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Cyclic Homooligomers of Furanoid Sugar Amino Acids

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Cyclic homooligomers of mannose-derived furanoid sugar amino acid **1** [H-Maa(Bn_2)-OH] were synthesized by using BOP reagent in the presence of DIPEA under dilute conditions that converted the sugar amino acid monomer directly into its cyclic homooligomers **3a** and **4a**. The glucose-based sugar amino acid **2** [H-Gaa(Bn_2)-OH] under the same reaction conditions gave a bicyclic lactam **5a** as the major product. Cyclic homooligomers of **2** were prepared by cyclizing their linear precursors **6** and **7** leading to the formation of cyclic peptides **8a** and **9a**, respectively. Conformational analysis by NMR and constrained MD studies revealed that all the cyclic products, **3**, **4**, **8**, and **9**, had symmetrical structures. The deprotected cyclic trimer of Maa **3b** displayed a conformation in which all the C═O and the N−H bonds of the molecule point in opposite directions. In the deprotected cyclic tetramer of Maa **4b**, the COs and NHs were in the plane of the ring with the former pointing to outside and the latter inside the ring. The structure of the cyclic Gaa dimer **8b** displayed an unusual six-membered intramolecular hydrogen bond between $NH_i \rightarrow C3{-}O_{i-1}$ and a syn orientation between the C2−H and CO. In this molecule, the C2-hydrogens and the COs can be seen on one side of the ring while the NHs point to the other side. Addition of the bicyclic lactam **5b** resulted in the influx of Na^+ ions across the lipid bilayer leading to the dissipation of valinomycin-mediated K^+ diffusion potential.

Introduction

Sugar amino acids have emerged as versatile templates that have been used extensively in recent years as conformationally constrained scaffolds in many peptidomimetic studies and as an important class of synthetic monomers leading to many de novo oligomeric libraries.[1] As part of our ongoing project on sugar amino acid based molecular designs, we were interested in synthesizing cyclic homooligomers[2] of furanoid sugar amino acids. Cyclization of linear peptides or covalent bridging of their constituent amino acids at appropriate places is a widely used method to constrain their conformational degrees of freedom and induce desirable structural biases essential for their biological activities, such as tubular structures for transporting ions or molecules across membranes.[3] It was envisaged that the cyclic homooligomers of sugar amino acids with structurally rigid molecular scaffolds could be moulded to build predisposed cavities of precise dimensions providing attractive tools to study diverse molecular recognition processes.[4] Herein we describe the synthesis and conformational studies of the cyclic homooligomers of mannose-derived furanoid sugar amino acid **1** and its glucose-based congener **2**.

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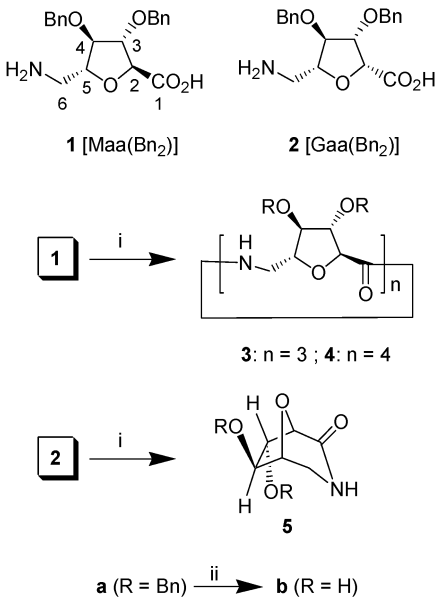
SCHEME 1[a]



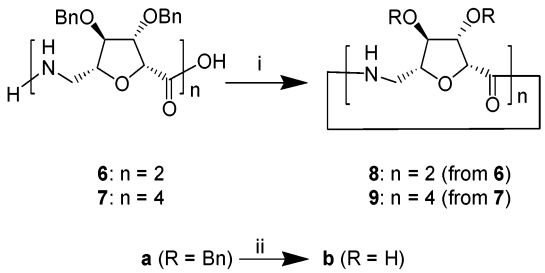
[a] Reagents and conditions: (i) BOP reagent, DIPEA, DMF, 0 °C, 7 h; (ii) H_2, $Pd(OH)_2$-C, MeOH, rt, 24 h.

Results and Discussions

Synthesis of the Cyclic Homooligomers. The method that we planned to use for the synthesis of these cyclic peptides is based on a reaction (Scheme 1) used earlier by us and others,[5] which was expected to convert the sugar amino acid monomers directly into their cyclic homooligomers, thus avoiding lengthy stepwise assembling of linear precursors, the process conventionally followed for synthesizing similar cyclic homooligomers.[2] Accordingly, the TFA-salt of H-Maa(Bn_2)-OH **1**,[6] dissolved in DMF (10^{-2} M), was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) at 0 °C, followed by the slow addition of *N*,*N*-diisopropylethylamine (DIPEA). After aqueous workup and chromatographic purification, the Bn-protected cyclic products **3a** and **4a** were isolated in 31% and 12% yields, respectively. Mass spectrometric analysis revealed that **3a** was the cyclic trimer of H-Maa(Bn_2)-OH and **4a** was its tetrameric homologue. Although not isolated, formation of other cyclic and/or linear oligomers in small quantities is not ruled out.

Next, it was decided to carry out the cyclohomooligomerization of the gluconic congener **2**. To our surprise, compound **2**, when subjected to the same oligomerizartion reaction under identical conditions as described above, furnished an intramolecularly cyclized bicyclic lactam **5a** as the major product in 75% yield. The *N*-Boc derivative of compound **5a** was isolated earlier by us as a side product during the synthesis of Boc-Gaa(Bn_2)-OH[6,7] and a debenzylated version of the same by Fleet, who also reported the synthesis of similar bicyclic lactams from different furanoid sugar amino acids.[8] Formation of other products from **2**, especially the expected cyclic oligomers or any linear oligomer, although not isolated, was negligible as revealed by the hplc analysis of the crude reaction mixture after aqueous workup.

