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Synthesis and Solution Conformation of Homo-β-peptides Consisting of *N*-Mannofuranosyl-3-ulosonic acids

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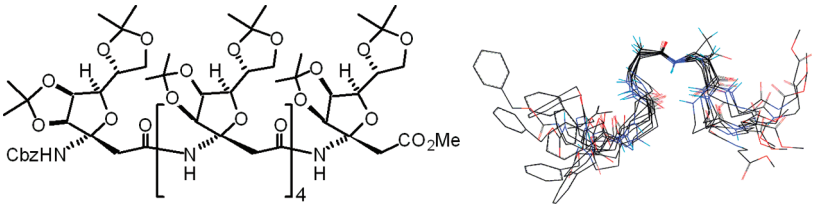

The synthesis and solution conformation of homo-oligomers of β-aminoacids, β-*N*-mannofuranosyl-3-ulosonic acids, have been studied by NMR, MD simulation, and circular dichroism. These oligomers feature a spirocyclic disubstitution and a N,O-acetal functionality at the β-carbon of the backbone, an unprecedented situation in the realm of β-peptides. Our study shows that tetramer **10** and hexamer **11** adopt a characteristic secondary structure. In the hexamer **11**, NMR investigations coupled with MD simulations suggest the preference for a double C_8 turn forming conformation.

Introduction

β-Peptides that are oligomers of β-amino acids have been the most studied class of foldamers[1] since the pioneering work of Gellman[2] and Seebach.[3] In β-peptides, the presence in the backbone of an additional carbon atom between the amino and the carboxyl groups allows a greater diversity compared with α-peptides, not only in term of primary structure but also, and this is the most striking observation, in term of secondary structure.[4] Indeed it has been demonstrated that linear and cyclic short β-peptidic sequences are able to fold into well-defined structures such as turn,[5] helical,[6] and sheet-like conformations.[7] In addition they exhibit a greater stability toward metabolization by microorganisms and to protease and peptidase degradations.[8] All of these interesting features make them the most thoroughly studied oligomers as peptidomimetics.[4c,9] It is now recognized that helical β-peptides are able to mimic protein

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secondary structures and thereby can act as protein−protein interaction inhibitors.[8,10] For example, they have shown promising biological activities as antibacterial agents[11] and somatostatin receptor binding[12] or anticancer drugs.[13] Self-association of helical β-peptides toward protein-like assemblies is also currently studied,[14] and mixed α/β-peptides designed for specific biological functions have also received much attention in recent years.[10c,15,16]

Sugar amino acids are sugars with both an amino group and a carboxyl group attached to the carbohydrate framework. Peptides containing sugar amino acid building blocks[17,18] have been used extensively in the area of peptidomimetic studies,[19] oligosaccharide mimetics,[20] and as structural element to induce secondary structures.[21]

β-Peptides consisting of sugar β-amino acids have also received much attention. Oligomers incorporating sugar β-amino acid residues were found to form helical secondary structures.[22,23] Glycosylated β-peptide[24] chains that retain typical helical secondary structure despite the presence of highly oxygenated carbohydrate appendages have also been described.[25] Sharma and Kunwar have designed C-linked carbo-β-peptides in which furanoid sugars are linked to a β-peptide backbone by the C-4 (sugar numbering). Oligomers derived from C-linked carbo-β^3-amino acids with alternating chirality form both 10/12 and 12/10 right-handed helices, whereas mixed β-peptides derived from alternating C-linked carbo-β^3-amino acids and β-hGly units adopt left-handed 10/12 and 12/10 helical structures.[26] A more surprising situation is when the anomeric center is merged into the β-carbon of a β-amino acid residue. We have previously shown that such structures, *N*-glycosyl-3-ulosonic acids, are readily prepared from *exo*-glycals.[27] They are useful building blocks for the synthesis of spiro sugar-diazepinediones heterocycles[28] and can be incorporated into small mixed peptides.[29] We recently described short homo-oligomeric cyclic peptides constituted of anomeric sugar $\beta^{3,3}$-amino acids.[30] We now give

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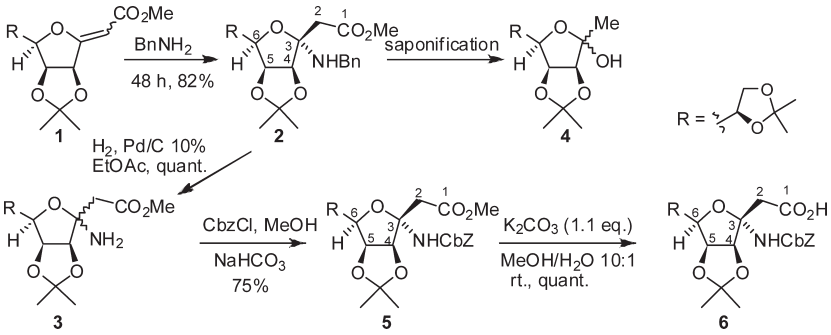
SCHEME 1. Synthesis of Building Blocks for Oligomerization



a full account of the synthesis and of the conformational preference of their linear precursors. Relatively little work concerns the conformational behavior of homo-oligomers consisting of β,β-disubstituted β-amino acids.[31] $\beta^{2,2}$- or $\beta^{3,3}$-amino acids do not adopt the most common secondary structures described in the β-peptide field.[8a] Oligomers **7**−**11** do not resemble other β-peptides previously reported in the literature. They are geminally disubstituted by two sides of a cycle at the β-carbon. This situation has been described at the α-carbon; the X-ray crystal analysis of a trimer consisting of 1-(aminomethyl)-cyclohexane-carboxylic residues features 10-membered hydrogen-bonded rings,[8a] while C-8 pseudocycles[32,33] are observed with oligomers bearing cyclopropylidene rings.[34] Geminally disubstituted β-amino acids in which the β-carbon is embedded in a cycloalkane ring have been used as turn inducers in short peptides[35] but have not been incorporated in β-peptide chains. To the best of our knowledge homo-oligomers **7**−**11** are the first ones featuring a spirocyclic substitution at the β-carbon. Moreover, the β-carbon of the peptide chain corresponds to the anomeric carbon of a sugar ring, and as a consequence this carbon features a N,O-acetal functionnality.[36]

Results and Discussion

Synthesis. The synthesis of the key building blocks for oligomerization is given in Scheme 1. *N*-Glycosyl-amino ester **2** was prepared by aza-Michael addition of benzylamine[29] to the *exo*-glycal (*manno* configuration) **1**.[27] Hydrogenolysis of the *N*-benzyl group lead to an α/β-mixture of *N*-glycosyl amine **3**.

