Chemoselective glycosylations using 2,3-unsaturated-4-keto glycosyl donors†

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2,3-Unsaturated-4-keto glycosyl acetates were found to exhibit low reactivity under several glycosylation conditions. Chemoselective glycosylations were effectively performed using 2,3-unsaturated glycosyl and 2,3-dideoxy glycosyl acetates as armed glycosyl donors, and 2,3-unsaturated-4-keto glycosyl acetates as disarmed glycosyl donors.

In the field of synthetic carbohydrate chemistry, significant attention has been paid to chemoselective glycosylation for the effective synthesis of oligosaccharides.[1] The "armed–disarmed" concept introduced by Fraser-Reid and co-workers has been one of the most influential ideas in this field.[2] Thus, the reactivity of a glycosyl donor can be controlled by the combinational use of C2 electron withdrawing and donating protecting groups. However, this approach cannot be directly applied to 2-deoxy glycosyl donors due to their lack of a C2 substituent. Therefore, an alternative strategy is required for the chemoselective glycosylation of 2-deoxy sugars. In this context, we earlier reported that a 2,3-unsaturated glycosyl donor exhibits much higher reactivity than the corresponding 2,3-saturated (dideoxy) glycosyl donor.[3] The high reactivity of 2,3-unsaturated glycosyl donors is apparently due to the half-chair conformation in the ground state induced by the double bond, and stabilization of the oxocarbenium intermediate in the transition state by the allylic cation (Fig. 1-(a)). Based on these findings, we anticipated that 2,3-unsaturated-4-keto glycosyl donors[4] would show much lower reactivity than the corresponding 2,3-unsaturated and/or 2,3-dideoxy glycosyl donor(s). This hypothesis was based on the expectation that the oxocarbenium intermediate, generated by the activation of the 2,3-unsaturated-4-keto glycosyl donor, would be very unstable due to the resonance effect of the α,β-unsaturated ketone system adjacent to the C1 cation (Fig. 1-(b)). Here, we report efficient chemoselective glycosylations using 2,3-unsaturated-4-keto glycosyl acetates as novel disarmed glycosyl donors.

To confirm our hypothesis, we first performed competitive glycosylations using either the 2,3-unsaturated glycosyl donor **1** (1.0 equiv.) or the 2,3-unsaturated-4-keto glycosyl donor **2** (1.0 equiv.) and a glycosyl acceptor **3** (1.0 equiv.) under several conditions. The glycosylations of **1** with **3** and **2** with **3** were separately conducted using TMSOTf, TBSOTf, $BF_3{\cdot}OEt_2$, TfOH or montmorillonite K-10 (MK-10) as activators; the results are shown in Table 1. It was found that the disaccharide **4**, resulting

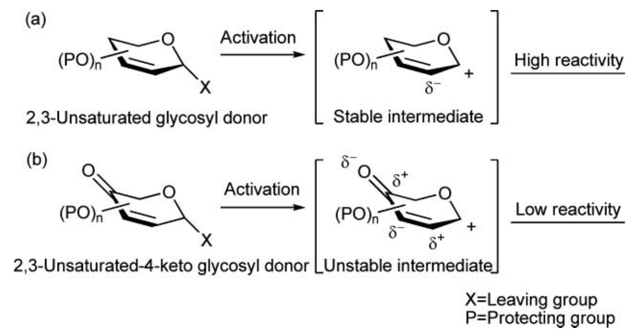

Fig. 1 Comparison of 2,3-unsaturated and 2,3-unsaturated-4-keto glycosyl donors.

from the activation of **1**, was produced in high yield even under conditions that produce insignificant amounts of the disaccharide **5** (Entries 1–5 *vs.* entries 6–10 in Table 1). In addition, in these cases, the glycosyl donor **2** did not react and was recovered in high yield (Entries 6–10 in Table 1). These results clearly show that the 2,3-unsaturated glycosyl donor is much more reactive than the corresponding 2,3-unsaturated-4-keto glycosyl donor, as expected. This tendency was essentially independent of the glycosylation activator used. Furthermore, it was confirmed that when glycosylation using **1** (1.0 equiv.), **2** (1.0 equiv.) and **3** (1.0 equiv.) took place in the same flask, similar results were obtained (for example, TMSOTf, MS 5Å, CH_2Cl_2, −60 °C, 1 h, **4**: 93% (α:β = 67 : 33), **5**: 3% (α:β = 64 : 36)).