SCHEME 2[a]



[a] Reagents and conditions: (i) BOP reagent, DIPEA, DMF, 0 °C, 7 h; (ii) H_2, $Pd(OH)_2$-C, MeOH, rt, 24 h.

The requisite cyclic homooligomers, however, could be synthesized from their linear precursors (Scheme 2). The linear dimer **6** and tetramer **7** of H-Gaa(Bn_2)-OH were prepared by conventional solution phase peptide synthesis methods, using 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and dry CH_2Cl_2 as solvent. While the *tert*-butoxycarbonyl (Boc) group was used for *N*-protection, the *C*-terminal was protected as a methyl ester (OMe). Deprotection of the former was done in TFA−CH_2Cl_2 and saponification of the later was performed with LiOH in THF−MeOH−H_2O. Reactions of **6** and **7** with BOP reagent in the presence of DIPEA under the conditions described above furnished the cyclized products **8a** in 56% yield and **9a** in 52% yield, respectively, as the major products.

Finally, the Bn-protections of all the products were removed by Pd-catalyzed hydrogenation to furnish the corresponding debenzylated compounds **3b**−**5b**, **8b**, and **9b** in quantitative yields.

Mass spectrometric analysis was used to characterize all the products. It is interesting to note here that the ESI[9] mass spectra of some of these products showed not only the expected $[M + H]^+$ peaks, but also signals of dimeric $[2M + H]^+$ or even higher order aggregates that were found to be concentration dependent. In such cases, the molecular weights were confirmed by matching the peak shapes to calculated isotopic distribution patterns.

Conformational Analysis: NMR Studies. The NMR spectra (both ^1H and ^{13}C) of the protected as well as the deprotected cyclic products displayed symmetric structures with only one set of resonances from their constitu-

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TABLE 1. ^{1}H Chemical Shifts (δ in ppm) and Coupling Constants (J in Hz) of Cyclic Peptides 3b, 4b, 8b, and 9b

protons	3b	4b	8b	9b
N*H*	8.36 (dd) (1.8, 7.5)	7.62 (dd) (5.2, 5.9)	8.11 (dd) (3.4, 8.0)	8.09 (t) (6.6)
C2-*H*	4.07 (d) (4.3)	4.11 (d) (3.2)	4.31 (d) (7.9)	4.31 (d) (3.9)
C3-*H*	4.09 (ddd) (4.3, 4.5, 5.2)	4.10 (ddd) (3.2, 3.9, 4.0)	4.15 (t) (7.9)	4.01 (ddd) (1.4, 3.9, 4.6)
C3−O*H*	5.56 (d) (5.2)	5.50 (d) (4.0)	5.72 (s) (−)	5.28 (d) (4.6)
C4-*H*	3.53 (dd) (4.5, 5.4)	3.67 (ddd) (3.4, 3.9, 4.2)	3.56 (ddd) (5.0, 7.9, 7.5)	3.87 (ddd) (1.4, 1.6, 4.3)
C4−O*H*	5.40 (d) (5.4)	5.24 (d) (4.2)	5.39 (d) (5.0)	5.30 (d) (4.3)
C5-*H*	3.53 (t) (6.5)	3.97 (dt) (3.4, 9.4)	3.78 (dd) (4.1, 7.5)	3.82 (m) (−)
C6-*H*	3.73 (dd) (7.5, 13.7)	3.33 (ddd) (3.4, 5.9, 13.8)	3.68 (dd) (8.0, 14.3)	3.57 (m) (−)
C6-*H*′	2.89 (ddd) (1.8, 6.5, 13.7)	3.24 (ddd) (5.2, 9.4, 13.8)	3.17 (ddd) (3.4, 4.1, 14.3)	3.25 (m) (−)

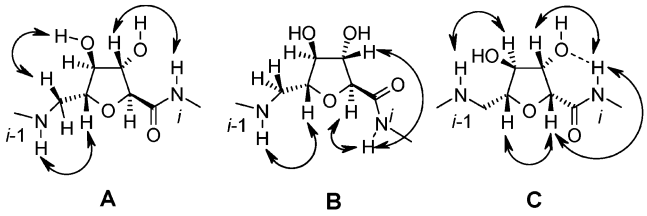

FIGURE 1. Schematic representation of the long-range rOes used as constraints in the MD studies of the deprotected cyclic trimer **3b** (A) and tetramer **4b** (B) of Maa and cyclic dimer **8b** of Gaa (C).

ent sugar residues in all the solvents they were studied. The NMR spectra of **3b**, **4b**, **8b**, and **9b** in DMSO-d_6 were well-resolved and most of the spectral parameters could be obtained easily and are reported in the Table 1. While the assignments were carried out with the help of total correlation spectroscopy (TOCSY), rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments provided the information on the proximity of protons, the details of which are provided in the Experimental Section. Variable-temperature studies were carried out to measure the temperature coefficients ($\Delta\delta/\Delta T$) of the amide proton chemical shifts that were used to determine their involvements in intramolecular hydrogen bonds. The cross-peak intensities in the ROESY spectra, shown schematically in Figure 1, were used for obtaining the restraints in the simulated molecular dynamics (MD) calculations, the detailed protocol of which is included in the Experimental Section.

Conformational Analysis of 3b. The mannose based sugar amino acid containing cyclic trimer **3b** is an 18-membered macrocyclic peptide. The vicinal coupling constants for the amide proton, $^3J_{\mathrm{NH-H6}(pro-S)} = 7.5$ Hz and $^3J_{\mathrm{NH-H6}(pro-R)} = 1.8$ Hz, imply the presence of a predominant single rotamer about the N−C6 bond.[10] The other vicinal couplings of $^3J_{\mathrm{H6}(pro-S)-\mathrm{H5}} \approx 0$ Hz and $^3J_{\mathrm{H6}(pro-R)-\mathrm{H5}} = 6.5$ Hz, as well as the appearance of rOe between $\mathrm{NH}_i \leftrightarrow \mathrm{C5-H}_i$, $\mathrm{NH}_i \leftrightarrow \mathrm{C3-H}_{i-1}$, and $\mathrm{C4-OH}_i \leftrightarrow \mathrm{C6-H}_i$(*pro-R*) indicate about 30° deviation from the negative synclinal (−*sc*) rotamer about the C5−C6 bond (Figure 2). The rOe between $\mathrm{NH}_i \leftrightarrow \mathrm{C3-H}_{i-1}$, the negative *synclinal* rotamer about the C5−C6, and a single rotamer about N−C6 are in agreement with the syn orientation of the C2−H and CO that practically ruled out the formation of intramolecular hydrogen bonding of the amide proton. This is further supported by the large magnitude of the temperature coefficient of the amide proton chemical shift ($\Delta\delta/\Delta T$).

