Glycosylation

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A Highly Reactive and Stereoselective β-Mannopyranosylation System: Mannosyl 4-Pentenoate/PhSeOTf**

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Although many efficient methods for the stereoselective construction of glycosyl linkages are available,[1] the stereospecific formation of the 1,2-*cis*-β-D-mannopyranosyl linkage still poses a great challenge. Several diverse and innovative strategies for β-mannopyranosylation have been developed,[2] and recently, Crich and co-workers have made a significant

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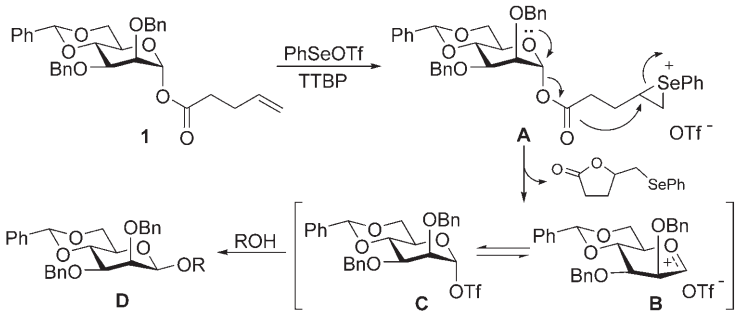
breakthrough in β-mannoside synthesis by employing 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides or thiomannopyranosides as glycosyl donors.[3] The effect of the 4,6-*O*-acetal group on the construction of β-mannosyl linkages was further confirmed with other mannosyl donors by us[4] and other workers.[5] Nevertheless, the effect of protecting groups at the 2-O and 3-O positions of the donor,[6] anomeric leaving groups, and acceptors on the stereoselectivity in this β-mannosylation of a 4,6-*O*-acetal-substituted sugar is not yet fully understood. More importantly, the β selectivity with certain glycosyl acceptors has never been satisfactory.[7] In the continuation of our effort to develop an efficient β-mannopyranosylation method, our attention focused on the use of 4,6-*O*-benzylidene mannosyl pentenoate **1** as a glycosyl donor in the presence of phenylselenyl triflate (PhSeOTf). Glycosyl pentenoates are not really new but have been reported as glycosyl donors with iodonium dicollidine perchlorate (IDCP) and *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS–TfOH) promoters by the research groups led by Kunz[8] and Fraser-Reid[9] independently. However, no detailed studies on the stereoselectivity and no application to oligosaccharide synthesis have been reported,[10] except that sialyl 4-pentenoate is reported to be inferior to 4-pentenyl sialoside as a glycosyl donor.[11] Herein we describe the use of **1** as the glycosyl donor and PhSeOTf as the promoter for the synthesis of β-mannopyranosides and the efficient construction of an oligosaccharide.

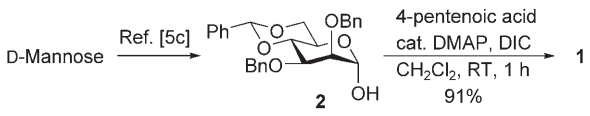
We envisioned that treatment of mannosyl pentenoate **1** with PhSeOTf in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[12] would induce the lactonization of **1** via selenonium ion **A** to generate γ-phenylselenylmethyl-γ-butyrolactone and oxocarbenium ion **B**, which might be in equilibrium with triflate **C** (Scheme 1). Subsequent reaction of **B** or **C** with a glycosyl acceptor would provide mannopyranoside **D**.



Scheme 1. Plausible mechanism of glycosylation with glycosyl pentenoate **1** as the donor and with PhSeOTf as a promoter. Bn = benzyl, Tf = trifluoromethanesulfonyl.

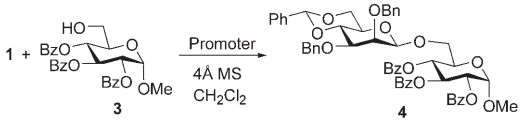
4,6-*O*-Benzylidene mannosyl pentenoate **1** (α/β = 10:1) was readily prepared from the corresponding 1-hydroxy sugar **2**[5c] by simple treatment with commercially available 4-pentenoic acid in the presence of 1,3-diisopropylcarbodiimide (DIC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) as shown in Scheme 2.

