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Conformational studies of the linear homooligomers of a glucose-derived furanoid sugar amino acid

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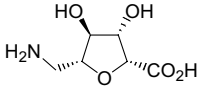
Abstract—Conformational analysis of the linear tetramer of the glucose-derived furanoid sugar amino acid **1** by NMR and constrained molecular dynamics studies revealed that the fully protected tetramer **2a** has a well-defined structure in $CDCl_3$ with repeating β-turns, each involving a 10-membered ring structure with intramolecular hydrogen bonds between $NH_i \rightarrow C{=}O_{i-2}$. Its deprotected versions **2b** and **2c** showed aggregation in organic solvents with structures similar to that of **2a**.

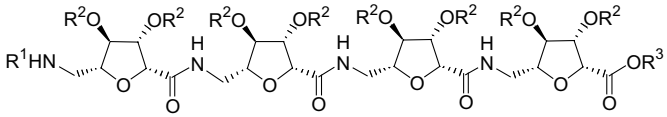
Oligomers of multifunctional monomeric building blocks have been extensively studied in recent years to mimic the structures and functions of biopolymers.[1] Such studies are also intended to develop new materials that can have wide-ranging applications.[2] Sugar amino acid[3] based oligomers, cyclic[4] as well as acyclic,[5] have been investigated by various groups leading to many interesting results. As part of our ongoing project on sugar amino acids and their uses in designing molecules, we report herein the conformational studies of a furanoid sugar amino acid, 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid **1** (Gaa) and its linear tetramer **2**. Fleet's group has shown that short oligomers of gluconic acid-based furanoid sugar amino acids form remarkably stable hydrogen-bonded secondary structures in non-polar organic solvents, the details of which have been published.[5b] We report here that the *O*-benzyl protected linear tetramer of Gaa, Boc-[Gaa(Bn_2)]$_4$-OMe **2a**,[6] has a structure, similar to the one found by Fleet in the acetate and acetonide protected oligomers of Gaa having an azido group at the N- and an ester at the C-termini, in $CDCl_3$ with repeating β-turns, each involving a 10-membered ring structure with intramolecular hydrogen bonds between $NH_i \rightarrow C{=}O_{i-2}$. Furthermore, its deprotected versions, the terminally deprotected compound, H-[Gaa(Bn_2)]$_4$-OH **2b**,[6] as well as the side-chain deprotected one, Boc-(Gaa)$_4$-OMe **2c**,[7] seem to have structures similar to that of the protected one **2a**, although both exhibit aggregation in organic solvents.

NMR studies of **2a** and **2b** were carried out in $CDCl_3$ and **2c** was studied in DMSO-d_6. The spectra were well resolved and most of the spectral parameters could be easily obtained.[8] While the assignments were carried out with the help of total correlation spectroscopy (TOCSY), rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments provided information on the proximity of the protons.[9] Solvent titration studies



1

(**Gaa**)



2

a: R^1 = Boc, R^2 = Bn, R^3 = Me; **b**: R^1, R^3 = H, R^2 = Bn;
c: R^1 = Boc, R^2 = H, R^3 = Me

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for **2a** and **2b** and variable temperature studies for **2c** were used to derive information about the involvement of the amide protons in intramolecular hydrogen bonds. The cross-peak intensities in the ROESY spectra were used for obtaining the restraints in the simulated molecular dynamics (MD) calculations.

