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An Efficient Modular Approach for the Assembly of *S*-Linked Glycopeptoids

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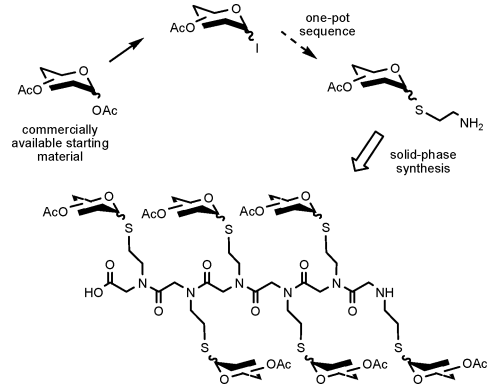
ABSTRACT



A short and convenient methodology for the synthesis of *S*-glycosylated peptoid models is described. The thioglycosylated building blocks were prepared from proper peracetylated sugars via glycosyl iodides in a one-pot fashion and directly employed in a submonomer solid-phase stategy.

Cellular surfaces of all living organisms are coated by glycans covalently attached to proteins, peptides, or lipids. The saccharidic moiety plays an essential role in the interaction with the environment and mediates many cell−cell recognition processes, such as signaling, cell growth and differentiation, immune response, and inflammation.[1]

All these processes are based on associative interactions between the proper saccharide sequences and their own specific receptors (lectins). The affinity enhancement of carbohydrate−protein interactions can be achieved by the so-called "cluster effect" through the employment of multivalent glycoligands, whose applications are useful especially when the protein targets are implicated in pathological events.[2] Several multiantennary carbohydrate-based systems have been created in the last two decades to serve as biological probes. Remarkable examples are represented by gold glyconanoparticles[3] and quantum dots,[4] glycodendrimers,[5] and glycoproteins.[6] However, their synthetic access is often very expensive and time-consuming. In this context, the peptidomimetic backbone of peptoids, or *N*-substituted oligoglycines,[7] is an attractive scaffold for immobilization of bioactive molecules, thanks to an easier preparation and

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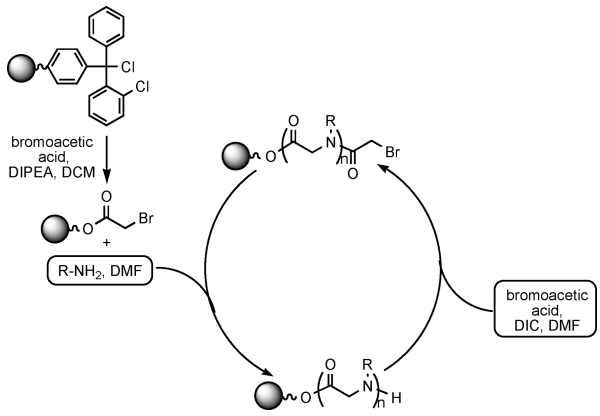
its ability to overcome pharmacokinetic instability and the poor cellular uptake, typical of natural peptides. Furthermore, the higher flexibility of the peptoid backbone facilitates the receptor interaction. Due to these advantages, a growing number of peptoid-based molecules are being investigated in the search for new therapeutics.[8]

In view of the widespread presence of glycopeptides in Nature, the development of a fast and general synthetic procedure toward glycosylated peptoids may represent an important goal. To date, a few synthetic approaches to *N*-linked,[9] *O*-linked,[10] and *C*-linked[11] glycopeptoids have appeared in the literature. Some alternative conjugation methods have also been reported.[12] To the best of our knowledge, examples of *S*-linked glycopeptoids have not yet been reported. Actually, the thioglycosidic linkage is known to be more resistant toward the hydrolytic action of glycosidases while maintaining biological properties of the *O*-analogues.[13] Indeed, this evidence has prompted the development of several methods for use of the thioglycoside bond in glycopeptide synthesis.[14]

Peptoids are generally obtained by a classical solid-phase peptide synthesis[15] (SPPS) or by the "sub-monomer" synthetic strategy,[16] relying on direct construction of the oligomer on the solid support starting from bromoacetic acid and suitable primary amine precursors (Scheme 1). In this

Scheme 1. Sub-monomer Peptoid Solid-Phase Strategy on a Trityl Resin

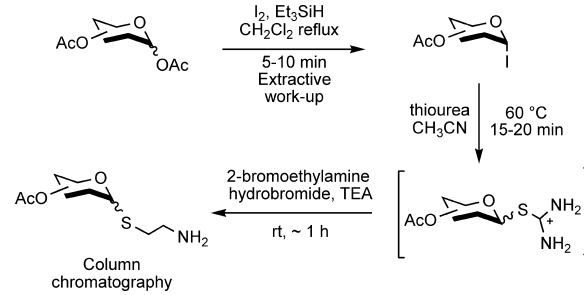


paper, we propose an easy and straightforward synthetic route to an array of thioglycosides appended to an ethylamino linker.

