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Minireview

Recent advances in the synthesis of 2-deoxy-glycosides

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ABSTRACT

Glycosides of 2-deoxy-sugars, monosaccharides in which the hydroxyl group at C-2 is replaced with a hydrogen atom, occur widely in natural products and therefore have been the subject of intense synthetic activity. The report summarizes recent advances in this area, with a particular focus on work published since an earlier review on the topic, in 2000 (Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385–8417).

Contents

1. Introduction

2-Deoxy-sugars, monosaccharides in which the hydroxyl group at C-2 is replaced with a hydrogen atom, are an important class of carbohydrates that occur widely in natural products.[1–3] Notably, 2-deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) is present in DNA as the skeletal sugar component. Other examples of such molecules are the 2,6-dideoxy-hexoses. All diastereomers of the 2,6-dideoxy-hexoses (Fig. 1) occur in nature and have been found to influence the biological activity of the molecules in which they are contained.[4] In particular, 2,6-dideoxy-hexoses are frequently present in antibiotics and anti-cancer agents such as anthracyclines, angucyclines, aureolic acid antibiotics, cardiac glycosides, enediynes, macrolides, and pluramycins.[1–3,5] Often, the occurrence of the deoxy-sugar components is crucial for the pharmacology and bioactivity of the drug.[6,7]

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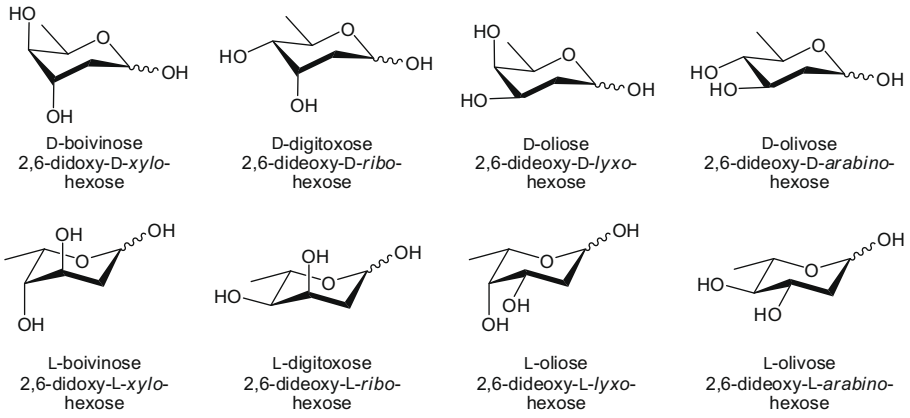


Figure 1. Examples of naturally occurring 2,6-dideoxy-hexoses.

1.1. General features of the 2-deoxy-glycosidic bond

As recognition of the biological importance of 2-deoxy-sugars has increased, so too have efforts to develop chemical methods for the assembly of oligosaccharides containing these residues.[5,8] However, once deoxygenation at C-2 of a glycosyl donor has been performed, the construction of the glycosidic bonds in a stereocontrolled fashion becomes a challenge. As outlined below, the absence of groups at C-2 that can act to direct the reaction often leads to syntheses of 2-deoxy-glycosides as mixtures of anomers. Another consideration is that 2-deoxy-glycosides can be more difficult to manipulate compared to the C-2 hydroxylated analogues because of their greater susceptibility to hydrolysis.[9]

1.2. Factors governing 2-deoxy glycosidic bond formation

Glycosidic bond formation is a complex process[10] that is often governed by the anomeric effect, which promotes axial (usually α-) glycoside formation.[11] The anomeric effect is the preference for the axial orientation of electronegative substituents, such as halides, and *O*-alkyl, *O*-aryl, *S*-alkyl, *S*-aryl derivatives, when they are attached to the anomeric center of a pyranose ring.[12,13] A widely accepted explanation for the anomeric effect is that the electron-withdrawing axial substituent (the α-anomer for D-sugars in the $^4C_1$ conformation) is stabilized by hyperconjugation between an unshared electron pair on O-5 and anti-bonding (σ^*) orbital of the axial (exocyclic) C–X bond (Fig. 2).[13]

With this background in mind, a more detailed discussion of glycosidic bond formation in 2-deoxy-sugars can be considered. The reaction pathways available to an oxocarbenium ion (**III**) with a substituent at C-2 that cannot stabilize the positive charge by participation (e.g., H) are shown in Figure 3. Such an oxocarbenium ion can be generated either by promoter-assisted departure of the leaving group from an activated donor (**I**) or, less commonly, by the addition of a proton (Y = H^+) to a glycal (**II**). The positive charge at the anomeric center in **IV** is stabilized by resonance from O-5. The nucleophile can react with the oxocarbenium ion from one of the two faces of the ring, which adopts a half-chair conformation. When a nucleophile approaches from the axial face, hyperconjugation between the one of the non-bonding orbitals of the ring oxygen and the anti-bonding orbital of the developing bond helps to stabilize the transition state, which resembles a chair conformer. This interaction is often referred to as the kinetic anomeric effect.[14] In contrast, when the nucleophile attacks from the equatorial face, in order for the appropriate orbital overlap to be present the transition state must develop as a boat-like species. This boat-like transition state is of higher energy than the chair-like transition state; therefore, the axial linkage is preferred.

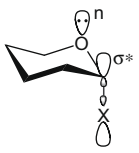


Figure 2. Stabilization of an axial C–X bond at the anomeric center of a pyranose ring by the anomeric effect.

Thus, in the synthesis of 2-deoxy-glycosides in which the group at C-2 is the non-participating hydrogen atom, the anomeric effect leads to the preferential formation of the α-glycoside. The selectivity of these reactions is, however, often not complete and various factors such as temperature, protecting group, solvent, promoter, and the leaving group affect actual glycosylation outcomes, including yield and stereoselectivity. Nevertheless, the important conclusion from this discussion is that the stereocontrolled formation of equatorial (usually β-) glycosides by this approach is difficult.

If one wants to prepare the equatorial 2-deoxy-glycosides, the most common method is an indirect approach, which is shown in Figure 4. In this case, the neighboring group participation of a C-2 substituent is used as a control element in the glycosylation reaction. The neighboring group Y is often a halogen, sulfur, or selenium, which can be introduced either several steps before the glycosylation reaction or during the reaction by use of a glycal donor. When this group is axial, it is proposed that participation leads to an intermediate in which the β-face is blocked, which favors attack. Alternatively, when this participating group is equatorial, the formation of a β-glycoside is possible. Following glycosylation, the C-2 substituent is removed to give the 2-deoxy-glycoside. The drawbacks of this strategy are that it requires two steps, and that the group at C-2 must be initially installed with the appropriate configuration. It should be mentioned that direct evidence for the participation of this substituent is, in most cases, lacking, and it is also possible that the stereocontrol arises simply from negative steric or electrostatic interactions between the incoming nucleophile and the (typically bulky) directing group at C-2.[15–19]

2. Scope

To date, a variety of approaches for the synthesis of 2-deoxy-glycosides in high yield and stereoselectivity have been developed. In 2000, Marzabadi and Franck compiled the progress in this area for the period 1988–1999.[8] In addition, studies focusing mainly

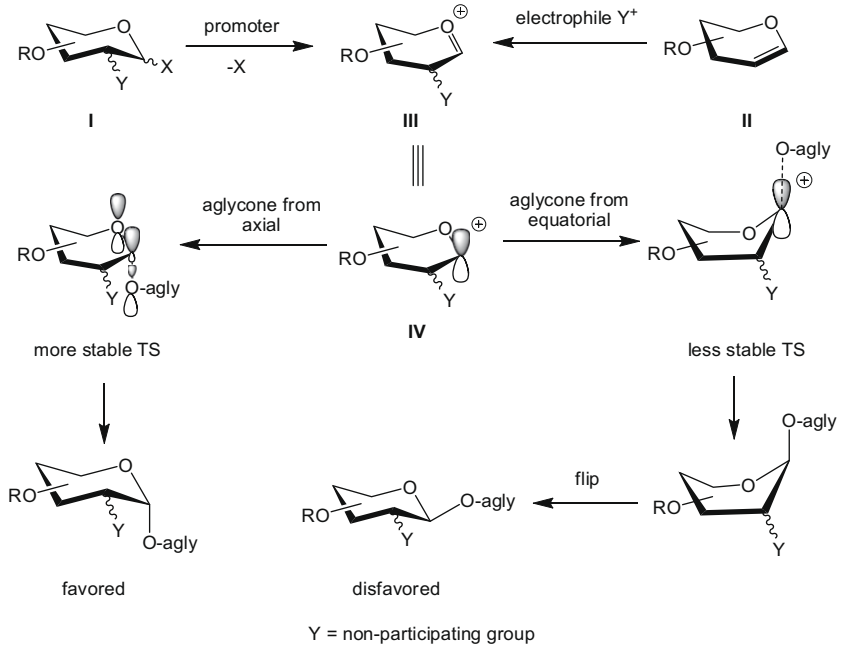


Figure 3. Glycosylation process with a non-participating group at C-2 position.

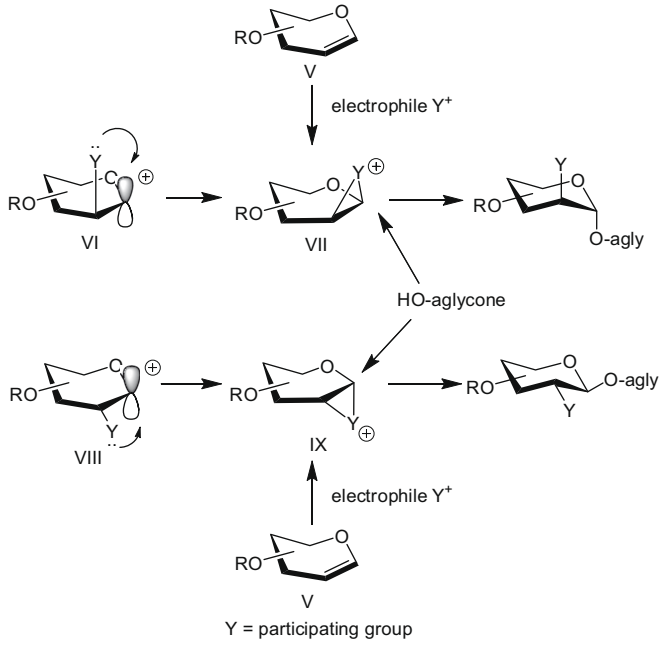


Figure 4. Glycosylation process with a participating group at C-2 position.

on the biochemical aspects of 2-deoxy-sugars and the mechanistic aspects of deoxy-sugar formation were reviewed in 1997,[2] 1999,[20] 2000,[1] and 2002.[3] More recently, a review on the synthesis and occurrence of deoxy-sugars, including the 2-deoxy-sugars, has appeared, but glycosylation methods were not included in the coverage.[4]

The objective of this review is to summarize recent progress toward establishing reliable chemical methods for the efficient preparation of 2-deoxy-glycosides and the application of these methods to suitable target molecules. The focus here is on work reported since the Marzabadi and Franck review,[8] and the coverage has been limited such that the synthesis of 2,3-dideoxy-glycosides by the Ferrier rearrangement[21] and enzymatic synthesis of 2-deoxy-glycosides are not covered. In addition, the formation of glycosides of sialic acid (*N*-acetylneuraminic acid) is not discussed because glycosylation reactions of this particularly unique '2-deoxy-sugar' have been the subject of a number of reviews.[22–24]

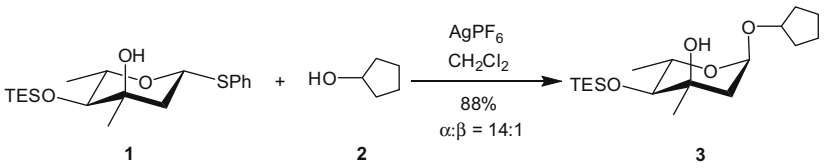
In the coverage below, the syntheses are organized by donor type. Use of thioglycosides is presented first, followed by the use of activated oxygen derivatives, glycosyl halides, and then glycals. These sections are further divided by methods that can be used for 'direct' and 'indirect' synthesis of 2-deoxy glycosides. The former are those that use 2-deoxy-glycosyl donors while the latter involve donors containing a group at C-2 that is reduced following glycosylation. A section describing the application of these methods to natural product synthesis is also included, as is a discussion of de novo approaches to 2-deoxysugar glycosides.

3. Use of thioglycoside donors

3.1. Direct synthesis

Thioglycosides are one of the most popular donors for glycosylation reactions,[25,26] and these species have been widely used as donors for the formation of 2-deoxy-glycosidic linkages via both direct and indirect approaches. For example, Hirama[27] and coworkers reported that $AgPF_6$ is a useful activator for α-selective glycosylation of 2-deoxy-thioglycoside donors (Scheme 1), and this method was broadly applied to 2-deoxy-thioglycoside systems such as those derived from L-mycarose, L-kedarosamine, L-digitoxose, L-olivomycarose, and D-olivose. One example is the coupling between the β-thioglycoside of L-mycarose (**1**) and cyclopentanol (**2**) (Scheme 1) in dichloromethane with the use of $AgPF_6$ as the sole promoter. This reaction gave a mixture of glycosides enriched in the α-anomer (α/β = 14:1, 0 °C, 2 h).

In other studies, three simple alcohols, phenethyl alcohol, *t*-BuOH, and *i*-Pr_2CHOH were screened as acceptors to test the scope of the methodology. It was shown that when both the phenylthio- and ethylthio-2-deoxy-glycosides were activated with $AgPF_6$–DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) and an alcohol acceptor (2–3 equiv), the corresponding 2-deoxy-glycosides were



Scheme 1. Glycosylation between **1** and **2** promoted by AgPF6.[27]

produced in 75–99% yields. When the reaction was performed at 0 °C for 0.5–2 h, the α-selectivity varied from 1:1 to 1:0 α:β. With other silver promoters (e.g., AgOTf), the selectivity was lower. It is interesting to note that with the L-olivomycarose donor **4**, the α:β ratio selectivity (1:8.1) is inverted using the same conditions (Scheme 2). However, the authors did not provide the yield of this reaction.

Despite the high selectivity of the reaction, no mechanistic work addressing the selectivity was provided. The method has, however, been used by other groups to synthesize analogues of doxorubicin, a clinically used anti-cancer agent that possess an α-linked 2,6-dideoxy-sugar moiety.[28–30]

In another study involving thioglycoside donors, Ye and co-workers have recently described an efficient method for the highly α-stereoselective formation of 2-deoxy-glycosides using a pre-activation approach.[31] The pre-activation procedure refers to the complete activation and consumption of the glycosyl donor to generate a reactive intermediate (e.g., a glycosyl triflate) in situ prior to the addition of the alcohol acceptor. In this investigation, a series of 3,4-*O*-carbonate protected thioglycoside donors were treated with a panel of acceptor alcohols. One example, in which the 2,6-dideoxysugar thioglycoside **7** was reacted with the glucose-derived alcohol **8**, is shown in Scheme 3. Glycosylations were performed at −72 °C in dichloromethane using benzenesulfinyl morpholine (BSM) and triflic anhydride (Tf_2O) as the promoter system. The coupling reactions proceeded with exclusive α-selectivity and in 87% yield.

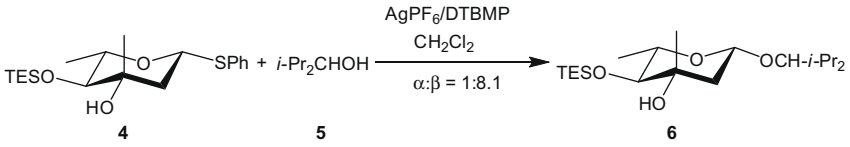
The authors proposed that the high α-selectivity resulted from the formation of a highly reactive β-glycosyl triflate intermediate after preactivation of the thioglycoside. After addition of the alcohol, this species would form the α-glycoside by way of an S_N2-like displacement reaction. The presence of 3,4-*O*-carbonate protecting group in the glycosyl donor was suggested to be essential to enhance the α-selectivity due to its ability to act as conformational constraint. However, a detailed description of this conformational effect, or experimental studies attempting to detect the presence of glycosyl triflate intermediates, was not reported.

In another study, Paul and Jayaraman described a facile preparation of either α- or β-2-deoxy-glycosides from a common 2-deoxy-thioglycoside donor, and applied this methodology to the synthesis of a series of 2-deoxy-disaccharides.[32] By employing the thiophilic activator *N*-iodosuccinimide–triflic acid (NIS–TfOH), 3,4,6-tri-O-acetylated donors (e.g., **10**, Scheme 4) were treated with seven different substituted phenols and naphthols in dichloromethane to afford the corresponding α-glycosides as the major products.

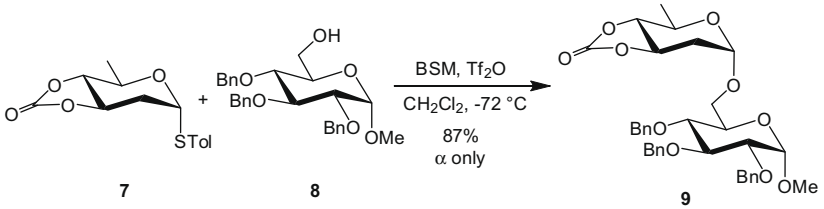
Studies of this NIS–TfOH mediated glycosylation indicated that solvents greatly influenced the stereochemical outcome. For example, a change of solvent from acetonitrile to dichloromethane gave a significant increase in the amount of the β-anomer. The authors ascribed this to the formation of an α-glycosyl nitrilium ion[33] as a result of a reaction between the solvent acetonitrile and the α-face of the oxocarbenium intermediate. However, this solvent effect was not enough to completely invert the stereoselectivity of the reaction, and, at best, a 3:2 α:β ratio was produced.

Nevertheless, the 2-deoxy-β-glycosides can be prepared from the same precursor thioglycosides by a different reaction protocol.[32] In this approach (Scheme 5), the thioglycoside **10** is converted to the glycosyl bromide upon reaction with bromine in dichloromethane. Treatment of the crude glycosyl bromide with a THF solution of a phenoxide generated in situ from the phenol and LHMDS affords the β-glycosylated product in more than 90% yield, presumably via an S_N2-like mechanism.