The amide proton signals of the protected tetramer **2a**, Boc-[Gaa(Bn_2)]$_4$-OMe, were very well resolved in $CDCl_3$. The downfield appearances of the amide protons at δ 7.71 ppm for Gaa(2)NH, 8.21 ppm for Gaa(3)NH, 8.30 ppm for Gaa(4)NH suggested their involvement in intramolecular H-bonding. Furthermore, these amide proton chemical shifts displayed no concentration dependence and very small changes during solvent titration studies with $\Delta\delta$ (in ppm)=0.23 for Gaa(2)NH, 0.14 for Gaa(3)NH and 0.14 for Gaa(4)NH,[10] with an increase in DMSO-d_6 concentration up to 33.3% in $CDCl_3$. Both concentration dependence and solvent titration studies confirmed their involvement in intramolecular hydrogen bonds with no aggregation. This was further corroborated by variable temperature studies in $CDCl_3$ recorded between 30 and 55 °C, which yielded temperature coefficients ($\Delta\delta/\Delta T$ in ppb/K) of −12.2 for Gaa(2)NH, −8.6 for Gaa(3)NH and −9.8 for Gaa(4)NH. The appearance of ROE cross-peaks between Gaa(2)NH ↔ Gaa(1)C5H, Gaa(2)NH ↔ Gaa(1)C6H, Gaa(3)NH ↔ Gaa(2)C5H, Gaa(3)NH ↔ Gaa(2)C6H, Gaa(4)NH ↔ Gaa(3)C5H, Gaa(4)NH ↔ Gaa(3)C6H, and weak ROE's between Gaa(1)NH ↔ Gaa(2)NH, Gaa(2)NH ↔ Gaa(3)NH, Boc ↔ Gaa(2) C6H, Boc ↔ Gaa(2)C4H coupled with the intramolecular H-bondings of Gaa(2)NH, Gaa(3)NH, Gaa(4)NH unequivocally support the presence of consecutive 10-membered β-turn like structures, which resemble a helical conformation throughout the molecule. The intensities of the ROE cross-peaks, shown schematically in Figure 1, were used for obtaining the restraints in the simulated molecular dynamics (MD) calculations.

A number of interatomic distances and torsional angle constraints obtained from NMR data were used in the MD simulations for durations of 240 ps using 40 cycles, each of 6 ps periods, following the simulated annealing protocol.[6] The results of these MD studies are summarized in Figure 2, which shows an ensemble of the backbone-superimposed turn structures of the 16 out of 20 samples collected during the simulation period.

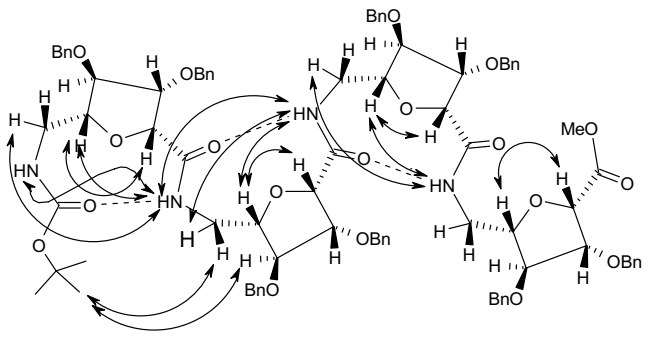

Figure 1. Schematic representation of the proposed structure of **2a** with some of the prominent long-range ROEs seen in its ROESY spectrum.

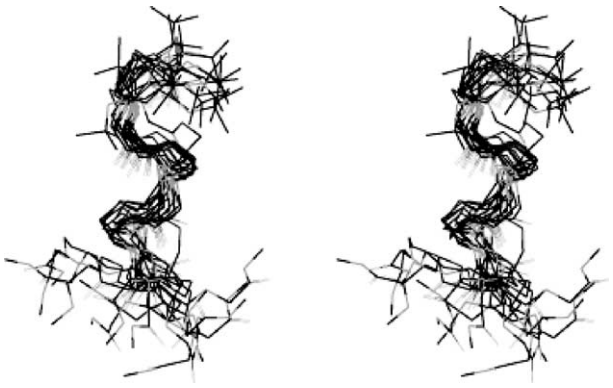

Figure 2. Stereoview of the 16 backbone-superimposed energy-minimized structures of **2a**, out of the 20 samples collected during 40 cycles of the 240 ps constrained MD simulations following the simulated annealing protocol. For clarity, only the backbones are shown here omitting all the C3 and C4 atoms of the sugar rings carrying the *O*-Bn groups.

Thus, the conformational analysis by NMR and constrained MD studies revealed that compound **2a** has a well-defined structure in $CDCl_3$ with repeating β-turns, each involving a 10-membered ring structure with intramolecular hydrogen bonds between $NH_i \rightarrow C{=}O_{i-2}$.

