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One-Pot Synthesis of 2-Deoxy-β-oligosaccharides

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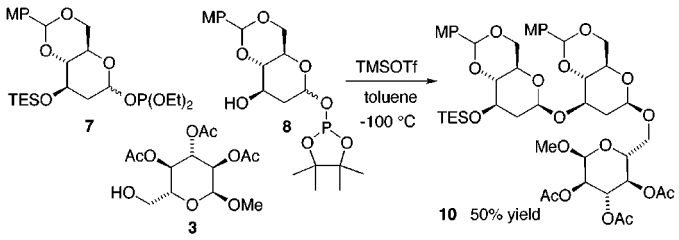
ABSTRACT



A new one-pot method using glycosyl phosphites for the synthesis of 2-deoxy-β-oligosaccharides is described.

Deoxysugars are ubiquitous structural components of many secondary metabolites that possess significant antitumor activity.[1] Common structural motifs include 2,6-dideoxyhexoses and 2,3,6-trideoxyhexoses interconnected by either 2-deoxy α- and/or β-glycoside linkages.[2] The 2-deoxy-β-glycoside linkage poses a particularly challenging synthetic problem since this isomer does not benefit from the anchimeric assistance of a C-2 oxygen substituent.[3] A majority of synthetic methods address this problem by the temporary placement of a C-2 directing group that requires removal after the glycosylation event.[4] An alternative approach to constructing 2-deoxy-β-glycoside linkages was reported by Hashimoto who found that 2-deoxyglycosyl phosphites provided good β selectivity without recourse to a C-2 directing group leading to a direct route to 2-deoxy-β-glycosides (Figure 1).[5]

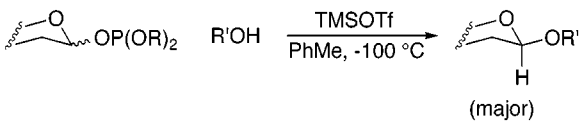


Figure 1. Hashimoto's glycosylation method.

Here we apply glycosyl phosphites to the expeditious assembly of oligosaccharides using a "one-pot sequential glycosylation" protocol.[6] These reactions assemble oligosaccharides from multiple monomers in a single reaction vessel without intermediate purification steps. To control the order of glycosylation, the reactivity of glycosyl donors and/or acceptors needs to be distinguished. Several approaches have been successfully applied toward the differential activation of anomeric leaving groups: (1) two orthogonal leaving groups (for example, thioglycosides and glycosyl fluorides) may be selectively activated using different reaction promoters,[7] (2) two glycosyl donors with identical leaving groups may be differentially activated depending on the nature of neighboring protecting groups,[8] and finally (3) a subtle

(1) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99−110.
(2) (a) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem*, **1997**, *188*, 1−84. (b) Hallis, T. M.; Liu, H.-W. *Acc. Chem. Res.* **1999**, *32*, 579−588. (c) Kirschning, A.; Jesberger, M.; Schöning, K.-U. *Synthesis* **2001**, 507−540.
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variation of leaving group capacity may be applied to a single "class" of leaving groups.[9] In this Letter we apply the latter approach using dialkyl glycosyl phosphites leading to the assembly of an all-β 2-deoxy-oligosaccharide.

Our general strategy is outlined in Figure 2 and depends

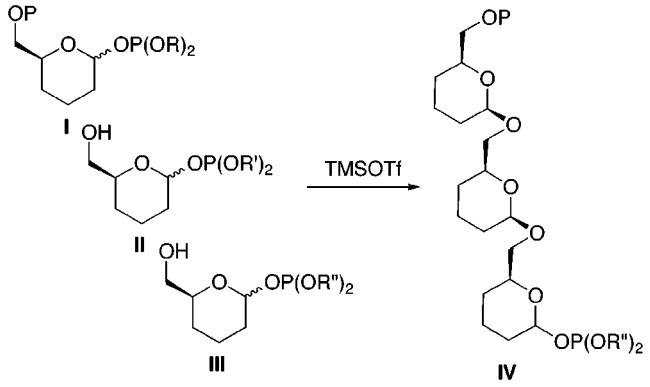
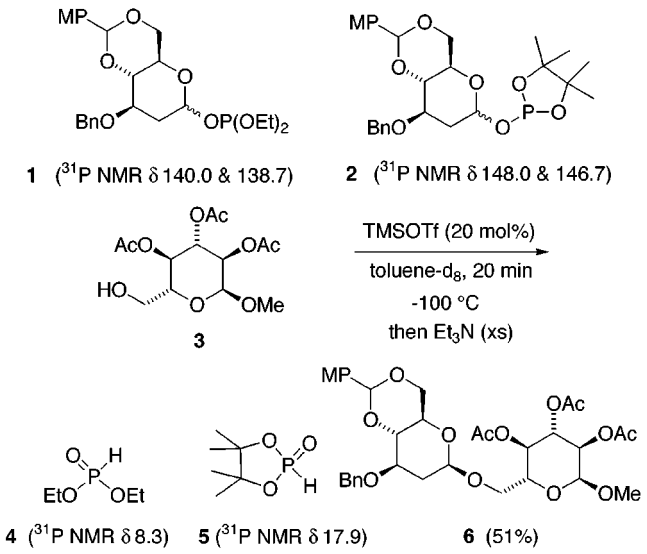


