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Synthesis and structural studies of oligomers of 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid

T. K. Chakraborty,[a,*] S. Jayaprakash,[a] P. Srinivasu,[a] M. Govardhana Chary,[a] P. V. Diwan,[a] R. Nagaraj,[b] A. Ravi Sankar[a] and A. C. Kunwar[a]

[a]*Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Centre for Cellular and Molecular Biology, Hyderabad 500 007, India*

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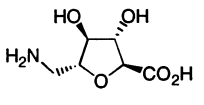
Abstract

A novel cycloetherification process involving a facile 5-*exo* S_N2-type ring closure by intramolecular opening of a terminal aziridine ring by a γ-hydroxyl group, led to the stereoselective synthesis of 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid (**1**). Oligomerization of **1** by solution phase peptide coupling methods gave oligomers **2**–**5**. While most of the oligomers, in either protected or deprotected form, did not show any significant secondary structure, octamer **5** (P = H) exhibited a very strong positive band at 216 nm in its CD spectrum in MeOH and TFE, indicating the possibility of the presence of an ordered structure in solution. Its ^{1}H NMR spectra in various polar solvents, however, failed to produce any distinct dispersion of the amide proton chemical shifts. Compounds **1**–**5** were found to be inactive in hypoglyceamic tests in rats.

During the past few years chemists have developed a large variety of oligomeric compounds that mimic biopolymers.[1–4] These synthetic oligomers are composed of unnatural and yet nature-like monomeric building blocks assembled together by iterative synthetic processes that are amenable to combinatorial strategies. The main objective in developing such oligomers is to mimic the ordered secondary structures displayed by the biopolymers and their functions. They are also expected to be more stable toward proteolytic cleavage in physiological systems than their natural counterparts. Rationally chosen monomeric units from the large repertoire of structurally diverse building blocks are woven together in specific sequences by iterative synthetic methods leading to the development of novel homo- and heteropolymers with architecturally beautiful 3-D structures and desirable properties.



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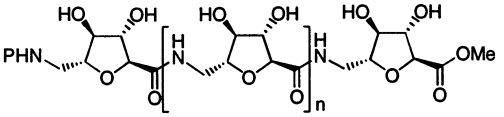

2: n=0; **3**: n=2; **4**: n=4; **5**: n=6
P=H or Boc

* Corresponding author.

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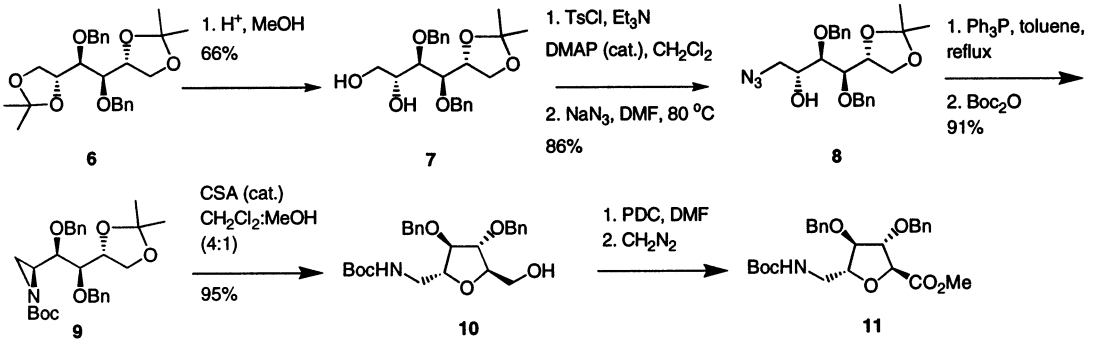
Sugar amino acids constitute an important class of synthetic monomers that have been used recently by several groups to construct oligomeric libraries.[5–19] The idea behind the development of sugar amino acids as a class of unique building blocks was the facile incorporation of these species, using their carboxyl and amino termini for attachments by well-developed solid- or solution-phase peptide synthesis methods, to construct any designed molecular framework. As part of our ongoing project on sugar amino acids and their uses in designing molecules, we report herein the synthesis and structural studies of a furanoid sugar amino acid, 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid (**1**) and its oligomers **2**–**5**.

Work on furanoid sugar amino acid oligomers has been reported by Fleet's group where even short oligomers, for example, a tetramer of gluconic acid-based furanoid sugar amino acid, formed remarkably stable hydrogen-bonded secondary structures in nonpolar organic solvents.[9–13] All the oligomers examined by them had their ring hydroxyls protected and carried an azido group at the N-terminus. Their structural studies by NMR were carried out in $CDCl_3$. We felt it necessary to prepare completely deprotected oligomers so that their structures and properties could be studied in water or other polar solvents in order to develop true mimics of natural biopolymers.

