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Chemoselective Synthesis of Oligosaccharides of 2-Deoxy-2-aminosugars

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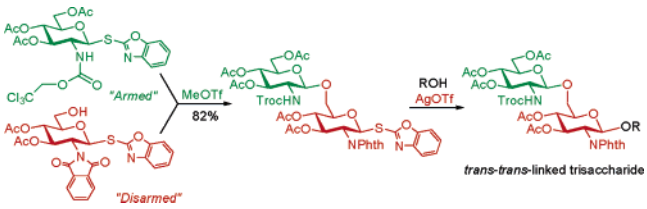

Along with the application of the *S*-benzoxazolyl glycosides to the high-yielding synthesis of disaccharides of the 2-amino-2-deoxy series, chemoselective assembly of oligosaccharides containing multiple residues of 2-amino-2-deoxyglycoses is reported. This modified armed−disarmed approach is relying on the observation that 2-*N*-trichloroethoxycarbonyl derivatives of *S*-benzoxazolyl glycosides are significantly more reactive than their 2-*N*-phthaloyl counterparts in MeOTf-promoted glycosylations. This allowed efficient chemoselective synthesis of 1,2-*trans*-linked oligosaccharides, the disarmed reducing end of which can be activated for immediate second step glycosidation in the presence of a more powerful activator, AgOTf. As a result of this two-step activation, *trans*−*trans*-patterned trisaccharides could be assembled in a highly efficient manner. This result differs from the classic armed−disarmed technique, according to which usually *cis*−*trans*-patterned oligosaccharides are generated.

The involvement of complex glycostructures in the pathogenesis of deadly diseases such as AIDS, cancer, pneumonia, meningitis, and hepatitis is now well-recognized. This knowledge has been translated into an appreciation of carbohydrates as targets for modern therapeutics.[1,2] Among a variety of biologically important carbohydrates are the prokaryotic and eukaryotic glycoconjugates, which are comprised mainly of residues of the 2-amino-2-deoxy-β-D-glucopyranosyl (D-glucosamino) series. Most representative examples include, but are not limited to, chitin, a linear homopolymer of 2-acetamido-D-glucosamine (GlcNAc) that is a component of fungal cell wall and arthropod integuments,[3] heparin, a linear sulfated polysackecharide consisting of alternating GlcNAc and L-iduronic acid units that is a major factor in diverse biological processes including blood coagulation, viral infections, cell growth, inflammation, etc.,[4,5] and the lipid-A region of antigenic lipopolysaccharides, an amphiphilic macromolecule composed of two D-glucosamine residues that has been shown to affect a variety of inflammatory processes.[6,7] Multiple glycosamino residues have also been found in a variety of tumor-associated glycosphingolipids.[8] Although it is now possible to selectively cleave, isolate, purify, and characterize certain classes of natural glycostructures, their accessibility in pure form is still limited. As a result, methods for the synthesis of glycosides and oligosaccharides containing 2-deoxy-2-amino residues have been the focus of a considerable amount of research.[9−11]

A vast majority of naturally occurring glycosamine residues are N-acetylated and linked via a 1,2-*trans* (β-D-gluco/galacto) linkage. However, it has been shown that glycosylation of complex aglycones with glycosyl donors bearing a 2-acetamido-2-deoxy functionality is usually impractical.[9,11] Unlike the reactive acyloxonium intermediate formed via participatory assistance of the 2-*O*-acetyl moiety in neutral sugars (see Scheme 1a), the 1,2-*O*,*N*-oxazoline intermediate (Scheme 1b) formed during glycosidation of N-acetylated glucosamine derivatives is rather stable. This significantly decreases the rate of glycosylation and yields, especially if unreactive or sterically hindered glycosyl acceptors are used.

