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Synthesis of Orthogonally Protected Cyclic Homooligomers from Sugar Amino Acids

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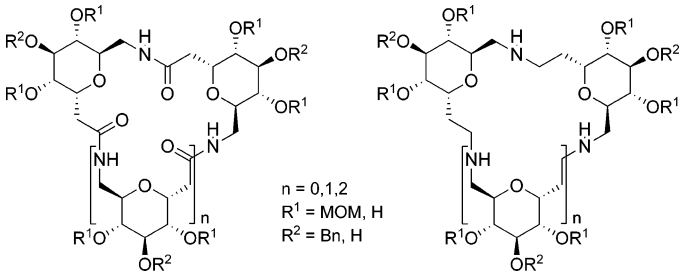

Two new families of orthogonally protected cyclic homooligomers with two to four sugar units were synthesized from pyranoid sugar amino acids. Cyclic oligomers composed of amide-linked sugar amino acids (**1**−**3**) were prepared by cyclization of linear oligomers of the novel orthogonally protected pyranoid sugar amino acid **12** using a solution-phase coupling method. These orthogonally protected cyclic molecules can be selectively or fully deprotected, affording the macrocycles ready to further functionalization. The straightforward reduction of the amide bonds in the cyclic oligomers **1**−**3** gave the corresponding amine-linked macrocycles **4**−**6**. This kind of amine-linked carbohydrate-based cyclic oligomer has never been reported before. These flexible molecular receptors could be studied as molecular hosts for molecular, cationic, and anionic recognition. Conformational analysis by molecular modeling (AM1) showed that all of the deprotected cyclic trimers and tetramers preferred a $^4C_1$ chair conformation with oxygen atoms of the sugar ring located on the interior of the cavity and the secondary hydroxyl groups outward. In the amide-linked macrocycles, all of the amide bonds are in s-*trans* conformation. The estimated size of the internal cavity is about 4.5 Å for the cyclic trimer and 6.9 Å for the cyclic tetramer. The amine-linked macrocycles displayed similar conformational behavior with a slight decrease in internal cavity.

Introduction

Host−guest recognition is implicated in a variety of physical, chemical, and biological processes. Progress toward the artificial recognition of ions and molecules may lead to the development of new chemical sensors design, purification, enantiomeric resolution, enzymatic mimics, or drug delivery systems. Various hosts such as cyclodextrines, crown ethers, cyclophanes, and calixarenes have been developed and widely studied in molecular or ionic recognition and inclusion. Among these molecular receptors, cyclodextrines, cyclic oligomers composed of α(1→4) linked D-glucopyranose units, have been most extensively studied as a result of their ability to include a variety of guest molecules in their hydrophobic cavities.[1] Development of analogues of cyclodextrines with a modified cavity would be of particular interest as potential specific host molecules.[2]

As part of our ongoing project on sugar amino acids based molecular design, we are interested in synthesizing analogues of cyclodextrines from sugar amino acids. An obvious advantage of this approach is that the amino and the carboxylic acid functionalities in the sugar amino acids can be linked via amide bonds following well-

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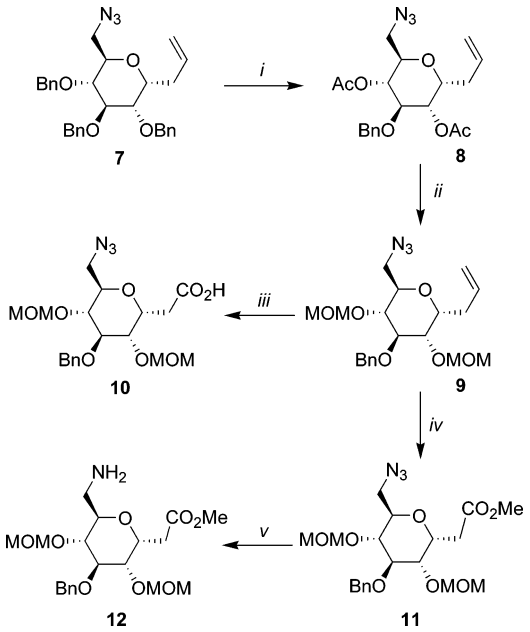
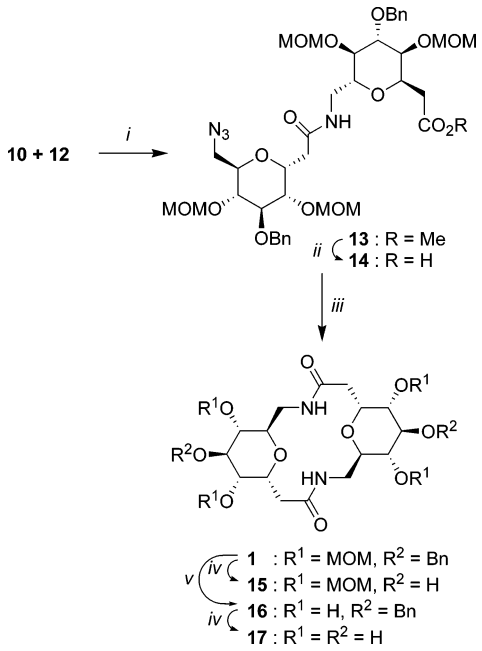
SCHEME 1[a]



[a] Reagents and conditions: (i) (1) BCl_3, CH_2Cl_2, −78 °C, (2) Ac_2O, pyridine, 100%; (ii) (1) MeONa, MeOH, (2) NaH, MOMCl, DMF, 97%; (iii) $KMnO_4$, AcOH, aliquat 336, H_2O, CH_2Cl_2, 69%; (iv) (1) $KMnO_4$, AcOH, aliquat 336, H_2O, CH_2Cl_2, (2) $NaHCO_3$, MeI, DMF, 49%; (v) PPh_3, H_2O, THF, 98.5%.

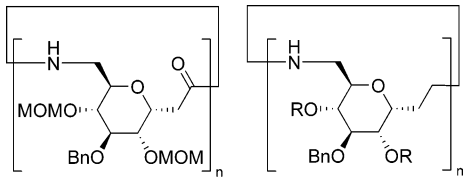
established peptide chemistry. Furthermore, a reduction of amide into amine would lead to a novel series of more flexible cyclic derivatives. Kessler and co-workers have first reported the synthesis of cyclic oligomers of pyranoid sugar amino acids as host molecules that could form inclusion complexes with *p*-nitrophenol and benzoic acid.[3] Cyclic oligomers of sugar amino acids bearing pyranoid *β*-anomer of sugar amino acids[4] or furanoid α- and *β*-anomers of sugar amino acids[4b,5] have been reported. Functionalization of these artificial receptors would be of interest for supramolecular chemistry. As selective modification of hydroxyl groups is still a challenge, orthogonally protected cyclic molecules are preferred for

SCHEME 2[a]



[a] Reagents and conditions: (i) DEPC, Et_3N, DMF, 83%; (ii) LiOH, H_2O/MeOH/THF, 93%; (iii) (1) H_2, Pd/C, MeOH, (2) DEPC, Et_3N, DMF, 60%; (iv) H_2, Pd/C, Pd black, AcOH, MeOH/EtOAc, 99% for **15**, 74% for **17**; (v) AcCl, MeOH, 98%.

further development. Herein we report the synthesis of novel orthogonally protected cyclic oligomers of pyranoid α-anomer of sugar amino acid (compounds **1**−**3**), their selective deprotection, and their transformation into amine-linked cyclic molecules (compounds **4**−**6**). Conformational analysis by molecular modeling (AM1) was performed on fully deprotected cyclic trimers and tetramers.



