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Polymer-supported oligosaccharide synthesis by a loading–release–reloading strategy

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Abstract

A new synthetic strategy for solid-supported oligosaccharide synthesis has been developed whereby a synthetic intermediate can be released from the solid support, purified and reloaded for further synthesis. Key to the success of this approach is the polymeric support polystyrylboronic acid, which allows saccharides to be loaded by heating in pyridine and released by treatment with a mixture of acetone and water. © 2000 Published by Elsevier Science Ltd.

Increased awareness of the biological importance of oligosaccharides and glycoconjugates[1,2] has stimulated the development of efficient methods for the preparation of these compounds. Improved chemical and enzymatic glycosylation procedures in combination with convergent synthetic strategies make it possible to execute multi-step synthetic sequences that give well-defined complex oligosaccharides in reasonable quantities.[3–6] It is to be expected that further improvements and eventually automation will come from polymer-supported oligosaccharide synthesis.[7] Several groups have successfully prepared relatively large 1,2-*trans*-linked oligosaccharides on solid support by employing glycosyl donors that have a neighboring group participating functionality at C-2. This approach gives absolute anomeric selectivities and reactions can be driven to completion either by using a relatively large excess of glycosyl donor or by performing repetitive glycosylations. On the other hand, attempts to introduce 1,2-*cis*-linked glycosides often resulted in the formation of mixtures of anomers. This lack of anomeric control is a major problem of solid-supported oligosaccharide synthesis. When several glycosidic linkages are formed as mixtures of anomers, a final product will constitute an intractable mixture of isomers.

In this communication, we address the problem of lack of anomeric control by the following sequence of manipulations: a protected oligosaccharide will be prepared on solid support and when a mixture of anomers is formed, the synthetic intermediate will be cleaved from the polymeric support and the anomers separated by silica gel column chromatography. The anomerically pure compound will be reloaded and used for further synthesis. This approach will only be attractive when the loading and cleavage step can be performed by very simple manipulations. In

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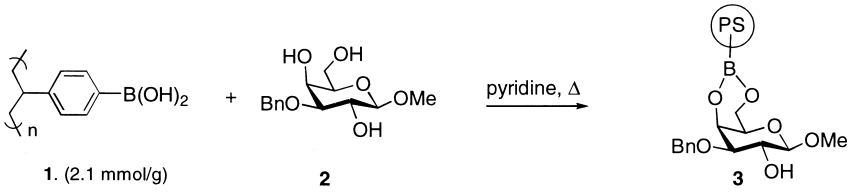
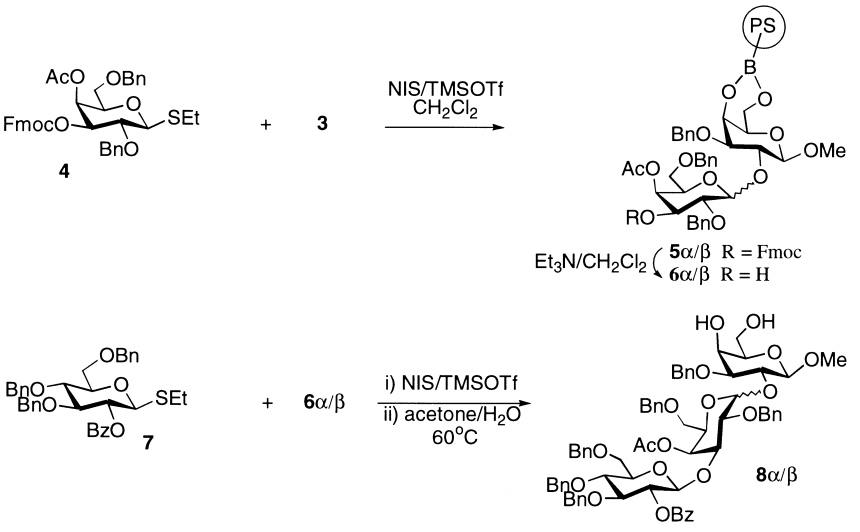
the preceding paper, we reported that polystyrylboronic acid[8a] requires only solvents for loading and cleavage and can be reused after a synthetic sequence. Therefore, this polymeric support should be ideally suited for the proposed synthetic strategy.

