

Synthetic Approaches for the Assembly of 1,2 *cis*- β -O-Glycosidic Linkages

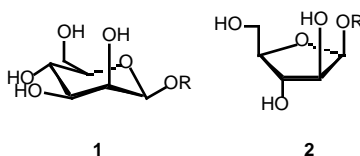
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ABSTRACT



Recent progress in the synthesis of 1,2-*cis*- β -O-glycosidic linkages of mannopyranosides (1) and arabinofuranosides (2) is discussed. These β -linkages are extremely important in many biological systems and are among the most difficult glycosidic bonds to form in a stereoselective fashion.

The many important roles that complex carbohydrates play in biology¹ have made synthesis of this class of molecules a major focus of synthetic organic chemistry.² Synthetic oligosaccharides are essential for biomedical studies³ on carbohydrate recognizing enzymes (glycosyltransferases and glycosidases) involved in the progression of diseases such as cancer, as well as viral and bacterial infections.⁴ The need for their synthesis stems from the fact that oligosaccharides can often only be isolated in small quantities from natural sources. Numerous methods for the assembly of glycosides have been developed, but the synthesis of some glycosidic linkages (Scheme 1A) remain a formidable challenge.² This situation is most evident for 1,2-*cis*- β -O-glycosidic linkages.

The most common 1,2 *cis*- β -glycosides found in nature are shown in the abstract. The β -D-mannopyranosidic (1) bond is found in the pentasaccharide core of all N-linked glycoproteins,^{5,6} various glycosphingolipids⁷ and lipopolysaccharides.⁸ β -D-arabinofuranosides (2) are a major component of mycobacterial arabinogalactan and lipoarabinomannan, and β -L-arabinofuranosides are key constituents of plant polysaccharides.⁹

Most methods for the assembly of oligosaccharides are based on a process (Scheme 1B) that involves activation of

a glycosyl donor (3), leading to an oxonium ion species (4), that is in turn trapped by an alcohol (the glycosyl acceptor) to give the product (6, 8). Depending upon the nature of the group at C-2, and the activation conditions, other intermediates (5, 7) can be formed from 4 en route to the glycoside. The key issue in the formation of glycosidic bonds is stereocontrol, and much effort has been focused on developing methods that provide one of the two possible glycosides as the sole product. Although stereocontrol is

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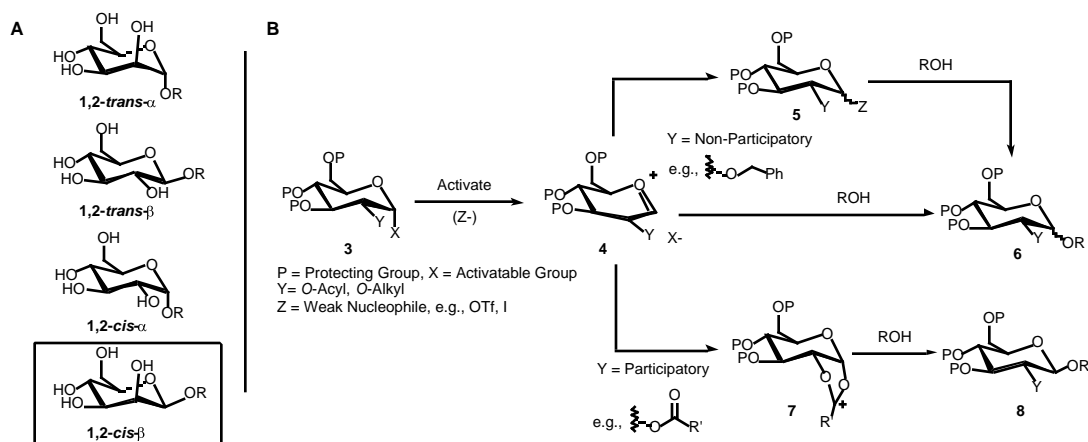
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Scheme 1.

