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Beneficial Participation of the Polymer : Improvement in Polymer-Supported Oligosaccharide Synthesis

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Abstract: The reagent combination scandium(III) trifluoromethanesulfonate and acetic anhydride efficiently cleaves oligosaccharides bound to the polyethylene glycol *(PEG)* polymer-support via the dioxyxylene (DOX) linker. Unexpectedly, the site of cleavage is between the DOX linker and the *PEG* polymer. This method of cleavage allows for the use of DOX as a linker for synthesis on polystyrene-polyethylene glycol, PS-*PEG* beads.

Polymer-supported synthesis is an emerging tool for the production of oligosaccharides.[1,2,3] The effective use of the polymer-support polyethylene glycol (*PEG*) for such syntheses is well demonstrated.[1,3] The dioxyxylene (DOX) linker, introduced by Krepinsky *et al.*, has been efficiently employed for the synthesis of up to a pentasaccharide.[4] This linker enables the use of base labile acyl groups as cleavable protecting groups. In spite of the considerable efforts to improve *PEG*-based oligosaccharide synthesis, a number of challenges remain. An increase in the repertoire of orthogonal protecting groups, as well as an increase in the efficiency of the glycosylation reactions are required.[1,3]

The propensity of *PEG* derivatives to complex metal cations has been demonstrated.[5] It is known that a number of conventional metal based reagents render *PEG* into an unfilterable slurry. This makes the usual purification procedure of precipitation and reprecipitation impossible.[6] Oligosaccharides linked via the benzyl-like DOX linker, to *PEG* can be released by Pd, Pt or Ni catalyzed hydrogenation.[4] However, hydrogenation is known to be inhibited by *PEG* derivatives and is substrate specific.[7] This paper describes the novel use of $Sc(OTf)_3$ for the cleavage of the DOX linker from the *PEG* polymer-support. This reaction likely proceeds *via* the coordination of the Sc^{3+} ions to the *PEG*, and represents a new type of reaction for polymer-supported chemistry, that is based on reagent-polymer interactions.

As a part of the process towards developing vaccines against Group B *Streptococcus* bacteria, we are involved in a program to synthesize oligosaccharide fragments of the serotype specific capsular polysaccharides.[8] In order to take advantage of the ease of purification of polymer bound products, we have employed polymer-supported methods based on the soluble polymer monomethyl polyethylene glycol ($MeO\text{-}(CH_2CH_2O)_nOH$ MW 5,000), *MPEG*.[1] Our initial test substrate was the β1,3-disaccharide bound to the *MPEG* polymer-support via the DOX linker **1** (Scheme 1). In this example the DOX linker has been modified by mono-α-methyl substitution to give MDOX. Stimulated by the report that $FeCl_3$ promoted benzyl ether cleavage,[9] we tested the cleavage of **1** with $FeCl_3$ and Ac_2O.[10] Although these conditions did lead to the cleavage of the disaccharide from the polymer, they resulted in decomposition. The useof the hard Lewis acid $Sc(OTf)_3$ was next examined. The combination $Sc(OTf)_3/Ac_2O$ did promote the cleavage of the disaccharide from the polymer-support. To our surprise, the site of bond cleavage was between the *MPEG* terminal oxygen and the benzylic carbon of the DOX linker, and not the expected site between the oligosaccharide and the DOX linker (Scheme 1). Thus, the free β1,3-disaccharide **2** was obtained. The cleavage was complete as only traces of the sugar bound to *MPEG* could be detected by ^1H NMR. Hydrogenation of the diastereomers **2** afforded the reducing disaccharide **3**,[11] a derivative that can be

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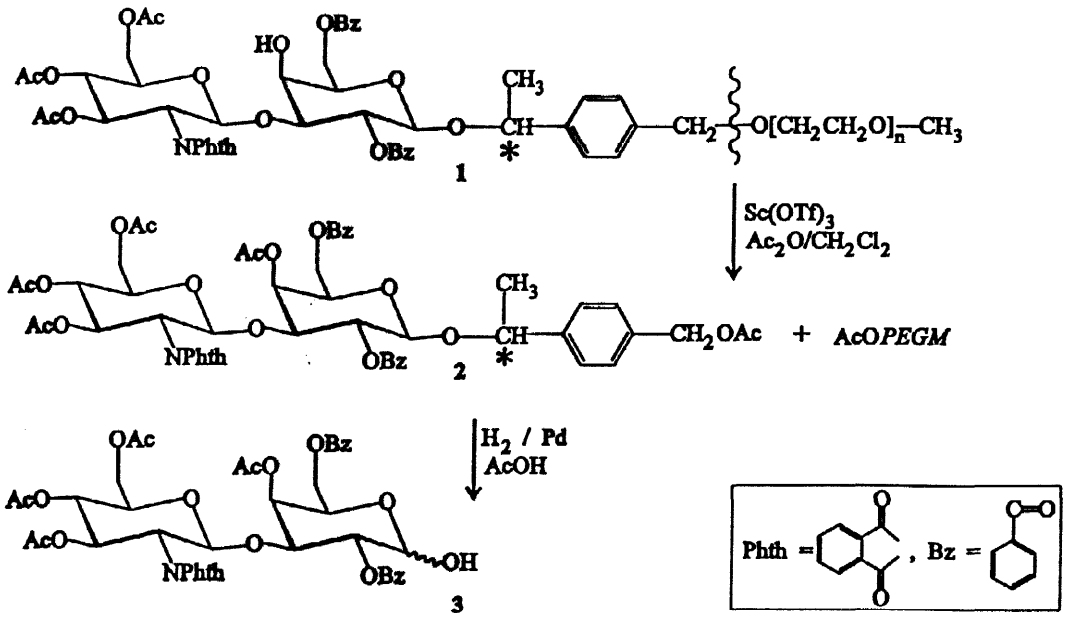
PII: S0040-4039(98)01260-X

