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A novel 5-thioglycosylation method with 1,5-dithioglycosyl donors: relevance to exo- versus endocyclic activation

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Abstract—5-Thioglucosylation of a 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivative was carried out with various 1,5-dithioglucosyl donors. The use of per-*O*-acetyl donors resulted in poor yields of an α-disaccharide. On the other hand, per-*O*-benzyl donors selectively gave an α-disaccharide in good to excellent yields regardless of the anomeric configuration of the donors. To study the relevance of the glycosylation results to the pre-equilibrium of exo- versus endocyclic sulfide activation, the relative nucleophilicities of exo- and endocyclic sulfides were estimated from the regioselectivities in the electrophilic oxidation of the per-*O*-benzyl donors with *m*-chloroperbenzoic acid. The results obeyed stereoelectronic effects and the endocyclic sulfides were more nucleophilic than the exocyclic sulfides for both anomers of per-*O*-benzyl-1,5-dithioglucosyl donors, the relative nucleophilicities of the endocyclic over exocyclic sulfides being 67% and 100%, respectively, for the α- and β-anomers. The results of the glycosidation and oxidation suggest that the glycosidation proceeded through an exocyclic cleavage mechanism despite the preferential endocyclic activation of 1,5-dithioglucosides.

The development of oligosaccharide-based drugs is one of the less explored frontiers in drug discovery history.[1] As are commonly important for biooligomer-based drugs,[2] the oligosaccharide drugs should be resistant to degrading enzymes in the digestive system or blood. Replacing the ring oxygen atom of a non-reducing sugar unit with sulfur atom is a promising way of making an oligosaccharide glycosidase-resistant.[3] Thus a number of oligosaccharide analogs capped with a thiosugar at the non-reducing end (S-oligosaccharides) have been synthesized both chemically[3c,4] and enzymatically.[3b,5]

Most chemical S-oligosaccharide syntheses have been carried out through glycosylation reactions with the trichloroacetimidate[4c,d] and bromide[4e] derivatives of 5-thioglycopyranosides. All of these chemical glycosidations stereoselectively gave α-glycosides even in the presence of 2-*O*-acyl groups, which are supposed to assist β-glycoside formations through anchimeric participation. Although thioglycosides have been generally used as versatile glycosyl donors in the synthesis of natural oligosaccharides,[6] there have been no reports on the use of 1,5-dithioglycosyl donors for the synthesis of S-oligosaccharides.

One might have hesitated to the use of 1,5-dithioglycosides because of a potential endocyclic sulfur (S_{endo}) activation that might lead to an endocyclic cleavage reaction to give an acyclic product, which is best exemplified by a dimethylboron bromide promoted ring opening reaction of glycopyranosides,[7] as opposed to an exocyclic cleavage through an exocyclic sulfur (S_{exo}) activation (Scheme 1). In practice, we found that the oxidation of a 1,5-thioglucopyranoside with *m*-chloroperbenzoic acid (*m*CPBA) gave both endo- and exocyclic mono sulfoxides,[8] which suggests that an electrophilic glycosylation promoter would partly activate S_{endo} of the same compound. On the other hand, Delorme and co-workers found that the reaction of 1,5-dithio-L-arabinopyranoside with bromine gave a corresponding glycosyl bromide, which is presumably produced through an exocyclic cleavage mechanism.[4e] In this study, we studied the 5-thioglycosylation reaction using 1,5-dithioglucopyranosides from the standpoint of the relation between the exo- versus endocyclic activation and the exo- versus endocyclic cleavage.

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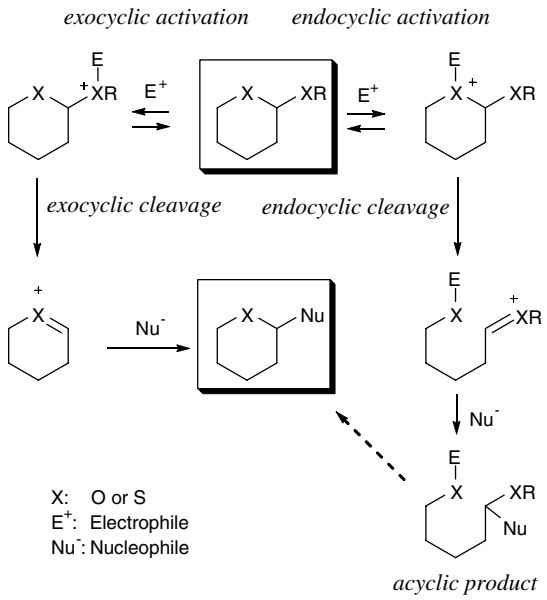


Scheme 1.

