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An efficient glycosidation method using 2,3-unsaturated glycosyl donors

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Dedicated to Professor K. C. Nicolaou on the occasion of his 60th birthday

Abstract—A novel class of 'armed' glycosyl donors containing a double bond at the C-2 position was designed by mimicking the mechanism of lysozyme-initiated hydrolysis. These donors were used to achieve chemoselective glycosidation of hex-2-enopyranosyl acetate and hexopyranosyl acetate, and synthesis of O-glycosidic linkages between highly deoxygenated sugars and tertiary alcohols.

Since the development by Koenigs and Knorr of a glycosidation method using glycosyl halides and a silver salt in 1901,[1] much attention has been paid to improving O-glycosidation reactions.[2] The 'armed–disarmed' concept introduced by Fraser-Reid and co-workers in 1988 has been one of the most influential ideas in this field over the past few decades.[3] Although glycosides consisting of a 2,3,6-trideoxysugar and a tertiary alcohol are found in several biologically important natural products, such as lactonamycin[4] and vineomycin B_2,[5] only a few attempts at constructing such a structure have been reported, including that of Sulikowski and co-workers.[6] The purpose of this paper is to demonstrate a novel glycosidation method inspired by an enzymatic reaction as a new concept in armed–disarmed methodology and as a powerful protocol for constructing glycosidic linkages between highly deoxygenated sugars and alcohols with low nucleophilicity.

The key idea in our study is lysozyme, which is known to recognize six hexose residues of mucopolysaccharides (A–F sugars) and to regioselectively cleave hexasaccharides between the D- and E-sugars, as shown in Figure 1.[7] The two most likely explanations for its regioselectivity are as follows: (1) Conformational distortion forces the D-sugar to adopt an unusual half-chair conformation ($^4H_5$), which is very similar to the conformation of the oxocarbenium intermediate;[8] and (2) the carboxylate anion of Asp 52 in the lysozyme stabilizes the generated oxocarbenium cation via electrostatic interaction.[9] These factors, which increase the reaction rate of hydrolytic cleavage of oligosaccharides, prompted us to design a novel class of glycosyl donors possessing an *endo* double bond at the C-2 position, as shown in Figure 1. The introduction of an unsaturated bond causes distortion of the glycosyl donor into a half-chair conformation in its ground state, similar to the change in conformation of the mucopolysaccharide D-sugar induced by lysozyme. In addition, when these glycosyl donors are used, the oxocarbenium intermediate of the glycosidation reaction may be stabilized in a similar fashion to that described above, because the cation center generated in the reaction is located at the allylic position of the double bond. Therefore, we anticipated that 2,3-unsaturated glycosyl donors would be very useful and effective in mild chemical glycosidation reactions.

To confirm our hypothesis, we examined glycosidation reactions using 2,3-unsaturated glycosyl donors (hex-2-enosyl donors) and 2,3-saturated glycosyl donors (hexosyl donors). Competitive glycosidation was investigated using the hex-2-enosyl donor **1** or **6** (1.0 equiv), the hexosyl donor **2** or **7** (1.0 equiv), and glycosyl acceptor **3** (0.9 equiv).[10,11] The results are shown in Table 1. It was found that the glycoside **4** was produced in preference to **5** in all glycosidations of **1** and **2** with **3** using

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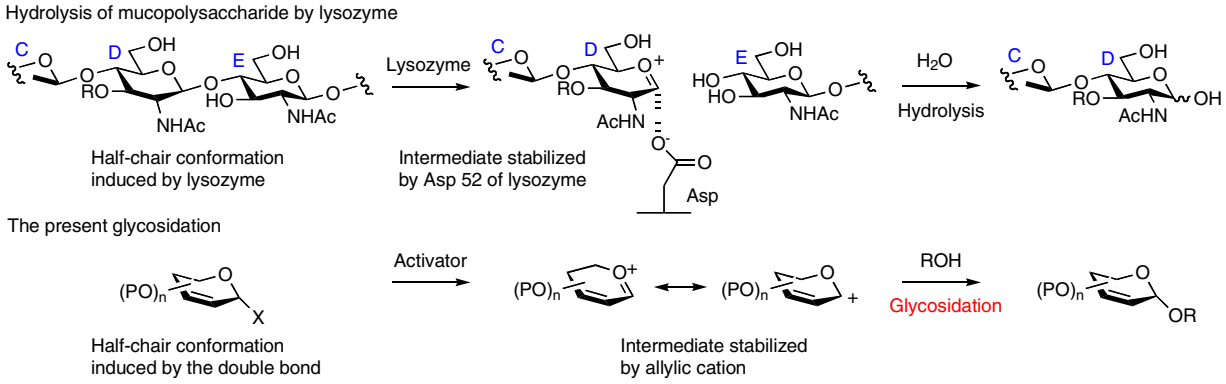
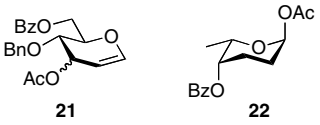


Figure 1. Regioselective hydrolysis of mucopolysaccharide by lysozyme (above), and the concept of the present glycosidation.



