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Novel Amphiphilic Cyclic Oligosaccharides: Synthesis and Self-Aggregation Properties

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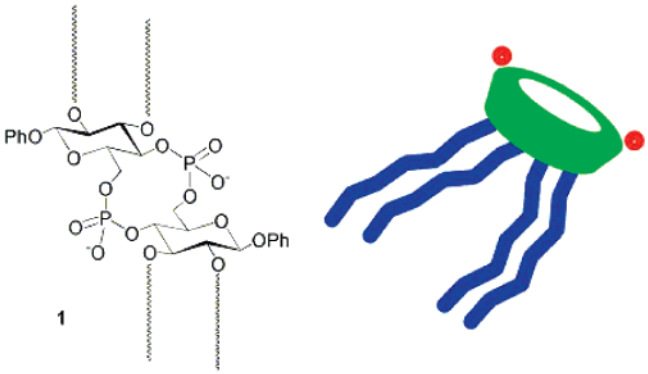
Received August 3, 2007



Novel amphiphilic cyclic disaccharide analogues, in which the saccharide units are connected through stable phosphodiester linkages (CyPLOS, Cyclic Phosphate-Linked OligoSaccharides) and decorated with long lipophilic tentacles at the 2- and 3-OH moieties, have been synthesized. Their propensity to self-aggregation has been investigated by means of ^{1}H and ^{31}P NMR experiments, making it possible to determine for these macrocycles critical aggregation concentration values in the millimolar range.

Introduction

Macrocycles, by virtue of their intrinsic preorganization, can show excellent recognition properties toward a wide range of different guests and therefore be of interest in several fields, from catalysis[1] to analytical applications.[2] Carbohydrates are in general very attractive scaffolds for the construction of macrocycles because they are rigidified building blocks, with well-defined stereocenters displaying multiple, selectively manipulable hydroxyl functional groups. Among the plethora of natural or artificial macrocycles known, cyclodextrins are the most commonly used hosts, exhibiting well-recognized ability to form stable complexes with different guests, low costs, and reduced, if not null, toxicity.[3] A great deal of attention is currently devoted to amphiphilic cyclodextrins,[4] obtained by grafting hydrophobic appendages on the oligosaccharide backbone. Oligosaccharide-based amphiphilic molecules are cell membrane mimics, envisaged to be biocompatible. These compounds may be inserted into lipid systems through their hydrophobic moieties and exploited as potential transmembrane ion channels.[5] Recent works on cyclodextrins, *ad hoc* derivatized to form artificial channels, showed that, in order to be efficiently included into membranes, they must be decorated with hydrophobic moieties approximately spanning the whole length of the lipid bilayer.[6] Upon adequate chemical modifications, such as per-substitution of one face of the truncated cone by hydrophobic tails, cyclodextrins can provide transient pores.[7] Indeed, skirt- or bouquet-shaped cyclodextrins, prepared by

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(3) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1753 and references therein.
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10.1021/jo7017087 CCC: $37.00
Published on Web 11/08/2007

esterification with fatty acids of all hydroxyl groups of the secondary face, or of both the primary and secondary face, are able to form nanoparticles in water.[8] Selective modification of preformed cyclodextrins[9] offers great opportunities but also severe chemical challenges, which generally prevent their massive exploitation. In principle, the total synthesis approach, involving the stepwise synthesis of the linear oligomer, followed by the circularization process, is a more general strategy, giving access to a wider repertoire of artificially modified macrocycles.

In the context of cyclodextrins mimicry, several groups have investigated cyclic oligosaccharide analogues having the canonical *O*-glycosidic bonds replaced by alternative linkages, such as amide,[10] *S*-glycosidic,[11] acetylenic,[12] or triazole[13] bridges. Recently, we described the synthesis and conformational properties of novel cyclic oligosaccharide analogues, 4,6-linked through phosphodiester bonds, that we named CyPLOS (*Cy*clic *P*hosphate-*L*inked *O*ligo*S*accharides).[14] We envisioned that a cyclic array of pyranose moieties alternated with negatively charged phosphate groups might lead to specific recognition, especially toward cations. These cyclic saccharide surrogates, designed to combine some constitutive elements of both small cyclodextrins and crown ethers and exhibiting, as a distinctive structural motif, stable phosphodiester bonds within their oligosaccharide core, were obtained through straightforward and high fidelity reactions, well-optimized in oligonucleotide synthesis. Cyclic dimer **2**, shown to adopt a concave conformation potentially able to bind metal ions, and key intermediate **3** are depicted in Figure 1.

