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Review

Glycosyl iodides. History and recent advances

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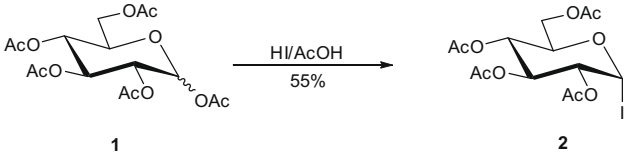
ABSTRACT

The use of glycosyl iodides as an effective method for the preparation of glycosides has had a recent resurgence in carbohydrate chemistry, despite its early roots in which these species were believed to be of limited use. Renewed interest in these species as glycosylating agents has been spurred by their demonstrated utility in the stereoselective preparation of O-glycosides, and other glycosylic compounds. This review provides a brief historical account followed by an examination of the use of glycosyl iodides in the synthesis of oligosaccharides and other glycomimetics, including *C*-glycosylic compounds, glycosyl azides and N-glycosides.

Contents

1. Introduction

Efficient formation of glycosidic linkages has played an important role in the development of modern synthetic carbohydrate chemistry.[1] Among the various types of donors that can be employed for the construction of glycosidic bonds, glycosyl iodides have long been underutilized. However, over the past 10 years, a number of advances in the preparation and use of glycosyl iodides



1 2

Scheme 1. First preparation of a glycosyl iodide from a per-O-acetylated monosaccharide.[5]

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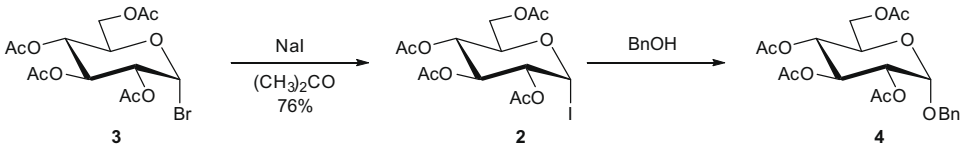


Scheme 2. Synthesis of benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside via a glycosyl iodide.[8]

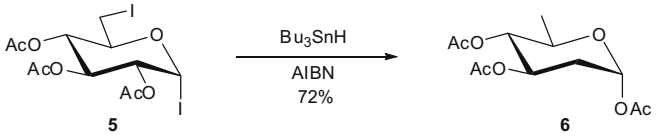
have been made. Of particular note, in head-to-head comparisons between glycosyl iodides and the more commonly used glycosyl bromide, thioglycoside and trichloroacetimidate donors, these species have often been shown to offer products in higher yield and/or with superior stereoselectivity. Thus, despite their relative lack of previous use, glycosyl iodides should now be viewed as versatile glycosylation reagents. In this review we summarize the history of glycosyl iodides in the field of synthetic carbohydrate chemistry and describe their use in the assembly of glycosidic bonds, with a particular focus on advances made since this area was last reviewed by Gervay-Hague.[2]

2. History and general features

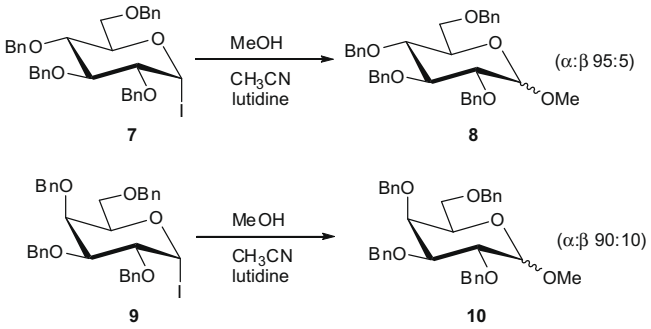
Glycosyl iodides were developed initially as an extension of the glycosyl chloride methodology developed by Michael[3] and the glycosyl bromide methodology developed by Koenigs and Knorr in 1901.[4] The first reported synthesis of a glycosyl iodide dates back almost a century, to 1910, with the successful preparation of several glycosyl iodides by Emil Fischer, upon treatment of a per-acetylated sugar (e.g., **1**) with HI in acetic acid[5] (Scheme 1). Shortly afterwards, several other preparations were reported, again involving the treatment of per-acetylated carbohydrates with HI in acetic acid.[6,7] The first glycosylation using a glycosyl iodide donor was conducted in 1929 when Helferich and Gootz prepared the crystalline 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide (**2**) and successfully produced the benzyl glycoside **4** upon treatment with benzyl alcohol in the absence of promoter[8] (Scheme 2). Despite this success, glycosyl iodides received little attention as glycosyl donors until more recently.

This lack of attention can mainly be attributed to the perceived high level of reactivity and instability of these species.[9] Glycosyl iodides are thermally unstable and subject to homolytic cleavage; however, this requires elevated temperatures of 70 °C or higher.[10] The ability of the carbon–iodine bond to undergo homolytic cleavage has been taken advantage of, offering efficient access to some 2-deoxy glycosides[10] (Scheme 3). Glycosyl iodides are also heterolytically unstable due to the good leaving group properties of the highly polarizable iodide ion.

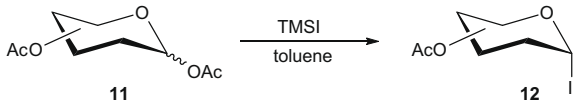
The first mechanistic study on the reactivity of glycosyl iodides was conducted by Kronzer and Schuerch who generated D-glucopyranosyl and D-galactopyranosyl iodides (**7** and **9**, respectively, Scheme 4) in situ from the corresponding chloride or bromide by treatment via Finkelstein exchange[11] with sodium iodide.[12] It was found that glycosyl iodides offered advantages over glycosyl chlorides and bromides including a significant rate enhancement; reaction times were typically reduced by at least 75%. It was also shown that glycosylations conducted with a glycosyl iodide were



Scheme 3. Preparation of 2-deoxy sugars via a glycosyl iodide.[10]



Scheme 4. Comparison of glycosyl iodides to glycosyl chlorides and bromides as glycosyl donors.[12]



Scheme 5. Generation of a glycosyl iodide from the corresponding anomeric acetate.[14]

found to be more stereoselective than those carried out with the corresponding bromide or chloride. Typically the α-anomer was produced in over 90% yield. It was proposed that this improvement in selectivity was due to the differences in the rates of anomerization of the halides prior to glycosylation.[12]

A short-lived resurgence of glycosyl iodides occurred in 1980 when it was reported that these donors could be generated from the corresponding anomeric acetate **11** upon treatment with iodotrimethylsilane (Scheme 5).[13,14] Thiem and Meyer not only successfully prepared a large library of glycosyl iodides, but were also able to fully characterize them.[14] However, it was nearly two decades later before Gervay-Hague et al. capitalized on the effectiveness of glycosyl iodides as donors and developed them into a versatile glycosylation technique.[15]

Another advance in the characterization of glycosyl iodides came in 2003, when Stachulski and co-workers prepared methyl 2,3,4-tri-*O*-pivaloyl-α-D-glucopyranuronate iodide and found that it possessed remarkable stability at room temperature. In fact, this

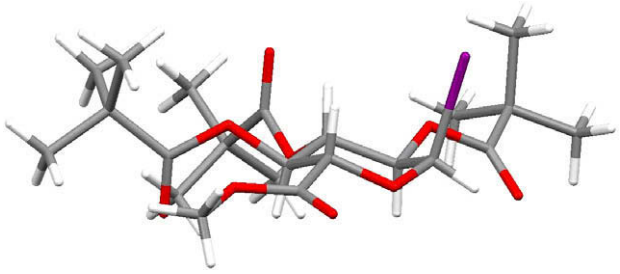
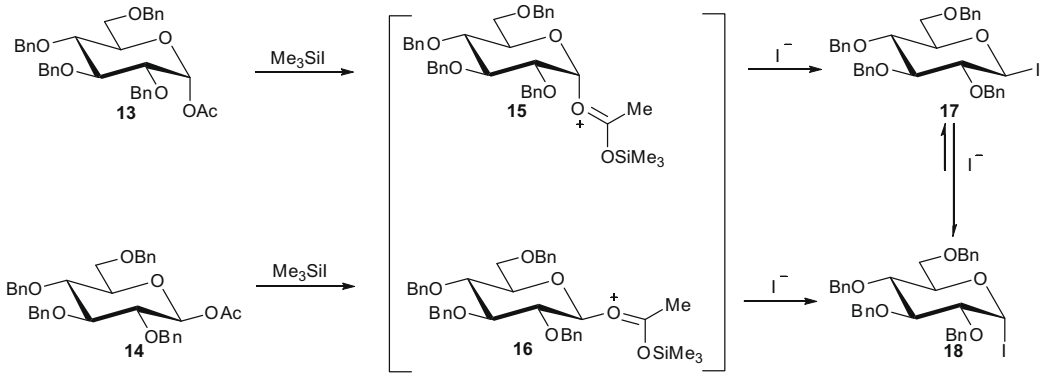


