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The First Polymer-Assisted Solution-Phase Synthesis of Deoxyglycosides

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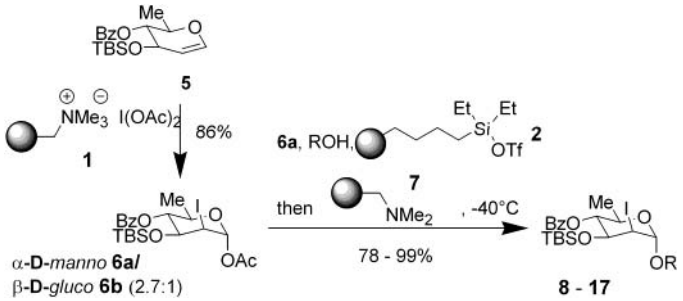
ABSTRACT



A glycosylation protocol for the synthesis of 2-deoxyglycosides has been developed which is based on the use of polymer-bound reagents. Glycals are transformed into 2-iodoglycosyl acetates using polymer-bound bis(acetoxy)iodate(I) complex (1). Activation of the anomeric center is achieved by employing polymer-bound silyl triflate (2). In the presence of different glycosyl acceptors, 2-deoxy-2-iodoglycosides are generated in very good yields. Furthermore, it is shown that this method can be embedded in multistep sequences toward glycosylated testosterone and rhodinosyl-olivosyl-olivoside.

Glycoconjugates composed of an (oligo)deoxysugar portion and an aglycon are widely distributed in nature and are of wide clinical importance.[1] Importantly, alterations of the saccharide structures can result in improved biological activity, in particular against drug-resistant microorganisms.[2] However, preparation of these glycoconjugates is still a challenging topic. In view of the importance and success of solid-phase chemistry, various polymer-supported syntheses of oligosaccharides including deoxysugar analogues[3] have been developed.[4]

One major disadvantage of solid-phase synthesis is its requirement of robust linkers which are stable under various reaction conditions. In addition, the target glycoconjugate needs to be cleaved from the linker without affecting the diverse functionalities present in both the saccharide and the aglycon domain.

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Recently, the development and application of polymer-supported reagents have seen a dramatic increase[5] which has moved functionalized polymers from an academic curiosity to a widely recognized synthetic technique. This hybrid solid/solution-phase technique possesses all the intrinsic advantages of classical solid-phase techniques (i.e., use of excess reagents to drive reactions to completion followed by a simple filtration step to isolate products). Additionally, all advantages associated with solution-phase chemistry are exploited here.

In conjunction with our research activities in this field,[6] we initiated a program dedicated to the polymer-assisted solution-phase synthesis of deoxysugar-based glycoconjugates using polymer-bound reagents.[7] In this Letter, we describe the first concise polymer-assisted preparation of oligodeoxysaccharides and glycconjugates derived therefrom. The strategy includes four steps: (1) glycal activation, (2) glycosidation, (3) deiodination, and (4) *O*-desilylation. The final step is necessary for creating a new glycosyl acceptor and thus opens up the opportunity for repeating the glycosidation.

We envisaged a set of polymer-bound reagents and activators, **1**−**4** (Figure 1), that we reckoned to be ideally

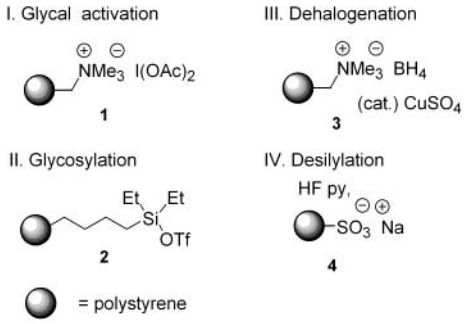
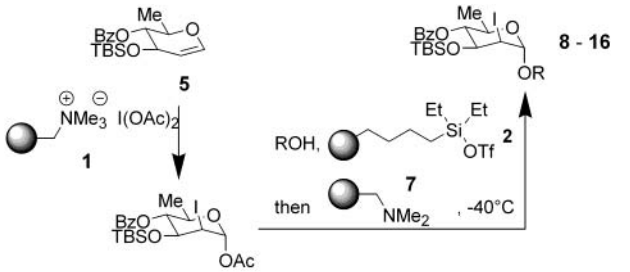


Figure 1. Functionalized polymers for polymer-assisted solution-phase synthesis of deoxygenated oligosaccharides.

suited for performing the steps mentioned above. These reagents can be easily prepared and have the potential to be recovered and recycled. More importantly, they are highly reactive and can overcome kinetic restrictions and diffusional limitations associated with polymer-assisted synthesis.

