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Efficient Installation of β-Mannosides Using a Dehydrative Coupling Strategy

Jeroen D. C. Codée, Laila H. Hossain, and Peter H. Seeberger*

Laboratorium für Organische Chemie, ETH Zürich, Wolfgang-Pauli Strasse 10, 8093 Zürich, Switzerland

seeberger@org.chem.ethz.ch

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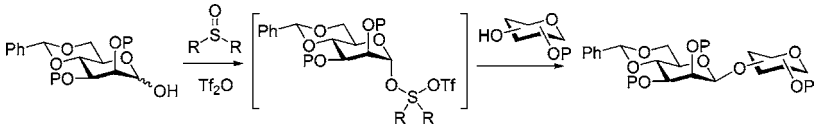
ABSTRACT



A new coupling procedure for the construction of the challenging β-mannosidic bond is described. Dehydrative mannosylation using 4,6-*O*-benzylidene mannopyranoses allows for the formation of β-mannosides in excellent yield. The stereoselectivity is generally good but influenced by the exact nature of the glycosylating agent and the nucleophile.

The development of efficient glycosylation methods is crucial for further advances in the rapid assembly of complex carbohydrates, particularly by automated solid-phase synthesis.[1] The stereoselective formation of 1,2-*cis*-glycosidic bonds still presents a major challenge in contemporary carbohydrate research.[2] This holds especially true for the β-mannose linkage, which is present in many biologically relevant oligosaccharides and glycoconjugates, including the N-linked core pentasaccharide[3] common to all N-linked glycoproteins.

Crich and co-workers developed several highly stereoselective β-mannosylation protocols based on the generation of α-mannosyl triflates from mannosyl sulfoxides or thiomannosides, a breakthrough in β-mannoside synthesis.[4] However, the immense reactivity of the anomeric triflates renders them too hydrolytically and thermally unstable for manipulation during automated synthesis.[5] In addition, electrophilic side products that can interfere with the integrity of the pentenol-linker system, often applied in solid-phase assembly, are generated during coupling.[6] To extend the repertoire of complex carbohydrates accessible with the automated oligosaccharide synthesizer, we set out to develop efficient glycosylation methods for the construction of the β-mannosidic bond employing monomeric building blocks compatible with the solid-phase format. Our attention was focused on the use of 4,6-*O*-benzylidene mannopyranoses for the synthesis of β-mannosides. Activation of 1-hydroxyl sugars can be readily achieved by a combination of a sulfoxide reagent such as diphenyl sulfoxide and trifluoromethane sulfonic anhydride[7] to provide an anomeric sulfonium triflate as the actual glycosylating species (Scheme 1). These sulfonium triflates should be more stable than their anomeric triflate counterparts as reflected by the higher reaction temperatures and longer reaction times required for glycosylations involving these species. A productive dehydrative condensation regenerates the starting sulfoxide with concomitant formation of triflic acid, which can be scavenged by an appropriate nonnucleophilic base.[8] The dehydrative protocol presents an efficient glycosylation method, but thus far it has found little application in the synthesis of complex

(1) (a) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523. (b) Seeberger, P. H.; Haasse, W. C. *Chem. Rev.* **2000**, *100*, 4339.

(2) Demchenko, A. V. *Synlett* **2003**, 1225.

(3) For a previous automated solid-phase assembly using a β-mannosidic dimer building block, see: (a) Ratner, D. M.; Swanson, E. R.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4717. (b) Wu, X.; Grathwohl, M.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4489.

(4) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435. (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321. (c) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. (d) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 667.

(5) For these reasons, Crich and Smith developed a donor-bound polymer-supported strategy for the synthesis of β-mannosides: Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867.

(6) (a) Codée, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057. (b) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081.