Results and Discussions

Synthesis of Cyclic Oligomers 1−3. The synthesis was started by preparing orthogonally protected sugar amino acids (Scheme 1). We have recently discovered a new regioselective debenzylation reaction of *C*-glycosides by boron trichloride.[6] Treatment of α-*C*-allyl glucoside **7** with BCl_3 followed by acetylation gave quantitatively the diacetate **8**.[6] Zemplén desacetylation and methoxymethylation of **8** furnished **9** in 97% yield. Oxidation of the alkene function with $KMnO_4$ led to carboxylic acid **10**, which was transformed into methyl ester **11**. Reduction of the azido function in **11** afforded amino ester **12** in 47% overall yield.

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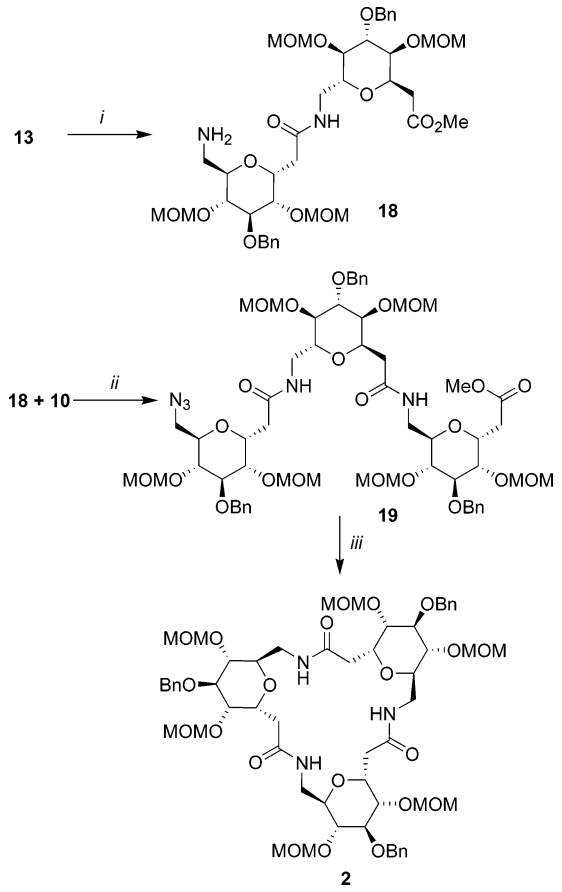
SCHEME 3[a]



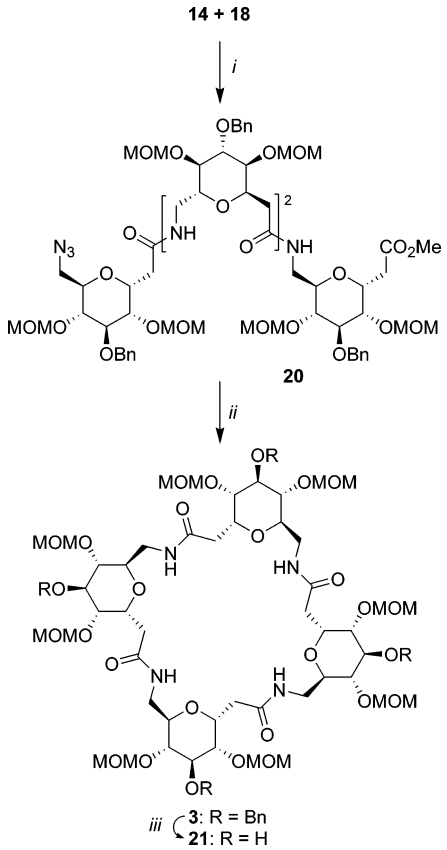
[a] Reagents and conditions: (i) PPh_3, H_2O, THF, 82%; (ii) DEPC, Et_3N, DMF, 53%; (iii) (1) LiOH, H_2O/MeOH/THF, (2) H_2, Pd/C, MeOH, (3) DEPC, Et_3N, DMF, 35%.

The coupling of amino ester **12** with azido acid **10** was carried out with diethyl phosphoryl cyanide (DEPC)[7]/Et_3N to give dimer **13** (Scheme 2). For final end-to-end cyclization, it was better to first convert ester **13** into acid **14** before the reduction of the azido function. It is to be noted that catalytic hydrogenation with Pd/C reduced selectively the azido function without debenzylation. Cyclic dimer **1** was obtained in 60% yield for the last two steps after cyclization using DEPC/Et_3N.

At this stage, we decided to deprotect selectively or totally compound **1**. The 3-*O*-benzyl group seemed to be particularly resistant under the usual debenzylation conditions. However, complete debenzylation could be achieved by Pd black-catalyzed hydrogenolysis in the presence of AcOH in a mixture of MeOH/EtOAc,[8] which led to **15** in 99% yield. Alternatively, treatment of **1** with AcCl/MeOH[9] gave cyclodimer **16** in 98% yield. Further debenzylation afforded the fully deprotected cyclic compound **17** in 74% yield.

Schemes 3 and 4 show the synthesis of cyclic trimer **2** and tetramer **3**. Reduction of azide **13** under Staudinger condition furnished amine **18** in 82% yield. Condensation of **18** with azido acid **10** gave the linear trimer **19** (53%).

SCHEME 4[a]



[a] Reagents and conditions: (i) DEPC, Et_3N, DMF, 100%; (ii) (1) LiOH, H_2O/MeOH/THF, (2) H_2, Pd/C, MeOH, (3) DEPC, Et_3N, DMF, 62%; (iii) H_2, Pd/C, Pd black, MeOH/EtOAc, 59%.

Subsequent saponification/reduction/coupling transformed **19** into the desired compound **2** in 35% yield (Scheme 3). Similarly, coupling of **14** with **18** produced quantitatively the linear tetramer **20**, which was converted into **3** in 62% yield (Scheme 4). Debenzylation of **20** afforded the partially deprotected cyclic compound **21** in 59% yield.

