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Formation of β-Glucosamine and β-Mannose Linkages Using Glycosyl Phosphates

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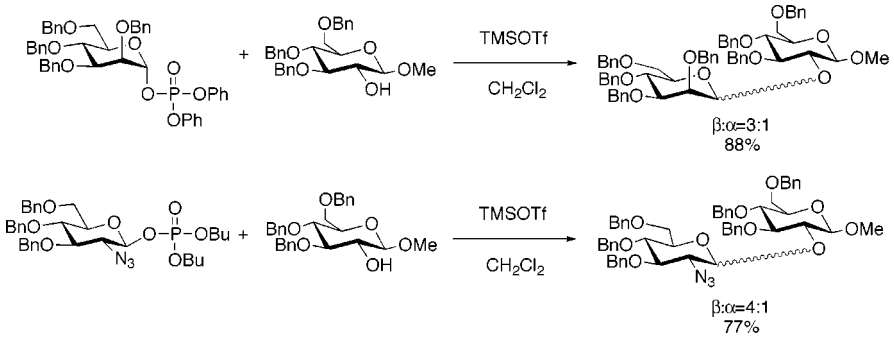
ABSTRACT



Glycosyl phosphates were examined for their utility in the synthesis of challenging glycosidic linkages. β-Glucosamine glycosides were formed preferentially and in good yield. β-Mannosides were constructed in high overall yield with modest anomeric selectivity. Interesting solvent and conformational influences on the stereochemical outcome of the coupling reactions were observed.

The biological importance of carbohydrates and glycosylated natural products[1] has resulted in an increased focus on the development of synthetic methods for the procurement of pure oligosaccharides and glycoconjugates. The selective and efficient installation of a variety of glycosidic linkages poses a major challenge for synthetic chemists. Much effort has been devoted to the development of glycosylation reactions to facilitate access to synthetic carbohydrate structures.[2] While many glycosidic linkages are now relatively straightforward to create, access to some glycosidic bonds remains difficult. Complete stereoselectivity of *trans*-glycosidic bond formation commonly relies on participating groups in the C2 position. The installation of *cis*-glycosidic linkages where participation is not feasible or *trans*-linkages in which a nonparticipating C2 group is desired is more difficult to control.

In nature, 2-amino glycosides are frequently encountered (e.g., *N*-linked glycoproteins and blood group determinants).[3] The construction of 2-amino β-glycosides commonly relies on the *N*-phthalimido functionality as a C2 participating group.[4] Due to difficulty of removing the *N*-phthalimide group, several other amine protecting groups have been investigated. Azides represent an attractive class of protecting groups since they are easily installed and removed.[5,6] Furthermore, the lack of anchimeric assistance in C2 azido donors could lead to glycosylating agents capable of constructing either *cis*- or *trans*-glycosides. Currently, there are few methods available for stereospecific glycosylation using C2 azido donors.

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(2) For a review, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(3) Hakomori, S.; Yongmin, Z. *Chem. Biol.* **1997**, *4*, 97.

(4) For a review, see: Debendham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann./Recueil* **1997**, 791.

(5) (a) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029. (b) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073. (c) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.

(6) Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580.

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cis-Glycosidic β-mannosides are another class of glycosides commonly found in nature as part of the core region of *N*-linked glycoproteins.[7] Steric inaccessibility of the β-face of mannose due to the C2 axial substituent combined with the anomeric effect favoring the thermodynamically more stable α-anomer render this type of linkage one of the most difficult to construct. Several approaches to the synthesis of β-mannosides have been reported.[8] Direct couplings using mannosyl donors resulted in preferential formation of β-glycosides only under heterogeneous conditions.[9] Glycosylations utilizing an intramolecular tether directly afforded the β-mannosidic linkage by acceptor delivery to the top face of the pyranose ring but necessitate multistep synthetic procedures.[10] More recently, conformationally constrained mannosyl donors have been shown to give high β-selectivity.[11]

Glycosyl phosphates showed high β-selectivity in glycosylations even when a nonparticipating group was present in the C2 position.[12,13] Encouraged by these findings, we investigated protocols for the formation of β-mannosidic and β-2-amino glucosidic linkages employing glycosyl phosphates.

