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On-resin generation and reactions of orthogonal glycosyl donors

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Abstract—An orthogonal series of glycosyl donors has been generated in situ from thiophenylglycosides appended to a hydroxymethylpolystyrene resin through a succinate linker. The conditions used to generate these donors and their subsequent reactions with sugar acceptors will be described.

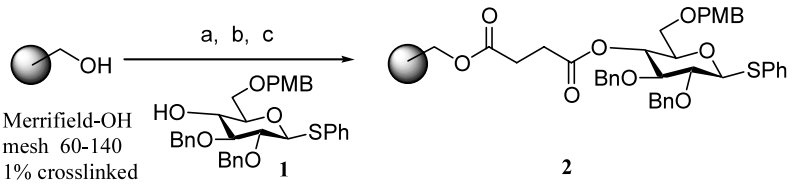
Introduction: The realization of the biological importance of oligosaccharides in such processes as cellular recognition and differentiation has spurred the development of a myriad of methods for the synthesis of these molecules over the past 20 years. Within the past decade, these methods have been expanded to include the techniques previously employed for other important biological molecules, namely the nucleic acids and peptides. In order to improve the synthetic efficiency of complex saccharide chains, solid phase techniques have been explored.[1] Recently, an automated synthesizer has been developed that promises to make the preparation of complex saccharides even more facile.[2]

Most of the solid phase procedures employed to date utilize the attachment of a glycosyl acceptor to a linker molecule on a resin. An excess of donor is added in solution along with the appropriate promoter. Using solid phase techniques, saccharide chains of varying lengths have been prepared.[1]

Resin-bound glycosyl donors have been used less frequently.[3] The major use of these donors has been to prepare branched saccharides on a resin.[1b,4] Some early work in this area successfully utilized the in situ activation of glycals on a resin to useful glycosyl donors.[3a,d] Usually donors have been prepared in solution and then attached to the resin prior to the coupling reaction. Donors for each coupling step are also prepared. Since each donor requires several synthetic steps, the overall synthetic efficiency of the process is low.

As part of an ongoing research program aimed at the synthesis of linear and cyclic 1,6-linked saccharides, we required an efficient method to carry out bi-directional glycosylations on a resin. Herein, we report on the successful in situ generation of a series of orthogonal glycosyl donors from a common sugar precursor. The groups investigated were the anomeric fluorides, sulfoxides and sulfones. These functionalities can be selectively activated in the presence of one another and are readily prepared from thioglycosides. The on-resin reactions of these donors with different sugar acceptors will be described.

Chemistry: Thiophenylglycosyl donor **1** was prepared from penta-*O*-acetyl-β-D-glucopyranose using estab-



Scheme 1. *Reagents and conditions*: (a) succinic anhydride (8 equiv.), Et_3N (10 equiv.), CH_2Cl_2, rt; (b) pivaloyl chloride (3 equiv.), Et_3N (5 equiv.), CH_2Cl_2; (c) phenyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside **1** (1 equiv.), Et_3N (1.5 equiv.), DMAP (0.2 equiv.), CH_2Cl_2.

Keywords: in situ generation; orthogonal donors; solid phase glycosylation.

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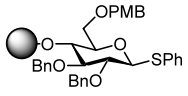
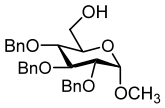
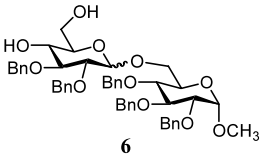
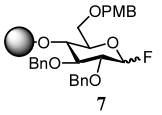
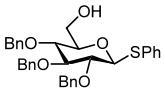
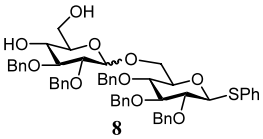
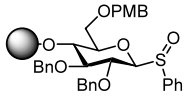
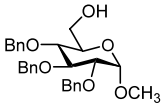
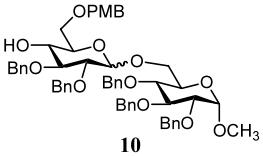
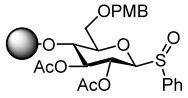
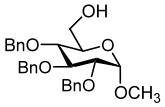
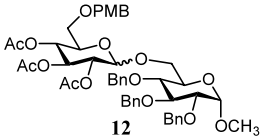
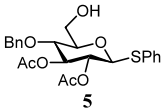
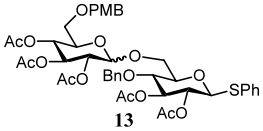
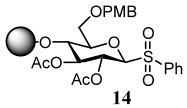
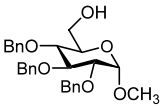
lished literature procedures.[5–7] The thiophenylglycosyl donor was appended to a resin through its 4-OH group using a succinate linker.[8] This linker was chosen because it can withstand the acidic conditions of most glycosylation reactions, yet it is labile under basic conditions, allowing for the easy cleavage of the product saccharides. The resin we employed for our studies was the insoluble, hydroxymethyl polystyrene resin (Argonaut, 1% cross-linked). The synthetic sequence used for the preparation of resin bound donor **2** is shown in Scheme 1.[9]