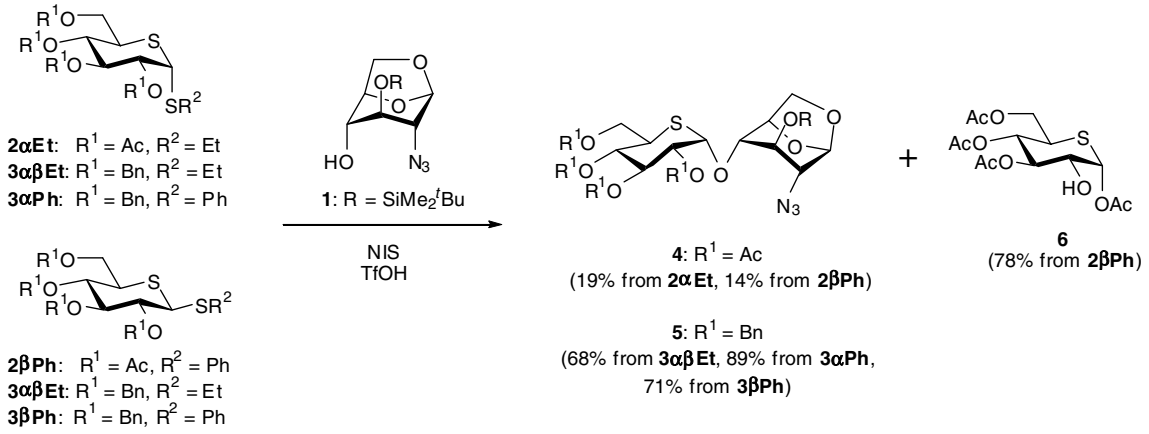
For the acid-catalyzed solvolyses of normal pyranosides, there have long been discussions as to whether the reactions are accompanied by endocyclic cleavages.[9] Elucidation of the reaction pathways is difficult because the solvolysis products are usually identical for two pathways and the activated intermediates are unisolable. On the other hand, the preferred activation sites of 1,5-dithioglucopyranosides are easily estimated, because the products of the electrophilic oxidation with *m*CPBA are isolable and its regioselectivity would indicate the relative nucleophilicities of the sulfides (S_{endo} vs S_{exo}).[8] The glycosidation promoter used in this study is *N*-iodosuccinimide (NIS), which is electrophilic toward sulfides[10] and thus predicted to cause a pre-equilibrium activation of S_{endo} and S_{exo} in favor of the more nucleophilic site. Then we may be able to reduce the potential acyclic products by using the 1,5-dithioglycoside with a less S_{endo} nucleophilicity.

We first examined per-O-acetylated ethyl and phenyl 1,5-dithioglucopyranosides (**2αEt** and **2βPh**) as glycosyl donors (Scheme 2), since these glycosides have distinct relative nucleophilicities regarding S_{endo} versus S_{exo} as estimated by *m*CPBA oxidation,[8] the relative S_{endo} nucleophilicity, $S_{endo}/(S_{endo}+S_{exo})$, being 0 and 0.91, respectively, for **2αEt** and **2βPh**. These relative nucleophilicities were interpreted by stereoelectronic effects. The main frame of the effects is the stabilizing interaction between a sulfur lone pair and the vacant σ^*-orbital of the adjacent C–S bond (n_S–σ^*_{CS}), which is maximized when the lone pair is antiperiplanar to the C–S bond. Among the four sulfur atoms in Fig. 1, only the S_{endo} of β-glycoside fails the stabilizing interaction, escaping a nucleophilicity reduction. The n_S–σ^*_{CS} interactions with a bias of the intrinsic congestion around S_{endo} leads to the relative nucleophilicities: $S_{endo} > S_{exo}$ for β-glycosides and $S_{endo} < S_{exo}$ for α-glycosides.

