Towards an unprotected self-activating glycosyl donor system: Bromobutyl glycosides

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Abstract: Bromobutyl mannopyranosides have been successfully used as both protected and unprotected glycosyl donors both with and without the use of an external activator.

Key words: glycosylation, unprotected glycosyl donors, oligosaccharides.

Résumé : On a utilisé avec succès des mannopyranosides de bromobutyle comme donneurs, tant protégés que non protégés, de glycosyles et avec ou sans l'aide d'activateur externe.

Mots clés : glycosylation, donneurs de glycosyles non protégés, oligosaccharides.

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Oligosaccharides and glycoconjugates are essential tools for the investigation of the enormous variety of biological functions that require specific carbohydrate-containing structures (1). Furthermore, their potential as therapeutic agents is clear (2). As a result, the formation of the glycosidic linkage continues to be a dominant theme in carbohydrate chemistry (3). Yet despite the development of many elegant strategies, there is still no generally efficient and stereoselective method available. To this end, a number of glycosyl-donor systems have been developed, but few chemical systems allow the use of unprotected glycosyl donors; one exception has been Hanessian's 3-methoxypyridyl (MOP) glycoside system (4). It has been estimated that, on average, the need for protecting groups introduces an additional six steps to each overall glycoside bond formation. If the use of protecting groups could, therefore, be avoided or limited, while maintaining control of reactivity, then overall efficiencies may be improved. To this end, and as part of an ongoing programme to develop novel glycosylation systems and strategies (5), we have begun to investigate a new class of glycosyl donors: 4-bromobutyl glycosides. This communication describes our first results in this area.

Our goal was to create a glycosylation system that (*i*) uses sufficiently stable donors to allow preparation in unprotected form but that can still be activated; and (*ii*) may self-activate or activate under mild conditions. We reasoned that spontaneous 5-*exo* cyclization (Scheme 1) through nucleophilic attack of the C-1 oxygen atom in **1**, for example, would yield an anomeric furanosyl cation, which would closely resemble those postulated as intermediates in the activation of Fraser-Reid's powerful pentenyl glycoside class of glycosyl donors. (6) This would not only yield THF as a volatile, non-nucleophilic leaving group, but such a cyclization would also be favoured over any potentially competing cyclic ether formation with the free hydroxyls of the unprotected donor through, for example, 8-*exo* cyclization of OH-2 onto the primary bromide of the aglycon.

Clearly, the use of activation conditions that are compatible with the presence of free hydroxyl groups is essential to the use of unprotected glycosyl donors. We chose to investigate two potential activation conditions: self-activation and soft Lewis acid activation (e.g., Hal^+, Ag^+).

Our first target donor, mannoside **1**, was prepared as shown in Scheme 2. Penta-*O*-acetyl-D-mannose **6** was synthesized in quantitative yield using well-established methods from D-mannose and acetic anhydride with pyridine as a catalyst. Our strategy for creating **1** relied on the different hard and soft Lewis basicities of the anomeric *O*-1 and the aglycon primary bromide of bromobutyl glycosides, respectively (Scheme 1). Formation of 4-bromobutyl tetra-*O*-acetyl-α-D-mannopyranoside **2** was accomplished through a glycosidation using pentaacetate **6** and 4-bromobutanol, in which the hard Lewis acid $BF_3{\cdot}Et_2O$ catalysed the loss of the acetate group from the anomeric position of **6** without affecting the soft Lewis base aglycon primary bromide or indeed without activating **2** as a glycosyl donor through the mechanism envisaged in Scheme 1. In this regard, an additional aiding factor is that because of the disarmed (7) nature of **2,** this should be less reactive than the target unprotected donor **1**. 4-Bromobutanol was readily prepared through the

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Dedicated to Professor J. Bryan Jones on the occasion of his 65th birthday.

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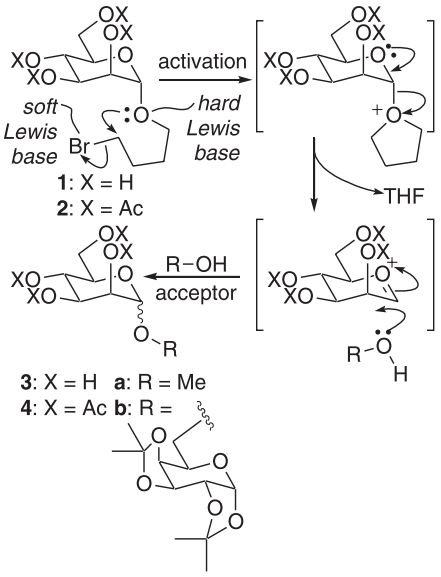
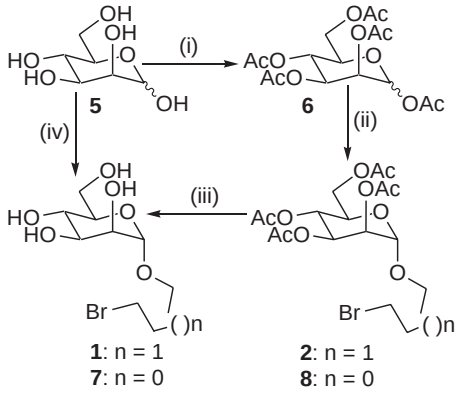
Scheme 1.