Synthesis of Cyclic Oligomers 4−6. These amine-linked macrocycles can be obtained by reduction of the amide bonds in compounds **1**−**3**. Reduction of compound **1** with BH_3·THF[10] (15 equiv/amide bond) gave the desired product **4** in 91% yield (Scheme 5). However, treatment of compounds **2** and **3** with BH_3·THF led to partial deprotection of the MOM groups. So we decided to remove all of the methoxymethyl substituants with AcCl/MeOH, which led to the partially deprotected cyclic compounds **5** and **6**. To the best of our knowledge, these amine-linked cyclic molecules have never been reported before. Replacement of the amide function by amine could make the macrocycle more flexible. Recently, a flexible cyclophane receptor with significantly improved host−guest recognition compared to that of the rigid parent host has been reported.[11] It would be of interest to study the host−guest basic attractive force with the more flexible cyclic compounds **4**−**6** and to compare their recognition properties with their parent compounds. Moreover, replacement

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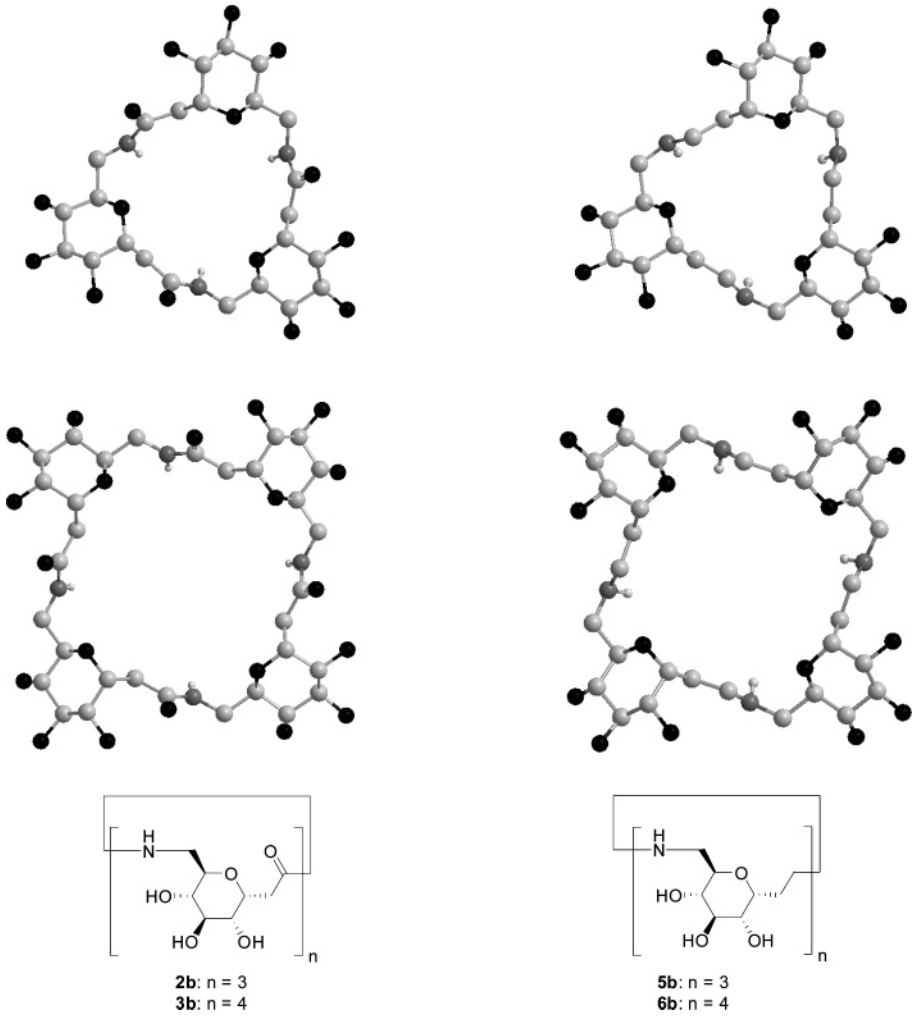

FIGURE 1. Energy-minimized structures of **2b** (top left), **3b** (bottom left), **5b** (top right), and **6b** (bottom right).

of the amide bond by amine in the macrocycles could allow recognition for both cationic and anionic guests.

Conformational Analysis. The ^{1}H and ^{13}C NMR spectra of all cyclic compounds displayed symmetric structure, since only one set of signals from their sugar unit is observed. However, because of the extensive overlapping of signals, the $^3J_{H,H}$ coupling constants could not be determined for either amide- or amine-linked cyclic oligomers. For amide-linked cyclic compounds, no significant chemical shifts of the amide protons were observed upon cyclization, with δ_{NH} ranges from 6.83 to 7.09 ppm in compounds **1**−**3**, **15**, and **21**, suggesting that N−H is not involved in intramolecular H-bonding. The geminal protons at C2 have, however, well-resolved chemical shifts. The geminal C2H resonating at lower field (arbitrarily assigned as H2b) displayed a large coupling constant with H1′ ($J_{1',2}$ = 11.7 Hz for cyclic dimer **1** and tetramer **3**, 9.6 Hz for cyclic trimer **2**). This indicates that compounds **1**−**3** adopt a similar conformation with H2b in an *anti* relationship relative to H1′. To find the most probable structures, conformational analysis was performed on corresponding fully deprotected cyclic trimers **2b**, **5b** and tetramers **3b**, **6b** by molecular modeling techniques (AM1 calculations in the GAMESS[12] suite of programs) (Figure 1).

In all cyclic compounds, the obtained energy-minimized structures displayed a $^4C_1$ chair conformation. The

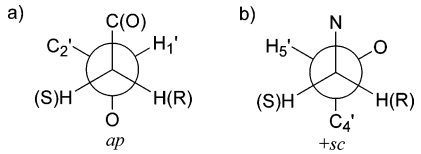

FIGURE 2. Rotamer conformation for the C2−C1′ bond (a) and the C6′−C5′ bond (b) of **2b** and **3b**.

oxygen atoms in the sugar ring are located on the interior and the secondary hydroxyl groups are oriented outward. No significant shape modification is observed between amide- and amine-linked macrocycles (**2b** vs **5b**, and **3b** vs **6b**). In amide-linked macrocycles, the s-*trans* orientation represents the most stable conformation, with all of the carbonyls pointing to the one side of the ring and the N−H bonds in the opposite direction, which practically ruled out the formation of intramolecular H-bonding between the amide proton and adjacent carbonyl group. This point is supported by the observed relative high field amide proton chemical shifts (δ_{NH} = 6.83−7.09 ppm). The minimized structures also reveal that the C2−C1′ bond adopts the *ap* conformation in **2b** and **3b** (Figure 2), with

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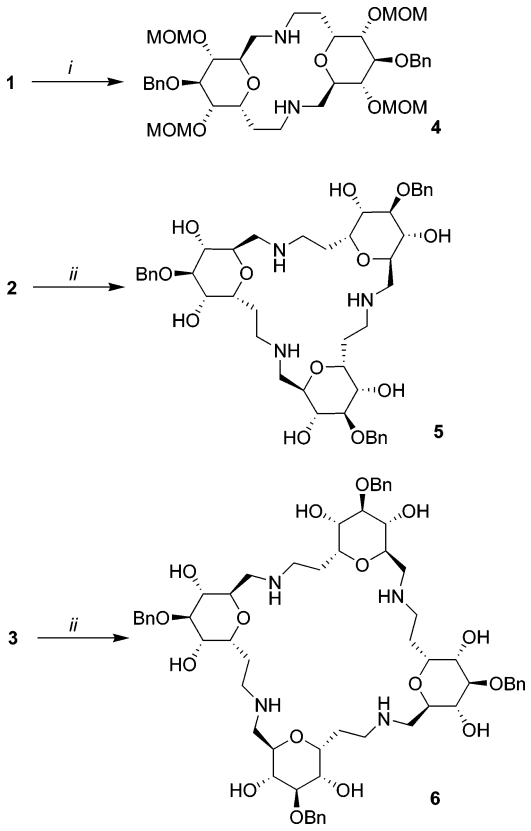
SCHEME 5[a]



[a] Reagents and conditions: (i) BH_3·THF, THF, reflux, 91%; (ii) (1) BH_3·THF, THF, reflux, (2) AcCl, MeOH; 42% for **5**; 68% for **6**.