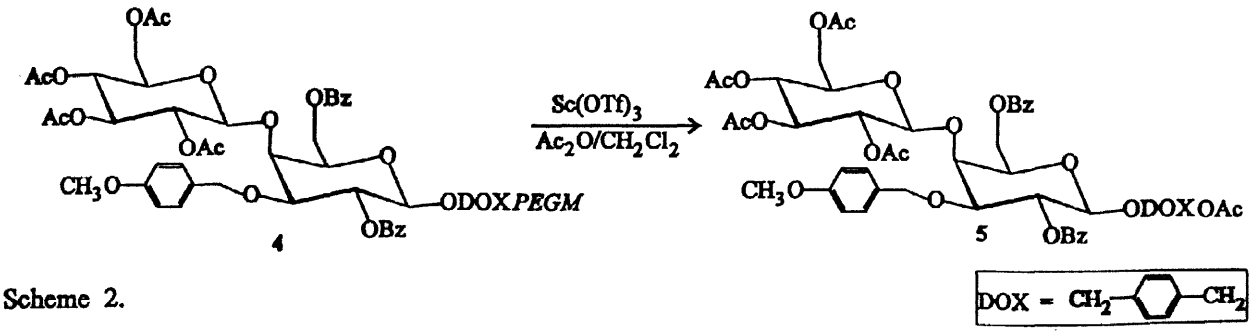


Scheme 1.

easily converted into a disaccharide donor.

Since this reagent combination has been reported to be an effective acylating system, the free hydroxyl group at the 4 position was acetylated under these reaction conditions.[12]

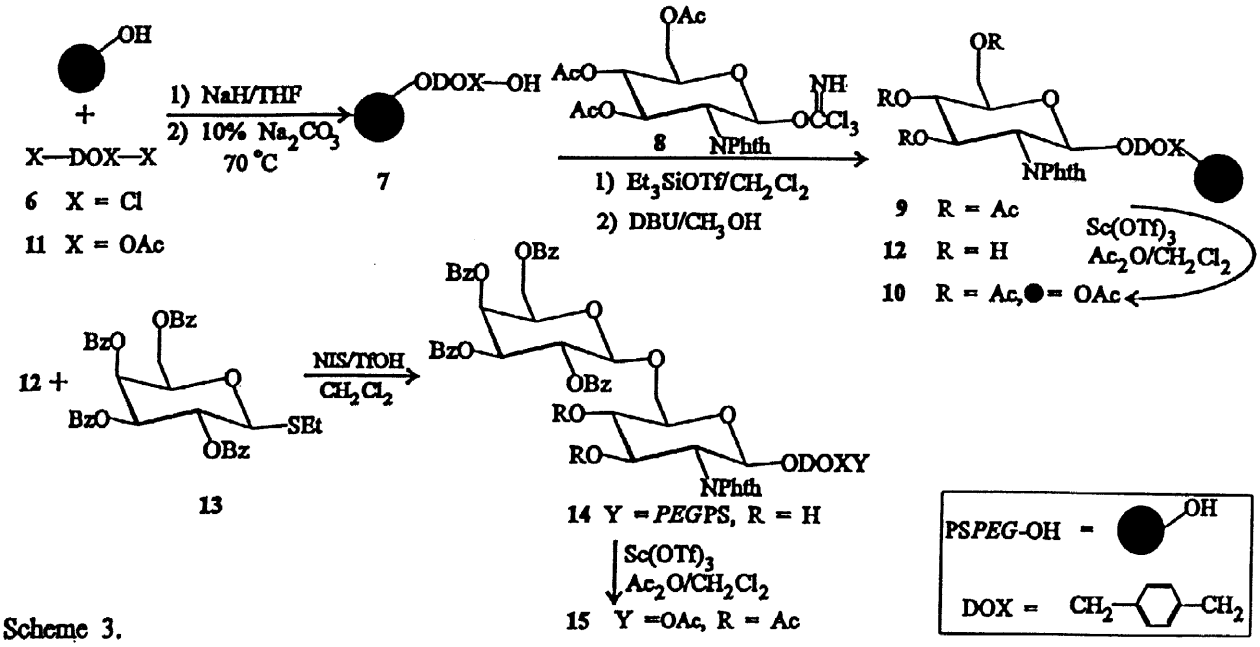
This unexpected position of cleavage led us to experiment with these cleavage conditions on the polymer-supported disaccharide **4**. The reaction of **4** with $Sc(OTf)_3/Ac_2O$ effected cleavage at the *MPEG*-DOX, C-O bond, and not at the anomeric position, to afford the free disaccharide **5**.[13]



Scheme 2.