We then examined chemoselective glycosylation using the 2,3-unsaturated glycosyl acetate **1** as a glycosyl donor and the 2,3-unsaturated-4-keto glycosyl acetate **6** as a glycosyl acceptor. As shown in Scheme 1, glycosylation using TMSOTf at −75 °C for 0.5 h proceeded chemoselectively to give the desired disaccharide **7** in high yield. Disaccharide **7** possesses an acetate leaving group at the C1 position, but no epimerization was observed. In contrast, no oligosaccharide(s) resulting from the undesired activation of **6** (which would lead to self-condensation) was detected. Furthermore, the reaction between disaccharide **7** and acceptor **3** proceeded smoothly using TMSOTf at −40 °C for 0.5 h in PhMe to afford trisaccharide **8** in a high yield with α-stereoselectivity. The use of PhMe as a solvent in the second glycosylation reaction was found to be highly effective in preventing the cleavage of the first glycosidic bond, and in increasing the α-stereoselectivity. Based on these results, the combination of the 2,3-unsaturated and the corresponding 2,3-unsaturated-4-keto glycosyl donors can define a new family of armed and disarmed glycosyl donors, respectively.

With these favourable results in hand, our attention next turned to comparison of the reactivity of 2,3-dideoxy glycosyl donors and 2,3-unsaturated-4-keto glycosyl donors, which are disarmed glycosyl donors for 2,3-unsaturated glycosyl donors. In this case,

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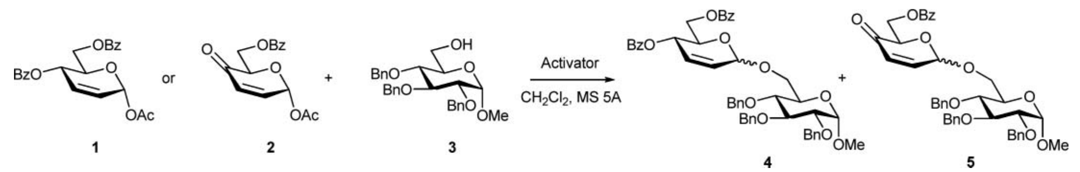
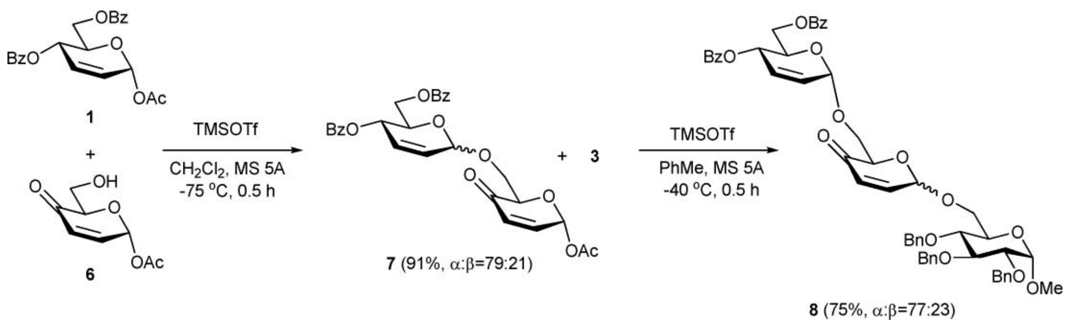
Table 1 Competitive glycosylations using **1** and **2**