Figure 2. One-pot glycosylation strategy for the synthesis of 2-deoxy-β-oligosaccharides.

on the different rates of activation of dialkyl glycosyl phosphites. In this way, oligosaccharide **IV** would be assembled in the sequence shown assuming the activation rate to be of the order $(RO)_2PO > (R'O)_2PO > (R''O)_2PO$. To establish the donor rates of different glycosyl phosphites, we monitored a competitive coupling reaction by ^{31}P NMR. The disappearance of starting glycosyl phosphite is accompanied by the appearance of the dialkyl phosphite byproduct (Scheme 1). The rate of glycosylation of **3** using

Scheme 1



diethyl glycosyl phosphite **1** and pinacol glycosyl phosphite **2** was determined by mixing **1** (1 equiv), **2** (1 equiv), and **3** (1.5 equiv) in anhydrous toluene-d_8, cooled to −100 °C and treated with 20 mol % of TMSOTf. After 20 min, the reaction was quenched with an excess of triethylamine and filtered through a plug of silica gel. The product mixture showed nearly complete consumption of **1** (**1**α, δ 140.0 and **1**β, δ 138.7)[10] in addition to the production of diethyl phosphite **4** (δ 8.3).[11] In contrast, pinacol phosphite **2** (**2**α, δ 148.0 and **2**β, δ 146.7) remained essentially unchanged while the formation of phosphite **5** (δ 17.9)[12] was not observed (Figure 3). Disaccharide **6** was isolated in 51% yield as a 5:1 mixture of β and α isomers.

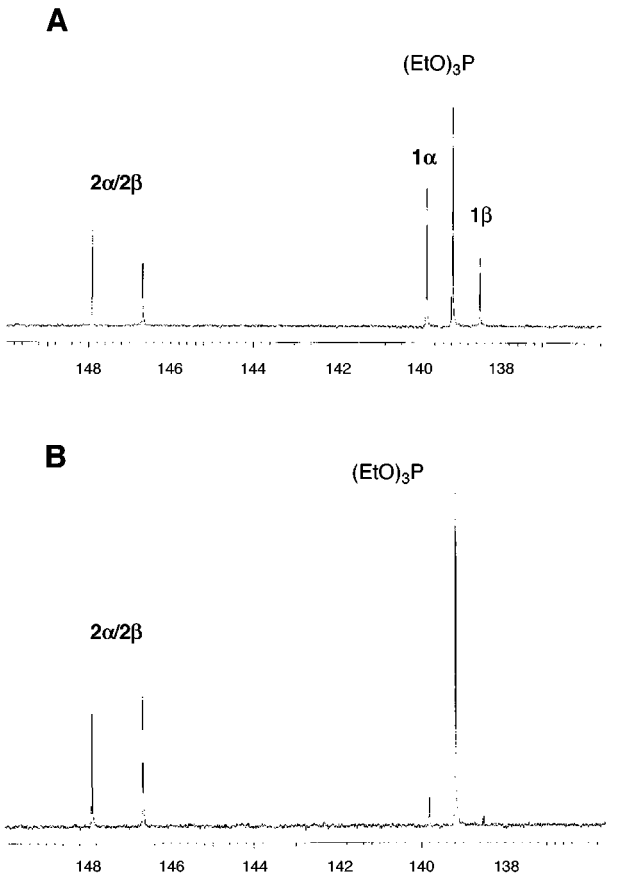


Figure 3. (A) ^{31}P NMR spectrum of initial reaction mixture containing glycosyl phosphites **1** and **2** and triethyl phosphite as an internal standard. (B) ^{31}P NMR spectrum of product mixture following triethylamine quench.