In contrast, the ^{1}H NMR spectrum of a 0.1 mM solution of **2b** in $CDCl_3$ showed downfield chemical shifts of all of its amide protons—Gaa(2)NH, Gaa(3)NH and Gaa(4)NH at δ 8.13, 8.6 and 8.9 ppm, respectively.[10] To examine whether these downfield shifts were due to aggregation or intramolecular hydrogen bonding, the spectra were recorded at eight different concentrations ranging from 0.1 to 20 mM. As shown in Figure 3, two of the amide signals, those of Gaa(3)NH and Gaa(4)NH show considerable concentration dependence in the specified range with $\Delta\delta = 0.408$ and 0.202 ppm, respec-

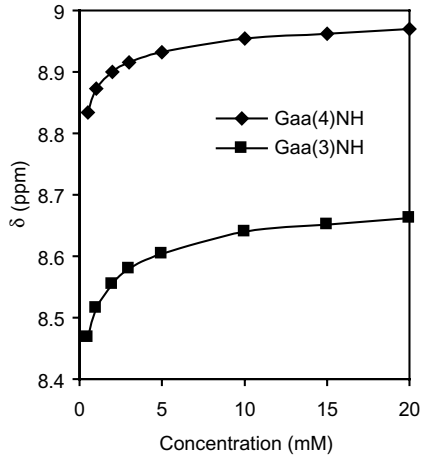

Figure 3. The concentration dependence study of the amide proton chemical shifts of **2b** in $CDCl_3$.

tively. The Gaa(2)NH signal remained unchanged. Nonlinear regression analysis of the NMR data of Gaa(3)NH revealed a dimerization constant of $7.92\times10^3\ M^{-1}$ and that of Gaa(4)NH led to a relatively smaller value of $1.06\times10^3\ M^{-1}$, suggesting strong aggregation of **2b** in nonpolar solvents.[11,12]

Solvent titration studies showed that addition of DMSO-d_6, a hydrogen bonding solvent, disrupted this aggregation inducing upfield shifts of the Gaa(3)NH and Gaa(4)NH resonances, $\Delta\delta = 0.116$ and 0.242 ppm, respectively, with the addition of up to 33.3% of DMSO-d_6 to the $CDCl_3$ solution. Once again the Gaa(2)NH, which does not participate in aggregation shows very small change in its chemical shift during the solvent titration studies, suggesting its involvement in an intramolecular hydrogen bonding, probably a six-membered one with the C3-oxygen of Gaa(1). Further support was lent by variable temperature (VT) study in DMSO-d_6, undertaken between 30 and 70 °C, yielding a temperature coefficient ($\Delta\delta/\Delta T$) of −3.5 ppb/K. The other two amide protons were expected to be involved in inter- as well as intra-molecular hydrogen bonding, which seemed likely from the ROESY spectrum of **2b** run in $CDCl_3$ containing 14% v/v DMSO-d_6. The ROE cross-peaks, some of which are shown in Figure 4, between Gaa(3)NH ↔ Gaa(2)C6H, Gaa(4)NH ↔ Gaa(3)C6H and Gaa(2)NH ↔ Gaa(3)NH confirm the presence of a 10-membered β-turn-like structure, shown in Figure 5, with H-bonds between Gaa(3)NH → Gaa(1)CO and Gaa(4)NH → Gaa(2)CO.