We initially examined the glycosylation of glycosyl acceptor **3** with pentenoate **1** and with various promoters (Table 1). The glycosylation with PhSeOTf at −78 °C to 0 °C afforded exclusively β-disaccharide **4** in 90 % yield (Table 1, entry 1). When PhSeBr was used, however, the reaction did not proceed at all (Table 1, entry 2). The use of IDCP gave β-disaccharide **4** exclusively but only in 31 % yield (Table 1, entry 3), whereas the use of NIS–TfOH provided a mixture of β-disaccharide **4** and its α anomer in a 7:1 ratio and in 41 % yield (Table 1, entry 4). These results indicated that PhSeOTf is much more efficient and stereoselective than other known promoters for glycosylation when used in combination with **1**.



Scheme 2. Synthesis of 4,6-*O*-benzylidene mannosyl pentenoate **1**.

Table 1: Glycosylation with donor **1** using various promoters.

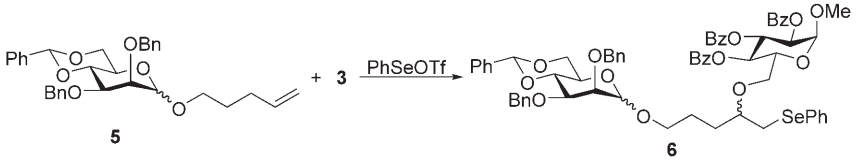


Entry	Promoter	Yield [%][a]	β/α[a]
1	PhSeOTf	90	β only
2	PhSeBr	0	–
3	IDCP	31	β only
4	NIS–TfOH	41	7:1[b]

[a] Determined after isolation of product. [b] Ratio was determined by ^{1}H NMR spectroscopy. Bz = benzoyl.

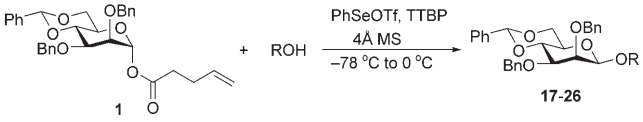
We also examined the glycosylation of **3** with 4-pentenyl 4,6-*O*- benzylidene mannoside **5** in order to compare the glycosyl 4-pentenoate with the well-known 4-pentenyl glycoside[13] as the glycosyl donor (Scheme 3). Reaction of pentenyl mannoside **5** and acceptor **3** in the presence of PhSeOTf, however, unexpectedly afforded a mixture of isomeric oxyselenides **6**, probably generated by addition of the alcohol **3** to the selenonium ion **A** (see Scheme 1).

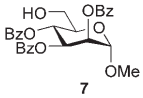
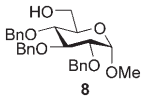
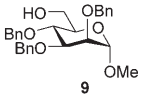
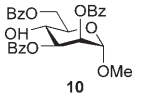
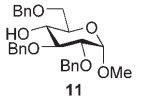
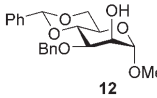
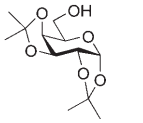
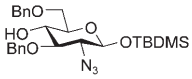
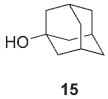
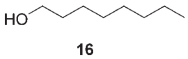
We used mannosyl pentenoate **1** and PhSeOTf to examine glycosylations of a number of other glycosyl acceptors (Table 2). Glycosylation was carried out with 5 equiv of PhSeBr and AgOTf in the presence of 4-Å molecular sieves (MS) and TTBP at −78 °C in CH_2Cl_2. Glycosylation proceeded smoothly with 1.5 or 2 equiv of PhSeBr and AgOTf, but 5 equiv of the



Scheme 3. Reaction of 4-pentenyl 4,6-*O*-benzylidene mannoside **5** as a donor with the acceptor **3**.

Table 2: Glycosylations of various acceptors **7–16** with donor **1** in CH_2Cl_2.



