ORGANIC LETTERS

2002
Vol. 4, No. 16
2751−2754

Linker Influence on the Stereochemical Outcome of Glycosylations Utilizing Solid Support-Bound Glycosyl Phosphates

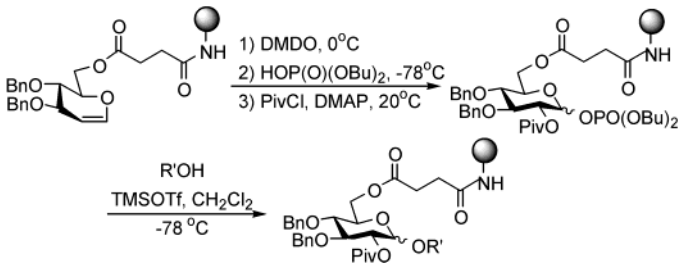
Diana K. Hunt and Peter H. Seeberger*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

seeberg@mit.edu

Received June 1, 2002

ABSTRACT



Glycosyl phosphates can be readily accessed on a solid support via a three-step procedure from support-bound glycals. These resin-bound glycosyl phosphates were successfully used as glycosylating agents for coupling with a series of nucleophiles. The stereochemical outcome of disaccharide formation was dependent on the nature of the linker connecting the saccharide to the polymer. Interestingly, other glycosyl donors such as thioglycosides and trichloroacetimidates did not exhibit such a dependence, indicating a different reaction mechanism for glycosylation.

Different strategies for the assembly of oligosaccharides on polymeric supports have recently received much attention.[1] The solid-phase approach is attractive due to increased yields resulting from the use of excess reagents and the ease of product purification. Recent success with automated solid-phase oligosaccharide synthesis offers additional benefits.[2]

Polymer-supported oligosaccharide synthesis may be approached from two different directions: linker attachment at the reducing end resulting in an immobilized acceptor or attachment at a "nonreducing" position providing a resin-bound glycosyl donor.[1,2a,3] Although the acceptor-bound method is most commonly employed, a variety of polymer-supported glycosyl donors have been explored. Effective glycosylations with resin-bound glycosyl fluorides, trichloroacetimidates, thioglycosides, and glycals have been demonstrated, whereby the latter two methods provided the best yields and purity.[3,4]

Glycosyl phosphates have proven to be competent donors that couple rapidly and in high yield in solution and in acceptor-bound glycosylations.[5] On the basis of the synthesis

(1) (a) *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Seeberger, P. H., Ed.; Wiley: New York, 2001. For recent reviews, see: (b) Ito, Y.; Manabe, S. *Curr. Opin. Chem. Biol.* **1998**, *2*, 701−708. (c) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349−4393.

(2) (a) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523−1527. (b) Sears, P.; Wong, C. H. *Science* **2001**, *291*, 2344−2350.

(3) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685−695.

(4) (a) Doi, T.; Sugiki, M.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2141−2144. (b) Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1997**, *119*, 5562−5566. (c) Kononov, L. O.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1997**, *38*, 1599−1602. (d) Manabe, S.; Ito, Y. *Chem. Pharm. Bull.* **2001**, *49*, 1234−1235. (e) Zhu, T.; Boons, G.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1898−1900.

10.1021/ol026276o CCC: $22.00
Published on Web 07/09/2002

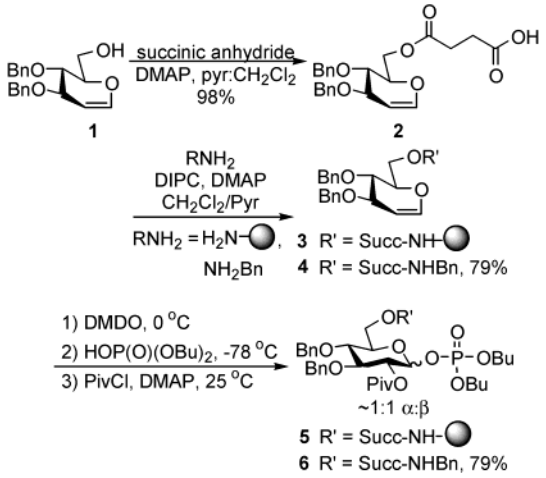
of glycosyl phosphates from glycals, an efficient route to resin-bound glycosyl phosphates was envisioned.[3,5]

Choice of an appropriate linker is an important consideration for any polymer-supported synthesis. The linker should be inert to all required manipulations, yet easily installed and readily cleaved to release the product. Donor-bound strategies have employed a variety of linkers, including trialkylsilyl[3,4a] and *p*-alkoxybenzyl[4b,d] groups, as well as base-labile succinic ester[4c] and succinamyl[4e] linkers.