NMR studies of **2c** had to be carried out in DMSO-d_6 as it was insoluble in $CDCl_3$. At higher concentrations the resonances broadened probably due to exchange or because of aggregation. The NMR experiments performed in ~3 mM solution of **2c** in DMSO-d_6 at 26 °C resulted in sharp spectral lines. The variable temperature experiments in DMSO-d_6 showed moderate values of $\Delta\delta/\Delta T$ for Gaa(2)NH (−4.1 ppb/K), Gaa(3)NH (−4.0 ppb/K) and Gaa(4)NH (−4.2 ppb/K), implying

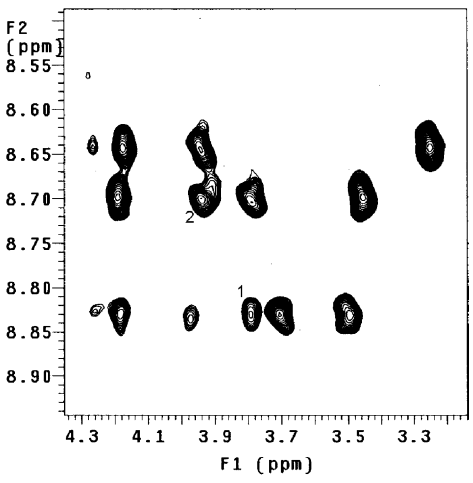

Figure 4. Some of the cross-peaks seen in the ROESY spectrum of **2b** (in $CDCl_3$ containing 14% v/v DMSO-d_6) between: (1) Gaa(4)NH ↔ Gaa(3)C6H, and (2) Gaa(3)NH ↔ Gaa(2)C6H.

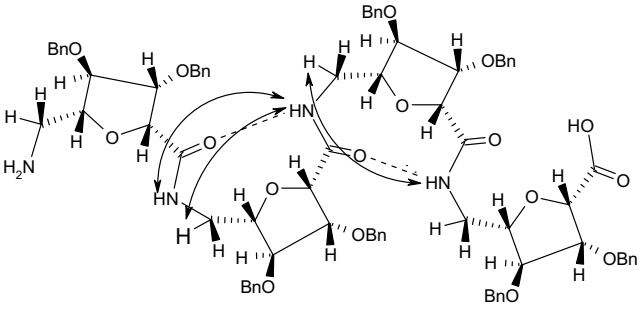

Figure 5. Schematic representation of the proposed structure of **2b** with some of the prominent long-range ROEs seen in its ROESY spectrum.

that there is a predominance of structures with these amides participating in hydrogen bonding. The ROE cross-peaks, shown schematically in Figure 6, between Gaa(2)NH ↔ Gaa(1)C6H, Gaa(4)NH ↔ Gaa(3)C6H and weak ROEs between Gaa(1)NH ↔ Gaa(2)NH, Gaa(3)NH ↔ Gaa(4)NH in the ROESY spectrum coupled with the above mentioned H-bonds corroborate the structure with successive 10-membered H-bonds between Gaa(2)NH → BocCO, Gaa(3)NH → Gaa(1)CO, Gaa(4)NH → Gaa(2)CO, which is very similar to that of **2a**. Because of limited NMR constraints, we were unable to ascertain the detailed structure for **2c**.

Compounds **2a** and **2b** self-assembled into beautiful three-dimensional structures as seen in their SEM pictures shown in Figure 7. The solution of **2a** in CH_2Cl_2 and of **2b** in MeOH formed white suspensions on addition of water. These wet suspensions were placed on aluminium stubs, air dried, gold coated in an HUS-5GB vacuum evaporator and observed using a Hitachi S-520 scanning electron microscope at an acceleration voltage of 10 kV. While compound **2a** self-assembled into dodecahedron shaped structures of ~6–7 μm dimensions (a in Fig. 7), the supramolecular self-assembly of **2b** showed round doughnut shaped structures (b in Fig. 7, <6.0 μm).

In summary, the linear homooligomers of a furanoid sugar amino acid with 2,5-*cis* relationships, like that in Gaa, displayed well-defined turn structures. However, the protected oligomer resulted in a more robust and

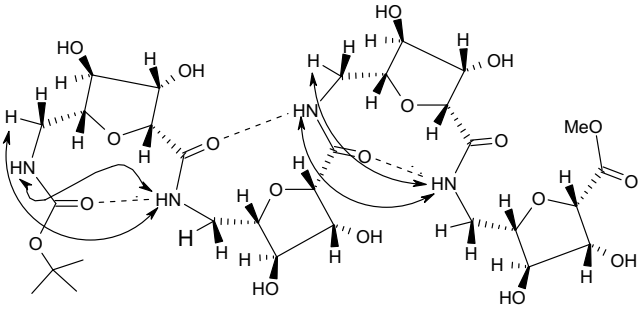

Figure 6. Schematic representation of the proposed structure of **2c** with some of the prominent long-range ROEs seen in its ROESY spectrum.