Entry	Glycosyl acceptor	Prod.	Yield [%][a,b]	β/α[a,b]
1		**17**	90 (87)	β only (β only)
2		**18**	88 (89)	β only (β only)
3		**19**	89 (87)	β only (β only)
4		**20**	87 (87)	β only (β only)
5		**21**	85 (85)	β only (β only)
6		**22**	90 (89)	17:1 (4:1)
7		**23**	82 (85) 86[c] 88[d]	β only (β only) 5.6:1[c] 2.1:1[d]
8		**24**	87	β only
9		**25**	89 (88)	β only (β only)
10		**26**	89 (89)	β only (β only)

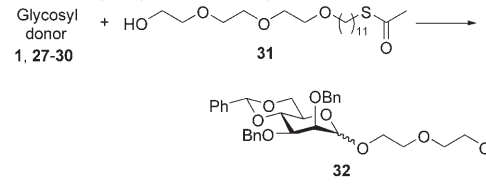
[a] Determined after isolation of product. [b] Yields and ratios in parentheses are those from reactions in toluene as a solvent. [c] The result by Crich's sulfoxide method, see Ref. [3e]. [d] The result with 3-*O*-allyl-2-*O*-benzyl-4,6-*O*-benzylidene mannopyranosyl trichloroacetimidate by Schmidt's method, see Ref. [5a]. TBDMS = *tert*-butyldimethylsilyl.

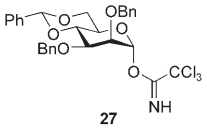
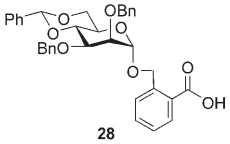
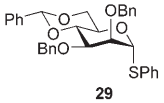
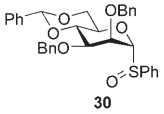
promoters guarantees high yield and stereoselectivity even when the promoter deteriorates slightly or the generation of PhSeOTf is incomplete. Although the glycosylation of various acceptors with **1** was so efficient that the glycosyl donor was consumed within 20 min at −78 °C based on TLC, the reaction mixture was further warmed to 0 °C to ensure completion of the reaction. Glycosylations of primary alcohol acceptors **7–9** with **1** afforded exclusively β-disaccharides **17–19** in high yields (Table 2, entries 1–3). The complete conversion of acceptors **10** and **11** to give the corresponding β-disaccharides **20** and **21** was also easily achieved (Table 2, entries 4 and 5). However, glycosylation of **12** gave a mixture of α- and β-disaccharide **22** (β/α = 17:1) in 90 % yield (Table 2, entry 6). Interestingly, diacetone galactose **13**, mannosylation of which is known to be less stereoselective than that of other glycosyl acceptors under Crich's sulfoxide conditions[3e] and Schmidt's tricholoroacetimidate conditions,[5a] reacted with **1** under the present conditions to afford β-disaccharide **23** exclusively in 82 % yield (Table 2, entry 7). Glycosylations of azido sugar **14**, hindered tertiary alcohol **15**, and the simple primary alcohol 1-octanol (**16**) also afforded only β-mannopyranosides in high yields (Table 2, entries 8–10). Moreover, toluene was also found to be a good solvent in the present PhSeOTf-mediated mannosylation method; the results with toluene were almost same as those with CH_2Cl_2 (Table 2) unlike the sulfoxide method for β-mannopyranosylation.[3a] The stereochemistries at newly generated anomeric centers of unknown disaccharides **19**, **20**, and **24** were determined unequivocally on the basis of ^1H and ^{13}C NMR spectroscopic data, in particular the C1′,H1′ coupling constants: $^1J(C1',H1') = 159.4$ Hz in compound **19**, $^1J(C1',H1') = 160.0$ Hz in compound **20**, and $^1J(C1',H1') = 160.8$ Hz in compound **24**.