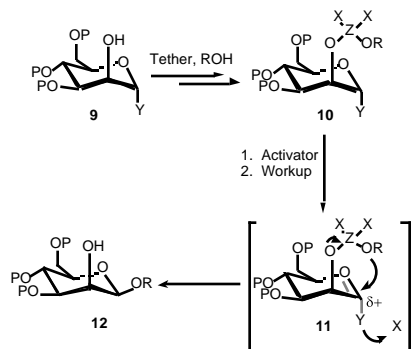
influenced by both steric and electronic effects in the donor and the acceptor, the nature of the C-2 substituent in the donor plays a predominant role.² This group can be termed either participating or non-participating. When donors with participating groups at C-2 are used (e.g., **3**, Y = O-Acyl) acyloxonium ion intermediates (**7**) are formed, which in turn afford glycosides with a 1,2-*trans* orientation (**8**). Glycosides with a 1,2-*trans* stereochemistry can be reliably made by this method in a stereoselective manner.

The stereoselective synthesis of 1,2-*cis* glycosides is more challenging. 1,2-*cis* α -glycosides can be generally prepared from donors with non-participatory groups at C-2 (e.g., **4**, Y = O-Alkyl), by taking advantage of the kinetic anomeric effect, which is the preference for nucleophiles to attack oxocarbenium ions (**4**) antiperiplanar to one of the lone pairs of the ring oxygen. In other cases, the formation of a transient intermediate (e.g., **5**, Z = I, β -glycosyl iodide) can be generated which in turn reacts with the alcohol via an S_N2-like displacement to yield the glycoside (**6**).

Using most classical strategies the assembly of 1,2-*cis*- β glycosides is difficult. The *cis* orientation of the groups at C-1 and C-2 prevents directing the stereoselectivity of the glycosylation reaction via a participating group at C-2 in the glycosyl donor. Furthermore, recourse cannot be made to donors possessing non-participating groups at C-2, because both stereoelectronic (kinetic anomeric effect) and steric effects favor the formation of the α -glycoside. The synthesis of 1,2-*cis*- β -glycosides by standard methods has resulted in the development of multiple protocols for their preparation. Some examples include the insoluble silver salt method,¹¹ the reduction of 2-uloses,¹² the C-2 inversion of β -glucosides,¹³ the inversion of the anomeric center in α -mannosides via radical methods,¹⁴ and the alkylation of 1,2-stannylene acetals.¹⁵ However, many of these methods are either not completely stereoselective, are highly substrate dependent, or require multiple steps. This review will focus on the two recently developed methods for the synthesis of 1,2-*cis*- β -glycosides: intramolecular aglycon delivery and glycosylations of conformationally restricted glycosyl sulfoxides and thioglycosides.

Intramolecular Aglycon Delivery

Intramolecular aglycon delivery (Scheme 2) is a two



Scheme 2.

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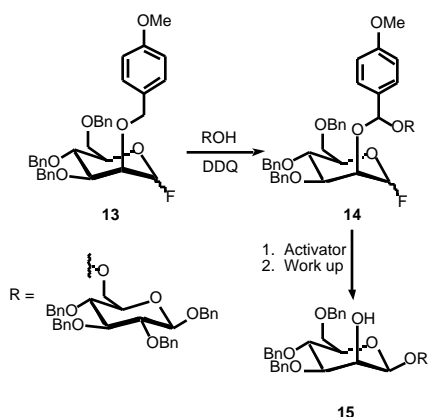
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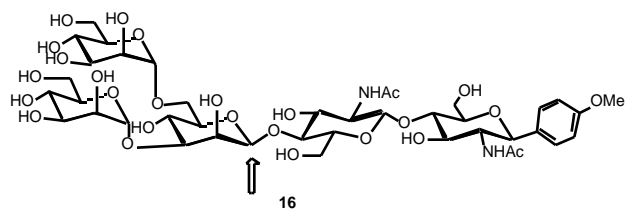
step process that first involves the synthesis of a glycosyl donor (**9**) in which the glycosyl acceptor is tethered to it at O-2 (**10**). Upon activation, the aglycon is delivered intramolecularly (**11**) to produce the β -mannoside (**12**). There are many possibilities for X, Y, and Z groups in this general strategy and their selection has been shown to be critical to the success of the method. For example, Baressi and Hindsgaul¹⁶ (Y = CH₃, Z = C, Y = SEt) first reported this method and used it in the synthesis of several β -mannosides in modest yields. Stork and LaClair¹⁷ later reported a variant using alkoxychlorosilanes (X = CH₃, Z = Si, Y = S(O)Ph) and were able to synthesize both *O* and *C*- β -mannosides.