Here, we report the synthesis and use of polymer-bound glycosyl phosphates for oligosaccharide synthesis. The nature of the linker was observed to have a profound influence on the stereochemical outcome of the glycosylation reactions. This dependence was found to stand in stark contrast to glycosylations involving other commonly used glycosyl donors such as glycosyl trichloroacetimidates and thioglycosides.

Glycal **1** was equipped on the C6 hydroxyl group with a base-labile[4e,6] succinate linker to furnish **2**. Immobilization of **2** on aminomethyl polystyrene provided resin-bound glycal **3**. Coupling of **2** with benzylamine provided solution-phase model **4** to facilitate reaction analysis (Scheme 1).

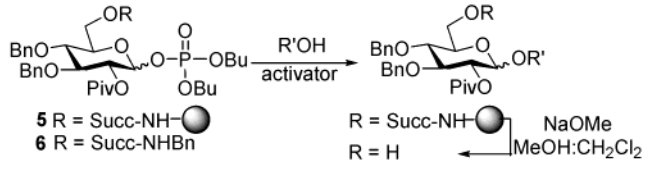
Scheme 1. Synthesis of Resin-Bound and Solution-Phase Model Glycosyl Phosphate Donor with a Succinamyl Linker

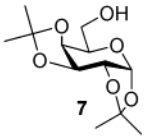
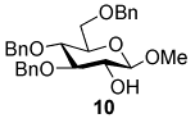
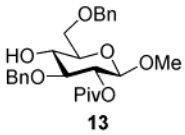


A three-step, one-pot procedure we had previously developed[5] for access to glycosyl phosphates provided **6** from **4** in excellent yield. The sequence of epoxidation with dimethyldioxirane (DMDO) followed by treatment with a phosphoric acid diester and pivaloylation was readily adapted to the synthesis of resin-bound glycosyl phosphate **5** (Scheme 1). A 1:1 mixture of α- and *β*-glycosyl phosphates in solution and on a solid support was observed by ^{31}P NMR and high-resolution magic angle spinning (HR-MAS) ^{31}P NMR.

With glycosyl phosphate **5** in hand, activation of the support-bound donor for union with a series of nucleophiles was explored. Coupling with glycosyl acceptors **7**, **10**, and **13**, exhibiting C6, C2, and C4 hydroxyl groups, respectively, followed by cleavage from the resin with sodium methoxide provided disaccharides **8**, **11**, and **14**, respectively (Table 1).

Table 1. Disaccharide Synthesis Using Resin-Bound Phosphates and a Solution-Phase Model with a Succinamyl Linker



donor	R'OH	product	R	yield (%, α:β)
5	 7	8	H	58%, α:β 1:2.2[a]
6		9	Succ-NHBn	85%, α:β 1:4[b]
5	 10	11	H	26%, α:β 1:2[a]
6		12	Succ-NHBn	98%, α:β 1:1.1[c] (38%, α:β 1:1.4)[b]
5	 13	14	H	27%, α:β 1:1.7[d]
6		15	Succ-NHBn	80% , α:β 1.1:1[c]

[a] Resin-bound phosphate **5** (1.0 equiv) was swelled in CH_2Cl_2; R′OH (2.5−6.5 equiv) was added, followed by TMSOTf (1.1 equiv) at −15 °C, and the reaction was shaken for 2 h. The procedure was repeated twice. [b] Phosphate **6** (1.1 equiv) and R′OH (1.0 equiv) were dissolved in CH_2Cl_2; TMSOTf (1.3 equiv) was added at −78 °C and the reaction warmed to −10 °C over 2 h. [c] Phosphate **6** (1.1 equiv) and R′OH (1.0 equiv) were dissolved in CH_2Cl_2, and TMSOTf (1.3 equiv) was added at −78 °C, followed by another 1.3 equiv of activator after warming to −30 °C over 1 h. [d] Resin-bound phosphate **5** (1.0 equiv) was swelled in CH_2Cl_2; R′OH (2.0 equiv) was added, followed by slow warming from −78 °C with addition of 3 × 1.1 equiv of TMSOTf added on 1 h delays at −78, −30, and −10 °C.

Surprisingly, despite the presence of a pivaloyl ester at C2, the resulting disaccharides were obtained as anomeric mixtures (Table 1). Solution-phase couplings employing glycosyl phosphate **6** and acceptors **7**, **10**, and **13** also produced anomeric mixtures, suggesting that the nature of the linker was responsible for these unexpected results (Table 1).