(7) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

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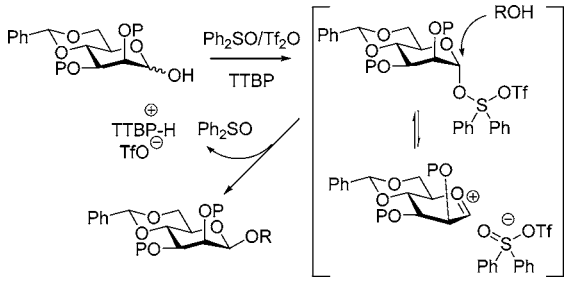
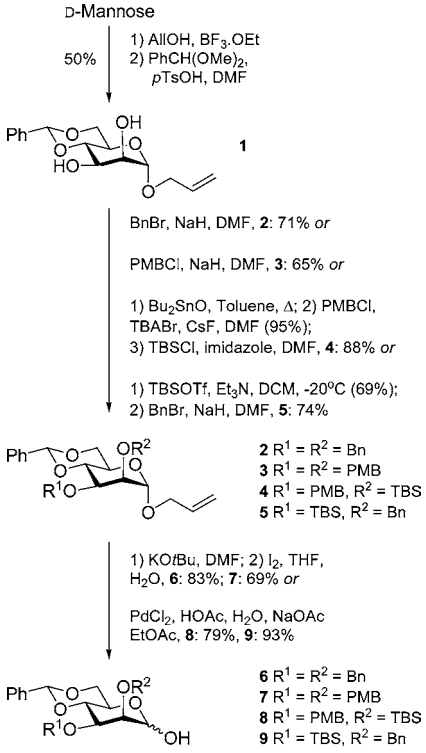
Scheme 1. Putative Mechanism of Dehydrative Mannosylations



oligosaccharides.[9] No detailed studies on the stereoselectivity of Ph_2SO/Tf_2O-mediated glycosylations have been reported. Here we present the use of the dehydrative glycosylation protocol for the solution-phase synthesis of β-mannosides.

To explore the scope and limitations of the dehydrative β-mannosylation protocol, we initially synthesized a set of 1-hydroxyl mannosides **6**−**9** (Scheme 2). Starting from 1-*O*-allyl-4,6-*O*-benzylidene-α-D-mannose **1**, building blocks **6** and **7** were readily obtained by (*p*-methoxy)benzylation, KO*t*Bu-induced allyl isomerization, and subsequent cleavage of the resulting enol ether by treatment with iodine. Selective protection of the C-4 hydroxyl group in **1** was effected by the formation of the dibutyltinketal that was reacted regioselectively with (*p*-methoxy)benzyl chloride to provide mannoside **4** after silylation of the remaining alcohol. Direct silylation of **1** and benzylation gave fully protected mannose **5**. The anomeric hydroxyl groups in **4** and **5** were exposed under the aegis of $PdCl_2$ in $HOAc/H_2O$ to furnish mannosides **8** and **9**.

Scheme 2. Synthesis of Differentially Protected 1-Hydroxyl Mannoses **6**−**9**



The sulfoxide/Tf_2O-mediated dehydrative condensations (Table 1) proceeded in excellent yield, with moderate to very good β-selectivities. The stereoselectivity of the condensation of 2,3-dibenzylated mannosides **6** and **7** with a variety of secondary hydroxyl acceptors (entries 1−5) remains good at temperatures as high as −25 °C.[10] The condensation of 1-hydroxyl mannoside **7** with thiomannoside **15** allowed for efficient access to the β-linked thiodisaccharide **16**, which can be used immediately in the next glycosylation.[11] For example, dimer **16** can find application in the assembly of (1→2)-linked β-mannans.[12] The use of more reactive primary hydroxyl nucleophiles such as *n*-pentenol and 1,2:3,4-diacetone galactose **23** leads to erosion in selectivity (entries 7 and 8). The pentenol moiety is stable under the condensation conditions (entries 6 and 7).

To enhance the β-selectivity for mannosylations involving **23**, we aimed to favor formation of the anomeric sulfoxonium triflate, or a close ion pair, over the generation of the promiscuous oxacarbenium ion by the use of a more apolar solvent system (toluene/CH_2Cl_2 5:1). Unfortunately, the solvent change did not have the desired effect (entry 8b). Tuning of the sulfoxide reagent by increasing the electron density on the sulfur atom of the anomeric sulfonium triflate should stabilize this glycosylating agent and shift the equilibrium between the covalent sulfonium triflate and the oxacarbenium ion toward the covalent bond.[13] However, no change in selectivity was observed when ditolyl sulfoxide was employed in combination with Tf_2O (entry 8c). Additionally, the use of BSP/Tf_2O[4c] also proved to be futile.

In line with the findings of Crich,[14] we observed that the use of 3-*O*-TBS-protected mannoside **9** completely eroded the stereoselectivity of the condensation. Also, no beneficial change in the stereochemical outcome of this reaction was observed by either lowering the reaction temperature or changing the polarity of the solvent.[15]

The last entry shows the use of a 1-hydroxyl mannose donor with a TBS group at the C-2 hydroxyl. As a result of

(8) In this work, tri-*tert*-butylpyrimidine (TTBP) was used as a nonnucleophilic base. Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.

