Organic LETTERS

Letter

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Scope and Limitations of 2-Deoxy- and 2,6-Dideoxyglycosyl Bromides as Donors for the Synthesis of β-2-Deoxy- and β-2,6-Dideoxyglycosides

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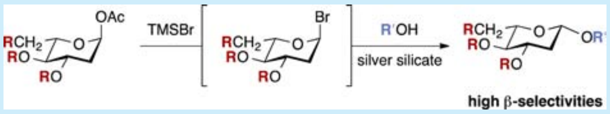
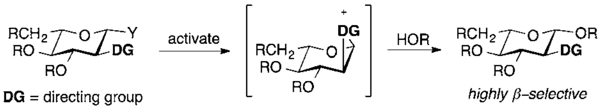
Ⓢ *Supporting Information*

ABSTRACT: It is shown that 2-deoxy- and 2,6-dideoxyglycosyl bromides can be prepared in high yield (72−94%) and engaged in glycosylation reactions with β:α selectivities ≥6:1. Yields of product are 44−90%. Fully armed 2-deoxyglycoside donors are viable, while 2,6-dideoxyglycosides require one electron-withdrawing substituent for high efficiency and β-selectivity. Equatorial C-3 ester protecting groups decrease β-selectivity, and donors bearing an axial C-3 substituent are not suitable. The method is compatible with azide-containing donors and acid-sensitive functional groups.



The difficulties associated with the syntheses of β-2-deoxy and β-2,6-dideoxyglycosides are related to the electron-rich nature of these donors, which favor α-selective, cationic pathways, and the absence of a C-2 substituent to bias β-selectivity.[1] In nature, glycosyltransferases convert α-linked donors to β-linked products by invertive displacement,[2] but few direct synthetic methods that employ aliphatic, oxygen-based acceptors have been reported.[3,4] The most intensively developed strategy involves introduction of a removable equatorial C-2 substituent to control stereoselectivity (eq 1).[5]



(1)

While this strategy reliably provides high β-selectivities, the synthesis of the diastereomerically pure C-2-substituted donor and removal of the directing group increase the number of steps associated with the glycoside construction. Alternative solutions to this problem include stereoselective addition to glycosyloxiranes,[6] strategic use of hydrogen-bonding[7] and conformational biasing elements,[8] stereoselective palladium-catalyzed allylic alkylation,[9] rhenium-catalyzed glucal hydroalkylation,[10] anomeric *O*-alkylation,[11] and reduction of anomeric radicals.[12]

Herein we show that glycosyl bromides, which form the basis of the Koenigs−Knorr method[13] and are among the first activated donors known,[14] can be employed in the direct construction of β-linked 2-deoxy- and 2,6-dideoxyglycosides and should be considered as a potential solution to this problem. Glycosyl halides exist predominantly, or exclusively, in the α-configuration, and in a seminal advance, Paulsen and coworkers reported that heterogeneous silver salts could mediate the formation of β-glycosides from these α-linked donors.[15] The stereochemical outcome of this process is commonly rationalized by invoking silver-assisted S_N2 displacement of the halogen by the acceptor, and sequestration of the liberated halide ion, which prevents donor anomerization. This strategy has been employed to construct stereochemically challenging products, such as β-mannosides.[15b] However, its application toward the syntheses of β-2-deoxy- and 2,6-dideoxyglycosides is limited to five isolated examples,[16] and a systematic study of predictive value has not been reported, to our knowledge. The limited application of deoxyglycosyl halides may be due to difficulties associated with their synthesis and handling: these electron-rich donors[17] readily ionize, leading to hydrolysis, elimination, and other decomposition products. We show below that under carefully controlled conditions a broad range of 2-deoxy- and 2,6-dideoxyglycosyl bromides can be prepared in excellent yield and purity and employed in highly β-selective glycosylation reactions. Donor substituent effects on efficiency and stereoselectivity are delineated.