Figure 1. Crystal structure of methyl 2,3,4-tri-*O*-pivaloyl-α-D-glucopyranuronate iodide.[16]



Scheme 6. Proposed mechanism of glycosyl iodide formation.[15]

glycosyl iodide was so stable that a crystal structure was obtained (Fig. 1). The crystal structure shows, as would be expected, that the α-D-glucoronyl ring adopts a $^4C_1$ conformation.[16]

3. Formation of glycosyl iodides

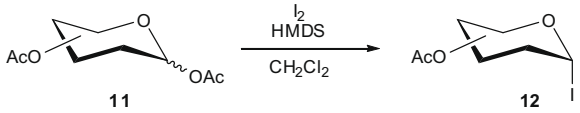
3.1. Iodotrimethylsilane

In 1997, Gervay et al. reported the stereoselective synthesis, full characterization and a mechanistic study of the formation of both α- and β-D-glucopyranosyl iodides using iodotrimethylsilane.[15] Treatment of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose with iodotrimethylsilane resulted in formation of the β-D-glucopyranosyl iodide **17** as the predominant product at −40 °C. Equilibration to the α-D-glucopyranosyl iodide occurred rapidly as the temperature was raised. The formation of the α-iodide **18** from the anomeric acetates (**13** and **14**) presumably occurs via O-silylation of the acetyl group to give the trimethylsilyl acetoxonium ion intermediates, followed by displacement by iodide ion to afford the glycosyl iodide; the anomeric effect favours the formation of the α-D-glucopyranosyl iodide **18**[15] (Scheme 6).

This technique for the generation of glycosyl iodides is by far the most popular method, primarily due to the fact that the only by-product is the volatile and easily removed trimethylsilyl acetate. Iodotrimethylsilane has not only been shown capable of generating glycosyl iodides from anomeric acetates but it has been reported to be efficient in the conversion of other anomeric esters,[14,15] anhydrosugars,[14] as well as trimethylsilyl[17,18] and methyl glycosides[14] to the corresponding iodide.

3.2. HMDS/I_2

Field and co-workers reported a slightly different approach to synthesize glycosyl iodides, preferring to generate the iodotrimethylsilane in situ through the treatment of hexamethyldisilane (HMDS) with molecular iodine (Scheme 7). The proposed mechanism of glycosyl iodide formation is identical to the method previously outlined using iodotrimethylsilane.[19,20] Murakami et al. extended this methodology using ZnI_2 as an additive, successfully

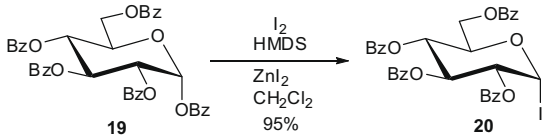


Scheme 7. Preparation of glycosyl iodides using HMDS and I_2.[19,20]

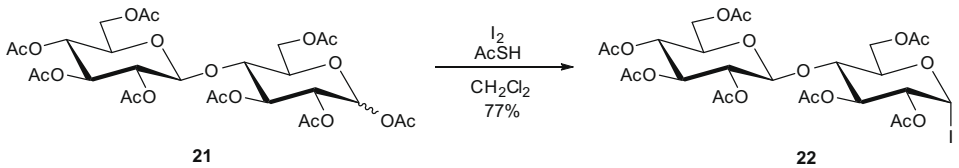
improving the yields reported by Field.[21] However, a drawback of the use of ZnI_2 is that an aqueous workup and column chromatography is required to isolate the glycosyl iodide product (Scheme 8).

3.3. HI

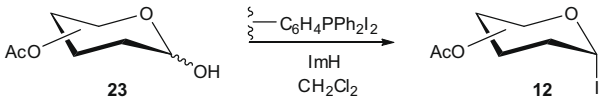
It has been known for over a century that treatment of per-*O*-acetylated sugars with anhydrous HBr–acetic acid results in the formation of the glycosyl bromide.[22] The corresponding reaction with per-acetylated sugars and HI was first reported by Fischer in 1910,[5] although this method has not been widely used, presumably due to the difficulty in preparing anhydrous HI.[6] Koreeda and co-workers circumvented this problem by generating HI in situ by the oxidation of thiolacetic acid with molecular iodine (Scheme 9).[23] This method proved effective in the generation of α-glycosyl iodides from the corresponding anomeric acetates. Reaction yields ranged from 54% to 77%; however, one could presume that the isolation of the α-glycosyl iodide through chromatography would be unpleasant due to the presence of thiolacetic acid. Ness et al. successfully prepared 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide from the corresponding 1,2,3,4,6-penta-*O*-benzoyl-α-D-glucopyranose by treatment with HI in acetic acid, in this case it



Scheme 8. Preparation of glycosyl iodides using HMDS, I_2 and ZnI_2.[21]



Scheme 9. Preparation of glycosyl iodides using in situ generated HI.[23]



Scheme 10. Formation of glycosyl iodides using polymer bound diphenylphosphane iodide complex.[26]

was generated by the addition of hydriodic acid to acetic anhydride, circumventing the problems associated with preparing anhydrous HI.[24] This technique was later applied by Gervay-Hague and Gregar to prepare the β-iodide of *N*-acetyl neuraminic acid.[25]

3.4. Miscellaneous techniques

Caputo et al. successfully developed a method of generating glycosyl iodides by taking advantage of a polymer-bound diphenylphosphane iodide complex.[26] Access to the iodide **12** is achieved directly from the hemiacetal **23** in the presence of imidazole acting as a proton trap (Scheme 10). Whilst this procedure offers distinct advantages to those mentioned above, it is yet to gain wide use as method for forming glycosyl iodides.

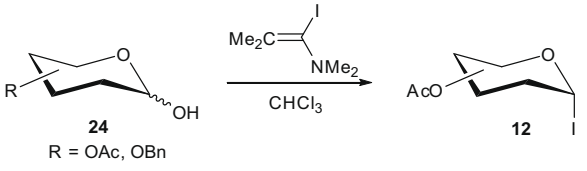
Another synthesis of these species was developed by Ernst and Winkler who converted a wide variety of furanose and pyranose hemiacetals to glycosyl iodides through the action of 1-iodo-*N*,*N*-trimethylpropyl-1-en-1-amine[27] (Scheme 11). The main disadvantage of this procedure is that a non-volatile amide by-product is generated during the reaction, thus requiring chromatographic separation to isolate the pure glycosyl iodide.

4. Formation of O-glycosides

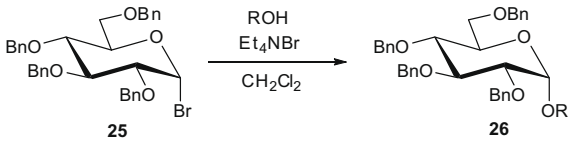
The formation of O-glycosides is an important aspect of modern synthetic carbohydrate chemistry particularly in the synthesis of complex, biologically relevant oligosaccharides. As mentioned previously, glycosyl iodides have increasingly been used for the synthesis of glycosidic bonds and in the discussion below, this work is organized based upon the relative stereochemistry of the groups at C1 and C2.[28] The use of these donors in the synthesis of the more difficult 1,2-cis linkages is presented first, followed by the more easily prepared 1,2-trans linkages.