Glycosyl acceptors both with and without a donor group were chosen for reaction with the resin-bound donors. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3** was prepared from methyl-α-D-glucopyranoside using

Table 1. Glycosylation reactions of resin-bound donors[a]

Entry	Donor	Acceptor	Disaccharide	Promoter (equiv)	%Yield[b] (α:β)[c]
1	 **2**	 **3**	 **6**	NIS (1.2) TfOH (1.0)	55 (1:4)
2	 **7**	 **4**	 **8**	$BF_3{\cdot}Et_2O$ (0.5)	74 (7:1)
3	" "	" "	" "	Tf_2O (0.5)	67 (1:3)
4	 **9**	 **3**	 **10**	Tf_2O (1.0)	58[d] (1:4) 57[e] (1:4)
5	 **11**	 **3**	 **12**	Tf_2O (1.0)	58[d] (1:9)
6	"	 **5**	 **13**	Tf_2O (1.0)	71[d] (1:9)
7	 **14**	 **3**	----------	$MgBr_2$ (2.2)	No Reaction

[a] All glycosylation reactions were carried out with one equiv of donor and an excess of acceptor (2-5 equiv) in CH_2Cl_2.except for Entry 7, in which a 1:1 mixture of THF:Et_2O as the solvent.

[b] Yields reported are isolated yields and were calculated by weighing the purified disaccharides from column chromatography and by comparing these weights to the predetermined loading weights of the donor sugars on the resin.[9] The purity of all compounds was established using NMR, MS and in some cases elemental analysis.

[c] Anomer ratios were determined by integration of anomeric resonances in the crude proton NMR.[19]

[d] Norbornylene (1.0 equiv) used as a scavenger.

[e] MPBT (1.5 equiv) used as a scavenger

● Denotes hydroxymethylpolystyrene resin with attached succinyl linker

a three-step sequence.[10] Thiophenylglycoside acceptors **4** and **5** were prepared from penta-*O*-acetyl-β-D-glucopyranose by a sequence similar to that used for the thiophenylglycosyl donor **1**.

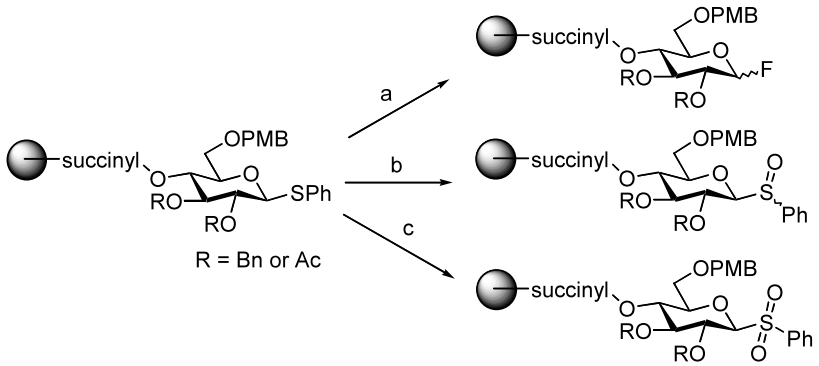
Using modified solution phase glycosylation procedures,[11] the resin-bound donor **2** (1 equiv.) was suspended in dichloromethane, treated with *N*-iodosuccinimide (NIS) (1.2 equiv.), trifluoromethanesulfonic acid (TfOH) (1.0 equiv.), and an excess of acceptor **3** (5 equiv.) and shaken on an orbital shaker for 24 h at room temperature. Following cleavage of the products from the resin with sodium methoxide and column chromatography on the filtrate, a 54% isolated yield of an anomeric mixture of disaccharide **6** was realized (1:4, α:β) (Table 1; entry 1). None of the unreacted donor **1** was recovered and the only byproducts isolated in quantities significant enough to characterize were the pyranose sugar from the reaction of water with the activated donor and the methyl glycoside from reaction of the donor with methanol used to rinse the resin. Unfortunately, under these reaction conditions the *p*-methoxybenzyl group (PMB) on the donor was labile and saccharides with a free 6-OH were recovered. Because a uniquely protected 6-OH group was required for the successful implementation of our protocol, we attempted to optimize the reaction to retain this group. Conducting the reaction at lower temperatures, for shorter periods of time, or with reduced amounts of promoter were unsuccessful and lead to diminished yields of disaccharide products.