With the purpose of exploring novel amphiphilic cyclic oligosaccharides, we reasoned that the synthesized CyPLOS could be suitable platforms to prepare different analogues, where the secondary hydroxyls at C-2 and C-3 of monosaccharide building block **4** (Scheme 1) are exploited as synthetic handles for further, selective derivatization. In this paper we report on the synthesis of cyclic, jellyfish-shaped phosphate-linked disaccharides, per-substituted at the 2- and 3-OH with lipophilic

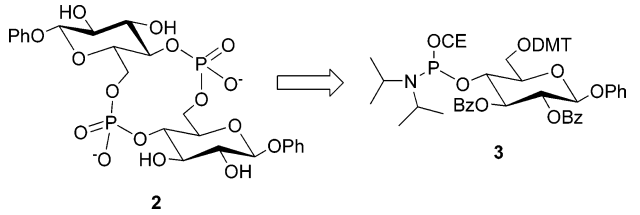

FIGURE 1. Dimer CyPLOS **2** and phosphoramidite derivative **3**.

tentacles (**1**). In addition to providing the desired amphiphilicity, these modifications introduce a high conformational freedom in the cyclic skeleton. In fact, once permanently masked, the 3-OH groups of the pyranose residues are not available for intramolecular H-bonding with the adjacent phosphate groups. Disruption of these strong H-bonds removes the structural motif further rigidifying the central cavity of the macrocycles, thus leading to more flexible structures, able to cover a wide conformational space in response to environmental stimuli.

Results and Discussion

Artificial compounds **1** are enantiopure, amphiphilic molecules endowed with a pseudo-C_2 symmetry, designed to produce reverse micellar aggregates in lipid systems, potentially useful for the transport of cations of biological interest (e.g., Na^+, K^+, Mg^{2+}, Ca^{2+}, etc.) through membranes or at the interface of water−organic solvents. In the retrosynthetic analysis, the cyclic molecule can be prepared by intramolecular condensation of a suitably protected linear dimer (**11**, Scheme 2), having at one end one phosphate moiety susceptible of further nucleophilic attack and at the other end one free hydroxyl group. In turn, the linear dimer is obtained by reacting phenyl-β-D-glucopyranoside-4-*O*-(2-chloro-phenylphosphate) **9** with 4-phosphoramidite derivative **10**, both derived from the common precursor 6-*O*-DMTr-phenyl-β-D-glucopyranoside **8**.

This compound was synthesized from phenyl-β-D-glucopyranoside **4** in four straightforward steps, involving, respectively, simultaneous protection of the 4- and 6-OH groups, insertion of the desired tentacles at the 2 and 3 positions, and then benzylidene removal followed by selective protection of the 6-OH group as 4,4′-dimethoxytritylether (Scheme 1).

In this context, as model hydrophobic tails to be attached at the 2- and 3-OH functions, we chose linear C11 hydrocarbon chains and tetra(ethylene glycol) (TEG) tails, thus providing a tetra-alkylated (type **a**), a tetra-polyether (type **b**), and a mixed dimer, containing one di-alkylated and one di-polyether-tailed sugar (type **c**), respectively. These hydrophobic residues, which in a fully extended conformation are, respectively, 15.4[15] and 17[16] Å long, were linked via stable ether bonds. In case **a**, this decoration was achieved by coupling the 4,6-benzylidene protected sugar **5** with 1-bromoundecane in the presence of NaH and NaI in DMF, giving **6a** in 90% yields.

The analogous step to introduce the TEG chain (case **b**) onto the sugar required previous synthetic elaboration of TEG, which was first protected with the benzyl (Bn) moiety, used as a convenient UV−vis label, leading to **I**, then activated at the remaining OH group with the mesyl (Ms) group, thus yielding

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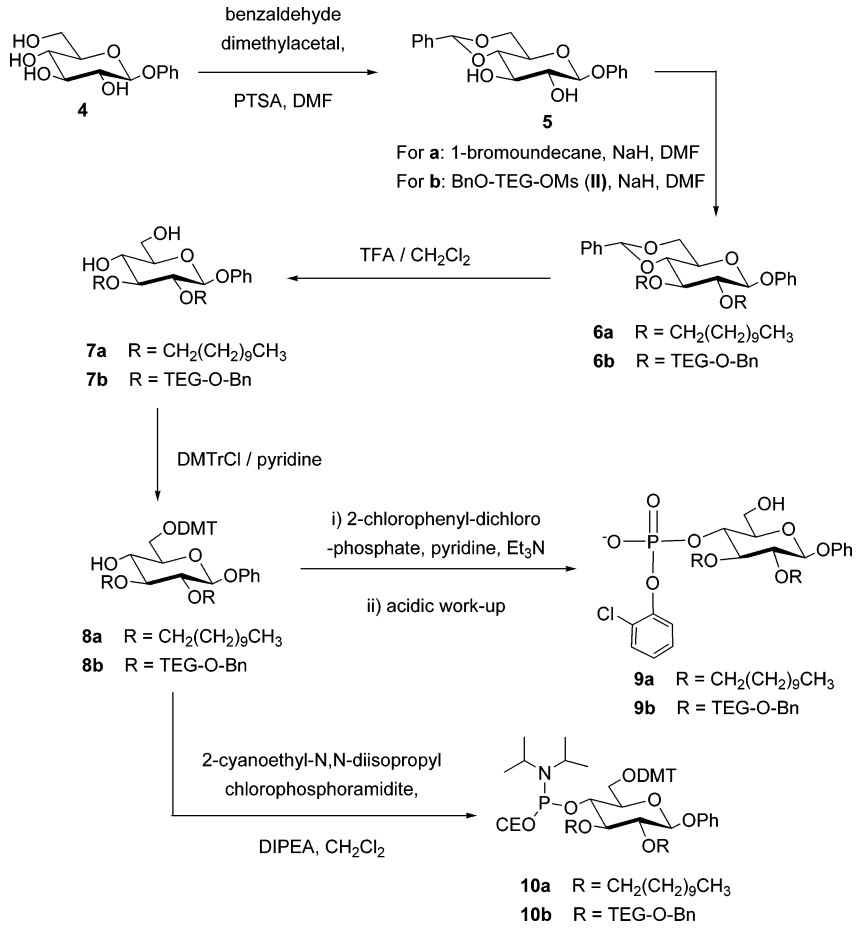
SCHEME 1. Synthesis of Building Blocks 9 and 10