However, starting from this *N*-glycosyl-amino ester mixture, amidation furnished a single anomer in which the anomeric nitrogen is *anti* to the 4,5-fused acetonide (ulosonic numbering). We next turned our attention to the saponification of the ester function of **2** in order to obtain the free carboxylic partner for the oligomerization study. Saponification of this compound resulted in a decarboxylation process whatever the reaction conditions used and gave ketose **4**. We reasoned that this reaction would be avoided by deactivation of the nucleophilic properties of the anomeric nitrogen. We therefore decided to protect the free amino group of **3** as a carbamate. A benzyloxycarbonyl protecting group, orthogonal to the sugar acetonides, was chosen and readily installed by reaction with benzyloxycarbonyl chloride (CbzCl) and $NaHCO_3$ in methanol. The resulting *N*-protected β-amino ester **5** was isolated as a single β anomer in accordance with our previous observation.[29] Hydrolysis of the ester was then performed with K_2CO_3 in aqueous methanol and yielded the expected carboxylic acid building block **6** quantitatively.

With the necessary building blocks **3** and **6** in hand, we turned to the synthesis of dimer **7**. The crude building blocks **3** and **6** were coupled using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate salt[37] (HATU) and diisopropylethylamine (DIPEA) in DMF giving a single glycosyl-β-dipeptide **7** in 70% yield after silica gel chromatography as an easily handled foam. The configuration at the anomeric center of each unit in **7** was established unambiguously by long-range NOE correlation (N-H→H-4, ulosonic numbering), and we therefore showed that starting from a α/β mixture of amines **3**, only the anomer having the two C3-NH links *trans* to the 4,5-dioxolane (ulosonic acid numbering) was obtained. Dipeptide **7** served as a common intermediate to prepare the two requisite units **8** and **9** for the tetramer synthesis. A portion of **7** was converted to the free carboxylic dipeptide unit **9** using the above-described procedure for saponification of the monomer **5**. The remainder of **7** was converted in the unmasked dipeptide amine **8** by hydrogenolysis. Finally, coupling of **8** and **9** using HATU and DIPEA in DMF yielded the tetramer **10** in 47% overall yield (three steps). Iteration of the process (saponification of the tetramer **10** and coupling with **8**) gave the hexamer **11** in 50% overall yield.

The solution conformation of these $\beta^{3,3}$-peptides was investigated using NMR and CD spectroscopies and molecular dynamic simulations.

NMR Spectroscopy. Spectra were recorded at 400 MHz in deuterated chloroform and/or benzene-d_6. The structure of the oligomers **7**, **10**, and **11** was unambiguously established. In particular the stereochemistry of the anomeric linkages was systematically confirmed using NOE correlations.

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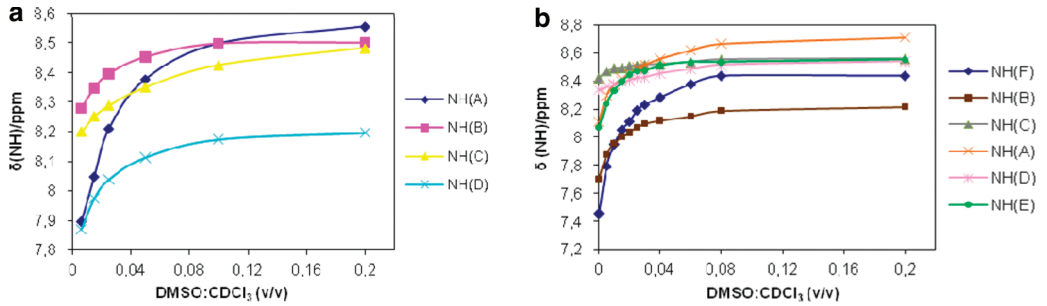
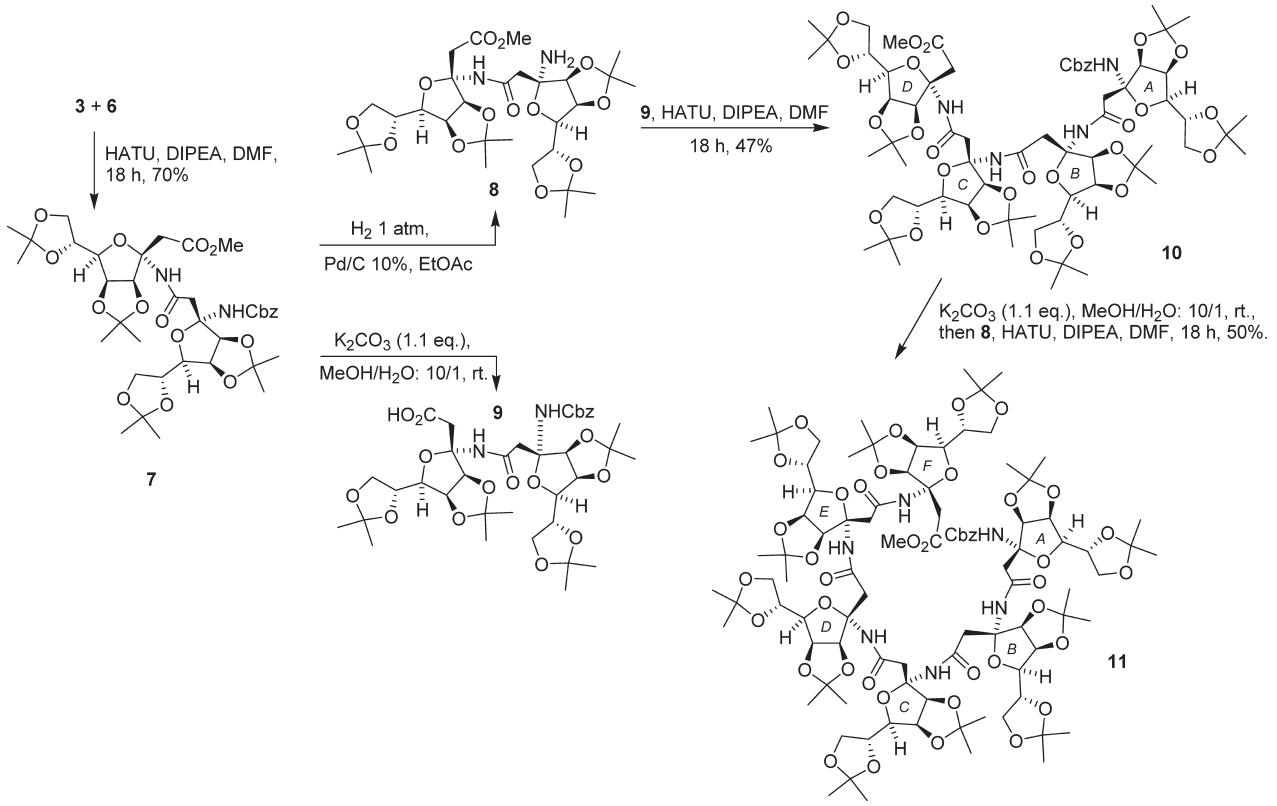


FIGURE 1. Solvent titration plot for the amide NH of tetramer **10** (a) and hexamer **11** (b) showing the variation of chemical shift with % of DMSO-d_6 to C_6D_6 at 298 K.