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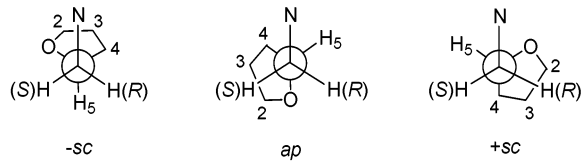

FIGURE 2. Schematic representation of the three possible rotamers about the C5−C6 bond: negative synclinal (−*sc*), antiperiplanar (*ap*), and positive synclinal (+*sc*).

The long-range distance restraints derived from the ROESY cross-peaks of **3b** in DMSO-d_6 (**A** in Figure 1) were used in the MD calculations. The MD studies were carried out by using the Simulated Annealing protocol for 50 cycles, each of 6 ps period with a total duration of 300 ps, and 25 structures were collected at regular intervals after every two cycles. The structures were subsequently energy minimized and superimposed aligning their backbones. Out of the 25 structures sampled during the 300-ps MD simulations, 5 structures that deviated considerably from the rest of them during backbone alignment were not included in the ensemble of the superimposed structures displayed in Figure 3. These structures clearly reveal that C2−H and CO are placed on one side of the ring while the NHs point to the other side.

Conformational Analysis of 4b. Mannose based sugar amino acid cyclic tetramer **4b** is a 24-membered macrocyclic peptide. The vicinal coupling constants of the amide proton, $^3J_{\mathrm{NH-H6}} = 5.9$ Hz and $^3J_{\mathrm{NH-H6'}} = 5.2$ Hz, are consistent with the value of |120°| for dihedral angles H−N−C6−H(*pro-S*) and H−N−C6−H(*pro-R*) about the N−C6 bond.[10] The coupling constants $^3J_{\mathrm{H6}(pro-R)-\mathrm{H5}} = 9.4$ Hz and $^3J_{\mathrm{H6}(pro-S)-\mathrm{H5}} = 3.4$ Hz, as well as the observation of strong rOe between $\mathrm{NH}_i \leftrightarrow \mathrm{C5-H}_i$, are consistent with the positive *synclinal* orientation (+*sc*) about the C5−C6 bond. This leads to the amide protons pointing into the ring and the carbonyls pointing to the outside, and unlike in other molecules, the C2−H and CO take an intermediate orientation about the C2−CO bond, which is neither a syn nor an anti orientation, as revealed by the structures, shown in Figure 4, sampled during the restrained MD calculations based on the ROESY cross-peaks found for **4b** in DMSO-d_6 (**B** in Figure 1). Here also, out of the 25 structures sampled during the 300-ps MD simulations, 5 structures that deviated considerably from the rest of them during backbone alignment were not included in the ensemble displayed in Figure 4. The backbone and the average pairwise heavy-atom RMSD are 1.03 ± 0.49 and 1.62 ± 0.34 Å, respectively, determined by analyzing the structures with the MOLMOL program.

FIGURE 3. Superimposition of the energy-minimized structures sampled during the MD simulations of **3b**.

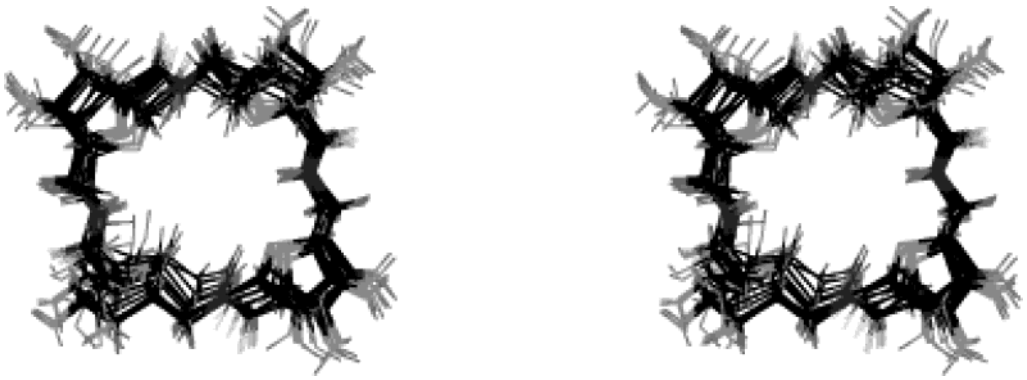

FIGURE 4. Superimposition of the energy-minimized structures sampled during the MD simulations of **4b**.

FIGURE 5. Superimposition of the energy-minimized structures sampled during the MD simulations of **8b**.

