# Glycosyldisulfides: a new class of solution and solid phase glycosyl donors†‡

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**Mixed glycosyl disulfides are not only glycomimetics but also glycosyl donors that may be readily constructed in either armed ether-protected or disarmed ester-protected and in soluble or solid-supported forms from corresponding glycosyl methanethiosulfonates and used in the glycosylation of a variety of representative acceptors.**

Oligosaccharides and glycopeptides 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 in which differences in their anomeric leaving groups have an often critical effect upon reactivity. Of the variety of glycosyl donor systems available, thioglycosides **1** have proved one of

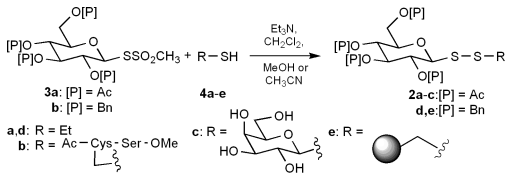

**1** **2**

the most popular.[4] Strategies for tuning their reactivity, including armed/disarmed[5] donors, active/latent donors[6] or the use of bulky leaving groups,[7] have culminated in elegant one-pot glycosylation systems.[8]

With the goal of extending the scope of glycosyl donor reagents with sulfur at the anomeric centre, we have examined the utility of glycosyl disulfides **2**. These appeared attractive for several reasons: (i) the mixed disulfide linkage is a flexible one that may be cleaved for ready aglycon adjustment in reactivity tuning methods.[9] (ii) If used as a linker in solid-supported glycosylations, the anomeric mixed disulfide linkage would allow bidirectional (reductive or hydrolytic) cleavage, that would be of great advantage in both the analysis and use of solid supported glycosylation systems. (iii) The coordination of a potential thiophile by both sulfur atoms may offer enhanced reactivity over single sulfur thioglycoside systems.[10]

Remarkably, despite these positive indications and the high utility of thioglycosides **1**, the use of glycosyl disulfides **2** as glycosyl donors in *O*-glycoside bond formation is unexplored.[11] This neglect of glycosyl disulfides may in part be due to the lack of efficiency in existing syntheses.[12] We therefore set ourselves the goals of (a) developing efficient and general methods for the construction of glycosyl disulfides and (b) exploring their utility as glycosyl donors in *O*-glycoside formation.

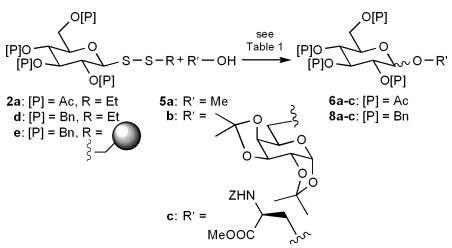
Methanethiosulfonate (MTS) reagents allow the rapid and efficient formation of mixed disulfides.[13] We have previously demonstrated the utility of glycosyl methanethiosulfonates in the site-selective glycosylation or proteins.[14] In order to test fully the efficiency and scope of their use as reagents we




**Scheme 1**

prepared a representative range of glycosyl disulfides **2a**–**e** (Scheme 1) in which the structure of the coupling thiol **4** was varied. Thus, addition of ethanethiol **4a** to equimolar glucoMTS **3a**[14] gave ethyl glucosyl disulfide **2a**† in an excellent 96% yield. Similarly, more complex dipeptide glucosyl disulfide **2b**[15] (62% yield), as a potential glycopeptide mimic, or galactosyl glucosyl disulfide **2c** (60% yield), as a potential trehalose analogue, were also prepared in fair yield simply by reaction of the appropriate thiol **4b**,**c**, respectively, with **3a**. It should be noted that in all cases the β anomeric stereochemistry of the glucoMTS was preserved in the product disulfides. This also demonstrated the compatibility of this method with partially-, **4b**, or even un-protected, **4c**, thiols. To investigate the effect of protecting groups in the glucoMTS **3**, we prepared perbenzylated glucoMTS **3b**, which also reacted smoothly with ethanethiol to give **2d** (78% yield).[16]

Having demonstrated the efficient synthesis of several different glucosyl disulfides **2a**–**d**, we chose ethyl glycosyl disulfides **2a**,**d** as model systems in which to investigate their utility as glycosyl donors with the representative selection of glycosyl acceptors **5a**–**c** (Scheme 2). As Table 1 shows, glucosyl disulfide **2a** allowed the successful preparation of simple **6a**, disaccharide **6b**[17] and glycopeptide **6c**[18] *O*-glucosides. In all three cases exclusive β-stereoselectivity was observed. However, consistent with the disarmed and peracetylated nature of **2a**, moderate yields and acetyl migration side-products[19] were obtained under a variety of conditions. The disarmed nature of **2a** was further confirmed by the lack of reactivity with $I_2$ but the efficient conversion of **2a** to acetobromoglucose **7** using IBr.[20] With the aim of improving efficiencies, the activation of armed perbenzylated glucosyl disulfide **2d** was investigated next. We were delighted to find that under the optimal conditions elucidated for the activation of **2a** (NIS, TESOTf, $CH_2Cl_2$), **2d** rapidly and smoothly[21] gave methyl glucoside **8a** in an excellent 90% yield. Furthermore, reaction of **2d** with more hindered acceptors **5b**,**c** gave good yields of disaccharide **8b**[22] and glycopeptide **8c**[23] *O*-glucosides, respectively.




