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Macrocyclic Carbohydrate/Amino Acid Hybrid Molecules - Synthesis and Evaluation as Artificial Receptors

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Synthesis of a C_3-symmetric macrocycle with alternating sugar amino acid and tyrosine residues

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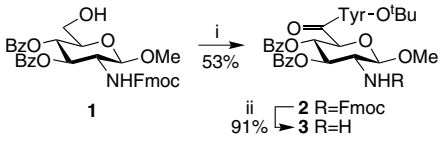
Abstract—A C_3-symmetric macrocycle with alternating sugar amino acid and tyrosine residues was synthesized in seven steps from tyrosine *tert*-butyl ester and a sugar amino acid precursor derived from D-glucosamine. An Fmoc-protected D-glucosamine derivative was oxidized at C-6 to give the sugar amino acid, which was immediately coupled to tyrosine *tert*-butyl ester to produce an orthogonally protected building block. This building block was subsequently elongated to the trimer via the dimer, and finally cyclized to give the C_3-symmetric macrocycle.

Cyclic sugar amino acid/amino acid hybrids have in recent years attracted interest as peptidomimetics[1–7] and have also been proposed as potential artificial receptors.[8–10] The sugar amino acids have mainly been used to induce turns, but in the present work a sugar amino acid that has previously been shown to induce an extended conformation[1] has been used in an attempt to obtain a rigid macrocycle that can form a central cavity without collapsing. Such molecules have the potential to form a binding site for guest molecules in the center and thus act as artificial receptors. We here present the synthesis of a C_3-symmetric macrocycle with alternating sugar amino acid and tyrosine residues. To the best of our knowledge, this is the first example of a C_3-symmetric macrocycle with alternating sugar amino acid and α-amino acid residues, although examples with β- or ε-amino acids have been prepared by others.[9,11]

The first building block for the macrocycle was synthesized by oxidizing sugar amino acid precursor **1**[10] using Jones' reagent and then directly coupling the crude sugar amino acid to tyrosine *tert*-butyl ester, which afforded **2** in 53% yield over two steps (Scheme 1). Sugar amino acid/amino acid hybrid **2** was deprotected using tetrabutylammonium fluoride (TBAF) and 1-octanethiol in THF[12] to give the second building block **3**.



Scheme 1. Synthesis of the building blocks for the macrocycle. Reaction conditions: (i) (a) CrO_3/H_2SO_4(aq)/acetone, (b) H–Tyr–O^{t}Bu/EDC·HCl/HOBt/*N*-methylmorpholine/THF, 16 h; (ii) TBAF/*n*-$C_8H_{17}SH$/THF, sonication, 5 min.

With the necessary building blocks in hand, we turned to the synthesis of the macrocycle (Scheme 2). In the first attempt, building block **2** was treated with 33% trifluoroacetic acid in CH_2Cl_2 with Et_3SiH as a scavenger[13] to cleave the *tert*-butyl ester and the crude product was directly coupled to building block **3** using *N*-(3-dimethylaminopropyl)-*N*′-ethyl carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) in an attempt to produce **4**. This yielded 27% of the desired material **4** along with 19% of epimerized product. Clearly, coupling conditions with lower epimerization were needed and we turned to diisopropylcarbodiimide (DIC) and HOBt in the absence of a base,[14] which gave 58% of **4** and only 6% of the undesired epimer after separation by flash chromatography.

The *tert*-butyl ester of compound **4** was cleaved with TFA/CH_2Cl_2/Et_3SiH and the crude product was coupled to building block **3** to afford **5** in 68% yield. No epimerization was observed in this coupling. The Fmoc

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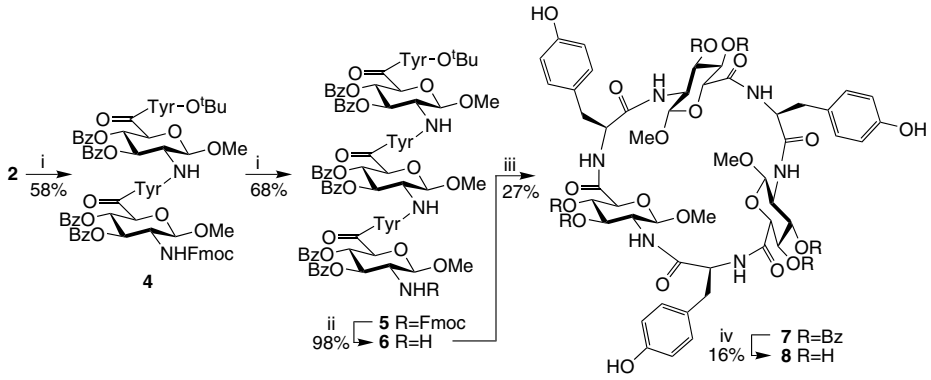