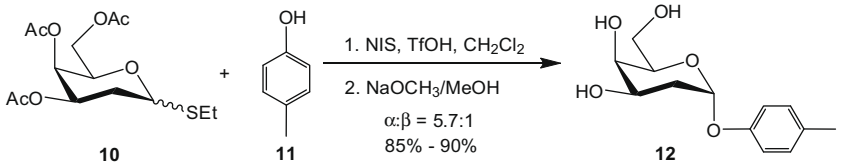
A polymer-assisted solution-phase approach to 2-deoxy-glycosides using thioglycosides as glycosyl donors, has been reported by Kirschning and co-workers (Scheme 6).[34] The use of polymer-supported reagents simplifies the work-up and purification to only filtration.[35,36] In the key glycosylation step, 2-deoxy-thiopyranosides were activated by functionalized polymers bearing a thiophilic promoter in the presence of various alcohols to afford the expected 2-deoxy-glycosides. Moderate to good α-selectivity (the α/β ratio ranged from 1.4:1 to 4:1) was observed when D-*arabino*-configured thiopyranosides (e.g., **14**) were employed. In



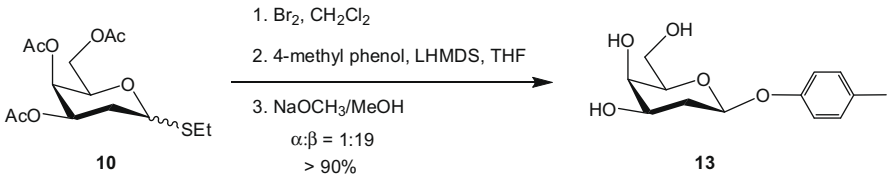
Scheme 2. Glycosylation between **4** and **5** under conditions reported by Hirama and co-workers.[27]



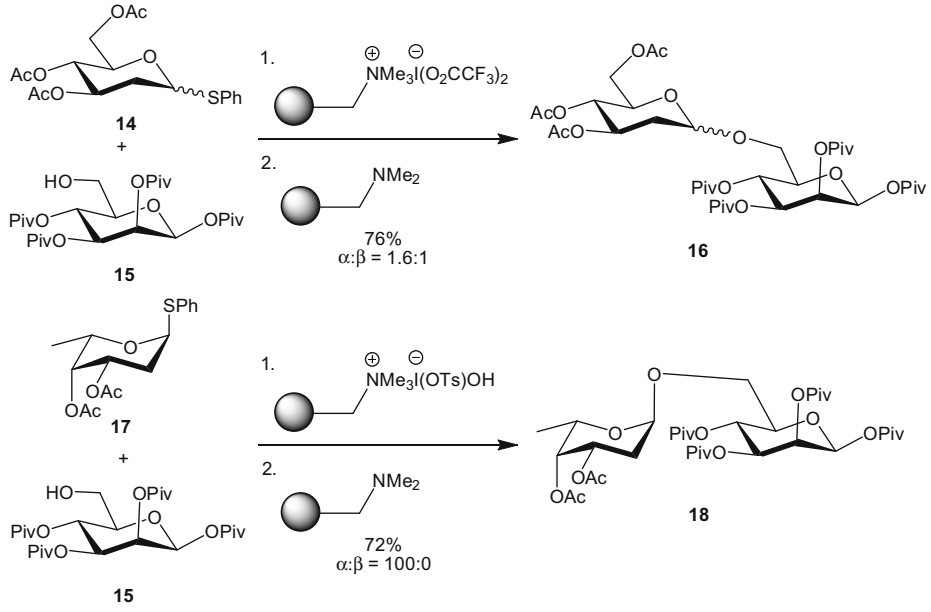
Scheme 3. Glycosylation of **8** with **7** under conditions developed by Ye and co-workers.[31]



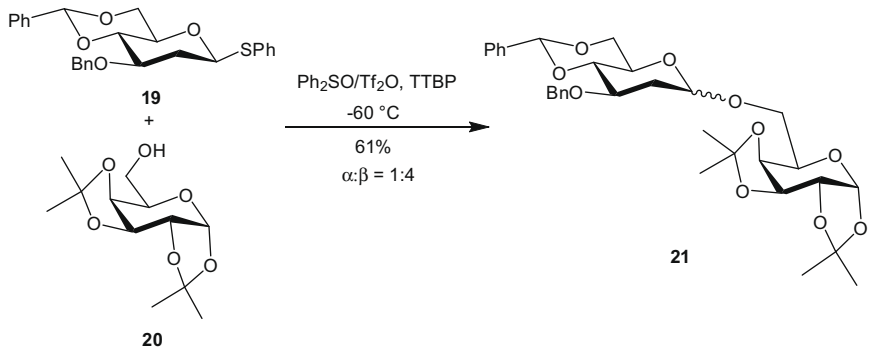
Scheme 4. Synthesis of aryl 2-deoxy-α-glycosides by Paul and Jayaraman.[32]



Scheme 5. Synthesis of aryl 2-deoxy-β-glycosides by Paul and Jayaraman.[32]



Scheme 6. Polymer-assisted solution-phase synthesis of 2-deoxy-glycosides by Kirschning and co-workers.[34]



Scheme 7. Glycosylation **19** with **20** as described by Crich and Vinogradova.[37]

contrast, L-*lyxo*-configured thiopyranosides (e.g., **17**) gave exclusively the α-anomers in good yields. The authors provided no rationale to explain the observed stereoselectivity.

In another study, Crich and Vinogradova[37] reported glycosylations with phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (**19**, Scheme 7). These reactions were achieved through activation of the donor with a combination of diphenyl sulfoxide (Ph_2SO) and triflic anhydride (Tf_2O) in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) at −60 °C, followed by the addition of the acceptor alcohol. A range of acceptors were

used, and the yields ranged from 30% to 75% but selectivity was modest to poor, ranging from a minimum of 1:1.5 α/β to a maximum of 4:1 α/β.

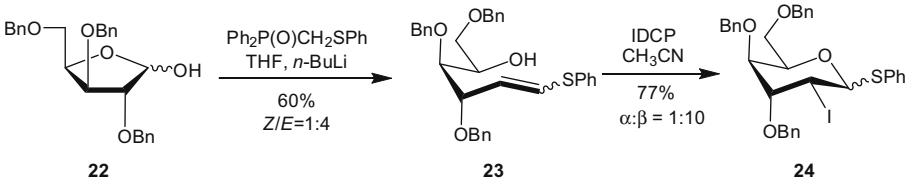
These studies were carried out to probe the mechanism and scope of the Crich β-mannopyranoside synthesis,[38,39] in which advantage is taken of a cyclic protecting group to generate significant quantities of α-mannopyranosyl triflates, which undergo an S_N2-like displacement upon addition of the alcohol. The lack of stereoselectivity in the glycosylation of **19** (a '2-deoxy-mannose' system) was ascribed to the instability of the corresponding glycosyl triflate, which in turn leads to high concentrations of an oxocarbenium ion that reacts with the acceptor to give glycoside mixtures. Indeed, low-temperature (−60 °C) NMR studies of the product mixture initially formed upon activation of **19** showed only trace amounts of the resonances expected for the glycosyl triflate intermediate.

3.2. Indirect synthesis

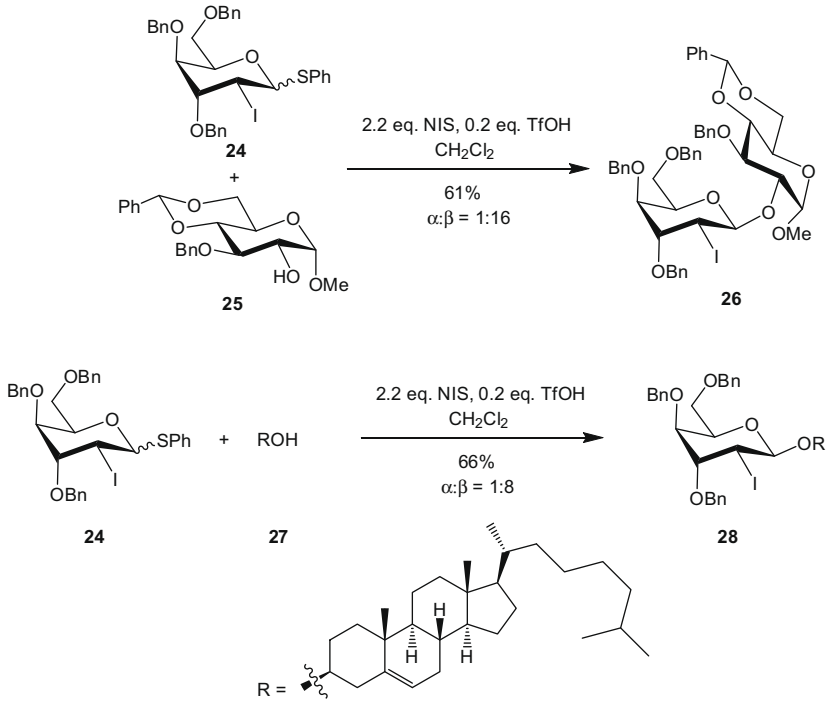
Recent investigations have also explored the use of thioglycosides possessing a substituent at C-2 for the preparation of 2-deoxy-glycosides. Although, in principle, this group can control the glycosylation stereocontrol by participation, in the cases described below an alternate rationale is provided. A new protocol, which utilizes phenyl 2-deoxy-2-iodo-1-thio-pyranosides as the glycosylating agents, has been developed by Castillón and co-workers.[40] The preparation of this type of glycosyl donor (Scheme 8) involved Wittig–Horner olefination of a protected pentose derivative and subsequent electrophilic cyclization induced by elemental iodine. For example, olefination of the 2,3,5-tri-*O*-benzyl-xylose (**22**) gave a *Z*/*E* mixture of alkenyl sulfanyl derivatives (**23**) in 60% yield. Generation of the thioglycosides was achieved under optimized conditions that involved cyclization using iodonium dicollidine perchlorate (IDCP) in acetonitrile, affording phenyl 2-deoxy-2-iodo-1-thio-gulopyranoside (**24**), as a 1:10 α/β mixture in 77% yield. Treatment of glycosyl donor **24** with methyl 4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (**25**, Scheme 9) or cholesterol **27** under typical activation conditions (NIS–TfOH) provided the corresponding products, **26** and **28**, in yields of 61% and 66% with an α/β ratio of 1:16 and 1:8, respectively.

The preference for the formation of the β-glycoside was rationalized on the basis of the reaction proceeding through one of two possible oxocarbenium ion conformers (**29** or **30**, Fig. 5). Although previous studies[41] indicated that **30** should be more stable than **29**, glycosylation of **30** in a stereoelectronically favored manner[14] would require the nucleophile to attack from the bottom face of the ring, which would be disfavored due to steric hindrance arising from the C-3 benzoyloxy group. On the other hand, the favored attack of the alcohol on **29** would proceed with less steric congestion and hence, although **29** is less stable, it is also the most reactive.

In a later study, Castillón and co-workers developed a 'one-pot' electrophile-induced cyclization–glycosylation sequence from the acyclic alkenyl sufanyl derivative to furnish the 2-deoxy-2-iodo



Scheme 8. Preparation of 2-deoxy-2-iodo-1-thio-D-gulopyranoside from 2,3,5-tri-*O*-benzyl-D-xylose.[40]



Scheme 9. Glycosylation of **25** and cholesterol **27** with 2-iodo-thioglycoside **24** as described by Castillon and co-workers.[40]

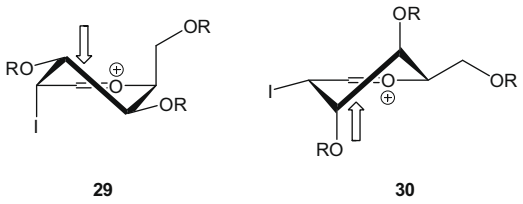


Figure 5. Pyranosyl oxocarbenium ions **29** and **30**.[40]

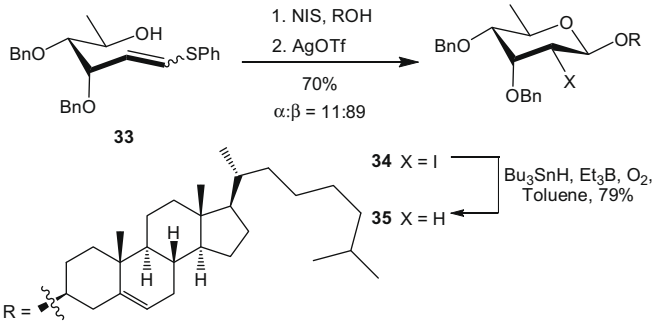
glycosides directly (Scheme 10).[42] Five acylic donors were examined with a variety of glycosyl acceptors including cholestanol, cholesterol (**27**), and methyl 4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (**25**) using NIS–TfOH activation in dichloromethane.

The glycosylation reactions provided the products in yields ranging from 50% to 76%. In all cases, the glycosidic bond formed as the major isomers was trans to the iodine substituent at C-2. The selectivities for the trans products varied from a low of 75:25 to a high of 97:3, and this stereochemical preference can be rationalized in a manner analogous to that described above (Fig. 5).

With the glycosylation methodology established, two representative 2-deoxy-2-iodo-glycosides were treated with Bu_3SnH under radical conditions to afford the corresponding 2-deoxy-glycosides. These reactions proceeded in 67–75% yield, thus demonstrating the potential of the method for synthesizing 2-deoxy-glycosides. The utility of the methodology was further established by its application to the synthesis of a model 2,6-dideoxy-glycoside (**35**) related to the pregnane glycoside (Scheme 11).

In a related investigation, the Castillón group has prepared 2-deoxy-2-phenylselenyl-thioglycosides to synthesize 2-deoxy-glycosides.[43] The synthetic route toward this new class of glycosyl donors is similar to that described above for the 2-iodo-derivative **24** (Scheme 12). Starting from the protected furanose derivative, olefination gave the expected alkenyl sufanyl derivative (**31**), which then underwent a selenonium ion-mediated 6-*endo* cyclization to generate the glycosyl donor **37**. When using *N*-(phenylselenenyl)phthalimide (NPSP) **36** and ZnI_2 as the promoters, the cyclization reactions were sluggish, and yields between 15% and 60% of the desired products were obtained; however, total regio- and stereoselectivity were observed.

Glycosylations were performed by treating a mixture of the 2-deoxy-2-phenylselenenyl-1-thioglycosyl donor **37** and the alcohol (e.g., **25**) with NIS–TfOH in toluene–dioxane (1:3). This protocol typically gave the desired products in yields of 50–70% (Scheme 12) and was particularly effective with donors leading to 2-deoxy-2-phenylselenenyl-β-D-gulopyranosides (α/β, 1:14; 50%) and 2-deoxy-2-phenylselenenyl-β-D-allopyranosides (**38**, α/β, 1:4; 66%). Although not described in this paper, the conversion of the products of these



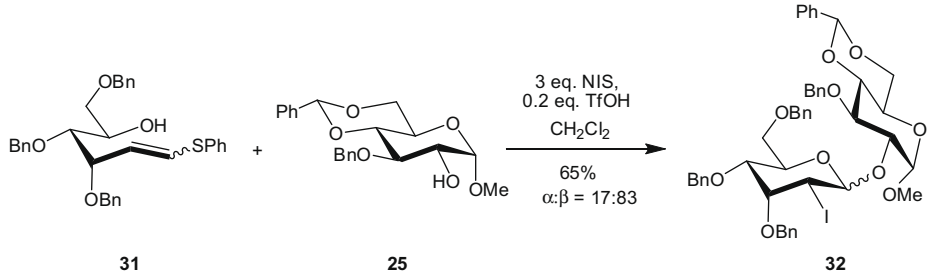
Scheme 11. Application of the cyclization–glycosylation procedure to the synthesis of 2,6-dideoxy-glycoside **35**.[42]

reactions to the 2-deoxy-glycosides can also be achieved by radical deselenylation with tin hydride reagents.[44]

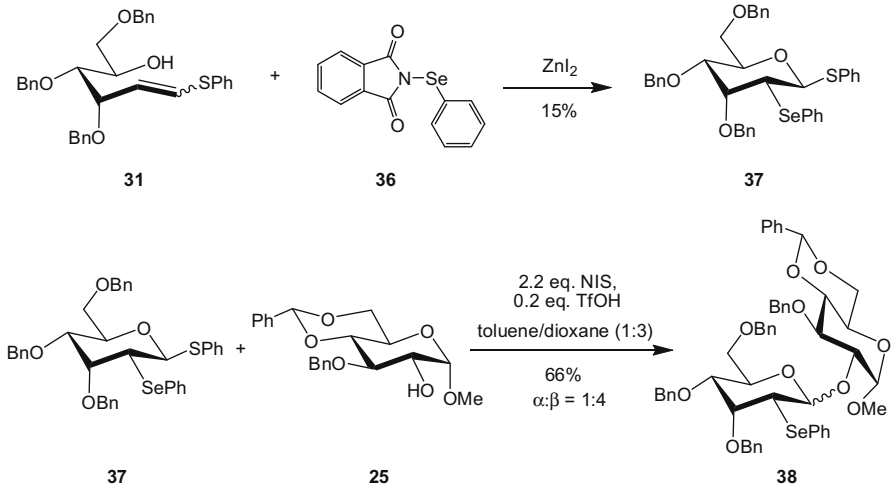
3.3. 1,2-Migration–glycosylations

Thioglycosides possessing a good leaving group at C-2 in a trans-configuration to the sulfur have been shown to undergo a tandem 1,2-migration–glycosylation sequence when treated with the appropriate promoters and an alcohol (Fig. 6). These reactions are proposed to proceed through the intramolecular displacement of a leaving group at C-2 by the neighboring nucleophilic sulfur atom at C-1 together with concomitant glycosylation. The formation of a transient episulfonium intermediate is often invoked, although there is not definitive proof for its existence.[19,45–52] Nevertheless, the intermediacy of such species is an attractive postulate as it explains the high stereoselectivity of the process, in which the relationship between the group at C-1 and C-2 in the product is trans. Desulfurization of the resulting 2-thioglycosides affords the corresponding 2-deoxy-glycosides. In earlier reports, donors such as 2-*O*-phenoxythiocarbonyl thioglycosides,[45] 2,3-orthoester-protected thioglycosides,[46,47] or 2-sulfonyloxyselenoglycosides[48,49] have been employed as precursors to the formation of 2-deoxy-glycosides by this route.

Yu and Yang have demonstrated the use of phenyl 2,3-*O*-thionocarbonyl-1-thio-α-L-rhamnopyranosides (e.g., **39**) as effective donors for the preparation of 2-deoxy-β-glycosides by this approach.[47,53] As illustrated in Scheme 13, typical reactions were performed in dichloromethane at room temperature using MeOTf as the promotor. Under these conditions, the expected 2-thio-β-glycosides (**41**) were obtained with complete stereocontrol in 64–90% yield. The list of acceptors includes benzyl alcohol, cyclohexanol, cholesterol, and three monosaccharide alcohols. Analogous transformations, leading to complex trisaccharides, have also been achieved using this method.



Scheme 10. Electrophile-induced cyclization–glycosylation sequence for the preparation of 2-deoxy-2-iodoglycosides.[42]



Scheme 12. Glycosylation of **25** with 2-phenylseleno-2-deoxy-thioglycoside **37** as described by Castillón and co-workers.[43]

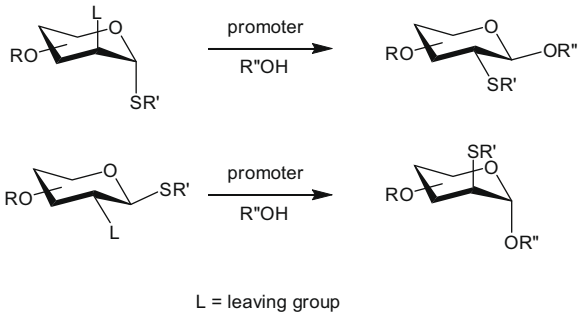


Figure 6. General 1,2-migration–glycosylation sequence.

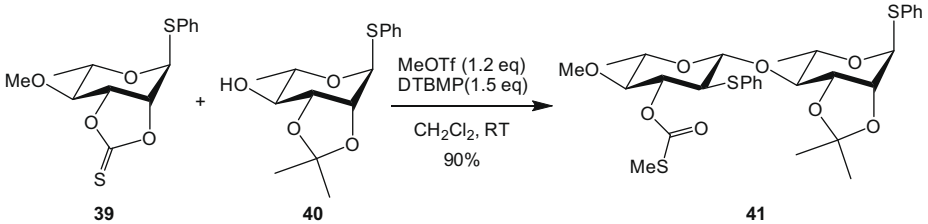
In a related investigation, the Castillón group has prepared 2-deoxy-2-phenylselenyl-thioglycosides to synthesize 2-deoxy-glycosides.[43] The synthetic route toward this new class of glycosyl donors is similar to that described above for the 2-iodo-derivative **24** (Scheme 12). Starting from the protected furanose derivative, olefination gave the expected alkenyl sufanyl derivative (**31**), which then underwent a selenonium ion-mediated 6-*endo* cyclization to generate the glycosyl donor **37**. When using *N*-(phenylselenenyl)phthalimide (NPSP) **36** and ZnI_2 as the promoters, the cyclization reactions were sluggish, and yields between 15% and 60% of the desired products were obtained; however, total regio- and stereoselectivity were observed.

When simple and activated primary carbohydrate alcohols are used, the reaction proceeds efficiently by treatment with 10 equiv of 4 Å molecular sieves in dichloromethane at reflux. Alternatively, with less reactive secondary carbohydrate alcohols, one equivalent of copper(II) triflate is needed to promote the glycosylation. The method was successfully applied to the synthesis of a trisaccharide (**51**) containing two 2-deoxyfuranosyl residues, which is a potential inhibitor of mycobacterial arabinosyltransferases[57] as illustrated in Scheme 14.