21 **22**

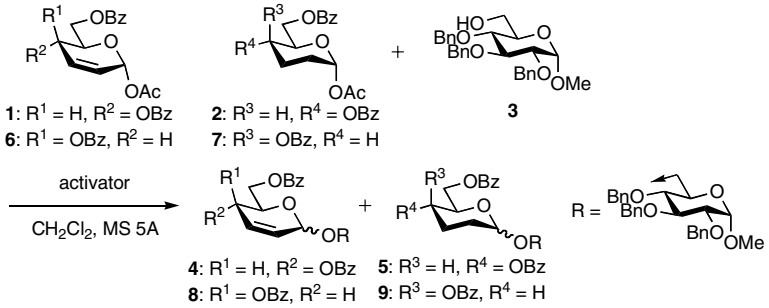
Figure 2. Glycal **21** and 2,3,6-trideoxyglycosyl acetate **22**.

$BF_3{\cdot}OEt_2$, montmorillonite K-10 (MK-10), TfOH, TMSOTf, and TBSOTf as activators (Table 1, entries 1–5).[12] Similarly, glycoside **8** was selectively obtained in preference to glycoside **9** in the glycosidation reactions of **6** and **7** with **3** (Table 1, entries 6 and 7). These results clearly show that the hex-2-enosyl donors, which mimic the mechanism of the lysozyme hydrolysis reaction, are much more reactive than the corresponding hexosyl donors.

Based on these results, we then examined chemoselective glycosidation using hex-2-enopyranosyl acetate **10** as a glycosyl donor and hexopyranosyl acetate **11** as a glycosyl acceptor to obtain hex-2-enosyl-hexose disaccharide **12**. Hex-2-enosyl-hexose disaccharides are found, for example, in the angucycline group of antibiotics as acurose–rhodinose disaccharides.[13] As shown in Scheme 1, glycosidation using TBSOTf at −78 °C for 24 h proceeded chemoselectively to give the desired disaccharide **12** in good yield with a high α-stereoselectivity. In contrast, the oligosaccharide **13** was generated only to a small extent, resulting from the undesired activation of **11**, which leads to self-condensation. Based on these results, we found that a pair consisting of a hex-2-enosyl donor and the corresponding hexosyl donor forms a new family of armed and disarmed donors.

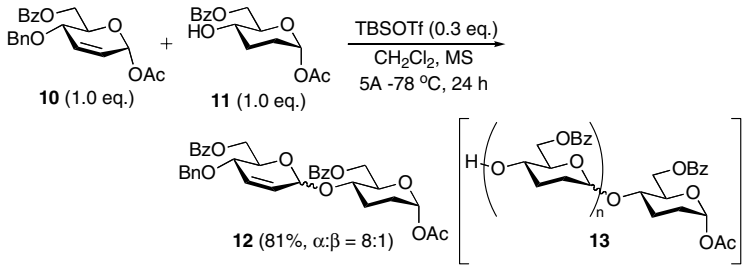
We then examined the possibility that this novel class of glycosyl donors could be a powerful tool in the construction of glycosides of tertiary alcohols. The formation of O-glycosidic linkages between 3°-alcohols and highly deoxygenated sugars is a challenging task, for the following two reasons: (1) tertiary alcohols have a tendency to generate carbocations along with elimina-

Table 1. Competitive glycosidation of **3** using **1** and **2** or **6** and **7**



