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Synthesis of Linear THF Amino Acid Homooligomers with *ribo* Configuration

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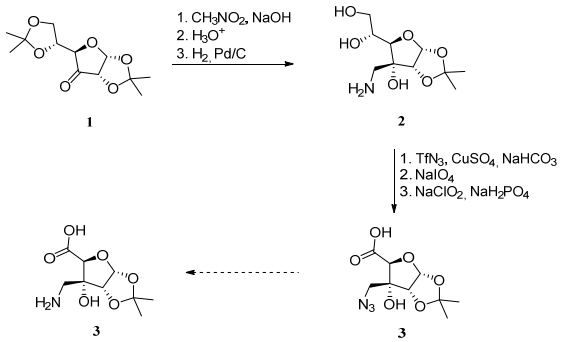
Sugar amino acids (SAAs) represent a structurally diverse class of compounds that can be used in foldamer synthesis and have a potential to act as biologically active analogues of natural biopolymers. SAAs are spread in nature [1], and a well-known example is the sialic acid family widely found peripherally on glycoproteins.

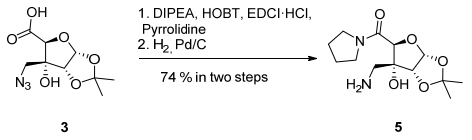
We developed a synthetic strategy towards a novel SAA – ribofuranose-γ-sugar-aminoacid. Commercially available diacetone-α-D-glucose was used as a starting material in a multistep synthesis. The process started with TEMPO catalyzed oxidation affording corresponding ketone **1** [2]. Further synthesis included a sequence of modifications at carbohydrate C(3) position. First diastereomerically pure nitromethyl product was prepared by the Henry reaction. After treatment with a Brønsted acid and the reduction of the nitro group, deprotected aminomethylalcohol **2** was obtained. Azide functionality was introduced by diazotransfer reagent TfN_3. Finally, SAA precursor – γ-azidoacid **3** was prepared by two subsequent oxidation reactions, the first one with sodium periodate followed by Pinnick oxidation. Product **3** can be easily transformed into corresponding amino acid **4**. Synthesis of **3** included six steps starting from ketone **1** with overall yield of 23% (Scheme 1).



Scheme 1. Synthesis of SAA's precursor **3**

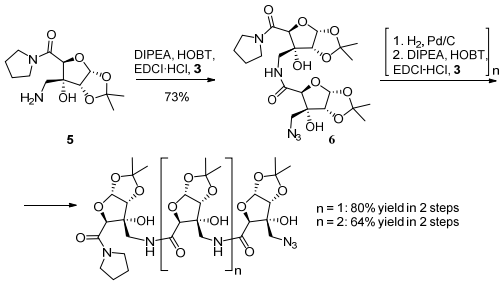
A few derivates of compound **3** were synthesized in order to obtain fully protected monosaccharide unit that could be utilized as a starting material in the synthesis of corresponding homooligopeptides. Some research was conducted to find an appropriate orthogonal protection/deprotection strategy for liquid phase synthesis.

We discovered that simultaneous deprotection of both carboxyl- and amino-termini led to γ-lactam formation. Using isopropyl ester [3] as a protecting group for carboxyl function, intramolecular cyclization also occurred, once free amine was obtained. As a result, we focused on the linear homooligomer synthesis strategy. While the azido group was used for *N*-protection, the *C*-end was protected as a pyrrolidine amide (Scheme 2).



Scheme 2. Synthesis of SAA amide **5**

Oligomers were synthesized from aminoamide **5** following standard solution phase peptide synthesis methods [4] using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI·HCl) and 1-hydroxybenzotriazole (HOBT) as coupling agents and dry DMF or DCM as solvents. Short chain oligopeptides were obtained in relatively good yields (Scheme 3).



Scheme 3. Oligopeptide synthesis

We assume that further elongation of tetrapeptide will lead to novel SAA oligomers that will form well-ordered secondary structures.

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