As such, following the general theory that neighboring group participation promotes efficient formation of 1,2-*trans*-linked glycosides, various 2-amino substituents have already been reported. These include *N*-trifluoroacetyl (trifluoroacetamido, NHTFA),[12] *N*-phthaloyl (phthalimido, NPhth),[13,14] *N*-trichloroethoxycarbonyl (trichloroethoxycarbamoyl, NHTroc),[15] and other substituents.[16−25] In spite of a variety of classes of glycosyl

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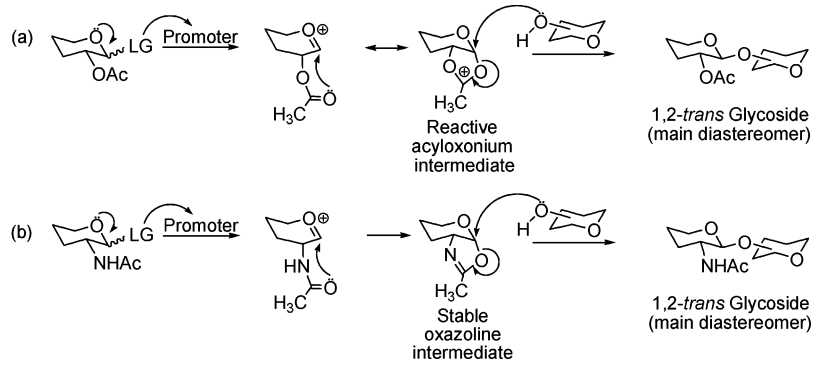
SCHEME 1



donors tested in these glycosylations, the yields achieved in these glycosylations are still far from being satisfactory.

The initial purpose of the study reported herein was to improve the yields for the introduction of 2-deoxy-2-*N*-substituted-β-D-glucopyranosyl residues in oligosaccharides. We assumed that this goal could be achieved by applying novel thioimidoyl glycosidation methodology, the development of which has been the primary focus of our research program. Among the thioimidates investigated, we have already reported that 1-*S*-benzoxazolyl (SBox) derivatives make excellent glycosyl donors due to their accessibility, stability, and high stereoselectivity and yields in glycosylations achieved under mild activation conditions.[26,27]

Nowadays, the majority of oligosaccharides are synthesized in a convergent-selective or chemoselective fashion.[28] Nevertheless, persistent attempts to apply these findings to 2-aminosugars have yet to emerge. Therefore, the ultimate goal of these studies would be the development of a chemoselective strategy for the synthesis of oligosaccharides containing multiple sequential residues of 2-amino-2-deoxysugars.

With these intentions in mind, we obtained four novel *N*-substituted SBox glycosides **1**−**4** (Figure 1), among which the 2-acetamido donor **4** was mainly intended for comparative studies. These compounds were synthesized from either glycosyl acetates with 2-mercaptobenzoxazole in the presence of a Lewis acid or glycosyl halides, bromides or chlorides, by reaction with 2-benzoxazolethione, potassium or sodium salt in the presence of a suitable crown ether, 18-crown-6 or 15-crown-5, respectively. High yields in the range of 80−95% and complete stereoselectivity were recorded for these transformations.

Having obtained SBox glycosides **1**−**4**, which were found to be stable crystalline or amorphous solids, we turned our attention to investigating their glycosyl donor properties in reactions with common glycosyl acceptors **5**−**8**.[29−32] We have already reported that benzoxazolyl derivatives of neutral sugars can be activated with mildly electrophilic promoters such as AgOTf, MeOTf, $Cu(OTf)_2$, or NIS/TfOH.[27,33] Also in application to our new targets, 2-*N*-substituted glycosyl donors, activations with either AgOTf or MeOTf gave the best outcome; the key reactions are summarized in Table 1. Glycosyl donors **1**−**3** performed very well in each reaction attempted, affording the corresponding disaccharide derivatives **9**−**12** in high yields and complete stereoselectivity (Table 1). As anticipated, glycosidation of 2-acetamido derivative **4** was sluggish and incomplete even in prolonged experiments (16−48 h). This reaction was negatively affected by the formation of a relatively unreactive 1,2-oxazoline intermediate.

We have also observed that, while AgOTf-promoted glycosidations of **1**−**3** were complete in less than 15 min, significantly different results have been recorded in MeOTf-promoted glycosylations. Thus, we noted that typically 1−2 h were required for glycosidation of NPhth (**1**) and NHTFA (**3**) derivatives, whereas NHTroc glycosyl donor (**2**) could be glycosidated in a matter of minutes (<5−15 min) under essentially the same reaction conditions. Therefore, we anticipated that this observation could give rise to a complementary glycosylation approach for chemoselective glycosidation of 2-aminosugars similar to that discovered by Fraser-Reid[34] and explored by others[29,35,36] for the neutral sugars.