By adapting a fast sequential procedure for the preparation of thioglycosides,[17] this method takes advantage of the in situ generation of a glycosyl thiolate via a glycosyl iodide[18] and its direct coupling with commercially available 2-bromoethylamine, as a hydrobromide salt, to give an *N*-homocysteinyl linkage[14a] (Scheme 2).

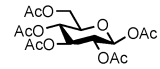
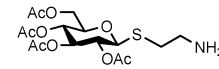
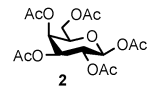
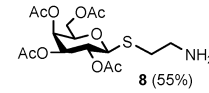
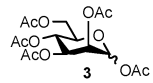
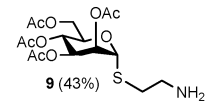
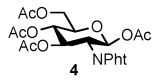
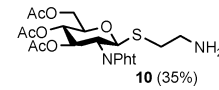
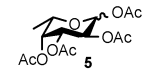
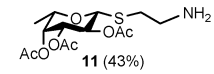
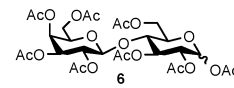
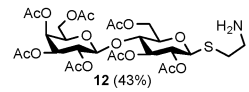
Starting from commercially available per-*O*-acetylated sugars **1** and **2** and easily prepared compounds **3**, **4**[19] and **5** (Table 1, entries 1−5), glycosylated building blocks **7**−**11** were prepared within 2 h without any intermediate purification, except for isolation of the crude glycosyl iodide by extractive workup. All the steps were operationally simple and did not require any special precaution. Only in the case of the lactose precursor **6** (entry 6) were longer reaction times required for the last step, and an inert atmosphere was strictly necessary to prevent disulfide formation. In all cases, the overall yields were satisfactory, and exclusive formation of the 1,2-*trans* glycosides was observed.

Scheme 2. One-Pot Sequence for Thioglycoamine Formation[a]



[a] Yields reported in Table 1.

Table 1. Synthesis of Thioglycoamines via the Sequence Reported in Scheme 2[a]

entry	starting material	products and yields (%)[b]
1	 **1**	 **7** (55%)
2	 **2**	 **8** (55%)
3	 **3**	 **9** (43%)
4	 **4**	 **10** (35%)
5	 **5**	 **11** (43%)
6[c]	 **6**	 **12** (43%)

[a] See the Supporting Information for experimental data. [b] Isolated overall yields. [c] Last step took 6 h rather than 1 h.

In order to test the behavior of the readily obtained glycosylated building blocks in a submonomer solid-phase protocol, we decided to prepare some *S*-linked glycopeptoid models (**13**−**15**, Figure 1).

Glycopeptoid **13** displays two β-D-galactose appendages. This residue is frequently incorporated into multiantennary constructs, owing to its specific interaction with human

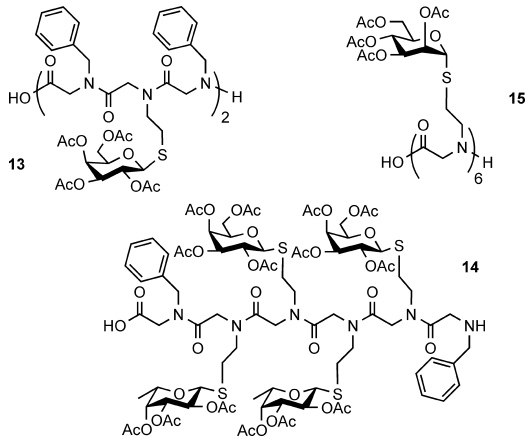


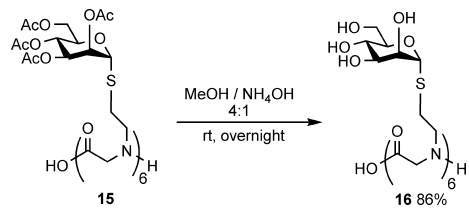
Figure 1. Linear *S*-linked glycopeptoids.

