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Chemoselective Glycosylations (Part 1): Differences in Size of Anomeric Leaving Groups can be Exploited in Chemoselective Glycosylations

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Abstract: We have developed a novel chemoselective glycosylation strategy. This glycosylation strategy is based on the fact that the glycosyl reactivity of an anomeric thiol group can be control by the bulkiness of this group whereby we have produced a new range of differentially reactive coupling substrates. The new approach will enable complex oligosaccharides of biological importance to be prepared in a highly convergent manner.

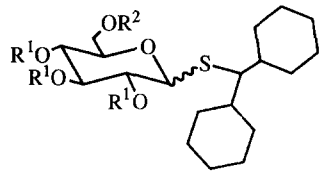
During the last few years, thioglycosides[1] and pentenyl glycosides[2] have attracted considerable attention in oligosaccharide synthesis. These substrates are stable under many different chemical conditions but are also suitable glycosyl donors in glycosylation reactions. Thio- and pentenyl glycosides have been used in an "armed-disarmed" glycosylation strategy.[2,3] This glycosylation approach relies on the fact that C-2 ethers activate (arm) and C-2 esters deactivate (disarm) the anomeric centre. Therefore, it is possible to couple a donor having a C-2 ether (armed) with an acceptor having a C-2 ester protecting group (disarmed). The anomeric centre of the resulting disarmed dimer may be activated with a more powerful activator and reaction with a suitable acceptor will yield a trisaccharide. It has been demonstrated[4] that a saccharide may also be regarded as disarmed when a cyclic acetal is attached to the pyranosyl ring. Recently, Ley *et al.* reported that thioglycosides, bearing a dispiroketal (dispoke)[5] or cyclohexane-1,2-diacetal (CDA) protecting group,[6] have reactivities between an armed and disarmed thioglycoside and therefore may be regarded as semi-disarmed substrates. Thus, at the moment three distinct levels of anomeric reactivity for thioglycosides have been described. It is important to note that a chemoselective glycosylation strategy avoids protecting group manipulations at the oligosaccharide stage and hence makes oligosaccharide synthesis more effective.

Despite the versatility of the armed-disarmed glycosylation approach, there remains an exciting opportunity to tune glycosyl donor leaving group ability further and, thus, realise a greater potential for these glycosylation reactions.[7]

Here, we wish to report the effect of the bulkiness of the anomeric thiol group on glycosyl reactivity whereby we have produced a new range of differentially reactive coupling substrates.

The thioglycosides **3**, **4**, **7** and **9** were prepared to investigate the effect of the bulkiness of the anomeric thiol group on the anomeric leaving group ability (Figure 1). Thus, treatment of peracetylated glucose with dicyclohexyl methanethiol[8] in the presence of a catalytic amount of trimethyl silyl triflate for 20 min. at 20°C gave, after silica gel column purification, **1**[9] as separate α/β anomers in a combined yield of 64%. Compound **1(β)** was deacetylated with NaOMe to give **2** and subsequent benzylation of **2** with benzyl bromide and

sodium hydride in DMF for 18 hr afforded **3** in an excellent yield (93%). Compound **4** was obtained by benzoylation of **2** with benzoyl chloride in pyridine. Regioselective protection of the 6-OH of **2** as a *tert*-butyldimethylsilyl (TBDMS) ether furnished **5** (76%). Compound **5** was benzylated with sodium hydride and benzyl bromide in DMF to afford **6** (92%), and the TBDMS group of **6** was removed by treatment with acetic acid-water (9/1, v/v) at 60° C to yield the requisite compound **7** (76%). Compound **8** was obtained by benzoylation of **5** with benzoyl chloride in pyridine and removal of the TBDMS group with acetic acid/water (9/1, v/v) at 60°C gave compound **9** (76% over-all yield).