While a significant disparity in reaction rates between NPhth- and NHTroc-protected derivatives has been observed,[15,37] no systematic studies have yet become available. The possibility of chemoselective activation of NTroc-protected donors over NPhth-protected acceptors for chemoselective oligosaccharide synthesis has only been applied once by Baasov's group in a sequential one-pot oligosaccharide synthesis employing tolyl thioglycosides.[38] Another relevant report explores the chemose-

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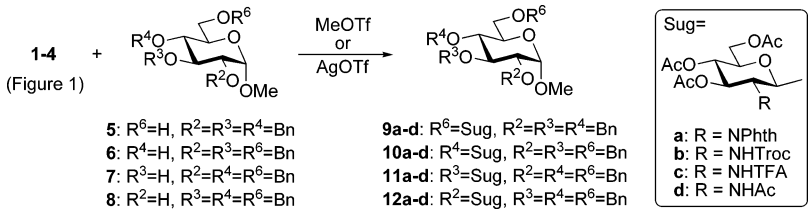
TABLE 1. Synthesis of 1,2-*trans*-Linked Disaccharides 9−12



entry	donor	acceptor	promoter	product	yield, % **a**−**b**−**c**−**d**
1	**1**−**2**−**3**−**4**	**5**	MeOTf	**9**	92−88−89−79[a]
			AgOTf		90−91−93−87[a]
2	**1**−**2**−**3**−**4**	**6**	MeOTf	**10**	84−89−78-nd[b]
			AgOTf		86−88−86-nd
3	**1**−**2**−**3**−**4**	**7**	MeOTf	**11**	87−88−84-nd
			AgOTf		85−90−89-nd
4	**1**−**2**−**3**−**4**	**8**	MeOTf	**12**	92−92−80-nd
			AgOTf		90−88−84-nd

[a] Synthesis of **9d**: incomplete reaction (ca. 70% conversion in 16 h); the yield is based on the acceptor recovered. [b] nd: no data reported; the reaction was too slow (ca. 20−40% conversion in 24 h) to have practical application.

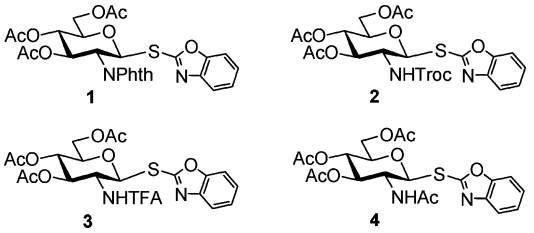


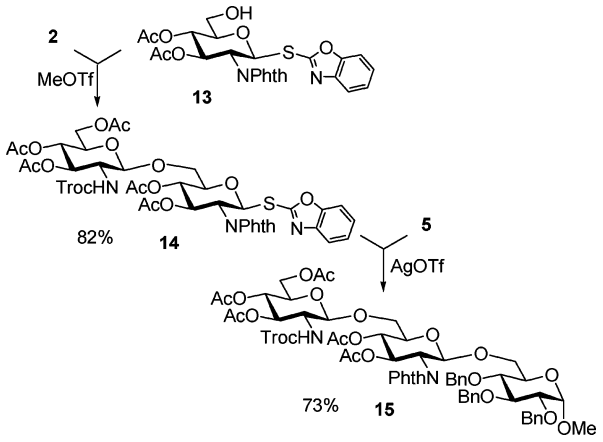
FIGURE 1. Differently *N*-substituted SBox glycosyl donors.

lective activation of the 2-NPhth-protected glycosyl donor over the 2-azido acceptor. Unfortunately, only a modest yield of 31% could be achieved.[39] Other representative examples of the selective activation of derivatives of the 2-deoxy-2-amino series make use of remote arming or disarming protecting groups[40] or the glycosyl donor preactivation concept.[41]

To explore this opportunity, we obtained a suitable glycosyl acceptor **13**, which was then glycosylated with glycosyl donor **2**, as illustrated in Scheme 2. We determined that this coupling is best accomplished at a reduced temperature (5 °C); under these reaction conditions, the disaccharide **14** was obtained in complete β-stereoselectivity and a high yield of 82%. Finally, to reiterate the potency of SBox 2-aminoglycosides as glycosyl donors, subsequent AgOTf-promoted glycosidation of disaccharide **14** with glycosyl acceptor **5** at room temperature gave trisaccharide **15** in 73% yield and with complete β-selectivity. In a similar fashion, based on the significant difference in the glycosylation rates, 2-TFA or 2-acetamido-protected glycosyl acceptors could also be glycosidated with NTroc glycosyl donor **2**.

