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A new efficient glycosylation method employing glycosyl pentenoates and PhSeOTf

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Abstract—The PhSeOTf promoted glycosylations of various glycosyl acceptors with mannosyl pentenoates and glucosyl pentenoates as glycosyl donors afforded corresponding disaccharides in high yields. And the present glycosyl pentenoates/PhSeOTf method showed that the complete α-selective mannosylation of secondary alcohol acceptors was achieved with 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl pentenoate to give α-disaccharides in good yields.

The development of efficient and stereoselective glycosylation methodologies has attracted a great deal of attention in the past a decade due to the explosive growth of important biological functions of complex oligosaccharides and glycoconjugates in glycobiology.[1] Devising new glycosyl donors and developing new activation systems for existing donors resulted in major advances in this area. While glycosyl trichloroacetimidates[2] and thioglycosides[3] have been the most commonly used methods for glycosylation, glycosyl sulfoxides,[4] glycals,[5] *n*-pentenyl glycosides,[6] glycosyl fluorides,[7] and glycosyl phosphates[8] have been also employed widely. Recently, there have been some reports on glycosylation methods using new glycosyl donors and employing new activation systems for existing glycosyl donors.[9] We have also reported a novel type of glycosyl donor, the 2′-carboxybenzyl (CB) glycosides that is useful for the stereoselective glycosylation.[10] Nevertheless, there is no generally applicable one single glycosylation method available for the construction of various glycosyl linkages and a combination of more than one glycosyl donors is usually required for the synthesis of complex oligosaccharides. In this regard, there still remains a need for new glycosylation methodologies, which might be highly efficient and generally applicable to the synthesis of oligosaccharides.

In the continuation of our effort to develop the efficient glycosylation method, our attention was focused on the use of glycosyl pentenoates, **1**–**3** (Fig. 1), as glycosyl donors and phenylselenyl triflate (PhSeOTf), which was readily generated in situ from PhSeBr and AgOTf, as a highly potent promoter. The glycosyl pentenoates themselves are not new but have been reported as the glycosyl donors in the combination with iodonium dicollidine perchlorate (IDCP), *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH), or 1,3-dithian-2-yl tetrafluoroborate as the promoter by Kunz[11] and Fraser-Reid[12] independently. However, the glycosylations using these promoters with the pentenoates appeared to be not quite efficient: examples were limited and yields of product disaccharides ranged from 53% to 65%. And no further studies on the glycosyl pentenoates and no application to the oligosaccharide synthesis have been reported until our recent paper, in which we showed a highly reactive and stereoselective procedure for the β-mannopyranosylation employing 4,6-*O*-benzylidene mannopyranosyl pentenoate **3** and PhSeOTf.[13] In order to explore the scope of glycosyl pentenoates/PhSeOTf method, we further carried out glycosylation reactions with mannopyranosyl pentenoates **1** and glucopyranosyl pentenoates **2**. Herein we report a highly reactive new glycosylation method using **1** and **2** as glycosyl donors and PhSeOTf as a highly potent promoter.

We envisioned that treatment of glycosyl pentenoate **A** with PhSeOTf in the absence or presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[14] would induce the

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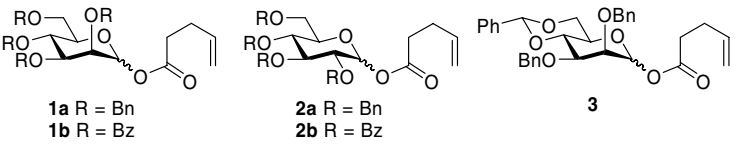


Figure 1. Various glycosyl pentenoates as glycosyl donors.

lactonization of **A** via selenonium ion **B** to generate γ-phenylselenylmethyl-γ-butyrolactone and oxocarbenium ion **C** (Fig. 2). Subsequent reaction of **C** with the glycosyl acceptor would provide desired glycoside **D**.

The glycosyl pentenoates **1** and **2** were prepared easily from the corresponding 1-hydroxy sugars by simple treatment with commercially available 4-pentenoic acid in the presence of 1,3-diisopropylcarbodiimide (DIC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in good yields as shown in Scheme 1. Since many glycosyl donors are prepared by anomeric oxygen exchange reactions and preparation of the glycosyl trichloroacetimidates from 1-hydroxy sugars requires a base such as K_2CO_3 or DBU,[2] the ready synthesis of glycosyl pentenoates from 1-hydroxy sugars through retention of anomeric oxygen atoms under the very mild condition would be one of advantages of the present glycosylation method.