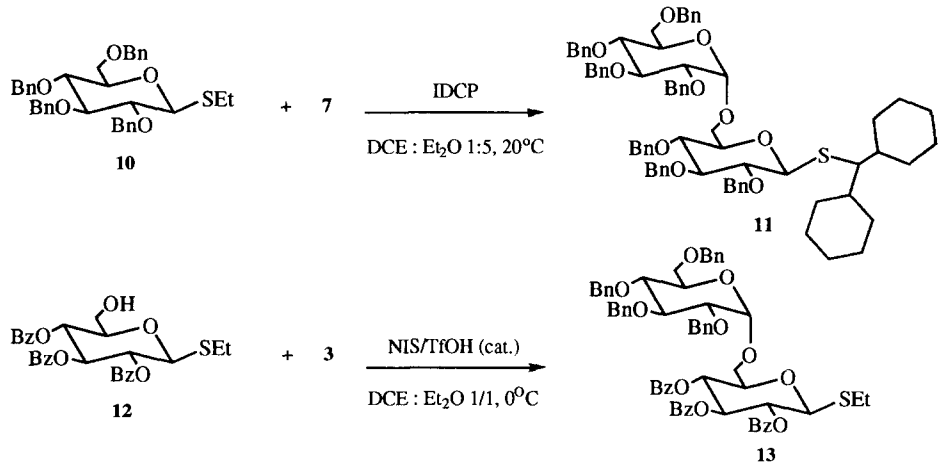


1 $R^1 = R^2 = Ac$
2 $R^1 = R^2 = H$
3 $R^1 = R^2 = Bn$
4 $R^1 = R^2 = Bz$

5 $R^1 = H, R^2 = TBDMS$
6 $R^1 = Bn, R^2 = TBDMS$
7 $R^1 = Bn, R^2 = H$
8 $R^1 = Bz, R^2 = TBDMS$
9 $R^1 = Bz, R^2 = H$

Figure 1. Synthesis of glycosyl donors and acceptors

Iodonium dicollidine perchlorate (IDCP) mediated chemoselective glycosylation of glycosyl donor **10** with glycosyl acceptor **7** in ether/dichloromethane after 2h, gave dimer **11** in an excellent yield of 71% as essentially one anomer (Scheme 1).[9] We were unable to detect any self-condensed or polymeric products and apart from the dimer **11** only small amounts of starting materials were isolated. To the best of our knowledge, this is the first example which demonstrates that the bulk of the anomeric leaving group has a profound effect on the leaving group mobility and the new methodology makes it possible now to couple chemoselectively benzylated thioglycosyl donors with benzylated thioglycosyl acceptors. In the next stage of the research, we have to establish whether there is a difference in reactivity between an electronically and a sterically deactivated substrate and whether such a difference in reactivity may be exploited in chemoselective glycosylation reactions. Thus, chemoselective coupling of the electronically deactivated glycosyl acceptor **12** with the sterically deactivated glycosyl donor **3** in the presence of the more powerful promoter system *N*-Iodosuccinimide/Triflic acid (NIS/TfOH) at 0°C, afforded dimer **13** in a 82% yield (α/β = 3/1).[9]

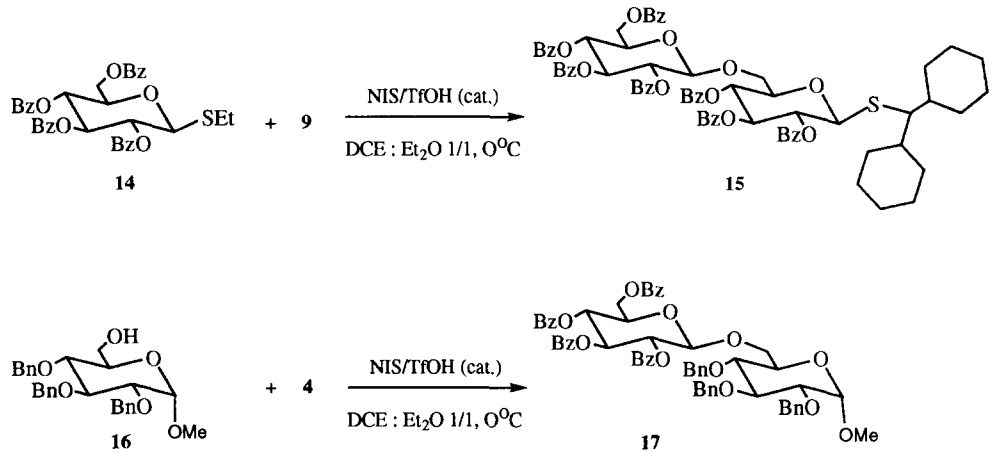


Scheme 1

These examples demonstrate that the reactivity of a C-2 benzylated dimethylcyclohexyl thioglycoside is of an order of magnitude between ethyl thioglycosides having a fully armed ether and disarmed ester protecting group on C-2 which implies that these novel thioglycosides may be regarded as semi-disarmed substrates.