Entry	Donor	Activator (equiv.)	Temp./° C	Time/h	Glycoside yield/% [a] (α:β ratio) [b]	Recovery yield of donors/% [a]
1	**1**	TMSOTf (0.3)	−60	1	**4**: 100 (66 : 34)	**1**: 0
2	**1**	TBSOTf (0.3)	−50	1	**4**: 92 (70 : 30)	**1**: 0
3	**1**	$BF_3\cdot OEt_2$ (2.0)	−60	48	**4**: 83 (76 : 24)	**1**: 8
4	**1**	TfOH (0.3)	−50	0.75	**4**: 92 (69 : 31)	**1**: 0
5	**1**	MK-10	0	8	**4**: 95 (64 : 36)	**1**: 0
6	**2**	TMSOTf (0.3)	−60	1	**5**: 0	**2**: 95
7	**2**	TBSOTf (0.3)	−50	1	**5**: 8 (63 : 37)	**2**: 83
8	**2**	$BF_3\cdot OEt_2$ (2.0)	−60	48	**5**: 2 (77 : 23)	**2**: 95
9	**2**	TfOH (0.3)	−50	0.75	**5**: 5 (76 : 24)	**2**: 94
10	**2**	MK-10 [c]	0	8	**5**: 8 (74 : 26)	**2**: 87

[a] Isolated yields. [b] α:β ratios were determined by ^{1}H-NMR analysis. [c] 100 wt% of MK-10 (relative to donor) was used.

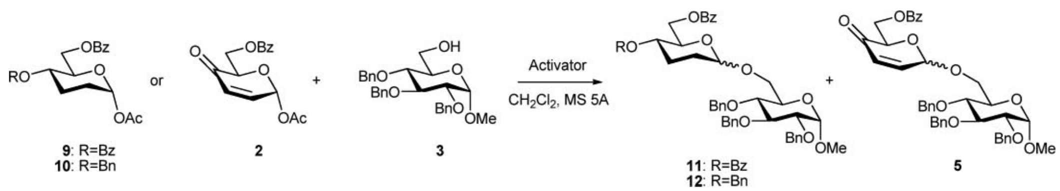


Scheme 1 Synthesis of trisaccharide **8** by chemoselective glycosylations using 2,3-unsaturated sugar **1** and 2,3-unsaturated-4-keto sugar **6**.

since the conformations and electronic characteristics of each glycosyl donor are quite different, it was not evident which would be most reactive. We therefore first conducted competitive glycosylations using the 2,3-dideoxy glycosyl donor **9** (1.0 equiv.), the 2,3-unsaturated-4-keto glycosyl donor **2** (1.0 equiv.) and the glycosyl acceptor **3** (1.0 equiv.) under several conditions. Although the reactivity of 2,3-dideoxy glycosyl donor **9** was found to be slightly higher than that of 2,3-unsaturated-4-keto glycosyl donor **2**, the difference was too small to utilize for chemoselective glycosylation (data not shown). Since an acyl protecting group on a glycosyl donor generally decreases the reactivity of the glycosyl donor,[5] we changed the protecting group at the C4 position of the 2,3-dideoxy glycosyl donor **9** from benzoyl (Bz) to benzyl (Bn) to improve its reactivity. Competitive glycosylations using the 2,3-dideoxy glycosyl donor **10** (1.0 equiv.), which has a benzyl protecting group at the C4 position, were conducted. The results are shown in Table 2. It was found that the disaccharide **12**, generated from **10** and **3**, was produced in high yield using TMSOTf, TBSOTf, $BF_3\cdot OEt_2$, TfOH or montmorillonite K-10 (MK-10) as the activator, even under conditions in which insignificant amounts of the disaccharide **5** were generated from **2** and **3** (Entries 1–5 *vs.* entries 6–10 in Table 2) and **2** was recovered in high yield (Entries 6–10 in Table 2). These results clearly indicate that the 2,3-dideoxy glycosyl donor is more reactive than the corresponding 2,3-unsaturated-4-keto glycosyl donor, and that the difference in reactivity between these glycosyl donors can be enhanced by optimal choice of the C4 protecting group of the 2,3-dideoxy glycosyl donor. In addition, the results confirmed that when glycosylation using **10** (1.0 equiv.), **2** (1.0 equiv.) and **3** (1.0 equiv.) occurred in the same flask, similar results were obtained (for example, TMSOTf, MS 5Å, CH_2Cl_2, −50 °C, 1 h, **12**: 99% (α:β = 71 : 29), **5**: 0%). Furthermore, as shown in Scheme 2, chemoselective glycosylation between 2,3-dideoxy glycosyl acetate **10** (glycosyl donor) and 2,3-unsaturated-4-keto glycosyl acetate **6** (glycosyl acceptor) using TMSOTf at −50 °C for 1 h afforded disaccharide **13** in a high yield with α-stereoselectivity; the disaccharide further gave trisaccharide **14** *via* glycosylation with **3** using TMSOTf at −35 °C for 0.5 h. In this case, 2,3-dideoxy and the corresponding 2,3-unsaturated-4-keto glycosyl donors function as the armed and disarmed glycosyl donors, respectively.