The same group also described the potential and scope of the pyranoside counterparts (Fig. 8), **52** and **55**) in these glycosylation reactions, particularly in the preparation of 2,6-dideoxy-sugar glycosides.[55] Glycosylation of a panel of alcohols with **52** and **55** afforded the corresponding 2-deoxy-2-thiotolyl glycoside products **53** and **56** in generally excellent yields with exclusive stereoselectivity. In this case, the 2-thiotolyl group was readily removed upon reaction with tri-*n*-butyltin hydride and AIBN to give the corresponding 2-deoxypyranosides **54** and **57**. This method was successfully applied to the synthesis of the disaccharide unit in apoptolidin and the trisaccharide moiety of Olivomycin A.

In a follow-up study, a series of experiments aimed at understanding the mechanism of the 2,3-anhydrosugar migration–glycosylation reaction were performed.[19] In these mechanistic studies, a range of techniques were employed, including low-temperature ^{1}H NMR spectroscopy, computational studies, chemical synthesis, and the measurement of deuterium kinetic isotope effects. Although episulfonium ion intermediates had previously been proposed to explain the typically high stereoselectivity observed in this[54] and similar migration–glycosylation processes,[19,45–52] the data obtained all pointed to the intermediacy of an oxacarbenium ion.

The deuterium kinetic isotope effects measured in this investigation represent the first direct experimental evidence of the nature of the intermediates formed in reactions of this type. On the basis of these investigations, it was proposed that the high stereoselectivity of the reaction occurs by 'inside-attack'[58,59] of the nucleophile onto the lowest energy conformer of the oxacarbenium ion intermediate, which adopts the ^{3}E conformation (Fig. 9).



Scheme 13. 1,2-Migration–glycosylation protocol developed by Yu and Yang.[47,53]

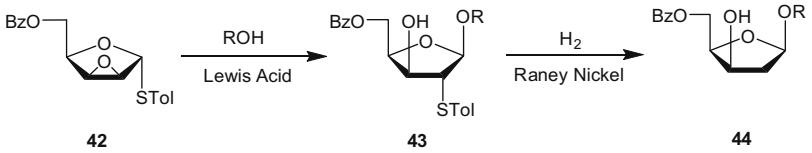
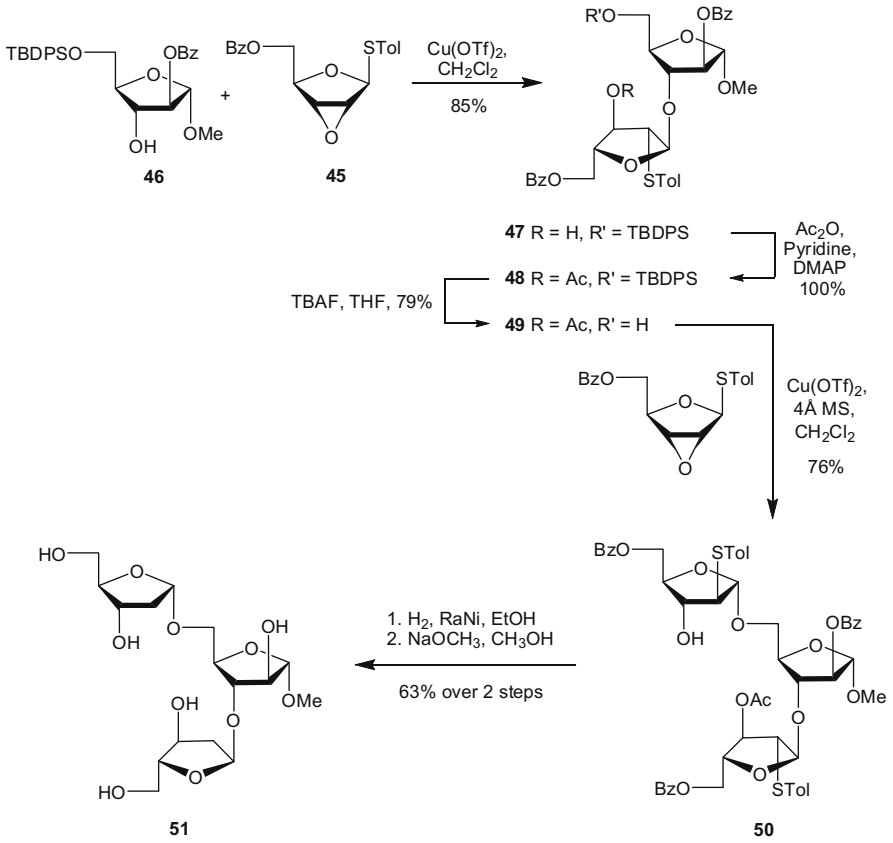


Figure 7. Two-step preparation of 2-deoxy-glycosides from 2,3-anhydrosugar thioglycosides.[54]



Scheme 14. Synthesis of trisaccharide **51**.[54]

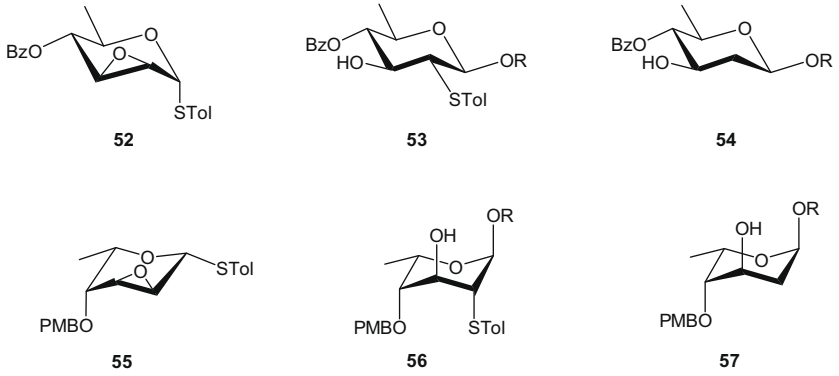


Figure 8. Structures of 2,3-anhydropyranosyl thioglycoside donors (**52** and **55**), glycosylation products (**53** and **56**), and 2,6-dideoxy-targets (**54** and **57**).[55]

4. Use of activated oxygen derivatives

4.1. Direct synthesis

A number of different classes of activated oxygen derivatives are used in the synthesis of glycosidic bonds, and most have been applied to the direct preparation of 2-deoxy-glycosides. In one recent investigation, Kim reported the application of (2′-carboxyl)benzyl (CB) glycosides as glycosyl donors for the direct synthesis of 2-deoxy-pyranosides.[60] An illustrative example is shown in Scheme 15, where activation of the readily accessible 3,4,6-tri-*O*-benzyl-protected 2-deoxy-pyranosyl CB glycoside **58**

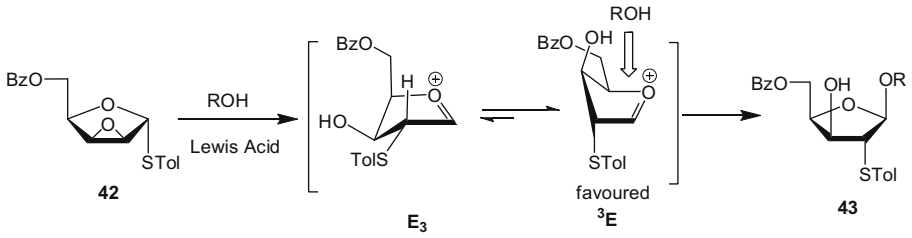
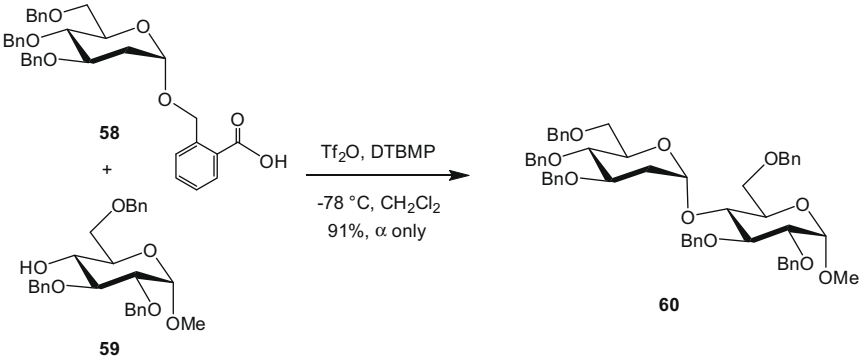


Figure 9. Proposed model for stereoselectivity in migration–glycosylation reactions with **42**.[19]



Scheme 15. Use of (2′-carboxyl)-benzyl (CB) glycosides in the synthesis of 2-deoxy-α-glycosides.[60]

with Tf_2O–DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) and the secondary alcohol **59** gave the disaccharide product **60** in excellent yield and stereoselectivity. In these reactions, it was shown that glycosylation of hindered secondary carbohydrate alcohols in which the other hydroxyl groups were protected with arming protecting groups (acetals or benzyl ethers) exhibited high α-selectivity (α/β ratio ranged from 9.4:1 to α-only). However, almost equal amounts of α- and β-anomers were formed when primary alcohols were used, regardless of the nature of groups protecting the other acceptor hydroxyl groups.

It should be noted that a change of the O-4 and O-6 protecting groups on the donor from benzyl ethers to a benzylidene acetal completely reverses the stereoselectivity from α to β (Scheme 16). Specifically, when the 4,6-*O*-benzylidene-protected donor **61** was treated with the same hindered secondary alcohols under the same reaction conditions, the β-anomer was favored (α/β ratio ranged from 1:8 to β-only) in good yield. As was seen with the tri-O-benzylated donor **58**, glycosylation of the primary alcohol acceptors afforded an anomeric mixture of disaccharides with no significant stereoselectivity in most cases.

The mechanism used to explain the stereoselectivity of the process assumed that the excellent β-selectivity in reactions involving **63** (Fig. 10) derived from an S_N2-like displacement mechanism of an α-glycosyl triflate intermediate that is formed in situ. The lack of, or poor, β-selectivity in reactions with primary alcohols was interpreted to indicate that these glycosylations proceed via the oxocarbenium ion intermediate **64**. No mechanistic work was performed to support these proposals and, in light of the study by Crich and Vinogradova[37] (see Scheme 7) it is likely that another mechanism is operating. In particular, the failure to detect a triflate

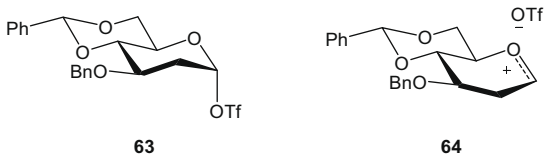
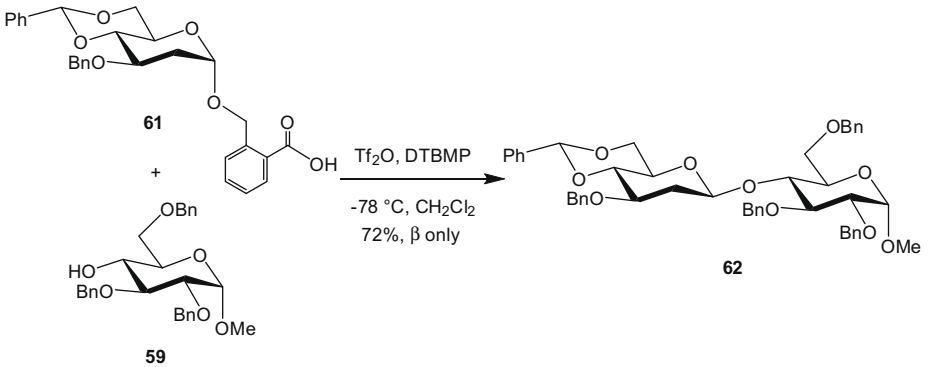


Figure 10. α-Glycosyl triflate **63** and oxocarbenium ion **64**.[60]



Scheme 16. Use of (2′-carboxyl)-benzyl (CB) glycosides in the synthesis of 2-deoxy-β-glycosides.[60]

species derived from donors with the protecting group pattern present in **63**[37] suggest that such species may not be viable intermediates in these reactions.

In another recent investigation, a unique approach to the synthesis of 2-deoxy-glycosides based on the oxidative activation of glycosyl trichloroacetimidates with I_2 at −94 °C has been developed by Takahashi and co-workers.[61] This approach successfully provides excellent β-selectivity: up to β:α > 95:5 in some reactions. Both the 3-*O*-benzyl-4-*O*-benzylsulfonyl-olivosyl (**65**, Scheme 17) and 3,4-*O*-dibenzoyl-digitoxosyl (**68**) imidates have been investigated and coupled with aglycones that include a range of primary and secondary carbohydrate alcohols. Protection of the hydroxyl group at C-4 in the donor with an electron-withdrawing benzylsulfonate group, rather than a benzyl ether, gave higher β-selectivity (β:α > 95:5) and better reaction yields. The high β-selectivity in the glycosylation when 3,4-*O*-dibenzoyl digitoxosyl imidate (**68**) was used as a donor was proposed to result from neighboring group participation by the axially oriented benzoyl group at C-3. No rationale was provided to explain the stereoselectivity of reactions involving donor **65**, which lacks a group that can participate to generate the β-glycoside.

The 4-*O*-benzylsulfonyl-oliosyl trichloroacetimidate (**70**, Fig. 11) and 4-*O*-benzylsulfonyl-amicetoxyl trichloroacetimidate (**71**) were also screened against olivosyl, mono-amicetosyl, and di-amicetosyl acceptors (**66**, **72**, and **73**, respectively) under the established conditions, to provide mixtures of di- and trisaccharides in yields of 57–95%. In all cases, the β-glycoside was favored, with the β:α ratio ranging from 60:40 to 80:20. To demonstrate the power of the methodology, a tetrasaccharide containing four β-(1→4)-linked olivose residues (**74**) was efficiently prepared.

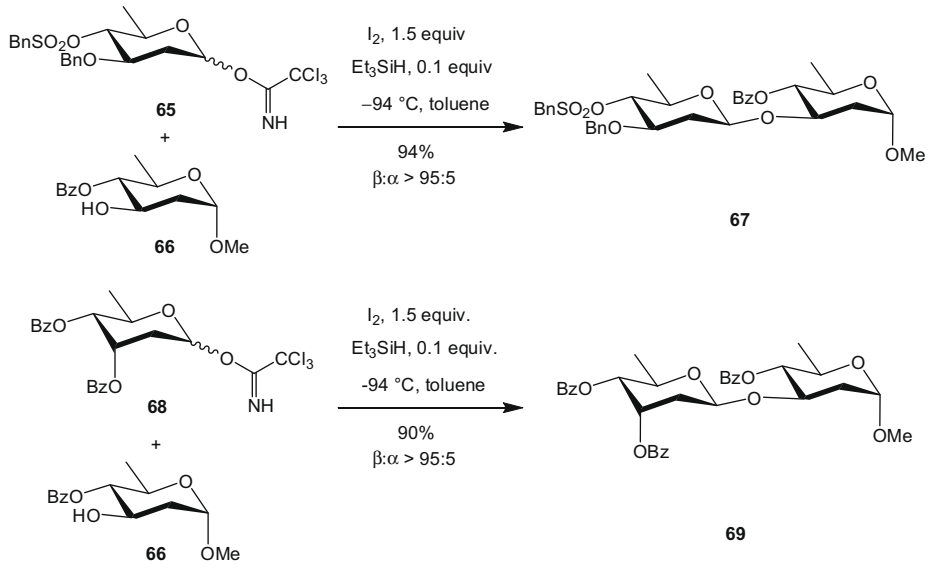
Another specialized method, limited to the synthesis of 2-deoxy-α-glycosides, has been developed by Boons and co-workers.[62] A 2-deoxy-glucopyranosyl trichloroacetimidate donor having a participating (*S*)-(phenylthiomethyl)benzyl moiety at C-6 was prepared and used in TMSOTf-mediated reactions with a range of acceptor substrates (Scheme 18). The glycosylation reactions led to the corresponding disaccharides in excellent yields (92–95%) with excellent α-selectivity; the α/β ratio ranged from 8:1 to 15:1. Similar glycosylations employing 2-deoxy-glucopyranosyl trichloroacetimidate donors with a benzyl ether or an acetyl ester at C-6 provided disaccharides as mixtures of anomers (the best α/β ratio was 5:1).

In the same paper, it was shown that allyl 2,6-dideoxy-glycosides can be employed in direct glycosylations using $BF_3{\cdot}Et_2O$ as the promoter (Scheme 19). Three allyl 2,6-dideoxy-glycosides, protected with either ester or benzyl ether protecting groups at C-3 and C-4, were employed in $BF_3{\cdot}Et_2O$-mediated glycosylations with the same panel of glycosyl acceptors used with the trichloroacetimidate donors. The glycosylations provided the disaccharides in good yields (65–85%) as mainly the α-anomer. With regard to the stereoselectivities observed with these allyl glycoside donors, no rationale was provided. However, the α-selectivity presumably arises as a consequence of the kinetic anomeric effect, as described above (see Section 1.2).

Glycosyl phosphites have also been used in the direct synthesis of 2-deoxy-glycosides. In a study published in 2005, Toshima and co-workers examined the activation of 2-deoxy-sugar phosphite donors using a heterogeneous solid acid, montmorillonite K-10 (Scheme 20).[63] Glycosylations using 3,4,6-*O*-tribenzyl-protected 2-deoxy-pyranosyl phosphite (**81**) and 3-*O*-benzyl-4-*O*-benzoyl olivosyl diethyl phosphite (**84**) as donors were performed in Et_2O at −78 °C in the presence of 100 wt % montmorillonite K-10. The acceptors screened included primary and secondary carbohydrate derivatives, as well as primary and secondary simple alcohols. Reaction yields ranged from 70% to 97%, and α:β ratios varied from a low of 29:71 to a high of 10:90. Diethyl ether was found to be the best solvent for these reactions. The origin of the β-selectivity for this reaction was not studied. However, because the product did not anomerize under the reaction conditions, it was suggested that the product distribution was the result of kinetic control.

In related work, Sulikowski has developed a one-pot sequential glycosylation protocol to construct β-linked 2-deoxy-oligosaccharides by taking advantage of the differential rates of activation of glycosyl phosphites possessing different alkyl groups.[64] By monitoring a competitive glycosylation reaction in anhydrous toluene-d_8 at −100 °C using ^{31}P NMR spectroscopy, it was established that the diethyl phosphite donor **87** (Fig. 12) is more reactive than the pinacol phosphite donor (**88**). The protocol was used to synthesize the trisaccharide **89** in 50% overall yield, by carrying out the two glycosylations in a single reaction vessel. The stereoselectivity of both reactions favored the β-anomer, but the origin of this preference was not discussed.