BnO-TEG-OMs **II** (Scheme 3). Condensation of **5** with **II** in DMF in the presence of NaH led to **6b** in 85% yields.

Phosphorylation of the 4-OH of **8**, followed by acidic workup of the reaction crude, directly gave detritylated compounds **9** in 92−95% yields; 4-phosphoramidite derivative **10** was obtained in 90% yields, essentially following protocols well-established in the elaboration of building blocks for the oligonucleotide synthesis.[17] The dimerization step was carried out by phosphoramidite chemistry, as described in Scheme 2. Coupling of **9a** and **10a** by activation with 0.45 M tetrazole in CH_3CN, followed by oxidation, afforded **11a**, obtained as a detritylated compound after column chromatography in 80% yield for the three steps.

In contrast, for the synthesis of **11b** and **11c**, the latter obtained by mixed coupling between **9b** and **10a**, the building blocks used proved to be quite reluctant to react under standard activation conditions. The desired linear dimers were successfully obtained using a 0.25 M 4,5-dicyanoimidazole (DCI) solution in CH_3CN as the activator at 40 °C for 2 h. After oxidation, the target compounds were isolated after column chromatography in the form of detritylated dimers with 75% yields for the three steps. Cyclization was then carried out by exploiting a phosphotriester methodology, well-optimized both in solution and in the solid phase, using 1-mesitylensulfonyl-3-nitro-1,2,4-triazole (MSNT) as the condensing agent; this strategy has been profitably exploited also for the solid-phase synthesis of cyclic oligonucleotides[18] and related analogues.[19] The fully protected cyclic molecules (**12a**−**c**, Scheme 2) were then deprotected in two steps: first, a basic, non-hydrolytic treatment to promote β-elimination of the 2-cyanoethyl protecting group (triethylamine, for **12a** and **12b**; a stronger base, such as piperidine, proved to be efficient for **12c**), followed by a basic hydrolytic treatment to cleave the 2-chlorophenyl group. The latter step, classically carried out by an overnight reaction with aqueous ammonia at 55 °C, required in this case more drastic basic treatments to go to completion. Optimal conditions were found leaving overnight the cyclic compounds **13a**−**c** in contact with a saturated LiOH solution in dioxane/water (1:5, v/v) at 50 °C. Following the described procedures, **1a**−**c** could be prepared in four steps in 50−58% yields from building blocks **9** and **10**, each obtained in five steps with 62−67% yields from phenyl-β-D-glucopyranoside **4**.

All of the synthesized compounds were purified by column chromatography, in all cases allowing the isolation of homogeneous compounds, and characterized by ^1H, ^{13}C (and ^{31}P, where present) NMR and ESI-MS data. Though ionic, the final cyclic dimers proved to be very lipophilic tools: **1a** could be dissolved in only $CHCl_3$ or CH_2Cl_2; on the contrary, final compounds **1b** and **1c** were fairly soluble in most organic solvents. On varying several solvent systems and conditions, none of the synthesized macrocycles exhibited a marked