Earlier studies have proven that iodate(I) complex **1** promotes 1,2-iodo-acetoxylation of glycals under mild conditions in excellent yields.[8] For example, fully protected D-olival **5** was converted into glycosyl acetates **6a**,**b** (α-*manno*/*β*-*gluco* 2.7:1) in excellent yield after separation (Scheme 1). The key step of this project, however, is the

Scheme 1 Polymer-Assisted Activation of Glycals and Subsequent Glycosidation (Refer Also to Table 1)



α-D-*manno* **6a**, β-D-*gluco* **6b** (86%)
(**6a**:**6b** = 2.7:1)

glycosidation step using acetate **6** as glycosyl donor and various alcohols as glycosyl acceptors. In solution phase, silyl triflates have proven to be powerful activating reagents for 2-iodo-2-deoxyglycosyl acetates[9] so we looked for the polymer-based variant. We found that Nafion R SAC-13 and TMS-Nafion,[10] which have occasionally been promoted as strong polymer-bound acid and Lewis acid, respectively,[11] turned out to be moderate promotors in this case.

Likewise, Montmorillonite K-10 was ineffective in this glycosidation step.[12] Polymer-bound silyl triflate **2**,[13] however, turned out to be a very powerful activator for 2-deoxy-2-iodoglycosyl acetates (Table 1). Starting from the α-*manno*-isomer **6a**, glycosylations of structurally diverse alcohols were achieved either in dichloromethane or diethyl ether with total stereocontrol in excellent yield. In most cases filtration and removal of the solvent gave pure α-glycosides **8**−**17**.[14] In some cases, concentration of the reaction mixture led to total decomposition of the products, which can be ascribed to the presence of TfOH. This problem was overcome by adding Amberlyst A-21 **7** prior to removal of the solvent.

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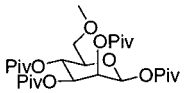
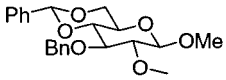
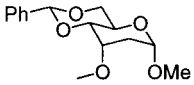
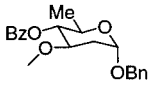
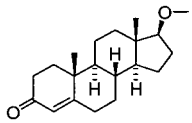
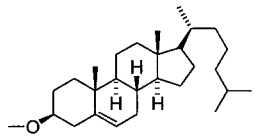
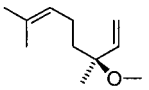
(14) In some cases, oligo- and polymeric impurities originated from the resins were present in the crude product as judged by ^{1}H NMR analysis. Under these circumstances, a simple gel-filtration step became necessary for obtaining analytically pure samples.

Table 1. Polymer-Assisted Glycosidation of 2-Deoxy-2-iodo-α-D-glycosyl Acetate **6a** (Refer Also to Scheme 1)

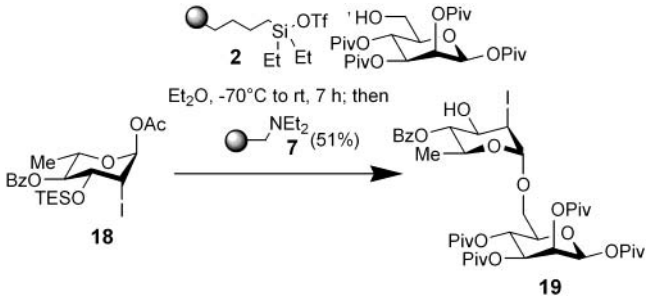
Entry	RO	Conditions[a]	Glycoside	Yield %[b]
1	MeO	CH_2Cl_2, -70°C to rt, 18h	**8**	95
2[c]	EtO	CH_2Cl_2, -70°C to 10°C, 18h	**9**	99
3	BnO	Et_2O, -78°C to -30°C, 6.5h	**10**	95
4		Et_2O, -70°C to 10°C, 7h,	**11**	97[d]
5		Et_2O, -65°C to --10°C, 5h	**12**	81[e]
6		Et_2O, -65°C to -10°C, 5h	**13**	99
7		Et_2O, -75°C to rt, 8h	**14**	95
8		Et_2O, -75°C to -50°C, 3h	**15**	97
9		Et_2O, -70°C to -rt, 22h	**16**	84
10		Et_2O, -65°C to -0°C, 5h	**17**	81

