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Solid-Phase Synthesis of β-Mannosides

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Abstract: The linkage of *S*-phenyl 2,3-di-*O*-benzyl-α-D-thiomannopyranoside to a cross-linked polystyrene support in the form of its 4,6-*O*-polystyrylborinate ester is described. The activation of this polymer-supported mannosyl donor is achieved at −60 °C in dichloromethane in the presence of 2,4,6-tri-*tert*-butylpyrimidine with the combination 1-benzenesulfinyl piperidine and trifluoromethanesulfonic anhydride. Addition of the donor alcohol at −60 °C followed by warming to room temperature and subsequent cleavage from the resin by gentle heating in aqueous acetone yields anomerically pure 2,3-di-*O*-benzyl-β-D-mannopyranosides in excellent yield. Successful, diastereoselective coupling is demonstrated with a range of primary, secondary, and tertiary glycosyl acceptors, including typical carbohydrates and threonine derivatives.

Introduction

Polymer-supported synthesis of oligosaccharides is a rapidly emerging field,[1−8] with remarkable successes using an automated synthesizer having been reported recently.[9] Nevertheless, the development of a truly versatile system for the automated, supported synthesis of oligosaccharides requires that methods for the highly diastereoselective assembly of all classes of glycosidic bonds be transposed to the solid phase. Presently, despite the enormous progress that has been made, we are clearly still some way from that goal, with several classes of glycosidic bonds still presenting a considerable challenge, even in solution. Here, we describe the first successful polymer-supported synthesis of the challenging β-mannopyranoside-type glycosidic bond.

Results and Discussion

The β-mannosides have long been recognized as one of the more important and challenging classes of glycosidic bonds.[10−12] As such, much effort has been spent on developing methods for their synthesis, culminating in several successful strategies.[13−23] With the exception of the work conducted in our laboratory,[21−23] these methods are largely indirect and consequently less than ideal for solid-supported synthesis because of the extra steps they introduce. The only method to have been transferred to the solid phase so far is the Ogawa group's adaptation of the intramolecular aglycon delivery method which, by its very nature, results in cleavage from the resin concomitant with formation of the β-mannoside linkage.[24]

In its original form, our own direct β-mannosylation reaction, a variation on Kahne's sulfoxide method,[25,26] involved the low-temperature activation of a 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxide, bearing additional nonparticipating protecting groups at O2 and O3, with triflic anhydride at low temperature to give the corresponding α-mannosyl triflate.[21,22,27] Subsequent addition of the acceptor alcohol results in an S_N2-like displacement of the triflate, with selective formation of the β-mannoside (Scheme 1). The reaction is typically conducted in the presence of a hindered base such as DTBMP or TTBP, which is our present choice owing to its ready availability and crystalline, nonhygroscopic nature.[28]

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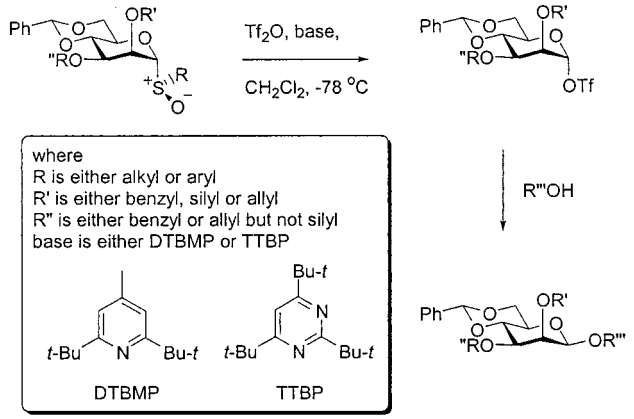
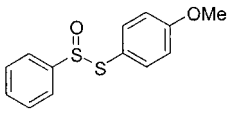
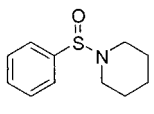
Scheme 1



To minimize manipulations of the hydrolytically and thermally unstable triflate intermediate, it was apparent that a donor-bound strategy should be followed in any polymer-supported version of this reaction. However, given the problems of monitoring stoichiometry and reaction progress commonly associated with solid-phase chemistry, it was considered unlikely that the key thioglycoside-to-glycosyl sulfoxide transformation could be accomplished in sufficiently high yield on the polymeric support. This does not, of course, exclude the use of the sulfoxide method in acceptor-bound polymer-supported oligosaccharide synthesis, as has been elegantly demonstrated by Kahne and co-workers.[1,2] To overcome the problem of supported sulfide-to-sulfoxide oxidation, over the course of several years we have consistently sought reagents for the rapid, direct conversion of thioglycosides to glycosyl triflates at low temperature. The first successful reagent for this purpose was benzenesulfenyl triflate,[22,23] but this suffers from its inconvenient preparation from benzenesulfenyl chloride and silver triflate. In particular, when this reagent is used to activate a polymer-bound thioglycoside, the beads tend to become coated in colloidal silver following decomposition of silver chloride, the byproduct of in situ generation. The combination of *S*-(4-methoxyphenyl)benzenethiosulfinate (MPBT, **1**) with triflic anhydride was found to achieve the desired transformation in solution,[29] but a still more powerful combination was eventually found in 1-benzenesulfinyl piperidine (BSP, **2**) and triflic anhydride,[30] and it is this reagent couple that has enabled the work described here.