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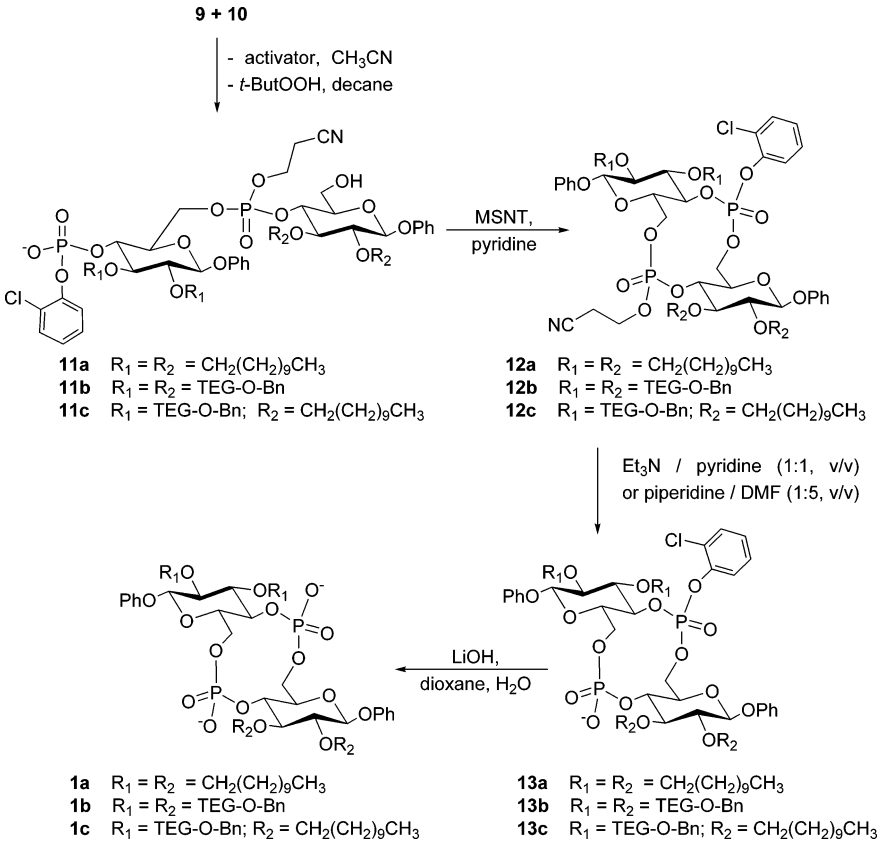
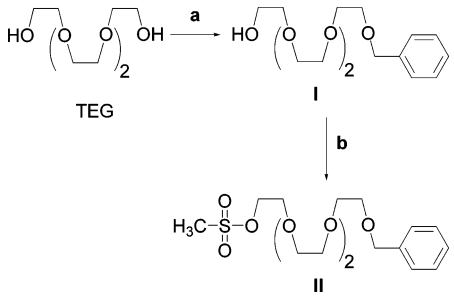
SCHEME 2. Synthesis of Macrocycles 1a−c



SCHEME 3. Synthesis of BnO-TEG-OMs II



tendency to form stable organogels at room temperature, though, of the growing list of known low molecular weight gelators, many are based on amphiphilic saccharide scaffolds.[20] Even though no gelling ability clearly emerged in these compounds, evidence for aggregation came from investigation of their NMR properties. $CDCl_3$ was the solvent of choice, first of all for being the best dissolving agent for **1a**, and second, because an apolar milieu can roughly mimic a lipid bilayer, thus offering useful, preliminary information about the ability of these amphiphilic macrocycles to self-assemble into ordered super-structures, potential carriers for cations through bulk membranes.

On a general basis, a net simplification of the NMR spectra is typically obtained when transforming an asymmetric dimer into a molecule possessing a C_2-symmetry, for which a monomer-like spectrum is expected as a result of fast equilibria between several conformations. Contrarily to our expectations, in cases **a** and **b**, a dramatic change could be observed when converting the cyclic dimers **13a** and **13b**, still protected at one phosphodiester moiety with the 2-chlorophenyl group, into final target compounds **1a** and **1b**. In Figure 2, ^{1}H and, in the insets, ^{31}P NMR spectra of **13b** are showed for comparison with those of fully deprotected **1b**.

The final cyclic compounds **1a**, **1b**, and **1c** exhibited different behaviors; however, they all showed concentration-dependent NMR spectra, clearly suggesting the presence of strong intermolecular interactions. Compound **1a** gave spectra with two distinguishable sets of signals, as if in the presence of two distinct species. NMR spectra of **1b** showed dramatic line broadening, diagnostic of slow equilibria on the NMR time scale, which could be explained assuming the formation of large aggregates in $CDCl_3$. Similar behavior was found in all the members of the **c**-series: when coupling **9b** and **10a** to finally yield **1c**, very broad, badly resolved signals in the NMR spectra were obtained already at the level of linear dimer **11c**, suggesting a strong propensity toward aggregation.

Preliminary experiments to investigate the self-aggregation properties of these amphiphilic macrocycles were carried out by analyzing the NMR data upon varying the temperature and concentration of the samples.[21]

Dimer **1a**, at 14 mM concentration, typically showed two separate signals for the anomeric protons, in approximately 1:1.2 ratio, in the ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) and two distinct, sharp signals in the ^{31}P NMR spectrum (Figure 3). In the VT-NMR study, no difference emerged in the temperature