Previous work, including couplings with glycosyl phosphates containing a 6-*O*-levulinate ester, had not indicated any interference of the C6 hydroxyl protecting group with the anomeric selectivity.[2a,5b] On the basis of these considerations, a levulinate-type linker was not expected to erode the stereoselectivity of the glycosylations, while hydrazine cleavage would allow rapid removal of the products from the resin under nonbasic conditions. A 3-benzoylpropionic ester linker, previously utilized at the anomeric position for

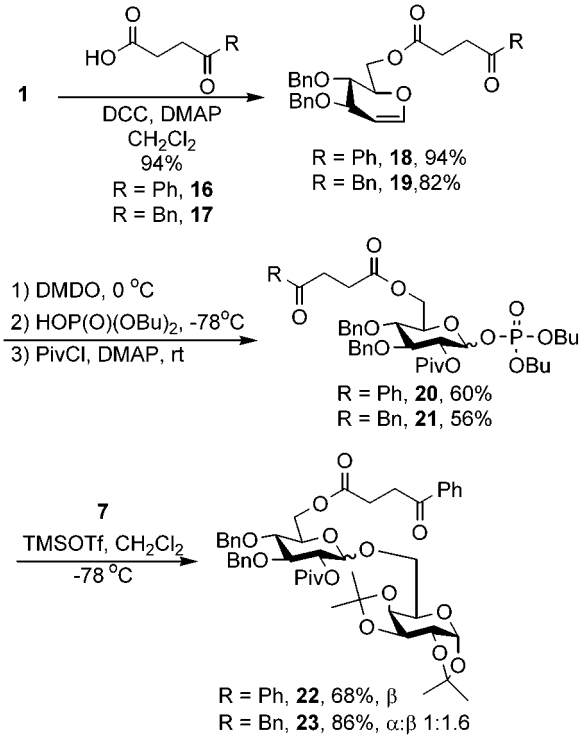
(5) (a) Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 585−589. (b) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545−9554.

(6) (a) Adinolfi, M.; Barone, G.; De Napoli, L.; Iadonisi, A.; Piccialli, G. *Tetrahedron Lett.* **1998**, *39*, 1953−1956. (b) Adinolfi, M.; Barone, G.; De Napoli, L.; Iadonisi, A.; Piccialli, G. *Tetrahedron Lett.* **1996**, *37*, 5007−5010.

the assembly of di-, tri-, and tetrasaccharides,[7] was selected to remedy the problem at hand.

Union of glucal **1** and 3-benzoylpropionic acid **16** afforded protected glucal **18** that was converted to the corresponding glycosyl β-phosphate **20** (Scheme 2).

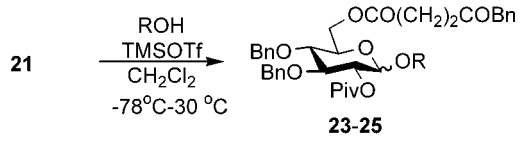
Scheme 2. Synthesis of 3-Benzoylpropionic Linker Model Phosphate from the Glycal and Coupling with the 6-OH Acceptor

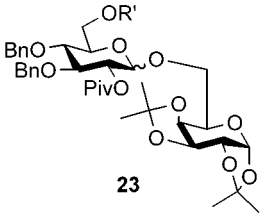
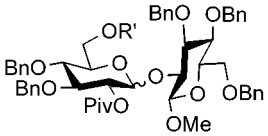
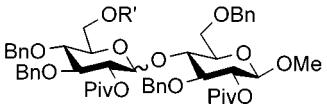


Subsequent coupling with **7** produced exclusively the expected β-disaccharide **22** (Scheme 2). Cleavage of the 3-benzoylpropionic ester with either excess hydrazine or hydrazine acetate proved to be very slow, requiring prolonged reaction times (18 h) even at elevated temperatures (80 °C). Addition of a methylene group to separate the phenyl ketone and relieve steric crowding was proposed to alleviate this problem. To assess this strategy, a 4-oxo-5-phenyl-valeric[8] ester on the C6 hydroxyl of a galactose model was cleaved with 2 equiv of hydrazine at ambient temperature in 90 min. On the basis of these initial observations, glycal **1** was equipped with the 4-oxo-5-phenyl-valeric ester at C6 and converted to the corresponding glycosyl phosphate **21**. Subsequent coupling with the acceptors **7**, **10**, and **13** unexpectedly produced an anomeric mixture of disaccharides **23**−**25** (Table 2).