In summary, we investigated the application of the SBox glycosyl donors to the stereoselective and high-yielding synthesis of the 1,2-*trans* glycosides of the 2-amino-2-deoxysugars. In addition, we discovered that 2-NTroc-protected SBox glycosides can be chemoselectively activated over a 2-NPhth SBox glycosyl acceptor. Two-step sequential activation leads to the *trans*−*trans*-linked oligosaccharides. This result significantly differs from the classic Fraser-Reid's armed−disarmed approach developed for neutral sugars, according to which a 1,2-*cis* linkage is usually introduced first.[34,42] It is to be expected that the strategy developed would also complement Baasov's approach based on *S*-aryl glycosides.[38] Since the SBox glycosides can be selectively activated over the *S*-alkyl/aryl moiety,[26] a longer oligosaccharide sequence could be obtained by the application of a combination of chemoselective and selective activation protocols.

SCHEME 2



Experimental Section

Preparation of the SBox Glycosides. Method A. Typical procedure for the preparation from glycosyl halides: Crown ether (18-crown-6, 0.2 mmol) and salt (KSBox, 3.0 mmol) were added to a stirred solution of a glycosyl halide (1.0 mmol) in dry acetone (10 mL) under argon. The reaction mixture was stirred for 1−16 h at rt. Upon completion, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1% aq NaOH (15 mL) and water (3 × 10

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mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford the corresponding SBox glycoside. **Method B.** Typical procedure for the preparation from glycosyl acetates: The solution of a glycosyl acetate (0.128 mmol), 2-mercaptobenzoxazole (0.256 mmol), and activated molecular sieves (3 Å, 100 mg) in CH_2Cl_2 (1.0 mL) was stirred under argon for 30 min at rt. The Lewis acid (BF_3−OEt_2, $AlCl_3$, $ZrCl_4$, or TMSOTf, 0.256 mmol) was then added dropwise, and the reaction mixture was kept for 45 min at rt. After that, another portion of 2-mercaptobenzoxazole (0.256 mmol) and Lewis acid (0.256 mmol) were added, and the reaction mixture was kept for 1.5−16 h at rt. Upon completion, the mixture was diluted with CH_2Cl_2 (10 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 10 mL). The combined filtrate (30 mL) was washed with 1% aq NaOH (15 mL) and water (3 × 10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford the corresponding SBox glycoside.

Benzoxazolyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (1) was obtained by Method B as white crystals in 85% yield: R_f = 0.53 (toluene−ethyl acetate, 3/2, v/v); mp 132−134 °C (ether−hexane); $[\alpha]_D^{25}$ 145 (c = 1.00, $CHCl_3$); mp 133−135 °C; ^{1}H NMR δ 1.89, 2.06, 2.07 (3s, 9H, 3 × $COCH_3$), 4.23−4.12 (m, 2H, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 2.1 Hz, H-6b, H-5), 4.36 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.68 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 5.29 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.98 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 6.52 (d, 1H, $J_{1,2}$ = 10.9 Hz, H-1), 7.86−7.26 (m, 8H, aromatic); ^{13}C NMR δ 20.6, 20.8, 20.9, 53.6, 62.0, 68.6, 71.5, 76.6, 77.4, 81.3, 110.3, 119.3, 124.1 (×2), 124.7 (×2), 129.2 (×2), 131.6, 134.7, 141.8, 152.1, 160.0, 169.7, 167.4, 170.2, 170.6; HRMS−FAB [M + H]$^+$ calcd for $C_{27}H_{25}N_2O_{10}S$, 569.1230; found, 569.1219.

Benzoxazolyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroethoxycarbamoyl-1-thio-β-D-glucopyranoside (2) was obtained as a white amorphous solid in 73% yield: R_f = 0.55 (toluene−ethyl acetate, 3/2, v/v); $[\alpha]_D^{25}$ 19.3 (c = 1.00, $CHCl_3$); ^{1}H NMR δ 1.96, 2.00, 2.01 (3s, 9H, 3 × $COCH_3$), 3.86−3.91 (m, 1H, $J_{5,6a}$ = 4.8 Hz, H-5), 4.05−4.12 (m, 2H, H-2, H-6b), 4.22 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.63 (s, 2H, CH_2CCl$_3$), 5.12 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-4), 5.28 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-3), 5.68 (d, 1H, $J_{1,2}$ = 10.7 Hz, H-1), 5.69 (d, 1H, NH), 7.20−7.53 (m, 4H, aromatic); ^{13}C NMR δ 20.8, 20.8, 20.9, 55.9, 62.0, 68.2, 73.5, 74.7, 76.9, 84.8, 95.4, 110.4, 118.9, 124.8, 128.8, 141.5, 152.1, 154.5, 161.9, 169.6, 170.9, 171.1; HRMS−FAB [M + H]$^+$ calcd for $C_{22}H_{24}Cl_3N_2O_{10}S$, 613.0217; found, 613.0217.

Benzoxazolyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-1-thio-β-D-glucopyranoside (3) was obtained as an off-white amorphous solid in 70% yield: R_f = 0.51 (toluene−ethyl acetate, 1/1, v/v); $[\alpha]_D^{25}$ 21.3 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 2.01, 2.03, 2.09 (3s, 9H, 3 × $COCH_3$), 3.95−4.00 (m, 1H, $J_{5,6a}$ = 4.9 Hz, $J_{5,6b}$ = 2.2 Hz, H-5), 4.15 (dd, 1H, $J_{6a,6b}$ = 12.6 Hz, H-6b), 4.27 (dd, 1H, H-6a), 4.50 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 5.19 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.46 (dd, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 5.76 (d, 1H, $J_{1,2}$ = 10.7 Hz, H-1), 7.21−7.56 (m, 4H, aromatic), 7.73 (d, 1H, NH); ^{13}C NMR δ 20.6, 20.8, 20.9, 62.1, 68.0, 73.8, 77.2, 84.0, 110.6, 113.8, 117.6, 118.7, 125.0, 125.0, 141.2, 152.2, 157.8, 161.8, 169.5, 170.9, 171.8; HRMS−FAB [M + H]$^+$ calcd for $C_{21}H_{22}F_3N_2O_9S$, 535.0998; found, 535.1000.

Benzoxazolyl-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (4) was obtained as white crystals in 70% yield: R_f = 0.53 (acetone−toluene, 1/1, v/v); mp 127−129 °C (ether−hexane); $[\alpha]_D^{25}$ 4.3 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 1.92, 2.02, 2.06, 2.07 (4s, 12H, $COCH_3$), 3.89−3.94 (m, 1H, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.2 Hz, H-5), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.6 Hz, H-6b), 4.27 (dd, 1H, H-6a), 4.45 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 5.19 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.26 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 5.68 (d, 1H, $J_{1,2}$ = 10.7 Hz, H-1), 6.02 (d, 1H, NH), 7.27−7.61 (m, 4H, aromatic); ^{13}C NMR δ 20.8, 20.9 (×2), 23.3, 53.6, 62.1, 68.1, 74.0, 77.4, 85.2, 110.5, 118.8, 124.7, 124.8, 141.6, 152.1, 162.5, 169.4, 170.5, 170.9, 171.6; HRMS−FAB [M + H]$^+$ calcd for $C_{21}H_{24}N_2O_9SNa$, 503.1100; found, 503.1093.

Preparation of Di- and Trisaccharides. Method A. Typical AgOTf-promoted glycosylation procedure (activation of the SBox glycosides): A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $ClCH_2CH_2Cl$ (2 mL) was stirred under argon for 1.5 h. Freshly conditioned AgOTf (0.22 mmol) was added, and the reaction mixture was stirred for 1−2 h at rt. The mixture was diluted with CH_2Cl_2, filtered to remove the solids, and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $NaHCO_3$ (15 mL) and water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford a di- or an oligosaccharide derivative. **Method B.** Typical MeOTf-promoted glycosylation procedure (activation of SBox glycosides): A mixture of the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $ClCH_2CH_2Cl$ (2 mL) was stirred for 2 h under argon. MeOTf (0.33 mmol) was added, and the reaction mixture was stirred for 1−2 h at rt. Triethylamine (0.5 mL) was added to neutralize the reaction, and the mixture was diluted with CH_2Cl_2 (30 mL), the solids were filtered off, and the residue was washed with CH_2Cl_2. The combined filtrate was washed with water (4 × 10 mL), and then the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to yield the corresponding disaccharide.

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Supporting Information Available: Extended experimental data, characterization, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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