reaction of THF with 48% HBr (aq.) (8), which was preferred for large-scale work over the use of Me_2BBr (9). More than five equivalents of $BF_3{\cdot}Et_2O$ were required for effective conversion of **6** to the α-anomer **2**[3] (the sole product); the exclusive stereoselectivity for this *trans*-glycoside may be attributed to neighbouring group participation by the C-2 acetate group. While higher conversions were obtained through the use of a large excess of 4-bromobutanol, the 43% yield of **2** obtained through the use of 1.1 equivalents represents an efficient 83% yield when based on recovered starting material and was, therefore, the preferred procedure for scale-up. The use of higher equivalents of Lewis acid or increased reaction times led to no significant change in the yield of **2**.

The final step in the formation of fully deprotected donor 4-bromobutyl tetra-*O*-acetyl-α-D-mannopyranoside **1**[4] was carried out in a single efficient (87% yield) Zemplén deacetylation. Small amounts of methyl glycoside **1** (7% yield) were also recovered, encouragingly suggesting that through its action as a glycosyl donor, substitution of the anomeric 4-bromobutoxy group by MeOH had occurred at some point during the deprotection process. Since methyl glycosides are not products of the deprotection of mannosides (for example, the corresponding 3-bromopropyl mannoside (vide infra)), the formation of these methanolysis products under conditions not typically associated with lability of the glycosidic bond gave us our first indication of the successful action of 4-bromobutyl glycosides as glycosyl donors. As a consequence of this methanolysis, care was required during deacetylation of **2**. As might be anticipated, removal of the disarming effect of the acetyl groups meant that **1** would potentially prove more reactive as a glycosyl donor than **2** and that, similarly, each of the intervening partially deacetylated intermediates would prove even more reactive than the previous. After extensive screening, the use of a ~0.017 M methoxide solution freshly prepared from anhydrous MeOH and reaction times of 18 h proved optimal; shorter reactions times led to incomplete deprotection, whereas extended reaction times led to significant accumula-

Scheme 2. Reagents and conditions: (*i*) Ac_2O, py (3:2), 100%; (*ii*) $Br(CH_2)_{3+n}OH$, DCM, $BF_3{\cdot}Et_2O$, 43% for **2**, 39% for **8**; (*iii*) MeONa, MeOH, 87% for **1**, 98% for **7**; (*iv*) $Br(CH_2)_{3+n}OH$, $BF_3{\cdot}Et_2O$, 18% for **1**, 25% for **7**.



[3] **2**: $BF_3{\cdot}Et_2O$ (6.00 g, 42.3 mmol, 5.5 equiv.) was added dropwise to a solution of **6** (3.00g, 7.69 mmol) and 4-bromobutanol (1.30 g, 8.47 mmol, 1.1 equiv.) in dry DCM (20 mL) at 0°C under N_2. After 1.5 h, the reaction solution was warmed to room temperature and stirred for a further 16.5 h, when TLC (EtOAc–hexane, 50:50) showed conversion of starting material (R_f = 0.5) to a major product (R_f = 0.65). The reaction mixture was poured into ice water (10 mL) and extracted with DCM (3 × 20 mL). The organic extracts were combined, washed with water (15 mL), dried ($MgSO_4$), filtered, and the solvent removed. The residue was purified by flash chromatography (EtOAc–hexane, 40:60) to give recovered bromobutanol, starting material **6** and product **2** (1.61 g, 43% yield, 83% based on recovered starting material) as a white solid; mp 61–62°C. $[\alpha]_D^{22}$ = + 46.4 (*c*, 0.34 in $CHCl_3$). IR (cm^{-1}): 1747 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 1.88 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 2.00, 2.05, 2.11, 2.16 (4s, 4 × 3H, 4 × Ac), 3.46 (m, 2H, CH_2Br), 3.72 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 3.96 (ddd, *J* = 10, 6, 3 Hz, 1H, H-5), 4.14 (dd, *J* = 12, 3 Hz, 1H, H-6), 4.29 (dd, *J* = 12, 6 Hz, 1H, H-6′), 4.81 (d, *J* = 2 Hz, 1H, H-1), 5.23–5.33 (m, 3H, H-2, H-3, H-4). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 20.7, 20.7, 20.8, 20.9 (4 × CH_3CO-), 27.9, 29.3 ($OCH_2CH_2CH_2CH_2Br$), 33.3 (CH2Br), 62.5, 66.1, 67.4, 68.6, 69.0, 69.6 ($OCH_2CH_2CH_2CH_2Br$, C-2, C-3, C-4, C-5, C-6), 97.6 (C-1), 169.8, 170.2, 170.3, 170.6 (4 × CH_3CO-). ES-MS *m*/*z* (MeOH): 505, 507 ($M+Na^+$). ES-HRMS calcd. for $C_{18}H_{31}BrNO_{10}$: 500.1131; found: 500.1131 ($[M + NH_4]^+$).