Another example of the direct synthesis of 2-deoxy-glycosides with activated oxygen derivatives is the use of a novel 1,6-lactone



Scheme 17. Synthesis of 2-deoxy-glycosides by oxidation of glycosyl trichloroacetimidates with I_2.[61]

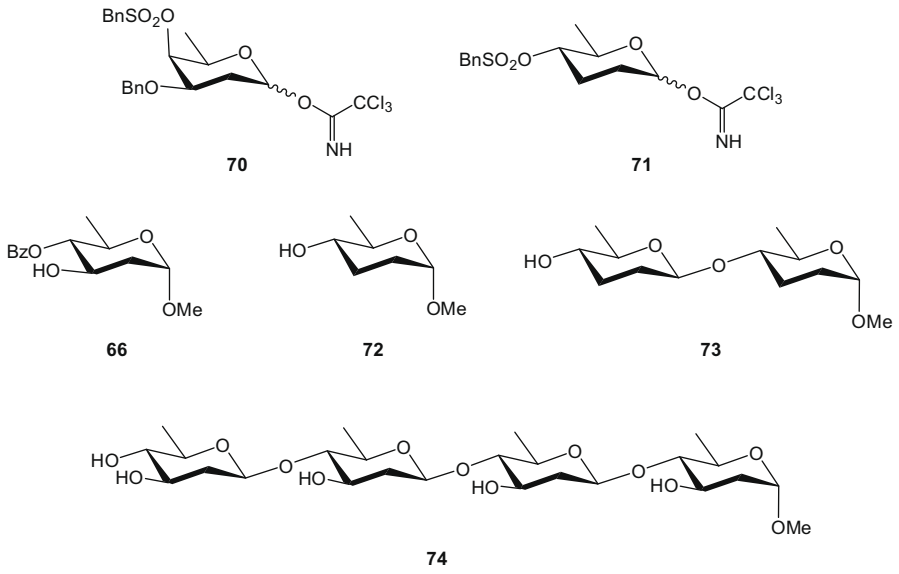
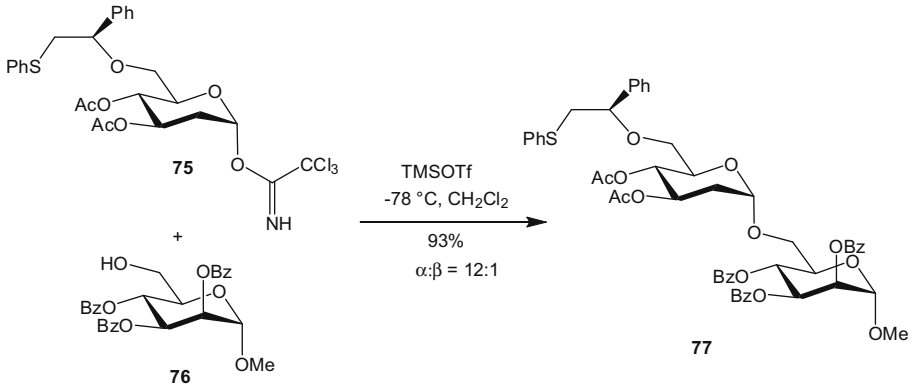
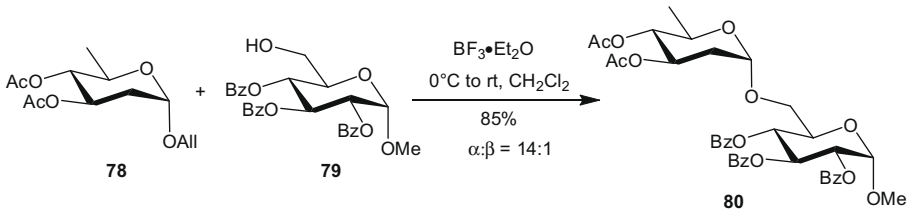


Figure 11. Structure of donors **70**, **71**, acceptors **66**, **72**, **73**, and tetrasaccharide **74**.[61]



Scheme 18. Synthesis of 2-deoxy-α-glycosides via using a trichloroacetimidate donor with a participating group attached to O-6.[62]

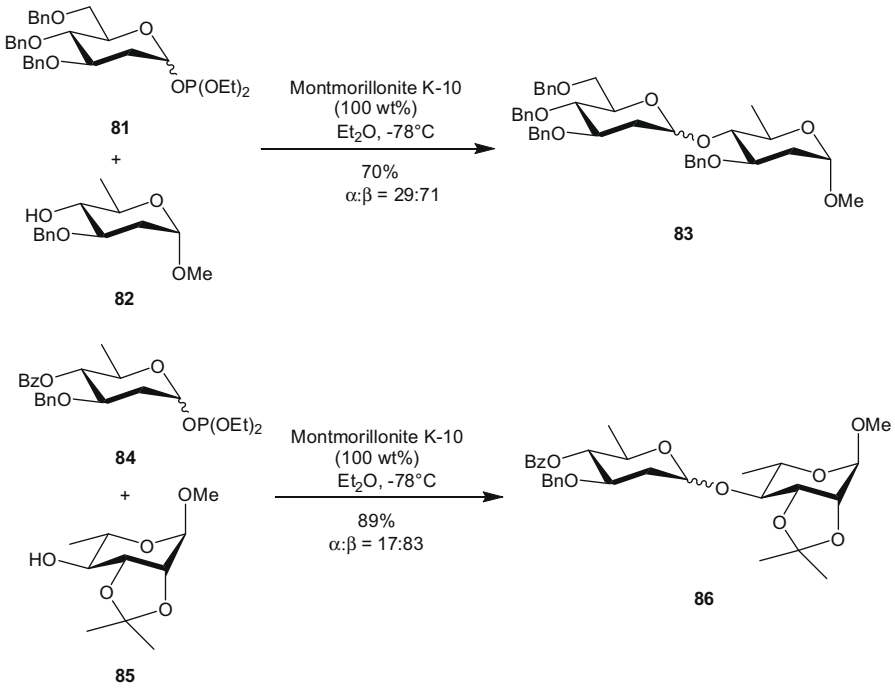


Scheme 19. Use of allyl glycosides in the direct synthesis of 2-deoxy-glycosides.[62]

donor (**90**, Scheme 21) in which the carboxylic acid acts as the leaving group in the reaction.[65] Using this approach, Murphy and co-workers synthesized **90** and treated it with one of four acceptors including trimethylsilyl azide, methyl trimethylsilyl ether, cyclohexyl trimethylsilyl ether, and a trimethylsilyl-protected threonine derivative **91** using tin (IV) chloride (0.33–1 equiv). The yields ranged from 41% to 66%, and only α-linked 2-deoxy-glucuronides were obtained. Because the glycosylation proceeded with an inversion of configuration at C-1, it was proposed that the reaction proceeded by way of an S_N2 mechanism.

In a recent investigation, Shair and Morris reported a novel approach to form highly stereoselective 2-deoxy-β-glycosides using anomeric O-alkylation/arylation.[66] Lactol **93**, shown in Scheme 22, when treated with NaH in dioxane at room temperature, can react with allyl bromide, 1-bromo-2,4-dinitrobenzene, and primary carbohydrate triflates such as **94** to afford the corresponding 2-deoxy-β-glycosides. The yields are around 90% and the products are obtained with high β-selectivity (α/β ranged from 1:18 to 1:20). However, reactions with secondary triflates **96** and **97** (Fig. 13) failed, which is not unexpected given previous literature demonstrating the limitations of the anomeric alkylation in the synthesis of carbohydrate glycosides.[67,68]

The lactols **98** and **99** (Fig. 14), derived from glucose and galactose were also screened against allyl bromide, 1-fluoro-2,4-dinitrobenzene, and primary carbohydrate triflates (**100**–**102**) under the established conditions. These reactions provided mixtures of



Scheme 20. Use of glycosyl phosphites in the preparation of 2-deoxy-glycosides.[63]

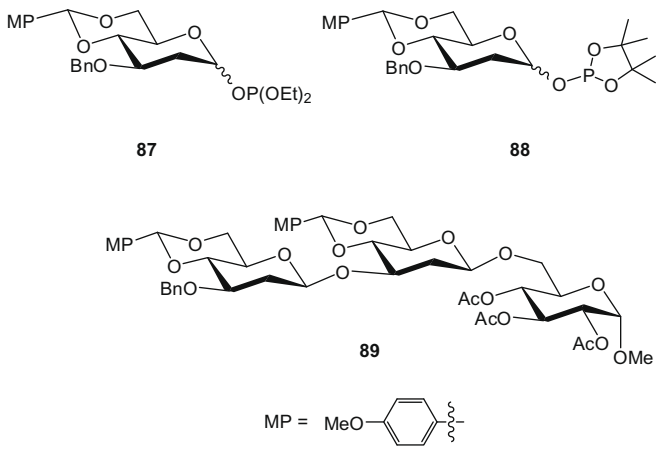


Figure 12. Structure of compounds **87**, **88**, and **89**.[64]

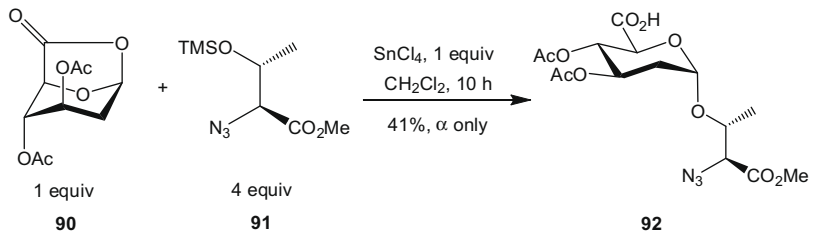
2-deoxy-β-glycosides in yields of 61–90%. In all cases, the β-glycoside was favored with β:α ratios ranging from 8:1 to 20:1.

The explanation for the high β-selectivity was proposed to involve the rapid equilibrium between axial and equatorial alkoxides. The enhanced nucleophilicity of the equatorial alkoxide, due to repulsion between the alkoxide and the ring oxygen lone pair leads to selective generation of the β-glycoside (Fig. 15).[69]

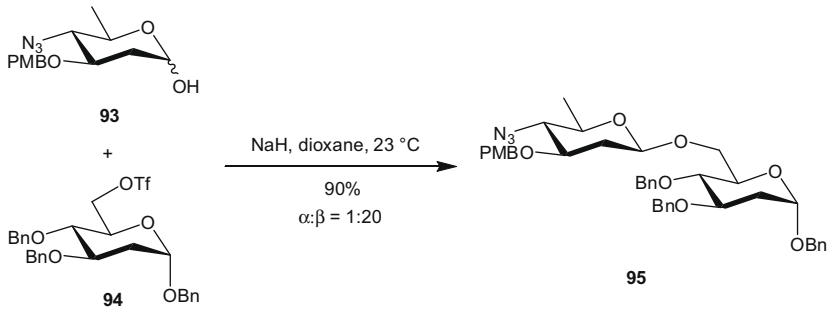
4.2. Indirect synthesis

The preparation of 2-deoxy-glycosides by an indirect approach using activated oxygen derivatives has also been reported. In one example, donors bearing thioacetyl functionality at C-2 leads to the stereoselective synthesis of 2-deoxy-β-glycosides, through neighboring group participation. An example of this approach, which has been developed by Knapp and Kirk, is shown in Scheme 23.[70] Glycosylation of various alcohols with 1,2,3,4,6-penta-*O*,*S*,*O*,*O*,*O*-acetyl-2-thio-β-D-glucopyranose (**105**) was performed in dichloromethane in the presence of 0.5 equiv of TMSOTf. A range of acceptors were used, and in all cases only the β-linked disaccharides were obtained in good yields (70–85%). The formation of an intermediate oxathiolium ion (**106**) is proposed to give rise to the high level of β-selectivity in these glycosylation reactions. Following glycosylation, reductive removal of the thioacetyl group with Raney Nickel provided the corresponding 2-deoxy-β-glycosides in yields of 73–77%.

A large volume of work in this area involves glycosyl donors possessing 2-deoxy-2-iodo- and 2-bromo-2-deoxy-glycosyl functionality (e.g., **109** and **110**, Fig. 16). Both glycosyl acetates and trichloroacetimidates serve as stereoselective glycosylating agents.[8,71,72]



Scheme 21. Use of 1,6-lactones in the preparation of 2-deoxy-glycosides.[65]



Scheme 22. Stereoselective 2-deoxy-β-glycosides using anomeric O-alkylation/arylation.[66]

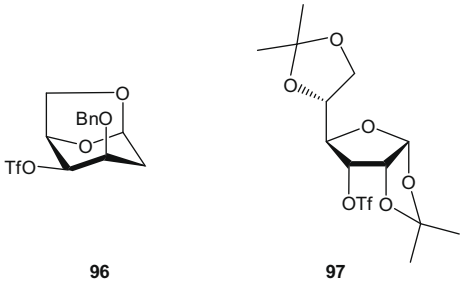


Figure 13. Structure of secondary triflates **96** and **97**.[66]

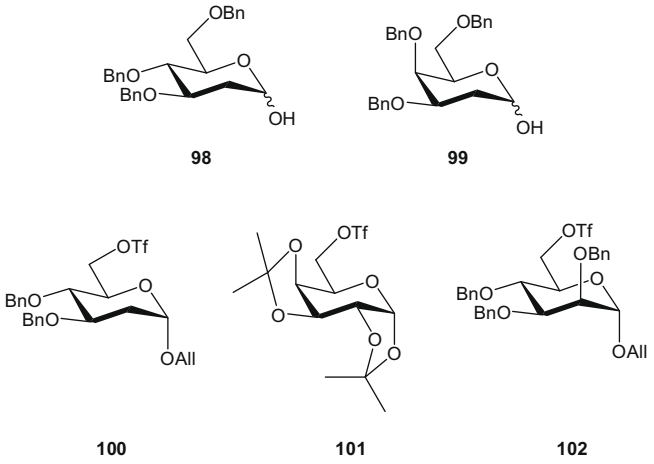


Figure 14. Structure of compounds **98**–**102**.[66]

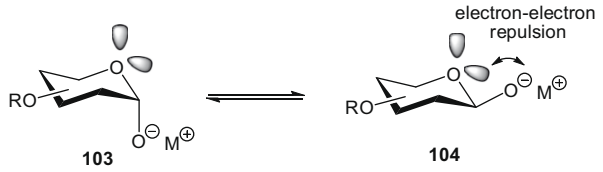


Figure 15. Proposed basis for the stereoselectivity in Shair's 2-deoxy-glycosides synthesis.[66]

The facile reductive removal of the halogen following glycosylation allows for the easy formation of 2-deoxy-glycosides.

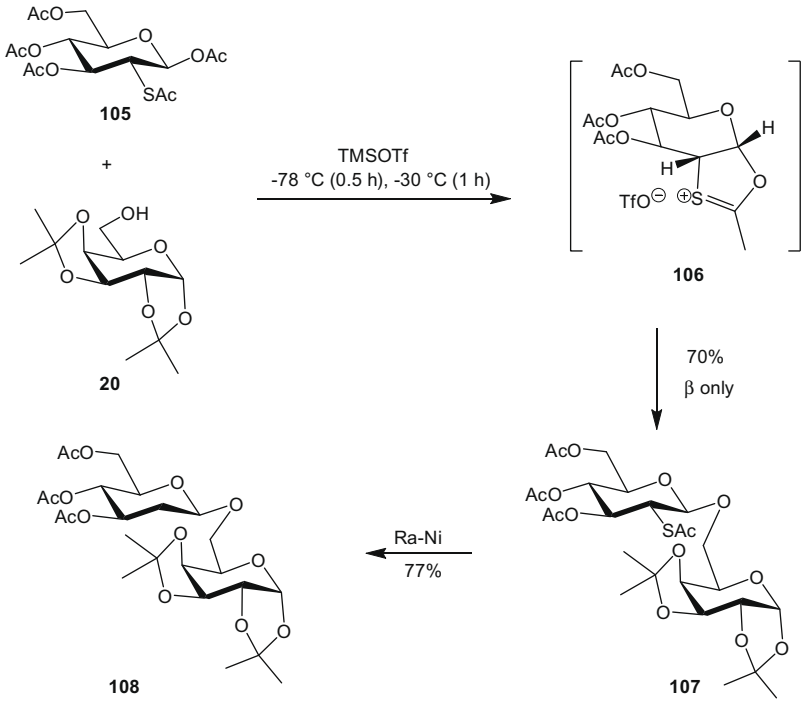
A leader in this area has been the Roush group, who has developed a series of powerful reagents for the assembly of 2-deoxy-glycosides.[71–75] For example, reactions employing 2-deoxy-2-iodo-β-D-glucopyranosyl acetates (**109**)[71] or 2-deoxy-2-iodo-α-D-glucopyranosyl trichloroacetimidates (**110**)[72] as the glycosyl donors proceeded in dichloromethane with excellent β-stereoselectivities (in most cases, ⩾19:1) using either TMSOTf or TBSOTf as the promoter. To investigate the origin of the high β-selectivity of these glycosylations, Roush and Chong used constrained 4,6-*O*-benzylidene-2-deoxy-2-iodo-glucopyranosyl glycosyl imidates **111** and **112** (Fig. 17) to probe the likely reaction pathway.[76] Glycosylations were performed by addition of catalytic TBSOTf to a solution of imidate **111** or **112** and acceptor **79**, **113**, or **114** in dichloromethane in the presence of 4 Å molecular sieves. It was found that the reactions were still highly β-selective (the β/α ratio ranged from 86:14 to β only).

An S_N2-like displacement pathway was ruled out because the stereoselectivity of glycosylation was independent of the starting donor configuration. Given the conformational constraint of the benzylidene acetal, the β-selectivity of the reaction was proposed to arise from the key reactive intermediate **115**, in which the pseudoaxial orientation of the iodine substituent hinders approach of the nucleophile from the α-face (Fig. 18). However, the iodonium ion intermediate **116**, which is difficult to distinguish experimentally from **115**, could be also invoked to rationalize the β-selectivity.

As an extension of these investigations, in 2003, Durham and Roush reported the use of 2-deoxy-2-halo-galactopyranosyl acetates and trichloroacetimidates for the synthesis of 2-deoxy-β-D-*lyxo*-hexopyranosides ('2-deoxy-β-D-galactopyranosides').[77] A number of 2-bromo-2-deoxy and 2-deoxy-2-iodo-glycosyl donors were evaluated in these investigations. When subjected to TBSOTf-promoted glycosylation, donors such as **117**–**122** (Fig. 19), displayed modest β-selectivity in yields of 38–93% in reactions with acceptors **113** and **79**.

The large amounts of α-glycosides produced in these reactions suggest that oxocarbenium ions instead of halonium ion intermediates play an important role in the glycosylation reactions of 2-deoxy-2-halo-galactopyranose donors. Therefore, the introduction of the cyclic 3,4-protecting group may encourage the key reactive intermediate (**123**, Fig. 20) to adopt the indicated boat-like conformation with the C(2)–X substituent in a pseudoaxial position. This would direct the glycosylation in a β-selective manner.

Thus, the 3,4-carbonate or isopropylidene protected 2,6-dideoxy-2-iodo-galactopyranosyl acetates **124** and **125**, and the 2-bromo-2-deoxy-galactopyranosyl trichloroacetimidates **126** and **127** (Fig. 21), were also screened against acceptors **113** and **79**. Donors **124** and **127** demonstrated only modest selectivity. The β-glycoside was favored with the β:α ratio ranging from 50:50 to 84:16. However, 6-deoxy donors **125** and **126** displayed good β-selectivity in reactions with **113** and **79** in yields of 62%–88% and β:α ratios ranging from 84:16 to 95:5.