Scheme 2. Synthesis of the C_3-symmetric macrocycle **8**. Reaction conditions: (i) (a) TFA/Et_3SiH/CH_2Cl_2, 4 h, (b) **3**/DIC/HOBt/THF, 16 h; (ii) DBU/*N*-(2-mercaptoethyl)aminomethyl polystyrene, 6 h; (iii) (a) TFA/Et_3SiH/CH_2Cl_2, 4 h, (b) HAPyU/DIPEA/THF, 3 h; (iv) NaOMe/MeOH (2 mM), 5 days.

group of **5** was cleaved using DBU with a solid-phase thiol as a scavenger[15] to give **6** in excellent yield.

After cleavage of the *tert*-butyl ester in compound **6**, the crude linear material was cyclized using 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridinylmethylene)pyrrolidinium hexafluorophosphate-3-oxide (HAPyU),[16] and *N,N*-diisopropylethylamine (DIPEA) in THF under dilute conditions to give **7** in 27% yield. Deprotection of **7** using 10 mM NaOMe in MeOH gave a number of products and only 11% of the desired compound **8** was obtained after purification by HPLC. The main product of the reaction was instead a compound that had a mass that was 18 lower than expected (HRMS 1061.3606, calculated for **8** + Na 1079.3709) and exhibited an NMR spectrum indicative of a nonsymmetrical compound with an unexpected signal in the olefinic region at ~6 ppm. This evidence led us to conclude that elimination of water or benzoic acid had taken place during the reaction. Deprotection at lower base concentration (2 mM) reduced the elimination somewhat and improved the yield to 16%. Deprotection in MeOH using either Et_3N, $MeNH_2$ or 4 Å molecular sieves[20] was also attempted, but these conditions gave even more side reactions.

The $^3J_{HH}$ coupling constants in the sugar amino acid residues decrease from 8–10 Hz to 7–8 Hz upon cyclization of **6** to **7**, which indicates that the $^4C_1$ conformation no longer is the only major conformation of the sugar amino acids. This prompted us to carry out a computational study on the conformation of **8** using Monte-Carlo conformational searches in MacroModel 8.5 (MMFFs force field with water as solvent, 20,000 steps, all backbone torsions were selected for random variation). The calculated low-energy conformers all had only one of the three sugar amino acid residues in the chair conformation, the other two were either in the boat or skew conformations (Fig. 1). Thus it appears that the macrocyclic ring is rather strained, which may be a reason for the difficulties experienced in the deprotection of the macrocycle.

In conclusion, we have prepared a C_3-symmetric macrocycle with alternating sugar amino acid and tyrosine residues in only five steps from the building blocks. The synthetic strategy is flexible in the sense that it will allow structural diversification by varying the amino acid building blocks to give symmetrical as well as nonsymmetrical macrocycles possessing up to three different amino acids, with potential to function as host molecules in an aqueous environment.

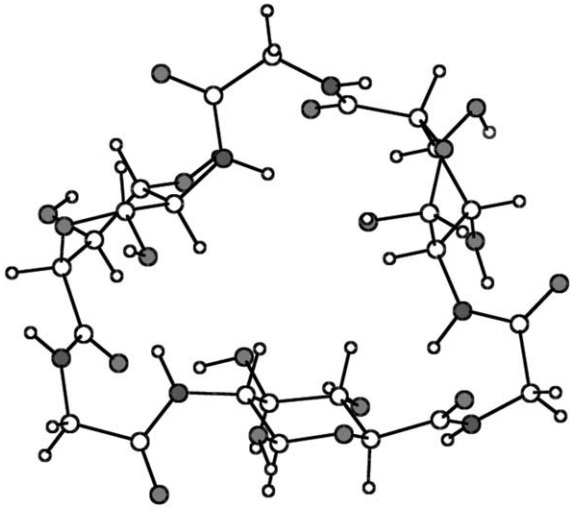

Figure 1. Representative calculated minimum conformation of **8**. Sidechains and methoxy groups omitted for clarity.

Acknowledgments

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Supplementary data

Experimental procedures and physical data for compounds **2**–**8**. Supplementary data associated with this

article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.038.

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