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Synthesis of Glycosyl-1-phosphates via Dehydrative Glycosylation

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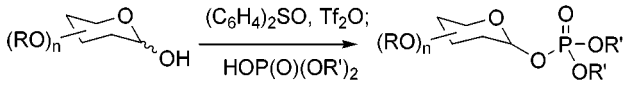
ABSTRACT



Direct synthetic access to glycosyl-1-phosphates is accomplished with the dehydrative coupling of carbohydrate hemiacetals and dialkyl phosphates, employing dibenzothiophene-5-oxide and triflic anhydride. The procedure offers a new and versatile method for efficient preparation of a host of glycosyl-1-phosphates of variable structure with good control over anomeric selectivity.

Glycosyl-1-phosphates are key intermediates in the chemical and biosynthesis of glycoconjugates. In the biosynthesis of complex carbohydrates, the controlled enzymatic assembly of oligosaccharides and glycoconjugates typically involves glycosyl nucleoside diphosphates[1] or glycosyl lipid diphosphates,[2] which function as effective glycosyl donors in glycosyl transferase catalyzed couplings. Moreover, glycosyl-1-phosphates have been shown to be effective glycosyl donors in Lewis acid catalyzed glycosylations[3,4] and also have been employed as useful biochemical probes.[5] Because of the importance of glycosyl-1-phosphates in both biology and chemistry, the efficient synthesis of this class of carbohydrate intermediates has attracted much attention.

Existing methods for the chemical synthesis of glycosyl-1-phosphates have involved the use of selected well-established glycosylation reactions employing nucleophilic phosphate glycosyl acceptors and electrophilic glycosyl donors such as glycosyl bromides,[6−8] thioglycosides,[9] glycosyl trichloroacetimidates,[10] and activated glycals.[4,11] While these methods have been shown to be effective in the introduction of the C(1)-phosphate moiety with varying degrees of anomeric selectivity, they must also entail multistep procedures for the preparation of the appropriate anomerically derivatized carbohydrate donors. Other strategies include the stereoselective synthesis of more stable glycosyl-1-phosphate precursors such as glycosyl-1-phosphites[12,13] or glycosyl-1-phosphoramidates;[14,15] however, access to glycosyl-1-phosphates by these strategies can only be accomplished with a subsequent oxidation step to generate the anomeric phosphate functionality. In a complementary method, nucleophilic hexopyranoses have also been coupled with chlorophosphate reagents to provide access to this class of carbohydrates.[3,16,17]

To date, there are no general and efficient methods for glycosyl-1-phosphate synthesis via the direct dehydrative

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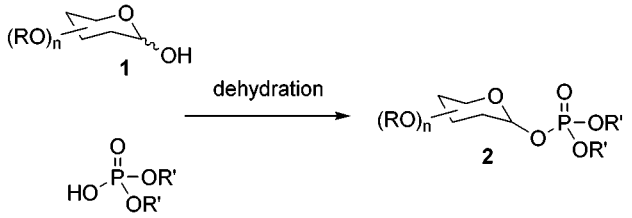
coupling of carbohydrate hemiacetals and dialkyl phosphates (Scheme 1) despite the potential advantages of such a

Scheme 1



strategy. The coupling process itself would be a one-pot procedure that obviates the need for the preparation and isolation of an anomerically derivatized glycosyl donor. However, such a dehydration process must necessarily be one in which unproductive side reactions, such as self-condensation of the hemiacetal donor or of the phosphate reagent, are minimized.