MPBT, **1**

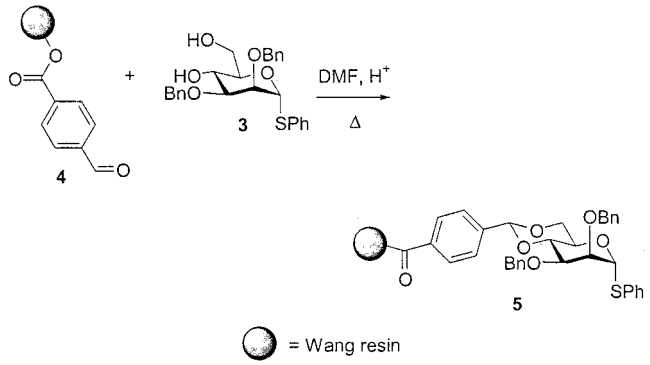


BSP, **2**

A requirement for high selectivity in our mannosylation reaction is the 4,6-*O*-benzylidene group[23,27] that serves to torsionally disarm[31,32] the intermediate mannosyl triflate and so reduces loss of selectivity potentially caused by the formation of free oxacarbenium ions. It is especially noteworthy that alternatively located six-membered cyclic protecting groups such as a Ley-type bis-acetal spanning the 3- and 4-positions are not suitable and are even α-selective.[33] The 4,6-*O*-benzylidene group, or its functional equivalent, must therefore be incorporated into the eventual polymer-bound mannosyl donor. This imposes limitations on the location at which the donor is bound to the polymeric support. We considered linkage through O2 to be too close to the site of reactivity and were dissuaded from linkers bound to O3 by the discoveries that both esters and silyl ethers at that position are α-directing,[33,34] the esters highly so, even in the presence of the 4,6-*O*-benzylidene group. Accordingly, immobilization via the benzylidene group, or its equivalent, was selected for study.

Both Fréchet and Hanessian have described the use of polymer-bond benzaldehyde derivatives as protecting groups in the glucose, but not mannose, series.[35,36] Initially, therefore, we investigated a commercial modified benzaldehyde derivative bound to the Wang resin. Thus, diol **3**, conveniently obtained by acid hydrolysis of the corresponding 4,6-*O*-benzylidene derivative, was stirred with resin **4** in DMF in the presence of *p*-toluenesulfonic acid, resulting in the formation of an immobilized thiomannoside **5** (Scheme 2). Unfortunately, incorporation, as determined by subsequent hydrolysis and recovery of the diol as well as by MAS NMR of the swollen beads,[37] was repeatedly found to be low; therefore, this method was not pursued further.

Scheme 2



Following the early work of Fréchet on the application of polystyrylboronic acid as a protecting group for carbohydrate diols,[38] and Boons' more recent extension to the immobilization of thioglucoside 4,6-diols and his subsequent use of the bound donors in coupling reactions,[39,40] we turned to the investigation of phenylboronic acid derivatives. To determine whether the 4,6-*O*-phenylboronate ester exhibited the same torsionally disarming properties as the benzylidene group, diol **3** was condensed with phenylboronic acid to give **6**. This was activated in dichloromethane at −60 °C in the presence of TTBP with BSP and then coupled to 1-adamantanol to give the crude β-mannoside **7**. Subjection of the residue to silica gel chroma-

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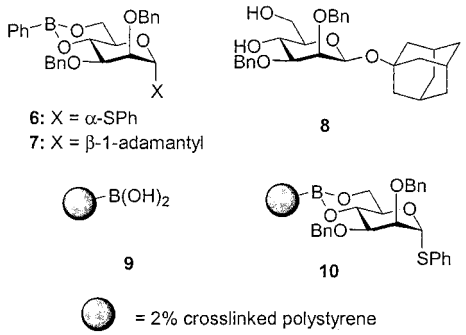
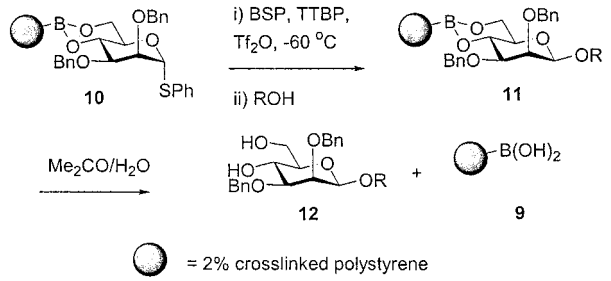
tography removed the phenylboronate ester to give the diol **8** in 72% yield. The anomeric stereochemistry of **8** was confirmed by the $^1J_{CH}$ coupling constant[41] of 152 Hz as well as by conversion of **8** into its known 4,6-*O*-benzylidene derivative,[23] with which it was identical in all respects.