Scheme 3.

Another variant of this protocol has been developed by Ito and Ogawa.¹⁸ This method involves the use of *p*-methoxybenzyl ether (PMB) as the tether. Starting from a 2-*O*-PMB mannose derivative (e.g. **3**, Scheme 3) treatment with alcohol in the presence of DDQ affords the mixed acetal (**14**). After activation the desired β -mannoside (**15**) is produced. This method has been used to synthesize the core pentasaccharide structure of the asparagine-linked glycoproteins (**16**).^{18c} This method has also been used to synthesize β -D-arabinofuranosides including a hexasaccharide containing two β -arabinofuranosides found at the non-reducing termini of mycobacterial arabinogalactan.¹⁹

Although complete stereochemical control has been

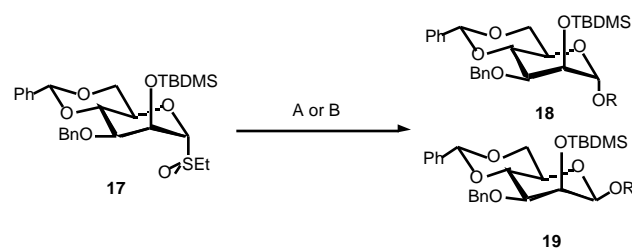


Scheme 4.

realized using this strategy, the manipulation of rather sensitive substrates (e.g., **10**, **14**) is required. Furthermore, the sequence is only compatible with a limited range of protecting groups and not all secondary alcohols are good substrates.

Glycosylations of Conformationally Restricted Glycosyl Sulfoxides and Thioglycosides.

A very efficient route to β -mannopyranosides has been reported by Crich and co-workers.^{20a} Using glycosyl sulfoxides²¹ as the donors it was found that the reaction stereochemistry was highly dependent upon the order of addition of the reagents (Scheme 5). When Tf₂O is added to a mixture of the glycosyl donor (**17**), glycosyl acceptor and di-*tert*-butyl-4-methyl pyridine (DTBMP) in diethyl ether at -78 °C, the selectivity in the glycoside product is α : β = 10:1 (**18**, **19**). If the glycosyl donor is allowed to first react with the Tf₂O at -78 °C, followed by addition of acceptor there is a reversal of selectivity in the glycoside product (α : β = 1:10.5).

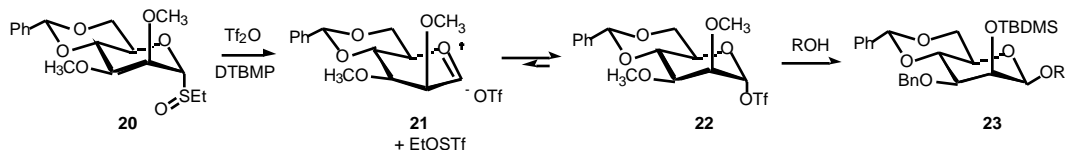


- A. Tf₂O, DTBMP, Et₂O, ArH, ROH, -78 to 0 °C (α : β = 10:1)
 B. 1) Tf₂O, DTBMP, Et₂O, ArH, -78 °C; 2) ROH, -78 to 0 °C (α : β = 1:10.5)

Scheme 5.