It was desirable to find a more reactive donor to carry out this transformation to avoid prolonged reaction times and loss of the PMB group. The glycosyl fluorides met this criterion. Treatment of resin-bound thiophenylglycosyl donor **2** with DAST and *N*-bromosuccinimide (NBS)[12] (50 min, rt), afforded a clean conversion to an anomeric mixture of glycosyl fluorides **7** (89%; 9:1, α:β) (Scheme 2).

We were interested in these donors because it is well documented in the literature that the anomeric selectivity of the glycosylation reaction changes with the use of different promoters. When the donor mixture **7** (1 equiv.) was treated with boron trifluoride diethyletherate ($BF_3{\cdot}Et_2O$) (0.5 equiv.)[13] and acceptor **4** (2 equiv.) at 25°C (1 h), disaccharides **8** were obtained in 74% yield (7:1, α:β) (Table 1; entry 2). With trifluoromethanesulfonic anhydride (Tf_2O) promotion (0.5 equiv.), the β-anomer was obtained as the major product (1:3, α:β 67%)[14] (Table 1; entry 3). In spite of the shorter reaction times and diminished amounts of promoter required, the PMB group was still lost using either set of glycosylation conditions. Again, attempts to optimize the reaction and prevent the loss of the PMB group using an acid scavenger[15] were unsuccessful.

Anomeric phenylsulfoxides have also shown promise as glycosyl donors.[16] These donors have been used in solution with acceptor-bound resin protocols.[16b] Treatment of resin-bound **2** with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 (16 h, rt) afforded sulfoxide **9** in 78% yield (Scheme 2). Overoxidation to the sulfone was the major side reaction and conditions had to be carefully controlled to avoid formation of this product. The reaction of donor **9** (1 equiv.) with Tf_2O (1 equiv.), di-*tert*-butylmethylpyridine (DTBMP) (3 equiv.) and acceptor **3** (2 equiv.), also gave modest yields of **6** (55%; 1:4, α:β). When the same reaction was carried out with the addition of stoichiometric amounts of the acid scavengers, norbornylene[16c] or *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT),[16d] the undesired removal of the PMB group was suppressed. Disaccharide **10** was obtained in 58 and 57%, respectively, for the two sets of conditions (Table 1; entry 4).[17] There was no change in anomeric selectivity with the addition of scavenger.

It is well known that β-anomeric selectivities can be enhanced using C-2 acyl groups that are capable of neighboring group participation. Diacetylated donor **11** was prepared by oxidation of resin-bound phenyl 2,3-di-*O*-acetyl-6-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside with MCPBA. Better selectivities for the β-disaccharide were observed when donor **11** was employed in the glycosylation reaction with acceptor **3** using Tf_2O and norbornylene as described above. Following reacetylation of the hydroxyl groups liberated during cleavage of the resin, disaccharide **12** was isolated as a α:β mixture (1:9) in 58% yield (Table 1; entry 5). Thiophenylglycosyl acceptor **5** afforded a 71% yield



Scheme 2. *Reagents and conditions*: (a) DAST (1.5 equiv.), then NBS (1.3 equiv.), CH_2Cl_2, rt; (b) MCPBA (1.2 equiv.), $NaHCO_3$ (1.2 equiv.), CH_2Cl_2, rt; (c) MCPBA (3 equiv.), $NaHCO_3$ (3 equiv.), CH_2Cl_2, rt.

of disaccharide **13** (1:9, α:β) when reacted with donor **11** and worked up under the same set of conditions (Table 1; entry 6).

Since sulfone was observed as a by-product from the MCPBA oxidation, we directly prepared this compound to observe its on-resin glycosylation capabilities. Ley[18] has demonstrated the usefulness of sulfones as orthogonal donors in solution phase glycosylation schemes with sulfoxides and thioglycosides. Treatment of donor **14** (1 equiv.) with magnesium bromide diethyletherate (2.2 equiv.), sodium bicarbonate (2.8 equiv.) and acceptor **3** (2 equiv.) at room temperature for 2 days failed to produce any disaccharide product (Table 1; entry 7). Only sulfone was recovered.

Discussion: Some general statements can be made about these reactions. All of the donors were readily prepared on the resin. Longer reaction times and/or higher reaction temperatures, compared to the reported solution phase syntheses, were necessary in every case to ensure the conversions had gone to completion.

The glycosylation experiments also required harsher reaction conditions. As predicted, the acyl-substituted donor **11** gave better reaction selectivities and β-disaccharides were formed predominately with this donor. Boron trifluoride activation of benzyl protected fluoride donor **7** afforded mainly α-disaccharide in good agreement with reports from solution phase experiments. The yields of products were modest with all donor/promoter combinations. The PMB group was cleaved under many of the conditions studied. The use of acid scavengers prevented the loss of the labile PMB group when used with sulfoxide donors **9** and **11**. Orthogonal strategies allowed the preparation of disaccharides from glycosyl fluoride donors and thiophenyl glycoside acceptors and from sulfoxide donors and thiophenyl glycosides. The extension of this work to the preparation of more complex saccharides using both unidirectional and bi-directional approaches is currently in progress and will be reported in due course.