The synthesis of an oligosaccharide on the polystyrylboronic acid solid support requires a temporary protecting group, which can be removed without effecting the boronic ester linkage. Boronic esters hydrolyze in protic solvents;[9] thus, protecting groups that are cleaved using this type of solvent should be avoided. Recently, it was demonstrated that the Fmoc group is an attractive hydroxyl-protecting group for oligosaccharide synthesis which can be cleaved by treatment with triethylamine in CH_2Cl_2.[10–12]

Thus, the Fmoc protected thioglycoside **4** was selected as the glycosyl donor for a NIS/TMSOTf mediated glycosylation. The immobilized acceptor **3** was easily obtained by heating a mixture of boronic acid modified cross-linked polystyrene and **2**[13] in pyridine (Scheme 1). Coupling of **3** with **4** to give immobilized **5** was performed in the presence of the promoter NIS/TMSOTf.[14–16] A small amount of beads was treated with acetone/water and TLC and MALDI-MS of the released product showed the absence of starting material and the presence of disaccharide. The Fmoc group of **5** was cleaved by treatment with Et_3N in CH_2Cl_2 to give glycosyl acceptor **6**, which was glycosylated with thioglycosyl donor **7**.[17] After cleavage from the solid support, the trisaccharide **8** was obtained in an overall yield of 55% (Scheme 2). Detailed NMR analysis of **8** showed that the first glycosidic linkage (D-Gal*p*-(1-2)-β-D-Gal*p*) was formed as a mixture of anomers (α:β = 1.6:1).



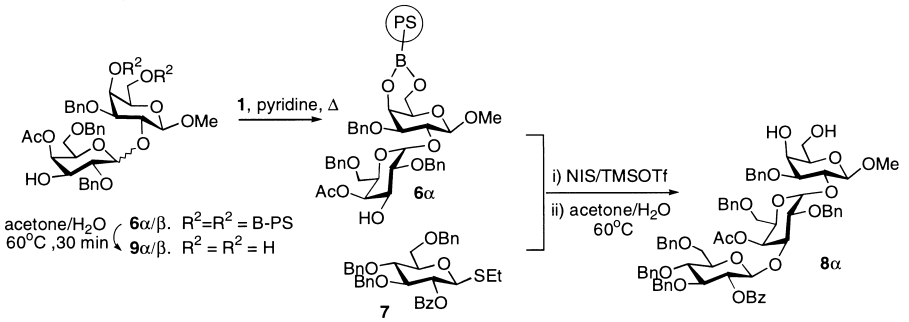
Scheme 1.



Scheme 2.

The favorable properties of boronic esters allow synthetic intermediates to be easily removed from the solid support, purified by column chromatography, reloaded onto the resin and used for further synthesis. This hybrid type of solid- and solution-phase chemistry may be the most attractive way to circumvent current shortcomings of solid supported glycosylation methodologies. To demonstrate this type of oligosaccharide synthesis, trisaccharide **8** was re-synthesized, but in this case the disaccharide intermediate **6** was released form the solid support to give **9**. Compounds **9**α/β were subjected to silica gel column chromatography and the two anomers separated. Compound **9**α was reloaded onto polymer **1** by heating in pyridine to give immobilized **6**α. Compound **6**α was glycosylated with **7** in the presence of NIS and TMSOTf to give, after cleavage from the support, trisaccharide **8**α as an anomerically pure compound (Scheme 3).[18]

In conclusion, it has been demonstrated that polystyrylboronic acid is an attractive polymeric support for oligosaccharide synthesis. The favorable properties of the boronic ester linker allow synthetic intermediates to be cleaved from the solid support, purified and reloaded for further synthesis.[19] This sequence of manipulations is particularly attractive when mixtures of anomers are formed.



Scheme 3.

Experimental. Procedure for loading 3-*O*-benzyl-β-D-galactopyranoside (**2**) onto polysytyrylboronic acid (**1**): The polymer (400 mg) was placed in a round-bottomed flask, just covered with pyridine and allowed to swell for 15 min. Compound **2** was added and the suspension was heated at 60°C for 1 h and at 80°C under reduced pressure for a further 1 h. After cooling, the solvent was removed by filtration and the polymer washed successively with pyridine (2×2 mL) and toluene (2×2 mL). The polymer was then co-evaporated twice from toluene and dried in vacuo over P_2O_5 for 24 h.

Procedure for detachment of trisaccharide **8**α from polystyrylbronic acid: a suspension of the loaded resin in acetone:water (4:1, v/v) was stirred for 30 min at 60°C. The resin was filtered and washed with dichloromethane (2×10 mL) and methanol (2×10 mL). The filtrate and the washings were combined and concentrated under reduced pressure.

Selected ^1H and ^{13}C NMR data for compound ***8***α: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.43 (d, 1H, H-1′, $J_{1',2'} = 3.5$ Hz), 5.41 (d, 1H, H-4′, $J_{3',4'} = 3.5$ Hz), 5.31 (t, 1H, H-2″, $J_{1'',2''} = J_{2'',3''} = 8.4$ Hz), 5.02 (d, 1H, H-1″), 3.40 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.65 (C-1), 101.00 (C-1″), 97.01 (C-1′), 56.70 (OCH_3), 21.11 (CH_3CO).

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