We present herein the first examples of direct dehydrative glycosylation of nucleophilic dialkyl phosphate acceptors with glycosyl-C(1)-hemiacetal donors for the facile preparation of glycosyl-1-phosphates (Figure 1). We have recently established that activated sulfonium reagents, derived from a diaryl sulfoxide and triflic anhydride, are effective activators of nucleophiles such as hemiacetals[18] and glycal enol ethers.[19,20] Using the reagent combination of dibenzothiophene-5-oxide (DBTO) and triflic anhydride, carbohydrate hemiacetals can be activated for the efficient one-pot synthesis of glycosyl-1-phosphates. In this procedure, triflic anhydride (1.4 equiv) is added to a solution of the hemiacetal donor **1** (1 equiv), DBTO (2 equiv), and the acid scavenger 2,4,6-tri-*tert*-butylpyridine (TTBP, 5 equiv) in dichloromethane at −78 °C. The solution is stirred at −45 °C for 1 h, and the dialkyl phosphate acceptor (3 equiv) is then added. The reaction mixture was stirred at −45 °C for 1 h, at 0 °C for 30 min, and then at 23 °C for 1 h before it was neutralized with the addition of triethylamine (10 equiv). It was observed that aqueous workup of the reaction mixture can lead to significant hydrolysis of the anomeric phosphate moiety. Thus, to minimize hydrolysis, the reaction solution is directly concentrated, and the residue is purified by flash column chromatography to afford the corresponding glycosyl-1-phosphate product.

The reaction protocol is straightforward and is amenable to the preparation of a variety of glycosyl-1-phosphates with high efficiency. Selectively protected gluco-, galacto-, manno-, and xylopyranoses, as well as furanose donors, can be readily transformed to their corresponding glycosyl-1-phosphates, as exemplified by the direct glycosylation of various dialkyl phosphates (Figure 1). On the basis of our

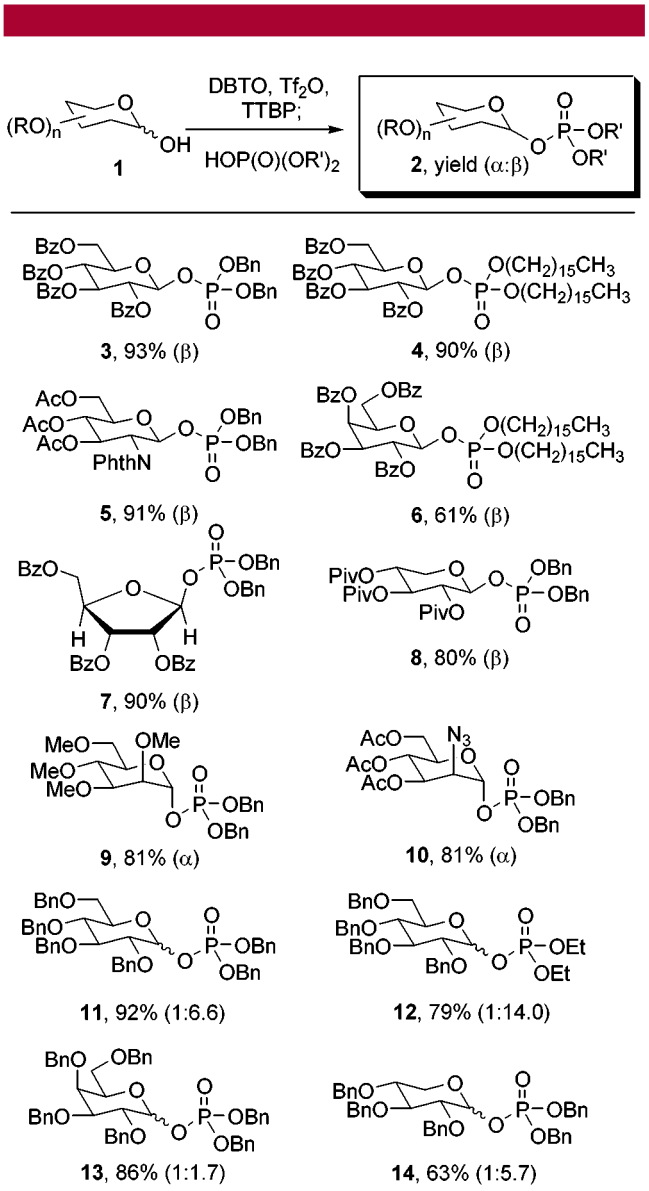
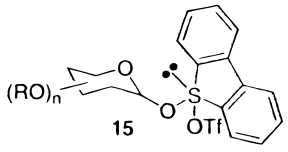