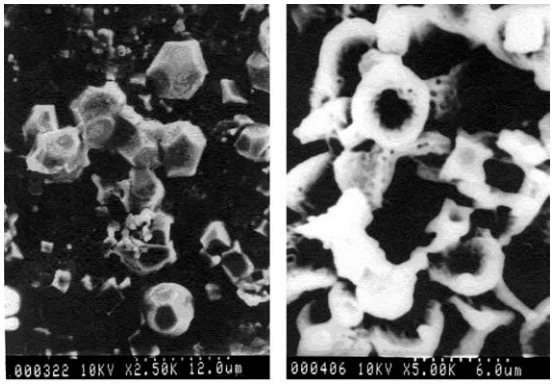

Figure 7. SEM pictures of the dried suspensions of **2a** (a) and **2b** (b).

well-defined structure compared to the deprotected one. The sugar moieties in these oligomers, especially those with deprotected sugar units that show a large propensity of helical structures, can play significant roles in recognizing and binding to suitable receptors in biological systems. These efforts would permit the design of compounds that will successfully mimic the structures and functions of biopolymers.

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References and notes

1. (a) Barron, A. E.; Zuckermann, R. N. *Curr. Opin. Chem. Biol.* **1999**, *3*, 681–687; (b) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530–535; (c) Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1997**, *1*, 120–129; (d) Gellman, S. H. *Acc. Chem. Res.* **1997**, *31*, 173–180; (e) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011.
2. Fox, M. A. *Acc. Chem. Res.* **1999**, *32*, 201–207.
3. For recent reviews on sugar amino acids see: (a) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; (b) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421–435; (c) Chakraborty, T. K.; Jayaprakash, S.; Ghosh, S. *Comb. Chem. High Throughput Screening* **2002**, *5*, 373–387; (d) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253; (e) Peri, F.; Cipolla, L.; Forni, E.; La Ferla, B.; Nicotra, F. *Chemtracts Org. Chem.* **2001**, *14*, 481–499.
4. For some important works on cyclic oligomers and homooligomers of sugar amino acids and related compounds see: (a) Mayes, B. A.; Stetz, R. J. E.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 153–156; (b) Mayes, B. A.; Simon, L.; Watkin, D. J.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 157–162; (c) Mayes, B. A.; Cowley, A. R.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 163–166; (d) van Well, R. M.; Marinelli, L.; Erkelens, K.; van der Marel, G. A.; Lavecchia, A.; Overkleeft, H. S.; van Boom, J. H.; Kessler, H.; Overhand, M. *Eur. J. Org. Chem.* **2003**, 2303–2313; (e) Stöckle, M.; Voll, G.; Günther, R.; Lohof, E.; Locardi, E.; Gruner, S.; Kessler, H. *Org. Lett.* **2002**, *4*, 2501–2504; (f) Campbell, J. E.; Englund, E. E.; Burke, S. D. *Org. Lett.* **2002**, *4*, 2273–2275; (g) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stöckle, M.; Kessler, H. *Chem. Eur. J.* **2002**, *8*, 4365–4376; (h) Locardi, E.; Stöckle, M.; Gruner, S.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189–8196; (i) Gruner, S. A. W.; Kéri, G.; Schwab, R.; Venetainer, A.; Kessler, H. *Org. Lett.* **2001**, *3*, 3723–3725; (j) van Well, R. M.; Overkleeft, H. S.; Overhand, M.; Carstenen, E. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 9331–9335; (k) Lohof, E.; Planker, E.; Mang, C.; Burkhart, F.; Dechantsreiter, M. A.; Haubner, R.; Wester, H.-J.; Schwaiger, M.; Hölzemann, G.; Goodman, S. L.; Kessler, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2761–2764.