We chose a 3-O-protected 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivative **1**[11] as a glycosyl acceptor, because this derivative has a relatively reactive axial secondary alcohol, which serves a good criterion as to whether the glycosidation is generally applicable to disaccharide syntheses. Glycosidation was carried out in the presence of a glycosyl donor (1.0 equiv), **1** (1.5 equiv), NIS (1.2 equiv), trifluoromethanesulfonic acid (TfOH, 0.25 equiv), and molecular sieves 4A in $ClCH_2CH_2Cl$ at −20 °C for 1 h, the conditions are enough to deplete all the glycosyl donors we tested.

The glycosidation with **2αEt** gave α-disaccharide **4** in 19% together with a complex mixture containing a 2-OH derivative **6**. The same disaccharide **4** was obtained in 14% yield from **2βPh**. The similar glycosidation results for two donors suggest that the reactions proceeded in the same mechanism regardless of the different preferred activating sites, S_{exo} versus S_{endo}, in the pre-equilibrium activation.

To circumvent the acyloxy migration and increase the reactivity toward glycosidation,[6b] O-benzylated glycosyl donors (**3αβEt**, **3αPh**, and **3βPh**)[12] were examined (Scheme 2). These glycosyl donors were synthesized from the corresponding per-O-acetylated derivatives through deacetylation and benzylation. All the glycosyl donors gave an α-disaccharide **5**[13] in good yields-68%,



Scheme 2.

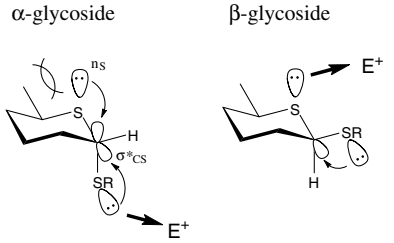
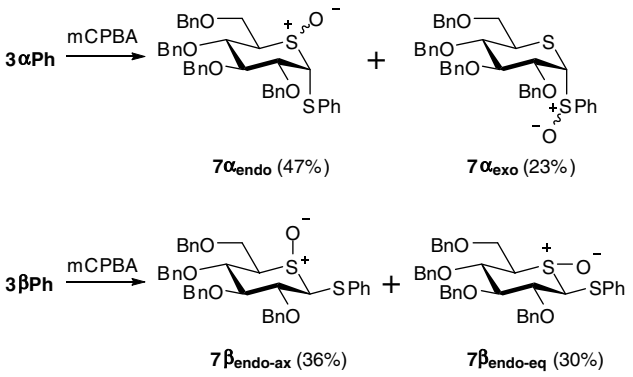


Figure 1. The stereoelectronic effects for the sulfur nucleophilicities of 1,5-dithioglycosides.

89%, and 71% from **3αβEt**, **3αPh**, and **3βPh**, respectively.

As expected, the use of the alkyl protecting group gave better glycosylation yields than those with acetyl protection. Again, α-selectivity was observed. The stereoelectronic effects predict that S_{endo} of each benzyl derivative is more nucleophilic than that of the acetate. To ensure this hypothesis, we carried out the oxidation of **3αPh** and **3βPh** using *m*CPBA (1.1 equiv) in CH_2Cl_2 at −20 °C for 30 min (Scheme 3). We obtained endo- and exo-sulfoxides ($\mathbf{7\alpha_{endo}}$ and $\mathbf{7\alpha_{exo}}$) in 47% and 23% yield, respectively, from **3αPh** and only the endo-sulfoxides ($\mathbf{7\beta_{endo\text{-}ax}}$ and $\mathbf{7\beta_{exo\text{-}eq}}$)[14] in 36% and 30% yield, respectively, from **3βPh**. The results indicate that the relative nucleophilicity of S_{endo} is 0.67 for **3αPh** and nearly 1.0 for **3βPh**.