Entry[a]	Donors	Activator (equiv)	Temperature, time	Yield/% (α:β ratio)[b]
1	**1** and **2**	$BF_3{\cdot}OEt_2$ (1.0)	−60 °C, 24 h	**4**: 72 (80:20), **5**: 3 (67:33)
2	**1** and **2**	MK-10[c]	0 °C, 4 d	**4**: 80 (56:44), **5**: 4 (35:65)
3	**1** and **2**	HOTf (0.5)	−70 °C, 24 h	**4**: 85 (80:20), **5**: 10 (60:40)
4	**1** and **2**	TMSOTf (0.3)	−78 °C, 3 h	**4**: 89 (69:31), **5**: 5 (60:40)
5	**1** and **2**	TBSOTf (0.3)	−70 °C, 3 h	**4**: 91 (68:32), **5**: 4 (58:42)
6	**6** and **7**	MK-10[c]	−20 °C, 4 d	**8**: 80 (80:20), **9**: 5 (90:10)
7	**6** and **7**	TBSOTf (0.3)	−78 °C, 24 h	**8**: 94 (94:6), **9**: 6 (90:10)

[a] The ratio of unsaturated donor (**1** or **6**) to saturated donor (**2** or **7**) to acceptor **3** was 1:1:0.9.
[b] Yields and α:β ratios were determined by HPLC analysis.
[c] 100 wt % of MK-10 to 2,3-unsaturated donor **1** or **6** was used.



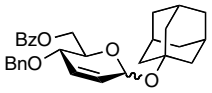
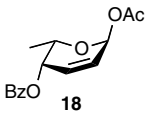
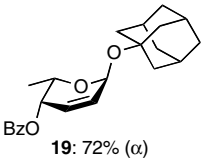
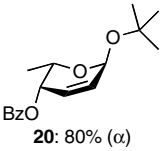
Scheme 1. Chemoselective glycosidation of **10** and **11**.

tion of a hydroxyl group under acidic conditions; and (2) because of the low nucleophilicity of tertiary alcohols, the active species—an oxocarbenium intermediate generated from a glycosyl donor—is easily converted to the corresponding glycal via deprotonation at the C-2 position. Our novel glycosidation method succeeded in overcoming these problems. Because hex-2-enopyranosyl glycosyl donors can be activated under much milder acidic conditions than the corresponding hexopyranosyl donors, acid-sensitive tertiary alcohols could be effectively glycosylated. In addition, the lack of a β-proton at the cationic center of the oxocarbenium ion prevents the side reaction mentioned above. As shown in Table 2, glycosidation of adamantan-1-ol (**14**) and *tert*-butanol (**16**) with an almost equal amount of the *erythro*-type hex-2-enopyranosyl acetate **10** proceeded effectively in the presence of a very mild Lewis acid, $Yb(OTf)_3$,[14] at 0 °C to give glycosides **15** and **17**, respectively, in high yields. For glycosidations using **18**, whose α-glycosides can easily be converted into naturally occurring L-rhodinosides, L-acurosides, L-cinerulosides, and L-rhamnosides by appropriate reduction and/or oxidation,[15] the corresponding glycosides **19** and **20** were also obtained in good to high yields with excellent α-stereoselectivities.

When the glycal **21**, which is the synthetic equivalent of **10** and can be converted into **15** and **17** by Ferrier rearrangement,[16] was used as a glycosyl donor for glycosidation of **14** under the same conditions used for **10**, the reaction did not proceed. In addition, when the hexopyranosyl donor **22** was used instead of **18** for glycosidation of **14**, it could not be activated below 0 °C in the presence of $Yb(OTf)_3$, and when the reaction was carried out between 0 and 25 °C, the corresponding α-glycoside was obtained in a yield of only 22%, accompanied by considerable amounts of by-products. These results indicate that glycosidation using hex-2-enosyl donors proceeds under conditions that are considerably milder than usual, and that this method can be used for effective construction of glycosidic linkages even for tertiary alcohols with low nucleophilicity (Fig. 2).

In conclusion, we have designed a novel class of glycosyl donors with a pyran ring containing an unsaturated bond, and clearly demonstrated that they can act as

Table 2. Glycosidation of 3°-alcohols with 2,3-unsaturated donor **10** or **18** using $Yb(OTf)_3$

Entry[a]	donor	ROH	Temperature, time	Yield/% (α:β ratio[b])
1	**10**	 **14**	0 °C, 19 h	 **15**: 74% (89:11)
2	**10**	 **16**	0 °C, 19 h	 **17**: 71% (86:14)
3	 **18**	**14**	−30 °C, 3 d	 **19**: 72% (α)
4	**18**	**16**	−30 °C, 3 d	 **20**: 80% (α)

[a] In all entries, the ratio of donor to ROH was 1.0:0.9.
[b] Isolated yield.

armed glycosyl donors. Furthermore, they were found to be very effective in the synthesis of O-glycosidic linkages between highly deoxygenated sugars and tertiary alcohols.