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17. Representative experimental procedures: Resin-bound donor **9** (0.10 g, 0.06 mmol), di-*tert*-butylmethylpyridine (0.02 mL, 1.74 mmol), and acceptor **3** (0.06 g, 0.12 mmol) were suspended in dry CH_2Cl_2 (2 mL), shaken and cooled to −78°C. Triflic anhydride (0.013 mL, 0.06 mmol) was added, the reaction mixed for 1 h at this temperature then allowed to warm to 25°C and mixed for 22 h longer. Excess reagents were removed by filtering the resin and washing it (3×) with ~20 mL portions of the following sequence of solvents: CH_2Cl_2, Et_2O, then CH_3OH. The resin was then resuspended in 1:1 mixture of THF:CH_3OH (20 mL) and sodium methoxide (0.4 mL) was added. The mixture was shaken for 4 h, then filtered and washed with CH_2Cl_2 and CH_3OH (3×). The filtrate was neutralized using an excess of Dowex 50W-X8, filtered and concentrated in vacuo. Column chromatography (SiO_2, 50% ethyl acetate in hexanes) afforded the two saccharides **6** (0.03 g, 0.033 mmol, 55%) (1:4, α:β). Data

for β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.30–7.20 (m, 25H), 4.96 (dd, 3H, $J=12.0$, 14.5 Hz), 4.79 (d, 2H, $J=11.5$ Hz), 4.75–4.72 (m, 2H), 4.66 (d, 2H, $J=11.5$ Hz), 4.60 (br s, 1H), 4.51 (d, 1H, $J=10.5$), 4.39 (d, 1H, $J=6.0$ Hz), 4.28–4.26 (m, 1H), 4.11 (d, 1H, $J=10.5$ Hz), 3.99 (dd, 1H, $J=9.0$, 8.0 Hz), 3.84–3.68 (m, 5H), 3.53–3.50 (m, 3H), 3.45–3.41 (m, 2H), 3.39 (s, 3H), 3.32–3.26 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ_C) 138.8, 138.4, 138.3, 138.1, 129.5, 128.7, 128.5, 128.42, 128.40, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 103.9, 98.1, 84.0, 81.9, 81.7, 79.77, 77.8 (2C), 75.7, 75.3, 74.9, 74.8, 73.4, 70.4, 69.8, 68.7, 62.6, 55.3. Positive-ion electrospray (ES) MS: 824.2 ($[M^+]+NH_4^+$).

Resin bound donor **9** (0.11 g, 0.06 mmol), di-*tert*-butylmethylpyridine (0.02 mL, 1.74 mmol), norbornylene (0.005 g, 0.06 mmol), acceptor **3** (0.06 g, 0.12 mmol) and Tf_2O (0.013 mL, 0.06 mmol) were shaken in CH_2Cl_2 (2 mL) (−78°C, 1 h; rt 22 h) and the mixture was worked up as described above. Column chromatography (SiO_2, 40% ethyl acetate in hexanes) afforded the two saccharides **10** (0.032 g, 0.035 mmol, 58%) 1:4, α:β. Data for β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.30–7.20 (m, 27H), 6.87 (d, 2H, $J=8.5$ Hz), 4.96 (d, 2H, $J=11.0$ Hz), 4.91–4.88 (m, 2H), 4.79 (d, 2H, $J=11.5$), 4.75–4.72 (m, 2H), 4.66 (d, 2H, $J=11.5$ Hz), 4.60 (br. s, 1H), 4.51 (d, 1H, $J=10.5$ Hz), 4.39 (d, 1H, $J=6.0$ Hz), 4.28–4.26 (m, 1H), 4.11 (d, 1H, $J=10.5$ Hz), 4.01–3.97 (m, 1H), 3.80 (s, 3H), 3.74–3.68 (m, 5H), 3.53–3.50 (m, 3H), 3.45–3.41 (m, 2H), 3.39 (s, 3H), 3.32–3.26 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ_C) 159.8, 143.2, 138.8, 138.6, 138.5, 138.4, 138.3, 138.1, 131.9, 129.4, 129.3, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 103.7, 98.1, 84.1, 81.9, 81.4, 80.4, 79.7, 77.5, 76.8, 75.7, 75.5, 74.8, 73.8, 73.3, 71.9, 70.3, 69.8, 68.5, 64.8, 55.3. Positive-ion electrospray (ES) MS: 944.2 ($[M]^+ +NH_4^+$).

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