Conformational Analysis of 8b. In the Gaa cyclic dimer **8b**, the vicinal coupling constants, $^3J_{\mathrm{NH-H6}(pro-R)} = 8.0$ and $^3J_{\mathrm{NH-H6}(pro-S)} = 3.4$ Hz, imply that the dihedral angle φ (CO−N−C_6−C_5) is about |90°|. The other vicinal couplings of $^3J_{\mathrm{H6}(pro-R)-\mathrm{H5}} \approx 0$ Hz and $^3J_{\mathrm{H6}(pro-S)-\mathrm{H5}} = 4.1$ Hz indicate the indisputable evidence for the deviation of ca. 30° from *synclinal* (−*sc*) orientation about the C5−C6 bond (Figure 2). Moderate magnitude of the temperature coefficient for the Gaa amide proton ($\Delta\delta/\Delta T = -3.0$ ppb/deg K in DMSO-d_6) in the variable-temperature experiments hints at its involvement in intramolecular hydrogen bonding. The observation of rOe cross-peaks between $NH_i \leftrightarrow C4-H_i$, $NH_i \leftrightarrow C2-H_{i-1}$, $NH_i \leftrightarrow C3-H_{i-1}$, $C2-H_i \leftrightarrow C5-H_i$ and the negative *synclinal* rotation about C5−C6, coupled with the intramolecular hydrogen bonding of NH indicate the presence of an unusual six-membered hydrogen bond between $NH_i \rightarrow C3-O_{i-1}$. This unusual six-membered hydrogen bonding and the rOe between $NH_i \leftrightarrow C4-H_i$ are in agreement with the syn orientation of C2−H and CO, as revealed in Figure 5 which shows the superimposed display of the structures sampled during the MD studies, using the long-range constraints derived from the rOe cross-peaks (**C** in Figure 1). In these structures, the C2-hydrogens and the COs can be seen on one side of the ring while the NHs point to the other side. The ^3J coupling constants between the protons of the sugar ring have the values of $^3J_{\mathrm{H2-H3}} = 7.9$ Hz, $^3J_{\mathrm{H3-H4}} = 7.9$ Hz, and $^3J_{\mathrm{H4-H5}} = 7.5$ Hz that are in agreement with $^3{}_4T$ sugar puckering (where 3 and 4 refer to C3 and C4, respectively).[11]

In the cyclic Gaa tetramer **9b**, due to exchange broadening of the resonances, we were unable to obtain any structural information.

Ion Flux Study. The abilities of the Bn-deprotected products **3b**, **4b**, **5b**, **8b**, and **9b** to transport ions across model membranes (large unilamellar vesicles from palmitoyl-oleoyl phosphatidylcholine[12]) were assessed by moni-

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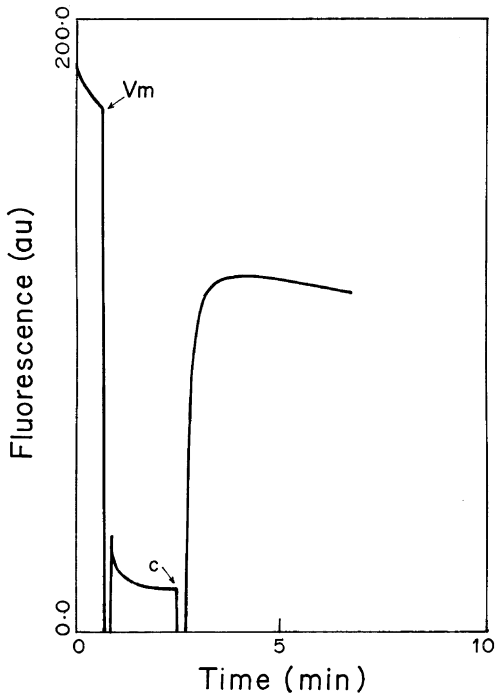

FIGURE 6. The profile shows that the addition of valinomycin at point Vm sets in diffusion potential as it triggers the transportation of K^+ ions, from inside to outside, across the model membrane of large unilamellar vesicles of palmitoyl-oleoyl phosphatidylcholine, which is reflected by a sharp fall in the fluorescence monitored by the fluorescent dye method. Addition of **5b** at point C in the profile resulted in the influx of Na^+ ions from the suspension medium back into the vesicles leading to the dissipation of the aforesaid diffusion potential as indicated by the increase in the fluorescence again.

toring the collapse of valinomycin-mediated K^+ diffusion potential on adding these substrates with use of the fluorescent dye method.[13] Addition of the deprotected bicyclic lactam **5b** resulted in the dissipation of the diffusion potential created by valinomycin (Figure 6) in a concentration-dependent manner indicating that the molecule is able to cause the influx of Na^+ ions across the lipid bilayer. The lipid−molecule ratio indicates that it is less effective than valinomycin in causing flux of Na^+ ions across the lipid bilayer. Hence, it is unlikely that a carrier mechanism involving complexation between Na^+ and **5b** is operative. It is possible that self-assembling structures are formed that can conduct ions across the bilayer.[4] The cyclic homoologomers of Maa **3b**, **4b**, and the Gaa-based compounds **8b** and **9b** did not show any significant ion influx.

Conclusion. Cyclic homooligomers of furanoid sugar amino acids constitute a new class of novel molecular scaffolds that display interesting 3-D structures. It is noteworthy that in case of mannose-derived sugar amino acid Maa **1**, having a trans relationship between C2−H and C5−H, the monomeric unit could be transformed directly into its cyclic homooligomers in a single-step process, an interesting finding that is expected to be applicable in the cyclohomooligomerization of other (C2,C5)-trans furanoid sugar amino acids. Detailed NMR studies in DMSO-d_6 and subsequent constrained MD simulations reveal that in the cyclic trimer of Maa **3b**, the C2−H and CO are placed on one side of the ring while the NHs point to the other side, with both CO and NH being perpendicular to the ring. In the cyclic tetramer of Maa **4b**, the amide protons point into the ring while the carbonyls are positioned outside. The structure of the cyclic Gaa dimer **8b** is characterized by an unusual six-membered intramolecular hydrogen bond between $NH_i \rightarrow C3{-}O_{i-1}$ and a syn orientation between C2−H and CO. This study will be useful in creating de novo cyclic peptides based on other furanoid sugar amino acids. The well-defined structures of these macrocyclic peptides will be useful in carrying out investigations on many interesting molecular recognition processes.

Experimental Section

Synthesis of 3a and 4a. To a solution of Boc-Maa(Bn_2)-OMe[6] (1.0 g, 2.1 mmol) in THF−MeOH−H_2O (3:1:1, 10 mL) at 0 °C was added LiOH·H_2O (265 mg, 6.3 mmol) with stirring from 0 °C to room temperature for 4 h. The reaction mixture was then acidified to pH 2 with 1 N HCl. It was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain the acid. The acid was dissolved in CH_2Cl_2 (7 mL) and to this solution was added trifluoroacetic acid (3 mL) with stirring from 0 °C to room temperature for 2 h. The reaction mixture was then concentrated in vacuo to give TFA.H-Maa(Bn_2)-OH.

