# Solid-Phase Synthesis of 6-Deoxyoligosaccharides

J. A. Hunt and William R. Roush*

*Department of Chemistry*
*Indiana University*
*Bloomington, Indiana 47405*

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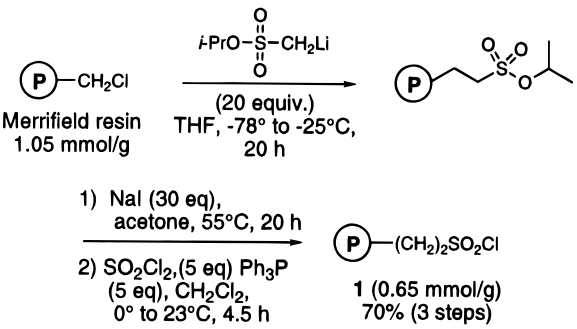
The structural information carried in the carbohydrate chains of oligosaccharides and glycoconjugates is essential to a host of biological recognition processes ranging from fertilization, growth, and development to inflammation and tumor metastasis.[1,2] The availability of a wide variety of structurally defined oligosaccharides, analogs, and mimetics should help to elucidate the myriad biological roles of this class of biopolymers and may also lead to the design of new drugs. Thus, there is a continuing demand for more efficient approaches to the synthesis of oligosaccharides.[3]

The success of solid phase methods in the synthesis of polypeptides[4] and oligonucleotides[5] has prompted investigation of polymer-supported methods for the synthesis of oligosaccharides.[6] Solid phase synthesis offers advantages over traditional, solution-based methods,[7,8] notably that large excesses of reagents can be used to drive reactions to completion and extensive workup procedures and chromatographic purifications are avoided. A diverse array of glycosylation methodology is available for the solution phase synthesis of oligosaccharides,[9] and several of these procedures have proved amenable to solid phase or polymer-supported solution synthesis.[10−17] However, no general method has emerged that is applicable to the solution phase synthesis of all classes of oligosaccharides;[9] this will no doubt prove equally true in polymer supported oligosaccharide synthesis.

Our interest in the synthesis of 2,6-dideoxyoligosaccharides,[18,19] which are integral components of many antibiotic and cytostatic agents,[20] led us to explore the synthesis of these compounds on a solid support. By linking sugar residues to the support through a sulfonate ester bond via the primary hydroxyl,[21] we recognized that synthesis of 6-deoxyoligosaccharides could be achieved via displacement of the oligosaccharides from the resin with iodide ion, coupled with a subsequent reduction step. We report herein the successful realization of this plan.

Sulfonyl chloride resin **1** was prepared following the solution phase method described by Widlanski.[22,23] Thus, treatment of Merrifield chloromethyl resin (ca. 1 mmol/g) with the lithium anion of isopropyl methanesulfonate gave an isopropyl sulfonate resin, which was converted to the corresponding sulfonic acid resin by treatment with NaI in refluxing acetone. The sulfonic acid resin was then converted to the sulfonyl chloride resin **1** by using $SO_2Cl_2$ and $PPh_3$. The loading of **1** was ca. 0.65 mmol/g, as determined by gravimetric analysis, corresponding to a 70% yield from the commercial Merrifield resin.




Resin **1** was treated with 3 equiv of glucose derivatives **2** and **3** ($CH_2Cl_2$, $Et_3N$, 23 °C), and then the acetate units were removed (guanidine, 2:1 MeOH−THF)[24] to give the monosaccharide resins **4** and **5** in 93−97% yield (determined by gravimetric analysis and displacement of the monosaccharides from the resin with NaI in DMF). The progress of the acetate deprotection is easily monitored by IR analysis (KBr disk). Resins **4** and **5** were subsequently treated, in independent experiments, with iodo acetate **6**[25] (3 equiv., TMSOTf, $CH_2Cl_2$, −78 to −65 °C, 4 Å molecular sieves, 20 h; procedure run twice) or the galactosyl trichloroacetimidate **7**[26] (5 equiv., TMSOTf, $CH_2Cl_2$, −15 to 23 °C, 4 Å molecular sieves, 20 h; procedure run twice). The resulting disacharide resins were acylated ($Ac_2O$, pyridine) to cap any unreacted **4** or **5**, and then the disaccharides were cleaved from the polymer support by treatment with NaI (2-butanone, 65 °C).[27] In this way, diastereomerically pure disaccharides **8**−**11** were isolated chromatographically in 91, 90, 87, and 85% yields, respectively; 4−11% of the 6-deoxy-6-iodo-monosaccharides corresponding to unreacted **2** and **3** were detected by $^1$H NMR analysis of the crude reaction mixtures. As a demonstration that this method is indeed useful for the synthesis of 6-deoxyglycosides, disaccharide **8** was reduced to **12** (92%) by treatment with $Bu_3SnH$ ($C_6H_6$, AIBN, 80 °C).

As a more demanding test of this methodology, we have synthesized trisaccharide **19**, a functionalized precursor of the C−D−E trisaccharide unit of olivomycin A.[18] Glycal **13** was coupled with resin **1**, and then the TES ether was removed by exposure of **14** to HF−pyridine in THF. The resulting glycal polymer **15** was then treated with trichloroacetimidate **16** (5

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(27) We have also demonstrated that sugars can be cleaved from the resin by treatment with NaOAc or $NaN_3$ in DMF, giving the corresponding 6-acetoxy or 6-azido sugars in high yield.