In order to explain this remarkable selectivity, Crich and co-workers have shown by ¹H, ¹³C and ¹⁹F NMR spectroscopy that the activation of glycosyl sulfoxides by triflic anhydride in the absence of the acceptor alcohol produces α -glycosyl triflate intermediates (e.g. **22**, Scheme 6).^{20c} Subsequent addition of the an alcohol results in an S_N2-like displacement of the triflate, thus affording the β -glycoside. This method has proven to be useful for the synthesis of a wide range of β -mannopyranosides with a high degree of stereocontrol. However, in order for good stereocontrol to be achieved the sulfoxide must possess a 4,6-*O*-benzylidene acetal

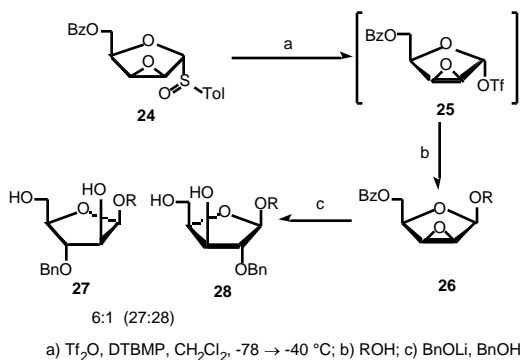
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Scheme 6.

protecting group. It is proposed that upon activation, the initially formed oxocarbenium ion pair (**21**) is converted to the triflate (**22**) and that the equilibrium between these two species lies in favor of the triflate. This protecting group would be expected to destabilize **21** relative to **22** due to increased torsional strain in the flattened chair form.²² It was also proposed that when the constraint is removed, the ion pair and the triflate are in rapid equilibrium, which leads to the reduced stereoselectivities. The stereoselective synthesis of β -mannosides via glycosyl triflates can also be achieved from thioglycosides upon activation with the appropriate promoters.²³

More recently, a variant of this method using 2,3-anhydro-lyxfuranosyl sulfoxides (e.g., **24**, Scheme 7)²⁴ has been reported by Lowary and co-workers. This substrate can be used to synthesize β -arabinofuranosides via a two step process. Initially, the donor is glycosylated to yield a 2,3-anhydro- β -lyxfuranosyl glycoside (**26**) followed by nucleophilic ring opening of the epoxide which can occur regioselectively at C-3 to yield the β -arabinofuranoside (**27**). These sulfoxides and thioglycosides glycosylate a wide range of alcohols with a high degree of stereocontrol and in excellent yields. The major or in many cases the sole product of the glycosylation is the β -glycoside. Like the Crich β -mannoside synthesis, activation of the sulfoxide is proposed to produce an α -glycosyl triflate (**25**) which is displaced by the alcohol in an S_N2 -like fashion. Activation of the corresponding thio-glycosides has also provided β -glycosides in good yields.



Scheme 7.

Outlook and Summary

The synthetic assembly of complex oligosaccharides has provided multiple challenges to organic chemists over the last thirty years. One of the most formidable challenges is the stereoselective synthesis of 1,2 *cis*- β -glycosides specifically **1** and **2**. Many synthetic approaches to these molecules have been developed and their synthesis has often proved to be cumbersome and somewhat substrate dependent. This review has focused on two of the most useful methods for the assembly of these systems: intramolecular aglycon delivery and the use of conformationally restricted donors. Future work in the area of IAD needs to involve the development of better linkers to increase the stability of the tethered intermediate (e.g., **10**, **14**). Also, other activation conditions need to be found with different glycosyl donors in order to improve the overall reaction yields and to make the method more reliable with secondary alcohols. The Crich sulfoxide method has been used to synthesize many β -mannosides with excellent stereoselectivity. However, further exploration of this method is desirable. For example, can other conformational restricting protecting groups be used instead of benzylidene acetal; if so this will increase the range of protecting group compatibilities and expand the overall scope of this method. The use of 2,3-anhydrofuranosyl donors is also a powerful method. Future work in this area requires further optimization of the ring opening step with various nucleophiles. It would also be interesting to see if this method can be expanded to 2,3-anhydropyranosyl donors with the same degree of stereoselectivity.

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