Scheme 23. Stereoselective synthesis of 2-deoxy-β-glycosides using a thioacetyl moiety at C-2 as a participating group.[70]

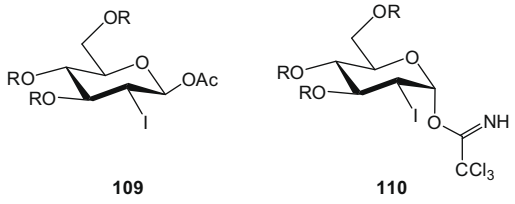


Figure 16. Donors **109** and **110**.[71,72]

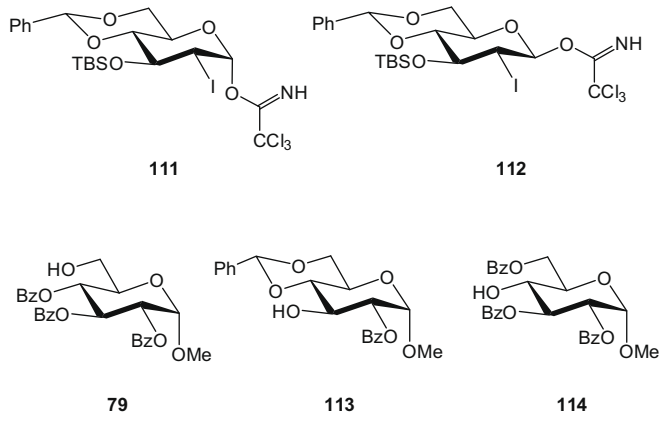


Figure 17. Structure of donors **111**, **112**, and acceptors **79**, **113**, **114**.[76]

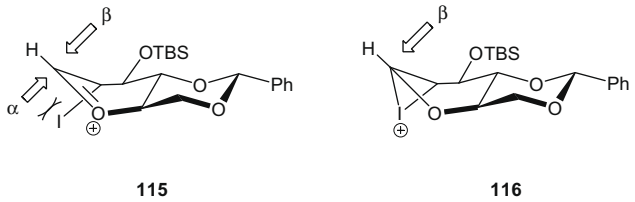


Figure 18. Oxocarbenium ion intermediate **115** and iodonium ion intermediate **116**.[76]

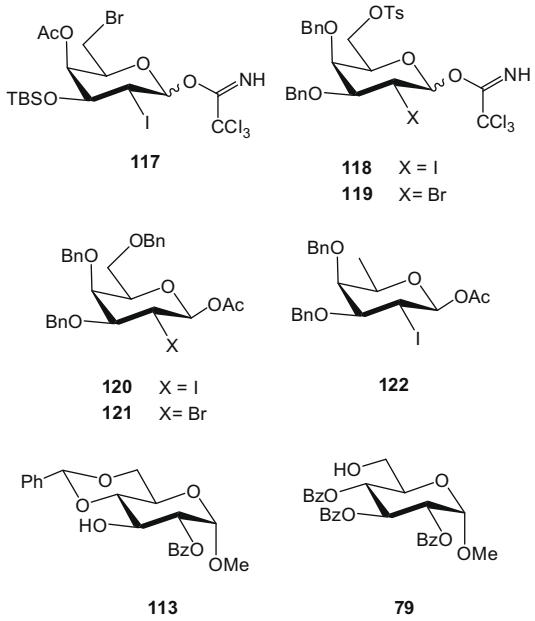


Figure 19. Structure of a series of 2-deoxy-2-halo-galactopyranosyl donors and acceptors used in the Durham and Roush approach.[77]

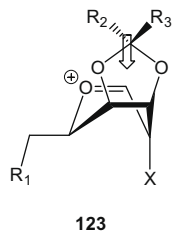


Figure 20. Stereochemical consideration of the key reactive intermediate **123**.[77]

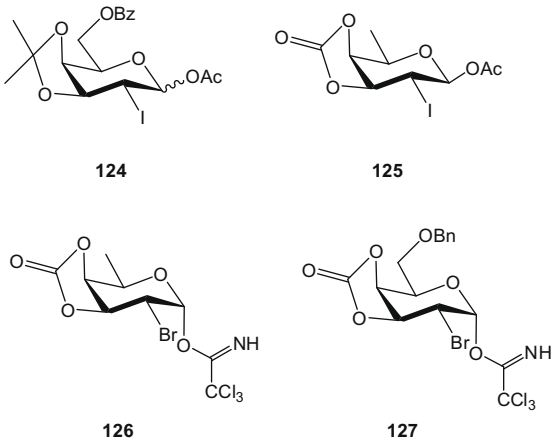


Figure 21. Structure of donors **124**–**127**.[77]

Once developed, this methodology was applied to the synthesis of the CDEF and CDE 2,6-dideoxy tetrasaccharide and trisaccharide unit of Durhamycins A and B.[78] These compounds, produced by *Actinoplanes durhamensis*, are potent inhibitors of HIV Tat transactivation and contain 2-deoxy-β-linked oligosaccharide moieties (Fig. 22).[79]

As shown in Scheme 24, glycosylation of acetate **128** with galactopyranosyl trichloroacetimidate **126** was achieved by treatment with TBSOTf at −78 °C, affording the corresponding β-linked disaccharide **129** in 94% yield. This product was converted in three steps into glycosyl fluoride **131**, which was then glycosylated with imidate **132** to provide trisaccharide **133** in 86% yield with 93:7 β:α selectivity.

Similarly, the CDEF tetrasaccharide was obtained by linking the disaccharide acceptor **131** to imidate donor **136** using the same catalytic conditions (Scheme 25). The route to the product began with glycosyl acetate **128** and imidate **134**, which were coupled to provide β-disaccharide **135** in 94% yield. Conversion of **135** to imidate **136** was done using standard procedures, and the product was used to glycosylate **131,** giving β-tetrasaccharide **137** in 74% yield.

As described above for the thioglycoside donors, the synthesis of 2-deoxy-glycosides through the use of polymer-supported thiophilic reagents has been developed by Kirschning et al.[80] A similar approach has been used in the preparation of 2-deoxy-2-iodo donors for the preparation of 2-deoxy-glycosides. The key glycosyl donor, 2,6-dideoxy-2-iodo-α-D-mannopyranosyl acetate **139**, was prepared from 3-*O*-*t*-butyldimethylsilyl-4-*O*-benzoyl-D-olival (**138**) by reaction with the polymer-supported iodate reagent (Scheme 26). The product was obtained, together with its stereoisomer **140**, in 86% combined yield.

With donor **139** prepared, it was treated with a polymer-bound silyl triflate and structurally diverse acceptors, resulting in the formation of α-linked disaccharides with complete stereocontrol (Scheme 27). The list of acceptors includes simple alcohols, carbohydrate-derived acceptors, steroids, and (−)-linalool. In some cases, pure α-glycosides were obtained in almost quantitative yield, and the lowest yield was 81%. This method was extended to the preparation of a steroid-derived glycoconjugate, as well as trisaccharide composed of two D-olivose units and the 2,3,6-trideoxy-hexose L-rhodinose.[80]

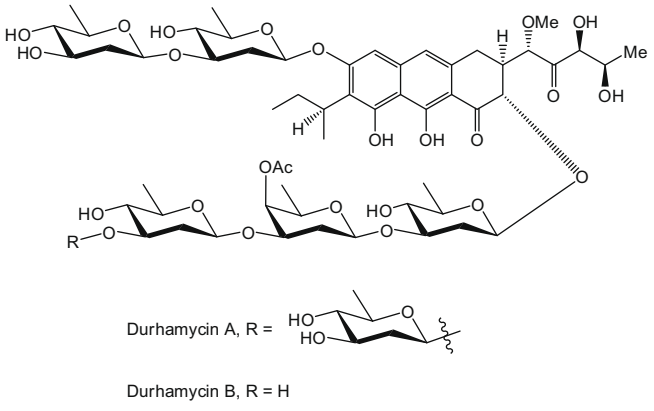


Figure 22. Structure of Durhamycins A and B.

5. Use of glycosyl halides

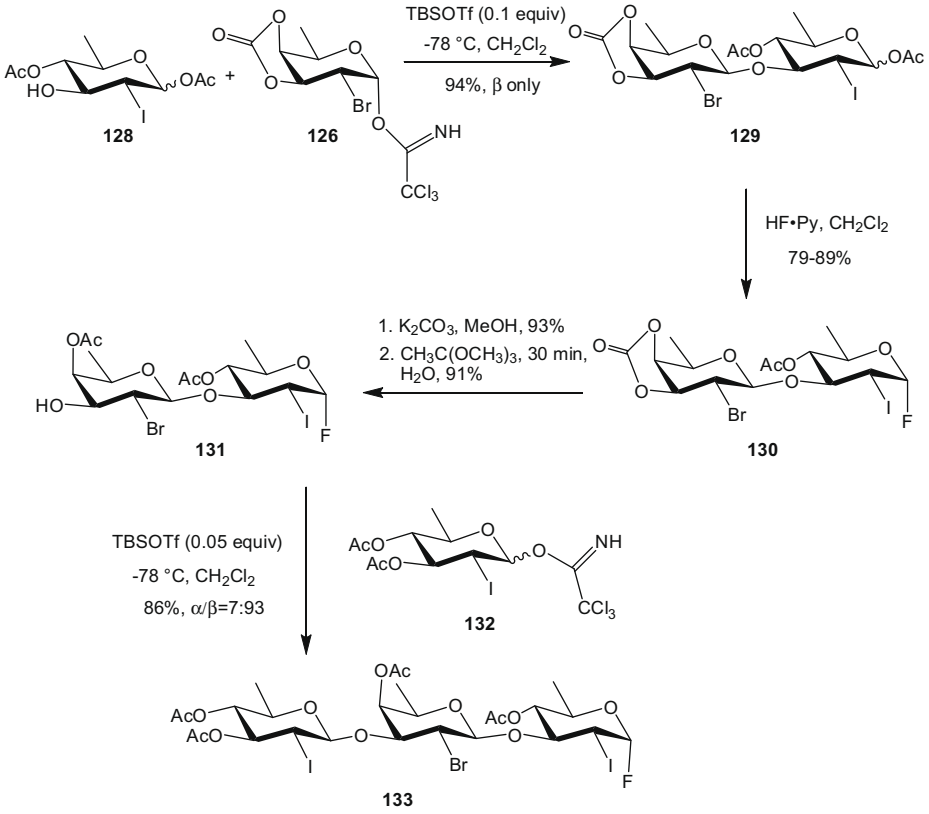
Glycosyl halides, one of the oldest classes of glycosyl donors,[81] have also been used for the preparation of 2-deoxy-glycosides. However, a limitation of using glycosyl halides deoxygenated at C-2 is their significant tendency for hydrolysis. Thus, a significant amount of these reactions have involved glycosyl fluorides, the most stable of the glycosyl halides, or rely on deoxygenation after glycosylation. In other cases, the 2-deoxy-glycosyl halide was generated and used with minimal purification.

One recent example of the use of glycosyl halides in this area was performed by Toshima et al., who have described a stereoselective synthesis of 2-deoxy-β-glycosides using a heterogeneous solid acid, montmorillonite K-10.[82] The glycosylation was performed by exposure of the 2,6-dideoxy-2-iodo-β-glucopyranosyl fluoride **142** to an alcohol (used in twofold excess) in dichloromethane at room temperature using 50 wt % montmorillonite K-10 in the presence of 50 wt % 5 Å molecular sieves (Scheme 28). The acceptor alcohols included cyclohexylmethanol, *n*-octanol, isopropanol, cyclohexanol, and glucopyranoside derivatives with a free hydroxyl group at C-4 and C-6. For all alcohols explored, the corresponding 2-deoxy-β-glycosides were obtained in yields of 88–97% and the α:β ratios ranged from 18:82 to 7:93. The stereoselectivity of the reactions favored the β-anomer, but the origin of this preference was not discussed.

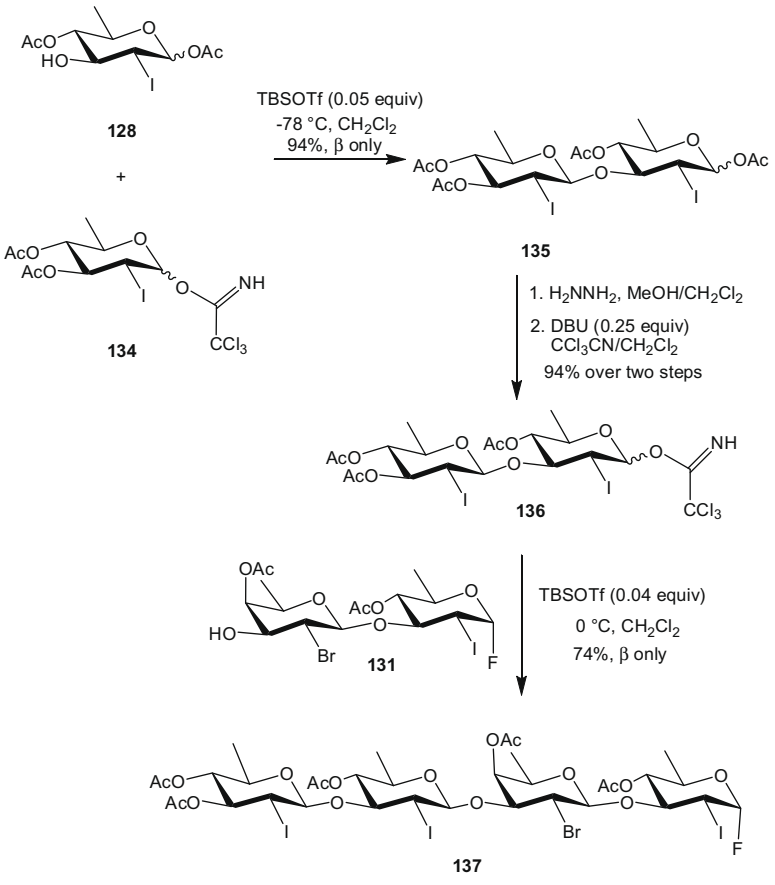
In subsequent work, the Toshima group reported that the 3,4,6-tri-*O*-benzyl-2-deoxy-α-glucopyranosyl fluoride **145** can be used to glycosylate cyclohexylmethanol (**143**, used in twofold excess) in 98% yield with α:β = 88:12 using the 5 wt % of a novel heterogeneous solid acid SO_4–ZrO_2 at 25 °C (Scheme 29).[83] The catalyst is also successful in glycosylating *n*-octanol, isopropanol, cyclohexanol, as well as primary and secondary carbohydrate alcohols. The yields ranged from 53% to 98% and α:β ratios were found from a low of 80:20 to a high of 88:12.

A striking observation was that the stereoselectivity of the glycosylation was reversed from α to β when diethyl ether was used as a solvent. In this solvent, the best case was an α:β ratio of 15:85, which was observed when the 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*xylo*-hexopyranosyl fluoride **145** was treated with *n*-octanol by employing 100 wt % of the SO_4–ZrO_2 activator in the presence of 500 wt % 5 Å molecular sieves at 0 °C (Scheme 30). Seven alcohols were glycosylated using this method and the yields ranged from 50% to 99%, and the minimum α:β ratio was 33:67.

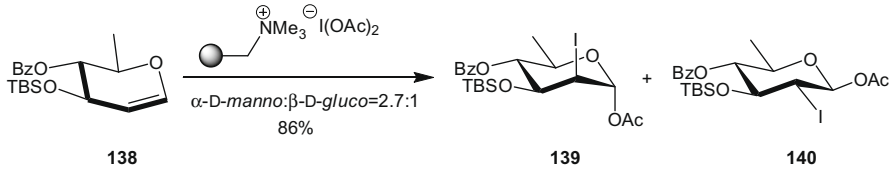
Other work on the use of glycosyl halides in the preparation of 2-deoxy-glycosides include investigations by Nicolaou et al., in which the scope of a 1,2-selenium migration to generate 2-seleno-glycosyl fluorides was probed.[44] The reaction was performed using both soluble and solid-phase intermediates starting from three β-selenopyranosides with the D-*gluco*, 6-deoxy-D-*gluco*, and



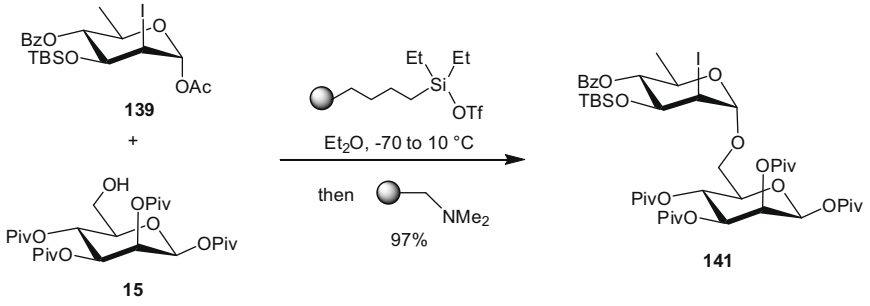
Scheme 24. Synthesis of the CDE trisaccharide of Durhamycins A and B by Roush and Durham.[78]



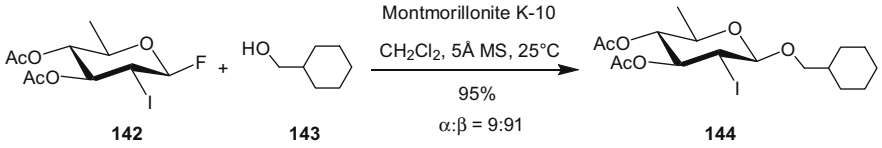
Scheme 25. Synthesis of the CDEF tetrasaccharide of Durhamycins A and B by Roush and Durham.[78]



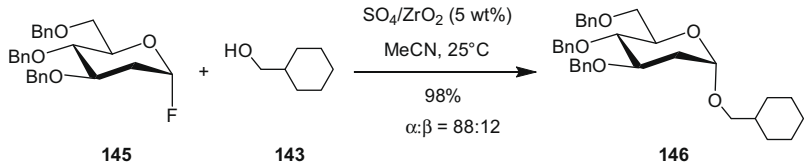
Scheme 26. Preparation of 2-deoxy-2-iodo-glycosyl acetate donor **139** using a polymer-supported reagent.[80]



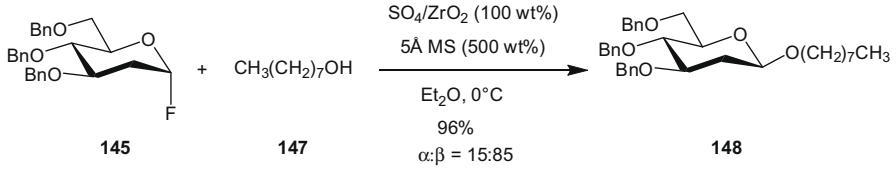
Scheme 27. Formation of 2-deoxy-2-iodo-glycosides from reaction of **139** with polymer-supported Lewis acids.[80]



Scheme 28. Synthesis of 2-deoxy-glycosides from 2-deoxy-2-iodo-glycosyl fluoride derivative **142**.[82]



Scheme 29. α-Selective glycosylations of alcohols by **145** using a SO_4–ZrO_2 promoter in acetonitrile solvent.[83]



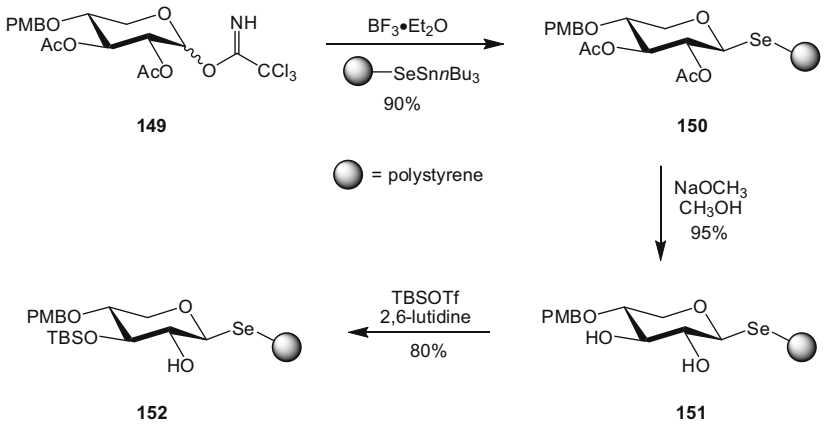
Scheme 30. β-Selective glycosylations of alcohols by **145** using a SO_4–ZrO_2 promoter in diethyl ether solvent.[83]

D-*xylo* configuration. These compounds were prepared from the corresponding glycosyl trichloroacetimidates as shown in Scheme 31. The polymer-bound case will be discussed here. Reaction of **149** with the tributylstannyl ether of resin-bound selenol was used to prepare the polymer-loaded β-selenopyranoside **150**. Next, the acetate protecting group was removed and the resulting compound **151** was treated with TBSOTf and 2,6-lutidine to give compound **152**.

Compound **152** was treated with diethylaminosulfur trifluoride (DAST), leading to a stereospecific 1,2-migration of the selenium group, with simultaneous installation of a fluoride group at C-1 (Scheme 32). Exposure of this polymer-bound 2-seleno-glycosyl fluoride **153** to alcohol **154** in the presence of $SnCl_2$, afforded the α-glycoside **155** in 89% yield. The 2-deoxy-glycoside **156** was liberated from the polymer obtained in 95% yield, by radical deselenation with *n*-Bu_3SnH.

An analogous series of transformations was performed to produce soluble selenoglycosides for solution-phase synthesis.[44] In these cases, the resin-bound selenol used in the conversion of **149** into **150** was replaced with benzeneselenol. For the solution-phase cases, the key glycosylation step (the transformation of **153** into **155**) provided the 2-deoxy-2-seleno-α-glycoside in yields of 66–95%.

In conjunction with other work on the use of glycosyl iodides as glycosylating agents, Gervay-Hague and Lam[84] have used these compounds as reagents for the synthesis of 2-deoxy-glycosides and 2,6-dideoxy-glycosides. The glycosyl iodides were efficiently prepared from the corresponding anomeric acetate (e.g., **157**) upon



Scheme 31. Preparation of polymer-bound β-selenoglycoside compound **152**.[44]

reaction with trimethylsilyl iodide (TMSI, Scheme 33). The formation of the α-glycosyl iodide was demonstrated by ^{1}H NMR spectroscopic data, which showed a dramatic downfield shift of the anomeric proton (to δ 6.95). After removal of the solvent, the mixture was dissolved in THF and a solution of KHMDS, 18-crown-6, and *O*-cresol or 1-naphthol was added, resulting in exclusive formation of β-*O*-aryl-glycosides in good yields. In the case of reactions with **158**, nucleophilic displacement with the potassium anions of *o*-cresol and 2-naphthol provided the β-glycoside in 42% and 49% yields, respectively. The low yields were ascribed to the propensity of the 2,6-dideoxy-glucosyl iodide to undergo 1,2-elimination under the basic reaction conditions. Presumably, the excellent β-selectivity results from an S_N2-like substitution of the iodide with aryloxy anions. To date, this method has not been applied to the preparation of alkyl 2-deoxy-glycosides.