A set of differentially protected glycosyl phosphates **1**−**4** (Figure 1) served as glycosylating agents in the coupling

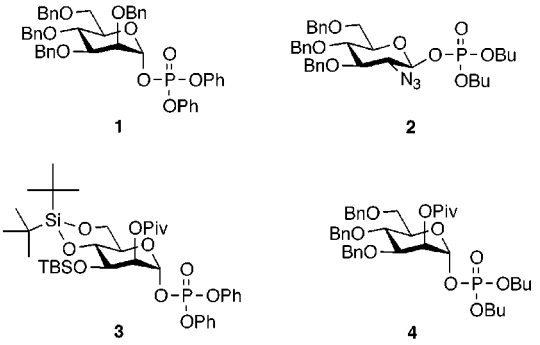


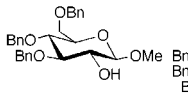
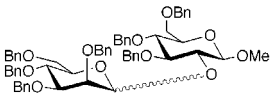
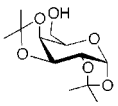
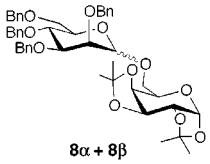
Figure 1. Phosphate-based glycosyl donors.

studies.[14] These donors were prepared either by reaction of the corresponding lactol precursors with a chlorophosphate[15] or by reaction of dibutyl phosphate with the corresponding 1,2 anhydro sugar.[16]

Initially, the direct formation of β-mannosidic linkages using a nonconstrained glycosyl donor and different acceptors was explored. Tetra-*O*-benzyl mannosyl phosphate **1** served as donor in glycosylation reactions with monosaccharide acceptors **5** and **7**. Activation of **1** by TMSOTf at −78 °C resulted in rapid glycosylation of the hindered acceptor **5** to furnish disaccharide **6**. Reaction with primary galactose acceptor **7** afforded disaccharide **8**. The selectivity of the glycosylation reactions was strongly dependent on two factors: the nature of the glycosyl acceptor and the solvent used for the coupling reaction. In dichloromethane, the desired β-mannoside **6**β was preferentially formed (β: α = 3:1). When the less hindered C6 hydroxyl group of galactose **7** served as an acceptor, the α-linked disaccharide **8**α was obtained as the main product (β: α = 1:1.6). In accordance with prior results, the configuration of the acceptor moeity was found to greatly influence the stereochemical outcome of glycosylation.[17]

A dramatic solvent effect was observed when the reaction was carried out in acetonitrile.[18] The selectivity of the coupling reaction between donor **1** and acceptor **5** was completely reversed in acetonitrile as disaccharide **6**α was preferentially obtained (β: α = 1:5.5) (Table 1). Even for

Table 1. Formation of α- and β-Mannosides Using Phosphate **1**

glycosyl acceptor	product	solvent	yield	α:β
		CH_2Cl_2	88	1:3.0
		CH_3CN[a]	83	5.5:1
5	**6α + 6β**			
		CH_2Cl_2	62	1.6:1
		CH_3CN[a]	80	2.9:1
7	**8α + 8β**			

Glycosylations were carried out with 1.2 equiv donor, 1.0 equiv acceptor and 1.3 equiv TMSOTf in dichloromethane at -78°C. [a]Reaction was carried out at -40°C.

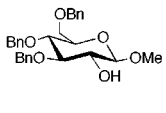
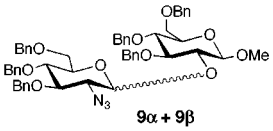
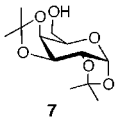
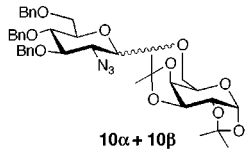
the coupling of the less hindered acceptor **7**, enhanced α-selectivity was observed in acetonitrile (β: α = 1:2.9).[19] These experimental results may be rationalized by the initial formation of either an anomeric α-triflate or a close ion pair followed by S_N2-type displacement by the acceptor nucleophile to yield a β-disaccharide. Crich and co-workers reported the existence of an α-triflate when glycosyl sulfoxides were activated by triflic anhydride.[17b,c] In a participating solvent such as acetonitrile, either a double displacement of the initial anomeric triflate may occur or the close ion pair may be

