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Conformational studies of glycosylated cyclic oligomers of furanoid sugar amino acids

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ABSTRACT

Glycosylation of molecules improve their pharmacological and pharmacokinetic properties. In the current manuscript, we have explored the effect of glycosylation on the structure and function of conformationally well-defined small ring homooligomers derived from a structurally diverse library of sugar amino acids (SAA). Conformational analyses carried out by NMR suggested that these cyclic dimers and trimers have well-defined structures in solution. MD simulations performed based on the restraints obtained from NMR revealed that C2H and CO are positioned outside the plane of the ring and NHs are pointed inside the ring. It was encouraging to note that while the cyclic non-glycosylated homooligomers did not show any antimicrobial activity at all, their glycosylated counterparts showed relatively better activity. The modular design developed here is amenable to further improvement and can serve as a tool to investigate many molecular recognition processes.

1. Introduction

Glycosylated natural products are abundant displaying wide ranging antimicrobial, antifungal and/or anticancer activities.[1] Many bacteria also use glycosylated small molecules as chemical weapons to gain a selective advantage or as signalling molecules for intra- and interspecies[1] communication.[2] Sugar moieties in these natural products and metabolites dramatically improve their pharmacological and pharmacokinetic properties, such as solubility, cellular permeability, distribution and metabolic stability.[3] They also impact the delivery of the natural product to the target, present high affinity and specificity for a given target, tissue, cell, as well as modulate both mechanism and in vivo properties.[4] Given that carbohydrates occupy a very large chemical space, differential glycosylation of natural products and/or synthetic small molecules offers a viable strategy to produce new chemical entities with improved pharmacological properties and biological activities.[5] This encouraged us to explore the effect of glycosylation on the structure and function of conformationally well-defined small ring homooligomers derived from a structurally diverse library of sugar amino acids (SAA). To begin with, the choice of the carbohydrate to be attached to these cyclic peptides stemmed from many naturally occurring C_2-symmetric cyclic diolides isolated from marine cyanobacteria, like clavosolides,[6] cyanolides,[7] cocosolide,[8] etc. (Fig. 1), all of which carry methylated xylopyranosides. In this paper, we describe the synthesis, conformational studies and biological activities of cyclic homooligomers **1**–**4** of furanoid sugar amino acids,[9] glycosylated with tri-*O*-methyl-D-xylopyranosyl sugar.

2. Results and discussion

The synthesis of the cyclic glycopeptides **1**–**4** was carried out in a similar fashion as reported by us and others[10] using solution phase peptide synthesis in which, the glycosylated sugar amino acid (SAA) monomers **5**–**8** (Fig. 2) were converted to their cyclic homooligomer counterparts efficiently. The construction of the monomers **5**–**8** (**5** for **1**, **6** for **2**, **7** for **3** and **8** for **4**) was initiated using 2-deoxy-D-ribose (for glycosyl acceptor residues **12** and **13**) and D-xylose (for glycosyl donor residue **14**) as the starting raw materials (Scheme 1). The monomers **5**–**6** differ from monomers **7**–**8** in the configuration of the stereocenter at C2 of the furanoid rings of their constituent δ-SAA moieties (Scheme 1). But the monomers **5** (or **7**) and **6** (or **8**) departed from each other with respect to the type of *O*-glycosidic linkage present in them, i.e.,

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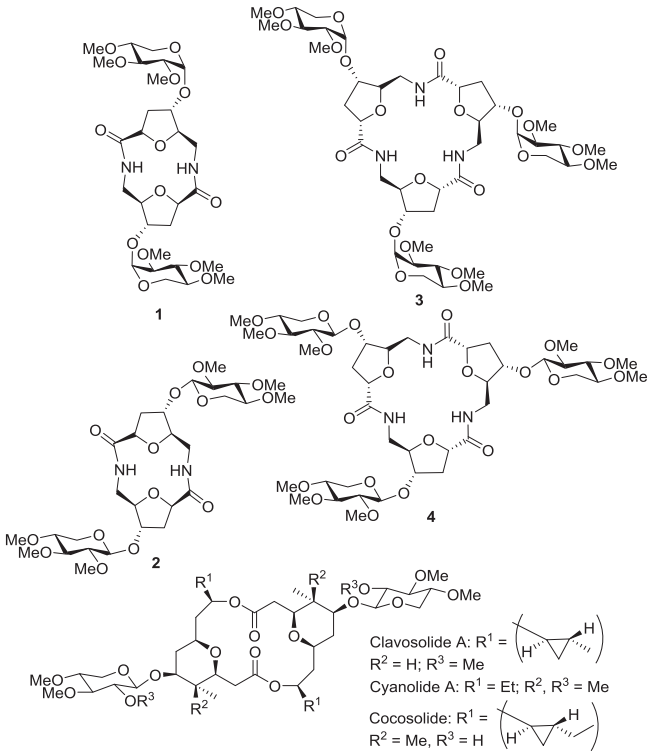


Fig. 1. Structures of glycosylated cyclic peptides of sugar amino acids, **1**–**4** and C_2-symmetric diolide natural products.