The viability of the 4,6-*O*-phenylboronates as torsionally disarming protecting groups was thus established, and we proceeded with the polymer-supported variant. Accordingly, diol **3** was heated in pyridine with polystyrylboronic acid (**9**)[38,42] to give the bound donor **10** with a loading of ~1 mmol/g as determined from the amount of diol liberated on cleavage. Activation of the bound thioglycoside **10** was achieved by stirring in dichloromethane with BSP (**2**) at −60 °C in the presence of TTBP and triflic anhydride for 20 min, followed by adding the acceptor alcohol, warming to room temperature, and quenching. After removal of the excess reagents, alcohol, and byproducts, the coupled β-mannosides **11** were released from the resin by heating in aqueous acetone for 1 h to give the 4,6-diols **12** (Scheme 3). The various β-mannosides so

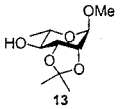
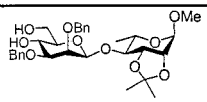
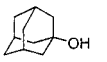
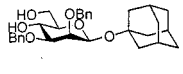
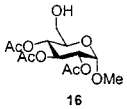
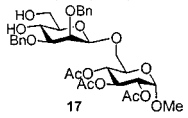
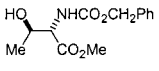
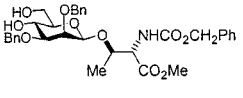
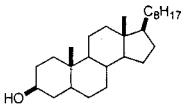
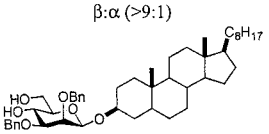
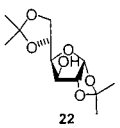
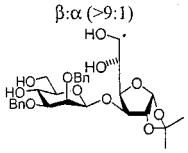
Scheme 3



prepared are collected in Table 1, from which it will be seen that a powerful method is at hand. The yields and selectivities presented in Table 1 require little further discussion except, perhaps, to draw attention to the hydrolysis of the 5,6-acetonide of the glucofuranose residue in the course of removal from the resin in the last entry.

All in all, a powerful method for the polymer-supported synthesis of β-mannosides is at hand using our potent BSP (**2**)/triflic anhydride combination for the activation of thioglycosides. Only very short activation times are required at low temperature, and the isolated yields of β-mannosides from this polymer-supported protocol are directly comparable with those obtained using the analogous solution-phase methodology. Finally, the method is both different from and complementary to that of Ogawa.[16,17] It differs fundamentally insofar as cleavage from the resin is not an integral part of the coupling reaction but rather the disaccharide is retained on the support and may, in principle,[43] be further extended. It is complementary in that after cleavage it provides β-mannosides bearing free hydroxyl groups at the 4- and 6-positions, whereas the Ogawa sequence affords the β-mannoside selectively deprotected at the 2-position.

Table 1. Polymer-Supported Synthesis of β-Mannosides with the Polystyrylboronate **10**[a]

Acceptor	Product[b]	Yield (%)	$^1J_{CH}$ (Hz)
 13	 14 β:α (>9:1)	77	158
	 15 β:α (>9:1)	88	152
 16	 17 β:α (>9:1)	73	155
 18	 19 β:α (>9:1)	79	154
 20	 21 β:α (>9:1)	78	154
 22	 23 β:α (>9:1)	84	157

[a] All reactions were conducted in dichloromethane at −60 °C. [b] Anomeric ratios of >9:1 are conservative minima; in all such cases, the minor isomer was not detected in the NMR spectra of the reaction mixtures.

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Supporting Information Available: Full experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) Further chain extension on the solid support may, in principle, take two forms. First, it is conceivable that a glycosyl fluoride bearing a free hydroxyl group may be used as an acceptor in the initial coupling, thereafter permitting extrapolation of the donor-bound strategy. Second, selective deblocking of a hydroxyl group after the initial coupling should permit further glycosylations in an acceptor-bound strategy. To date, we have examined only the second of these two strategies but report that we have so far been thwarted by the relative instability of the polystyrylboronate linker, which curtails the options for protecting group manipulation.