Using the mannopyranosyl pentenoate **1** and PhSeOTf, glycosylations of a number of glycosyl acceptors were examined (Table 1). The glycosylation was carried out with 5 equiv of PhSeBr and AgOTf in the presence of 4 Å molecular sieves and TTBP at −78 °C in CH_2Cl_2. Although TTBP is not essential for all glycosylations, it is necessary in the glycosylation of the acceptors having the benzylidene or the isopropylidene protective group in order to prevent their decomposition by triflic acid generated during the glycosylation. The glycosylation proceeded smoothly with 1.5 or 2 equiv of PhSeBr and AgOTf, but 5 equiv of the promoters guarantee the high yield even in the case of slight deterioration of the promoters or incomplete generation of PhSeOTf.

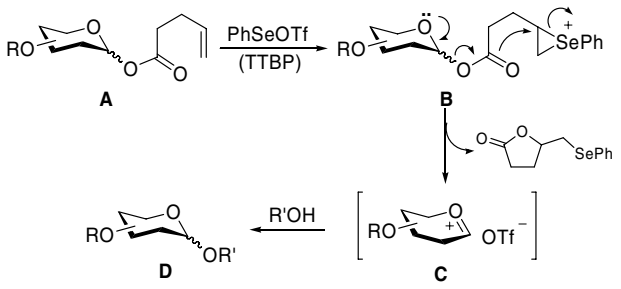
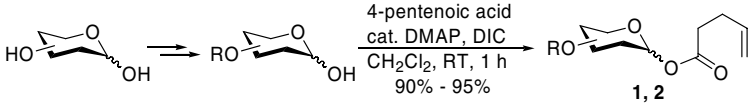


Figure 2. Plausible mechanism of glycosylation with glycosyl pentenoate as the donor using PhSeOTf as a promoter.

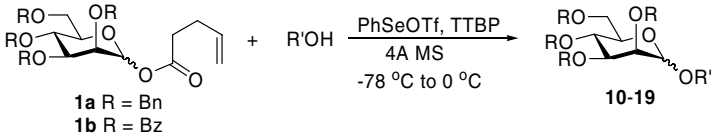
Although glycosylations of various acceptors with tetrabenzyl mannosyl pentenoate **1a** were so efficient that the glycosyl donor disappeared in 20 min at −78 °C based on TLC, the reaction mixture was further warmed to 0 °C to make sure the completion of the reaction. In case of disarmed tetrabenzoyl mannosyl pentenoate **1b**, the donor **1b** started to be activated at −40 °C and the glycosylation was completed after the reaction temperature was reached to 0 °C. Glycosylations of primary alcohol acceptors **4** and **5** with **1a** gave a mixture of α- and β-disaccharides **10**[15] (α/β = 1.1:1) and **11** (α/β = 1.4:1), respectively, in high yields (entries 1 and 2), while the glycosylation of secondary alcohol acceptor **6** with **1a** afforded exclusively α-disaccharide **12** in 84% yield, in spite of no participating group effect of benzyl-protected glycosyl donor (entry 3). Interestingly, the complete α-selective mannosylation of secondary alcohol acceptors **7**–**9** was also achieved with **1a** to give α-disaccharides **13**–**15** in good yields (entries 4–6). Namely, in the case of the less-reactive secondary alcohol acceptors, complete α-selectivities were observed in the mannopyranosylation with **1a**. Glycosylations of primary and secondary alcohol acceptors **4**, **5**, **6**, and **7** with **1b** afforded the corresponding α-disaccharides **16**, **17**, **18**, and **19** exclusively in high yields (entries 7–10). This result indicates that not only the 4,6-*O*-benzylidene-protected mannosyl pentenoate[13] but also mannosyl pentenoates with other protective groups are efficient mannosyl donors.

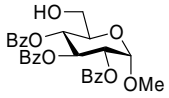
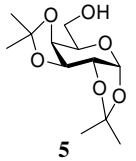
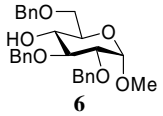
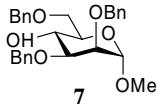
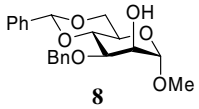
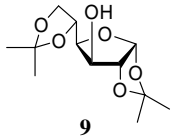
Glycosylations of various glycosyl acceptors with the glucosyl pentenoate **2** using PhSeOTf as the promoter were also carried out under the same reaction condition as described above for the mannosyl pentenoate **1** (Table 2). Reactions of the benzyl-protected glucosyl donor **2a** with primary alcohol acceptors **4** and **5** afforded a mixture of α- and β-disaccharides **20** in 90% yield and **21** in 86% yield, respectively (entries 1 and 2), while it has been reported that the reaction of **2a** with **5** using 1,3-dithian-2-yl tetrafluoroborate as promoter gave **21** in 56% yield.[11] Glycosylations of secondary alcohol acceptors **6** and **7** with **2a** also afforded the anomeric mixture of disaccharides **22** and **23**, respectively, in high yields (entries 3 and 4). Reaction of **2a** with diacetone glucofuranose **9** under the present glycosylation condition also provided an anomeric mixture of disaccharide **24** in 85% yield (entry 5), while it has been reported that the same reaction by Fraser-Reid group gave **24** in 65%



Scheme 1. Synthesis of glycosyl pentenoates **1** and **2**.