To demonstrate the utility of this differential glycosyl donor reactivity, trisaccharide **10** was prepared in one pot from diethyl glycosyl phosphite **7**, pinacol phosphite **8**, and glycosyl acceptor **3**. In a typical reaction, glycosyl donors **7**

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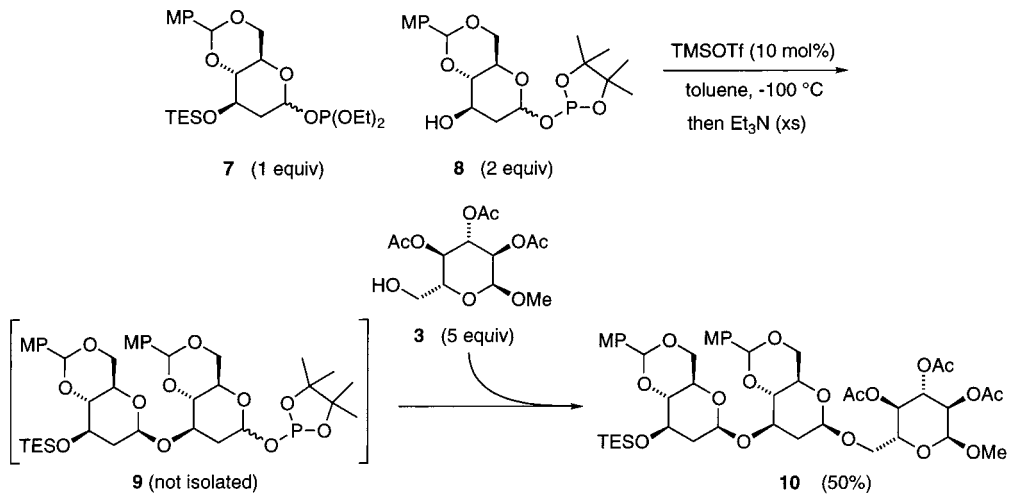
(10) α- and β-glycosides were assigned by analysis of $^3J_{PH}$ couplings.

(11) Quin, L. D.; Ionkin, A. S. *J. Org. Chem.* **1995**, *60*, 5186−5189.

(12) Munzo, A.; Hubert, C.; Luche, J.-L. *J. Org. Chem.* **1996**, *61*, 6015−6017.

Scheme 2



and **8** were dissolved in freshly distilled toluene and cooled to −100 °C. TMSOTf was added as the activating agent, and after 10 min acceptor **3** was introduced as a solution in toluene. After an additional 10 min, the reaction was quenched by addition of excess triethylamine (Scheme 2).

Optimization of the conditions for the one-pot glycosylation revealed that toluene was the best solvent and that a stoichiometry of 1:2:5 for **7**, **8**, and **3**, respectively, provided more consistent results. Improved yields and stereoselectivity were observed upon a reduction in the amount of TMSOTf employed with a concentration of 10 mol % providing the best results. Also, the timing of the coupling reactions was found to be crucial as prolonged exposure to the reaction conditions during either coupling resulted in increased decomposition of substrates and/or products. In most cases, stereoisomers (4:1, β/α) were produced at the glycosidic linkage between monosaccharides **7** and **8** as determined by 500 MHz ^{1}H NMR. In some trials, a trace amount of a disaccharide corresponding to coupling between residues **7** and **3** was also isolated (β isomer only).

In conclusion, we have demonstrated that two different dialkyl glycosyl phosphites glycosylate at different rates utilizing ^{31}P NMR. We have extended this concept to a proof-of-principle synthesis of the targeted trisaccharide **10** employing our newly found one-pot glycosylation protocol to construct multiple 2-deoxy-β-glycosidic linkages in a single operation, thus bypassing the necessity for intermediate purification steps. In order for this procedure to be applied to larger oligosaccharides, other dialkyl glycosyl phosphites need to be evaluated. Further investigations along these lines and the use of this procedure in the construction of oligosaccharide portions of various natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **2**, **7**, **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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