These results led us to examine oligosaccharide synthesis using polystyrene-polyethylene glycol (PS-*PEG*) beads. Thus, α,α-dichloroxylene **6**, was attached to PS-*PEG*-OH with NaH in tetrahydrofuran, followed by hydrolysis to give **7**. The alcohol **7** was glycosylated with 5 equivalents of the glycosyl donor **8**[14] under TESOTf promotion, in dichloromethane to afford the resin bound monosaccharide **9**. Upon cleavage with $Sc(OTf)_3/Ac_2O$, the expected free monosaccharide **10** and the diacetate of DOX **11**, were obtained (about 3:1). The formation of the diacetate **11** suggested that no side reactions had occurred but that some sites on the beads had remained unreacted. Repetitive treatments or even more vigorous glycosylation conditions did not improve the yield, suggesting that some sites on the beads are not accessible to the glycosyl donor. Deacetylation of **13** in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene afforded the PS-*PEG* bound triol **12**. The glycosylation of the triol **12** with glycosyl donor **13**, under promotion by *N*-iodosuccinimide / triflic acid, afforded the resin

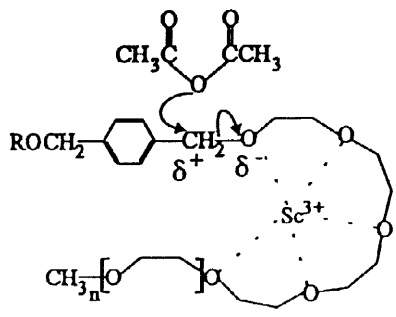
bound disaccharide **14**.[15] Upon cleavage from the resin with $Sc(OTf)_3/Ac_2O$, the free disaccharide **15** was obtained in 10% yield for 6 steps, based on 100% derivatization of the beads.[16] Traces of monosaccharide **10** and the diacetate **11** were obtained as well as traces of other regio- and stereoisomeric disaccharides. Thus, this new method of cleavage allows each step of the solid-phase synthesis to be easily monitored. It also allows the combination of the stable DOX linker, and base labile acyl protecting groups to be used with PS-*PEG* beads.



Scheme 3.

Typically 0.5 equivalents of $Sc(OTf)_3$ were used. Some cleavage could be detected even after 1 min, however 2-4 hours were necessary to obtain complete cleavage.[17] In the case of soluble *MPEG*DOX bound substrates, *MPEG*OAc was the major by-product.

The dominant reaction at the *MPEG*DOX ether linkage is highly suggestive of a complexation mechanism,[18] since other benzylic ethers, such as the electronically activated MDOX (Scheme 1) were stable. The observation of the cleavage of the DOX linker from sites that are inaccessible to the glycosyl donor suggest that steric effects are also not important. Furthermore, two control experiments support the premise of a complexation driven mechanism. Firstly, $Sc(OTf)_3$ is insoluble in dichloromethane but is freely soluble in the presence of MPEG. Secondly, the subjection of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside to $Sc(OTf)_3/Ac_2O$ conditions for 90 hours, in the absence of MPEG, led to its complete decomposition. However, in an analogous reaction conducted in the presence of 1 equivalent of MPEG, the sugar was recovered intact. The benzyl protecting groups were not cleaved under these reaction conditions. These observations suggest that the Sc(III) ion forms a complex with the PEG in such a way that its reactivity is tuned to the cleavage of the DOX-*PEG*, C-O linkage only (Scheme 4).



Scheme 4.

Thus, we have not only discovered a useful reagent for polymer-supported oligosaccharide synthesis, but we have discovered a new type of reaction that utilizes the complexation properties of the polymer-support to promote a useful reaction. It can be envisaged that the deliberate design of polymeric-supports that complex reagents is now feasible. Furthermore, this reaction opens up the use of *PEG*DOX combinations for so called "traceless" linker synthetic applications to compounds other than oligosaccharides.[19]

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11. **3**: $[\alpha]^{20}_{D}$: 19.2° (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.67 (1H, brd, *J* = 2.7 Hz, H-4), 5.53 (1H, d, *J* = 8.2 Hz, H-1'), 5.45 (1H, d, *J* = 3.8 Hz, H-1), 4.15 (1H, m, H-3); HRMS (FAB) calcd for $C_{42}H_{40}NO_{17}$: 830.2294, found *m/z* 830.2309 (M+ - OH).
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17. On an analytically scale to 15-30 mg of resin is added sequentially CH_2Cl_2 (0.5 mL), Ac_2O (0.5 mL) and $Sc(OTf)_3$ (2-3 mg). This mixture is stirred for 3-4 hours, cooled, quenched with TBME, and filtered. The filtrate is evaporated and analysed by TLC, NMR, MS etc. On a larger scale silica gel chromatography can be used to purify the products.
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