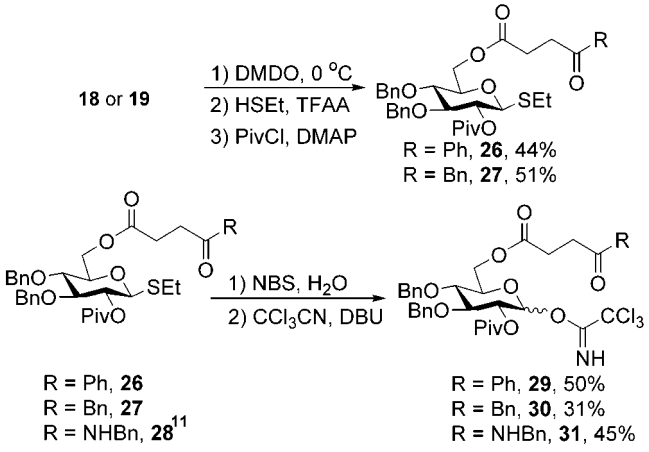
To explore the generality of the observed linker effect for different anomeric leaving groups, the corresponding thioglycoside and glycosyl trichloroacetimidate donors, containing a C2 pivaloyl ester and each of the three C6 model linkers, were prepared according to standard protocols (Scheme 3).[4e,9−11] Glycosylating agents **26**−**31** were then coupled with galactose acceptor **7** (Table 3).

Table 2. Disaccharide Synthesis Using Glycosyl Phosphates Containing a 4-Oxo-5-phenyl-valeric Ester at C6



ROH	product (R' = $CO(CH_2)_2COBn$)	yield (%, α:β)
7	 **23**	86% (α:β 1:1.6)
10	 **24**	94% (α:β 1:2.2)
13	 **25**	53% (α:β 1:1.8)

Scheme 3. Synthesis of Thioglycosides and Glycosyl Trichloroacetimidates Containing Various Linkers



(7) (a) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368−373. (b) Excoffier, G.; Gagnaire, D. Y.; Vignon, M. R. *Carbohydr. Res.* **1976**, *46*, 201−213.

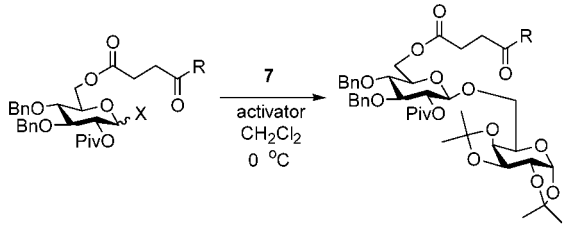
(8) Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth.* **1996**, *73*, 215−220.

(9) (a) Demchenko, A.; Stauch, T.; Boons, G. J. *Synlett* **1997**, *7*, 818−820. (b) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.

(10) Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(11) Thioglycoside **28** was prepared by an alternate route; see Supporting Information.

Table 3. Glycosylations with Thioglycosides and Glycosyl Trichloroacetimidates Containing Various Linkers



X	activator	donor	R	product	yield
—SEt	NIS TMSOTf (cat)	**26**	Ph	**22**	70%
		27	Bn	**23**	37%
		28	NHBn	**9**	73%
—O, CCl_3, NH	TMSOTf (cat)	**29**	Ph	**22**	82%
		30	Bn	**23**	79%
		31	NHBn	**9**	69%

Both donor types exhibited complete β-selectivity in all cases. The influence of a C6 linker on glycosylation stereoselectivity for glycosyl phosphates and the absence of such a dependence for thioglycosides and glycosyl trichloroacetimidates suggest the presence of different intermediates along the reaction pathway. The exact nature of the linker interference during glycosylation is not understood at this time but must be taken into consideration in the development of new linkers for the synthesis of oligosaccharides and carbohydrate libraries on a solid support.

In conclusion, we have demonstrated the preparation of glycosyl phosphates from support-bound glycals using a three-step procedure. These glycosyl phosphates served as resin-bound glycosyl donors in the formation of several disaccharides. The nature of the linker connecting the C6 hydroxyl group to the support was found to fundamentally influence the stereoselectivity of glycosylations involving these donors. Influence of the linker on glycosylation with glycosyl phosphates will have to be considered during synthetic planning of oligosaccharide assembly under the donor-bound regime.

Acknowledgment. Financial support from Boehringer-Ingelheim for partial support of this research is gratefully acknowledged. P.H.S. is a Glaxo-Smith-Kline Research Scholar and an Alfred P. Sloan Scholar. Funding for MIT-DCIF Inova 501 and 5 mm Broadband CP/MAS probe was provided by NSF (Grant CHE-9808061). Funding for the MIT-DCIF Inova 500 was provided by NSF (Grant DBI-9729592). Funding for MIT-DCIF Avance (DPX) 400 was provided by NIH (Grant ISIORR13886-01). Funding for the MIT-DCIF Mercury 300 was provided by NSF (Grants CHE-9808061 and DBI-9729592).

Supporting Information Available: Detailed experimental procedures, including synthesis of **28**, 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.

OL026276O