H2(*pro-S*) in an *anti* conformation in relation to H1′ and H2(*pro-R*) pointing into the interior of the cavity. Consequently, the diastereotopic proton resonating at lower field (H2b, $J_{1',2b} = 9.7-11.7$ Hz) can be assigned as a H2(*pro-S*). Otherwise, the C6′−C5′ bond prefers a positive synclinal orientation (+*sc*), which makes the amide protons slightly pointing into the ring, in parallel to H5′. These last two points are different from the conformational behavior of the reported β-anomer of **2b**, where the most populated rotamer for both C2−C1′ and C6′−C5′ adopts the −*sc* conformation.[4b] However, these two anomeric cyclic trimers displayed a similar tripod bowl-shaped structure. The estimated size of the internal cavity is about 4.5 Å for **2b** and 6.9 Å for **3b** (by the calculated average distance between two opposite closest protons (H2*pro-R*)). So the cavity of cyclic tetramer **3b** is intermediate to that of α- and β-cyclodextrines (5.7 and 7.8 Å, respectively).

In amine-linked macrocycles **5b** and **6b**, the C6′−C5′ bond prefers also a positive synclinal orientation *(+sc)*, which makes the amine protons slightly pointing into the ring as their amide analogues. The calculated average distance between two opposite closest protons is about 4.2 Å for **5b** and 6.7 Å for **6b**.

Conclusions

We have accomplished the synthesis of three orthogonally protected cyclic oligomers of pyranoid α-anomer of sugar amino acids that constitute a new class of molecular scaffolds. These molecules have been selectively and fully deprotected, offering possibilities for further functionalization. These macrocycles can be used as host molecules in both organic and aqueous environment. Furthermore, we have realized the direct conversion of the amide-linked macrocycles into amine-linked ones, which represent the first example of this type of carbohydrate-derived host molecules. Conformational analysis by molecular modeling (AM1) showed that all of the deprotected cyclic trimers and tetramers displayed a $^4C_1$ chair conformation with oxygen atoms of the sugar ring located on the interior of the cavity and the secondary hydroxyl groups outward. This would provide a hydrophobic internal cavity as in the case of cyclodextrines. These information will be useful for further recognition studies of these novel cyclic compounds.

Experimental Section

Conformational Analysis by Molecular Modeling. A coarse drawing of the structure leads to a geometry that is first improved using molecular mechanics technics (MM2) implemented in ChemBats3D 5.0, and the resulting structure is then optimized by the semiempirical Hamiltonian AM1 in the GAMESS[12] suite of programs. These programs were run on RS/6000 System Regatta Power4 machines. To perform the optimization, no symmetry constraint was imposed, allowing the whole (3N-6) degrees of freedom. The minimum in energy was obtained by minimizing the gradient norm using the default (BFGS) algorithm. A search for other possible conformations (for example in the amide link) leads to worse energies, so the proposed conformations appear the best ones, and the structures obtained show serendipitous symmetry.

Reduction of Azido Function (General Method A). To a solution of azido-sugar (1 equiv) in freshly distilled THF (0.1 M) under an argon atmosphere were added water (11.1 equiv) and triphenylphosphine (1.1 equiv), and the mixture was stirred at room temperature for 24 h. Then, an additionnal amount of PPh_3 (0.11 equiv) was added, and the solution was stirred for another 24 h. The solvent was removed, and the residue was purified over silica gel (EtOAc, then 9:1 CH_2Cl_2/MeOH) to afford the corresponding amino-sugar.

Reduction of Azido Function (General Method B). A stirred solution of azido-sugar and Pd/C (10% w/w) in methanol was hydrogenated under H_2 atmosphere overnight. The mixture was filtered over a Celite pad, washed with MeOH, and evaporated to give the corresponding amino-sugar.

Amide Formation (General Method C). DEPC (1.5 equiv) and Et_3N (3 equiv) were successively added, at 0 °C under an argon atmosphere, to a stirred solution of amine (1 equiv) and acid (1 equiv) in DMF (73 mM). The solution was allowed to warm to room temperature and stirred for 1−3 days. Then, the mixture was partitioned in EtOAc/H_2O (1:1), the organic layer was washed with brine, and the aqueous layers were combined and extracted with EtOAc (2×). The organic layers were combined, dried ($MgSO_4$), evaporated, and purified over silica gel to give the corresponding amide.

Saponification (General Method D). LiOH·H_2O (1.5 equiv) was added to a solution of methyl ester (1 equiv) in a mixture of THF/MeOH/H_2O (1:1:1; 0.33 M). The solution was stirred for 1−2 days at room temperature and then acidified to pH 4 with HCl (10%). The mixture was extracted with EtOAc, and the organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give the corresponding acid.

Oligomer Cyclization (General Method E). Cyclization was realized in dilute DMF (2.2 mM) following the general method C.

Debenzylation (General Method F). Pd/C and Pd black (1:1, 10% w/w) were added to a solution of benzylated cyclic oligomer in a mixture of MeOH/EtOAc (1:1). The resulting

suspension was stirred under H_2 atmosphere (1 atm) for 1−4 days. The mixture is filtered over a Celite pad, washed with MeOH, and evaporated to give the corresponding debenzylated cyclic oligomer.

Deprotection of the MOM Group (General Method G). A solution of HCl (0.3 M) in MeOH was prepared by addition of AcCl (213 μL, 3 mmol) to distilled MeOH (10 mL). To this solution was added methoxymethylated oligomer (1 equiv HCl/MOM), and the solution was heated at 50 °C overnight. After evaporation, the mixture was diluted in EtOH and evaporated to give the corresponding deprotected oligomer.