(9) Gin's dehydrative glycosylation methodology has recently been employed in the synthesis of the complex triterpene glycoside QS-21A (Wang, P.; Kim, Y.-J.; Navarro-Villalobos, M.; Rohde, B. D.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 3256) and in the assembly of heparin oligosaccharides (Codée, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767).

(10) Condensations were started at this temperature and then allowed to warm slowly to room temperature. No fine-tuning of the reaction temperature has been investigated. It is clear, however, that relatively high reaction temperatures are tolerated by the reported glycosylation system.

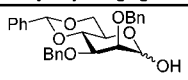
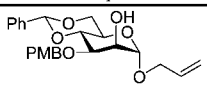
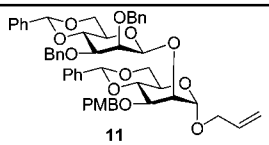
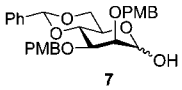
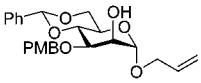
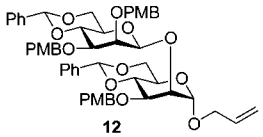
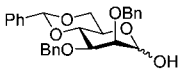
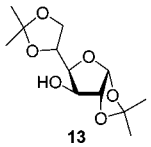
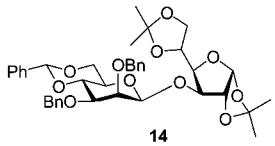
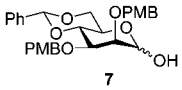
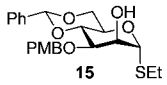
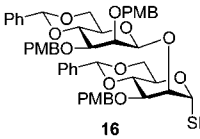
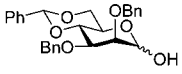
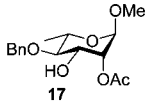
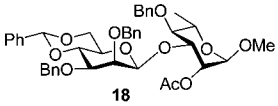
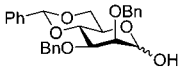
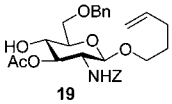
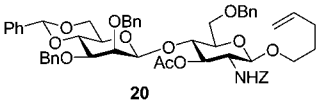
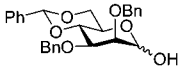
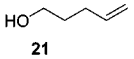
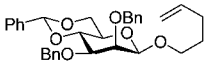
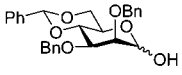
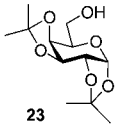
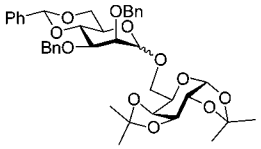
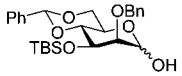
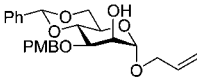
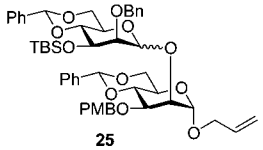
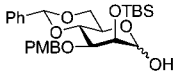
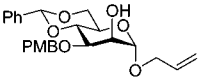
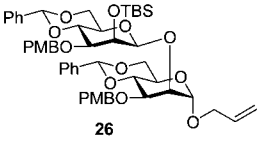
(11) Codée, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947.

(12) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930.

(13) For tuning of the sulfoxide reagent in dehydrative sialylations, see: Haberman, J.; Gin, D. Y. *Org. Lett.* **2003**, *5*, 2539.

(14) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643.

Table 1. Dehydrative β-Mannosylations

Entry	Glycosylating agent	Nucleophile	Conditions	Product[b]	Yield (β/α)[c]
1	 **6**	 **10**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **11**	81% (>9:1)
2	 **7**	 **10**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **12**	70% (>9:1)
3	 **6**	 **13**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **14**	95% (>9:1)
4	 **7**	 **15**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **16**	67% (>9:1)
5	 **6**	 **17**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **18**	90% (3.5:1)
6	 **6**	 **19**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **20**	80% (2.5:1)
7	 **6**	 **21**	Ph_2SO, Tf_2O, TTBP DCM, -50°C to rt	 **22**	81% (3:1)
8a	 **6**	 **23**	Ph_2SO, Tf_2O, TTBP DCM, -50°C to rt	 **24**	89% (3:1)
8b			Ph_2SO, Tf_2O, TTBP Toluene/DCM 5:1, -50°C to rt		97% (3:2)
8c			$(tol)_2SO$, Tf_2O, TTBP DCM, -50°C to rt		91% (3:1)
8d			BSP, Tf_2O, TTBP DCM, -50°C to rt		52% (3:2)
9a	 **9**	 **10**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **25**	92% (3:2)
9b			Ph_2SO, Tf_2O, TTBP DCM, -50°C to rt		88% (3:2)
9c			Ph_2SO, Tf_2O, TTBP Toluene/DCM 5:1 -50°C to rt		82% (2:3)
10	 **8**	 **10**	Ph_2SO, Tf_2O, TTBP DCM, -25°C to rt	 **26**	79% (4:1)