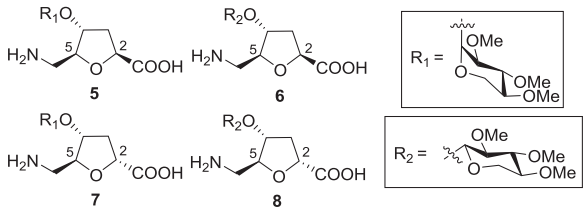
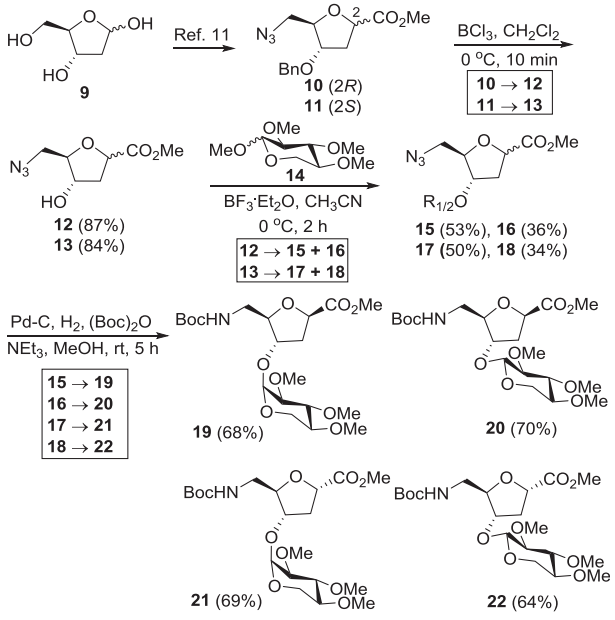
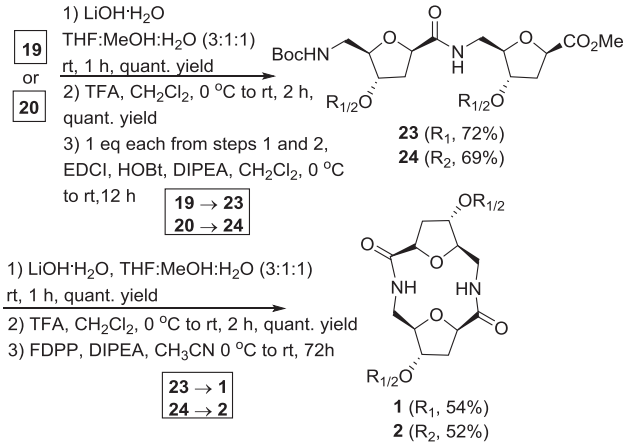


Fig. 2. Glycosylated δ-SAA monomers **5**–**8**.

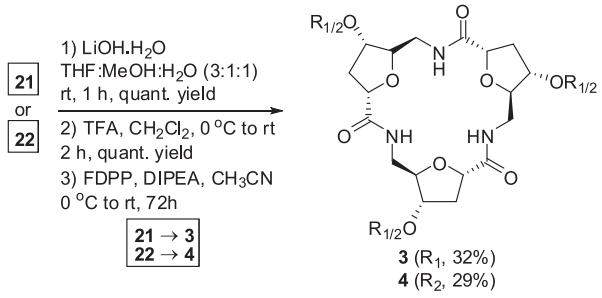


Scheme 1. Synthesis of *O*-glycosylated and protected precursors **19**–**22**.

monomer **5** (or **7**) possesses α-*O*-glycosidic linkage while monomer **6** (or **8**) carry β-*O*-glycosidic linkage. While monomers **5** and **6** were used to get solely the C_2-symmetric glycosylated homooligomers **1** and **2**, respectively, monomers **7** and **8** furnished C_3-symmetric glycosylated homooligomers **3** and **4**, respectively as the major products (Schemes 2 and 3).



Scheme 2. Synthesis of the C_2-symmetric glycosylated cyclodimers **1** and **2**.



Scheme 3. Synthesis of the C_3-symmetric glycosylated cyclotrimers **3** and **4**.

The synthesis of the protected SAA precursors (**19**–**22**), each representing the monomers **5**–**8** sequentially, was carried out by *O*-glycosylation of **12**–**13** using the glycosyl donor **14** (Scheme 1). The preparation of **12**–**13** commenced from commercially available 2-deoxy-D-ribose (**9**) which was easily and efficiently converted into diastereomeric intermediates **10** and **11** as reported earlier from our lab (Scheme 1).[11] BCl_3-mediated benzyl ether deprotection[12] of intermediates **10** (C2-*R*-isomer) and **11** (C2-*S*-isomer) furnished **12** and **13**, respectively, in excellent yields. Thereafter, $BF_3 \cdot Et_2O$ mediated *O*-glycosylation reaction[13] was implemented between substrates **12**–**13** and the glycosyl donor substrate, permethylated-D-xylose[14] **14**, resulting in the formation of α-*O*-glycosylated product **15** along with β-*O*-glycosylated product **16** (from **12**, overall 89% yield) and α-*O*-glycosylated product **17** along with β-*O*-glycosylated product **18** (from **13**, overall 84% yield), respectively in a ratio of 1.5:1 (α:β) after chromatographic separation. The azido moiety in the intermediates **15**–**18** were subjected to in situ one-pot reduction and Boc-protection reactions using Pd-C/H_2 and $(Boc)_2O$-NEt_3, furnishing compounds **19**–**22** in good yields (Scheme 1).

After acquiring the monomeric building blocks **19**–**22**, we proceeded for the synthesis of glycosylated cyclic homooligomers **1**–**4**. Firstly, syntheses of C_2-symmetric cyclic peptides **1** and **2** were accomplished from the monomers **19** and **20**, respectively