**Scheme 2**

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b0/b008734n/

‡ Some of this work was presented at a joint meeting of the RSC Carbohydrate and Bioorganic groups, Warwick, July 6 2000 and at the 20th International Carbohydrate Symposium, Hamburg, August 30, 2000.

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**Table 1** Results of glycosylation reactions using dithioglycosides **2** as donors

| Donor | Conditions[a] | Reaction time/h | Acceptor | Product | Yields (%)[b] |
|---|---|---|---|---|---|
| **2a** | NIS, reflux | 24 | **5b** | **6b** | 32[c] (β only) |
| **2a** | NIS, TfOH | 22 | **5b** | **6b** | 26[c] (β only) |
| **2a** | NIS, TfOH, $CH_3CN$ | 24 | **5b** | **6b** | 2[c] (β only) |
| **2a** | NIS, TMSOTf | 4.5 | **5b** | **6b** | 30[c] (β only) |
| **2a** | NIS, TMSOTf, $CH_3CN$ | 6 | **5b** | **6b** | 16[c] (β only) |
| **2a** | NIS, TESOTf | 2 | **5b** | **6b** | 36[c] (β only) |
| **2a** | $I_2$ | 168 | **5b** | — | — |
| **2a** | IBr | 30 min | — | **7** | 82 (α only) |
| **2a** | NIS, TESOTf | 15 min | **5a** | **6a** | 24[c] (β only) |
| **2a** | NIS, TESOTf | 24 | **5c** | **6c** | 34[c] (β only) |
| **2d** | NIS, TESOTf, 0 °C | 40 min | **5b** | **8b** | 75 (9:11 α:β) |
| **2d** | NIS, TESOTf 0 °C | 1 | **5a** | **8a** | 90 (9:15 α:β) |
| **2d** | NIS, TESOTf, 0 °C | 1.5 | **5c** | **8c** | 73[d] (1:1 α:β) |
| **2e** | NIS, TESOTf | 4 | **5a** | **8a** | 67[e] (1:2 α:β) |

[a] All reactions at rt in $CH_2Cl_2$ unless otherwise stated. [b] All yields are for isolated products. [c] See ref. 19. [d] See ref. 23. [e] Yield over two steps: mercaptomethylpolystyrene **4e** with **3b** then glycosylation.

To test the applicability of glycosyl disulfides to solid-supported glycosylation strategies we used mercaptomethylpolystyrene **4e** as a suitable thiolfunctionalized support (Scheme 3). Such was the reactivity of **3b** that even with solid-supported thiol **4e** reaction proceeded rapidly (1 h) to give solid-supported glycosyl disulfide **2e**.[24] The cleavage of **2e** as a representative disulfide-linked glycoside from the support in a bidirectional manner was then demonstrated. Firstly, a small portion of **2e** was taken and treated with tributylphosphine to yield configurationally stable tetrabenzyl 1-thio-β-D-glucose **9**. The potential ability to retune **9** in a latent/active manner to create a glycosyl donor bearing an alternative aglycon (in this case bearing a methyl) was demonstrated by smooth conversion into **10**[25] using methyl methanethiosulfonate. This also showed the release of solid-supported glycosyl disulfide glycosyl donor **2e** from the resin in the form of a solution phase glycosyl donor **10**, thereby demonstrating the potential of the resin as a platform for the creation of solution-phase donors. Next, the ability of **2e** to act as a solid-supported glycosyl donor was clearly demonstrated by activation with NIS, TESOTf in the presence of glycosyl acceptor **5a** to yield methyl glycoside **8a** in a good overall yield (67% over 2 steps). This is also a traceless cleavage method that installs reducing end functionality.

In summary, we have demonstrated the ready and efficient preparation of a wide range of glycosyl disulfides using differently protected glycosyl methanethiosulfonates. Furthermore, we have shown for the first time that glycosyl disulfides may be used as efficient glycosyl donors in both solution- and solid-phase systems for the preparation of *O*-glycosides including disaccharides and glycopeptides. The disulfide linkage offers enhanced utility in aglycone alteration, use as a linker to solid supports and higher activation rates, the full potential of which is the subject of current investigations.

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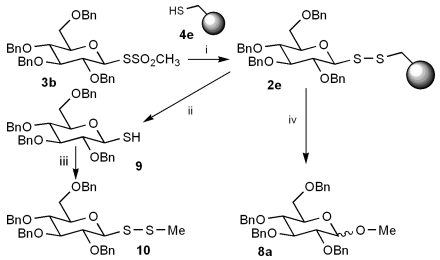


**Scheme 3** *Reagents and conditions:* i, $Et_3N$, $CH_2Cl_2$; ii, $PBu_3$, $CH_2Cl_2$; iii, $MeSSO_2Me$, $Et_3N$, $CH_2Cl_2$; iv, MeOH, $CH_2Cl_2$, NIS, TESOTf.

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