[4] **1**: A freshly prepared solution of NaOMe–MeOH (3 mL, 0.1 M) was added to a solution of **2** (1.00 g, 2.07 mmol) in dry methanol (15 mL) at room temperature under nitrogen. After 18 h, TLC (ethyl acetate–hexane, 50:50) showed the conversion of **2** (R_f = 0.65) to **1** (R_f = 0.05). The mixture was run through a Dowex 50W (H^+) plug (1 × 4 cm, eluant MeOH) and the solvent removed. The residue was purified by flash chromatography (15% MeOH–$CHCl_3$) to yield **1** (0.57 g, 1.82 mmol, 87%); mp 104–105°C. $[\alpha]_D^{22}$ = + 36.0 (*c*, 0.2 in MeOH). ^1H (250 MHz, CD_3OD) δ: 1.78 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 1.98 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 3.50 (m, 2H, CH_2Br), 3.70 (m, 2H, $OCH_2CH_2CH_2CH_2Br$), 3.60–3.90 (m, 5H, H-2, H-3, H-4, H-5, H-6), 3.96 (dd, *J* = 12, 3 Hz, 1H, H-6′), 4.78 (d, *J* = 2 Hz, 1H, H-1). ^{13}C (250 MHz, CD_3OD) δ: 30.0, 31.9 ($OCH_2CH_2CH_2CH_2Br$), 35.1 (CH_2Br), 63.8, 68.5, 69.5, 73.1, 73.5, 75.6 ($OCH_2CH_2CH_2CH_2Br$, C-2, C-3, C-4, C-5, C-6), 102.4 (C-1). ES-MS *m*/*z* (MeOH): 337, 339 ($[M + Na]^+$, 100%). ES-HRMS calcd. for $C_{10}H_{23}BrNO_6$: 332.0709; found: 332.0716 ($[M + NH_4]^+$). Anal. calcd. for $C_{10}H_{19}BrO_6$: C 38.11, H 6.08; found: C 37.95, H 6.04.

Table 1. Results of glycosylation reactions using bromobutylglycosides **1** and **2** as donors.

Donor	Activator[a]	Solvent	Reaction time (h)	Acceptor	Product	Yield(%)[b]	Product α:β ratio
1	—	DMF	10	MeOH[c]	**3a**	20	9:1
1	—	DMF	60	MeOH[c]	**3a**	53	9:1
1	IBr	DMF	12	MeOH[c]	**3a**	36	8:1
1	AgOTf	DMF	24	MeOH[c]	**3a**	66	9:1
1	AgOTf	DMF	20	DAG[d]	**3b**	60	5:1
2	—	DCM	60	MeOH[c]	—	—	—
2	IBr	DCM	60	MeOH[c]	—	—	—
2	AgOTf	DCM	24	MeOH[c]	**4a**	43	α only
2	AgOTf	DCM	20	DAG[d]	**4b**	51	α only

[a]All reactions at room temperature.
[b]All yields are for isolated products.
[c]5 equivalents used.
[d]1 equivalent used.

tion of methyl mannoside products. The anomeric mixture of glycosides formed (the formation of some methyl β-D-mannopyranoside suggests that there was a lack of neighbouring group participation and therefore the lack of a C-2 acetate) and the disarming effect (7) of the acyl groups in **2**, likely means that methanolysis occurred when the donor was fully deprotected as **1**. It should be noted that although **1** is an effectively active glycosyl donor, it is nonetheless stable even to flash column chromatography on silica: an unusual and highly convenient stability that may be attributed to silica as a mild, hard rather than soft, Lewis acidic medium. As an alternative direct method for the direct synthesis of **1** from D-mannose **5**, Fischer glycosidation was also investigated. Treatment of a suspension of **5** in neat 4-bromobutanol with $BF_3{\cdot}Et_2O$ gave, after extensive purification, a low yield (18%) of **1**; although this was only a one-step procedure, inferior overall yield and use of large quantities of 4-bromobutanol meant preparation via **2** was selected as a superior route.