The electronic effect of protecting groups is tremendous toward the relative nucleophilicity and S_{endo} of **3βPh** is overwhelmingly nucleophilic over S_{exo}. Thus the exocyclic activation by NIS is presumed to be less than 0.5% in the pre-equilibrium stage for the glycosidation with **3βPh**. On the other hand, the fact that only the α-glycosides were obtained as with the other 5*S*-glycosyl donors suggests that these glycosidations proceeded through an exocyclic cleavages despite the unfavorable pre-equilibrium S_{exo} activations, because the α-selectivities are presumably due to the kinetic anomeric effect that is available only for the exocyclic cleavage mechanism. If the endocyclic cleavage were the principal mechanism, we would most probably have obtained both anomeric isomers. Indeed, the anomeric mixtures have been obtained for the acyclic products in the ring-opening reactions of glycopyranosides with Me_2BBr,[3c,7,15] suggesting that the endocyclic cleavage pathway would not be stereospecific.



Scheme 3.

In conclusion, 1,5-dithioglycopyranosides can be used for the syntheses of S-oligosaccharides, if appropriate protecting groups are used. The α-selectivity is expected for this 5-thioglycosylation reaction as with the other 5*S*-glycosyl donors. Possibility for the formation of acyclic products is low, even though the relative nucleophilicity of S_{endo} is high and S_{endo} activation would predominate over S_{exo} activation. Though the reaction pathways with regard to exo- versus endocyclic cleavage were not determined, the observed α-selectivity favors the exocyclic cleavage mechanism.

