ORGANIC LETTERS

1999
Vol. 1, No. 2
211−214

Synthesis and Use of Glycosyl Phosphates as Glycosyl Donors

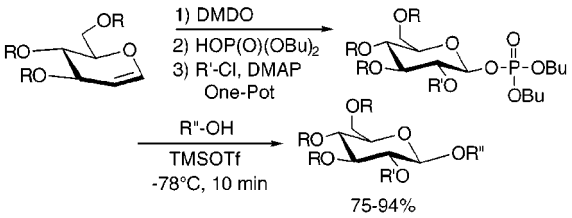
Obadiah J. Plante, Rodrigo B. Andrade, and Peter H. Seeberger*

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

seeberg@mit.edu

Received March 30, 1999

ABSTRACT



Differentially protected glycosyl phosphates prepared by a straightforward synthesis from glycal precursors are used as powerful glycosyl donors. Activation of β-glycosyl phosphates by TMSOTf at −78 °C achieves the selective formation of β-glycosidic linkages in excellent yields with complete stereoselectivity. Reaction with thiols results in the conversion of glycosyl phosphates into thioglycosides in nearly quantitative yield. An orthogonal coupling strategy using glycosyl phosphate donors and thioethyl glycoside acceptors allows for the rapid synthesis of a trisaccharide.

Complex glycoconjugates have been implicated in many cell−cell recognition events important in inflammation, immune response, and tumor metastasis.[1,2] Much effort has been devoted to the development of novel, powerful glycosylation reactions to facilitate access to defined synthetic oligosaccharide and glycoconjugate structures.[3] A wide range of anomeric groups, including most notably trichloroacetimidates,[4] thioethyl glycosides,[5] glycosyl sulfoxides,[6] fluorides,[7] and pentenyl glycosides[8] have been explored as glycosyl donors. While these methods have proven very useful for the installation of a variety of glycosidic linkages, they still suffer in many cases from lengthy syntheses, long reaction times, and the use of toxic activating agents. Thus, the need for the development of new, easily accessible glycosylating agents which may be coupled selectively and in high yield using nontoxic activators persists.

In biosynthesis, glycosyl transferases make use of glycosyl phosphates in the form of nucleotide diphosphate sugars (e.g. UDP-Glc) for the construction of glycosidic linkages.[9] To study these enzymatic reactions, a number of synthetic approaches for the preparation of glycosyl phosphates have been developed.[10] While several phosphate analogues, including phosphites,[11] phosphoramidates,[12] and phosphorodithioates,[13] have been employed as glycosyl donors in

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10.1021/ol9905452 CCC: $18.00
Published on Web 05/29/1999

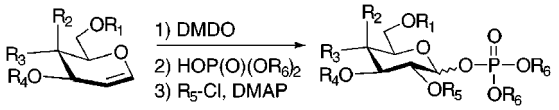
oligosaccharide synthesis, glycosyl phosphates have received surprisingly little attention for this application.[14]

We now report the efficient synthesis of glycosyl phosphates from glycals and their use as powerful glycosyl donors in the high-yielding and completely selective construction of β-glycosidic linkages requiring very short reaction times.

A three step, "one-pot" procedure was used to selectively prepare a variety of differentially protected glycosyl phosphates (Table 1). Conversion of a glycal into the 1,2-anhydrosugar by epoxidation with dimethyldioxirane (DMDO) was followed by opening of the epoxide with a phosphoric acid at −78 °C and protection of the generated C2 hydroxyl group at 0 °C. We[13] and others[16] have recently described the synthesis of anomeric phosphate derivatives using 1,2-anhydrosugars. A strong solvent dependence for the ratio of α- and β-glycosyl phosphates prepared by this method was observed. While reactions in toluene and dichloromethane produced preferentially β-phosphates, reactions in THF resulted almost exclusively in α-phosphates (Table 1). Using this approach, differentially protected glucosyl (**1**, **2**, **4**−**6**, **8**), galactosyl (**3**), and lactosyl phosphates (**7**) were prepared. Introduction of participating groups in the C2 position by acylation proved straightforward and high-yielding. Silylation of the C2 hydroxyl to install a nonparticipating TES group was also feasible, while introduction of a C2 TBS group failed. Efforts to equip the C2 position with a benzyl ether protecting group did not meet with success but rather resulted in the isolation of benzyl C2 phosphate glycosides. Similar results had previously been observed in the dithiophosphate series.[13]