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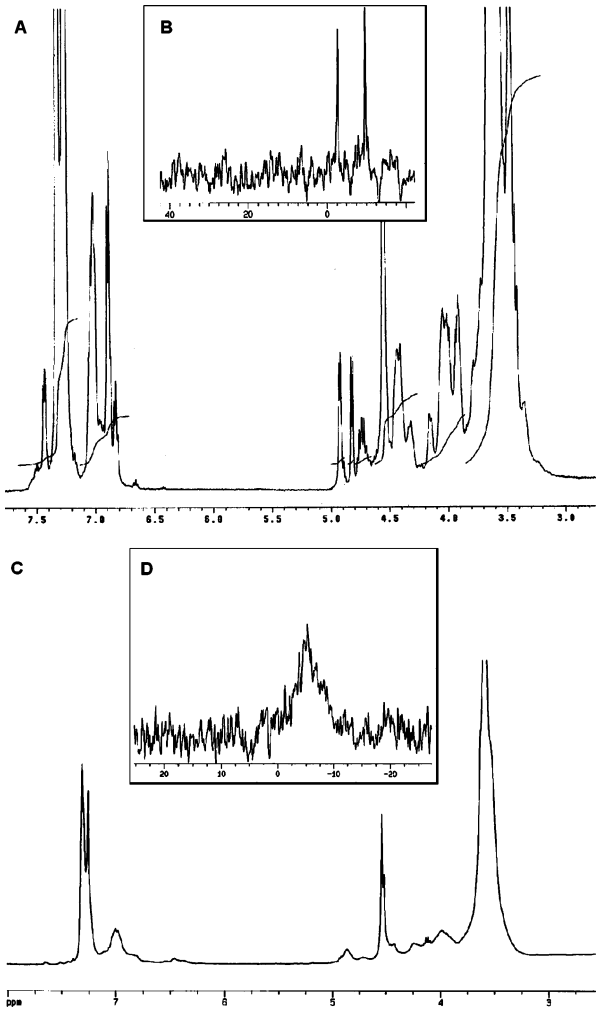

FIGURE 2. ^{1}H NMR (400 MHz, 298 K, $CDCl_3$) and, in the inset, ^{31}P NMR (161.98 MHz, 298 K, $CDCl_3$) spectra of compounds **13b** (panels A and B, respectively) and **1b** (panels C and D, respectively), both at 10 mM concentration.

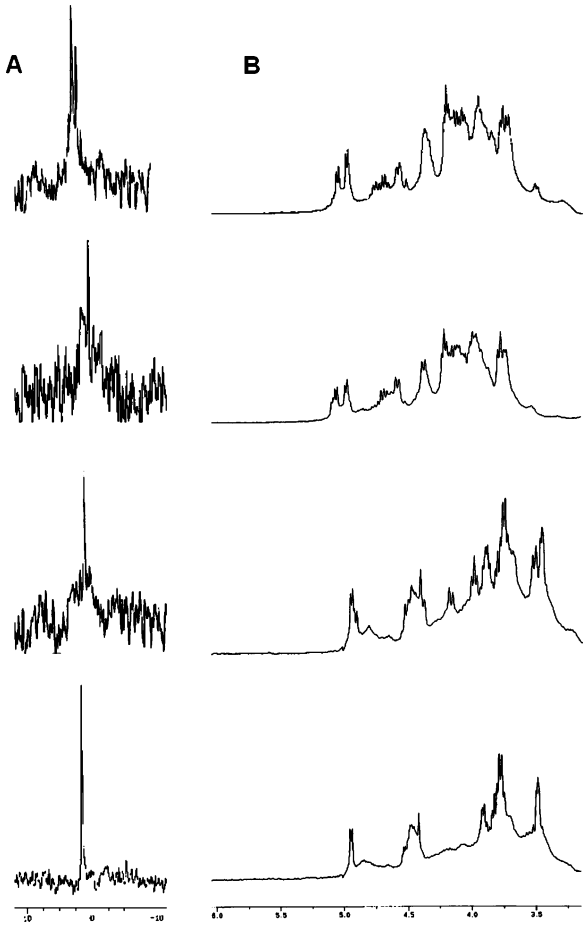

FIGURE 3. ^{31}P NMR (161.98 MHz, 298 K, $CDCl_3$) and ^{1}H NMR (400 MHz, 298 K, $CDCl_3$) spectra (panels A and B, respectively, with the latter ones limited at the sugar regions) of compound **1a** registered at different concentrations (from the top to the bottom: 14.0, 7.5, 3.5, and 1.8 mM, respectively).

range 273−323 K. However, when heated at 328 K, a highly simplified system was obtained, with only one signal in the region of the anomeric protons and one signal in the ^{31}P NMR spectrum (see Supporting Information).