SCHEME 2. Oligomerization Reactions[a]



[a]To facilitate the discussion, the residues in tetramer **10** and hexamer **11** are identified alphabetically from the N- to C-terminus. Letters that identify the residues are drawn inside of each sugar ring.

Proton assignments for each residue were established from a combination of 2D (COSY45, HMQC, TOCSY) techniques, and the sequential assignment of the four (compound **10**) and six (compound **11**) residues was established using through-bond long-range $^1H-^{13}C$ correlations (HMBC).

Despite the fact that both tetramer **10** and hexamer **11** are homo-β-peptides, consisting of up to six identical residues, signal dispersion was observed throughout their ^1H NMR ($CDCl_3$ and C_6D_6) spectra, suggesting the occurrence of a conformational preference. Well-dispersed chemical shifts of the amide resonances (from 7.48 to 8.21 ppm for compound **10** and from 7.58 to 8.51 ppm for compound **11**), particularly in d_6-benzene, allowed the assignment of all the NH signals. This dispersion of the amide protons was also indicative of a hydrogen-bonding structure in solution. DMSO-d_6 titration into a benzene solution showed distinct amide environments for hexamer **11** (Figure 1b). The $\Delta\delta$ ppm values exhibited by the NH groups were 0.60, 0.51, 0.13, 0.21, 0.48, and 1.10 for NH_A, NH_B, NH_C, NH_D, NH_E, and NH_F, respectively, showing that NH_F was the most shifted one and thus the most exposed to the solvent. The internal NH_C and NH_D appeared to be more involved in intramolecular H-bonds. DMSO-d_6 titration of tetramer **10** was also performed ($\Delta\delta$ NH ppm 0.38, 0.27, 0.34, and 1.10 for NH_A, NH_B, NH_C, and NH_D). Again, the NH group at the N-terminus was the most exposed to the solvent (Figure 1a).

Usually in β-peptides, the NH−CH(β) coupling constants for individual residues allow to establish the relative disposition of the corresponding H-atoms and the torsion angles found can be used as restraints, in addition to NOEs, in

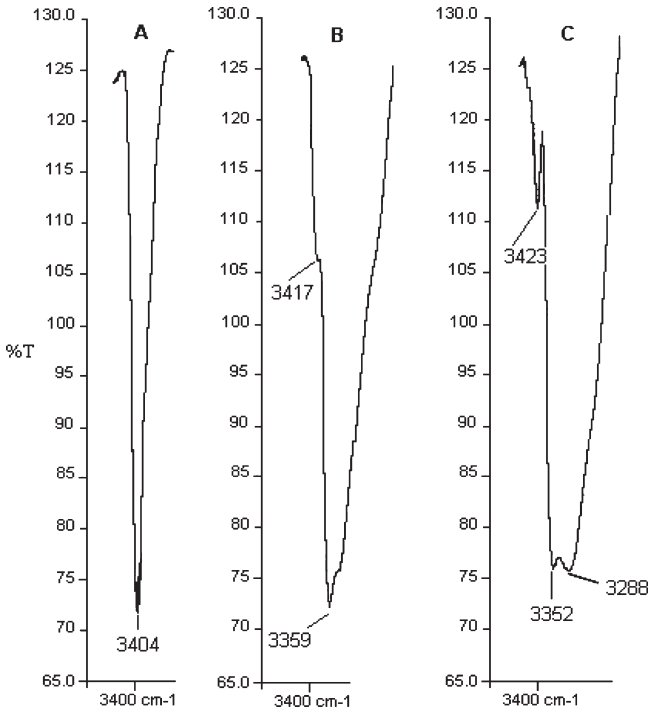


FIGURE 2. Solution infrared spectra (2 mM in $CHCl_3$) of monomer **5** (A), dimer **7** (B), and hexamer **11** (C).

molecular dynamics simulations. In contrast, the absence of CH(β) in β,β-disubstituted β-amino acids and their oligomers makes them more difficult to analyze from a conformational point of view. Due to important overlapping in the ^{1}H NMR spectrum of **11**, only few cross-peaks could be considered unambiguously from the 2D ROESY experiments. All the cross-peaks identified except one ($NH_A \rightarrow H4_c$) were NH→H4 NOEs, involving the NHs and H4 of neighboring residues ($NH_A \rightarrow H4_B$, $NH_B \rightarrow H4_C$, $NH_E \rightarrow H4_F$, $NH_B \rightarrow H4_A$, $NH_D \rightarrow H4_C$).

Solution IR spectrum of compound **11** in $CHCl_3$ (Figure 2) was also used to differentiate hydrogen-bonded from non-hydrogen-bonded amides and as such gave further evidence of the presence of hydrogen-bonded conformations.

The solution IR spectrum of the monomeric unit **5** (Figure 2A) exhibited only one sharp band at 3404 cm^{-1} corresponding to the carbamate N−H stretch. Shoulders at 3417 and 3423 (Figure 2B and C, respectively) were assigned to the N−H carbamate. Dimer **7** (Figure 2B) showed only one amide environment at 3359 cm^{-1} consistent with a non-hydrogen-bonded amide, whereas the hexamer **11** (Figure 2C) showed a broad signal with two N−H stretches at 3352 and 3288 cm^{-1} consistent with non-hydrogen-bonded and hydrogen-bonded amides.[34]

MD Simulation.[38] The previously obtained set of NOEs was used to restrain the MD simulation by fixing a set of distances ranging from 2 to 5 Å. The simulation system was generated by placing the hexamer **11** in a cubic solvent box (39/38/42 Å) containing 512 molecules of benzene. After one first minimization over the entire system, MD simulation was performed at 600° K during 200 000 step integrations of 1 fs. The system was equilibrated for 5000 fs in the NVT ensemble. The resulting ten most stable structures for **11** have been extracted and minimized with constraints.