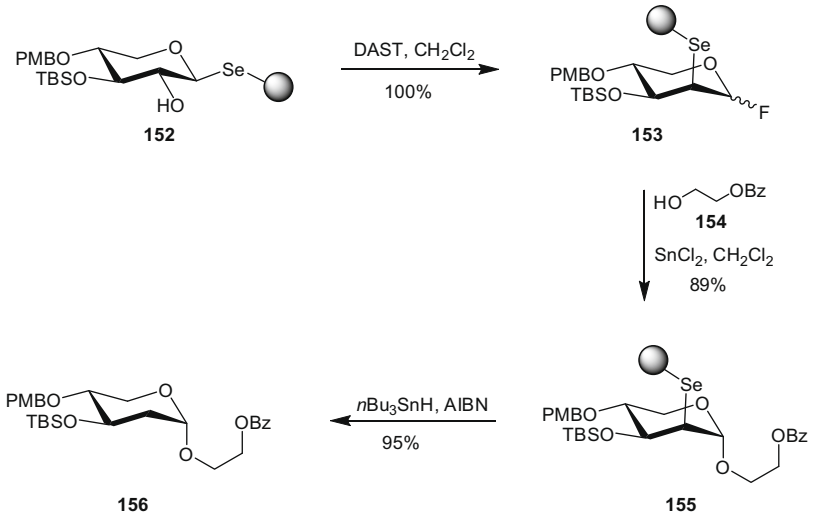
6. Use of glycals

6.1. Direct synthesis

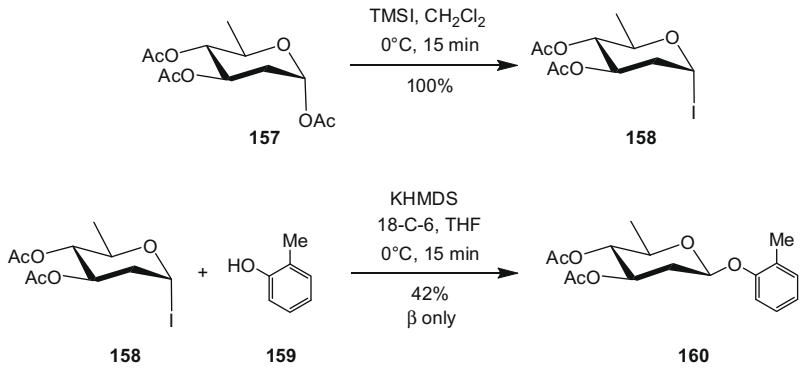
Glycals, cyclic enol ether derivatives of sugars that have a double bond between C-1 and C-2, have been increasingly used in the preparation of oligosaccharides[10,85] and it is therefore not surprising that a number of groups have used these compounds as intermediates in the preparation of 2-deoxy-glycosides. With glycals, both the direct and indirect syntheses of 2-deoxy-glycosides are possible. In the case of direct conversion, the reaction proceeds through an anomeric oxocarbenium ion intermediate produced by the addition of an acid to the double bond. In the majority of these cases, the axial (α-) glycoside is formed as the major product due to the preference for the alcohol to add to this oxocarbenium ion in a manner favored by the anomeric effect.

A number of protic and Lewis acids have been used to activate glycals in the presence of an alcohol leading to 2-deoxy-glycosides.[86–92] A recent paper by Yadav et al. reported a mild and efficient method for preparing 2-deoxy-glycosides from glycals using the $CeCl_3{\cdot}7H_2O$–NaI reagent system (Scheme 34).[93] Glycals such as 3,4,6-tri-*O*-acetyl-D-glucal, 3,4,6-tri-*O*-acetyl-D-galactal, and 3,4-di-*O*-acetyl-D-xylal were evaluated to determine the scope and generality of this protocol, and a range of simple alcohol acceptors (e.g., allyl alcohol, *n*-octanol, phenyl allyl alcohol, and (*E*)-hex-2-en-1-ol) were examined. The reactions proceeded smoothly in the presence of the promotor in acetonitrile at reflux, resulting in the exclusive formation of 2-deoxy-α-glycosides in yields of 78–90%. In the absence of sodium iodide, however, the reactions underwent Ferrier rearrangement to afford the corresponding 2,3-unsaturated hexopyranosides in favor of the 2-deoxy-α-glycosides.

In later work, the Yadav group disclosed that the glycals can be used for the synthesis of 2-deoxy-thioglycosdes using gallium(III)



Scheme 32. Conversion of polymer-bound selenoglycoside **152** into 2-deoxy-glycoside **156** by way of a glycosyl fluoride intermediate.[44]



157 158 158 159 160

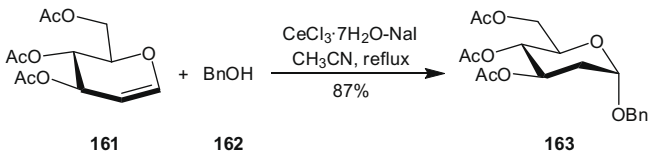
Scheme 33. Synthesis of 2-deoxy-glycosyl iodide **158** and its use in the preparation of aryl 2-deoxy-glycosides.[84]

trichloride as a catalyst (Scheme 35).[94] Reactions between 3,4,6-tri-*O*-acetyl-D-glucal, 3,4,6-tri-*O*-acetyl-D-galactal, and 3,4-di-*O*-acetyl-D-xylal, and ten substituted thiophenols and thionaphthols provided thioglycosides in 75–95% yields with a high α-selectivity (the α/β ratio ranged from 8:2 to 19:1). Not unsurprisingly, reactions of substance with electron-donating substituents on the aromatic ring gave higher yields than for those bearing the electron-withdrawing substituents.

In a similar series of reactions, Colinas and co-workers have described the optimization of a simple method for producing *N*-sulfonyl glycosides using 3,4,6-tri-*O*-benzyl-D-galactal (**166**) or 3,4,6-tri-*O*-benzyl-glucal (**169**) as donor (Scheme 36).[95] The glycosylation protocol was performed with 1.1 equiv of sulfonamide in dichloromethane catalyzed by 5 mol % $HBr{\cdot}PPh_3$. A range of sulfonamides bearing alkyl or aryl moieties serve as acceptors in the reaction. In all cases, only the 2-deoxy-β-sulfonamidoglycosides were isolated. Sulfonamides with more sterically demanding groups required stronger conditions, for example, heating at reflux in dichloromethane for over 12 h, and these substrates afforded the corresponding products in lower yields. It was suggested that the β-selectivity of the process results from the preferential attack of the sterically demanding sulfonamide from the less hindered equatorial position. Alternatively, it was proposed that the reaction is under thermodynamic control and that the α-sulfonamide product could isomerize to the β-isomer under the conditions of the reaction. However, no mechanistic studies were performed to test these hypotheses.

Another approach to 2-deoxy-α-glycosides, involving catalysis by a high-oxidation-state rhenium-oxo complex, was developed by Toste and co-workers (Scheme 37).[96] 3,4,6-Tri-*O*-benzyl-D-glucal (**169**) and 3,4,6-tri-*O*-benzyl-D-galactal (**166**), as well as related derivatives with different protecting groups, underwent the reaction with a range of alcohols when performed in toluene in the presence of 1 mol % of $[ReOCl_3(SMe_2)(Ph_3PO)]$ as the catalyst. The catalytic system tolerated a number of commonly used protecting groups, including isopropylidene acetals, silyl ethers, acetates, and benzoates.

Reactions with the galactal derivatives proceeded with complete α-selectivity, whereas the glucal derivatives generally gave



161 162 163

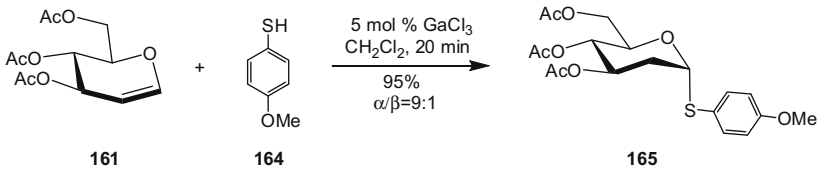
Scheme 34. Synthesis of 2-deoxy-α-glycosides from glycals using the $CeCl_3{\cdot}7H_2O$–NaI reagent system.[93]

mixtures of products in which the α-isomer was favored by about a 3:1 ratio over the β-isomer. However, some reactions with the glucal derivatives gave only the α-glycoside as the sole product. Through the use of a deuterium-labeling experiment, the authors concluded that the selectivity of the reaction is determined not in the olefin activation step, but in the transfer of the nucleophile to the complex formed between the glycal and the catalyst. Product yields ranged from 56% to 86%, and the catalyst system also allows for the use of sulfonamides and thiols as nucleophiles.

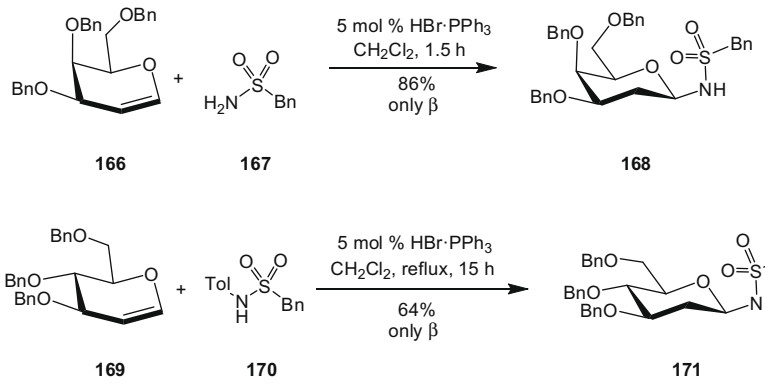
Another recently reported method, developed by Vankar and co-workers,[97] involves the ceric ammonium nitrate (CAN) oxidation of the glucal **169** and galactal **166** in the presence of an alcohol (Scheme 38). The couplings were performed in anhydrous acetonitrile in the presence of the alcohol and 2 mol % of CAN as a catalyst. Galactal **166** gave the 2-deoxy-glycoside in 60% yield with modest α-selectivity. Another eight examples were performed using both simple and carbohydrate alcohols, which led to products in yields of 26–78% with modest to excellent selectivity for the α-glycoside. On the other hand, reactions between glucal **169** and simple alcohols such as methanol, allyl alcohol, cyclohexanol, and *t*-butanol led to the formation of 2-deoxy-glycosides in 34–65% yield together with the corresponding Ferrier by-product. The Ferrier by-products can be suppressed by using four equivalents of CAN. It was proposed that the reaction proceeds via the generation of HNO_3 in solution, which then protonates the glycal, generating an oxocarbenium ion that reacts with the alcohol.

In a follow-up of previous work from the Falck and Mioskowski groups,[87] Wandzik and Bieg examined the stereoselectivity of the addition of various alcohols to L-rhamnal derivatives promoted by triphenylphosphine hydrobromide (TPHB).[98] The stereoselectivity of the outcome in the Falck–Mioskowski method is influenced by the protecting group at C-3 in the glycal. Significant predominance of the α anomer was obtained when 4-*O*-acetyl-3-*O*-*t*-butyldimethylsilyl-L-rhamnal (**177**, Scheme 39) was used in reactions with glycerol derivatives and monosaccharide alcohols. It was proposed that the use of the bulky *t*-butyldimethylsilyloxy group at the C-3 position blocks the approach of the nucleophile from the bottom face of the ring, and leading to the observed α-stereoselectivity.

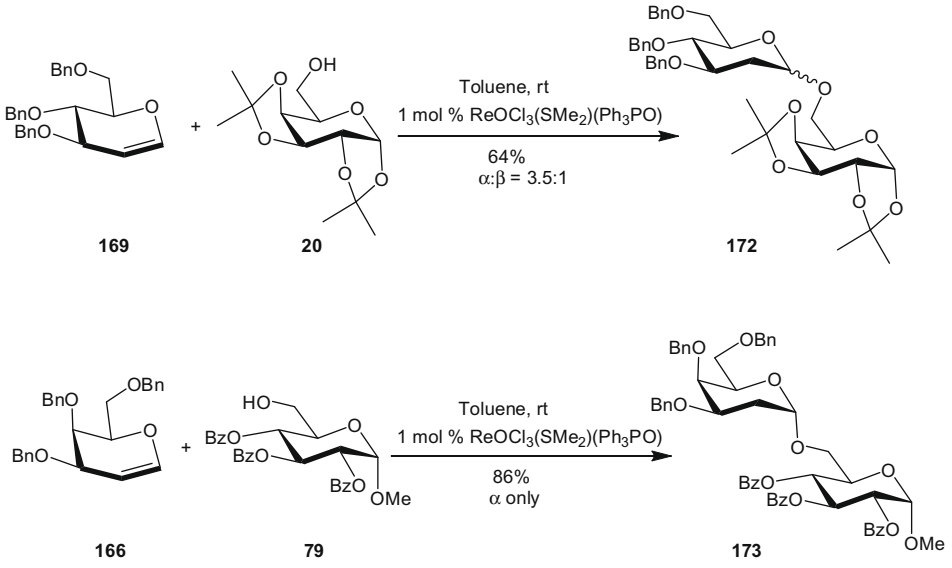
In a related investigation, Kirschning and co-workers showed that polymer-bound diphenylphosphine hydrobromide can be employed in the activation of glycals to suppress the formation of by-products arising from the Ferrier rearrangement (Scheme 40).[99] It was further demonstrated that only 0.1 mol % of the polymer-attached catalyst can promote two glycosylations in a one-pot procedure. For instance, addition of disilylated L-fucal (**182**) to the reaction mixture after coupling of L-fucal derivative (**180**) to decarestrictine (**179**) to generate **181**, initiated the second glycosylation, affording glycoconjugate **183** in 62% overall yield and with



Scheme 35. Synthesis of 2-deoxy-α-thioglycosides from glycals using the $GaCl_3$.[94]



Scheme 36. Formation of *N*-sulfonyl glycosides from benzylated glycals using catalytic $HBr{\cdot}PPh_3$.[95]



Scheme 37. $[ReOCl_3(SMe_2)(Ph_3PO)]$-catalyzed formation of 2-deoxy-glycosides from glycals.[96]

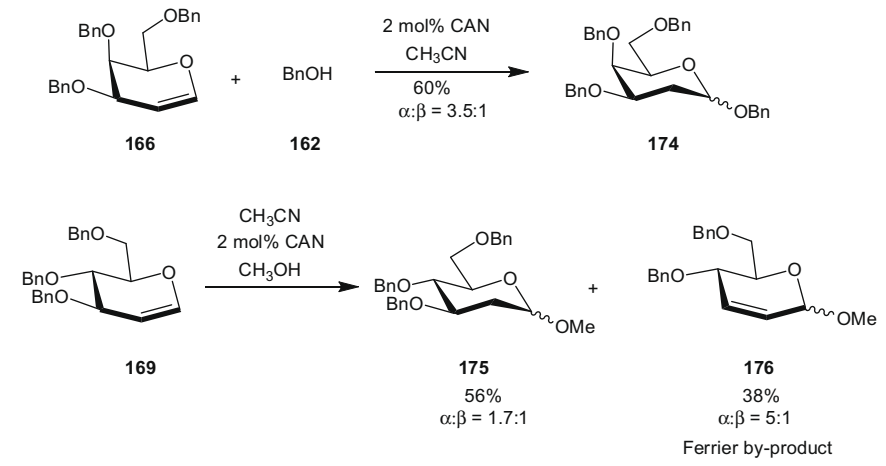
excellent selectivity (only the α-anomer was produced in both glycosylation steps).

6.2. Indirect synthesis

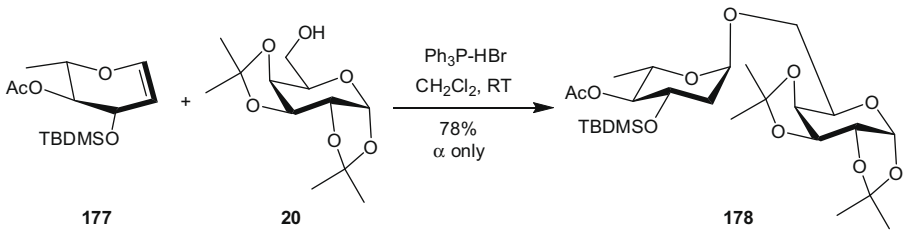
The indirect synthesis of 2-deoxy-glycosides has also been performed using a number of different approaches. In one particularly elegant study, Capozzi and co-workers reported that carbohydrate-fused 1,4-oxathiine derivatives, prepared by cycloaddition reaction of glycals with oxothioheterodienes, are effective donors for the stereospecific synthesis of 2-deoxy-2-thio-β-glycosides.[100] For example, starting from 3,4,6-tri-*O*-benzyl-D-glucal (**169**), the α-*gluco* adduct (**185**) was obtained in 83% yield and excellent stereoselectivity (19:1 α-*gluco*:β-*manno*) upon reaction with β-diketone **184** (Scheme 41).

The direct activation of cycloadduct **185** with acid promoters in nitromethane led to the sluggish formation of β-glycosides. Improvement on the reaction could be accomplished by conversion of the unsaturated ketone into an allyl acetate or the corresponding allyl *t*-butyldimethylsilyl ether, by reduction of the ketone and derivatization (Scheme 42).