4.1. Preparation of 1,2-cis linkages

The preparation of difficult 1,2-cis linkages[29] is a challenge to which the glycosyl iodide methodology has been shown to excel. The use of glycosyl halides to prepare 1,2-cis linkages was pioneered by Lemieux in 1975 with the development of halide-ion catalysis.[30] In this seminal work, Lemieux et al. showed that treatment of an α-glycosyl bromide **25** in the presence of tetraethylammonium bromide and an alcohol afforded the 1,2-cis glycoside **26** selectively and in excellent yield (Scheme 12). The stereoselectivity of the reaction was proposed to arise from a Curtin–Hammett kinetic scheme involving the in situ generation of the more reactive



Scheme 11. Formation of glycosyl iodides using 1-iodo-*N*,*N*-trimethylpropyl-1-en-1-amine.[27]

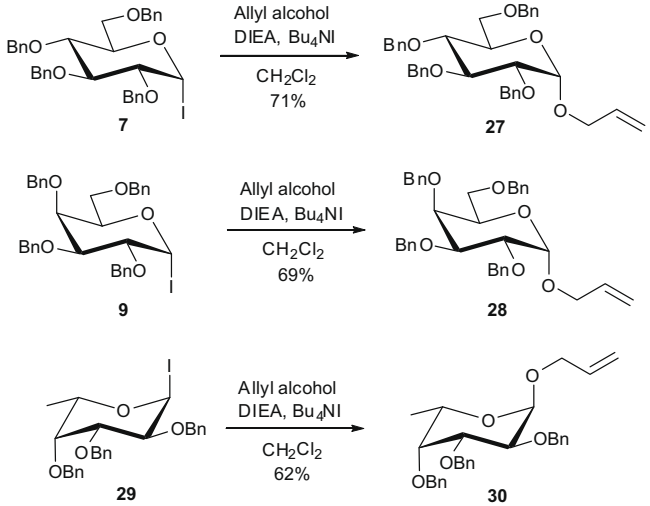


Scheme 12. Preparation of 1,2-cis linkages using halide catalysis.[30]

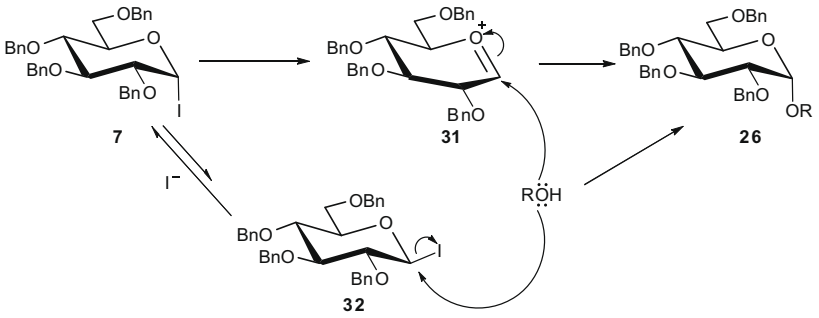
β-glycosyl bromide, which reacted in an S_N2-like manner to afford the product.

Gervay-Hague and Hadd capitalized on the effectiveness of halide-ion catalysis using glycosyl iodides as the donors, successfully preparing several α-D-glucopyranosides, α-D-galactopyranosides and α-L-fucopyranosides.[31] In the D-glucopyranose series, treatment of the α-glycosyl iodide **7** with tetra-*n*-butylammonium iodide and an alcohol, in the absence of a participating group at C2, results in the highly selective formation of the α-D-glucopyranoside (**27** Scheme 13).[32] Based on the earlier work of Lemieux, it was proposed that the tetra-*n*-butylammonium iodide catalyzes the rapid interconversion of the α- and β-D-glucopyranosyl iodides.[30] The α-glycoside **26** is then formed by preferential attack on the oxocarbenium ion **31** from the bottom face of the ring, or by attack of the neutral alcohol on the more reactive β-D-glucopyranosyl iodide **32**, via an S_N2-like displacement (Scheme 14).

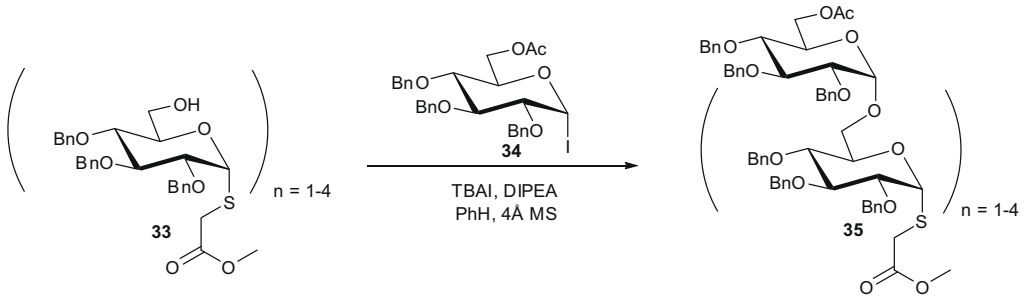
In subsequent work, Gervay-Hague and Lam took advantage of this technique to prepare oligosaccharides via solution-phase synthesis[33] (Scheme 15). Shortly afterwards, this technique was extended with the development of a solid-phase glycosylation approach to prepare a tetrasaccharide attached to TentaGel resin (Scheme 16), thus removing much of the cumbersome chromatography involved in traditional oligosaccharide synthesis.[34] A direct comparison of solution- and solid-phase approaches was also conducted; the solution-phase synthesis was found to be more effective in terms of reaction times, yields and efficiency. For example, yields in the solution-phase synthesis ranged from 87% to 93% whilst in the solid phase lower yields of 64–88% were reported. It should be noted that similar solid-phase glycosylations were conducted by Frechet and Schuerch utilizing a glycosyl bromide donor; however, they were found to be far less efficient.[35] The reactions required days to complete and 12 equiv of the glycosyl bromide donor were required. In contrast with the use of glycosyl iodides, the reactions were complete in 12 h and only 7.5 equiv of donors were needed.



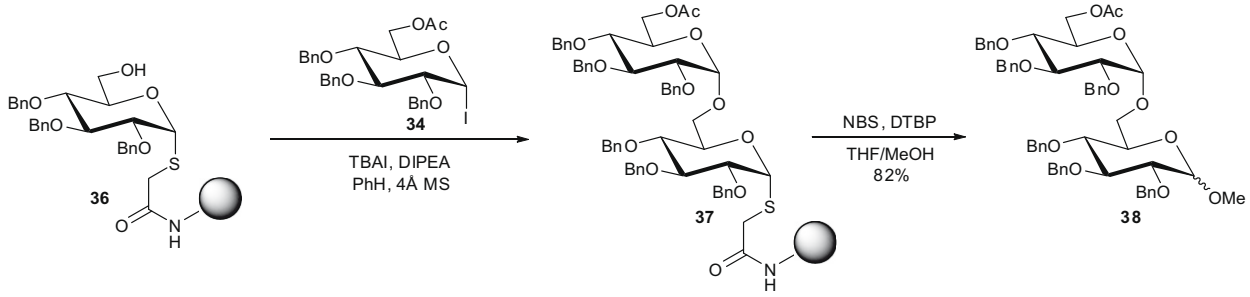
Scheme 13. Preparation of 1,2-cis linkages from a glycosyl iodide.[31]



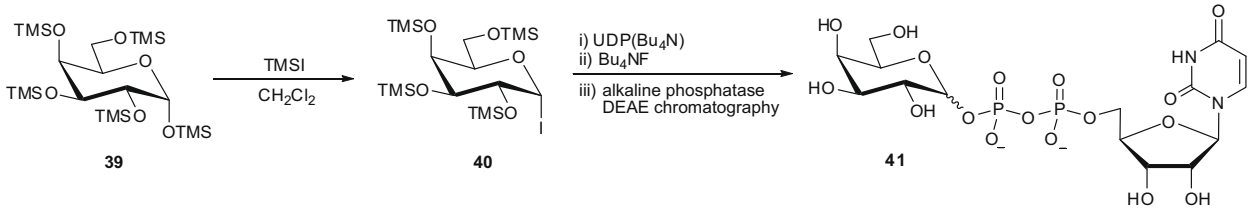
Scheme 14. Mechanism of glycoside formation in the presence of TBAI.[2]



Scheme 15. Solution-phase oligosaccharide synthesis using a glycosyl iodide donor.[33]



Scheme 16. Solid-phase oligosaccharide synthesis using a glycosyl iodide donor.[34]

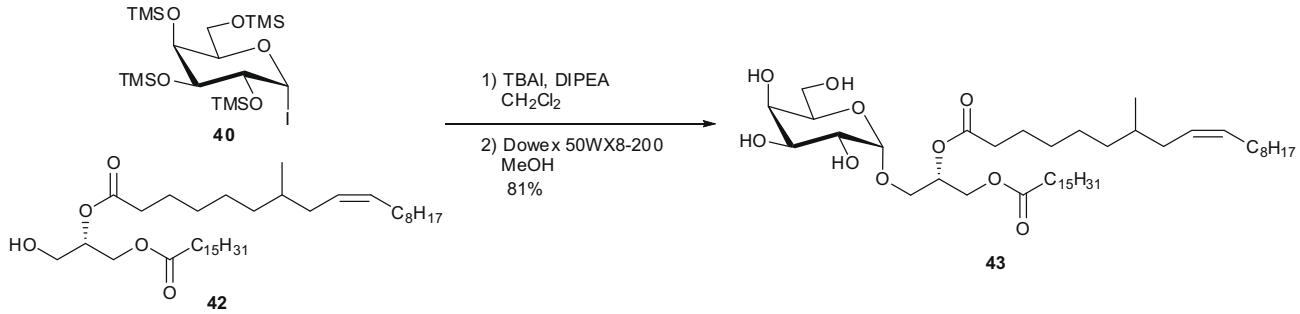


Scheme 17. Preparation of UDP-Gal via 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranosyl iodide.[17]