As glycosyl bromides are intermediate in reactivity between glycosyl chlorides and iodides, we focused on these donors. Classically, glucosyl bromides have been prepared by treatment of anomeric acetates with hydrobromic acid in acetic acid,[14] conditions that are almost certain to be incompatible with deoxy donors. Thiem[18] and Gillard[19] independently described the conversion of glycosyl acetates (including 2-deoxyglycosyl acetates)[18] to glycosyl bromides by treatment with trimethylsilyl bromide in chloroform or benzene. These conditions are attractive because the side product in the reaction, trimethylsilylacetate, is easily removed in vacuo (bp = 107 °C at 760 Torr), and aqueous workup of the glycosyl bromide product can be avoided. Accordingly, we investigated the transformation of the deoxyglycosyl acetates **1a−d** to the bromides **2a−d** by treatment with trimethylsilyl bromide (2.25 equiv) in dichloromethane at 0 °C (Table 1). After stirring for 20 min−2.5 h at 0 °C, the product mixture was concentrated in

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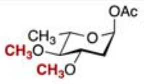
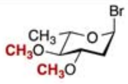
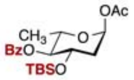
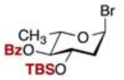
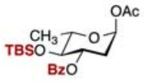
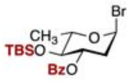
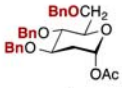
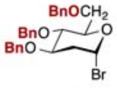
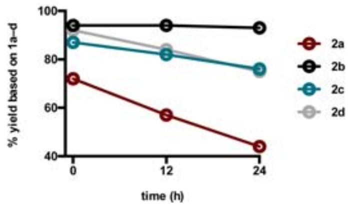
Table 1. Syntheses of Glycosyl Bromide Donors 2a−d

entry	donor	β:α	product	β:α[a]	yield α[a]
1	 **1a**	1:2.1	 **2a**	α-only	72%
2	 **1b**	1:1.8	 **2b**	α-only	94%
3	 **1c**	1:4.2	 **2c**	α-only	87%
4	 **1d**	1:7.4	 **2d**	α-only	92%

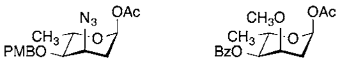
Stability of glycosyl bromides **2a**–**2d** in benzene-d_6 at 24 °C.



[a] Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.

vacuo (100 mTorr, 0 °C, 10 min). Residual trimethylsilyl bromide and trimethylsilyl acetate were removed by codistillation with benzene under reduced pressure. Under these conditions, the glycosyl bromides **2a−d** were reproducibly formed in yields of 72−94%, as determined by ^{1}H NMR analysis against an internal standard. Solutions of **2a−2d** in benzene-d_6 at 24 °C were monitored by ^{1}H NMR spectroscopy to assess their stability (Table 1, bottom). These studies revealed the stability ranking **2b** > **2c** ≈ **2d** > **2a**. The minor (≤8%) extent of decomposition of **2b−2d** after 12 h suggested they may be viable in the glycosylation step. Attempted aqueous workup of the bromide **2d** (dilution with saturated aqueous sodium bicarbonate solution) led to hydrolysis and decomposition. Chlorodeacetoxylation of the donor **1a** (chlorotrimethylsilane, 5 equiv, 24 °C) did not proceed to completion. The donors **1e** and **1f**, which contain an axial C-3 substituent, did not form stable glycosyl bromides (Figure 1).

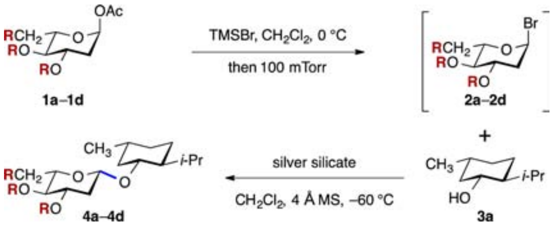
We then sought to evaluate the suitability of the donors **2a−2d** in glycosylation reactions and to elucidate the influence of substituents and protecting groups on efficiency and stereoselectivity (Table 2). We employed (−)-menthol (**3a**) as the acceptor. The donors **1a−1d** were transformed to the corresponding glycosyl bromides **2a−2d**, as described above, and then redissolved in dichloromethane. The resulting solution was added to a mixture of **3a** (1.5 equiv), silver silicate (1.6 g/mmol donor), and activated 4 Å MS (860 mg/mmol donor) in dichloromethane at −60 °C. Under these conditions, the products **4a−4d** were obtained in 53−81% yield (yields are based on the glycosyl acetates **1a−1d**). The experiments outlined in Table 2 define the structural parameters of the donor that lead to high efficiency and β-selectivity. The fully armed 2,6-dideoxyglycoside donor **1a** provided modest β-selectivity (β:α = 3.4:1), and the glycosylation proceeded in only 53% yield (entry 1). The modest yield and selectivity may be due to the lower yield in the formation of **2a** (vide supra) and competitive ionization, which leads to α-selective pathways and decomposition. The partially deactivated donor **1b**, which contains a C-4 benzoyloxy substituent, provided an 81% yield of product and 18:1 β-selectivity (entry 2). Notably, the isomeric donor **1c**, which contains a C-3 benzoyloxy substituent, was selective

