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# Orthogonally Protected Sugar Diamino Acids as Building Blocks for Oligosaccharide Mimetics

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## Introduction

Sugar amino acids (SAAs) [1] have received considerable interest as building blocks for oligosaccharide and peptide mimetics and as pharmacophor-presenting scaffolds. Used as monomers with a rigid pyran ring, functional pharmacophoric groups attached to the hydroxy, amino, and carboxyl groups can be presented in a distinct spatial arrangement following seminal studies by Hirschmann et al. [2]. Linear and cyclic oligomers of SAAs have been synthesized taking advantage of well-established peptide chemistry, and in certain cases adopting defined secondary structures [1, 3]. Branched structures employing sugar diamino acids, however, are not known.

Here we introduce the protected derivative **1** of 2,6-diamino-2,6-dideoxy-$\beta$-D-glucopyranosyl carboxylic acid, the first example of a sugar diamino acid (SDA) amenable to solid-phase synthesis (Figure 1). Compared to SAAs, the additional amino group can be used to increase diversity by selective functionalization and to form branched oligomers. Oligomeric SDAs with unprotected amino groups, on the other hand, are potential aminoglycoside mimetics.

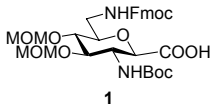


*Fig. 1. Orthogonally protected sugar diamino acid (SDA).*

## Results and Discussion

The synthesis of **1** started from glycosyl cyanide **2** which was prepared according to a published procedure [4]. After deacetylation the obtained triol was regioselectively tosylated at the 6 position followed by azide substitution to give **3** (Figure 2). Hydrolysis of both the nitrile and acetamide under acidic conditions led to the free amino acid. To facilitate isolation, methyl ester **4** was formed by treatment with 2,2-dimethoxypropane and concentrated HCl. First attempts to obtain the free amino acid by basic hydrolysis of **3** ($Ba(OH)_2$, $H_2O$, reflux) were, however, not successful. Under these conditions the reaction stopped at the acetamido carboxylate stage.

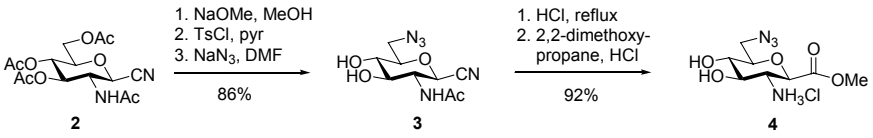


*Fig. 2. Formation of azido amino ester **3**.*

The amino group of **4** was protected by the Boc group with concomitant cleavage of the methyl ester. Methoxymethyl (MOM) groups were introduced by treatment with dimethoxymethane and $P_2O_5$ in order to circumvent toxic MOM-Cl to give **5** (Figure 3). The MOM ester contained in **5** was cleaved with NaOH. Finally, hydrogenation of the azide and subsequent Fmoc protection of the amine gave SDA building block **1**.

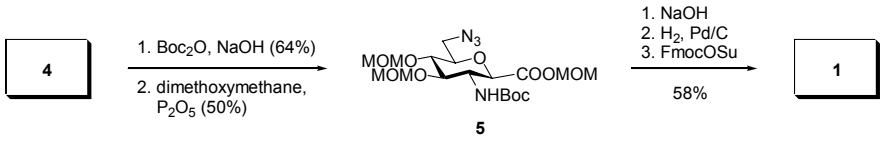


*Fig. 3. Synthesis of SDA building block **1**.*

Building block **1** is suited for peptide coupling reactions in solution and on solid support using the Fmoc strategy as demonstrated in Figure 4. Diphenylmethyl protected $\beta$-alanine amide **6** served as a model for a solid-phase linked amino acid. Stepwise coupling of **1** using HATU/HOAt as coupling reagents followed by complete deprotection led to $\beta$-alanine-linked pseudo disaccharide **8** within 5 steps (Figure 4).

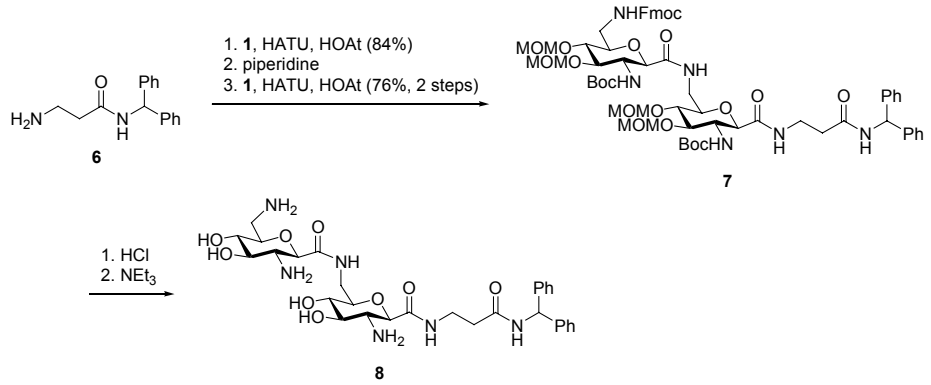


*Fig. 4. Application of SDA building block **1** in peptide coupling reactions.*


## Acknowledgments

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