All α-phosphates as well as the C2-silyl β-glycosyl phosphates **7** and **8**β were completely stable to silica column chromatography and could be stored at 4 °C for several weeks without decomposition. The phosphates **1**β, **2**β, and **5**β, however, were more difficult to handle, as they decomposed upon prolonged exposure to silica gel. Butyl phosphates proved more stable than benzyl phosphates and were easier to handle. Filtration through a short plug of silica gel yielded the pure desired compounds in all cases. Even these less stable β-phosphates could be stored at −20 °C for several weeks without decomposition.

Table 1. Synthesis of Glycosyl Phosphates from Glycal Precursors[15]



entry	R_1	R_2	R_3	R_4	R_5	R_6	solvent	yield, %	β:α
1	Bn	H	OBn	Bn	Piv	Bn	CH_2Cl_2	74	10:1[a]
							THF	71	1:10
							toluene	84	17:1
2	Bn	H	OBn	Bn	Piv	Bu	CH_2Cl_2	65	11:1
							THF	59	1:4
							toluene	60	8:1
3	Bn	OBn	H	Bn	Piv	Bu	CH_2Cl_2	57	4:1
4	TIPS	H	OBn	Bn	Piv	Bn	CH_2Cl_2	65	1:0
5	TIPS	H	OBn	Bn	Piv	Bu	THF	70	1:1
6	TBS	H	OPiv	Piv	Piv	Bu	CH_2Cl_2	75	1:0
7	Bn	H	OY[b]	Bn	TES	Bu	CH_2Cl_2	71	1:0
8	Bn	H	OBn	Bn	TES	Bu	THF	79	2:1

[a] When the reaction was carried out at 0 °C, a ratio of 4:1 (β:α) was observed. [b] Y = 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside-(1→4)-.

After having established a straightforward synthetic route for the preparation of differentially protected glycosyl phosphates, we evaluated the performance of these compounds as donors in glycosylation reactions. Anomeric β-phosphates served as powerful donors in the high-yielding, selective formation of β-glycosidic linkages in only 10 min upon activation with trimethylsilyl triflate (TMSOTf) at −78 °C (Table 2). Participation of the protecting group in the C2 position was not required for the selective formation of β-glycosidic linkages, as the C2-TES protected donor **8**β yielded exclusively the desired β-disaccharide **16**, although the TES group was lost during the reaction. While primary and hindered secondary alcohols such as the C2 hydroxyl could be coupled in very good yields, tertiary acceptors failed to react. Efficient conversion of glycosyl phosphate **2**β into the corresponding thioethyl glycoside **17** was achieved by coupling with ethanethiol.

The more stable α-phosphates could also serve as glycosyl donors upon activation with TMSOTf but required higher temperatures for efficient activation. While no reaction was observed at −78 °C, donor **2**α was activated at −20 °C and coupled to galactosyl acceptor **9** to yield 87% of the desired β-disaccharide **13** within 10 min (Table 2). Couplings to more hindered acceptors and to thiols were also accomplished in good yields.

Exclusive formation of β-glycosides using a nonparticipating group in C2 suggests that, upon activation of the phosphate by TMSOTf, an anomeric triflate or a close ion pair of an oxonium ion intermediate is formed. Anomeric triflates have been proposed as intermediates in the formation of β-mannosides from thioglycosides by Crich.[17]

Since thioethyl glycosides were completely stable under the conditions used to activate β-glycosyl phosphates, we investigated an orthogonal coupling strategy employing both

Scheme 1. Orthogonal Glycosylation Strategy Using Glycosyl Phosphates and Thioethyl Glycosides

