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

Shunichi Kusumi, Sainan Wang, Tatsuya Watanabe, Kaname Sasaki, Daisuke Takahashi and Kazunobu Toshima\*

Received 4th December 2009, Accepted 17th December 2009 First published as an Advance Article on the web 7th January 2010 DOI: 10.1039/b925587g

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.<sup>2</sup> 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 2,3unsaturated glycosyl donor exhibits much higher reactivity than the corresponding 2,3-saturated (dideoxy) glycosyl donor.<sup>3</sup> 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<sup>4</sup> 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 2,3unsaturated-4-keto glycosyl donor, would be very unstable due to the resonance effect of the  $\alpha,\beta$ -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<sub>3</sub>·OEt<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, –60 °C, 1 h, 4: 93% ( $\alpha$ : $\beta$  = 67:33), **5**: 3% ( $\alpha$ : $\beta$  = 64:36)).

We then examined chemoselective glycosylation using the 2,3unsaturated glycosyl acetate 1 as a glycosyl donor and the 2,3unsaturated-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  $\alpha$ -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  $\alpha$ -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,

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan. E-mail: toshima@applc.keio.ac.jp; Fax: +81-45-566-1576; Tel: +81-45-566-1576 † Electronic supplementary information (ESI) available: Procedure for chemoselective glycosylation reactions and characterization of glycosides. See DOI: 10.1039/b925587g

#### Table 1 Competitive glycosylations using 1 and 2



a Isolated yields. <sup>b</sup> α:β ratios were determined by <sup>1</sup>H-NMR analysis. <sup>c</sup> 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,<sup>5</sup> 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<sub>3</sub>·OEt<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, -50 °C, 1 h, 12: 99% ( $\alpha$ : $\beta$  = 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  $\alpha$ -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, 2,3unsaturated-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



" Isolated yields. <sup>b</sup> α:β ratios were determined by <sup>1</sup>H-NMR analysis. <sup>c</sup> 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

This research was supported by the High-Tech Research Center Project for Private Universities: Matching Fund Subsidy, 2006-2011.

### Notes and references

1 Handbook of Chemical Glycosylation: Advances in Stereochemistry and Therapeutic Relevance, ed. A. V. Demchenko, Wiley-VCH, Weinheim, 2008; H. Tanaka, H. Yamada and T. Takahashi, Trends in Glycosci. Glycotech., 2007, 19, 108; G. A. Van der Marel, L. J. Van den Bos, H. S. Overkleeft, R. E. J. N. Litjens and J. D. C. Codee, ACS Symposium

Series, 2007, 960, 190; B. Fraser-Reid, K. N. Jayaprakash, J. C. Lopez, A. M. Gomez and C. Uriel, ACS Symposium Series, 2007, 960, 91; K. Toshima and K. Tatsuta, Chem. Rev., 1993, 93, 1503

- 2 D. R. Mootoo, P. Konradsson, U. Udodong and B. Fraser-Reid, J. Am. Chem. Soc., 1988, 110, 5583.
- 3 K. Sasaki, S. Matsumura and K. Toshima, Tetrahedron Lett., 2006, 47, 9039; K. Sasaki, S. Matsumura and K. Toshima, Tetrahedron Lett., 2007, 48, 6982
- 4 6-Acyl-2H-pyran-3(6H)-one system was effectively used in palladiumcatalyzed glycosylation, see: A. C. Comely, R. Eelkema, A. J. Minnaard and B. L. Feringa, J. Am. Chem. Soc., 2003, 125, 8714; R. S. Babu and G. A. O'Doherty, J. Am. Chem. Soc., 2003, 125, 12406; R. S. Babu, M. Zhou and G. A. O'Doherty, J. Am. Chem. Soc., 2004, 126, 3428.
- 5 For a typical example, see: K. Toshima, G. Matsuo and M. Nakata, J. Chem. Soc., Chem. Commun., 1994, 997.

1

2

3

4

5

6

7

8

9