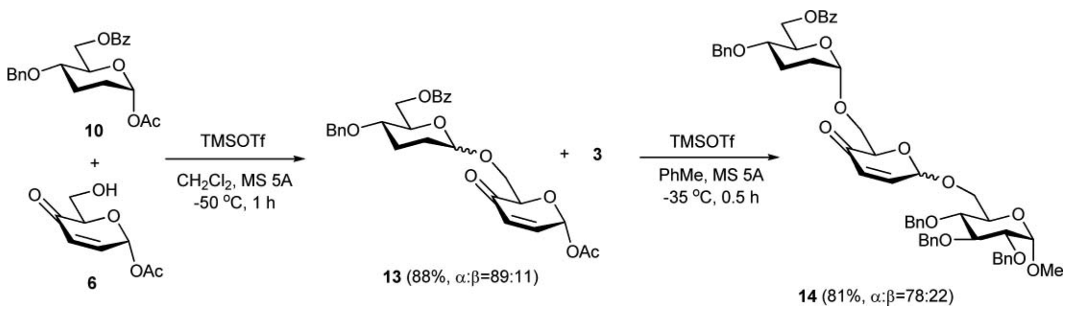
In conclusion, we have established new families of armed and disarmed glycosyl donors using 2,3-unsaturated-4-keto glycosyl donors as new disarmed glycosyl donors. Chemoselective glycosylations by combinational use of 2,3-unsaturated, 2,3-unsaturated-4-keto, and 2,3-dideoxy glycosyl donors should find wide application in the efficient synthesis of biologically important natural products which have 2,3-dideoxy and/or 2,3-unsaturated sugar(s), such as the antibiotic vineomycin B_2.

Table 2 Competitive glycosylations using **10** and **2**



Entry	Donor	Activator (equiv.)	Temp./°C	Time/h	Glycoside yield/% [a] (α:β ratio)[b]	Recovery yield of donors/%[a]
1	**10**	TMSOTf (0.3)	−50	1	**12**: 99 (68 : 32)	**10**: 0
2	**10**	TBSOTf (0.3)	−45	1	**12**: 98 (68 : 32)	**10**: 0
3	**10**	$BF_3 \cdot OEt_2$ (2.0)	−50	36	**12**: 94 (69 : 31)	**10**: 0
4	**10**	TfOH (0.3)	−45	1	**12**: 96 (73 : 27)	**10**: 0
5	**10**	MK-10	25	25	**12**: 84 (68 : 32)	**10**: 9
6	**2**	TMSOTf (0.3)	−50	1	**5**: 0	**2**: 91
7	**2**	TBSOTf (0.3)	−45	1	**5**: 4 (66 : 34)	**2**: 96
8	**2**	$BF_3 \cdot OEt_2$ (2.0)	−50	36	**5**: 6 (81 : 39)	**2**: 93
9	**2**	TfOH (0.3)	−45	1	**5**: 4 (84 : 16)	**2**: 91
10	**2**	MK-10[c]	25	25	**5**: 0	**2**: 91

[a] Isolated yields. [b] α:β ratios were determined by ^{1}H-NMR analysis. [c] 100 wt% of MK-10 (relative to donor) was used.



Scheme 2 Synthesis of trisaccharide **14** by chemoselective glycosylations using 2,3-dideoxy sugar **10** and 2,3-unsaturated-4-keto sugar **6**.

Acknowledgements

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Notes and references

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