3-(6′-Azido-3′-*O*-benzyl-6′-deoxy-2′,4′-di-*O*-methoxymethyl-α-D-glucopyranosyl)-prop-1-ene (9). MeONa in MeOH (1 M, 50 mL) was added to a solution of **8**[6] (11.64 g, 28.21 mmol) in MeOH (250 mL), and the mixture was stirred overnight. After acidification with HCl (10%) to pH 4, the solvent was removed, the residue was partitioned (EtOAc/H_2O, 1:1, 400 mL) and extracted (EtOAc, 2 × 100 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting oil was diluted in DMF (40 mL) and added dropwise to a cold (0 °C) suspension of washed NaH (3.95 g, 98.70 mmol, 60% in oil) in DMF (90 mL) under an argon atmosphere. The mixture was stirred for 1 h and warmed to room temperature. Then, the methoxymethyl chloride (7.50 mL, 98.70 mmol) was added dropwise, and the solution was stirred at room temperature overnight. After addition of methanol (20 mL), the solvent was evaporated, and the resulting residue was partitioned (EtOAc/H_2O, 1:1, 400 mL) and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **9** (11.12 g, 97%) as a slightly yellow oil: R_f 0.43 (1:4 EtOAc/cyclohexane); $[\alpha]_D$ +55.1 (*c* 2, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.36−2.61 (m, 2H), 3.35 (s, 3H), 3.36 (s, 3H), 3.37−3.54 (m, 3H), 3.62−3.73 (m, 2H), 3.77 (dd, J = 5.5, 8.9 Hz, 1H), 4.07−4.19 (m, 1H), 4.61 (d, J = 6.5 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 4.83 (d, J = 11.1 Hz, 1H), 4.84 (d, J = 6.5 Hz, 1H), 5.08−5.24 (m, 2H), 5.76−5.97 (m, 1H), 7.27−7.42 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 30.4, 51.7, 56.0, 56.4, 71.3, 74.1, 75.1, 77.1, 77.9, 81.1, 97.5, 98.3, 117.3, 127.8, 128.5, 134.4, 138.3. Anal. Calcd for $C_{20}H_{29}N_3O_6$ (407.46): C, 58.95; H, 7.17; N, 10.31. Found: C, 58.64; H, 7.28; N, 10.19.

(6′-Azido-3′-*O*-benzyl-6′-deoxy-2′,4′-di-*O*-methoxymethyl-α-D-glucopyranosyl)-ethanoic Acid (10). Acetic acid (8 mL, 140.10 mmol) and aliquat 336 (490 mg) were added to a solution of **9** (3 g, 7.37 mmol) in a mixture of CH_2Cl_2/H_2O (1:1; 75 mL). The reaction mixture was cooled to 0 °C, $KMnO_4$ (4.314 g; 27.27 mmol) was added in two portions, and the solution was allowed to warm to room temperature and stirred for 24 h. After dilution in CH_2Cl_2 (100 mL), the excess of $KMnO_4$ was reduced with Na_2SO_3 (4.8 g). The aqueous layer was extracted, and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified over silica gel (1:3 EtOAc/cyclohexane, then 95:5 CH_2Cl_2/MeOH) to give **10** (2.16 g, 69%) as a colorless oil: R_f 0.65 (9:1 CH_2Cl_2/MeOH), $[\alpha]_D$ +60.1 (*c* 2, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.78 (dd, J = 15.5, 8.5 Hz, 1H), 2.84 (dd, J = 15.5, 5.7 Hz, 1H), 3.37 (s, 3H), 3.39 (s, 3H), 3.42−3.55 (m, 2H), 3.56 (t, J = 8.2 Hz, 1H), 3.66 (t, J = 8.2 Hz, 1H), 3.76−3.90 (m, 2H), 4.64 (d, J = 6.5 Hz, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.74 (d, J = 11.3 Hz, 1H), 4.78 (d, J = 6.8 Hz, 1H), 4.85 (d, J = 11.3 Hz, 1H), 4.87 (d, J = 6.5 Hz, 1H), 7.22−7.41 (m, 5H), 10.2 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.7, 51.2, 55.9, 56.2, 71.4, 72.1, 74.9, 76.3, 76.4, 80.4, 97.1, 98.0, 127.7, 128.4, 138.0, 176.2. Anal. Calcd for $C_{19}H_{27}N_3O_8$ (425.43): C, 53.64; H, 6.40; N, 9.88. Found: C, 53.88; H, 6.21; N, 9.67.

Methyl (6′-Azido-3′-*O*-benzyl-6′-deoxy-2′,4′-di-*O*-methoxymethyl-α-D-glucopyranosyl)-ethanoate (11). Compound **9** (5.74 g, 14.099 mmol) was oxidized as described previously to afford crude **10** (6.20 g). $NaHCO_3$ (4.74 g, 56.40 mmol) and methyl iodide (3.51 mL, 56.40 mmol) were added to the solution of **10** in DMF (22 mL) under an argon atmosphere. After 24 h of stirring, an additional amount of methyl iodide (1.75 mL, 28.20 mmol) was added, and the mixture was stirred for 48 h. The solvent was removed, and the resulting residue was partitioned (EtOAc/H_2O,1:1, 200 mL) and extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), evaporated, and purified over silica gel (1:5 then 1:4 EtOAc/cyclohexane) to give **11** (3.01 g, 6.86 mmol, 49%) as a colorless oil: R_f 0.55 (2:3 EtOAc/cyclohexane), $[\alpha]_D$ +46.6 (*c* 2, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.59 (d, J = 7.4 Hz, 2H), 3.17 (s, 3H), 3.19 (s, 3H), 3.22−3.30 (m, 2H), 3.33 (t, J = 8.5 Hz, 1H), 3.45 (t, J = 8.5 Hz, 1H), 3.56 (s, 3H), 3.57−3.67 (m, 1H), 3.65 (t, J = 8.5 Hz, 1H), 4.39−4.47 (m, 1H), 4.43 (d, J = 6.5 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 6.5 Hz, 1H), 7.05−7.24 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.6, 51.4, 52.0, 56.0, 56.3, 71.6, 72.2, 75.0, 76.5, 80.5, 97.2, 98.1, 127.7, 127.8, 128.4, 138.1, 171.4. Anal. Calcd for $C_{20}H_{29}N_3O_8$ (439.46): C, 54.66; H, 6.65; N, 9.56. Found: C, 54.82; H, 6.78; N, 9.26.

Methyl 2-(6′-Amino-3′-*O*-benzyl-6′-deoxy-2′,4′-di-*O*-methoxymethyl-α-D-glucopyranosyl)-ethanoate (12). Compound **11** (2.33 g, 5.31 mmol) was reduced using general method A to give amine **12** (2.16 g, 98.5%) as a slightly yellow oil: R_f 0.19 (9:1 CH_2Cl_2/MeOH), $[\alpha]_D$ +68.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.79 (s, 2H), 2.68 (dd, J = 15.2, 4.8 Hz, 1H), 2.78 (dd, J = 15.2, 9.7 Hz, 1H), 2.89 (dd, J = 15.0, 4.6 Hz, 1H), 2.95 (dd, J = 15.0, 4.6 Hz, 1H), 3.35 (s, 6H), 3.45 (t, J = 8.0 Hz, 1H), 3.55 (td, J = 4.6, 8.0 Hz, 1H), 3.61 (t, J = 8.0 Hz, 1H), 3.70 (s, 3H), 3.75 (dd, J = 8.0, 5.4 Hz, 1H), 4.54 (ddd, J = 4.8, 9.7, 5.4 Hz, 1H), 4.57 (d, J = 6.5 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 4.86 (d, J = 6.5 Hz, 1H), 7.23−7.39 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.8, 42.6, 52.0, 56.1, 56.3, 70.9, 73.7, 74.9, 75.9, 76.8, 80.6, 97.2, 98.0, 127.8, 128.5, 138.2, 171.9. Anal. Calcd for $C_{20}H_{31}NO_8$ (413.46): C, 58.10; H, 7.56; N, 3.39. Found: C, 57.89; H, 7.76; N, 3.28.