5. For some important works on acyclic oligomers and homooligomers of sugar amino acids and related compounds see: (a) Hunter, D. F. A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3831–3839; (b) Smith, M. D.; Claridge, T. D. W.; Sansom, M. S. P. *Org. Biomol. Chem.* **2003**, *1*, 3647–3655; (c) Vescovi, A.; Knoll, A.; Koert, U. *Org. Biomol. Chem.* **2003**, *1*, 2983–2997; (d) Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Shimada, I.; Ichikawa, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1999–2013; (e) Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Chary, M. G.; Diwan, P. V.; Nagaraj, R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2000**, *41*, 8167–8170; (f) Brittain, D. E. A.; Watterson, M. P.; Claridge, T. D. W.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655–3665; (g) Hungerford, N. L. H.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3666–3679; (h) Hungerford, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3680–3685; (i) Smith, M. D.; Long, D. D.; Martín, A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2191–2194; (j) Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195–2198; (k) Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2199–2202; (l) Smith, M. D.; Long, D. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2039–2040; (m) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041–2042.
6. For the syntheses of **2a** and **2b** see: Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; Kiran Kumar, S.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257–6263.
7. Compound **2c** was synthesized from **2a** by hydrogenation using $Pd(OH)_2$–C as catalyst in methanol.
8. For selected physical data of **2a** see Ref. 6. Selected physical data of **2b**: $[\alpha]_D^{26}$ 54.2 (*c* 0.87, $CHCl_3$); IR (KBr) ν_{max} 3388, 2886, 2839, 1662, 1529, 1200, 1098 cm^{-1}; ^1H NMR ($CDCl_3$+14% v/v DMSO-d_6, 30 °C, 500 MHz) δ 3.00 (m, 1H, Gaa(1)C6*H*), 3.11 (m, 1H, Gaa(1)C6*H*′), 3.25 (m, 1H, Gaa(2)C6*H*), 3.46 (m, 1H, Gaa(3)C6*H*), 3.52 (m, 1H, Gaa(4)C6*H*), 3.70 (m, 1H, Gaa(4)C6*H*′), 3.79 (m, 1H, Gaa(3)C6*H*′), 3.95 (m, 1H, Gaa(2)C6*H*′), 4.18 (m, 1H, Gaa(3)C5*H*), 4.19 (m, 2H, Gaa(2)C5*H* and Gaa(4)C5*H*), 4.20–4.26 (m, 4H, Gaa(1)C4*H*, Gaa(2)C4*H*, Gaa(3)C4*H*, Gaa(4)C4*H*), 4.28 (m, 1H, Gaa(1)C5*H*), 4.35–4.49 (m, 4H,