The superposition of the 10 lowest energy conformers is shown in Figure 3. Three structures are in the first half of the MD simulation and the other seven are distributed throughout the second half. The N- and C-terminus, which do not participate in hydrogen bonding, display important fraying while the backbone of the central residues C and D is more well-defined. Depending on the conformations, NH_E adopts two well distinct orientations. One of them allows the NH_E-CO_B hydrogen bond to be formed (12-membered ring), but the latter is not corroborated by DMSO NMR titration. Conformers displaying this hydrogen bond appear in the second half of the simulation (see for example structure B in Figure 4 obtained after 119 700 steps), they are characterized by a central turn that brings residues B and E close together and by backbone lengths ranging from 12.4 to 9.8 Å (Figure 3, b). Whatever the conformation, NH_B is never involved in H-bonding while NMR data ($\Delta\delta$ NH_B = 0.51 ppm, DMSO-d_6 titration) could suggest that it is weakly H-bonded. A reasonable interpretation is that a weak H-bond could be established occasionally with the highly crowded and oxygenated sugar portions of the oligomer.[39] This kind of hydrogen bond is observed in some of the 10 lowest energy conformations (see Supporting Information). The more extended structure at ca. 18 Å length (Figure 4a) is actually the one in best agreement with NMR titration. This conformation shows two consecutive eight-membered ring hydrogen bonds, NH_C-CO_A and NH_D-CO_B.

These C_8 conformations are also found individually among some of the 10 lowest energy structures and are believed to occur in the tetramer **10**. It is worth mentioning that eight-membered hydrogen-bonded rings between N−H (i) and C=O (i − 2) have been observed in a cyclic homo-β-peptide prepared from tetramer **10**.[30] Consecutive C_8 pseudocycles have been observed in the field of β-peptides when a hydroxy group is present in the 2-position of each amino acid residue,[32] in the crystal structures of a dimer, a trimer, and a tetramer consisting of 1-(aminomethyl)cyclopropanecarbonyl moieties[34], and in a dimer and trimer of a family of oxanorbornene β-peptides.[40] Eight-membered hydrogen-bonded rings were also found in oligomers composed of α-aminooxy acids[41] and in aza-β^3-peptides.[42]

Modeling of H-8 and H-12 Helices. NMR titration and MD simulations tend to show that the secondary structure of hexamer **11** is mainly governed by two hydrogen bonds between CO and NH of amides in the backbone, namely, the NH_C-CO_A and NH_D-CO_B. Nevertheless it seemed of interest to evaluate whether helices described in the β-peptide field could be conceivable in our case. To answer this question, the construction of several models of helices for the hexamer **11**, by fixing the torsional angles in the backbone was performed. H-8 (ϕ −69°, ψ −64, θ 120°),[43] H-12

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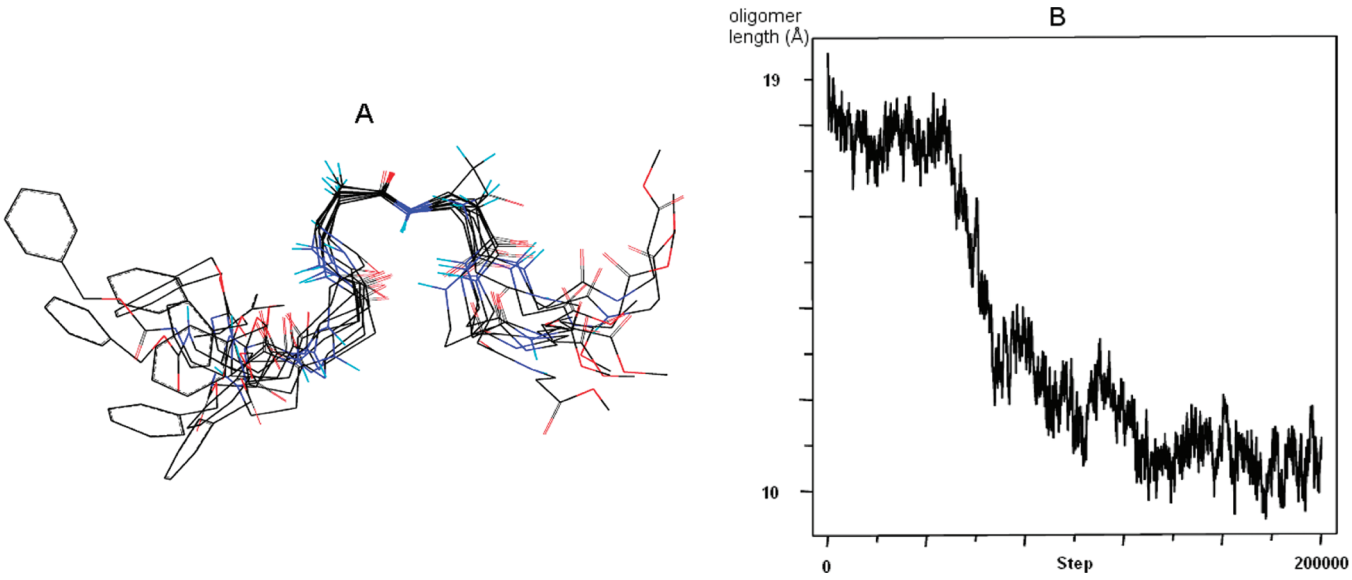

FIGURE 3. (A) Structure of β-hexapeptide **11**. Bundles of the 10 lowest energy conformers incorporating NOE-derived distances constraints (first structure obtained after 39 900 steps). Carbon atoms are in black, nitrogens in blue, and oxygens in red. Side chains and hydrogens atoms (except amide NH) omitted for clarity. (B) Variation of the length (Å) of **11** during MD simulation.

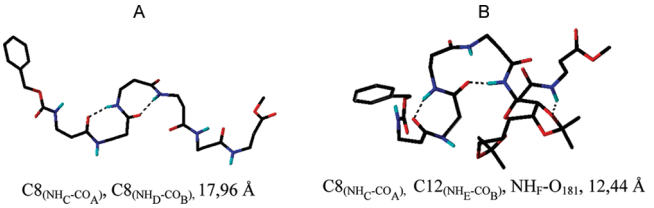

FIGURE 4. Stick view of two representative structures among the 10 lowest energy conformations obtained from constrained MD simulations. (A) Structure that most satisfies the DMSO NMR titration, this structure shows two consecutive eight-membered ring hydrogen bonds, $NH_C{-}CO_A$ and $NH_D{-}CO_B$, and was obtained after 39 900 steps. (B) One example of structure displaying the 12-membered ring hydrogen bond $NH_E{-}CO_B$ in addition to the eight-membered ring hydrogen bond $NH_C{-}CO_A$ (119 700 steps). The total number of integration steps is equal to 200 000. The length (Å) of the structures are calculated from the C(CO) at the N-terminus to the C(CO) at the terminal carboxylic moiety. Dashed lines correspond to hydrogen bonding.