Figure 1. Glycosyl-1-phosphates derived from dehydrative glycosylation.[21]

recent mechanistic studies of hemiacetal activation using activated sulfoxides,[22] it is likely that anomeric bond formation proceeds via initial in situ generation of an anomeric oxosulfonium or sulfurane species such as **15**, which functions as a potent carbohydrate electrophile.



Of particular interest is the stereochemical outcome of the coupling products depicted in Figure 1. In the examples where the hemiacetal donors incorporate C(2)-acyl protective groups, exclusive formation of 1,2-*trans*-glycosyl-1-phosphates is observed (**3**−**8**) as a result of neighboring group

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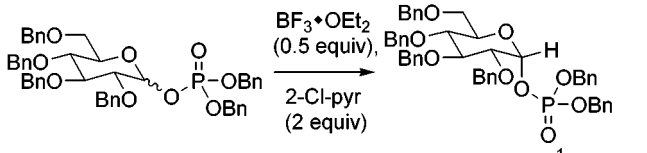
participatory effects. Although the C(2)-acyl-participatory effect is a well-known means for controlling anomeric selectivity in the glycosylation of a variety of nucleophilic acceptors, it has not always led to predictable anomeric selectivity in the case of glycosyl-1-phosphate synthesis as a result of the propensity of the anomeric phosphate ester to anomerize. For example, in glycosylation reactions to form glycosyl-1-phosphates in which the anomeric bond forming event is acid catalyzed, variables such as reaction duration and purity of the phosphate reagents have dramatic effects on anomeric selectivity even in the presence of a C(2)-participatory group.[10,23] However, with this dehydrative glycosylation protocol using TTBP as a mild acid scavenger, complete 1,2-trans-selectivity is observed, and no post-coupling anomerization is detected.

Although the *β*-glucosyl-, *β*-galactosyl-, and *β*-xylosyl-1-phosphates **3**−**8** can be stereoselectively accessed through neighboring group participatory effects using the above-mentioned protocol, complementary access to their corresponding α-anomers by employing donors devoid of a C(2)-acyl group was less successful (**11**−**14**). For these glycosyl donors, the anomeric ratio of the glycosyl-1-phosphate products appear to vary with the nature of the coupling partners.[24] As a result, efforts subsequently focused on exploring methods for dehydrative phosphate glycosylation that would proceed under thermodynamic control to access the α-anomers of **11**−**14** with high selectivity. In preliminary investigations (Scheme 2), it was found that treatment of a

Scheme 2



β-rich anomeric mixture of dibenzylphosphoryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside anomers (**11***β*; 1:6.6, α:*β*) with BF_3·OEt_2 (0.5 equiv) and 2-chloropyridine (1 equiv) in dichloromethane (23 °C, 1 h) led to its anomerization to afford **11**α (7.3:1, α:*β*) with minimal hydrolysis (<5%) of the anomeric phosphate linkage.[25] The presence of the mild acid scavenger 2-chloropyridine is essential for the controlled epimerization of the C(1)-phosphate. Attempts to anomerize **11** with BF_3·OEt_2 alone led to rapid decomposition of **11**, and the use of a stronger acid scavenger such as TTBP in combination with BF_3·OEt_2 did not lead to anomeric equilibration.[26]

With this promising result, the BF_3·OEt_2/2-chloropyridine reagent combination was then incorporated into the dehydrative coupling procedure in the absence of TTBP with the goal of achieving direct access to the α-glycosyl-1-phosphate of **11**−**14** with good selectivity (Figure 2). In the event, triflic