With a novel method at our disposal to control the anomeric leaving group mobility, it should now be possible to generate glycosyl donors or acceptors with new reactivities. We envisaged that the sterically and electronically deactivated glycosyl acceptor **9** should have a lower reactivity than the electronically deactivated glycosyl donor **14**. Indeed, coupling of glycosyl donor **9** with glycosyl acceptor **14** in the presence of NIS/TfOH at 0°C gave dimer **15** in a 61% yield. In this case, no self-condensed or oligomeric products were observed (Scheme 2).

Finally, we have to prove that an electronically and sterically deactivated substrate is still a suitable glycosyl donor. Thus, glycosyl donor **4** was coupled with **16** in the presence of NIS/TfOH at room temperature and dimer **17** was isolated in a good yield (73%).



Scheme 2

The research described in this communication has shown, for the first time, that the reactivity of a thioglycoside can be controlled by the bulk of the anomeric thiol group and has produced glycosyl donors and acceptors with new levels of reactivity. The armed-disarmed glycosylation strategy has gained in versatility since the anomeric reactivity of glycosyl donors and acceptors can now be regulated by the bulkiness of the leaving group as well as the nature of protecting groups.

Preliminary studies have shown that the methodology is also applicable for secondary sugar alcohols. The new methodology will be applied to the preparation of oligosaccharides of biological importance.