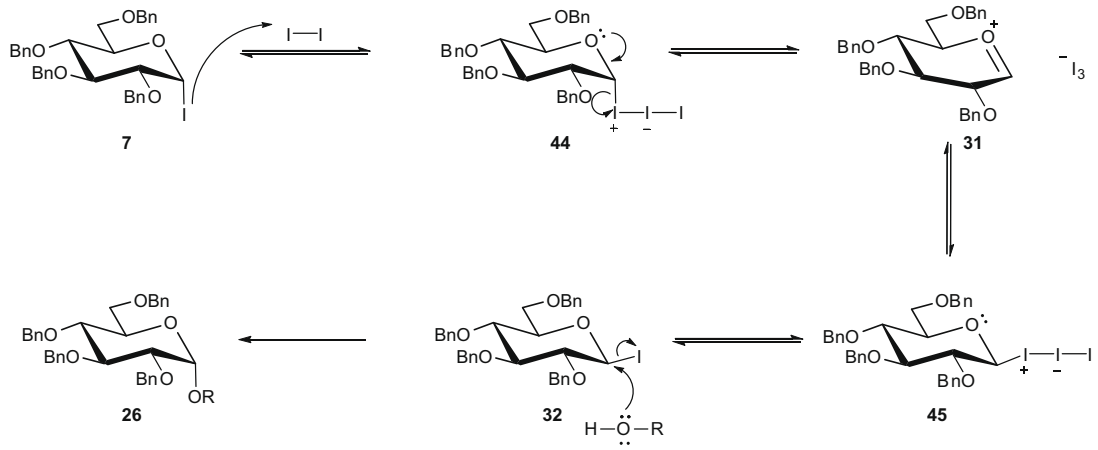
The preparation of most glycosyl donors involves multistep synthesis and purification of the intermediates using silica gel chromatography. In an effort to circumvent this obstacle, a more efficient protecting group strategy was explored. Hindsgaul and Uchiyama successfully employed the readily prepared per-O-trimethylsilylated glycosyl iodides as an effective glycosyl donor for the preparation of their corresponding UDP derivatives (Scheme 17).[17] In addition, this approach was applied to the preparation of α-fucopyranosides.[18]

This work was extended by Gervay-Hague and co-workers, who capitalized on the effectiveness of this technique, successfully preparing several biologically active α-linked glycolipids, related to the natural killer T-cell ligand α-galactosyl ceramide[36] (Scheme 18). Yields appeared to be substrate dependent; in some cases yields above 70% while in other yields were around 30–40%. However, in all cases only the α-anomer was observed. In contrast, previously reported syntheses utilized glycosyl trichloroacetimidate[37] and glycosyl fluoride[38–40] donors, typically offering lower yields (30–60%) and complex α/β mixtures.

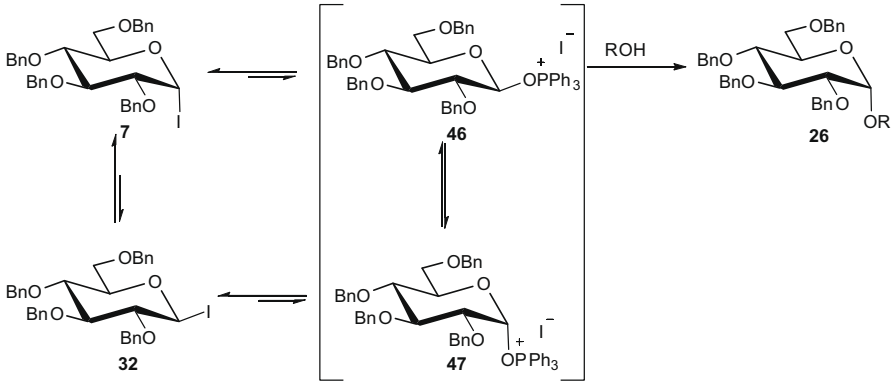
To expand the methods for activating glycosyl iodides, Field and co-workers developed molecular iodine as a promoter that could replace tetra-*n*-butylammonium iodide.[19] Field proposed the



Scheme 18. Glycolipid synthesis utilizing per-O-trimethylsilylated galactopyranosyl iodides.[36]



Scheme 19. Proposed mechanism of glycosylation of glycosyl iodides using I_2 as the promoter.[19]



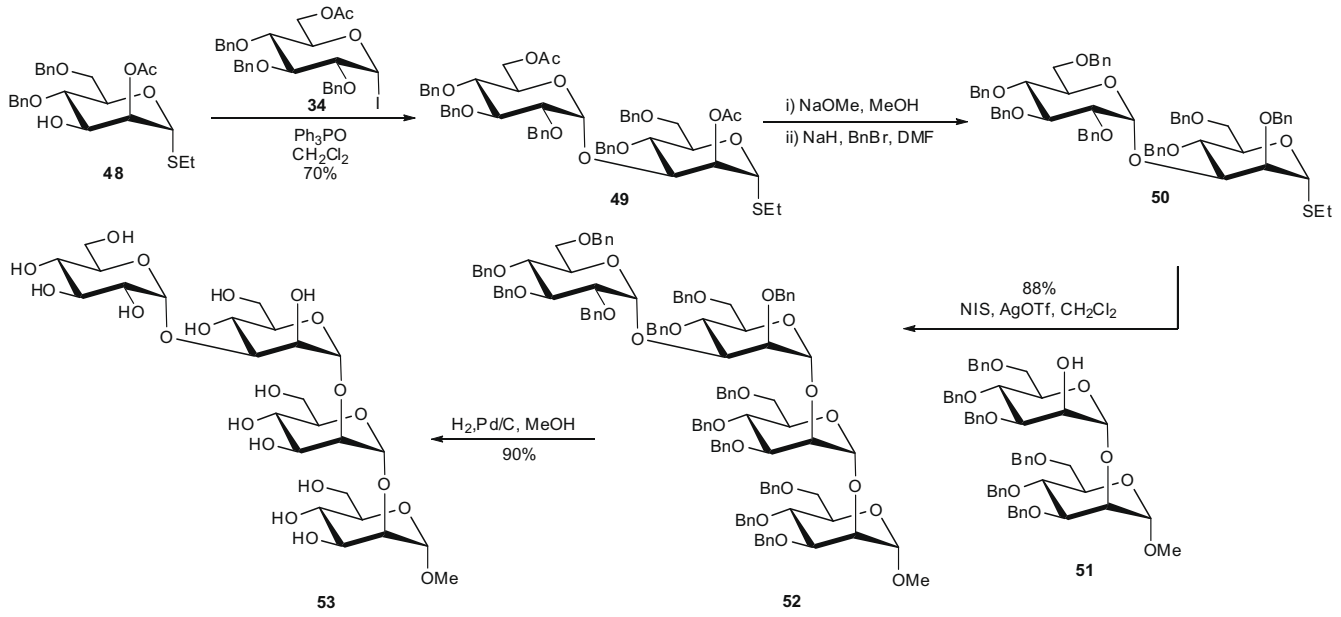
Scheme 20. Proposed mechanism of glycosyl iodide promotion with triphenylphosphine oxide.[43]

mechanism shown in Scheme 19 to explain the observed selectivity, again relying on the concept of halide-ion catalysis.

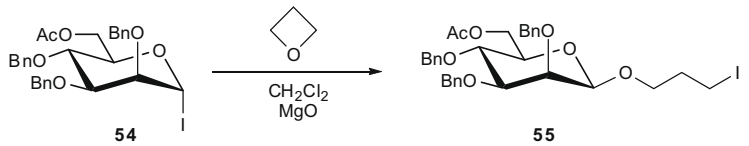
Mukaiyama and Kobashi recently reported the activation of both glycosyl iodides and glycosyl bromides using various trialkylphosphine oxides.[41,42] The phosphine oxide also served to neutralize hydrogen iodide generated during the course of the reaction, thus removing the need for the addition of a base to maintain near-neutral conditions. The use of the phosphine oxide also minimized elimination of the glycosyl iodide in turn resulting in the formation of a glycal by-product, which complicates purification of the product (see discussion below). In the D-glucopyranose series, the α-selectivity possibly arises due to S_N2 attack on the more reactive β-D-glucosyloxyphosphonium iodide **46**. The glucosyloxyphosphonium iodide has not been observed in NMR studies, which indicates that, if present, only very small amounts of this reactive intermediate exist in equilibrium with the α-D-glycosyl iodide **7** and phosphine oxide (Scheme 20).[41,42]

Oscarson and co-workers took advantage of triphenylphosphine oxide promotion to prepare successfully α-D-glucopyranosides with complete stereoselectivity (Scheme 21).[44] The stability of the thioglycoside to these conditions (as opposed to activation using I_2) was taken advantage of and the subsequent glycosylation of the disaccharide product **50** was conducted to afford the tetrasaccharide **53**, recognized by the lectins Calrecticulin and Calnexin.