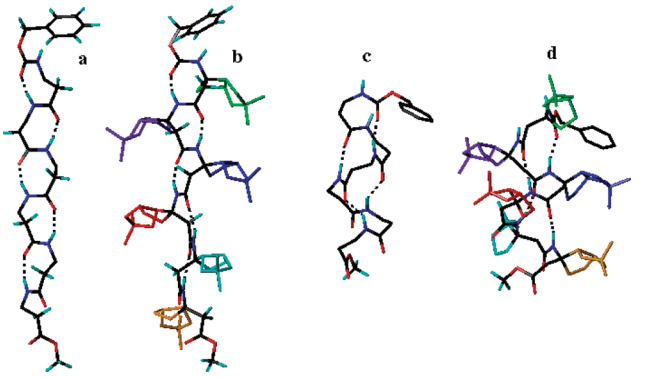

FIGURE 5. 3D structures of H-8 (a, b) and H-12 (c, d) helices. Dashed lines correspond to hydrogen bonding. The models were generated with the SYBYL package and energetically minimized using the Tripos Force Field with Gasteiger-Hückel charges (distance-dependent dielectric constant 5) up to a root-mean-square (rms) gradient of 0.05 kcal/mol·Å (Powell Algorithm). In (a) and (c) all carbohydrate moieties have been omitted for clarity, carbons are shown in black, nitrogens in blue, and oxygens in red. For models (b) and (d) only the dioxolane moieties at the non-reducing end of the sugars have been omitted, and the same code of color has been used for the peptidic backbone while the sugar moieties are represented in different colors.

(ϕ −87°, ψ −109°, θ 92°),[44] and H-14 (ϕ −148°, ψ −138°, θ 61°)[44] helices were chosen, the first two because eight- and 12-membered hydrogen bonds have been found along the MD simulation, and the H-14 because the latter is known to be impossible for $\beta^{3,3}$-peptides and as such represent a comparison model. Figure 5 shows the resulting models for H-8 and H-12 after minimization. As expected the H-14 secondary structure do not withstand the minimization process and is completely destabilized (not shown). H-8 and H-12 helices that were not found in our MD simulation do not satisfy all of the NOE constraints (see Supporting Information).

Circular Dichroism Spectroscopy. Circular dichroism (CD) spectroscopy is a useful method to probe the secondary structure of synthetic oligomers. For β-peptides for which structural information from NMR or RX are known, CD fingerprints have been correlated to typical secondary structures such as 3_{14}, 2.5_{12}, 12/10 helices, and hairpin turns. CD spectra for dimer **7**, tetramer **10** and hexamer **11** were recorded in methanol and acetonitrile at 25 °C and at an amide bond concentration of 100 μM, for example, 33 μM for the tetramer that has three amide bonds in the backbone. Monomer **5**, which has no amide chromophore, was also analyzed to ensure that it does not exhibit any significant CD signal in the far UV (Figure 6). In acetonitrile, tetramer **10** and hexamer **11** display a minimum at ca. 229 nm, a maximum at ca. 200 nm and a zero-crossing at ca. 213 nm. A very similar pattern is observed in MeOH: a minimum at 228 nm, a maximum at 199 nm, and a zero-crossing at 212 nm. First of all, whatever the solvent, CD spectra do seem to indicate

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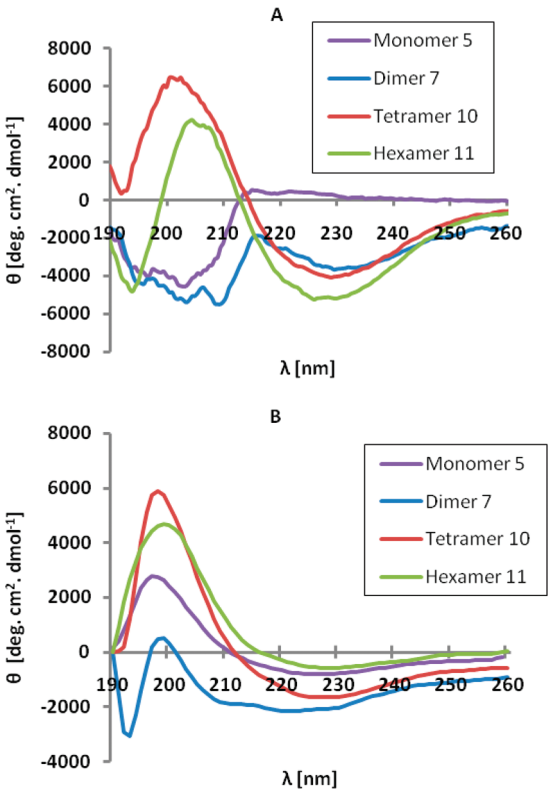

FIGURE 6. CD spectra of oligomers **7**, **10**, and **11** in acetonitrile (A) and in methanol (B). All spectra were recorded at room temperature and have been normalized as amide bond concentration.

that the tetramer and hexamer adopt the same regular conformation. The Cotton effect does not increase on going from the tetramer to the hexamer. This could suggest that the tetramer is long enough to adopt a local conformation that is also observed for the hexamer. The spectra of the dimer **7** are somewhat different in methanol and acetonitrile. In acetonitrile, the dimer does not display a positive peak around 200 nm, and in both solvents an additional trough is observed at ca. 270 nm. The benzyloxycarbonyl group should account for this CD signal, and it would suggest that this group is in a very different environment in the dimer as compared to the tetramer and the hexamer. Nevertheless, the dimer also exhibits the negative Cotton effect around 225−229 nm, suggesting that it is conformationally preorganized in a manner similar to that of longer oligomers.

The absorption patterns found in methanol and acetonitrile are distinct from those that have been correlated to secondary structures in the β-peptide field. For example, both H-14 and H-12 helices display a maximum around 200 nm, the CD spectra of oligomers **10** and **11** also feature a maximum at ca. 200 nm, but the wavelengths of the minima, around 228 nm, are red-shifted in comparison to typical values for H-14 (ca. 215 nm) or H-12 (ca. 220 nm) helices derived from α-L-amino acids. In the field of β-peptides, one can find CD fingerprints featuring red-shifted signal above 225 nm. For example $\beta^{3,3}$-oligomers from Seebach's group show CD pattern with a weak trough around 230 nm and two peaks at 215 and 200 nm.[45] The presence of the additional signal at 215 nm makes the general shape different and as a consequence do not allow any future comparison. The polyproline I helix and oligomers of (*S*)-nipecotic acids also feature CD signals above 225 nm, until 232 nm in aliphatic alcohol,s[46] but their whole spectra are once again different from those that characterize our oligomers.

Actually the characteristics of our curves can be compared to values (max ∼195 nm, min ∼225, zero-crossing 212−222) reported by Yang et al. for turns and helices consisting of α-aminoxy acids that display eight-membered hydrogen bonds.[41] At the moment, in the field of β-peptides, no CD pattern is associated to C8 pseudocycle secondary structure. The combination of NMR and simulation also suggest that eight-membered hydrogen bonds are present, but for the moment comparison of our data with that of oligomers consisting of α-aminoxy acids remains hazardous since α-aminoxy acids may display specific CD patterns.