To begin with, we decided to prepare the oligomers of mannonic acid based sugar amino acid **1**. Synthesis of **1** is depicted in Scheme 1. The salient feature of the synthesis is a facile cycloetherification step to construct the 2,5-anhydro furanoid ring. Based on the known susceptibility of linear molecules having S_N2 active sites to undergo spontaneous ring-closure, induced by a heteroatom at the γ-position, to produce thermodynamically favourable 5-membered cyclic products,[20,21] we envisaged that a terminal aziridine ring could be opened regio- and stereoselectively by a γ-hydroxy group, to build the targeted tetrahydrofuran ring of **1**.[22,23] Monodeprotection of acetonide rings of 3,4-di-*O*-benzyl-1,2:5,6-diisopropylidene-D-mannitol (**6**) gave a diol intermediate **7** in 66% yield.[24] The primary hydroxyl of **7** was converted to an azide **8** in two steps in 86% overall yield. Next, the azido alcohol **8** was treated with 2 equivalents of Ph_3P in refluxing toluene leading to the formation of the aziridinyl intermediate, which was protected in situ with Boc_2O to give the target intermediate **9** in 91% yield. The aziridine formation followed an S_N2 mechanism executing inversion at the C5 position. The stage was now set to try out the crucial cyclisation step. When **9** was treated with a catalytic amount of camphor sulfonic acid in MeOH–CH_2Cl_2 (1:4), it underwent facile acetonide deprotection with concomitant and spontaneous intramolecular ring closure by 5-*exo* S_N2-type opening of the aziridine ring by the γ-OH group giving the desired 2,5-anhydro-D-mannitol framework **10**, in 95% yield. Finally, oxidation of the primary hydroxyl in **10** using PDC in DMF followed by esterification with CH_2N_2 gave the protected monomer **11** in 77% yield.[24]



Scheme 1. Stereoselective synthesis of methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-mannonate (**11**)

Oligomerization of **1** was achieved by standard solution phase peptide coupling methods using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and CH_2Cl_2 and/or amine-free dry DMF as solvents. Saponification of **11** gave the free carboxyl group that was reacted with the Boc-deprotected unit using the above-mentioned reagents to furnish the dimer. Two dimers were joined together to build the tetramer, followed by the synthesis of other oligomers in similar fashion. Up to the tetramer, Bn-deprotections were done by hydrogenation in MeOH using Pd on C (10%) as catalyst giving 85% (dimer) and 70% (tetramer) yields. For the hexamer and octamer, the final deprotections were carried out using 10% trifluoromethanesulfonic acid in TFA, in the presence of 10% *p*-cresol. After completion of the reaction, the reaction mixture was poured into an excess of dry ether and the precipitated solids were collected by centrifugation. The residual solids were washed three times with dry ether and dried under vacuum to obtain ~70% yields in both cases. They were used directly for further studies.[24]

The conformational analyses of **2**–**5** were carried out by studying their circular dichroism (CD) spectra in methanol, trifluoroethanol (TFE) and water. The CD spectra of the octamer **5** (P=H) in MeOH and TFE exhibited very strong positive bands at ~216 nm, as shown in Fig. 1(A), indicating the possibility of the presence of a turn structure in solution.[25,26] Dilution of the MeOH solution almost up to 50% with H_2O did not change the nature of the band much. Unfortunately, the ^1H NMR spectra of **5** in various polar solvents, like DMSO-d_6, CD_3OH, CD_3OH–H_2O mixture and H_2O, did not exhibit any significant dispersion of the amide proton chemical shifts. Fleet's group also had similar experiences with the *O*-acetylated tetramer of the same sugar amino acid in $CDCl_3$.[11] Acylation of the N-terminus of the tetramer with fatty acid (**3**, P=$CH_3(CH_2)_{12}CO$), designed to model a membrane-bound oligomer, also failed to separate the amide proton peaks in its NMR spectrum.

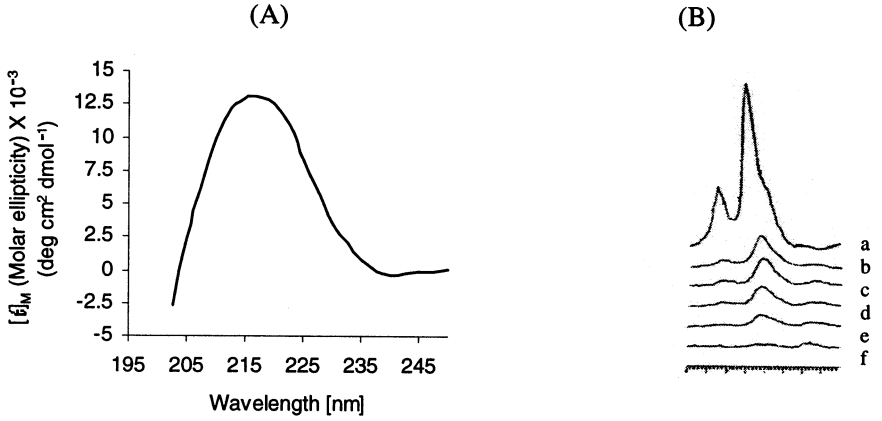


Figure 1. (A) CD spectrum of **5** (P=H) in MeOH. (B) Studies on NH/ND exchanges in **5** (P=H): amide proton peaks in CD_3OH–H_2O (4:1) (a); in CD_3OD–D_2O (4:1) after 20 (b), 30 (c), 40 (d), 60 (e) and 120 (f) minutes

Next, attempts were made to study the NH/ND exchange rates in **5** (P=H) by running its ^1H NMR first in CD_3OH–H_2O (4:1). Subsequently, spectra in CD_3OD–D_2O (4:1) were recorded 20, 30, 40, 60 and 120 minutes after solution preparation. The results are summarised in Fig. 1(B).

Most of the amide protons exchanged rapidly, while one proton showed much slower solvent exchange. This peak gradually disappeared over a period of time and almost totally exchanged in 120 minutes. The study indicates that at least one amide proton is probably buried inside and less accessible to the solvents or involved in some kind of intramolecular H-bond. However, further structural studies are required to identify the exact nature of the ordered structure displayed in its CD spectrum.

Finally, compounds **1**–**5** were tested for their hypoglyceamic activities in normal Wistar rats and were found not to reduce their blood sugar levels. Modifications of the sugar backbone and further improvements in design are expected to lead to many such novel molecular frameworks that may exhibit interesting structures and also have useful properties.

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