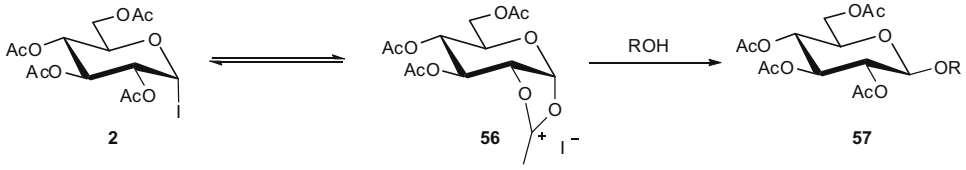
A direct comparison of the thioglycoside, trichloroacetimidate and glycosyl iodide methodology was conducted by Stick and co-



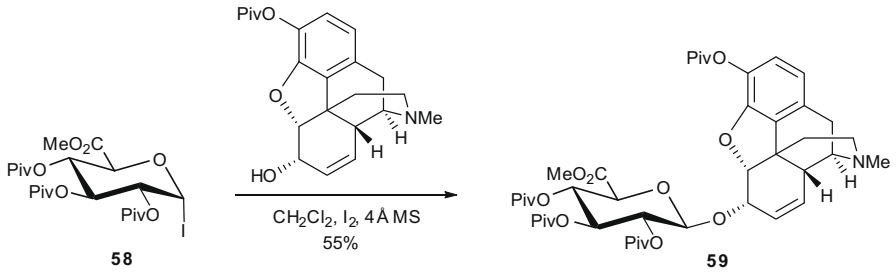
Scheme 21. Glycosylation utilizing a glycosyl iodide donor and triphenylphosphine oxide promoter.[44]



Scheme 22. Synthesis of β-mannopyraosides using α-mannopyranosyl iodides and oxetane as the acceptor.[45]



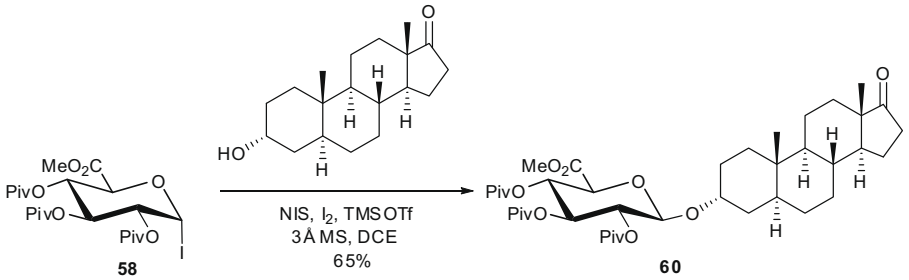
Scheme 23. Preparation of 1,2-trans linkages using a C2 participating group.



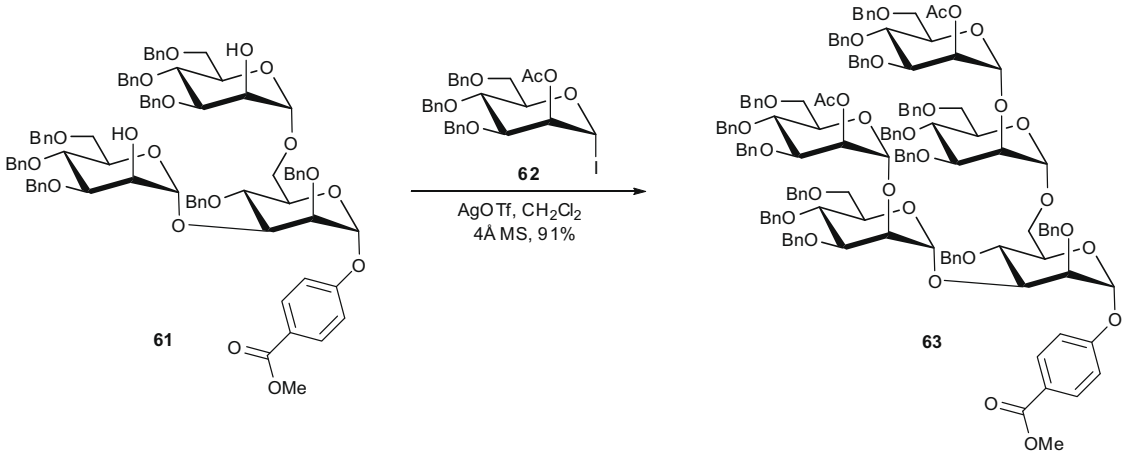
Scheme 24. Preparation of glycosylated morphine using a glucuronyl iodide.[16]

workers in the synthesis of several α-D-glucopyranosides.[43] The glycosyl iodide methodology was explored using the triphenylphosphine oxide promoter reported by Mukaiyama and the TBAI–DIPEA promoter reported by Gervay-Hague.[31,41,42] Both promoter systems were shown to offer significantly better selectivity in the formation of α-D-glucopyranosides compared to the trichloroacetimidate methodology. However, the trichloroacetimidate methodology was found to be more efficient in that large excesses of the donor were not required to ensure reaction completion. The thioglycoside methodology was found to offer lower stereoselectivity than both the trichloroacetimidate and glycosyl iodide methodologies.

The stereoselective formation of β-mannopyranosides remains one of the most challenging synthetic transformations in carbohydrate chemistry as both the anomeric effect and C2 axial substituent favour the formation of the α-mannopyranoside.[45] In an effort to apply this class of donors to this problem, Gervay-Hague and coworkers reported a detailed computational and mechanistic study, in which β-mannopyranosides were prepared from the corresponding mannopyranosyl iodide **54** using oxetane as the acceptor



Scheme 25. Glucuronidation of a steroidal alcohol.[46]



Scheme 26. Preparation of a mannose pentasaccharide using AgOTf as the promoter.[47]

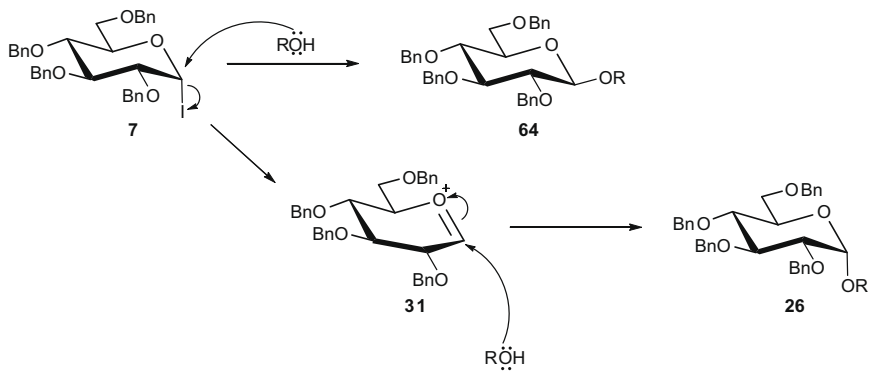
(Scheme 22).[45] This technique, however, is yet to be demonstrated in the synthesis of oligosaccharides containing β-mannopyranoside residues, or to be widely used.

4.2. Preparation of 1,2 trans linkages

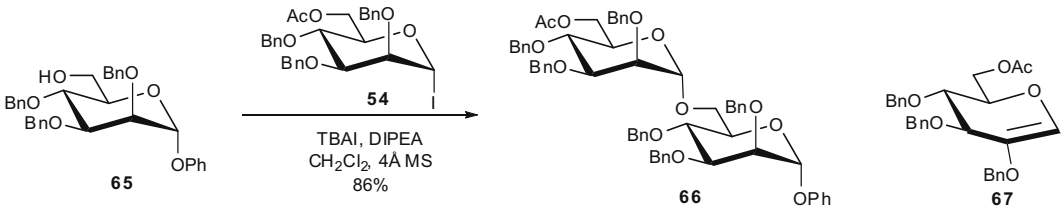
Most glycosylations used to prepare 1,2-trans linkages take advantage of an ester participating group at C2 and the resulting orthoester **56** to control stereoselectivity (Scheme 23). However, activation of the donor is often slower than those typically used in the synthesis of 1,2-cis linkages, due primarily to the disarming effect of the acyl-protecting groups required to control stereoselectivity.[30] Thus, glycosyl iodides have been used in cases where reactions with less reactive glycosyl donors have failed.