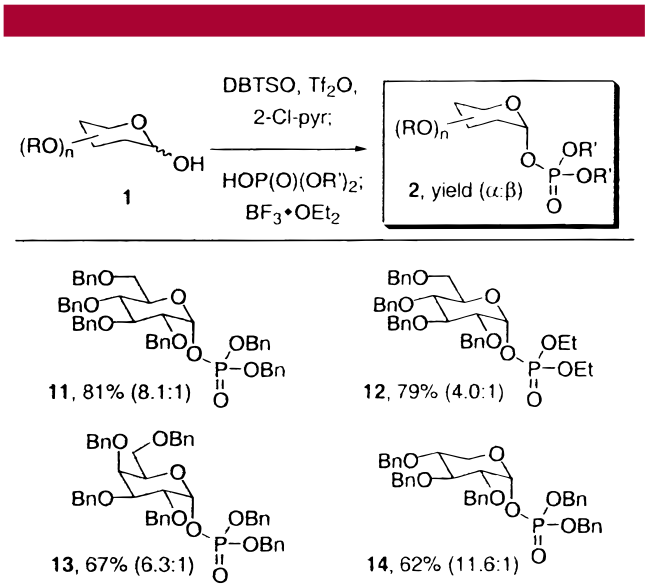


Figure 2. Glycosyl-1-phosphates derived from dehydrative glycosylation.

anhydride (1.4 equiv) is added to a solution of the hemiacetal donor **1** (1 equiv), DBTO (2 equiv), and 2-chloropyridine (5 equiv) in dichloromethane at −78 °C. As before, the solution is stirred at −45 °C for 1 h, and the dialkyl phosphate acceptor (3 equiv) is then added. The reaction mixture was stirred at 23 °C for 1 h, and BF_3·OEt_2 (1 equiv) was introduced. After a further 1 h at 23 °C, the reaction is neutralized with the addition of triethylamine (10 equiv). The solution is concentrated, and the residue is purified by flash column chromatography to afford the glycosyl-1-phosphate with good selectivity for the thermodynamically favored anomer (Figure 2).[27]

In summary, an efficient method for the preparation of glycosyl-1-phosphates is reported. The procedure involves the first examples of direct dehydrative coupling of carbohydrate hemiacetals with dialkyl phosphates, mediated by DBTO and Tf_2O. This protocol offers a new and versatile method for efficient access to a host of glycosyl-1-phosphates of variable structure.

(21) For the preparation of **9**, **10**, and **12**, Ph_2SO was substituted for DBTO to facilitate chromatographic purification of the product. Efficiencies and stereoselectivities were to those of similar reactions with either sulfoxide reagent as indicated by ^{1}H NMR analysis of the crude reaction mixtures.

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(24) The use of mannopyranose donors led to high α-selectivity for the product glycosides even in the absence of C(2)-neighboring group participants (i.e., **9** and **10**).

(25) Determined by ^{1}H NMR analysis of the reaction mixture.

(26) The effectiveness of 2-chloropyridine may be due to its possible role as a nucleophile in the displacement of the anomeric phosphate moiety to facilitate anomeric epimerization in the presence of BF_3·OEt_2. For evidence of the intermediacy of glycosyl-2-chloropyridinium species in this dehydrative glycosylation reaction, see ref 22.

(27) Glycosylations to prepare C(2)-acyl-protected glycosyl-1-phosphates such as **3** in the presence of 2-chloropyridine and BF·OEt_2 led to the isolation of only 28% of **3***β* and 58% recovery of the hemiacetal donor. The corresponding α-glycosyl phosphate was not deteced. It is likely that, in the presence of 2-chloropyridine and BF·OEt_2, the C(2)-acyloxy group promoted hydrolysis rather than epimerization of the anomeric phosphate moiety during the reaction/purification process.

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Supporting Information Available: Experimental details and spectral/analytical data for the glycosylation products. This material is free of charge via the Internet at http://pubs.acs.org.

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