[a] For details refer to the Supporting Information. [b] Yields refer to isolated pure products. [c] L-**6a** was employed. [d] In this case, Nafion-TMS (4 equiv, Et_2O, −70 °C to rt, 4.5 d) gave 39% of the desired glycoside **11**. [e] Reduced yield due to partial decomposition of glycosl acceptor.

Besides simple alcohols (Table 1, entries 1−3), carbohydrate-derived glycosyl acceptors (entries 4−7), steroids (entries 8 and 9), and even hindered alcohols such as (−)-linalool (entry 10) were employed successfully. Neighboring group participation of the adjacent iodine atom completely governs the selectivity as is also seen in solution-phase variants. The good efficiency of the process can be rationalized by assuming that the reactive oxonium-type intermediates are located on the polymeric support at isolated spots so that interactions between activated species are suppressed to a large extent. It is noteworthy that polymer-bound silyl triflate **2** can be regenerated after use by treatment with TMSCl for removing traces of water followed by treatment with an excess of TMSOTf.

While the TBS-protection is tolerated under the glycosidation conditions decribed Table 1, entry 4) the polymer-bound Lewis acid **2** may also cleave the TES group as is demonstrated for glycosyl acetate **18** in Scheme 2.

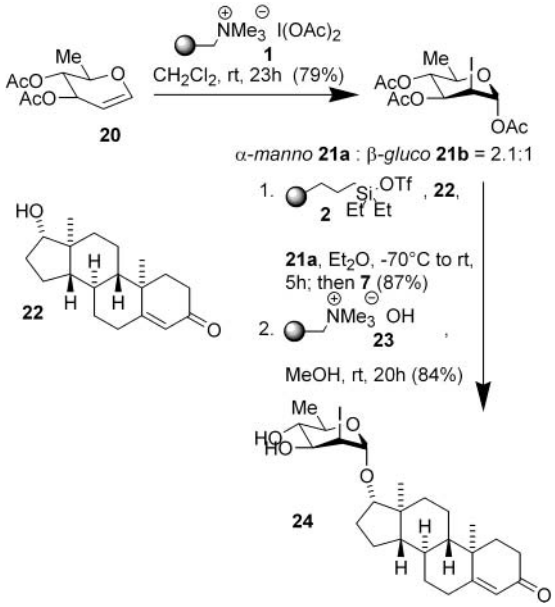
Scheme 2



Next, we extended the concept of polymer-assisted solution-phase glycosidation to the preparation of a steroid-derived glycoconjugate as well as a deoxytrisaccharide.

For the glycosylation of testosterone **22**, a three-step synthesis based on polymer-bound reagents was devised. 1,2-Iodoacetoxylation of per-*O*-acetylated 6-deoxy-D-glucal **20** afforded an α-*manno*/*β*-*gluco* diasteromeric mixture from which the major 1,2-addition product **21a** was employed for the next step after chromatographic isolation (Scheme 3).