In one example, Stachulski and co-workers developed this technique to glycosylate 3-*O*-pivaloyl morphine, using methyl 2,3,4-tri-*O*-pivaloyl-α-D-glucopyranuronate iodide **58**[16] (Scheme 24). This work was further extended to the glucuronidation of several steroidal alcohols, which are important in the metabolism of a number of steroid-based chemotherapy pharmaceuticals (Scheme 25).[46] The glycosyl iodide methodology was contrasted with the trichloroacetimidate methodology and was shown to offer distinct advantages, most notably the absence of transacylation from the donor to the acceptor.

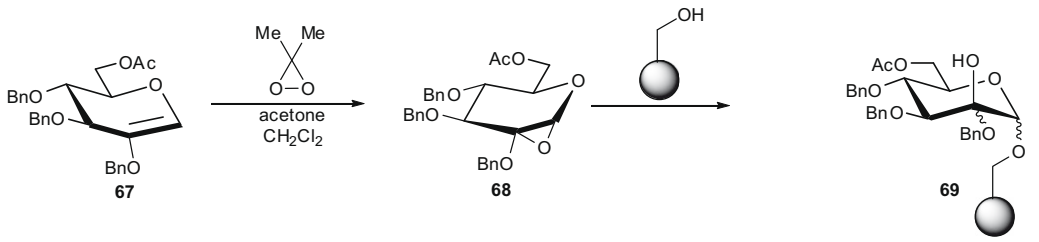
In another example of the use of 2-O-acetylated glycosyl iodides, Gervay-Hague and Lam successfully prepared a mannose pentasaccharide (**63**, Scheme 26), which is a protected derivative of a fragment of the N-glycan chains of HIV-1 gp120.[47] All of the glycosidic linkages between carbohydrate residues in **63** were prepared using 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl iodide **62**, promoted by AgOTf. The final glycosylation step in the synthesis of **63** is shown in Scheme 26. In this reaction, an excess



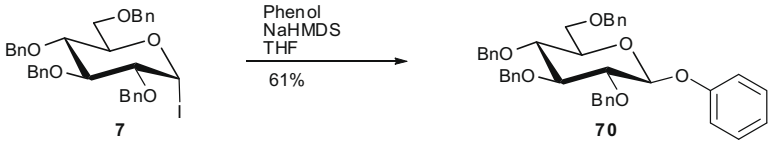
Scheme 27. Preparation of 1,2-trans linkages in the absence of a C2 participating group by direct displacement.



Scheme 28. Preparation of α-mannopyranosides utilizing the glycosyl iodide methodology.[48]



Scheme 29. Phase trafficking technique used to remove glycal generated during glycosylation.[48]



Scheme 30. Glycosylation using a glycosyl iodide donor and phenol acceptor.[49]

of **62** was used to glycosylate trisaccharide diol **61**, leading to a 91% yield of the desired pentasaccharide.

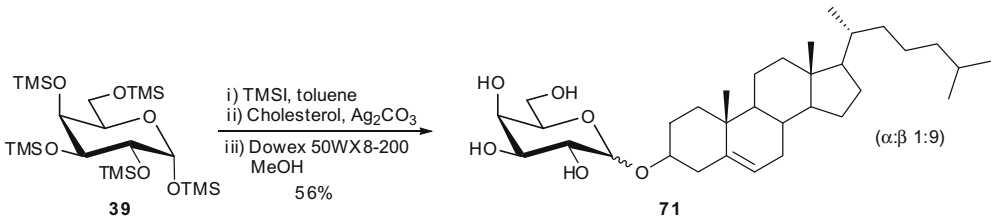
There are also several instances where glycosyl iodides have been used to synthesize 1,2-trans linkages in the absence of a participating group at C2 of the donor. In the case of α-glycosyl iodides in the *gluco*- or *galacto*-series, when an iodide source is not present, in situ anomerization would not occur, and thus one would expect that direct S_N2 displacement of the iodide **7** would provide the 1,2-trans linkage (**64**, Scheme 27). In contrast, nucleophilic attack on the oxonium ion **31** would presumably afford the α-glycoside **26**.

In the *manno*-series, the situation is different. The first reported synthesis of an α-D-mannopyranoside utilizing a glycosyl iodide was conducted by Gervay-Hague and Lam in 2005 using their standard TBAI–DIPEA promoter system.[48] The donor employed possessed a benzyloxy group at C2 and thus this reaction probably proceeds in a manner similar to the halide catalysis discussed in the context of 1,2-cis glycoside synthesis. Unfortunately, these conditions generated significant quantities of the glycal **67** by-product, which was inseparable from the desired product by chromatography (Scheme 28). The glycal **67** could be removed by conversion to the 1,2-anhydrosugar **68** via electrophilic epoxidation, followed by immobilization on divinylbenzene cross-linked polystyrene beads (Scheme 29).[48]

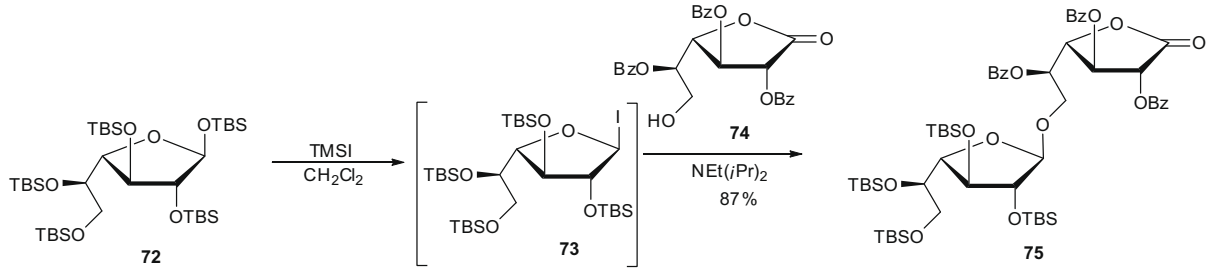
Another example of a glycosylation conducted with a glycosyl iodide in the absence of a participating group is the preparation of the phenyl β-glucopyranoside **70** (Scheme 30).[49] Promotion was achieved by the treatment of phenol with NaHMDS, resulting in the generation of the highly nucleophilic phenoxy anion. Gervay-Hague and Kulkarni were then able to adapt this method into a viable approach for the synthesis of more complex glycosides, by taking advantage of the 1,2,3,4,6-penta-*O*-trimethylsilyl-D-galactopyranose **39** to prepare an immunogenic bacterial glycolipid (**71**, Scheme 31).[50] In the latter case, silver carbonate, not a base, was used to promote the reaction.

The effective synthesis of furanosides is a topic of emerging importance, particularly, when one considers that furanose polysaccharides are a vital component of the cell wall of many pathogenic bacteria such as *Mycobacterium tuberculosis* and *Trypanosoma cruzi*.[51,52] Baldoni and Marino recently reported the first use of a galactofuranosyl iodide to prepare several glycosides in good yield and high stereoselectivity (Scheme 32).[53] In particular, carbohydrate-based acceptors such as **74** resulted in formation of the β-glycoside as the sole product; in all but one case the yields were above 69%.