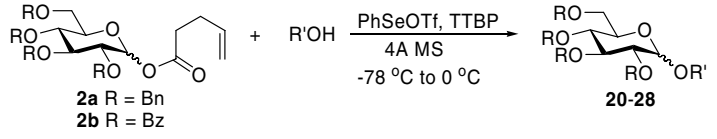
Table 1. Glycosylations of various acceptors with mannosyl pentenoate **1** in CH_2Cl_2



Entry	Glycosyl donor	Glycosyl acceptor (R′OH)	Product	Yield[a] (%)	Ratio (α/β)[a]
1	**1a**	 **4**	**10**	92	1.1:1
2	**1a**	 **5**	**11**	89	1.4:1
3	**1a**	 **6**	**12**	84	α Only
4	**1a**	 **7**	**13**	82	α Only
5	**1a**	 **8**	**14**	80	α Only
6	**1a**	 **9**	**15**	83	α Only
7	**1b**	**4**	**16**	85	α Only
8	**1b**	**5**	**17**	87	α Only
9	**1b**	**6**	**18**	90	α Only
10	**1b**	**7**	**19**	87	α Only

[a] Determined after isolation.

Table 2. Glycosylations of various acceptors with glucosyl pentenoate **2** in CH_2Cl_2



Entry	Glycosyl donor	Glycosyl acceptor (R′OH)	Product	Yield[a] (%)	Ratio (α/β)[a]
1	**2a**	**4**	**20**	90	1:1
2	**2a**	**5**	**21**	86 (56)[b]	1.3:1 (1:1)[b]
3	**2a**	**6**	**22**	88	1:1.1
4	**2a**	**7**	**23**	90	1:1.9
5	**2a**	**9**	**24**	85 (65)[c] (62)[d]	1:1.1 (3:1)[c] (1:1)[d]
6	**2b**	**4**	**25**	89	β Only
7	**2b**	**5**	**26**	88	β Only
8	**2b**	**6**	**27**	89	β Only
9	**2b**	**7**	**28**	93	β Only

[a] Determined after isolation.
[b] The result with 1,3-dithian-2-yl tetrafluoroborate as promoter by Kunz, see Ref. 11.
[c] The result with IDCP as promoter by Fraser-Reid, see Ref. 12.
[d] The result with NIS–TfOH as promoter by Fraser-Reid, see Ref. 12.

yield using IDCP and 62% yield using NIS–TfOH, respectively.[12] Clearly, using PhSeOTf instead of IDCP, NIS–TfOH, or 1,3-dithian-2-yl tetrafluoroborate as the promoter for the glycosylation with **2a** enhanced the efficiency of the reaction. Reactions of the benzoyl-protected glucosyl donor **2b** with acceptors **4**, **5**, **6**, and **7** afforded the corresponding β-disaccharides **25**, **26**, **27**, and **28** exclusively in high yields without any problem (entries 6–9).

In conclusion, we have described a new efficient glycosylation method employing the glycosyl pentenoate as the glycosyl donor and PhSeOTf as the highly potent promoter. We found that PhSeOTf is much more efficient promoter than IDCP, NIS–TfOH, and 1,3-dithian-2-yl tetrafluoroborate, which are used to date, for glycosylations with glycosyl pentenoates as donor. Moreover, the present methodology showed that the complete α-selective mannosylation of secondary alcohol acceptors was achieved with 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl pentenoate (**1a**) to give α-disaccharides in good yields.

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15. *General procedure* (**10**, Table 1, entry 1): A solution of PhSeBr (81 mg, 0.34 mmol) and AgOTf (88 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) in the presence of 4 Å molecular sieves (100 mg) was stirred for 15 min at room temperature and cooled to −78 °C, then a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl pentenoate (**1a**) (42 mg, 0.067 mmol) and TTBP (2,4,6-tri-*tert*-butylpyrimidine) (85 mg, 0.34 mmol) in CH_2Cl_2 (1.5 mL) was added. After the resulting solution was stirred at −78 °C for 15 min, methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**4**) (45 mg, 0.088 mmol) was added. The reaction mixture was stirred at −78 °C for 20 min, allowed to warm over 1 h to 0 °C, stirred for further 20 min at 0 °C, quenched with saturated aqueous $NaHCO_3$ (10 mL), and then extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc/CH_2Cl_2, 4:1:1) to afford the desired mannopyranoside **10** (92%, $\alpha/\beta = 1.1:1$).