The results of glycosylation reactions[5] with **1** and **2** are shown in Table 1. We were delighted to see that simply by stirring **1** with MeOH as a glycosyl acceptor and *without activator*, methyl mannoside **3a** (10) was formed in a low 20% yield after 10 h, but in a fair 53% yield after 60 h. The α:β stereoselectivity (9:1) observed is consistent with the stereoselectivities of other non-participatory mannosyl donors. (3) Although these results were encouraging, we reasoned that use of a soft Lewis acid might increase rate and (or) efficiency because of the differing nature of the Lewis basicities of **1** (Scheme 1). Thus, the use of IBr (11) led after 12 h to increased rate and yield when compared with glycosylations without an activator. Unfortunately, prolonged reaction times with IBr did not lead to enhanced yield and so AgOTf was tested as an alternative halophilic Lewis acid. Using AgOTf, we were extremely pleased to observe a yield of 66% of **3a**. These improved conditions were also successfully applied to the synthesis of disaccharide **3b** (60% yield) through the use of diacetone galactose (DAG) as an acceptor, thereby demonstrating potential for oligosaccharide synthesis and confirming the compatibility of the method with acid-sensitive protecting groups. The possibility exists that although none was isolated, self-condensation of **1** may account for the only fair yield of **3b**, and we are now investigating the use of *O*-6 protected donors.

Having demonstrated the ability of **1** to act as a glycosyl donor, peracetylated **2** was examined next. Consistent with our earlier hypothesis (vide supra) and with the disarmed (7) nature of **2**, glycosylation did not proceed either in the absence of an activator or in the presence of IBr. Through the use of AgOTf, however, fair yields of methyl mannoside **4a** (12) (43%) and disaccharide **4b** (51%) were obtained. The exclusive α-stereoselectivity that was observed for **4a**,**b** may be attributed to neighbouring group participation by the C-2 acetate group.

Finally, to test the hypothesis that cyclization to form a furanosyl oxonium leaving group is an essential precursor step in the mechanism of glycosylation, two analogous peracetylated (**8**) and deprotected (**7**) 3-bromopropyl mannopyranosides were prepared using analogous routes to those used for the preparation of **1** and **2** (Scheme 2). Consistent with the need for cyclization, neither **7** or **8** were able to act as glycosyl donors under the conditions that had proved successful for **1** or **2**.[6]

In summary, this communication describes the first examples of a new class of glycosyl donor: bromobutylglycosides (BBGs). Deprotected BBG **1** appears to possess a remarkably balanced reactivity that allows its ready preparation and

[5]General procedure for glycosylation reactions: To a solution of **1** (100 mg, 0.32 mmol, 1 equiv.) in DMF (5 mL) under nitrogen, was added acceptor MeOH (64 μL, 1.6 mmol, 5 equiv.). The solution was stirred at room temperature for 60 h, any precipitate removed by centrifugation and the solvent removed. The residue was purified by flash chromatography (15% MeOH– $CHCl_3$) to yield **3a** (33 mg, 53%, α:β = 9:1) as a white solid. Parallel reactions were repeated under similar conditions using, IBr (66 mg, 0.32 mmol, 1 equiv.) or silver triflate (82 mg, 0.32 mmol, 1 equiv.) to yield 22 mg (α:β, 8:1, 36%, after 12 h) or 41 mg (α:β, 9:1, 66%, after 24 h) of **3a**, respectively.

[6]As usefully highlighted by a referee, the inactivity of 3-bromopropyl glycosides does not exclude the possibility of direct Fischer glycosylation that could be catalyzed by the equivalent of HBr (in spontaneous and IBr-activated reactions) or TfOH (in AgOTf-activated reactions) that is liberated. To test this hypothesis, **1** was used to glycosylate MeOH activated with AgOTf in the presence of the hindered base 2,4,6-tri-*tert*-butylpyridine (TTBP) [D. Crich D, M. Smith, Q.J. Yao, J. Picione, Synthesis, 323 (2001).] and yielded 64% of **3a** after 24h; near identical to that obtained without base. Other aspects of the mechanism, including the detection of THF, are currently in progress.

purification and yet is sufficiently reactive to act as an *unprotected* glycosyl donor *even in the absence of activator*. In addition, although **1** is strongly activated by soft Lewis acid catalysis its relative resistance to hard Lewis acid catalysis allows, for example, its direct preparation through Fischer glycosidation. Although the yields for glycosylations using BBGs are thus far only fair or low,[7] the potential to avoid the use of protecting groups might offset overall glycosylation efficiencies. The breadth of the utility of **1** with other acceptors and the investigation of bromobutylglycosides of other parent carbohydrates is underway, the results of which will be presented in due course.

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[7] The possibility of competing 1,6-anhydromannose formation was raised by a referee as a reason for the moderate yields. Although none was isolated as a by-product, the synthesis of 6-*O*-protected donors to test this hypothesis is underway.