Acknowledgements

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10. The 2,3-unsaturated glycosyl donor **1** was prepared from the known methyl α-D-*erythro*-hex-2-enopyranoside in two steps including benzoylation followed by acetolysis (Ac_2O, H_2SO_4, −40 °C): Fraser-Reid, B.; Boctor, B. *Can. J. Chem.* **1969**, *47*, 393–401.
11. The 2,3-dideoxy glycosyl donor **2** was synthesized by hydrogenation of **1** using Rh/Al_2O_3 in EtOAc–PhMe; Sasaki, K.; Wakamatsu, T.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2006**, *47*, 8271–8274.
12. The configurations at the anomeric positions of the 2,3-unsaturated glycosides were determined by the ^1H NMR analyses of the corresponding 2,3-saturated glycosides which were obtained by standard hydrogenations. Representative ^1H NMR (300 MHz, $CDCl_3$): spectra [δ (TMS), J (Hz)] are the following. Compound **4α**: 8.02–7.95 (4H, m, ArH), 7.66–7.52 (2H, m, ArH), 7.52–7.22 (19H, m, ArH), 6.02 (1H, ddd, $J_{2',3'} = 10.2$, $J_{1',3'} = J_{3',4'} = 0.9$, H-3′), 5.91 (1H, ddd, $J_{2',3'} = 10.2$, $J_{1',2'} = 2.4$, $J_{2',4'} = 2.1$, H-2′), 5.68 (1H, ddd, $J_{4',5'} = 7.2$, $J_{2',4'} = 2.1$, $J_{3',4'} = 0.9$, H-4′), 5.16 (1H, dd, $J_{1',2'} = 2.4$, $J_{1',3'} = 0.9$, H-1′), 4.99 and 4.80 (2H, ABq, $J = 10.8$, $ArCH_2$), 4.91 and 4.64 (2H, ABq, $J = 11.4$, $ArCH_2$), 4.78 and 4.67 (2H, ABq, $J = 12.0$, $ArCH_2$), 4.61 (1H, d, $J_{1,2} = 3.6$, H-1), 4.46 (1H, dd, $J_{6',6'} = 8.7$, $J_{5',6'} = 4.5$, H-6′), 4.37 (1H, ddd, $J_{4',5'} = 7.2$, $J_{5',6'} = 5.1$, $J_{5',6'} = 4.5$, H-5′), 4.34 (1H, dd, $J_{6',6'} = 8.7$, $J_{5',6'} = 5.1$, H-6′), 4.01 (1H, dd, $J_{6,6} = 11.4$, $J_{5,6} = 4.8$, H-6), 4.00 (1H, dd, $J_{2,3} = J_{3,4} = 9.3$, H-3), 3.82–3.72 (2H, m, H-5, 6), 3.53 (1H, dd, $J_{3,4} = J_{4,5} = 9.3$, H-4), 3.49 (1H, dd, $J_{2,3} = 9.3$, $J_{1,2} = 3.6$, H-2), 3.38 (3H, s, OMe). Compound **4β**: 8.04–7.96 (4H, m, ArH), 7.61–7.46 (2H, m, ArH), 7.46–7.22 (19H, m, ArH), 6.10 (1H, ddd, $J_{2',3'} = 10.2$, $J_{3',4'} = 3.6$, $J_{1',3'} = 1.5$, H-3′), 5.92 (1H, ddd, $J_{2',3'} = 10.2$, $J_{1',2'} = J_{2',4'} = 1.5$, H-2′), 5.55 (1H, ddd, $J_{4',5'} = 11.4$, $J_{3',4'} = 3.6$, $J_{1',3'} = 1.5$, H-4′), 5.16 (1H, dd, $J_{1',2'} = J_{1',3'} = 1.5$, H-1′), 4.98 and 4.80 (2H, ABq, $J = 11.1$, $ArCH_2$), 4.87 and 4.61 (2H, ABq, $J = 11.1$, $ArCH_2$), 4.78 and 4.66 (2H, ABq, $J = 12.0$, $ArCH_2$), 4.59 (1H, d, $J_{1,2} = 3.6$, H-1), 4.54 (1H, dd, $J_{6',6'} = 11.7$, $J_{5',6'} = 6.0$, H-6′), 4.49 (1H, dd, $J_{6',6'} = 11.7$, $J_{5',6'} = 5.4$, H-6′), 4.31 (1H, ddd, $J_{4',5'} = 11.4$, $J_{5',6'} = 6.0$, $J_{5',6'} = 5.4$, H-6′), 4.08–4.01 (1H, m, H-6), 3.97 (1H, dd, $J_{2,3} = J_{3,4} = 9.3$, H-3), 3.79–3.71 (2H, m, H-5, 6), 3.57 (1H, dd, $J_{3,4} = J_{4,5} = 9.3$, H-4), 3.53 (1H, dd, $J_{2,3} = 9.3$, $J_{1,2} = 3.6$, H-2), 3.30 (3H, s, OMe). Compound **5α**: 8.02–7.95 (2H, m, ArH), 7.93–7.88 (2H, m, ArH), 7.58–7.48 (2H, m, ArH), 7.42–7.22 (19H, m, ArH), 5.11–5.01 (1H, m, H-4′), 5.00 and 4.80 (2H, ABq, $J = 10.8$, $ArCH_2$), 4.98 and 4.68 (2H, ABq, $J = 10.8$, $ArCH_2$), 4.73 (1H, br dd, H-1′), 4.78 and 4.68 (2H, ABq, $J = 12.0$, $ArCH_2$), 4.63 (1H, d, $J_{1,2} = 3.6$, H-1), 4.46 (1H, dd, $J_{6',6'} = 9.9$, $J_{5',6'} = 2.1$, H-6′), 4.26 (1H, dd, $J_{6',6'} = 9.9$, $J_{5',6'} = 6.0$, H-6′), 4.22 (1H, ddd, $J_{4',5'} = 9.3$, $J_{5',6'} = 6.0$, $J_{5',6'} = 2.1$, H-5′), 4.01 (1H, dd, $J_{2,3} = J_{3,4} = 9.3$, H-3), 3.96 (1H, dd, $J_{6,6} = 11.1$, $J_{5,6} = 4.8$, H-6), 3.81 (1H, ddd, $J_{4,5} = 10.2$, $J_{5,6} = 4.8$, $J_{5,6} = 1.2$, H-5), 3.68 (1H, dd, $J_{6,6} = 11.1$, $J_{5,6} = 1.2$, H-6), 3.53 (1H, dd, $J_{4,5} = 10.2$, $J_{3,4} = 9.3$, H-4), 3.48 (1H, dd, $J_{2,3} = 9.3$, $J_{1,2} = 3.6$, H-2), 3.40 (3H, s, OMe), 2.21–2.11 (1H, m, H-3′), 2.05–1.80 (3H, m, H-2′ × 2, H-3′). Compound **5β**: 8.02–7.95 (4H, m, ArH), 7.61–7.47 (2H, m, ArH), 7.44–7.22 (19H, m, ArH), 5.02 (1H, ddd, $J_{3',4'} = 9.3$, $J_{4',5'} = 9.0$, $J_{3',4'} = 5.1$, H-4′), 4.98 and 4.80 (2H, ABq, $J = 10.5$, $ArCH_2$), 4.88 and 4.59 (2H, ABq, $J = 11.1$, $ArCH_2$), 4.78 and 4.65 (2H, ABq, $J = 12.3$, $ArCH_2$), 4.60 (1H, d, $J_{1,2} = 3.6$, H-1), 4.56 (1H, dd, $J_{6',6'} = 12.0$, $J_{5',6'} = 3.9$, H-6′), 4.43 (1H, br dd, $J_{1',2'} = 9.0$, H-1′), 4.40 (1H, dd, $J_{6',6'} = 12.0$, $J_{5',6'} = 6.0$, H-6′), 4.09 (1H, br dd, $J_{6,6} = 10.5$, H-6), 3.98 (1H, dd, $J_{2,3} = J_{3,4} = 9.6$, H-3), 3.93 (1H, ddd, $J_{4',5'} = 9.0$, $J_{5',6'} = 6.0$, $J_{5',6'} = 3.9$, H-5′), 3.75 (1H, br ddd, $J_{4,5} = 9.6$, $J_{5,6} = 3.9$, H-5), 3.64 (1H, dd, $J_{6,6} = 10.5$, $J_{5,6} = 3.9$, H-6), 3.56 (1H, dd, $J_{3,4} = J_{4,5} = 9.6$, H-4), 3.54 (1H, dd, $J_{2,3} = 9.6$, $J_{1,2} = 3.6$, H-2), 3.33 (3H, s, OMe), 2.40–2.30 (1H, m), 1.92–1.57 (3H, m).

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