Conclusion

We have synthesized and studied the solution conformation of short homo-oligomers build from *N*-mannofuranosyl-3-ulosonic acids. In these β-peptides, the amino group of each β-amino acid is part of a N,O-acetal, an unprecedented situation in the field of β-peptides. To the best of our knowledge homo-oligomers from β-amino acids with a cyclic disubstitution at the β-carbon also represents a non-documented topological situation. The lack of CH(β) made the NMR analysis less informative than that of more traditional β-peptide chains; nevertheless, NMR and IR gave evidence of the existence of a defined solution conformation stabilized by H-bonding. Constrained MD simulations, in addition to the DMSO NMR titration suggest the presence of two consecutives C_8 turns. The CD curves could be reminiscent to that observed with helices consisting of α-aminoxy acids that display eight-membered hydrogen bonds, even though the peptidic chains are different. The propensity of this novel family of β-peptide oligomers for local folding, involving eight-membered ring H-bonding, should be confirmed with *N*-glycosyl-3-ulosonic acid building blocks of different configurations in their protected and deprotected forms to probe the conformational preference in aqueous environments.

Experimental Section

Compounds **1**[27a] and **2**[29] have been previously reported.

Methyl 3-Amino-2,3-dideoxy-4,5:7,8-bis-*O*-isopropylidene-D-manno-3-octulofuranosonate 3. The synthesis of compound **3** has been previously reported.[28] Oil, R_f 0.34 (Hex/EtOAc 1:2); $[\alpha]^{20}_D$ −5.3 (*c* 0.3; $CHCl_3$); ν_{max} (thin film) 3416 (NH_2), 1734 (C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.86−4.77 (m, 1H, H_4), 4.51−4.46 (m, 1H, H_5), 4.38−4.31 (m, 1H, H_7), 4.14−3.90 (m, 2H, H_6, $H_{8'}$), 3.71, 3.70 (2s, 3H, CO_2CH_3), 3.58 (dd, 1H, H_8, $J_{7,8}$ = 3.0, J_{gem} = 7.0 Hz), 2.91 (d, J_{gem} = 17.0 Hz, H_2), 2.66 (d, J_{gem} = 17.0 Hz, H_2), 2.63 (br s, H_2), 2.25 (br s, 2H, NH_2), 1.52, 1.46, 1.44, 1.34, 1.31 (5s, 12H, 4 × $C(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9, 170.2 (C=O), 112.9, 109.5, 109.3 (2 × $C(CH_3)_2$), 92.9, 92.8 (C_3), 81.0, 80.6, 78.9, 78.4, 77.5, 76.4, 73.5, 70.2 (4C, C_4, C_5, C_6, C_7), 67.5, 67.2 (C_8), 52.2, 51.9 (CO_2CH_3), 41.8, 40.6 (C_2), 27.2, 26.4, 26.2, 25.6, 25.4, 24.9 (4 × CH_3).

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Methyl 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-(benzyloxycarbonyl)-amino-α-D-manno-3-octulofuranosonate 5. To a cold solution of the free amine **3** (3.83 g, 11.56 mmol) in MeOH (60 mL) were added successively, in one portion, solid Na_2CO_3 (3.9 g, 46 mmol, 4 equiv) and dropwise benzyl chloroformate (2 mL, 14 mmol, 1.2 equiv). The reaction mixture was stirred 1 h at room temperature, after which it was concentrated under reduced pressure. The residue was taken up by CH_2Cl_2 (30 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, giving the crude residue which was purified by column chromatography on silica (EtOAc in hexane, 20%) to afford compound **5** (4.0 g, 8.67 mmol, 75%) as an oil. $[\alpha]^{25}_D$ −8.3 (*c* 0.4, $CHCl_3$); ν_{max} (thin film) 1731 (C=O, ester), 3344 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.37 (m, 5H, Ar), 6.10 (s, 1H, NH), 5.13 (d, 1H, H_4), 5,07 (br s, 2H, $-CH_2Ph$), 4.95 (dd, 1H, J_{4-5} = 5.8 Hz, J_{5-6} = 3.6 Hz, H_5), 4.35 (m, 1H, H_7), 4.15 (dd, 1H, J_{6-7} = 7.3 Hz, H_6), 4.05 (dd, 1H, $J_{7-8'}$ = 5.8 Hz, $H_{8'}$), 3.97 (dd, 1H, J_{7-8} = 5.1 Hz, J_{gem} = 8.8 Hz, H_8), 3,6 (s, 3H, OMe), 3,05 (d, 1H, $H_{2'}$), 2.85 (d, 1H, J_{gem} = 16.0 Hz, H_2), 1.48, 1.42, 1.35, 1.32 (4s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8 (CO_2Me), 155.1 ($C{=}O_{(Cbz\ group)}$), 135.9 (C_{ipso}), 128.0−128.5 (4 × C_{Ar}), 109.0, 112.8 (2 × $C(CH_3)_2$), 92.4 (C_3), 85.0 (C_4), 80.9 (C_5 and C_6), 73.3 (C_7), 66.7 ($-CH_2Ph$), 66.6 (C_8), 51.8 (CO_2CH_3), 38.1 (C_2), 26.7, 25.7, 25.3, 24,3 (4 × CH_3). ESI-HRMS: calcd for $C_{23}H_{32}O_9N$ $[M + H]^+$ 466.2077, found 466.2097.

2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-(benzyloxycarbonyl)-amino-α-D-manno-3-octulofuranosonic Acid 6. The ester compound **5** was dissolved in MeOH (10 mL/mmol), and potassium carbonate (1.1 equiv) and water (1 mL/mmol) were added. After completion, the reaction mixture was neutralized by adding Amberlite resin (IR 120), filtered, and concentrated in vacuo to get a crude free carboxylic acid, which was used directly in the next step. Compound **6** (730 mg, 1.61 mmol) was synthezised from **5** (750 mg, 1.61 mmol) in a quantitative yield, following the general procedure of saponification described above, and was used directly in the next step. R_f 0−0.2 (Hex/EtOAc 1:1); ^1H NMR (400 MHz, d_6-DMSO) δ 12.2 (s, 1H, OH), 8.0 (s, 1H, NH), 7.5−7.3 (m, 5H, Ar), 5.06 (d, 1H, *J* = 12.7 Hz, H-benz), 5.02 (d, 1H, H-benz), 4.90 (d, 1H, $J_{4,5}$ = 5.8 Hz, H_4), 4.74 (dd, 1H, $J_{5,6}$ = 3.5 Hz, H_5), 4.20 (m, 1H, H_7), 3.97 (dd, 1H, $J_{8,8'}$ = 8 Hz, $J_{7,8}$ = 6.5 Hz, H_8), 3.84 (dd, 1H, $J_{6,7}$ = 7.2; H_6), 3.74 (dd, 1H, $J_{7,8'}$ = 5.3 Hz, $H_{8'}$), 3.25 (d, 1H, $J_{2,2'}$ = 16.6 Hz, H_2), 2.7 (d, 1H, $H_{2'}$), 1.5−1.3 (4s, 12H, CH_3); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 171.3 (CO_2H), 155.3 (C=O), 137.7 (C-ipso), 129.2−128.4 (C Ar), 112.3, 108.9 ($C(CH_3)_2$), 92.9 (C_3), 85.0 (C_4), 81.0 (C_5), 80.0 (C_6), 73.3 (C_7); 67.0 (C_8), 66.0 (CH_2Ph), 27.4, 26.5, 25.9, 25.2 (4 × CH_3).