To a solution of the above-prepared TFA-salt of Maa(Bn_2) **1** (429 mg, 0.91 mmol) in amine-free dry DMF (91 mL, 10^{-2} M) was added BOP reagent (604 mg, 1.36 mmol) at 0 °C and the reaction mixture was stirred for 15 min. This was followed by the slow addition of DIPEA (1.12 mL, 6.37 mmol) to the reaction mixture and stirring was continued at 0 °C for 7 h. Evaporation of the DMF under reduced pressure gave a residue that was dissolved in EtOAc, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, 60−65% EtOAc in petroleum ether eluant) to afford **3a** (96 mg, 31%) and **4a** (37 mg, 12%) as solids. Data for **3a**: R_f =0.5 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 38.1 (*c* 0.975, $CHCl_3$); mp 88−90 °C; IR (KBr) ν_{max} 3396, 2909, 2847, 1670, 1513, 1098, 1066, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (m, 10 H, Ar*H*), 6.72 (dd, J = 7.4, 3.0 Hz, 1 H, N*H*), 4.76 (d, J = 11.8 Hz, 1 H, PhCH_2O), 4.60 (d, J = 11.8 Hz, 1 H, PhCH_2O), 4.51 (d, J = 11.5 Hz, 1 H, PhCH_2O), 4.48 (t, J = 3.2 Hz, 1 H, C3-*H*), 4.47 (d, J = 3.2 Hz, 1 H, C2-*H*), 4.43 (d, J = 11.5 Hz, 1 H, PhCH_2O), 3.85 (dt, J = 7.0, 2.7 Hz, 1 H, C5-*H*), 3.83 (t, J = 3.3 Hz, 1 H, C4-*H*), 3.76 (ddd, J = 13.8, 7.4, 2.6 Hz, 1 H, C6-*H*), 3.23 (ddd, J = 13.8, 9.6, 3.0 Hz, 1 H, C6-*H'*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 137.4, 136.9, 128.4, 128.2, 128.0, 127.94, 85.6, 85.2, 82.9, 81.4, 72.2, 72.1, 42.0; MS (LSIMS) *m*/*z* (%) 1018 (74) $[M + H]^+$, 1040 (30) $[M + Na]^+$.

Data for **4a**: R_f 0.4 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 40.5 (*c* 0.80, $CHCl_3$); mp 75−77 °C; IR (KBr) ν_{max} 3396, 2917, 2862, 1662, 1521, 1090, 823, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.13 (m, 10 H, Ar*H*), 6.82 (dd, J = 6.5, 5.4 Hz, 1 H, N*H*), 4.71 (d, J = 11.9 Hz, 1 H, PhCH_2O), 4.60 (d, J = 11.9 Hz, 1 H, PhCH_2O), 4.56 (d, J = 2.1 Hz, 1 H, C2-*H*), 4.45 (t, J = 2.1 Hz, 1 H, C3-*H*), 4.39 (d, J = 11.2 Hz, 1 H, PhCH_2O), 4.28 (d, J = 11.2 Hz, 1 H, PhCH_2O), 3.97 (dt, J = 9.1, 3.4 Hz, 1 H, C5-*H*), 3.78 (dd, J = 3.4, 1.9 Hz, 1 H, C4-*H*), 3.50 (ddd, J = 13.7, 9.4, 5.2 Hz, 1 H, C6-*H*), 3.38 (ddd, J = 13.7, 6.7, 3.8 Hz, 1 H, C6-*H'*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 137.3, 137.2, 128.5, 128.4, 128.0, 127.9, 127.8, 84.6, 84.5, 84.1, 83.4, 77.2, 71.9, 71.6, 41.0; MS (ESI) *m*/*z* (%) 702 (12) $[^1/_2M + Na]^+$, 1381 (<1) $[M + Na]^+$.

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(13) Sims, P. J.; Waggoner, A. S.; Wang, C. H.; Hoffman, J. F. *Biochemistry* **1974**, *13*, 3315.

Synthesis of 3b. To a solution of **3a** (71 mg, 0.07 mmol) in MeOH (2 mL) was added $Pd(OH)_2$ on C (20%, 50 mg) and the mixture was hydrogenated under atmospheric pressure with use of a H_2 balloon for 24 h. The reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed with MeOH. The filtrate and the washings were combined and concentrated in vacuo to get a quantitative yield of **3b** (30 mg). Data for **3b**: R_f 0.43 (silica gel, *n*BuOH:AcOH:H_2O = 4:2:2); $[\alpha]^{20}_D$ 97.6 (*c* 0.59, H_2O); IR (KBr) ν_{max} 3396, 2854, 1639, 1529, 1035, 823 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) see Table 1; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.8, 82.8, 81.6, 80.2, 80.0, 41.8; MS (ESI) *m*/*z* (%) 500 (10) $[M + Na]^+$.

Synthesis of 4b. Compound **4b** was synthesized from **4a** in quantitative yield following the same procedure described above for the synthesis of **3b**. Data for **4b**: R_f 0.31 (silica gel, *n*BuOH:AcOH:H_2O = 4:2:2); $[\alpha]^{20}_D$ 46.5 (*c* 0.41, MeOH); IR (KBr) ν_{max} 3396, 2894, 1639, 1529, 1066 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) see Table 1; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.6, 84.1, 83.9, 79.9, 78.8, 41.5; MS (ESI) *m*/*z* (%) 660 (40) $[M + Na]^+$.