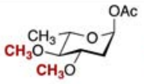
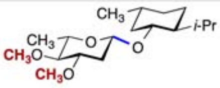
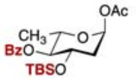
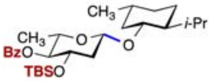
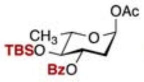
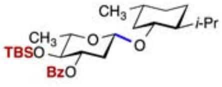
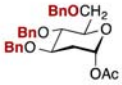
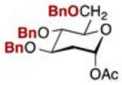


1e **1f**

Figure 1. Donors that did not form stable glycosyl bromides.

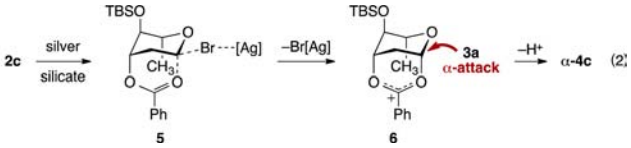
Table 2. Evaluation of Carbohydrate Substituents on Efficiency and Selectivity



entry	donor	product	β:α[a]	yield β[b]
1	 **1a**	 **4a**	3.4:1	53%
2	 **1b**	 **4b**	18:1	81%
3	 **1c**	 **4c**	1:1.5	67%[c]
4	 **1d**	 **4d**	22:1	74%
5[d]	 **1d**	 **4d**	14:1	77%

[a] Determined by ^{1}H NMR or LC/MS analysis of the unpurified product mixture; see Supporting Information. [b] Isolated yield after purification by flash-column chromatography. Yield based on **1a−d**. [c] Isolated as a mixture of α- and β-anomers. [d] Glycosylation conducted at −40 °C.

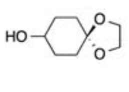
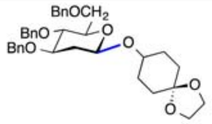
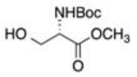
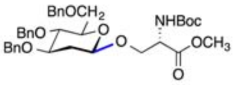
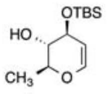
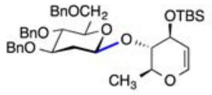
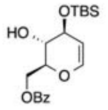
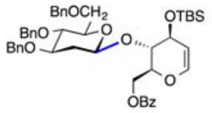
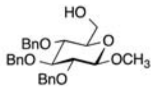
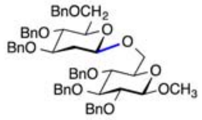
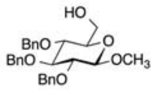
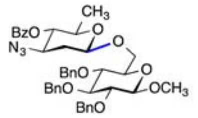
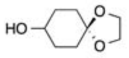
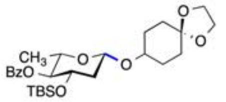
for the α product (β:α = 1:1.5), and the glycoside **4c** was isolated in 67% yield as a mixture of anomers (entry 3). The lower β-selectivity with the C-3-benzoyloxy donor **1c** may be due to anchimeric assistance from the ester, which leads to a bridged oxacarbenium ion such as **6** and α-selective addition (eq 2).[20] The fully armed 2-deoxydonor **1d** was a suitable substrate for the glycosylation and provided the product **4d** in 74% yield and with 22:1 selectivity in favor of the β-anomer (entry 4). To probe the influence of temperature on selectivity and yield, this experiment was also conducted at −40 °C. Under these conditions, the product **4d** was obtained in 77% yield and the selectivity in the reaction was only slightly diminished (β:α = 14:1, entry 5).



