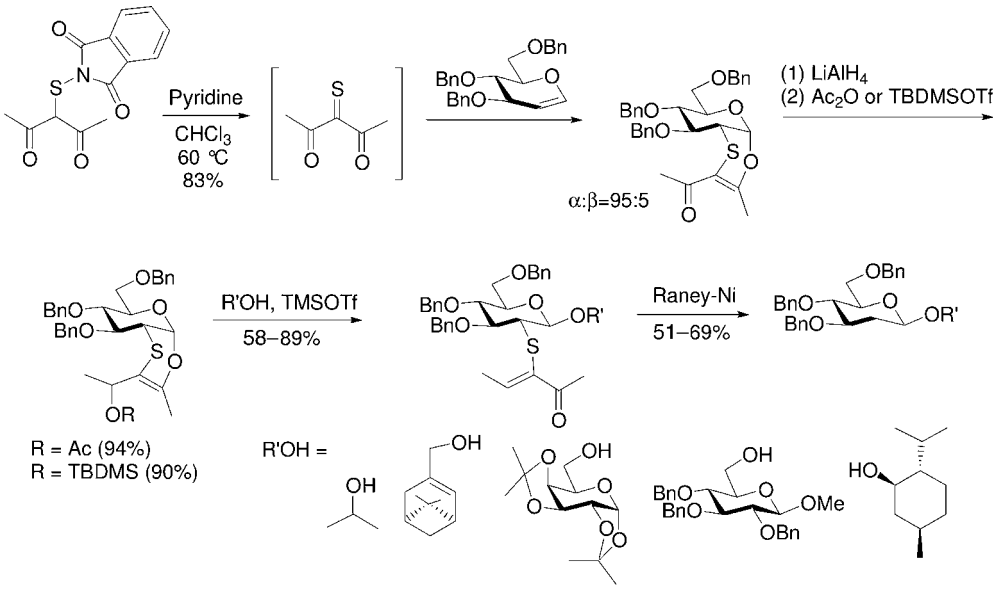
Scheme 5.119

these initial Diels–Alder adducts with alcohols under acidic conditions, 2-hydrazino-glycosides are formed stereoselectively that can be reduced to 2-amino-glycosides (Scheme 5.119). The initial cycloadducts are *cis*-configurated and are opened with alcohols by a S_N2 mechanism giving exclusively 1,2-*trans*-configurated 1-aminoglycosides.

Table 5.8 summarizes the glycals that had been converted into 2-aminoglycosides so far. In general, photolytic *cis*/*trans* isomerization of *trans*-azodicarboxylates is necessary to accomplish good yields of the initial cycloadducts [335–337]. However, bis-trichloroethyl azodicarboxylate also reacts under thermal conditions and also gives a more reactive cycloaddition product [338,339].

Table 5.8 [2 + 4] Cycloadditions according to Scheme 5.19.

Entry	Glycal	[4+2] Adduct	Yield %	Alcohol	Product	Yield %	References
1			70	MeOH		64	[335]
2			73	MeOH		84	[335]
3			80	MeOH		78	[335]
4			71	MeOH		63	[335]
5							
	R = TBDMS	R = TBDMS	71			95	[336]
6	R = 	R = 	92	MeOH		48	[339]