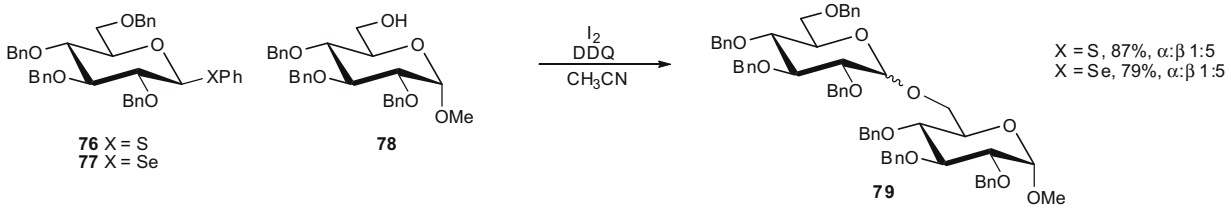
Field and co-workers have extended their previously developed glycosyl iodide promotion systems to include thioglucoside and selenoglucoside donors.[54] In this case the treatment of a thiogluco-



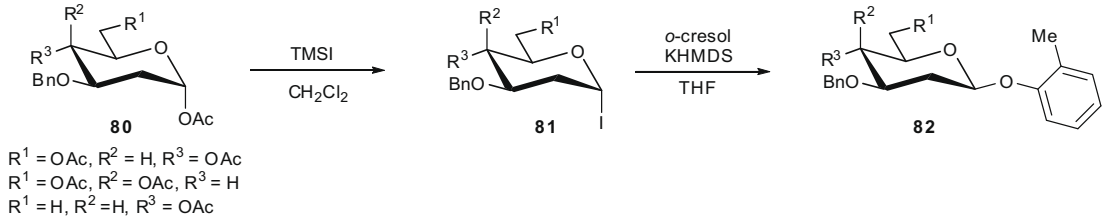
Scheme 31. Synthesis of BbGL1 from 1,2,3,4,6-penta-*O*-trimethylsilyl-D-galactopyranose.



Scheme 32. Synthesis of galactofuranosides utilizing a glycosyl iodide intermediate.[53]



Scheme 33. Glycosylation using a thioglucoside and selenoglucoside donor, through proposed formation of a glycosyl iodide intermediate.[54]



Scheme 34. Preparation of 2-deoxy-β-D-glycopyranosides by direct displacement of an α-D-glycopyranosyl iodide.[60]

side **76** or selenoglucoside **77** with iodine and DDQ, followed by an acceptor, resulted in moderately selective formation of the β-glucopyranoside **79** in good yield. The mechanism of the promotion is not fully understood; however, it was suggested that a variety of intermediates were possible including a glycosyl iodide, oxocarbenium ion or an α-glycosyl nitrilium ion (Scheme 33).

4.3. Preparation of 2-deoxy glycosides

Deoxygenated carbohydrates are an important component of modern pharmaceuticals including the important anti-tumour antibiotics olivomycin, chromomycin, mithramycin and UCHC9.[55–57] These compounds are members of the aureolic acid family and possess several 2,6-dideoxy glycosidic linkages.[58] The synthesis of 2-deoxy-β-glycosides presents a significant challenge, because in the absence of a participating group at C2, the kinetic anomeric effect favours the axial (usually α) glycoside.[59] Gervay-Hague and Lam reported the successful preparation of several 2-deoxy-β-D-glycopyranosides **82** via direct displacement of the α-D-glycopyranosyl iodide **81** (Scheme 34).[60]

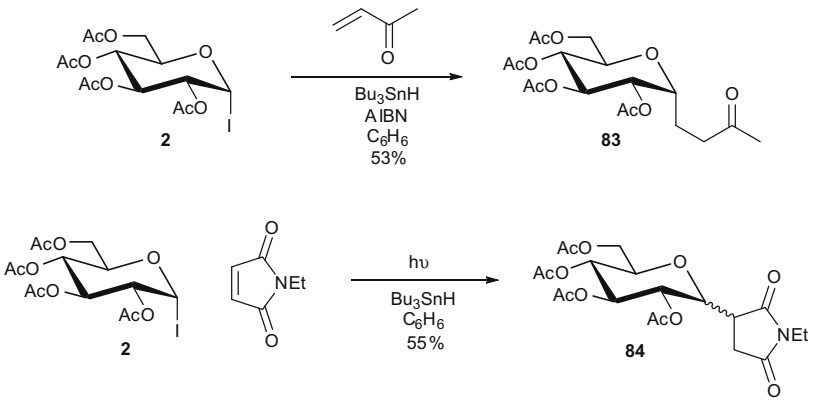
Access to the 2-deoxy-α-D-glycopyranosyl iodide **81** required for these glycosylations was achieved from the anomeric acetate **80**, which was, in turn, easily produced from the corresponding glycal. Treatment of the 2-deoxy-α-D-glycopyranosyl iodide **81** with the aryloxy anion generated in situ by treatment of the appropriate phenol with KHMDS afforded the β-D-glycoside **82**.[60] Whilst this technique shows significant promise in the synthesis aryl 2-deoxy-β-glycosides, it is yet to be proven in the synthesis of 2-deoxy oligosaccharides.

5. Formation of *C*-glycosylic compounds (C-glycosides)

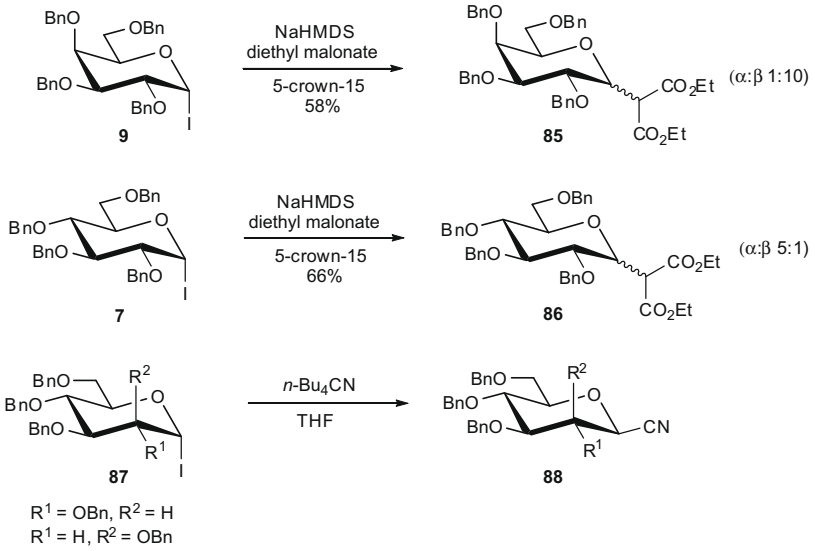
The importance of C-glycosides is evident by the diverse array of biologically relevant natural products possessing this linkage.[61] In the context of glycomimetics, an advantage of C-glycosides is that, being ethers, they are as not susceptible to enzymatic or chemical hydrolysis thus rendering them potentially more suitable as biological tools and therapeutics.[62,63]

The first synthesis of C-glycosides utilizing a glycosyl iodide was conducted by Nagasawa and co-workers in 1987.[64] This work took advantage of the formation of a glycosyl radical by treatment of the glycosyl iodide **2** with Bu_3SnH in the presence of either AIBN or light, and its subsequent addition to an electron-deficient olefin. A direct comparison to glycosyl bromides was also made. In the case of the reaction of glycosyl iodide **2** with methyl vinyl ketone, a slightly higher yield was observed whilst requiring only one quarter of the quantity of Bu_3SnH. This effect was rationalized by preferential homolytic cleavage of the carbon–iodine bond compared to the carbon–bromine bond (Scheme 35).[64]

The formation of C-glycosides via an anionic addition to a glycosyl iodide was developed by Gervay-Hague and Hadd, initially utilizing simple nucleophiles such as diethyl malonate or *n*-Bu_4NCN.[49] In the case of α-D-galactopyranosyl **9** and α-D-mannopyranosyl iodides **87**, excellent β-selectivity was observed, whilst in the reaction of the α-D-glucopyranosyl iodide **7** with diethyl malonate, the α-anomer was favoured.[49] This stereochemical outcome was rationalized by the in situ anomerization of the iodide, although an S_N1 mechanism could not be ruled out (Scheme 36).[49]



Scheme 35. Preparation of C-glycosides using a glycosyl radical addition.[64]



Scheme 36. Preparation of C-glycosides using anionic addition.[49]

Direct access to more complex C-glycosides via glycosyl iodides has not been reported, but has been achieved by the introduction of the C-glycoside followed by subsequent elaboration to the target. For example, Gervay-Hague and Kulkarni successfully prepared a C-glycoside analogue **94** of the immunogenic bacterial glycolipid BbGL2 by first introducing the C-glycoside using a Grignard reaction, followed by olefin cross metathesis to introduce a functionalized carbon chain and consecutive DCC couplings to insert the lipid (Scheme 37).[65]

The preparation of C-glycosides utilizing a carbohydrate-based electrophile was achieved by Beau and co-workers by taking advantage of a reductive samariation.[66] Treatment of glycosyl iodide **7** with an aldehyde or ketone in the presence of samarium iodide afforded C-glycoside **96** bearing a hydroxyl group at the 'glycosidic' carbon, which was then deoxygenated in good yield.[66] Whilst this technique is promising, its main disadvantage lies in the multistep sequence required to deoxygenate and obtain the C-glycoside (Scheme 38).