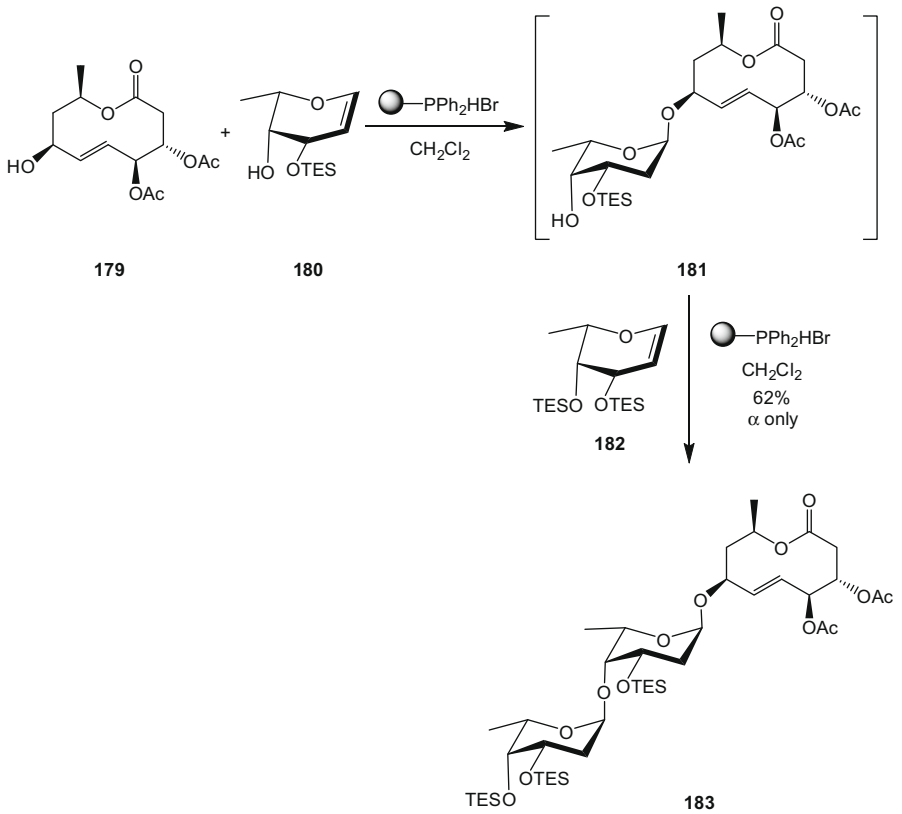
Subsequent glycosylation of these modified cycloadducts **186** and **187**, was achieved by reaction with an alcohol and methyl triflate in either nitromethane or dichloromethane, which provided exclusively the β-glycosides (Scheme 43). The yields of glycosides obtained ranged from 38% to 89%. Desulfurization was



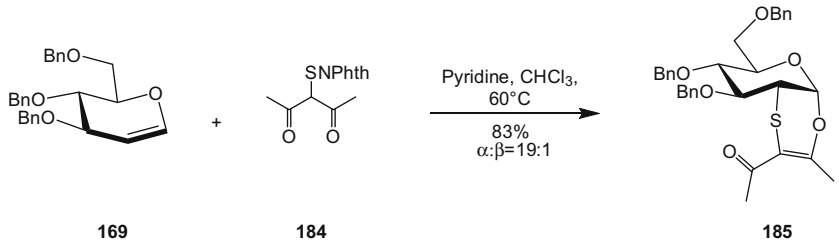
Scheme 38. Activation of glycals with CAN for the synthesis of 2-deoxy-glycosides.[97]



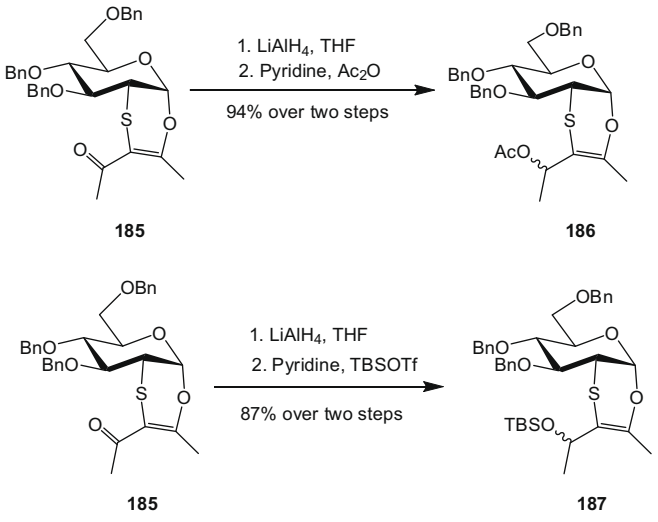
Scheme 39. Triphenylphosphine hydrobromide promoted glycosylation of glycals.[98]



Scheme 40. Preparation of **183** through a one-pot diglycosylation process.[99]



Scheme 41. Cycloaddition between glucal **169** and β-diketone **184**.[100]



Scheme 42. Synthesis of **186** and **187**.[100]

accomplished using Raney Nickel in wet THF to afford the corresponding 2-deoxy-β-glycosides in 51–69% yield.

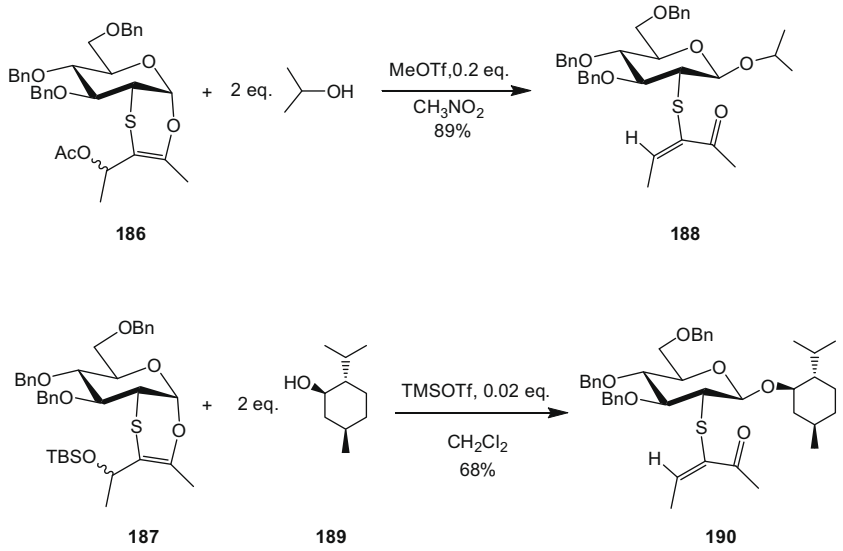
7. De novo synthesis

De novo synthesis of 2-deoxy-glycosides starting from non-carbohydrate precursors by employing asymmetric synthesis has been carried out with increasing frequency. For example, O'Doherty and Zhou have described a highly stereoselective approach to the cardiac glycoside digitoxin and its trisaccharide moiety digoxose from achiral 2-acylfuran.[101,102] The key steps of the synthetic strategy involve the iterative application of the palladium-catalyzed glycosylation of a pyranone derivative **191** (obtained in three steps from 2-acyl furan), Myers' reductive 1,3-alkene transposition,[103,104] and diastereoselective dihydroxylation (Scheme 44).

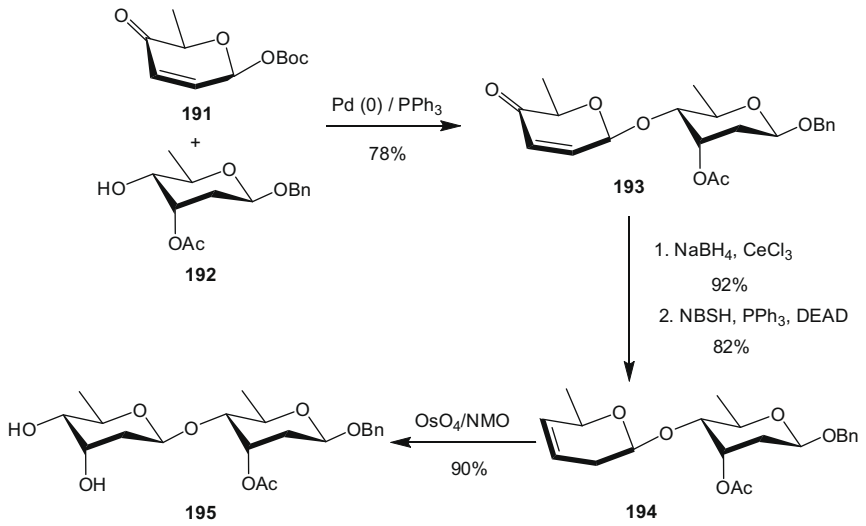
In the presence of 5 mol % Pd and 10 mol % PPh_3, glycosylation of the C-4 secondary alcohol in **192** with 2 equivalents of pyranone **191** provided the β-(1→4)-linked disaccharide **193** in 78% yield. Reduction of the ketone under Luche conditions[105] and isomerization of the double bond gave **194** in 75% yield over the two steps. Dihydroxylation with a catalytic amount of osmium tetroxide and *N*-methyl-morpholine oxide gave a 90% yield of disaccharide **195**. Iteration of this approach led to the target molecule digitoxin **199** (Scheme 45).

In 2008, O'Doherty and Zhou applied a similar strategy to the preparation of the α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose trisaccharide portion in Landomycin A (Scheme 46).[106] The glycosylation of disaccharide acceptor **201** and α-L-pyranone **200** afforded the trisaccharide pyranone **202** in 95% yield with complete stereocontrol at anomeric center. Luche reduction proceeded in 93% yield to give exclusively the alcohol, which had inverted stereochemistry compared to the target compound. Mitsunobu reaction afforded the desired product **203** in 97% yield. After removal of benzoate, diimide reduction of the olefin and desilylation, the repeating trisaccharide unit of Landomycin A, **204**, was successfully achieved.

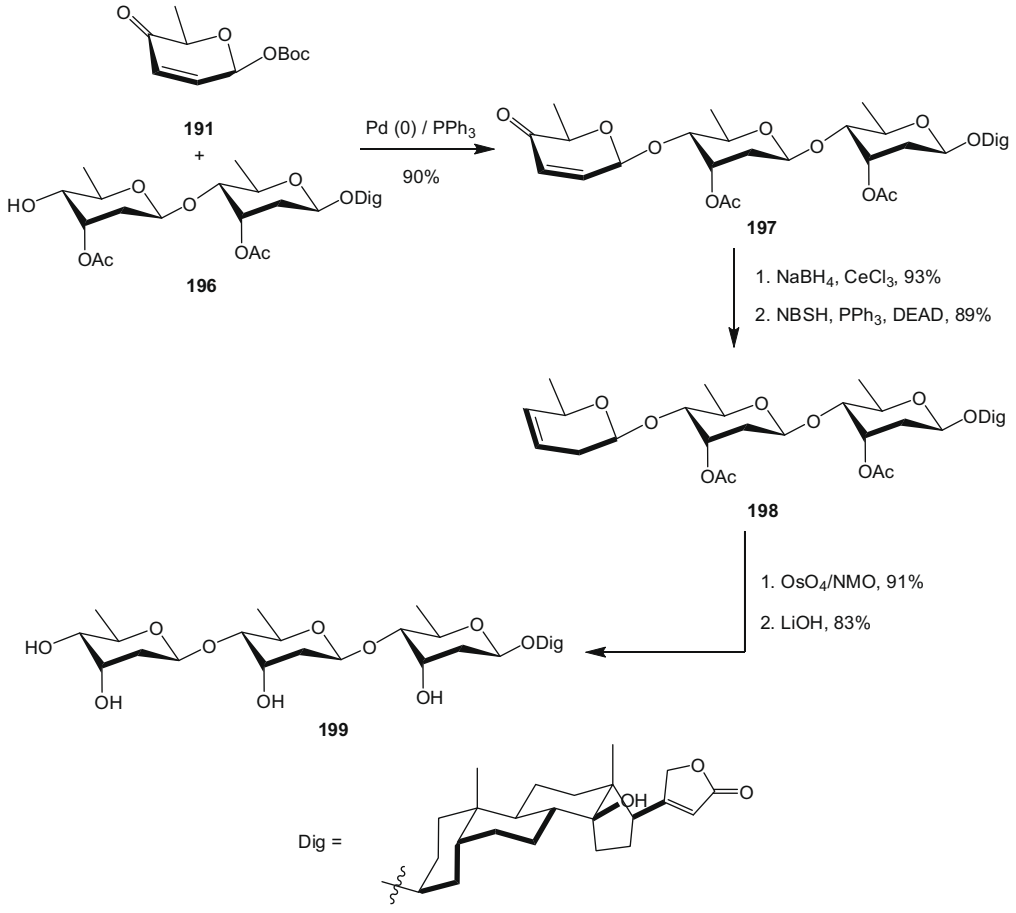
Another fundamentally different approach to 2-deoxy-glycosides has been reported by McDonald et al. (Scheme 47). Key to



Scheme 43. Glycosylation of alcohols with **186** and **187**.[100]

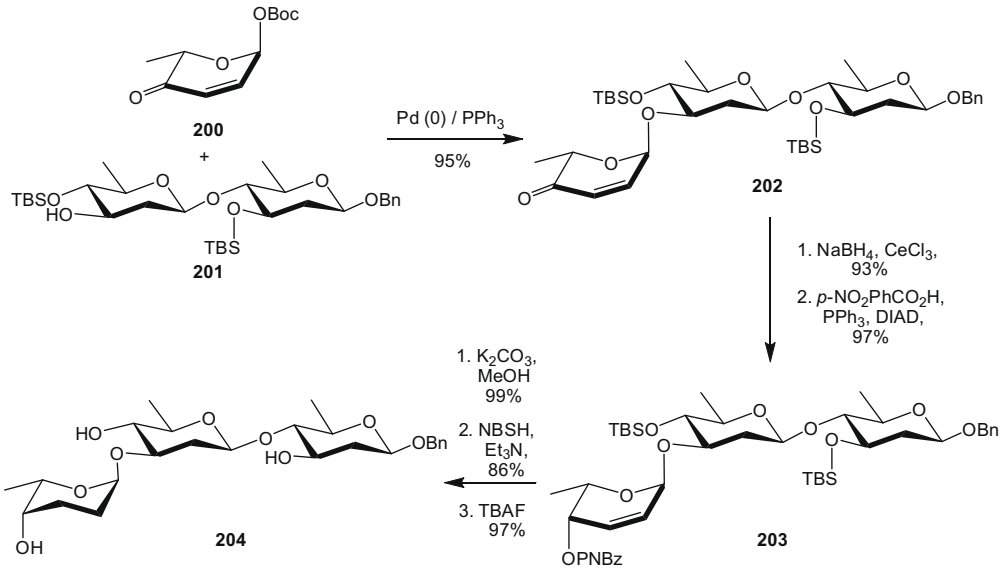


Scheme 44. The key steps used in the de novo synthesis.[102]



Scheme 45. Synthesis of target molecule digitoxin **199**.[102]

their method is a tungsten-catalyzed alkynol cycloisomerization, which is applied to the synthesis of 6-deoxy-glycals.[107] This single-step cycloisomerization is accomplished when the alkynol substrates (e.g., **205**) are photolyzed at 350 nm in THF at reflux in the presence of triethylamine using catalytic amounts of $W(CO)_6$ (25 mol %). The reaction was shown to be applicable to the preparation D-*ribo*, L-*lyxo*, D-*arabino*, L-*xylo* configured glycals in yields of 77–98%. The successful *endo*-selectivity is highly dependent on maintaining anaerobic conditions, as the exocyclization by-product is produced when such conditions are not used. This cycloisomerization transformation has been accomplished, for instance, with alkynol substrates **205**, providing the corresponding D-*ribo* glycal **206** in 98% yield, as shown in Scheme 47. To synthesize oligosaccharides via this approach, the glycal product (**206**) is reacted

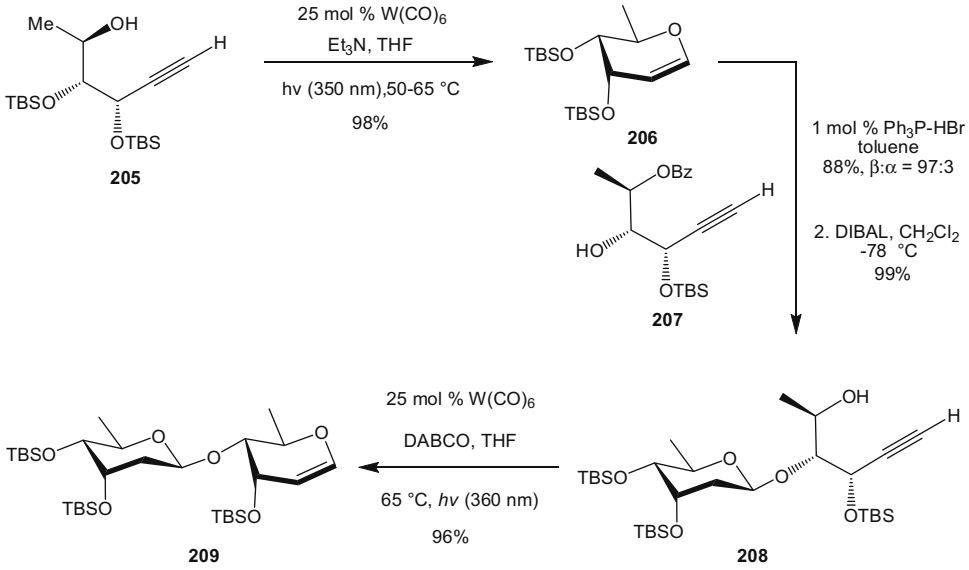


Scheme 46. Synthesis of the repeating trisaccharide **204** in Landomycin A.[106]

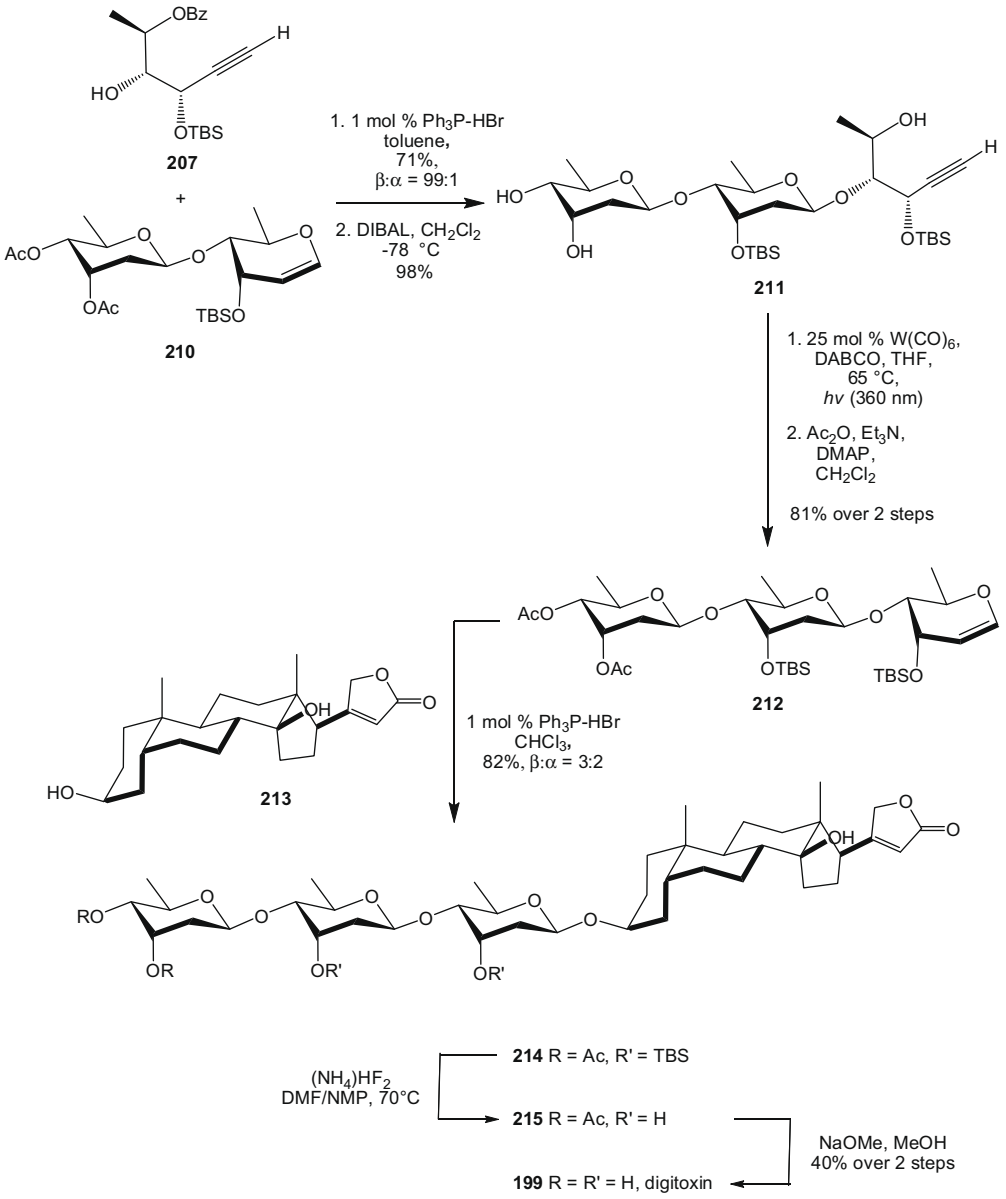
with an alkynol (**207**) in the presence of $HBr{\cdot}PPh_3$ to generate a product (**208**) that, following removal of the benzoate ester, is a substrate for the application of the $W(CO)_6$-catalyzed cycloisomerization reaction. In the case of **208**, the reaction gave the 2-deoxydisaccharide glycal **209** in 96% yield.

This strategy can be iterated and has been applied for the synthesis of digitoxin.[108] As shown in Scheme 48, the synthesis used protic acid-catalyzed stereoselective glycosylation of glycal **210** with alkynyl alcohol **207**. Upon reaction with Ph_3P–HBr in toluene, the reaction provided the 2-deoxy-glycoside with excellent anomeric stereoselectivity on multimillimol scale. Reductive debenzoylation and tungsten carbonyl catalyzed endo-selective cycloisomerization of alkynol substrate followed by acetylation gave the trisaccharide glycal **212**. Ph_3P–HBr-catalyzed glycosylation in $CHCl_3$ between the trisaccharide glycal **212** and digitoxigenin aglycone **213** afforded a β:α 60:40 mixture of 2′-deoxyglycoconjugate (Scheme 48). Deprotection of the TBS protective groups of **214** was achieved by ammonium hydrogen fluoride in dimethylformamide–*N*-methylpyrrolidine solvent. The remaining acetate protective groups of **215** were then removed to give digitoxin **199**.