Like Seeberger et al. indicated,[5c] we observed that the mannosylation of more reactive primary alcohol acceptors showed poorer β stereoselectivity with known 4,6-*O*-benzylidene-substituted mannosyl donors. Therefore, we investigated the efficiency of the present mannosyl pentenoate/PhSeOTf method for the preparation of β-mannopyranoside **32** (which we needed to make a self-assembled β-mannoside monolayer on a gold surface) from primary alcohol **31** and compared the results with those from other mannosylation methods (Table 3). The glycosylation of **31** with the pentenoate donor **1** afforded β-mannopyranoside **32** exclusively in 87 % yield (Table 3, entry 1). While the glycosylation with the trichloroacetimidate donor **27** gave a mixture of α- and β-mannopyranoside **32** (β/α = 2:1, $^1J(C1'\text{-}H1') = 161.8$ Hz for β-mannoside and $^1J(C1'\text{-}H1') = 169.6$ Hz for α-mannoside) in 85 % yield (Table 3, entry 2), the use of 2′-carboxybenzyl glycoside **28**[4] as the mannosyl donor provided the undesired α anomer of **32** as the major product in good yield (Table 3, entry 3). On the other hand, glycosylations with thioglycoside **29** and with glycosyl sulfoxide **30** as glycosyl donors afforded a mixture of α- and β-mannopyranoside **32** (β/α = 1:2 for **29**, 11:1 for **30**) in yields of 70 % and 81 %, respectively (Table 3, entries 4 and 5). Accordingly, the present method appears to be more efficient than other known methods for the β-mannosylation of simple primary alcohols.

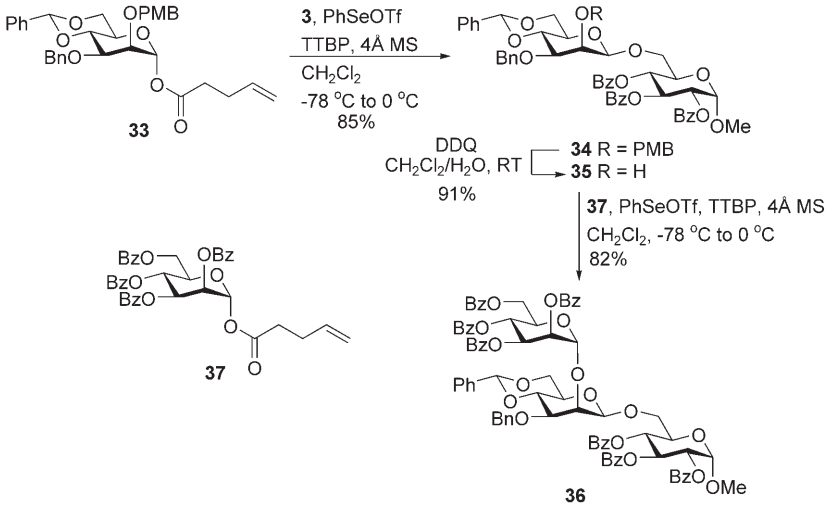
We applied this new glycosylation method to the synthesis of trisaccharide **36**, which has both α- and β-mannopyranosyl linkages, to show its effectiveness for oligosaccharide synthesis (Scheme 4). Mannosyl pentenoate donors **33** and **37** were readily prepared from D-mannose via the corresponding 1-hydroxy sugars (see the Supporting Information). Reaction of 4,6-*O*-benzylidene mannosyl donor **33** and acceptor **3** under the present glycosylation conditions using PhSeOTf afforded only β-disaccharide **34** in 85 % yield. Subsequent removal of the *p*-methoxybenzyl (PMB) group of **34** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave alcohol **35**. Glycosylation of the disaccharide **35** as an acceptor with benzoyl-protected mannosyl pentenoate **37** as a donor under

Table 3: Glycosylation of acceptor **31** with various donors, **1**, and **27–30**.



Entry	Glycosyl donor	Promoter	Yield [%][a]	β/α[a]	Reaction conditions
1	**1**	PhSeOTf TTBP	85	β only	Present work
2	 **27**	TMSOTf	87	2:1	Ref. [5a]
3	 **28**	Tf_2O DTBMP[b]	91	1:6	Ref. [4]
4	 **29**	BSP[c] Tf_2O TTBP	70	1:2	Ref. [3g]
5	 **30**	Tf_2O TTBP	81	11:1	Ref. [3b]

[a] Determined after isolation of product. [b] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine. [c] BSP = benzenesulfinylpiperidine. TMS = *tert*-butyldimethylsilyl.



Scheme 4. Synthesis of trisaccharide **36**.

the same reaction conditions smoothly provided the diastereomerically pure α-trisaccharide **36** in 82% yield.