Acknowledgments

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12. Compound **3αPh**: mp 112–114 °C; +194.1 (*c* 0.99, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48–7.15 (m, 25H), 4.98 (d, $J = 10.6$ Hz, 1H), 4.89 (d, $J = 10.9$ Hz, 1H), 4.79 (d, $J = 10.6$ Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.56 (d, $J = 10.9$ Hz, 1H), 4.49 (d, $J = 12.2$ Hz, 1H), 4.44 (d, $J = 5.3$ Hz, 1H), 4.43 (d, $J = 12.2$ Hz, 1H), 4.12–4.07 (m, 1H), 4.00 (dd, $J = 4.3$, 9.9 Hz, 1H), 3.88–3.80 (m, 2H), 3.62–3.54 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.8, 138.3, 137.84, 137.79, 134.2, 133.1, 128.9, 128.4, 128.3, 128.0, 127.92, 127.89, 127.82, 127.76, 127.69, 127.5, 84.1, 83.9, 81.8, 76.2, 75.6, 73.2, 72.3, 67.8, 55.2, 42.6. HR-ESIMS: Calcd for $C_{40}H_{40}O_4S_2Na$ *m/z* $[M+Na]^+$: 671.2268; found, 671.2279. Anal. Calcd for $C_{40}H_{40}O_4S_2$: C 74.04, H 6.21, S 9.88. Found: C 74.15, H 6.06, S 9.37. Compound **3βPh**: mp 103–107 °C; +71.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.60–7.09 (m, 25H), 4.99–4.49 (m, 8H), 4.11 (d, $J = 8.9$ Hz, 1H), 3.85 (t, $J = 9.6$ Hz, 1H), 3.78 (dd, $J = 4.9$, 9.6 Hz), 3.71 (dd, $J = 8.9$, 10.2 Hz, 1H), 3.64 (dd, $J = 2.6$, 9.6 Hz, 1H), 3.46 (t, $J = 10.2$ Hz, 1H), 2.95 (ddd, $J = 2.6$, 4.9, 10.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.6, 138.1, 137.7, 133.9, 132.5, 129.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.49, 127.46, 88.2, 85.1, 81.8, 76.5, 76.1, 75.6, 73.4, 67.8, 53.8, 47.4. HR-ESIMS: Calcd for $C_{40}H_{40}O_4S_2Na$ *m/z* $[M+Na]^+$: 671.2268; found, 671.2270. Anal. Calcd for $C_{40}H_{40}O_4S_2$: C 74.04, H 6.21. Found: C 73.77, H 6.60.
13. Compound **5**: +91.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39–7.16 (m, 20H), 5.58 (s, 1H), 4.92 (d, $J = 10.5$ Hz, 1H), 4.90 (d, $J = 10.6$ Hz, 1H), 4.80 (d, $J = 11.6$ Hz, 1H), 4.77 (d, $J = 10.5$ Hz, 1H), 4.73 (d, $J = 11.6$ Hz, 1H), 4.66 (d, $J = 2.6$ Hz, 1H), 4.63 (br s, 1H), 4.55 (d, $J = 10.6$ Hz, 1H), 4.52 (d, $J = 12.2$ Hz, 1H), 4.48 (d, $J = 12.2$ Hz, 1H), 4.17 (d, $J = 6.9$ Hz, 1H), 4.17 (t, $J = 9.5$ Hz, 1H), 3.95 (s, 1H), 3.89 (dd, $J = 4.7$, 9.8 Hz, 1H), 3.83 (dd, $J = 2.6$, 9.8 Hz, 1H), 3.81 (t, $J = 9.8$, 1H), 3.72 (t, $J = 6.6$ Hz, 1H), 3.62 (dd, $J = 2.6$, 9.8 Hz, 1H), 3.51 (s, 1H), 3.42 (ddd, $J = 2.6$, 4.7, 9.5 Hz, 1H), 2.84 (s, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 139.0, 138.5, 138.4, 137.9, 128.4, 128.3, 128.0, 127.8, 127.69, 127.66, 127.58, 127.5, 127.4, 100.7, 84.2, 82.7, 82.1, 81.2, 77.0, 76.0, 75.6, 75.3, 73.4, 73.2, 70.4, 67.9, 64.8, 60.9, 42.1, 25.6, 17.7. HR-ESIMS: Calcd for $C_{46}H_{57}N_3O_8SSiNa$ *m/z* $[M+Na]^+$: 862.3535; found, 862.3511. Anal. Calcd for $C_{46}H_{57}N_3O_8SSi$: C 65.76, H 6.84, N 5.00. Found: C 65.46, H 7.08, S 4.68.
14. Compound $\mathbf{7\beta_{endo\text{-}ax}}$: mp 102–106 °C; +18.1 (*c* 0.52, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.63–7.08 (m, 25H), 5.54–4.43 (m, 8H), 4.19 (dd, $J = 9.2$, 11.2 Hz, 1H), 4.12 ($J = 9.2$, 11.2 Hz, 1H), 4.00 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.79 (t, $J = 9.6$ Hz, 1H), 3.77 (d, $J = 11.2$ Hz, 1H), 3.67 (t, $J = 9.2$ Hz, 1H), 2.73 (dt, $J = 4.0$, 11.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.3, 137.7, 137.34, 137.30, 133.8, 123.0, 129.4, 128.6, 128.48, 128.39, 128.1, 128.03, 127.96, 127.89, 127.6, 127.2, 87.6, 78.0, 77.2, 76.3, 76.0, 75.4, 73.7, 70.4, 65.3, 61.1. (ESI-MS.): Calcd for $C_{40}H_{41}O_5S_2$ *m/z* $[M+H]^+$: 665.2397; found, 665.2424. Anal. Calcd for $C_{40}H_{40}O_5S_2$: C 72.26, H 6.06. Found: C 72.05, H 6.20. Compound $\mathbf{7\beta_{exo\text{-}eq}}$: +50.9 (*c* 0.43, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.70–7.13 (m, 25H), 5.00–4.60 (m, 6H), 4.65 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.15 (dd, $J = 2.3$, 10.8 Hz, 1H), 4.06 (dd, $J = 2.3$, 10.8 Hz, 1H), 3.99 (d, $J = 11.2$ Hz, 1H), 3.87 (dd, $J = 9.2$, 11.2 Hz, 1H), 3.72 (t, $J = 9.2$ Hz, 1H), 3.87 (dd, $J = 9.2$, 11.2 Hz, 1H), 3.72 (t, $J = 9.2$ Hz, 1H), 3.58 (dd, $J = 9.2$, 11.2 Hz, 1H), 2.87 (dt, $J = 2.3$, 11.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.1, 137.7, 137.5, 137.45, 133.9, 133.1, 129.2, 128.5, 128.1, 127.9, 127.8, 127.7, 127.4, 81.1, 77.3, 77.2, 76.5, 76.0, 75.8, 73.7, 73.6, 67.0, 62.8. HR-ESIMS: Calcd for $C_{40}H_{41}O_5S_2$ *m/z* $[M+H]^+$: 665.2397; found, 665.2391.
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