Synthesis of 5a. Compound **5a** was synthesized from **2** in 75% yield, following the same procedure described above for the cyclooligomerization of **1** with the same reagents in identical molar equivalents and under identical reaction conditions. Data for **5a**: R_f 0.4 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −28.6 (*c* 0.76, $CHCl_3$); IR (neat) ν_{max} 3254, 2870, 2807, 1678, 1262, 1074, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.29 (m, 10 H, Ar*H*), 5.65 (br s, 1 H, N*H*), 4.79 (d, *J* = 11.1 Hz, 1 H, PhCH_2O), 4.70 (d, *J* = 6.4 Hz, 1 H, C2-*H*), 4.53 (d, *J* = 11.7 Hz, 1 H, PhCH_2O), 4.48 (d, *J* = 11.1 Hz, 1 H, PhCH_2O), 4.48 (d, *J* = 11.7 Hz, 1 H, PhCH_2O), 4.36 (d, *J* = 4.7 Hz, 1 H, C5-*H*), 4.34 (dd, *J* = 6.4, 3.0 Hz, 1 H, C3-*H*), 4.05 (d, *J* = 3.0 Hz, 1 H, C4-*H*), 3.70 (dd, *J* = 11.6, 4.7 Hz, 1 H, C6-*H*), 3.17 (dd, *J* = 11.6, 2.6 Hz, 1 H, C6-*H′*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 137.3, 137.1, 128.5, 128.45, 128.39, 128.05, 127.98, 127.9, 87.5, 78.6, 77.3, 72.9, 71.7, 45.5; MS (ESI) *m*/*z* (%) 679.8 (100) $[2M + H]^+$, 340.3 (50) $[M + H]^+$; HRMS (LSIMS) calcd for $C_{20}H_{22}NO_4$ $[M + H]^+$ 340.1549, found 340.1558.

Synthesis of 5b. Compound **5b** was synthesized from **5a** in quantitative yield, following the same procedure described above for the synthesis of **3b**. Data for **5b**: R_f 0.5 (silica gel, *n*BuOH:AcOH:H_2O = 4:2:2); $[\alpha]^{20}_D$ −35.7 (*c* 0.54, MeOH); IR (KBr) ν_{max} 3490, 3278, 2909, 1678, 1425, 1098, 1027 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.34 (dd, *J* = 2.6, 1.0 Hz, 1 H, N*H*), 5.41 (d, *J* = 4.0 Hz, 1 H, C3−O*H*), 5.32 (d, *J* = 4.7 Hz, 1 H, C4−O*H*), 4.09 (ddd, *J* = 7.0, 4.0, 2.4 Hz, 1 H, C3-*H*), 4.08 (d, *J* = 7.0 Hz, 1 H, C2-*H*), 4.04 (d, *J* = 5.0 Hz, 1 H, C5-*H*), 3.88 (dd, *J* = 4.7, 2.4 Hz, 1 H, C4-*H*), 3.38 (ddd, *J* = 11.9, 5.0, 1.0 Hz, 1 H, C6-*H*), 3.04 (dd, *J* = 11.9, 2.6 Hz, 1 H, C6-*H′*); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.4, 83.0, 81.9, 80.2, 80.1, 44.8; MS (ESI) *m*/*z* (%) 341 (15) $[2M + Na]^+$, 182 (38) $[M + Na]^+$; HRMS (LSIMS) calcd for $C_6H_9NO_4$ $[M]^+$ 159.0531, found 159.0527.

Synthesis of H-[(Gaa(Bn$_2$)]$_2$-OH (6). To a solution of Boc-Gaa(Bn$_2$)-OMe[6] (1.0 g, 2.1 mmol) in THF−MeOH−H_2O (3:1:1, 10 mL) at 0 °C was added LiOH·H_2O (265 mg, 6.3 mmol) with stirring from 0 °C to room temperature for 4 h. The reaction mixture was then acidified to pH 2 with 1 N HCl and then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain the acid.

In another round-bottom flask a solution of Boc-Gaa(Bn$_2$)-OMe (1.0 g, 2.1 mmol) in CH_2Cl_2 (7 mL) was added. To this solution was added trifluoroacetic acid (3 mL) with stirring from 0 °C to room temperature for 2 h. The reaction mixture was then concentrated in vacuo to give TFA.H-Gaa(Bn$_2$)-OMe.

The above-prepared crude acid was dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C. Then it was sequentially treated with HOBt·H_2O (315 mg, 2.3 mmol) and EDCI (447 mg, 2.3 mmol). After 10 min, TFA.H-Gaa(Bn$_2$)-OMe prepared above and dissolved in CH_2Cl_2 (6 mL) was added to the reaction mixture followed by the addition of DIPEA (0.75 mL, 4.2 mmol). After being stirred for 12 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 45−50% EtOAc in petroleum ether eluant) afforded the protected linear dimer Boc-[(Gaa(Bn$_2$)]$_2$-OMe (1.26 g, 74%). Data for **Boc-[(Gaa(Bn$_2$)]$_2$-OMe**: R_f 0.4 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 25.1 (*c* 1.2, $CHCl_3$); mp 38−40 °C; IR (neat) ν_{max} 3356, 2901, 1686, 1654, 1529, 1190, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.75 (t, *J* = 5.2 Hz, 1 H, Gaa(2)-N*H*), 7.35−7.18 (m, 20 H, Ar*H*), 5.73 (t, *J* = 5.5 Hz, 1 H, Gaa(1)N*H*), 4.78 (d, *J* = 6.3 Hz, 1 H, Gaa(2)C2-*H*), 4.61 (d, *J* = 3.7 Hz, 1 H, Gaa(1)C2-*H*), 4.56−4.36 (m, 8 H, PhCH_2O), 4.32 (dd, *J* = 6.3, 3.3 Hz, 1 H, Gaa(2)C3-*H*), 4.27 (d, *J* = 3.7 Hz, 1 H, Gaa(1)C3-*H*), 4.18 (dt, *J* = 5.9, 4.3 Hz, 1 H, Gaa(2)C5-*H*), 4.14 (dt, *J* = 7.6, 2.6 Hz, 1 H, Gaa(1)C5-*H*), 3.98 (dd, *J* = 4.3, 3.3 Hz, 1 H, Gaa(2)C4-*H*), 3.77 (s, 3 H, OCH_3), 3.74 (d, *J* = 2.6 Hz, 1 H, Gaa(1)C4-*H*), 3.70 (ddd, *J* = 14.2, 5.2, 4.3 Hz, 1 H, Gaa(2)C6-*H*), 3.62 (dt, *J* = 14.2, 5.8 Hz, 1 H, Gaa(2)C6-*H′*), 3.46 (ddd, *J* = 14.3, 6.3, 3.0 Hz, 1 H, Gaa(1)C6-*H*), 3.38 (ddd, *J* = 14.3, 7.5, 6.0 Hz, 1 H, Gaa(1)C6-*H′*), 1.39 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 168.7, 156.2, 137.6, 137.4, 137.3, 137.0, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 126.8, 84.5, 83.7, 83.6, 82.5, 82.3, 82.2, 81.6, 79.0, 77.2, 72.6, 72.4, 72.1, 71.7, 52.2, 43.0, 39.8, 28.3; MS (LSIMS) *m*/*z* (%) 711 (30) $[M^+ + H - C_5H_8O_2]$, 811 (6) $[M + H]^+$; HRMS (ESI) calcd for $C_{46}H_{55}N_2O_{11}$ $[M + H]^+$ 811.3850, found 811.3806.