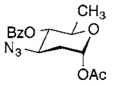
The scope of the glycosylation was then evaluated (Table 3). For all entries, 1.5 equiv of the acceptor was employed, and the yields are based on the glycosyl acetates **1b**, **1d**, and **1g**. The α and β diastereomers were readily distinguished by the chemical shift and vicinal coupling constants of the anomeric proton.[21] Coupling of the donor **1d** with 1,4-dioxaspiro[4.5]decan-8-ol (**3b**) provided the glycoside **4e** in 90% yield and with 27:1 β-selectivity (entry 1). Coupling of *N*-Boc-L-serine methyl ester (**3c**) with **1d** provided the glycoside **4f** as a 6:1 mixture of β and α isomers in 80% yield (entry 2). This result is important because β-hydroxy carbonyl compounds are known to be poor acceptors in glycosylation reactions.[5m] The glucals **3d** and **3e** were coupled to the donor **1d** in 44% and 46% yield, respectively, and with high β-selectivities (entries 3 and 4). The methyl glycoside **3f** was glycosylated with the donor **1d** in 78% yield and with 47:1 β-selectivity (entry 5). The azide-containing disaccharide **4j** was obtained in 72% yield and with 13:1 β-selectivity from the azidosugar **1g** and the acceptor **3f** (entry 5). Finally, the donor **1b** could be coupled with 1,4-dioxaspiro-[4.5]decan-8-ol (**3b**), to provide the glycoside **4k** in 90% yield and with 20:1 β-selectivity. The result in entry 6 demonstrates that the method is compatible with azide-containing donors. The results in entries 1−4 and 7 establish the method as compatible with acid-sensitive functional groups. It is noteworthy that hindered secondary alcohols, such as **3a**, **3d**, and **3e**, are suitable acceptors in this transformation.

Several experimental parameters are critical to the success of these reactions. First, it is essential that excess trimethylsilyl bromide is removed under strictly anhydrous conditions. Trace amounts of hydrobromic acid, formed by reagent hydrolysis, decompose the donors. Second, the bromide donors we have prepared are unstable toward TLC analysis; ^{1}H NMR analysis provides a reliable method to assess conversion in the bromination step. The rates of bromination are dependent on the electron-density of the donor (as expected), and for all donors we investigated, except **1g**,[22] this step was complete within 2.5 h at 0 °C. Finally, all of the trimethylsilylacetate byproduct must be removed prior to the glycosylation step to prevent regeneration of the glycosyl acetate. This is readily assessed by ^{1}H NMR analysis of the unpurified glycosyl bromide (chemical shifts for trimethylsilylacetate in benzene-d_6: δ 1.71, 0.23).

Table 3. Scope of the Glycosylation Reaction

entry	donor	acceptor	product	β:α[a] yield β[b]
1	**1d**	 **3b**	 **4e**	27:1 90%
2	**1d**	 **3c**	 **4f**	6:1 80%[c]
3	**1d**	 **3d**	 **4g**	β only 44%
4	**1d**	 **3e**	 **4h**	13:1 46%
5	**1d**	 **3f**	 **4i**	47:1 78%
6	**1g**[d]	 **3f**	 **4j**	13:1 72%
7	**1b**	 **3b**	 **4k**	20:1 90%

[a] Determined by ^{1}H NMR or LC/MS analysis of the unpurified product mixture, see Supporting Information. [b] Isolated yield after purification by flash-column chromatography. Yield based on the glycosyl acetates **1b**, **1d**, and **1g**. [c] Isolated as a mixture of anomers. [d] Structure of **1g**:



In summary, we have demonstrated that 2-deoxy- and 2,6-dideoxyglycosyl bromides can be employed in high-yielding, β-selective glycosylation reactions and delineate several useful reactivity trends. Fully armed 2-deoxyglycoside donors are suitable, while 2,6-dideoxyglycosides require at least one electron-withdrawing substituent. Equatorial C-3 ester protecting groups decrease β-selectivity,[23] and donors bearing axial C-3 heteroatom substituents do not form stable activated bromides. Hindered and deactivated acceptors, acid-sensitive functional groups, and azide-containing donors are compatible with the method. The use of glycosyl acetates is strategically advantageous, as it provides protection of the C-1 hydroxyl group in the event that additional manipulations of the donor are required. The studies outlined herein should motivate the application of glycosyl bromides in this difficult bond construction.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) Bromodeacetoxylation of **1g** required 6 h at 25 °C to acheive full conversion, see Supporting Information.

(23) Though not investigated here, it seems plausible that formation of the α-anomer using donors such as **2c** could be suppressed by decreasing the electron-donating ability of the C-3 ester substitutent and increasing the steric bulk of the C-4 oxygen substituent.