In the concentration-dependent analysis, the ^{31}P NMR spectra showed the two signals coalesced into a unique, broad peak at 7 mM, giving sharp and better resolved signals upon successive dilution. In this case the ^{1}H NMR study was more informative, showing the two anomeric signals to progressively overlap on decreasing the concentration (Figure 3). A final coalescence into a unique, sharp signal was observed at 1.8 mM concentration, thus indicating that a fast equilibrium among the different species was operative, with only one form finally predominating, at a concentration between 2 and 3 mM. These spectral features may be consistent with the aggregation into small micelles, but they do not support the formation of large aggregates.[22]

On the contrary, as far as **1b** and **1c** are concerned, inspection of the ^{1}H and ^{31}P spectra cleanly suggested the presence of strongly self-aggregated systems, with typical chemical shift anisotropy and line broadening. In no case did the ^{1}H NMR spectra give the expected simplification upon dilution or by increasing the temperature. When varying the temperature or the concentration, the ^{31}P NMR study gave a deeper insight into the behavior of **1b**. In detail, a very broad signal, dispersed over a 10 ppm region, was found in the ^{31}P NMR spectrum, when analyzing the sample at 10 or 9 mM ($CDCl_3$, 161.98 MHz, 298 K). This signal was significantly shrunk at 5 mM and progressively simplified upon further dilution, thus allowing evaluation of the critical aggregation concentration (cac) between 6 and 8 mM (see Supporting Information).

The same trend could be observed for **1c**, which in the ^{31}P NMR spectra registered at 9 mM concentration showed a high number of close resonances, densely populating a region of 10 ppm. When decreasing the concentration, the chemical shift anisotropy of the ^{31}P NMR signals progressively reduced only at concentrations lower than 1 mM, with an apparent cac determined between 300 and 400 μM (see Supporting Information).

VT-^{31}P NMR spectra showed for both **1b** and **1c** a tendency toward only partial simplification of the peaks on increasing the temperature; no apparent modification was found up to 338 K, thus indicating the formation of thermally stable aggregates (see Supporting Information).

Taken together, these data suggest the following order in terms of increasing preference for self-aggregation in $CDCl_3$:

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1a < **1b** < **1c**, with the latter two compounds able to generate larger aggregates responsible for severe line broadening and chemical shift anisotropy in the NMR spectra. The van der Waals interactions between the dangling lipophilic tentacles of these macrocycles may be in all cases indicated as the main driving force for self-aggregation, with the TEG residues more efficient than the sole C11 alkyl chains in promoting the formation of stable aggregates in organic solvents.

Studies to investigate in detail the ability of these cyclic compounds to form organized supramolecular architectures, as well as to selectively extract metal ions from aqueous into organic solvents, or to transport them through bulk liquid membranes, are currently underway in our laboratories. Possible applications of the above-described artificial structures can be foreseen in the fields of sensory systems and drug delivery, as well as in the development of new biocompatible functional materials.

Conclusions

In this work, novel amphiphilic macrocycles **1a**−**c** have been synthesized, profitably exploiting both phosphoramidite and phosphotriester chemistry, respectively, for the oligomerization and the circularization reactions. Insertion of the long lipophilic tentacles was cleanly realized by classical Williamson reactions on the 2- and 3-OH groups of 4,6-protected sugar **5**. The final ionic compounds were fairly soluble in most organic solvents yet displayed very different self-aggregation properties. ^{1}H and ^{31}P concentration-dependent and VT-NMR studies showed that the presence of the hydrophobic TEG tentacles inserted onto the cyclic core produces amphiphilic tools with a marked propensity to aggregation, **1b** and **1c**, with critical aggregation concentrations in the millimolar range, whereas the insertion of the sole alkyl tails in **1a** is not sufficient to generate large self-aggregated species. Particularly, cyclic compounds conjugated with TEG residues may form stable inverted micellar aggregates in $CDCl_3$, which could account for the large anisotropy and line broadening observed in the NMR spectra.

With the synthesis of model, cyclic molecules **1a**−**c** we demonstrated the feasibility of a more general synthetic platform, giving access to a variety of diverse jellyfish-shaped oligomers, the properties of which can be finely tuned by *ad hoc* varying the nature of the monosaccharides and of the tentacles inserted on the phosphate-linked oligosaccharide backbone.

Experimental Section

Synthesis of 5. Phenyl-β-D-glucopyranoside **4** (3.00 g, 12.0 mmol, 1 equiv) was dissolved in 25 mL of anhydrous *N*,*N*-dimethylformamide (DMF). *p*-Toluensulfonic acid (PTSA, 110 mg, 0.60 mmol, 0.05 equiv) and, dropwise, benzaldehyde dimethylacetal (4.0 mL, 26.0 mmol, 2.2 equiv) were sequentially added to the stirred mixture, which was left at 0 °C for 48 h. The reaction mixture was then diluted with $CHCl_3$, transferred into a separatory funnel, and washed twice with water. The organic phase, dried over anhydrous Na_2SO_4 and filtered, was then concentrated under reduced pressure and purified by crystallization in $CHCl_3$, furnishing pure **5** (3.92 g, 11.4 mmol) in 95% yield: white amorphous powder, mp (from ethanol/acetone) 191−193 °C (lit.[23] 194−195 °C). R_f = 0.4 ($CHCl_3$/CH_3OH, 98:2, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52−7.00 (complex signals, 10H, aromatic protons); 5.54 [s, 1H, (Ph-C*H*)]; 5.02 (d, J = 7.5 Hz, 1H, H-1); 4.36 (dd, J = 6.6 and 10 Hz, 1H, H-3); 3.96−3.54 (overlapped signals, 5H, H-2, H-4, H-5, H-6_a and H-6_b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 129.5, 129.3, 128.3, 126.9, 126.2, 123.2 and 116.8 (aromatic carbons); 101.9 (Ph-*C*H); 101.0 (C-1); 80.2 (C-5); 74.2 (C-3); 73.1 (C-2); 68.5 (C-4); 66.4 (C-6). ESI-MS (positive ions): calcd for $C_{19}H_{20}O_6$ 344.126; *m/z*, found 367.19 (M + Na^+), 383.25 (M + K^+). HRMS (MALDI-TOF): *m/z* calcd for $C_{19}H_{20}O_6Na$ 367.1158; found 367.1209 (M + Na^+).