In conclusion, we have described a highly reactive and stereoselective procedure for the β-mannopyranosylation employing 4,6-*O*-benzylidene mannopyranosyl pentenoate **1** and PhSeOTf. This method for the β-mannopyranosylation was found to be comparable to and even better than other known methods for the mannosylation of the simple reactive primary alcohol. The versatility of the present methodology was readily demonstrated by the efficient synthesis of trisaccharide **36**, which has both α- and β-mannopyranosyl linkages, with perfect stereoselectivity in high yields.

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[1] For selected reviews on glycosylation, see: a) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; b) P. Sinaÿ, *Pure Appl. Chem.* **1991**, *63*, 519–528; c) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531; d) G.-J. Boons, *Tetrahedron* **1996**, *52*, 1095–1121; e) B. G. Davis, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2137–2160; f) A. V. Demchenko, *Lett. Org. Chem.* **2005**, *2*, 580–589.

[2] For selected reviews on β-mannosylation, see: a) H. Paulsen, *Angew. Chem.* **1982**, *94*, 184–201; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155–173; b) F. Barresi, O. Hindsgaul in *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood , Amsterdam, **1996**, pp. 251–276; c) V. Pozsgay in *Carbohydrates in Chemistry and Biology, Vol. 1* (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, **2000**, pp. 319–343; d) J. J. Gridley, H. M. I. Osborn, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1471–1491; e) A. V. Demchenko, *Synlett* **2003**, 1225–1240.

[3] a) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506–4507; b) D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198–1199; c) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223; d) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1998**, *120*, 435–436; e) D. Crich, S. Sun, *Tetrahedron* **1998**, *54*, 8321–8348; f) D. Crich, W. Cai, Z. Dai, *J. Org. Chem.* **2000**, *65*, 1291–1297; g) D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.

[4] K. S. Kim, J. H. Kim, Y. J. Lee, Y. J. Lee, J. Park, *J. Am. Chem. Soc.* **2001**, *123*, 8477–8481.

[5] a) R. Weingart, R. R. Schmidt, *Tetrahedron Lett.* **2000**, *41*, 8753–8758; b) S.-i. Tanaka, M. Takashina, H. Tokimoto, Y. Fujimoto, K. Tanaka, K. Fukase, *Synlett* **2005**, 2325–2328; c) J. D. C. Codée, L. H. Hossain, P. H. Seeberger, *Org. Lett.* **2005**, *7*, 3251–3254.

[6] a) A. A. H. Abdel-Rahman, E. Jonke, E. S. H. El Ashry, R. R. Schmidt, *Angew. Chem.* **2002**, *114*, 3100–3103; *Angew. Chem. Int. Ed.* **2002**, *41*, 2972–2974; b) D. Crich, P. Jayalath, *Org. Lett.* **2005**, *7*, 2277–2280; c) D. Crich, P. Jayalath, T. K. Hutton, *J. Org. Chem.* **2006**, *71*, 3064–3070.

[7] For examples, see: Refs. [3e,g,4,5a].

[8] H. Kunz, P. Wernig, M. Schultz, *Synlett* **1990**, 631–632.

[9] J. C. Lopez, B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.* **1991**, 159–161.

[10] 3-*n*-Pentenoyl glycals were used for the synthesis of 2,3-unsaturated disaccharides: a) J. C. Lopez, B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.* **1992**, 94–96; b) J. C. Lopez, A. M.

Gomez, S. Valverde, B. Fraser-Reid, *J. Org. Chem.* **1995**, *60*, 3851 – 3858.
[11] K. Ikeda, J. Fukuyo, K. Sato, M. Sato, *Chem. Pharm. Bull.* **2005**, *53*, 1490 – 1493.
[12] D. Crich, M. Smith, Q. Tao, J. Picione, *Synthesis* **2001**, 323 – 326.
[13] For reviews, see: a) B. Fraser-Reid, U. E. Udodong, Z. Wu, H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts, R. Madsen, *Synlett* **1992**, 927 – 942; b) B. Fraser-Reid, R. Madsen in *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1997**, pp. 339 – 356.