Synthesis of Azido Ester 13. Amine **12** (2.02 g, 4.88 mmol) and acid **10** (2.07 g, 4.88 mmol) were coupled using general method C and purified over silica gel (6:4 EtOAc/cyclohexane) to give **13** (3.31 g, 83%) as a white solid: R_f 0.44 (6:4 EtOAc/cyclohexane), mp 114 °C, $[\alpha]_D$ +62.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57 (dd, J = 16.3, 3.1 Hz, 1H), 2.56−2.75 (m, 2H), 2.85 (dd, J = 16.3, 10.5 Hz, 1H), 3.31 (s, 3H), 3.32 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.37−3.68 (m, 8H), 3.70 (s, 3H), 3.73−3.90 (m, 4H), 4.46 (ddd, J = 10.5, 3.1, 3.1 Hz, 1H), 4.53−4.84 (m, 13H), 6.80−6.93 (m, 1H), 7.21−7.40 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.7, 34.2, 38.7, 51.4, 52.0, 56.1, 56.2, 67.8, 71.3, 72.1, 73.0, 73.6, 75.2, 76.0, 76.4, 77.4, 80.0, 73.9, 74.7, 96.9, 97.1, 97.9, 127.8, 128.0, 128.4, 128.5, 137.7, 138.1, 170.1, 172.5. MS (MALDI) *m/z* 843.7 $[M + Na]^+$.

Synthesis of Azido Acid 14. Ester **13** (1.63 g, 1.98 mmol) was saponified using general method D to give acid **14** (1.49 g, 93%) as a white solid: R_f 0.47 (4:1 EtOAc/cyclohexane), mp 102 °C, $[\alpha]_D$ +65.8 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48−2.75 (m, 2H), 2.61 (dd, J = 15.5, 3.5 Hz, 1H), 2.84 (dd, J = 15.5, 11.0 Hz, 1H), 3.29−3.91 (m, 12H), 3.33 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.37 (s, 3H), 3.43−3.84 (m, 14H), 6.78−6.88 (m, 1H), 7.21−7.40 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.3, 34.2, 39.5, 51.3, 56.1, 56.2, 56.3, 56.4, 69.3, 71.5, 71.8, 72.3, 74.4, 74.7, 74.9, 75.9, 76.1, 77.0, 78.7, 79.8, 97.1, 97.19, 97.24, 97.8, 127.9, 128.6, 137.9, 138.1, 170.5, 174.2. MS (MALDI): *m/z* 829.3 $[M + Na]^+$.

Synthesis of Cyclic Dimer 1. Compound **14** (706 mg, 0.876 mmol) was reduced using general method B, cyclized using general method E, and purified over silica gel (1:1 EtOAc/CH_2Cl_2 then 9:1 CH_2Cl_2/MeOH) to give **1** (400 mg, 60%) as a white solid: R_f 0.63 (9:1 CH_2Cl_2/MeOH), mp 266 °C, $[\alpha]_D$ +84.7 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.62 (dd, J = 17.3, 2.5 Hz, 2H), 2.76 (dd, J = 17.3, 11.7 Hz, 2H), 2.99−3.15 (m, 2H), 3.28−3.38 (m, 2H), 3.33 (s, 6H), 3.41 (s, 6H), 3.53−3.65 (m, 4H), 3.72 (dd, J = 5.6, 8.9 Hz, 2H), 4.11−4.26 (m, 2H), 4.43 (ddd, J = 2.5, 11.7, 5.6 Hz, 2H), 4.59 (d, J = 6.8

Hz, 2H), 4.60 (d, J = 6.5 Hz, 2H), 4.68 (d, J = 11.4 Hz, 2H), 4.74 (d, J = 6.5 Hz, 2H), 4.78 (d, J = 11.4 Hz, 2H), 4.87 (d, J = 6.8 Hz, 2H), 6.83−6.95 (m, 2H), 7.22−7.40 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.3, 40.4, 56.2, 56.6, 71.3, 72.2, 75.3, 77.2, 77.3, 80.0, 97.7, 98.2, 127.9, 128.6, 138.1, 170.2. MS (MALDI): *m/z* 785.6 $[M + Na]^+$.

Synthesis of Cyclic Dimer 15. Compound **1** (50 mg, 0.066 mmol) was debenzylated with Pd/C and Pd black (1:1, 20% w/w) in a MeOH/EtOAc/AcOH (1:1:0.4, 2.4 mL) mixture according to general method F and purified over silica gel (95:5 CH_2Cl_2/MeOH) to give **15** (38 mg, 99%) as a white solid: R_f 0.25 (9:1 CH_2Cl_2/MeOH), mp 211 °C, $[\alpha]_D$ +77.6 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57−2.80 (m, 4H), 2.91−3.05 (m, 2H), 3.14 (dd, J = 8.3, 9.5 Hz, 2H), 3.39 (s, 6H), 3.45 (s, 6H), 4.48−4.76 (m, 6H), 4.10−4.23 (m, 2H), 4.40−4.51 (m, 2H), 4.672 (d, J = 6.8 Hz, 2H), 4.674 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 6.8 Hz, 2H), 4.87 (d, J = 6.8 Hz, 2H), 6.90−7.00 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.7, 40.7, 56.0, 56.3, 70.2, 71.6, 72.1, 77.7, 81.4, 97.7, 98.0, 171.0. MS (MALDI): *m/z* 605.2 $[M + Na]^+$.

Synthesis of Cyclic Dimer 16. Compound **1** (50 mg, 0.066 mmol) was deprotected using general method G to give **16** (38 mg, 98%) as a pale yellow solid: R_f 0.64 (1:1 acetone/MeOH), mp 131 °C (decomp), $[\alpha]_D$ +73.5 (*c* 1, MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ 2.54 (dd, J = 15.6, 2.7 Hz, 2H), 2.72 (dd, J = 15.6, 12.2 Hz, 2H), 3.24−3.38 (m, 4H), 3.44 (t, J = 8.5 Hz, 2H), 3.55−3.73 (m, 4H), 3.76 (dd, J = 5.7, 8.7 Hz, 2H), 4.34 (ddd, J = 2.7, 12.2, 5.7 Hz, 2H), 4.85 (s, 4H), 7.21−7.37 (m, 6H), 7.38−7.47 (m, 4H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 33.2, 42.1, 71.8, 73.5, 73.7, 74.2, 75.8, 82.7, 128.5, 129.1, 129.2, 140.3, 173.4. MS (MALDI): *m/z* 609.3 $[M + Na]^+$.

