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A Stereoselective Synthesis of a *C*-Glycosylated Peptoid Building Block

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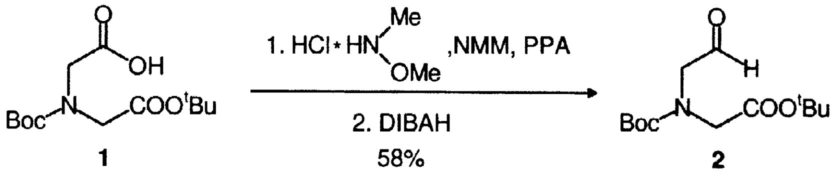
Abstract: A *C*-glycosylated peptoid analogue of the Ser-*O*-GlcNAc with a single carbon chain between the sugar residue and the peptoid was prepared by the coupling of a peptoid aldehyde with a glycosyl dianion of the glucosamine.

Peptoids are *N*-substituted oligoglycines with alkylated N^{α}-atoms.[1] These highly flexible molecules show higher stability towards proteolytic degradation [2] and still resemble their peptidic analogues.[3] During the last years, this modification of the peptide backbone has provided a new concept in the search for new lead structures and for the synthesis of libraries.

R. Roy et al. combined the advantages of peptoids with the glycopeptide approach. They presented several glycopeptoids and glycopeptoid libraries with *O*- and *N*-linked glycans.[4] One motivation for the use of glycopeptoids was to overcome shortcomings of peptides as potential drugs.[5]

Herein we present the synthesis of a novel *C*-glycosylated peptoid analogue of the naturally occurring Ser-*O*-GlcNAc.[6] The use of this peptoid building block should exhibit two major advantages over the *O*-glycosylated peptoids. The spacer length between the backbone and the carbohydrate moiety is isosteric to the serine containing *O*-glycosides which could not be realized in an *O*-glycopeptoid yet. In addition, the *C*-glycosidic linkage is more stable against enzymatic cleavage than the *O*-glycosidic linkage.

The synthesis is analogous to the one for a *C*-glycosylated amino acid that we presented recently.[7] The key step is the coupling of the peptoid aldehyde **2** with a dianion of the glucosamine.



Scheme 1. Preparation of the peptoid aldehyde **2**.

The aldehyde was prepared in two steps from Boc-Nasp-*O*-^{t}Bu **1** [8] as outlined in **Scheme 1**. The carboxylic acid was transformed into the Weinreb amide [9] using *N*,*O*-dimethylhydroxylamine hydrochloride, *N*-methylmorpholine (NMM) and propylphosphonic acid anhydride (PPA) as coupling reagent. Subsequently, the Weinreb amide was transformed into aldehyde **2** by reduction with diisobutylaluminium hydride (DIBAH).

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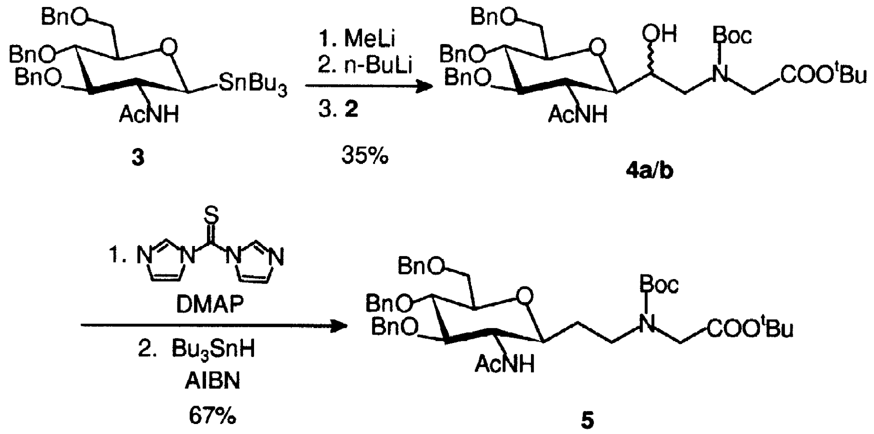
To generate the dianion, tin compound **3** [10] was first deprotonated with methyllithium and then transmetallated with n-butyllithium [11] (**Scheme 2**). After the addition of aldehyde **2** the two diastereomeric *C*-glycosylated peptoids **4a/b** were obtained in 35% yield.[12]



Scheme 2. Synthesis of the *C*-glycosylated peptoid building block **5**.

To remove the hydroxy group, **4a/b** were transformed into the corresponding thiocarbonylimidazoles by using 1,1′-thiocarbonyldiimidazole and 4-(dimethylamino)pyridine (DMAP).[13] The subsequent reduction with tributyl tin hydride and AIBN gave the desired *C*-glycosylated peptoid building block **5** in 67% yield.[14]

Although the coupling yield of aldehyde **2** with the dianion was only moderate, the described procedure offers an easy access to a new glycopeptidomimetic. After removing the ^{t}Bu and the Boc protecting group in one step, this glycopeptoid building block can be easily converted into derivatives useful for peptide synthesis.[15]

References and Notes

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[8] Boc-Nasp-O^{t}Bu was synthesized by reductive amination of H-Gly-O^{t}Bu and glyoxylic acid with subsequent Boc-protection.[1]

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[12] The ratio of **4a**:**4b** was approximately 1:2. Exclusively the β configurated glycopeptoid was obtained.

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[14] $[\alpha]^{20}_D = +10.2°$ ($c = 1.0$, $CHCl_3$); ^{1}H-NMR (500 MHz, DMSO): $\delta = 7.95, 7.91$ (2*d, 1H, NH), 7.36-7.15 (m, 15H, arom. H), 4.73-4.62 (m, 3H), 4.57-4.45 (m, 3H), 3.85-3.12 (m, 11H), 1.80 (s, 3H), 1.74 (m, 1H), 1.43 (m, 1H), 1.39-1.34 (4*s, 18 H); $J_{H(1)-H(2)} = 9\text{-}10$ Hz.

[15] A sample of **5** was converted into the corresponding Fmoc derivative by deprotection with trifluoracetic acid (+10% H_2O) and subsequent protection with Fmoc-Cl.