hepatic lectins[20] or as epitope mimics of bacterial toxins.[21] Compound **14** is a hybrid glycopeptoid decorated with both L-fucose and D-galactose units. Multiligands containing both sugars could be of biological interest due to their role in adhesion mechanisms of the pathogen *Pseudomonas aeruginosa*.[22] Finally, the fully mannosylated peptoid **15** allows an improved synthesis of a previously reported *O*-linked counterpart[23] used for interaction analysis with the model lectin concavalin A.[24] It may be included among the mannoside clusters useful for their potential roles in preventing bacterial adhesion.[25]

The synthesis of compounds **13**−**15** (Figure 1) started after loading bromoacetic acid onto a 2-chlorotrityl resin through an ester linkage. The oligomerization was carried out in DMF through cycles consisting of primary amine substitution and *N*,*N*-diisopropylcarbodiimide (DIC)-mediated bromoacetylation (Scheme 1). Both reactions were accomplished in 30 min at room temperature and in very high yields as verified by HPLC and mass spectrometry analysis of the crude peptoids **13** and **14**. In the case of fully mannosylated hexamer **15**, a partial deacetylation was observed. However, the efficiency of the oligomerization was confirmed by the HPLC profile and mass analysis of the crude mixture after reacetylation. Feasible global deacetylation of the linear glycopeptoids was demonstrated by treating hexamannosylated peptoid **15** with ammonia in methanol to afford compound **16** in high yield (Scheme 3).

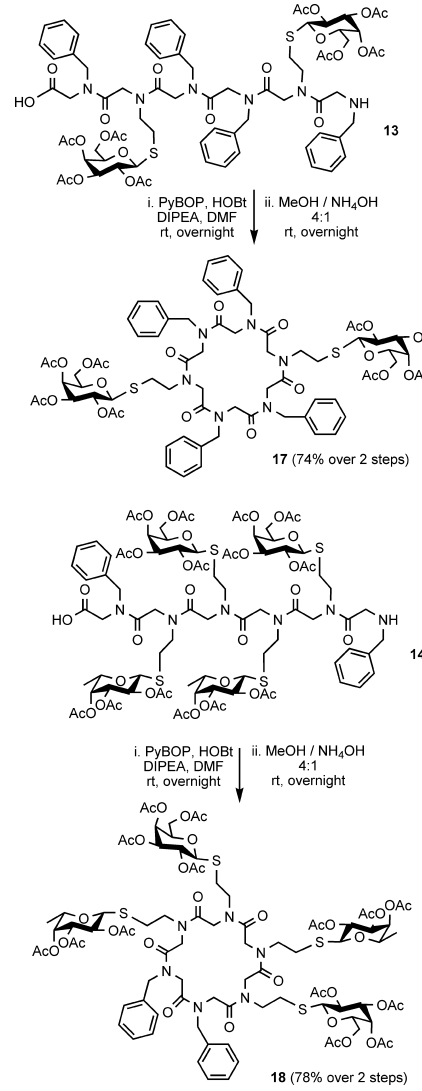
Furthermore, since a more constrained structure may be more efficient for some applications,[8] we performed head-to-tail macrocyclization for peptoids **13** and **14** under high dilution conditions with the use of PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) and HOBt (1-hydroxybenzotriazole) in DMF.[26] The corresponding cyclic compounds were directly deacetylated with ammonia in methanol to give compounds **17** and **18** in good overall yields (Scheme 4).

Scheme 3. Deprotection of Hexamannopeptoid **15**



15 **16** 86%

Scheme 4. Macrocyclization Reaction and Global Deprotection



13 **17** (74% over 2 steps) **14** **18** (78% over 2 steps)

The complexity of the rt ^{1}H NMR spectra recorded for the linear and cyclic oligomers **13**−**18** invoked the simultaneous presence of more than one conformer in slow exchange on the NMR time scale.[27]

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In conclusion, we have developed a straightforward general method for preparation of *S*-glycosylated peptoids and a high yield method for their cyclization. The reported strategy relies on the combination of a rapid synthesis of glycosylated building blocks from inexpensive precursors and their direct incorporation into a time-effective and high-yielding submonomer solid-phase approach. The versatility of the method has been demonstrated by the easy preparation of three glycopeptoids with variable saccharide content. Due to the therapeutic potential associated with the tuning of carbohydrate−receptor interactions, the herein presented overall strategy is expected to be a useful tool for sugar-based drug discovery.

Acknowledgment. We acknowledge the financial support of University of Salerno.

Supporting Information Available: Full experimental details and characterization of all compounds are reported as well as NMR spectra and HPLC chromathograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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