Dimer 7. A solution of compound **5** (750 mg, 1.61 mmol) was dissolved in MeOH (16 mL), and potassium carbonate (245 mg, 3.2 mmol, 2 equiv) and water (2.2 mL) were added. After completion, the reaction mixture was neutralized by adding Amberlite IR-120(H^+) resin, filtered, and concentrated in vacuo to give the crude carboxylic acid **6**.

Amine **3** (460 mg, 1.4 mmol) and the carboxylic acid **6** (710 mg, 1.4 mmol, 1.0 equiv) were dissolved in dry DMF (120 mL) at room temperature under an argon atmosphere. HATU (0.800 g, 2.1 mmol, 1.5 equiv) was added in one portion followed by dropwise addition of DIPEA (0.23 mL, 2.1 mmol, 1.5 equiv). The resulting solution was stirred for 15 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with CH_2Cl_2 (50 mL), and washed successively with saturated aq $NaHCO_3$ (3 × 20 mL), brine (20 mL), and water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was purified by column chromatography on silica (EtOAc in hexane, 30%) to yield the dimer **7** as a glassy white solid (0.810 g, 1.06 mmol, 70%). Mp 78 °C; $[\alpha]^{25}_D$ −0.9 (*c* 0.9, $CHCl_3$); ν_{max} (thin film) 1720 (C=O, ester), 1685 (C=O, amide I) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 5H, aromatics), 7.15 (s, 1H, NH_B), 6.63 (s, 1H, NH_A), 5.25 (d, 1H, H_{4A}), 5.15 (d, 1H, H_{4B}), 5.13 (d, 1H, $-CH_2Ph$), 5.05 (d, 1H, J_{gem} = 12.3 Hz, $-CH_2Ph$), 4.96 (dd, 1H, J_{4A-5A} = 5.9 Hz, H_{5A}), 4.88 (dd, 1H, J_{4B-5B} = 5.9 Hz, J_{5B-6B} = 3.8 Hz, H_{5B}), 4.33−4.40 (m, 2H, H_{7A}, H_{7B}), 4.22 (dd, 1H, J_{5A-6A} = 3.8 Hz, J_{6A-7A} = 7.5 Hz, H_{6A}), 4.13 (dd, 1H, J_{6B-7B} = 6.6 Hz, H_{6B}), 4.04−4.09 (m, 2H, H_{8A}, H_{8B}), 3.93−3.99 (m, 2H, $H_{8'A}$, $H_{8'B}$), 3.64 (s, 3H, OMe), 3.04 (d, 1H, J_{gem} = 15.9 Hz, H_{2B}), 2.90−2.98 (m, 2H, $H_{2'B}$, H_{2A}), 2.77 (d, 1H, J_{gem} = 14.7 Hz, $H_{2'A}$), 1.54, 1.48, 1.45, 1.42, 1.37, 1.31 (8s, 24H, 8 × CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.7 (CO_2Me), 170.3 (2 × C=O(NH)), 155.7 ($C{=}O_{(Cbz\ group)}$), 136.5 (C_{ipso}), 128.4−128.9 (4 × C_{Ar}), 113.3 (2 × $C_{acetal\ 4-5}$), 109.4, 109.6 ($C_{acetal\ 7-8}$), 93.5 (C_{3A}), 93.1 (C_{3B}), 85.1 (C_{4A}), 84.8 (C_{4B}), 81.8 (C_{6A}), 81.5 (C_{6B}), 81.1 (2 × C_5), 73.8 (C_{7B}), 73.4 (C_{7A}), 67.2 ($-CH_2Ph$), 67.0 (C_{8A}), 66.8 (C_{8B}), 52.3 (OMe), 42.6 (C_{2A}), 37.8 (C_{2B}), 24.6, 24.7, 25.5, 25.7, 26.2, 26.3, 27.1, 27.3 (8 × CH_3); *m*/*z* (ES^+) 765 ($M + H^+$, 100%). Anal. Calcd for $C_{37}H_{52}N_2O_{15}$ (764.8): C, 58.11; H, 6.85; N, 3.66. Found: C, 58.06; H, 6.93; N, 3.59.

Tetramer 10. To a solution of compound **7** (190 mg, 0.25 mmol) in methanol (5 mL) were added successively potassium carbonate (190 mg, 0.25 mmol, 2 equiv) and water (0.2 mL). After reaction completion, the reaction mixture was neutralized by adding Amberlite IR-120(H^+) resin, filtered, and concentrated in vacuo to give the crude dimer acid **9**.

To a solution of compound **7** (930 mg, 1.21 mmol) in EtOAc (20 mL) was added 10% Pd/C (93 mg), and the mixture was stirred overnight under hydrogen at atmospheric pressure. The catalyst was then removed by filtration through a short pad of Celite, and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo to give the crude dimer amine **8**.