Synthesis of Cyclic Dimer 17. Compound **16** (20 mg, 0.034 mmol) was deprotected using general method F and purified by precipitation in a MeOH/acetone mixture and centrifugation (2×), giving **17** (10 mg, 74%) as a pale yellow solid: R_f 0.35 (1:1 acetone/MeOH), mp 192 °C, $[\alpha]_D$ +57.3 (*c* 0.7, MeOH); ^{1}H NMR (250 MHz, D_2O) δ 2.54 (dd, J = 15.5, 3.1 Hz, 2H), 2.72 (dd, J = 15.5, 12.4 Hz, 2H), 3.19 (t, J = 9.1 Hz, 2H), 3.36−3.64 (m, 8H), 3.72 (dd, J = 6.1, 10.2 Hz, 2H), 4.36 (ddd, J = 3.1, 12.4, 6.1 Hz, 2H); ^{13}C NMR (62.9 MHz, D_2O) δ 32.3, 41.4, 70.8, 70.6, 72.9, 73.3, 73.7, 174.2. MS (MALDI): *m/z* 429.1 $[M + Na]^+$.

Synthesis of Amino Ester 18. Azido ester **13** (1.28 g, 1.56 mmol) was reduced using general method A to give **18** (1.02 g, 82%) as a white solid: R_f 0.33 (9:1 CH_2Cl_2/MeOH), mp 200 °C, $[\alpha]_D$ +68.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.86 (s, 2H), 2.55 (dd, J = 15.4, 3.4 Hz, 1H), 2.60 (dd, J = 16.1, 3.7 Hz, 1H), 2.69 (dd, J = 15.4, 10.6 Hz, 1H), 2.82 (dd, J = 16.1, 10.3 Hz, 1H), 2.85−3.01 (m, 2H), 3.33 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.36 (s, 3H), 3.39−3.49 (m, 3H), 3.71 (s, 3H), 3.56−3.80 (m, 7H), 4.42−4.57 (m, 2H), 3.55−3.86 (m, 12H), 6.91−7.04 (m, 1H), 7.27−7.37 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.7, 34.3, 39.0, 42.4, 52.1, 56.2, 56.3, 68.4, 70.6, 74.1, 74.7, 72.9, 73.6, 74.0, 75.5, 75.7, 76.6, 77.8, 80.1, 97.0, 97.7, 127.9, 128.0, 128.6, 137.8, 138.2, 170.7, 172.5. MS (MALDI): *m/z* 795.6 $[M + H]^+$, 817.6 $[M + Na]^+$.

Synthesis of Trimer 19. Compound **18** (642 mg, 0.809 mmol) and compound **10** (344 mg, 0.809 mmol) were coupled using general method C and purified over silica gel (8:2 EtOAc/cyclohexane) to give **19** (514 mg, 53%) as a white solid: R_f 0.35 (8:2 EtOAc/cyclohexane), mp 131 °C, $[\alpha]_D$ +57.8 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.40−2.95 (m, 6H), 3.13−3.97 (m, 40 H), 4.35−4.91 (m, 20H), 6.75−6.89 (m, 1H, NH), 7.09−7.39 (m, 16H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.6, 34.0, 35.3, 38.6, 38.8, 51.4, 52.0, 56.0, 56.1, 56.2, 56.3, 67.8, 67.9, 71.5, 71.9, 72.8, 72.9, 73.4, 73.7, 73.8, 74.0, 74.8, 75.2, 76.1, 76.4, 77.3, 80.6, 96.7, 96.9, 97.0, 97.9, 127.67, 127.71, 127.80, 127.83, 127.9, 128.0, 128.4, 128.5, 137.7, 137.8, 138.3, 170.2, 170.8, 172.5. MS (MALDI): *m/z* 1224.8 $[M + Na]^+$.

Synthesis of Cyclic Trimer 2. Compound **19** (216 mg, 0.180 mmol) was saponified (method F), reduced (method B), then cyclized (method E), and purified over silica gel (1:1 EtOAc/CH_2Cl_2 then 9:1 CH_2Cl_2/MeOH) to give **2** (72 mg, 35%) as a white solid: R_f 0.45 (9:1 CH_2Cl_2/MeOH), mp 226 °C, $[\alpha]_D$ +63.8 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57 (dd, J = 15.4, 4.3 Hz, 3H), 2.68 (dd, J = 15.4, 9.6 Hz, 3H), 3.32 (s, 9H), 3.35 (s, 9H), 3.36−3.49 (m, 6H), 3.64 (t, J = 6.3 Hz, 3H), 3.70 (dd, J = 4.0, 6.3 Hz, 3H), 3.78−3.88 (m, 6H), 4.47 (ddd, J = 4.0, 4.3, 9.6 Hz, 3H), 4.58 (d, J = 6.8 Hz, 3H), 4.63 (d, J = 11.4 Hz, 3H), 4.68 (d, J = 6.8 Hz, 3H), 4.72 (d, J = 6.5 Hz, 3H), 4.73 (d, J = 11.4 Hz, 3H), 4.75 (d, J = 6.5 Hz, 3H), 6.99−7.09 (m, 3H), 7.21−7.40 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.1, 39.2, 56.0, 56.2, 69.2, 72.4, 74.1, 74.8, 75.7, 78.5, 97.2, 97.3, 127.90, 127.94, 128.5, 137.9, 170.8. MS(MALDI): *m/z* 1166.9 $[M + Na]^+$.

Synthesis of Tetramer 20. Compound **18** (383 mg, 0.467 mmol) and compound **14** (395 mg, 0.490 mmol) were coupled using general method C and purified over silica gel (9:1 CH_2Cl_2/MeOH) to give **20** (739 mg, 100%) as a white solid: R_f 0.11 (9:1 CH_2Cl_2/MeOH), mp 171 °C, $[\alpha]_D$ +56.9 (*c* 1.35, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.32−2.94 (m, 8H), 3.21−3.92 (m, 52 H), 4.33−4.85 (m, 27H), 6.74−6.91 (m, 1H), 7.13−7.42 (m, 22H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.1, 33.4, 33.8, 35.0, 38.69, 38.72, 38.8, 40.1, 51.3, 51.9, 55.90, 55.92, 55.93, 56.03, 56.04, 56.08, 56.11, 56.19, 59.61, 67.99, 71.09, 71.45, 71.83, 72.07, 72.55, 72.61, 72.65, 72.66, 73.60, 73.72, 73.87, 76.09, 76.12, 76.29, 76.41, 77.24, 79.83, 80.66, 96.57, 96.67, 96.70, 96.85, 96.88, 97.01, 97.55, 97.82, 97.99, 127.61, 127.69, 127.71, 127.78, 127.79, 127.87, 127.97, 128.37, 128.42, 128.46, 128.47, 128.51, 137.60, 137.66, 137.85, 137.91, 138.27, 170.23, 170.62, 170.93, 172.47. MS (MALDI): *m/z* 1606.1 $[M + Na]^+$.