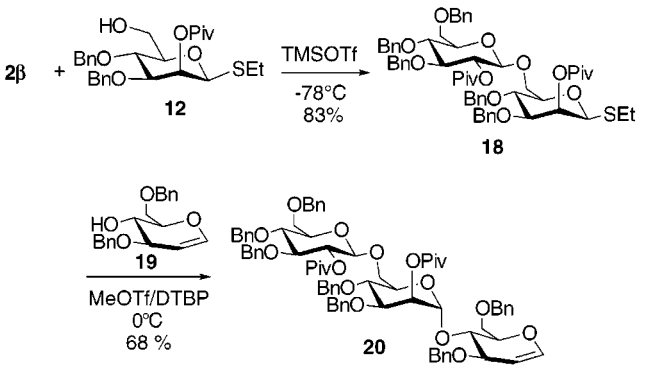
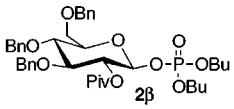
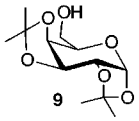
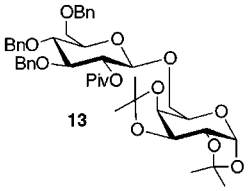
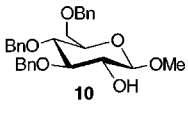
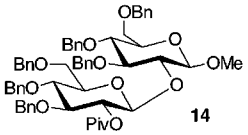
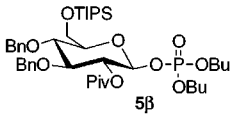
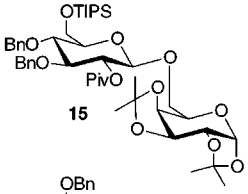
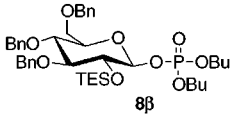
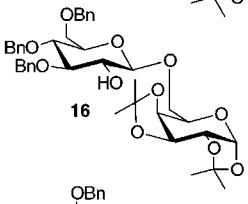
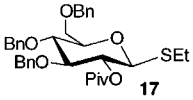
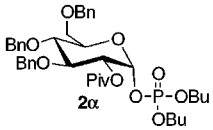


Table 2. Glycosylations with Glycosyl Phosphates and Trimethylsilyl Triflate[a]

Entry	Glycosyl Donor	Glycosyl Acceptor	Product	Yield
1	 **2β**	 **9**	 **13**	94
2	**2β**	 **10**	 **14**	83
3	 **5β**	**9**	 **15**	82
4	 **8β**	**9**	 **16**	71
5	**2β**	 **11**	 **17**	90
6[b]	 **2α**	**9**	**13**	87
7[b]	**2α**	**10**	**14**	73
8[b]	**2α**	**11**	**17**	70

[a] Glycosylations were carried out with 1.2 equiv of donor, 1.0 equiv of acceptor, and 1.2 equiv of TMSOTf in dichloromethane at −78 °C. [b] The reaction was carried out at −20 °C.

glycosyl phosphates and thioethyl glycosides (Scheme 1). Thioethyl mannoglycoside **12** served as glycosyl acceptor in the reaction with glycosyl phosphate **2**β to yield 83% of disaccharide **18**. Without any further manipulations, **18** was used as a glycosyl donor and coupled to glycal acceptor **19** under previously described coupling conditions.[18] The glycal double bond of trisaccharide **20** allows for further elongation by the glycal assembly method.[19]

In summary, we have described the efficient synthesis of differentially protected glycosyl phosphates from glycals. We have further demonstrated that α- and β-glycosyl phosphates serve as powerful glycosyl donors in the formation of β-glycosidic linkages in high yield and with complete stereoselectivity. Efficient conversion of glycosyl phosphates into thioethyl glycosides was also achieved. Additionally, glycosyl phosphates and thioethyl glycosides were employed in the synthesis of a trisaccharide using an orthogonal glycosylation scheme, thus minimizing tedious protecting group manipulations. Efforts to employ glycosyl phosphates in the construction of other glycosidic linkages as well as in

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(15) General procedure: 1.0 equiv of glycal, 1.5 equiv of 0.08 M dimethyldioxirane, 1.10 equiv of dialkyl phosphate, 1.5 equiv of pivaloyl chloride and 3.0 equiv of DMAP. All steps were carried out in dichloromethane unless noted otherwise.

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the solid support synthesis of oligosaccharides are currently underway and will be reported in due course.

Acknowledgment. Financial support from the Department of Chemistry at the Massachusetts Institute of Technology, from the Kenneth M. Gordon Scholarship Fund (Fellowship for O.J.P.), and from the NSF (Predoctoral Fellowship for R.B.A.) is gratefully acknowledged.

Supporting Information Available: 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.

OL9905452