The crude acid **9** (200 mg, 0.23 mmol) and the crude amine **8** (175 mg, 0.23 mmol, 1.0 equiv) were dissolved in dry DMF (5 mL) at room temperature under an argon atmosphere. HATU (131 mg, 0.35 mmol, 1.5 equiv) was added in one portion followed by dropwise addition of DIPEA (57 μL, 0.35 mmol, 1.5 equiv). The resulting solution was stirred for 15 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with CH_2Cl_2 (5 mL), and washed successively with saturated aq $NaHCO_3$ (3 × 5 mL), brine (5 mL), and water (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to yield the tetramer **10** as a glassy white solid (150 mg, 0.11 mmol, 47%). R_f 0.64 (ethyl acetate/hexane 7:3). Mp 113 °C; $[\alpha]^{25}_D$ +3.6 (*c* 0.6, $CHCl_3$); ν_{max} (thin film) 3367 (NH) cm^{-1}; *m*/*z* (ES^+) 1363 $[(M + H)^+$, 21%], 1385 $[(M + Na)^+$; 100%]. Anal. Calcd for $C_{65}H_{94}N_4O_{27}$ (1363.4): C, 57.26; H, 6.95; N, 4.11. Found: C, 57.39; H, 6.87; N, 4.10. ^1H NMR (400 MHz, C_6D_6) δ 7.29−7.22 (m, 5H, Ar), 5.30, 5.07 (2 × d, 2H, J_{gem} = 12.4 Hz, $-CH_2Ph$), 3.45 (s, 3H, OMe), 1.60, 1.59, 1.52 (s), 1.48 (s), 1.46 (s), 1.45, 1.44, 1.40 (s), 1.24 (s), 1.23 (s), 1.22, 1.17(s) (48H, 16 × CH_3).

	ring			
	A	B	C	D
NH	7.81	8.21	8.14	7.48
$H_2/H_{2'}$	3.23, 3.23	3.11, 3.39	3.04, 3.47	3.26, 3.38
H_4	5.40	5.53	5.52	5.45
H_5	4.92−4.96	4.92−4.96	4.66, 4.70	4.83
H_6	4.60−4.65	4.53−4.58	4.41−4.46	4.41−4.46
H_7	4.66−4.70	4.60−4.65	4.60−4.65	4.53−4.58
$H_8/H_{8'}$	4.41−4.46	4.46−4.50	4.25−4.31	4.21, 4.25−4.31

^{13}C NMR (100.6 MHz, C_6D_6) δ 172.9 (CO_2Me), 171.4, 171.1, 170.8, (3 × $C{=}O_{(NH)}$), 156.1 ($C{=}O_{Cbz}$), 137.5 (C_{ipso}), 128.7

(4 × C_{Ar}), 66.9 (−CH_2Ph), 52.0 (OMe), 113.0, 112.7, 112.5, 112.4, 109.1, 109.0, 108.8 (8 × $C(CH_3)_2$), 94.5, 93.9, 93.8, 93.7 (4 × C_3),85.6, 85.2, 84.8, 84.7 (4 × C_4), 82.3, 82.2 (4 × C_6), 81.7, 81.5, 81.0 (4 × C_5), 74.2, 73.9, 73.6 (4 × C_7), 67.6, 67.5, 67.0, 66.6 (4 × C_8), 42.2, 41.9, 40.8, 38.5 (4 × C_2), 27.4, 27.3, 27.2, 26.9, 26.2, 26.0, 25.9, 25.7, 25.6, 25.4, 24.5, 24.4, 24.35, 24.3 (16× CH_3).

Hexamer 11. To a solution of compound **10** (300 mg, 0.20 mmol) in methanol (5 mL) were added potassium carbonate (360 mg, 0.40 mmol, 2 equiv) and water (0.4 mL). After reaction completion, the mixture was neutralized by adding Amberlite IR-120(H^+) resin, filtered, and concentrated in vacuo to give the crude acid.

The crude acid (270 mg, 0.20 mmol) and the crude amine **8** (80 mg, 0.14 mmol, 0.7 equiv) were dissolved in dry DMF (5 mL) at room temperature under an argon atmosphere. HATU (112 mg, 0.30 mmol, 1.5 equiv) was added in one portion followed by dropwise addition of DIPEA (49 μL, 0.30 mmol, 1.5 equiv). The resulting solution was stirred for 15 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with CH_2Cl_2 (5 mL), and washed successively with saturated aq $NaHCO_3$ (3 × 5 mL), brine (5 mL), and water (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to yield the hexamer **11** (140 mg, 0.071 mmol, 50%). R_f 0.55 (ethyl acetate/hexane 7:3), $[\alpha]^{25}_D$ +3.2 (*c* 0.6, $CHCl_3$); ν_{max} (thin film) 3350 (NH), 1735 (C═O ester), 1674, 1668, 1662, 1652 (C═O amides) cm^{-1}; *m*/*z* (ES^+) 1984 [$(M + Na)^+$; 100%]. Anal. Calcd for $C_{93}H_{136}N_6O_{39}$ (1960.8): C, 56.93; H, 6.99; N, 4.28. Found: C, 56.91; H, 7.02; N, 3.93. ^{1}H NMR (400 MHz, C_6D_6) δ 7.32−7.19 (m, 5H, Ar), 5.33, 5.15 (2 × d, 2H, J_{gem} = 12.4 Hz, −CH_2Ph), 3.47 (s, 3H, OMe), 1.17−1.60 (m, 72H, 24 × CH_3).

^{13}C NMR (100.6 MHz, C_6D_6) δ 172.8 (CO_2Me), 171.7, 171.4, 171.2, 170.9, 170.8 (5 × C═$O_{(NH)}$), 156.2 (C═O_{Cbz}), 137.7 (C_{ipso}), 128.8, 128.6, 128.5 (5 × C_{Ar}), 113.0, 112.9, 112.7, 112.6, 112.5, 109.2, 109.1, 109.0, 108.9, 108.8 (12 × $C(CH_3)_2$), 94.5, 94.3, 94.2, 94.0, 93.9, 93.6 (6 × C_3), 85.6, 85.3, 85.1, 84.9, 84.6 (6 × C_4), 82.3, 82.2, 82.1, 82.0 (6 × C_6), 81.9−81.1 (6 × C_5), 74.2, 74.1, 74.0, 73.9, 73.7 (6 × C_7), 67.6−66.6 (6 × C_8), 66.9 (CH_2Ph), 52.0 (OMe), 42.3, 41.9, 41.3, 41.2, 41.1, 38.6 (6 × C_2) 27.4, 27.3, 27.2, 26.9, 26.2, 26.1, 25.9, 25.8, 25.6, 25.5, 25.3, 24.6, 24.5, 24.4, 24.3 (24 × CH_3).

	ring					
	A	B	C	D	E	F
NH	8.22	7.79	8.51	8.43	8.17	7.58
$H_2/H_{2'}$	3.27, 3.30	3.19, 3.44	3.16, 3.43	3.08, 3.29	3.04, 3.39	3.25, 3.32
H_4	5.51	5.41	5.60	5.57	5.62	5.47
H_5	4.86−4.39	4.94−4.96	4.86−4.90	5.05−5.03	4.94−4.96	4.86−4.90
H_6	4.49−4.50	4.55−4.57	4.55−4.57	4.55−4.57	4.51−4.54	4.55−4.57
H_7			4.60−4.69			
$H_{8/}H_{8'}$			4.19−4.52			

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Supporting Information Available: General experimental, results of constrained molecular dynamic simulation including the 10 lowest energy structures, selected distances measured over the course of the simulation, the view of a H-14 helix model and measurement of distances in minimized H-8 and H-12 helices, ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.