Synthesis of 6a. Compound **5** (1.9 g, 5.65 mmol, 1 equiv), dissolved in anhydrous *N*,*N*-dimethylformamide (35 mL), was treated with sodium hydride (540 mg, 22.5 mmol, 4 equiv). The mixture was left under stirring for 10 min, and then 1-bromoundecane (5.0 mL, 22.5 mmol, 4 equiv) and sodium iodide (425 mg, 2.82 mmol, 0.5 equiv) were sequentially added. The reaction, left at room temperature for 4 h under stirring, was quenched by addition of CH_3OH, and the resulting mixture concentrated under reduced pressure. The crude was then diluted with $CHCl_3$, transferred into a separatory funnel, washed three times with water, concentrated under reduced pressure, and purified by column chromatography. Eluting the column with *n*-hexane, containing growing amounts of ethyl acetate (from 1 to 10%) gave pure **6a** (3.3 g, 5.08 mmol) in 90% yield: white amorphous powder, R_f = 0.8 (*n*-hexane/ethyl acetate, 4:1, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50−7.03 (complex signals, 10H, aromatic protons); 5.56 (s, 1H, Ph-C*H*); 5.02 (d, J = 8.0 Hz, 1H, H-1); 4.36 (dd, J = 10.0 and 4.5 Hz, 1H, H-6_a); 3.91−3.83 [m, 2H, 1x(CH_2-CH_2-O-sugar)]; 3.81−3.71 [m, 3H, H-6_b and 1x(CH_2-CH_2-O-sugar)]; 3.64 (t, J = 9.0 and 9.5 Hz, 1H, H-4); 3.55 (t, J = 8.5 and 9.0 Hz, 1H, H-3); 3.50 (m, 1H, H-5); 3.45 (t, J = 8.5 and 8.5 Hz, 1H, H-2); 1.61−1.52 [m, 4H, (CH_2-CH_2-O-sugar)]; 1.31−1.24 [overlapped signals, 32H, 2x(-CH_2-)$_8$]; 0.88 [t, 6H, 2x(CH_3)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1, 138.3, 129.4, 128.8, 128.1, 125.9, 122.8 and 116.8 (aromatic carbons); 102.1 (*C*H-Ph); 101.1 (C-1); 82.1 (C-5); 81.2 and 81.0 [2x(CH_2-*C*H_2-O-sugar)]; 73.6 (C-3); 73.5 (C-2); 68.7 (C-4); 66.2 (C-6); 31.8, 30.2, 29.6 and 26.0 [(-CH_2-)$_8$]; 22.6 [2x(*C*H_2-CH_3)]; 14.0 [2x(CH_3)]. ESI-MS (positive ions): calcd for $C_{41}H_{66}O_6$, 654.476; *m/z*, found 677.49 (M + Na^+), 693.44 (M + K^+). HRMS (MALDI-TOF): *m/z* calcd for $C_{41}H_{66}O_6Na$ 677.4757; found 677.4720 (M + Na^+).

Synthesis of 7a. Compound **6a** (3.3 g, 5.08 mmol) was treated with 50 mL of a TFA/CH_2Cl_2/H_2O 1:10:0.5 (v/v/v) solution. The reaction was left at 0 °C. After 4 h, the reaction mixture was diluted with CH_2Cl_2. The organic phase was washed twice with water and concentrated under reduced pressure. The crude was purified by column chromatography. Eluting the column with $CHCl_3$, containing growing amounts of CH_3OH (from 1 to 5%) gave pure **7a** (2.4 g, 4.3 mmol) with 85% yield: white amorphous powder, R_f = 0.5 ($CHCl_3$/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−6.99 (complex signals, 5H, aromatic protons); 4.97 (d, J = 7.5 Hz, 1H, H-1); 3.97−3.91 [overlapped signals, 3H, H-6_a and 1x(CH_2-CH_2-O-sugar)]; 3.78 (m, 1H, H-5); 3.71−3.63 [overlapped signals, 3H, H-6_b and 1x(CH_2-CH_2-O-sugar)]; 3.50 (m, 1H, H-4); 3.38 (t, J = 8.5 and 8.0 Hz, 1H, H-3); 3.30 (t, J = 9.0 and 9.0 Hz, 1H, H-2); 2.42 (bd, 1H, 4-OH); 2.01 (t, 1H, 6-OH); 1.61−1.52 [m, 4H, 2x(CH_2-CH_2-O-sugar)]; 1.31−1.23 [overlapped signals, 32H, 2x(-CH_2-)$_8$]; 0.88 [t, 6H, 2x(CH_3)]. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.2, 129.5, 122.6 and 116.6 (aromatic carbons); 101.7 (C-1); 84.2 [2x(CH_2-*C*H_2-O-sugar)]; 81.9 (C-5); 75.2 (C-3); 73.5 (C-2); 72.9 (C-4); 62.7 (C-6); 31.8, 30.3, 29.5, 29.2 and 26.1 [2x(-CH_2-)$_8$]; 22.6 [2x(*C*H_2-CH_3)]; 13.9 [2x(CH_3)]. ESI-MS (positive ions): calcd for $C_{34}H_{60}O_6$, 564.439; *m/z*, found 587.20 (M + Na^+), 603.20 (M + K^+). HRMS (MALDI-TOF): *m/z* calcd for $C_{34}H_{60}O_6Na$ 587.4288; found 587.4301 (M + Na^+).