6. Formation of N-glycosides

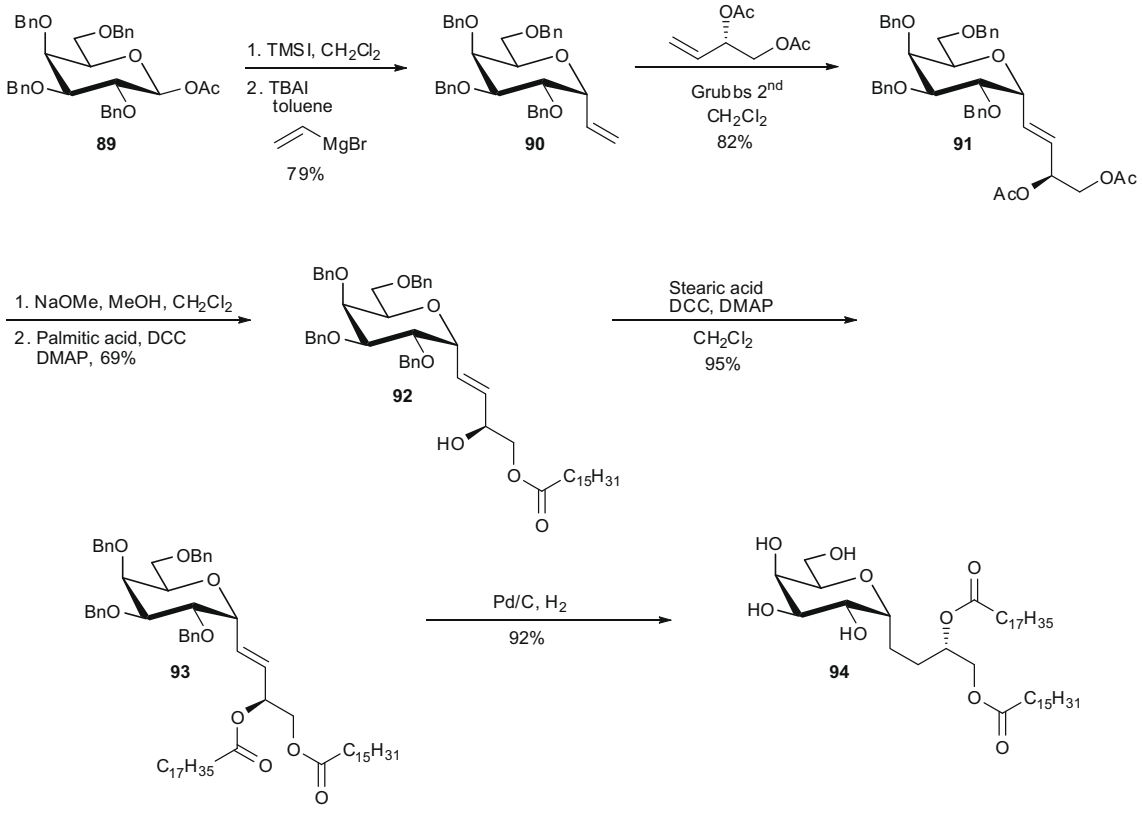
The importance of N-glycosides is highlighted by nucleosides and nucleotides, constituents of RNA and DNA.[67] The first reported synthesis of an N-glycoside via a glycosyl iodide methodology was the synthesis of protected derivatives of the nucleosides uridine, cytidine and adenosine by Beránek and co-workers.[13] In most cases the yields obtained were greater than 80% and the reactions were completely stereoselective (Scheme 39).

Gervay-Hague and Ying took advantage of a glycosyl iodide donor to prepare a range of glycosyl azides, important intermediates in the incorporation of carbohydrates onto solid supports for solid-phase strategies.[68] These azides, once reduced to the corresponding amine, have also been used to great effect in the synthesis of amide linked oligomers,[69–72] and glycopeptides.[73] Treatment of glycosyl iodides derived from several monosaccharides and disaccharides with either tetrabutylammonium azide ($TBAN_3$) or tetramethylguanidinium azide (TMGA) led to 70–90% yields of the glycosyl azide (Scheme 40).[68]

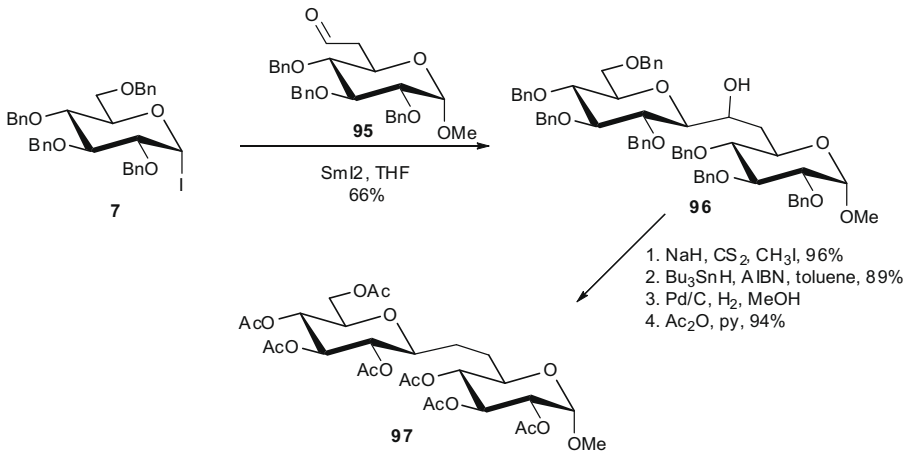
Indigo N-glycosides show considerable activity against a variety of human tumour cell lines. Langer and co-workers took advantage of a glycosyl iodide methodology to successfully prepare several indigo N-glycosides in 15–22% yield. Despite the low yields, this synthesis was the first reported for a fully deprotected indigo N-glycoside[74] (Scheme 41).

7. Conclusions

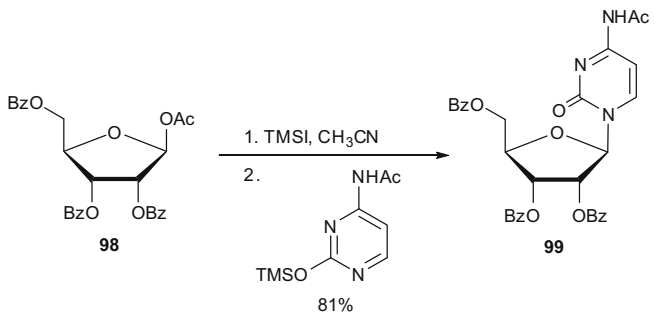
Advances over the past several years have now established glycosyl iodides as a useful class of glycosylating agents, which can be employed in the synthesis of a number of different types of glyco-



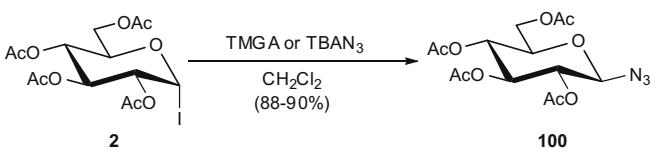
Scheme 37. Formation of C-analogue of bacterial glycolipid BbGL2.[65]



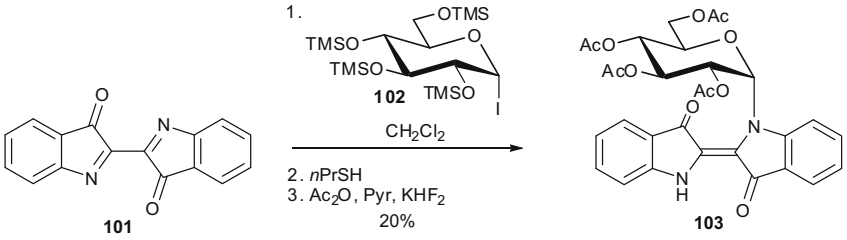
Scheme 38. Preparation of C-glycoside **97** via a reductive samariation.[66]



Scheme 39. Preparation of protected nucleosides via a glycosyl iodide.[13]



Scheme 40. Preparation of glycosyl azides via a glycosyl iodide.[68]



Scheme 41. Synthesis of *N*-(α-D-glucopyranosyl)indigo.

sidic linkages, including O-, N- and C-glycosides. One of their main strengths lies in the preparation of the difficult 1,2-cis O-glycosides, usually offering excellent stereoselectivity, comparable or better to those obtained with other classes of glycosyl donors. These donors have also been used for the synthesis of other classes of glycosidic linkages, but in many cases their advantage over other glycosylating agents is less clear. It remains to be determined whether this is due to undeveloped potential or limitations that are inherent in these donors.

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