[a] Typically, the glycosylating agent (1.5 equiv) was preactivated by sulfoxide (3 equiv)/Tf_2O (1.5 equiv) in the presence of TTBP (3.75 equiv) at −40 to −20 °C before addition of the acceptor glycoside (1 equiv). [b] Anomeric configurations were assigned on the basis of the very characteristic mannose H-5 shift.[4] [c] Ratios of >9:1 are conservative minima; no α-product was isolated.

the steric bulk of this protecting group, the stereoselectivity is somewhat impaired when compared to the 2-*O*-benzyl case, while the yield was unaffected.

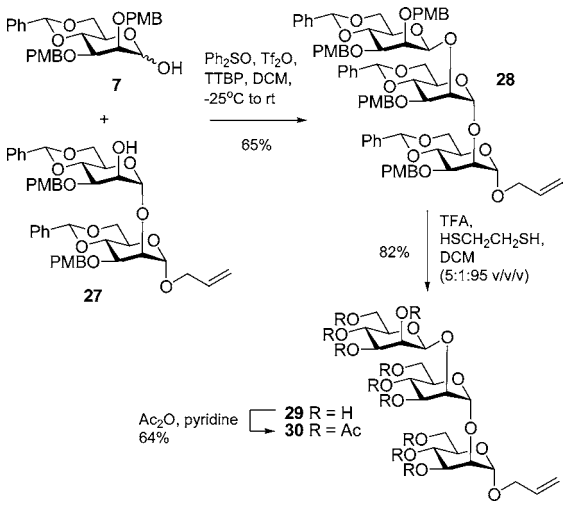
The repeating trimannoside **29** of the O5 antigen of the opportunistic gram-negative pathogen *Klebsiella*[16] was assembled by the new method. The mild conditions employed

to induce glycosylation makes it possible to utilize acid-labile protecting groups such as benzylidene acetals and PMB ethers throughout the synthesis. Global deprotection can be readily achieved at the final stage of the synthesis by mild acidolysis, thereby obviating the need for heterogeneous catalysis or Birch reduction. This protecting group strategy can present a significant advantage in future solid-phase oligosaccharide assembly.

Thus, the β-(1→2)-mannosidic bond in **28** was stereoselectively installed by Ph_2SO/Tf_2O-mediated dehydrative condensation of glycosylating agent **7** and dimannoside **27** (Scheme 3). Deprotection of the three benzylidene acetals and four PMB-ethers was then readily effected by treatment of **28** with 5% TFA in CH_2Cl_2, in the presence of 1,2-ethanedithiol as a cation scavenger, to provide the target trisaccharide in good yield. Transformation of **29** into deca-*O*-acetate **30** simplified purification and characterization.

In conclusion, we have shown that the challenging β-mannosidic linkage can be efficiently installed using a dehydrative glycosylation protocol. Secondary alcohol nucleophiles showed good to excellent selectivities. Mannosylation of reactive primary alcohols on the other hand proceeded only with moderate selectivity. The effects of protecting groups in the glycosylation agent parallel those observed for Crich's thioglycoside/glycosyl sulfoxide method. Finally, the dehydrative glycosylation method is compatible with *n*-pentenol functional groups, a key feature in anticipation of automated solid-phase oligosaccharide assembly. The global use of acid-labile protecting groups throughout the construction of the oligosaccharides is also significant in the context of the overall efficiency of oligosaccharide preparation.

Scheme 3. Assembly of a Trimannoside Antigen of *Klebsiella*[a]



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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The Crich laborarory recently employed the 2-*O*-propargyl ether as a minimally intrusive protecting group to overcome this poor selectivity: Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277.

(16) Griffiths, A, J.; Davies, D. B. *Carbohydr. Polym.* **1991**, *14*, 241.