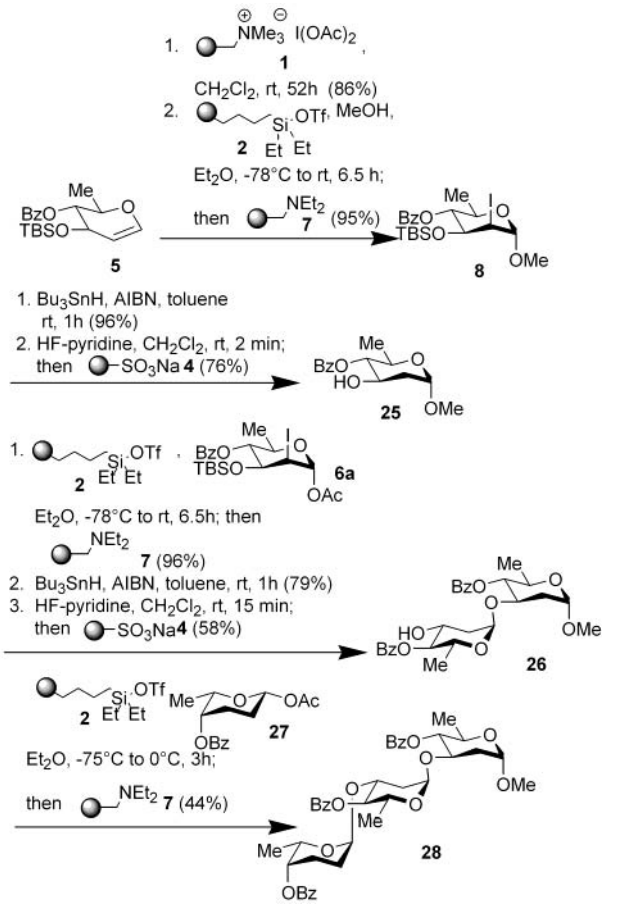
Scheme 3. Polymer-Assisted Glycosylation of Testosterone



Activation of the anomeric center using reagent **2** followed by coupling with steroid **22** and debenzoylation with Amberlyst A-26 (OH^- form) **23** afforded the unprotected α-glucoside **24** in very good yield with high purity (>95%). The final product was purified by gel filtration and the analytical data confirmed the structure of **24**.

In a more advanced study, we envisaged the preparation of a trisaccharide composed of two D-olivose units and 2,3,6-trideoxyhexose L-rhodinose (Scheme 4). These deoxyhexoses are widely found as carbohydrate components in various glycoconjugates from microbial sources such as the lando-

Scheme 4. Synthesis of a Rhodinosyl-olivosyl-olivoside



mycine group of antibiotics.[15] Activation of D-glucal derivative **5** was the starting point of the synthesis of trisaccharide **28** as described previously.

Separation of the diastereomeric mixture and glycosidation of **6a** with methanol as acceptor led to methyl glycoside **8** (Table 1, entry 1) which was further modified after deiodination and *O*-desilylation. It has been reported that polymer-bound borohydrides doped with metal salts such as $Ni(OAc)_2$, or $CuSO_4$ **3** are powerful reductants for alkyl iodides.[16] However, in our hands these reagents gave only minor amounts of deiodinated products when reacted with 2-iodoglycoside **8**. Likewise, polymer-bound tin hydrides[17] were found to be inefficient reducing agents in this context. Therefore, we turned to a conventional deiodination protocol (Bu_3SnH, AIBN) at this point. Subsequently, desilylation was achieved using the HF−pyridine complex.[18] Excess desilylating reagent was removed with Amberlite A-200 (Na^+ form) **4**. This scavenging reagent turned out to be very efficient for trapping protonated pyridine as well as the fluoride anion as its sodium salt. Both solids were simply filtered off. Now, the stage was set for a second glycosidation step using olivosyl acetate **6a** and polymer-bound silyl triflate **2**. After neutralization, filtration, and removal of the solvent in the usual manner, methyl glycoside **25** was deiodinated and desilylated as described previously to yield the next glycosyl acceptor **26**. The sequence toward trisaccharide **28** was terminated by a third glycosidation step, this time using rhodinosyl acetate **27** as the glycosyl donor. In the presence of the usual set of polymer-bound reagents **1** and **7**, the coupling afforded the α-glycosidation product **28** as a single isomer.

In conclusion, we have developed the first synthetic approach to 2-deoxyoligosaccharides and glyconjugates which relies on polymer-supported reagents. The strategy includes polymer-assisted glycal activation, glycosidation, and *O*-desilylation and affords glycosides in good to excellent yield without tedious workup and product isolation. Hence, this synthetic strategy should have the potential to be applicable for automated parallel synthesis.

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Supporting Information Available: Spectra and descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) In analogy to tetra-*n*-butylammonium fluoride, Amberlyst A-26 (F^- form) was employed for the treatment of various silyl ethers. While both primary and secondary triethylsilyl groups can rapidly be removed, this polymer-bound reagent is not reliable when cleaving secondary primary TBS ethers.