Acknowledgement

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References and Notes -

1. P. Fugedi, P.J. Garegg, H. Löhn, T. Norberg, *Glycoconjugate J.*, **1987**, *4*, 97.
2. B. Fraser-Reid, U.E. Udodong, Z. Wu, H. Ottesson, J.R. Merritt, C.S. Rao, C. Roberts, R. Maden, *Synlett*, **1992**, 927-942.
3. a) G.H. Veeneman, J.H. van Boom, *Tetrahedron Lett.*, **1990**, *31*, 275; b) G.H. Veeneman, S.H. van Leeuwen, J.H. van Boom, *Tetrahedron Lett.*, **1990**, *31*, 1331.
4. B. Fraser-Reid, Z. Wu, C.W. Andrews, E. Skowronski, J.P. Bowen, *J. Am. Chem. Soc.* , **1988**, *110*, 5583.
5. G.J. Boons, P. Grice, S.V. Ley, L.L. Yeung, *Tetrahedron Lett.* **1993**, *34*, 8523.
6. S.V. Ley, H.W.M. Priepke, *Angew. Chem. Int. Ed. Eng.*, **1994**, *33*, 2292.
7. For other chemoselective and orthogonal glycosylations see: R.W. Friesen, S.J. Danishefsky, *J. Am. Chem. Soc.*, **1989**, *111*, 6656; S. Mehta, B.M. Pinto, *Tetrahedron Lett.*, **1991**, *32*, 4435; R. Roy, F.O. Anderson, M. Telellier, *Tetrahedron Lett*, **1992**, *33*, 6053; S. Raghavan, D. Kahne, *J. Am. Chem. Soc.*, **1993**, *115*, 1580; S. Mehta, B.M. Pinto, *J. Org. Chem.*, **1993**, *58*, 3269; L.A.J.M. Sliedrecht, K. Zegelaar-Jaarveld, G.A. van der Marel, J.H. van Boom, *Synlett*, **1993**, 335-337; G.J. Boons, S. Isles, *Tetrahedron Lett.*, **1994**, *35*, 3593; H. Yamada, T. Harada, H. Miyazaki, T. Takahishi, *Tetrahedron Lett.*, **1994**, *35*, 3979; O. Kanie, Y. Ito, T. Ogawa, *J. Am. Chem. Soc.*, **1994**, *116*, 12073.
8. Dicyclohexyl methanethiol was prepared from the corresponding commercial available alcohol according to the three-stepprocedure of Kellogg *et al.*; B. Strijtveen, R.M. Kelogg, *J. Org. Chem.*, **1986**, *51*, 3664.
9. All new compounds gave satisfactory NMR spectroscopic, mass spectroscopic and elemental analytical data.
   Selected data:
   11: Syrup. Fab-MS: *m/z* 1166 (M^++Na); ^{1}H NMR (400MHz): δ = 1.0 -1.8 (m, 20H), 1.97 (m, 2H), 2.37 (t, 1H), 3.11 (dd, 1H, H-2, $J_{1,2}$ 9.7, $J_{2,3}$ 9.2), 3.32 (m, 1H, H-5), 3.56 - 3.64 (m, 4H, H-2', H-3, H-4', H6'a), 3.70 (dd, 1H, H-6'b $J_{6'a,6'b}$ 10.8, $J_{5',6'b}$ 3.8), 3.76 - 3.81 (m, 3H, H-4, H-5', H-6a), 3.87 (dd, 1H, H-6b, $J_{6a,6b}$ 12.4, $J_{6b,5}$ 3.5), 3.97 (t, 1H, H-3', $J_{2,3}$ $J_{3,4}$ 9.2), 4.34 (d, 1H, H-1), 4.99 - 4.46 (m, 14 H, 7x CH_2, Bn), 5.20 (d, 1H, H1' $J_{1,2}$ 3.5), 7.15 - 7.45 (m, 35H, H-Arom.); ^{13}C NMR (75MHz, $CDCl_3$), δ 138.9-127.6 (7 $C_6H_5CH_2$), 97.5 (C-1'), 88.1 (C-1), 86.8 (C-3), 82.7 (C-2), 81.8 (C-3'), 80.2 (C-2'), 79.0 (C-5), 77.7 (C-4'), 77.4 (C-4 or C-5'), 75.7, 75.6, 75.0, 73.5 and 71.8 (7 $C_6H_5CH_2$), 70.5 (C-4 or C-5'), 68.8 (C-6'), 66.1 (C-6), 60.3 (*C*HS), 41.4 and 39.5 (2 *C*H DCHM), 32.0-26.6 (2 CH_2 DCHM).
   15: White glass. Fab-MS: m/z 1287 (M^++Na); ^{1}H NMR (400MHz): δ = 0.6-1.8 (m, 12H), 2.28 (t, 1H), 3.77 (dd, 1H, H6a, $J_{6a,6b}$ 11.0, $J_{6a,5}$ 4.0), 4.10 (m, 1H, H-5'), 4.18 (dd, 1H, H6b, $J_{6b,5}$ = 2.5), 4.45 (dd, 1H, H6'a, $J_{6'a,6'b}$ 12.1, $J_{6'a,5'}$ 5.0), 4.55 (dd, 1H, H6'b, $J_{5'6'b}$ 3.4), 4,65 (m, 1H, H-5), 4.93 (d, 1H, H-1', $J_{1',2'}$ 7.8), 5.18 (dd, 1H, H-2, $J_{1,2}$ 5.6, $J_{2,3}$ 10.5), 5.45 (t, 1H, H-4, $J_{3,4}$ $J_{4,5}$ 9.8) 5.55 (dd, 1H, H-2', $J_{2',3'}$ 9.6), 5.61 (d, 1H, H-1), 5.62 (t, 1H, H-4', $J_{3',4'}$ $J_{4'5'}$ 9.6), 5.90 (t, 2H, H-3, H-3'), 7.22-7.55 and 7.75 - 8.10 (m, 35H, H-Arom.); ^{13}C NMR (75MHz, $CDCl_3$), δ 166.06, 165.81, 165.44 and 165.11 (7 C_6H_5CO), 133.2-128.3 (7 $C_6H_5CH_2$), 101.4 (C-1'), 85.5 (C-1), 73.0 (C-3 or C-3'), 72.3 (C-5'), 71.7 (C-2, 2'), 70.7 (C-3 or C-3'), 69.7 (C-4'), 69.3 (C-4), 69.0 (C-5), 67.7 (C-6), 63.1 (C-6'), 61.4 (*C*HS), 41.0 and 39.4 (2 *C*H DCHM), 32.0-26.1 (10 CH_2 DCHM).

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