To a solution of Boc-[Gaa(Bn$_2$)]$_2$-OMe (250 mg, 0.30 mmol) in THF−MeOH−H_2O (3:1:1, 2.5 mL) at 0 °C was added LiOH·H_2O (38 mg, 0.93 mmol) with stirring from 0 °C to room temperature for 4 h. The reaction mixture was then acidified to pH 2 with 1 N HCl. It was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain the acid that was dissolved in CH_2Cl_2 (7 mL). To this solution was added trifluoroacetic acid (3 mL) with stirring from 0 °C to room temperature for 2 h. The reaction mixture was then concentrated to give the TFA-salt of **6** that was used directly in the synthesis of **8a**.

Synthesis of H-[(Gaa(Bn$_2$)]$_4$-OH (7). To a solution of Boc-[Gaa(Bn$_2$)]$_2$-OMe (502 mg, 0.62 mmol) in THF−MeOH−H_2O (3:1:1, 5 mL) at 0 °C was added LiOH:H_2O (78 mg, 1.86 mmol) with stirring from 0 °C to room temperature for 4 h. The reaction mixture was then acidified to pH 2 with 1 N HCl and then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain the acid.

In another round-bottom flask a solution of Boc-[Gaa(Bn$_2$)]$_2$-OMe (502 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added. To this was added trifluoroacetic acid (2 mL) with stirring from 0 °C to room temperature for 2 h. The reaction mixture was then concentrated to give TFA.H-[Gaa(Bn$_2$)]$_2$-OMe.

The above-prepared crude acid was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. Then it was sequentially treated with HOBt·H_2O (92 mg, 0.68 mmol) and EDCI (130 mg, 0.68 mmol). After 10 min, TFA.H-[Gaa(Bn$_2$)]$_2$-OMe prepared above and dissolved in CH_2Cl_2 (4 mL) was added to the reaction mixture followed by the addition of DIPEA (0.21 mL, 1.23 mmol). After being stirred for 12 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 50−60% EtOAc in petroleum ether eluant) afforded the protected linear tetramer Boc-[Gaa(Bn$_2$)]$_4$-OMe (563 mg, 61%). Data for **Boc-[Gaa(Bn$_2$)]$_4$-OMe**: R_f 0.3 (silica gel, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 38.0 (*c* 0.25, $CHCl_3$); mp 65−68 °C; IR (neat) ν_{max} 3278, 2901, 1662, 1537, 1098, 1058, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.30 (t, *J* = 5.6 Hz, 1 H, Gaa-(4)N*H*), 8.21 (t, *J* = 5.9 Hz, 1 H, Gaa(3)N*H*), 7.71 (t, *J* = 5.7 Hz, 1 H, Gaa(2)N*H*), 7.38−7.10 (m, 40 H, aromatic protons), 5.08 (t, *J* = 5.8 Hz, 1 H, Gaa(1)N*H*), 4.68−4.15 (m, 16 H, OCH_2-Ph), 4.67 (d, 1 H, Gaa(4)C2-*H*), 4.67 (d, 1H, Gaa(3)C2-*H*), 4.59

(d, 1 H, Gaa(1)C2-*H*), 4.56 (d, 1 H, Gaa(2)C2-*H*), 4.28 (m, 1 H, Gaa(3)C3-*H*), 4.24 (m, 1 H, Gaa(2)C3-*H*), 4.21 (m, 1 H, Gaa-(1)C3-*H*), 4.18 (m, 1 H, Gaa(4)C3-*H*), 4.16 (m, 1 H, Gaa(4)C5-*H*), 4.14 (m, 1 H, Gaa(3)C5-*H*), 4.14 (m, 1 H, Gaa(2)C5-*H*), 3.99 (m, 1 H, Gaa(1)C5-*H*), 3.92 (m, 1 H, Gaa(2)C4-*H*), 3.88 (m, 1 H, Gaa(3)C4-*H*), 3.86 (m, 1 H, Gaa(4)C4-*H*), 3.75 (m, 1 H, Gaa-(2)C6-*H*), 3.70 (m, 1 H, Gaa(4)C6-*H*), 3.70 (m, 1 H, Gaa(3)C6-*H*), 3.65 (s, 3 H, OCH_3), 3.64 (m, 1 H, Gaa(4)C6-*H′*), 3.63 (m, 1 H, Gaa(3)C6-*H′*), 3.59 (m, 1 H, Gaa(1)C4-*H*), 3.57 (m, 1 H, Gaa(1)C6-*H*), 3.17 (m, 1 H, Gaa(2)C6*H′*), 3.14 (m, 1 H, Gaa-(1)C6*H′*), 1.40 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.7, 169.5, 169.4, 156.6, 137.7, 137.62, 137.57, 137.4, 137.3, 137.1, 128.44, 128.36, 128.33, 127.89, 127.85, 127.81, 127.76, 127.71, 127.66, 127.6, 127.52, 127.48, 127.43, 85.4, 85.1, 84.6, 84.0, 83.8, 83.6, 83.4, 83.3, 82.7, 82.6, 82.5, 82.1, 81.9, 81.8, 80.1, 79.4, 73.1, 72.9, 72.8, 71.8, 71.6, 71.5, 71.4, 71.3, 51.9, 43.0, 41.8, 40.9, 28.3; MS (LSIMS) *m*/*z* (%) 1390 (10) [M^+ + H − $C_5H_8O_2$].