(7) Merritt, J. R.; Naisang, E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4443.
(8) For a review ,see: Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471.
(9) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102.
(10) (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376. (b) Stork, G.; Guncheol, K. *J. Am. Chem. Soc.* **1992**, *114*, 1087.
(11) Crich, D.; Sanxing, S. *Tetrahedron* **1998**, *54*, 8321.
(12) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211.
(13) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, *11*, 685.
(14) For the synthesis of **1**, see: Sabesan, S.; Niera, S. *Carbohydr. Res.* **1992**, *223*, 169. For the synthesis of **2**-**4**, see Supporting Information.
(15) Inagem, M.; Chaki, H.; Kusumoto, S.; Shiba, T. *Chem.Lett.* **1982**, 1281.
(16) Du, Y.; Kong, F. *J. Carbohydr. Chem.* **1995**, *14*, 341.
(17) (a) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180. (b) Crich, D.; Sanxing, S. *J. Am. Chem. Soc.* **1998**, *120*, 435. (c) Crich, D.; Weiling, C. *J. Org. Chem.* **1999**, *64*, 4926.
(18) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141.
(19) Wulff, G.; Rohle, G. *Angew. Chem.* **1974**, *86*, 173.

disrupted, thus resulting in the preferential formation of the α-disaccharide.[20] Efforts to obtain direct experimental evidence for the formation of a triflate intermediate by low-temperature NMR spectroscopy are in progress.

The influence of a nonparticipating, equatorial substituent on the selectivity of glycosylation reactions was examined by using C2 azido glycosyl phosphate donors. Activation of glycosyl donor **2** with TMSOTf required higher temperatures (−40 °C) and longer reaction times (2 h) than those for mannose donor **1** (Table 2). Coupling of **2** to methyl

Table 2. Formation of α- and *β*-2-Azido Glucosides Using Phosphate **2**

glycosyl acceptor	product	solvent	yield	α:β
 **5**	 **9α + 9β**	CH_2Cl_2	77	1:4
		CH_3CN	61	1:4
 **7**	 **10α + 10β**	CH_2Cl_2	60	1:5
		CH_3CN	60	1:5

Glycosylations were carried out with 1.2 equiv donor, 1.0 equiv acceptor and 1.3 equiv TMSOTf at -40°C.

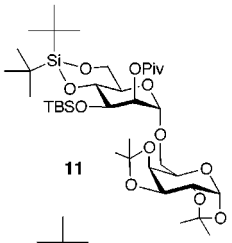
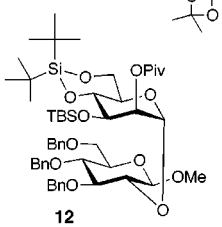
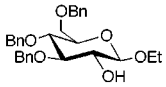
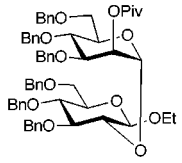
glycoside **5** resulted preferentially in the formation of *β*-linked disaccharide **9***β* in both dichloromethane and acetonitrile (*β*: α = 4:1). A strong preference for the formation of the *β*-anomer (*β*: α = 5:1) was again obtained upon reaction of **2** with primary galactose acceptor **7**, resulting in a mixture of disaccharides **10**α and **10***β*. Interestingly, no solvent effect for couplings involving C2 azide donor **2** was observed.

Finally, we explored the use of mannosyl phosphates **3** and **4** for the formation of α-mannosidic linkages. In all cases, only the desired α-isomer was obtained by virtue of the participating pivaloyl group as expected.[21] The reactions were high-yielding, fast, and completely selective (Table 3).

In summary, we have described glycosyl phosphates as useful donors in the synthesis of the challenging *β*-mannosidic and *β*-2-amino glucosidic linkages. Anomeric phosphates can be readily installed, require short reaction times, and are compatible with a variety of protecting groups. The stereoselectivity of the glycosylations involving mannosyl phosphates is strongly influenced by solvent effects and by the steric nature of the acceptor nucleophile. Investigations

(20) Waldmann, H.; Bohm, G.; Schmid, U.; Rottele, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1944.
(21) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647.

Table 3. Synthesis of α-Mannosides Using Glycosyl Phosphate Donors

donor	acceptor	product	yield
3	**7**	 **11**	85%
3	**5**	 **12**	75%
4	 **13**	 **14**	82%

Glycosylations were carried out with 1.2 equiv donor, 1.0 equiv acceptor and 1.3 equiv TMSOTf at -78° → -50°C in CH_2Cl_2.

into the mechanism of glycosyl phosphates activated by TMSOTf are underway and should allow for further modification of the selectivity and potency of these donors.

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Note Added in Proof: This Letter was inadvertantly released ASAP on 11/10/00 before a final correction was made. The last line of the first paragraph on the third page should read “temperature NMR spectroscopy are in progress”. The print and final Web version are correct.

Supporting Information Available: One additional scheme along with detailed experimental procedures and compound characterization data, including ^{1}H, ^{13}C, and ^{31}P NMR spectral data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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