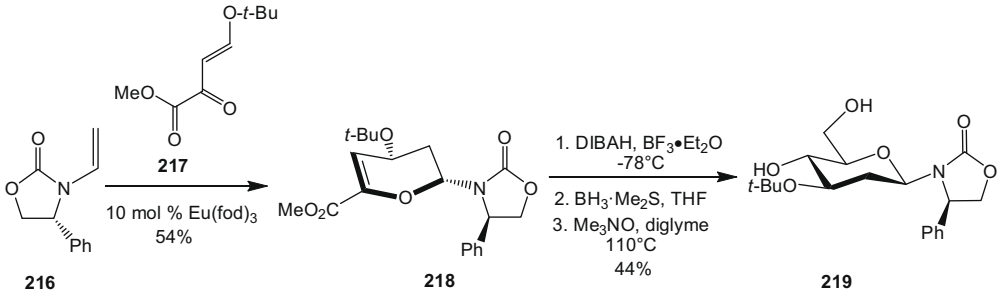
Another de novo approach is a [4+2]-based protocol for the preparation of the simple 2-deoxy N-glycosides, which has been reported by Dujardin and co-workers (Scheme 49).[109] This heterocycloaddition method involves the use of *N*-vinyl-2-oxazolidinones as a chiral dienophile. Under $Eu(fod)_3$(10 mol %)-catalyzed conditions, a variety of dienophiles were reacted with 4-*tert*-butoxymethylene pyruvic acid ester (**217**) to afford heteroadducts with a nearly total *endo*-selectivity and a high facial selectivity (from 95:5 to 98:2) in yields of 40–66%. The adducts derived from *N*-vinyl-2-oxazolidinones could then be converted to either D-*arabino* or L-*arabino* configured 2-deoxy-*N*-β-glycosyl oxazolidinones. The transformations in this sequence include reduction of the ester at C-6 to the hydroxymethyl group and subsequent regio- and stereoselective hydroboration–oxidation of the double bond. As a consequence, the final *N*-glycosyl oxazolidinones were isolated in 32–58% overall yields and in a high overall diastereomeric purity (>98% in all cases).



Scheme 47. De novo synthesis of 2-deoxy-β-glycosides using McDonald's cycloisomerization strategy.[107]



Scheme 48. Synthesis of the digitoxin **199**.[108]



Scheme 49. De novo synthesis of 2-deoxy-*N*-β-glycosyl oxazolidinone **219**.[109]

8. Applications to natural product synthesis

The methods discussed in the previous sections have, in most cases, been applied to preparation of biologically relevant oligosaccharides. While a few of these were discussed above, additional examples are summarized in this section.

Apoptolidin (Fig. 23), isolated from the soil bacteria *Nocardiopsis* sp. by Hayakawa et al. in 1997, contains a 20-membered macrocyclic ring and carries a disaccharide moiety consisting of D-oleandrose and L-olivomycose, as well as a 6-deoxy-glucose residue.[110,111]

Roush and co-workers reported the construction of the 2-deoxy-β-glycosidic linkage in the disaccharide moiety by

employing their 2-deoxy-2-iodo-glycosyl acetate donors (Scheme 50).[112] Specifically, treatment of a mixture of 2-deoxy-2-iodo-β-glucopyranosyl acetate **220** and acceptor **221** with 1.0 equiv of TBSOTf at 0 °C gave the desired 2-deoxy-β-disaccharide **222** in 60% yield without the formation of regio- or stereoisomers. The activated disaccharide acetate **224**, which serves as the glycosyl donor for glycosylation of late stage intermediates en route to completion of a total synthesis of apoptolidin A, was accomplished by a two-step procedure. Treatment of **222** with ceric ammonium nitrate (CAN), followed by acetylation provided the targeted disaccharide donor **224** in 87% yield as a ca. 6:4 mixture of anomeric acetates.

The same disaccharide moiety was prepared by, Nicolaou et al.[113] using a method involving 1,2-phenylsulfeno migration to prepare a 2-deoxy-2-phenylthio glycosyl fluoride (**226**), a crucial donor in directing the formation of desired β-linkage (Scheme 51). In the preparation of this donor, the 6-deoxy-α-*manno*-thioglycoside **225** was treated with DAST, which gave glycosyl fluoride **226** in quantitative yield, accompanied by inversion of configuration at C-2. Glycosylation between glycosyl fluoride **226** and acceptor **227** in diethyl ether, promoted by tin(II) chloride, furnished the desired 2-deoxy-β-glycoside **228** in 45% yield together with its 3-*O*-regioisomer (26% yield). Glycosylation of C-3-protected derivatives (TMS, TBS, and OAc) failed, presumably due to steric shielding exerted by the protecting group over the neighboring C-4 position. The activated glycosyl donor **231** used for the completion

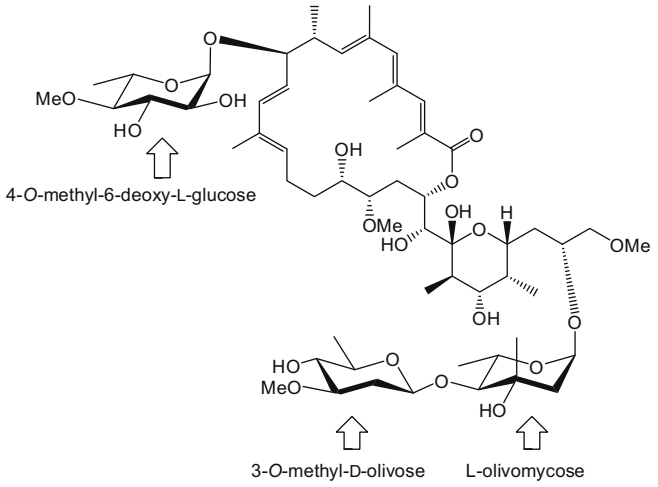


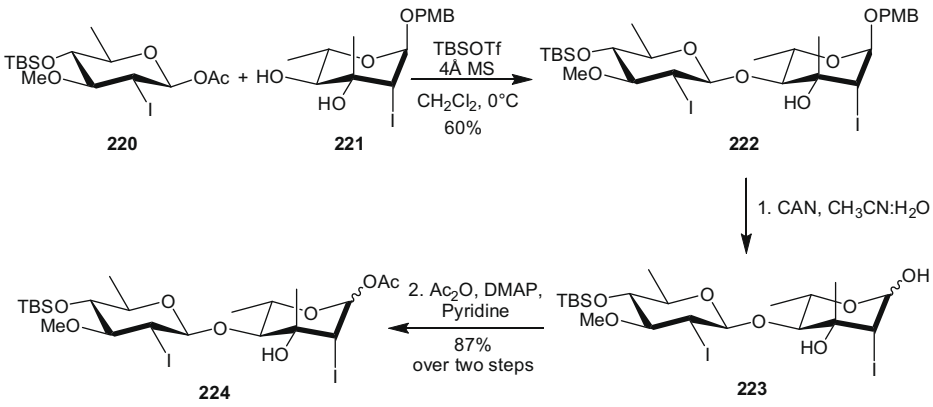
Figure 23. Structure of apoptolidin.

of the total synthesis of apoptolidin proceeded in a three-step procedure. Initially, installment of a TES group onto the tertiary alcohol afforded **229** in 84% yield. Exposing **229** to Raney Nickel resulted in the removal of the two thiophenyl groups and the benzyl moiety in 92% yield. After treatment of the resulting lactol **230** with DAST, the activated glycosyl donor **231** was obtained in quantitative yield in a 3:1 ratio of anomers.

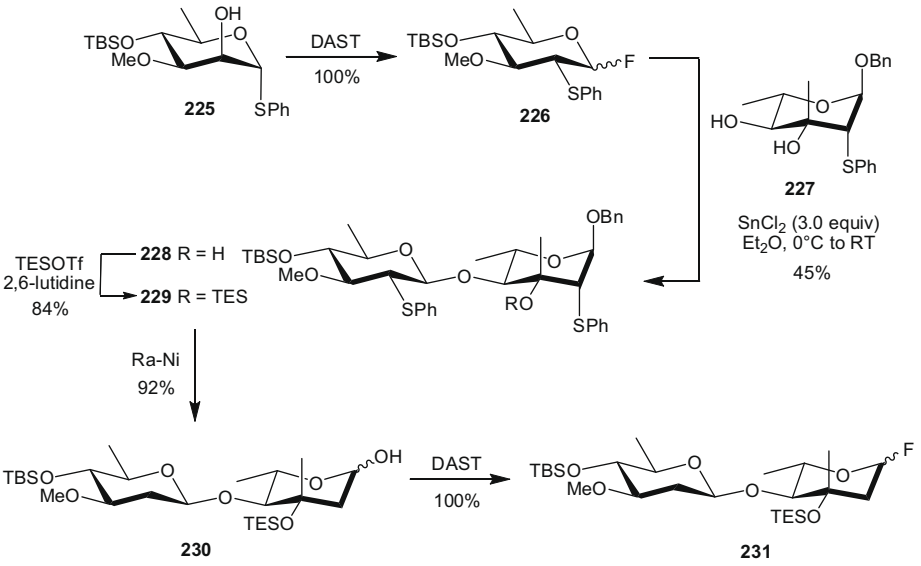
A third approach to this target was reported by Koert and co-workers, who reported the successful application of the 2-deoxy-2-phenylthio-glucopyranosylimidate (**233**) to assemble the 2-deoxy-β-disaccharide unit in apoptolidin (Scheme 52).[114] The key glycosidic linkage was formed by treatment of acceptor **232** and donor **233** in the presence of TMSOTf, leading to the disaccharide **234** in 87% yield with a 95:5 β-selectivity. The glycosylation in diethyl ether gave better yield than that performed in dichloromethane. Subsequently, the tosylate in **234** was converted into an iodide by treatment with NaI in *N,N′*-dimethylformamide (DMF) at 90 °C. The preparation of the protected 2-deoxy-disaccharide **236** was accomplished by reductive removal of the iodo and the thioaryl groups upon *n*-Bu_3SnH and AIBN in toluene at 100 °C.

The preparation of the 2-deoxy-β-disaccharide unit toward the total synthesis of apoptolidin described by the Crimmins group employed a glycosylation between **238** and **239** in the presence of Ag_2O–silica gel (Scheme 53).[115] The glycosyl bromide **238** was generated in situ by exposure of hemiacetal **237** to Me_3SiBr in benzene. The reaction between **238** and **239** produced the desired 2-deoxy-β-disaccharide **240** in 68% yield in a β:α ratio of 6:1. Only trace amounts of disaccharide linked via the tertiary hydroxyl group were detected. Protection of the tertiary hydroxyl group using triethylsilyl triflate and 2,6-lutidine in dichloromethane followed by hydrogenolysis with 10% Pd/C in ethanol afforded the hemiacetal **241** in 72% yield over two steps.

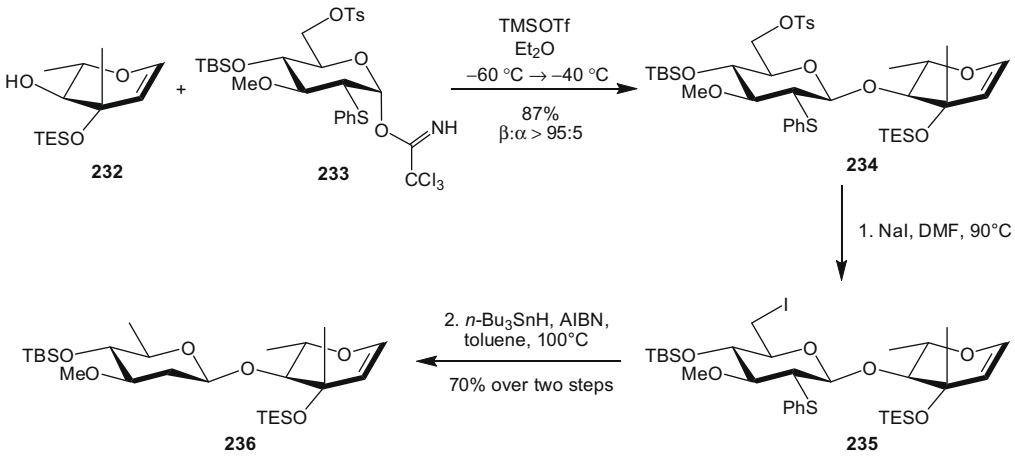
Landomycin A, a member of the angucycline antibiotic family, was first reported in 1990 from *Streptomyces cyanogen*. The molecule bears a hexasaccharide comprising two repeating α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose trisaccharides.[116,117] Yu and co-workers utilized phenyl 2,3-*O*-thionocarbonyl-1-thioglycosides **242** as a precursor for the stereoselective synthesis of β-linkage in this trisaccharide (Scheme 54).[118] The iterative glycosylation steps in the synthetic approach, for example, coupling of 4-hydroxy thioglycoside **243** and donor **242**, was performed in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and MeOTf, providing β-(1→4)-linked disaccharide **244** in 88% yield. Construction of the α-glycosidic bond was achieved by using 1,4-di-*O*-acetyl-L-rhodinose **246** as donor. Removal of 2-thiophenyl groups and benzyl protecting groups was accomplished by Raney Nickel at 40 °C, affording the target hexasaccharide **249**.



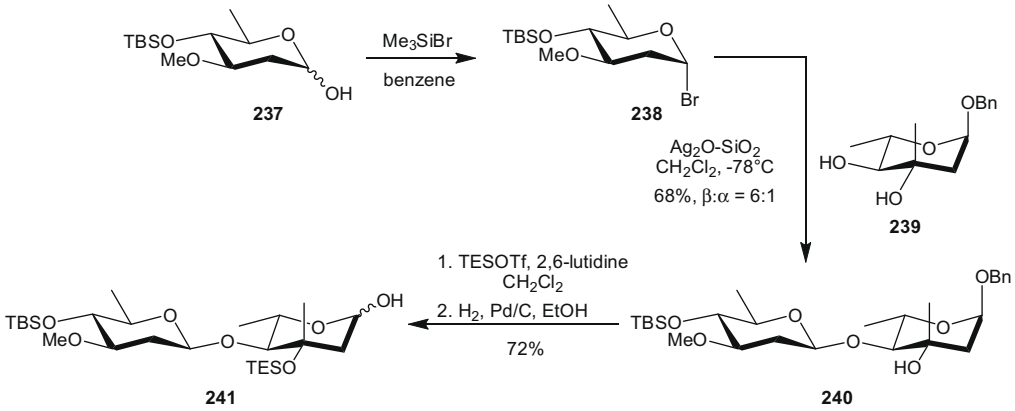
Scheme 50. Key glycosylation reaction in synthesis of the apoptolidin disaccharide moiety by Roush and co-workers.[112]



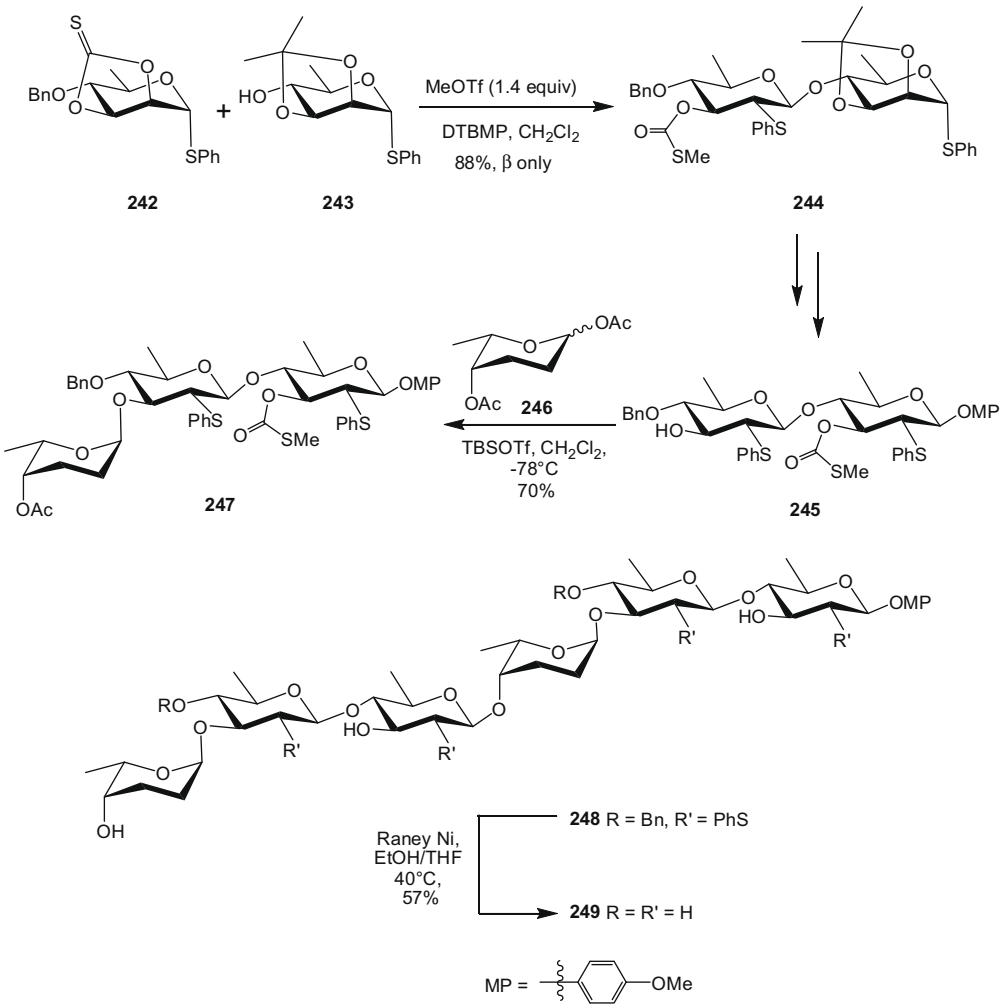
Scheme 51. Key steps in the synthesis of the apoptolidin disaccharide moiety by Nicolaou et al.[113]



Scheme 52. Key steps in the synthesis of the apoptolidin disaccharide moiety by Koert and co-workers.[114]



Scheme 53. Key steps in the synthesis of the apoptolidin disaccharide moiety by Crimmins and Long.[115]



Scheme 54. Synthesis of the Landomycin A hexasaccharide by Yu and Wang.[118]

9. Summary

This review concentrated on the most recent progress in the development of methods for the synthesis of 2-deoxy-glycosides. Several approaches have been outlined. As was true at the time of an earlier review on this topic,[8] a number of strategies for the synthesis of 2-deoxy-glycosides rely on an indirect approach in which the presence of a group such as a halide, alkylthio, or alkylseleno substituent at the C-2 position directs the stereoselectivity of the reaction. These substituents generally promote highly selective glycosylations either through anchimeric assistance, or by inducing conformational effects in the donor that favor formation of the product in which the algycone is trans to the group at C-2. In addition, the presence of the substituent at C-2, being electron-withdrawing compared to a hydrogen, minimizes anomerization under acidic glycosylation conditions. However, these methods require a subsequent reduction step of the group at C-2.

On the other hand, the direct strategy, which uses 2-deoxy-glycopyranosyl donors to form the 2-deoxy-glycoside in only one step, is more efficient and has been the focus of a number of more recent studies. 'Stable' glycosyl donors, for example, glycosyl acetates, fluorides, thioglycosides, and glycals, are widely employed in both direct and indirect strategies, offering reliable and efficient methods for the preparation of 2-deoxy-glycosides. The trichloroacetimidate donors have been particularly useful for the glycosylation of less reactive acceptors. Regardless of the selected technique, the best stereoselectivities are typically obtained when the glycosylations are performed under mild reaction conditions; the influence of other factors such as a protecting group pattern in both glycosyl donor and glycosyl acceptor, solvent effects, and steric hindrance must be taken into consideration; however, in general these effects are not well understood. Clearly, this is an area that would benefit from detailed mechanistic investigation.

Acknowledgments

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