Synthesis of Cyclic Tetramer 3. Compound **20** (364 mg, 0.230 mmol) was saponified (method F), reduced (method B), then cyclized (method E), and purified over silica gel (1:1 EtOAc/CH_2Cl_2 then 9:1 CH_2Cl_2/MeOH) to give **3** (218 mg, 62%) as a white solid: R_f 0.13 (95:5 CH_2Cl_2/MeOH), mp 183 °C, $[\alpha]_D$ +57.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.51 (dd, J = 15.4, 1.8 Hz, 4H), 2.79 (dd, J = 15.4, 11.7 Hz, 4H), 3.14−3.32 (m, 4H), 3.33 (s, 12H), 3.34 (s, 12H), 3.36−3.44 (m, 4H), 3.64 (t, J = 7.1 Hz, 4H), 3.75 (dd, J = 4.6, 7.1 Hz, 4H), 3.79−3.92 (m, 4H), 3.93−4.09 (m, 4H), 4.50−4.85 (m, 28H), 6.87−7.03 (m, 4H), 7.19−7.40 (m, 20H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.9, 40.3, 56.1, 56.3, 69.9, 71.3, 74.2, 76.0, 76.4, 79.0, 97.0, 97.3, 127.7, 127.8, 128.5, 138.1, 170.9. MS (MALDI): *m/z* 1547.9 $[M + Na]^+$.

Synthesis of Cyclic Tetramer 21. Compound **3** (20 mg, 0.013 mmol) was debenzylated using the general method F and purified over silica gel (95:5 CH_2Cl_2/MeOH) to give **21** (9 mg, 59%) as a white solid: R_f 0.31 (9:1 CH_2Cl_2/MeOH), mp 120 °C, $[\alpha]_D$ +51.2 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.52 (dd, J = 15.3, 2.9 Hz, 4H), 2.67 (dd, J = 15.3, 12.2 Hz, 4H), 2.89−3.04 (m, 4H), 3.19 (t, J = 8.9 Hz, 4H), 3.42 (s, 12H), 3.46 (s, 12H), 3.65 (dd, J = 5.8, 8.9 Hz, 4H), 3.69−3.81 (m, 4H), 3.83 (t, J = 8.9 Hz, 4H), 3.91−4.04 (m, 4H), 4.42−4.56 (m, 4H), 4.68 (d, J = 6.8 Hz, 4H), 4.71 (d, J = 6.8 Hz, 4H), 4.80 (d, J = 6.8 Hz, 4H), 4.83 (d, J = 6.8 Hz, 4H), 6.93−7.06 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.4, 41.6, 56.0, 56.3, 69.8, 71.3, 72.1, 78.0, 81.9, 97.4, 98.2, 170.9. MS (MALDI): *m/z* 1187.6 $[M + Na]^+$.

Synthesis of Cyclic Dimer 4. BH_3·THF (1.5 M in THF, 1.05 mL, 1.572 mmol) was added to a solution of compound **1** (40 mg, 0.0525 mmol) in distilled THF (4 mL), and the mixture was heated at 66 °C overnight. A few drops of EtOH were added after cooling the solution, then the solvent was removed, and the residue diluted in EtOH (4 mL) and refluxed for 48 h. After evaporation, the residue was partitioned in a CH_2Cl_2/NaOH (1 M in H_2O) mixture. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were dried ($MgSO_4$) and evaporated to give **4** (35 mg, 91%) as a colorless oil: R_f 0.26 (95:5:1 CH_2Cl_2/MeOH/Et_3N), $[\alpha]_D$ +60.1 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.77−1.84 (m, 2H), 2.01−2.27 (m, 2H), 2.56−5.82 (m, 4H), 2.98−3.19 (m, 4H), 3.25 (t, J = 8.2 Hz, 2H), 3.32 (s, 6H), 3.35 (s, 6H), 3.58−3.73 (m, 4H), 3.84−4.02 (m, 2H), 4.07−4.22 (m, 2H), 4.58 (d, J = 6.8 Hz,

2H), 4.61 (d, J = 6.8 Hz, 2H), 4.68 (d, J = 11.1 Hz, 2H), 4.74 (d, J = 6.5 Hz, 2H), 4.78 (d, J = 11.1 Hz, 2H), 4.83 (d, J = 6.5 Hz, 2H), 7.21−7.40 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.9, 48.6, 51.6, 55.9, 56.4, 70.1, 75.2, 75.5, 78.1 (2 × C), 80.9, 97.4, 98.0, 127.8, 128.5, 138.3. MS (MALDI): *m/z* 735.2 $[M + H]^+$, 757.2 $[M + Na]^+$.

Synthesis of Cyclic Trimer 5. Compound **2** (23 mg, 0.02 mmol) in distilled THF (1.5 mL) was treated with BH_3·THF (1.5 M in THF, 670 μL, 1.01 mmol) as described previously. Subsequent deprotection with AcCl/MeOH (method G) and purification over silica gel (8:2 CH_2Cl_2/MeOH) afforded **5** (7 mg, 42%) as a slightly yellow solid: R_f 0.30 (8:2 CH_2Cl_2/MeOH), mp 163 °C, $[\alpha]_D$ +42.7 (*c* 0.7, MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ 2.06−2.30 (m, 6H), 3.05−3.42 (m, 12H), 3.46 (t, J = 6.8 Hz, 3H), 3.57 (t, J = 6.8 Hz, 3H), 3.76 (dd, J = 4.3, 6.8 Hz, 3H), 3.99−4.23 (m, 6H), 4.81 (s, 6H), 7.21−7.48 (m, 15H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 24.7, 46.9, 49.6, 71.1, 72.1, 72.8, 73.3, 75.1, 81.2, 128.7, 129.1, 129.3, 139.9. MS (MALDI): *m/z* 838.3 $[M + H]^+$, 860.3 $[M + Na]^+$.

Synthesis of Cyclic Tetramer 6. Compound **3** (20 mg, 0.013 mmol) in distilled THF (2 mL) was reduced with BH_3·THF (1.5 M in THF, 525 μL, 0.787 mmol) as described previously. Subsequent deprotection with AcCl/MeOH (method G) afforded **6** (10 mg, 68%) as a white solid: R_f 0.07 (8:2 CH_2Cl_2/MeOH), mp 157 °C, $[\alpha]_D$ +39.0 (*c* 0.6, MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ 2.00−2.46 (m, 8H), 3.14−3.39 (m, 12H), 3.45 (t, J = 8.5 Hz, 4H), 3.47−3.59 (m, 4H), 3.67 (t, J = 8.5 Hz, 4H), 3.79 (dd, J = 5.1, 8.5 Hz, 4H), 3.98−4.10 (m, 4H), 4.10−4.24 (m, 4H), 4.80−4.89 (m, 8H), 7.32−7.51 (m, 20H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 22.9, 46.2, 50.2, 69.7, 70.8, 72.4, 74.0, 76.0, 81.1, 129.4, 129.5, 129.7, 138.4. MS (MALDI): *m/z* 1117.6 $[M + H]^+$, 1139.5 $[M + Na]^+$.

Supporting Information Available: General methods and ^{1}H and ^{13}C NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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