To a solution of Boc-[Gaa(Bn_2)]$_4$-OMe (447 mg, 0.3 mmol) in THF−MeOH−H_2O (3:1:1, 5 mL) at 0 °C was added LiOH·H_2O (38 mg, 0.9 mmol) with stirring from 0 °C to room temperature for 4 h. The reaction mixture was then acidified to pH 2 with 1 N HCl and diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain the acid that was dissolved in CH_2Cl_2 (3.5 mL). To this solution was added trifluoroacetic acid (1.5 mL) with stirring from 0 °C to room temperature for 2 h. The reaction mixture was then concentrated to give the TFA-salt of **7** that was used directly in the synthesis of **9a**.

Synthesis of 8a. Compound **8a** was synthesized from **6** in 56% yield, following the same procedure described above for the cyclooligomerization of **1** with the same reagents in identical molar equivalents and under identical reaction conditions. Data for **8a**: R_f 0.3 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −15.5 (*c* 0.91, $CHCl_3$); IR (KBr) ν_{max} 2924, 1670, 1538, 1218, 1086, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (dd, J = 6.7, 5.4 Hz, 1 H, N*H*), 7 33−7.16 (m, 10 H, Ar*H*), 4.72 (d, J = 6.6 Hz, 1 H, C2-*H*), 4.57 (d, J = 11.9 Hz, 1H, PhCH_2O), 4.53 (d, J = 11.9 Hz, 1 H, PhCH_2O), 4.43 (dd, J = 6.6, 4.3 Hz, 1 H, C3-*H*), 4.39 (d, J = 11.7 Hz, 1 H, PhCH_2O), 4.27 (d, J = 11.7 Hz, 1 H, PhCH_2O), 4.25 (dd, J = 5.4, 4.3 Hz, 1 H, C5-*H*), 3.93 (t, J = 4.3 Hz, 1 H, C4-*H*), 3.77 (dt, J = 14.4, 5.4 Hz, 1 H, C6-*H*), 3.59 (dd, J = 14.4, 6.7 Hz, 1 H, C6-*H′*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 137.6, 136.5, 128.7, 128.6, 128.4, 127.8, 127.4, 84.6, 82.3, 82.0, 81.0, 73.3, 72.2, 40.2; MS (ESI) *m*/*z* (%) 1359 (2) [2M + H]$^+$, 680 (94) [M + H]$^+$; HRMS (ESI) calcd for $C_{40}H_{43}N_2O_8$ [M + H]$^+$ 679.3019, found 679.3046.

Synthesis of 8b. Compound **8b** was synthesized from **8a** in quantitative yield, following the same procedure described above for the synthesis of **3b**. Data for **8b**: R_f 0.45 (silica gel, *n*BuOH:AcOH:H_2O = 4:2:2); $[\alpha]^{20}_D$ −70.8 (*c* 0.36, MeOH); IR (KBr) ν_{max} 3444, 3300, 2928, 1647, 1546, 1419, 1166, 1126, 1064 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) see Table 1; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.7, 81.4, 76.3, 75.9, 75.1, 37.4; MS (ESI) *m*/*z* (%) 659.21 (40) [2M + Na]$^+$, 643.24 (38) [2M + Li]$^+$, 341.07 (100) [M + Na]$^+$, 325.11 (76) [M + Li]$^+$; HRMS (ESI) calcd for $C_{12}H_{19}N_2O_8$ [M + H]$^+$ 319.1141, found 319.1135.

Synthesis of 9a. Compound **9a** was synthesized from **7** in 52% yield, following the same procedure described above for the cyclooligomerization of **1** with the same reagents in identical molar equivalents and under identical reaction conditions. Data for **9a**: R_f 0.2 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 82.5 (*c* 0.21, $CHCl_3$); mp 58−60 °C; IR (KBr) ν_{max} 3404, 3060, 3032, 2924, 1668, 1536, 1455, 1097, 739, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.23 (m, 10 H, Ar*H*), 7.01 (dd, J = 7.2, 5.0 Hz, 1 H, N*H*), 4.58 (d, J = 3.9 Hz, 1 H, C2-*H*), 4.54 (d, J = 12.1 Hz, 1 H, PhCH_2O), 4.48 (d, J = 12.1 Hz, 1 H, PhCH_2O), 4.39 (s, 2 H, PhCH_2O), 4.25 (dd, J = 3.9, 1.1 Hz, 1 H, C3-*H*), 4.11 (ddd, J = 8.4, 3.6, 2.2 Hz, 1 H, C5-*H*), 3.92 (ddd, J = 14.4, 7.2, 2.2 Hz, 1 H, C6-*H*), 3.70 (dd, J = 3.6, 1.1 Hz, 1H, C4-*H*), 3.20 (ddd, J = 14.4, 8.4, 5.0 Hz, 1 H, C6-*H′*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 137.5, 137.2, 128.5, 128.4, 127.9, 127.8, 127.6, 84.5, 84.2, 82.8, 82.3, 72.8, 71.8, 42.1; MS (ESI) *m*/*z* (%) 1359 (100) [M + H]$^+$.

Synthesis of 9b. Compound **9b** was synthesized from **9a** in quantitative yield, following the same procedure described above for the synthesis of **3b**. Data for **9b**: R_f 0.3 (silica gel, *n*BuOH:AcOH:H_2O = 4:2:2); $[\alpha]^{20}_D$ 25.5 (*c* 0.18, MeOH); IR (neat) ν_{max} 3424, 2921, 1636, 1399, 1097 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) see Table 1; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.2, 85.5, 82.1, 78.0, 77.5, 41.1; MS (ESI) *m*/*z* (%) 659.2 (70) [M + Na]$^+$, 643.2 (100) [M + Li]$^+$.

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Supporting Information Available: General experimental procedures, NMR spectroscopy, molecular dynamics and ion flux studies; ^{1}H and ^{13}C NMR spectra of all the products; ROESY spectra of **3b**, **4b**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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