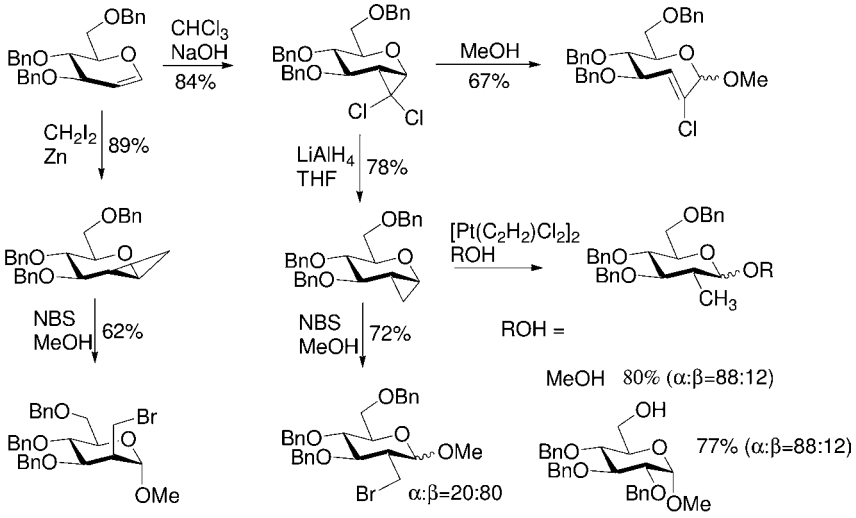
Scheme 5.120

Yet another hetero-dien for cycloaddition reactions of glycals that had been used for the preparation of 2-deoxyglycosides is 2,4-dioxo-3-thioxo-pentane, generated *in situ* from 3-thiophthalimido-pentane-2,4-dion. The cycloaddition occurs with high 1,2-*cis* selectivity, giving thioxins [340,341]. The latter can be reacted with alcohols under Lewis acid catalysis to afford 2-thio-glycosides that finally give 2-deoxy-glycosides upon desulfuration with Raney-Ni. [342] (Scheme 5.120). Yields are medium to high, but more examples need to be investigated to judge the broad applicability of this approach. At least this special method is a considerable alternative for the preparation of β-2-deoxy-glycosides that are otherwise difficult to obtain.

5.4.2.2 **1,2-Cyclopropanated Sugars**

1,2-Cyclopropanated sugars, easily available from glycols [343,344] react with alcohols to give 2-*C*-branched glycosides. As both diastereomeric cyclopropanated sugars can be obtained, this special method for the preparation of glycosides is highly flexible and affords a wide variety of 2-*C*-branched glycosides. For example, tri-*O*-benzyl-D-glycal affords the β-manno-configurated 1,2-cyclopropane derivative upon Simmons–Smith cyclopropanation, whereas the α-gluco-configurated counterpart is obtained through cyclopropanation with dichlorocarbene followed by dehalogenation. Upon methanolysis, the dichlorocyclopropane sugar reacts under ring opening to give an oxepine derivative whereas the cyclopropane counterparts afford the corresponding 2-bromomethyl mannosides and glycosides when treated with NBS and methanol [344]. 2-*C*-Methyl glycosides can be obtained by Pt-catalyzed ring opening of the cyclopropane ring [254,345] (Scheme 5.121).

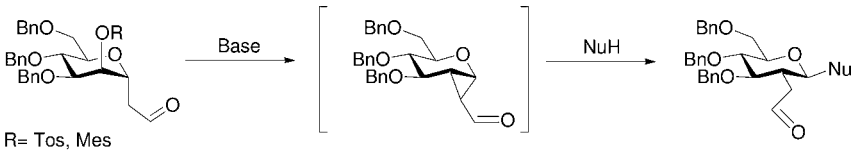
Similarly, *tri-O*-benzyl-glucal affords the corresponding manno-configurated methoxycarbonyl cyclopropanes upon treatment with methyl diazoacetate under



Scheme 5.121

rhodium acetate catalysis [346]. The latter can get opened at the cyclopropane ring with NIS and methanol, and the formed intermediates can be converted into 2-*C*-aminomethyl-glycosides.

Yet another indirect method for the preparation of *O*-glycosides makes use of intermediate cyclopropanated sugars. Treatment of benzyl-protected 2-(*C*-2-*O*-mesyl-α-D-mannosyl)acetaldehyde with alcohols and base results in the intermediate formation of cyclopropanated sugar that undergoes immediate ring opening to afford the corresponding 2-*C*-formylmethyl glycosides [347,348] (Scheme 5.122). The method is also suitable for the preparation of 1-thio-glycosides and glycosyl azides.



R	Base	NuH	Yield%
Mes	Et_3N	MeOH	72
Mes	Et_3N	EtOH	71
Tos	Et_3N	H_2C=CH-CH_2OH	76
Tos	K_2CO_3	H_2C=CH-$(CH_2)_4$OH	78
Tos	K_2CO_3	Ph-CH_2OH	75
Tos	K_2CO_3	Ph-OH	62
Tos	K_2CO_3	Ph-SH	86
Tos	K_2CO_3	*p*-MeOPh-SH	85
Tos	K_2CO_3	*p*-ClPh-SH	83
Tos	Et_3N	NaN_3/MeOH	52

Scheme 5.122

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Index

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