Gaa(1)C3*H*, Gaa(2)C3*H*, Gaa(3)C3*H*, Gaa(4)C3*H*), 4.35–4.66 (m, 16H, OCH_2Ph), 4.59 (m, 1H, Gaa(1)C2*H*), 5.60 (m, 1H, Gaa(2)C2*H*), 4.62 (m, 1H, Gaa(3)C2*H*), 4.70 (d, $J = 4.7$ Hz, 1H, Gaa(4)C2*H*), 7.16–7.33 (m, 40H, aromatic protons), 8.54 (br s, 2H, Gaa(1)N*H*), 8.65 (dd, $J = 5.9$, 7.0 Hz, 1H, Gaa(2)N*H*), 8.70 (t, $J = 6.4$ Hz, 1H, Gaa(3)N*H*), 8.83 (t, $J = 6.3$ Hz, 1H, Gaa(4)N*H*); MS (LSIMS) m/z (%) 1375 (8)$[M+H]^+$. Selected physical data of **2c**: $R_f = 0.64$ (silica gel, *n*-BuOH/AcOH/H_2O=4:2:2); $[\alpha]_D^{26}$ 93.2 (*c* 0.72, MeOH); IR (neat) ν_{max} 3466, 2917, 2839, 1725, 1403, 1145 cm^{-1}; ^1H NMR (DMSO-d_6 at 26 °C, 500 MHz) δ 1.39 (s, 9H, *Boc*), 3.13–3.20 (m, 2H, Gaa(1)C6*H* and C6*H*′), 3.18 (m, 1H, Gaa(3)C6*H*), 3.20 (m, 1H, Gaa(4)C6*H*), 3.22 (m, 1H, Gaa(2)C6*H*), 3.43 (m, 1H, Gaa(3)C6*H*′), 3.50 (m, 1H, Gaa(4)C6*H*′), 3.61 (m, 1H, Gaa(2)C6*H*′), 3.62 (s, 3H, OCH_3), 3.88–3.80 (m, 8H, Gaa(1)C5*H* and C4*H*, Gaa(2)C4*H* and C5*H*, Gaa(3)C4*H* and C5*H*, Gaa(4)C4*H* and C5*H*), 4.01 (m, 2H, Gaa(1)C3*H* and Gaa(2)C3*H*), 4.04 (m, 1H, Gaa(3)C3*H*), 4.11 (m, 1H, Gaa(4)C3*H*), 4.29 (d, $J = 3.4$ Hz, 1H, Gaa(1)C2*H*), 4.30 (d, $J = 3.6$ Hz, 1H, Gaa(3)C2*H*), 4.31 (d, $J = 3.9$ Hz, 1H, Gaa(2)C2*H*), 4.33 (d, $J = 3.7$ Hz, 1H, Gaa(4)C2*H*), 5.06 (d, $J = 4.0$ Hz, 1H, Gaa(3)C3O*H*), 5.13 (d, $J = 4.2$ Hz, 1H, Gaa(2)C3O*H*), 5.21 (d, $J = 3.6$ Hz, 1H, Gaa(1)C3O*H*), 5.24 (d, $J = 3.5$ Hz, 1H, Gaa(1)-C4O*H*), 5.25 (d, $J = 4.1$ Hz, 1H, Gaa(4)C4O*H*), 5.26 (d, $J = 3.7$ Hz, 1H, Gaa(3)C4O*H*), 5.27 (d, $J = 3.8$ Hz, 1H, Gaa(2)C4O*H*), 5.52 (d, $J = 4.5$ Hz, 1H, Gaa(4)C3O*H*), 7.06 (t, $J = 5.8$ Hz, 1H, Gaa(1)N*H*), 7.77 (t, $J = 6.1$ Hz, 1H, Gaa(4)N*H*), 7.97 (t, $J = 6.0$ Hz, 1H, Gaa(2)N*H*), 7.99 (t, $J = 6.0$ Hz, 1H, Gaa(3)N*H*); MS (LSIMS) m/z (%) 775 (22) $[M+Li]^+$, 675 (12) $[M+Li-C_5H_8O_2]^+$.

9. (a) Cavanagh, J.; Fairbrother, W. J.; Palmer, A. G., III; Skelton, N. J. *Protein NMR Spectroscopy*; Academic: San Diego, 1996; (b) Wüthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986.
10. The individual units of Gaa in **2** are numbered in ascending order from N- to C-termini.
11. The concentration dependent chemical shift data for Gaa(3)NH and Gaa(4)NH in **2b** were subjected to nonlinear regression analysis fitting the following equation: $\delta_{obs} = \delta_{free}\ ((1 + 8K_{dim}[\mathbf{2b}]_{tot})^{1/2} - 1)/4K_{dim}[\mathbf{2b}]_{tot} + \delta_{bound}(4K_{dim}[\mathbf{2b}]_{tot} - (1 + 8K_{dim}[\mathbf{2b}]_{tot})^{1/2} + 1)/4K_{dim}[\mathbf{2b}]_{tot}$, where δ_{obs} = observed chemical shift, δ_{free} = minimum chemical shift, δ_{bound} = maximum chemical shift, $[\mathbf{2b}]_{tot}$ = total concentration of **2b** in solution, and K_{dim} = dimerization constant (for details see Ref. 12).
12. (a) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: New York, 1991; p 123; (b) Nowick, J. S.; Chung, D. M.; Maitra, K.; Maitra, S.; Stigers, K. D.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654–7661.