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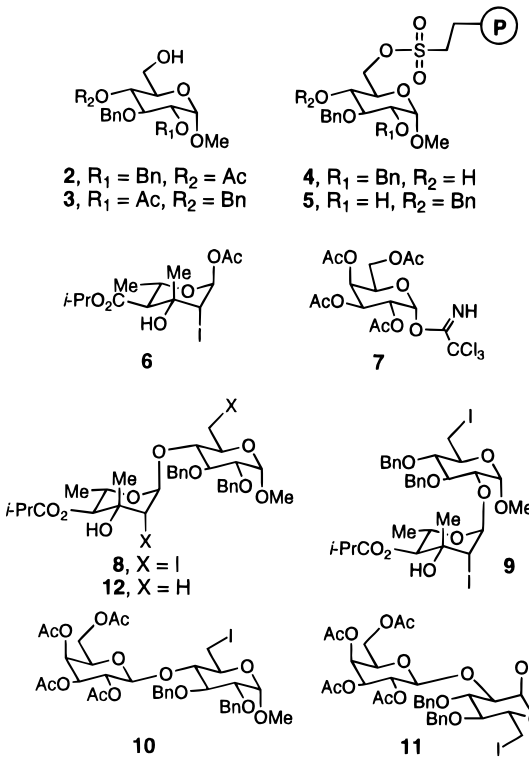
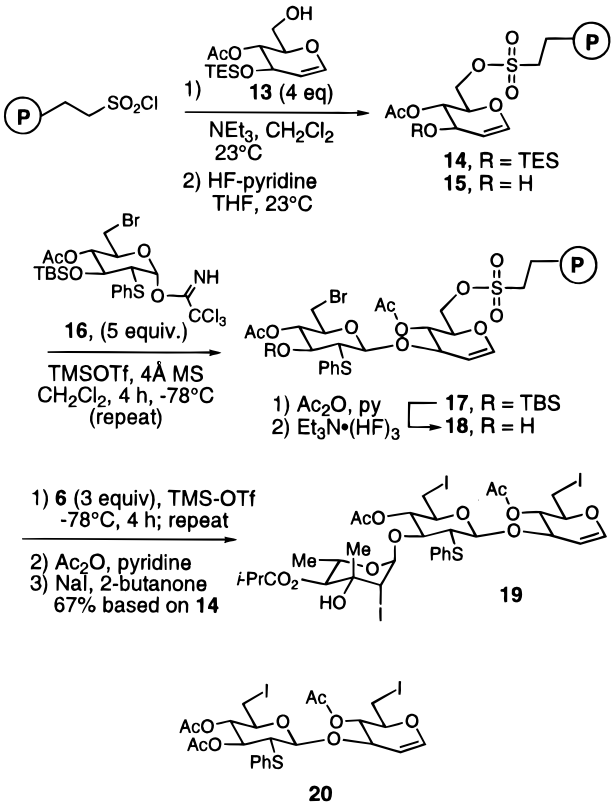



equiv.) and TMS−OTf (1.0 equiv.) in $CH_2Cl_2$ at −78 °C in the presence of 4 Å molecular sieves for 4 h; this experiment was repeated a second time to give disaccharide resin **17**. The resin was then treated with $Ac_2O$ and pyridine to cap any unreacted **17**, and then the 3′-TBS ether was removed by treatment with $Et_3N-(HF)_3$ in $CH_2Cl_2$ to give disaccharide resin **18**. Acylation of a sample of **18** followed by treatment with excess NaI (2-butanone, 65 °C) provided disaccharide glycal **20** in 87% isolated yield. $^1$H NMR analysis of the crude reaction mixture indicated that only trace amounts (≤5−10%) of the α-linked disaccharide were produced. By comparison, the analogous reaction in solution provides a 4−5:1 mixture of *β*- and α-disaccharides.[18] *It is clearly quite significant, and most unanticipated, that the reaction of* ***16*** *and* ***17*** *is much more selective on the solid support than in solution.*[28] Finally, glycosylation of **18** with iodo acetate donor **6** (3 equiv.) and TMS−OTf (1.0 equiv) in $CH_2Cl_2$ at −78 °C for 4 h (this experiment was repeated a second time), acylation of the resulting trisaccharide resin, and treatment with excess NaI (2-butanone, 65 °C) provided diastereomerically homogeneous trisaccharide glucal **19** in 67% isolated yield. The trisaccharide isomer with an α linkage between the C and D residues was not observed.




In summary, we have demonstrated that precursors of 6-deoxy di- and -trisaccharides are easily prepared in high yield by using sulfonyl chloride resin **1** as an insoluble solid support. The sulfonate ester linkage has proven compatible with several different classes of glycosylation and alcohol deprotection conditions, and the mono-, di-, and trisaccharides are readily removed from the resin by treatment with various nucleophiles such as NaI, NaOAc, and $NaN_3$.[27] Finally, it has not escaped our notice that resin **1**, along with other chlorosulfonated polystyrenes,[23] should also be useful for a wide range of substitution reactions on solid supports. Further applications of this strategy for the synthesis of deoxyoligosaccharides will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds (23 pages). See any current masthead page for ordering and Internet access instructions.

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(28) Similar claims are implicit in other reports of polymer-based oligosaccharide synthesis (for example, see: refs 13−15).