Synthesis of 8a. Compound **7a** (2.4 g, 4.3 mmol, 1 equiv), dissolved in anhydrous pyridine (12 mL), was reacted with DMTrCl (1.9 g, 5.6 mmol, 1.3 equiv). The reaction mixture, left at room temperature overnight under stirring, was then diluted with CH_3OH and concentrated under reduced pressure. The crude was next purified on a silica gel column, eluted with CH_2Cl_2 containing

(23) Rivaille, R.; Szabó, L. *Bull. Soc. Chim. Fr.* **1963**, 716−721.

growing amounts of CH_3OH (from 1 to 5%) in the presence of a few drops of pyridine, affording pure **8a** (3.5 g, 4.1 mmol) in 95% yield: glassy compound, mp dec > 90 °C. $R_f = 0.7$ ($CHCl_3/CH_3OH$, 98:2, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−6.77 (complex signals, 18H, aromatic protons), 4.91 (d, $J = 7.5$ Hz, 1H, H-1); 3.91−3.82 [overlapped signals, 3H, H-6_a and 1x(CH_2-CH_2-O-sugar)]; 3.77 (s, 6H, OCH_3 of the *DMTr group*); 3.70−3.64 [overlapped signals, 3H, H-6_b and 1x(CH_2-CH_2-O-sugar)]; 3.60−3.25 [overlapped signals, 4H, H-4, H-5, H-2 and H-3]; 1.62−1.50 [m, 4H, 2x(CH_2-CH_2-O-sugar)]; 1.37−1.20 [overlapped signals, 32H, 2x(-CH_2-)$_8$]; 0.88 [t, 6H, 2x(CH_3)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 144.7, 135.8, 123.0, 129.5, 129.3, 129.0, 128.7, 128.1, 127.7, 127.0, 126.6, 124.9, 122.4, 116.9 and 113.0 (aromatic carbons); 101.6 (C-1); 85.0 (quaternary C of the *DMTr group*); 84.4 [2x(CH_2-CH_2-O-sugar)]; 81.8 (C-5); 73.6 (C-3); 73.0 (C-2); 71.2 (C-4); 63.8 (C-6); 55.1 (OCH_3 of the *DMTr group*); 31.8, 30.3, 29.5, 29.5, 29.2 and 26.1 [2x(-CH_2-)$_8$]; 22.6 [2x(CH_2-CH_3)]; 14.0 [2x(CH_3)]. ESI-MS (positive ions): calcd for $C_{55}H_{78}O_8$, 866.570; *m/z*, found 889.20 ($M + Na^+$), 905.18 ($M + K^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{55}H_{78}O_8Na$ 889.5594; found 889.5623 ($M + Na^+$).

Synthesis of 6-*O*-(4,4′-*O*-Dimethoxytriphenylmethyl)-2,3-di-*O*-undecyl-phenyl-β-D-glucopyranoside-4-*O*-(2-cyanoethyl-*N*,*N*-diisopropyl)phosphoramidite, 10a. To a solution of compound **8a** (1.0 g, 1.1 mmol, 1 equiv), dissolved in anhydrous CH_2Cl_2 (9.4 mL) were added sequentially *N*,*N*-diisopropylethylamine (DIPEA) (765 μL, 4.4 mmol, 4 equiv) and 2-cyanoethyl-*N*,*N*-diisopropyl-chlorophosphoramidite (490 μL, 2.2 mmol, 2 equiv) under stirring at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure. The crude was chromatographed on a silica gel column, eluting with *n*-hexane containing growing amounts of ethyl acetate (from 20 to 50%) in the presence of a few drops of triethylamine, furnishing the desired compound **10a** (1.0 g, 0.99 mmol) in 90% yield: oil, as a mixture of diastereomers, $R_f = 0.5$ (*n*-hexane/ethyl acetate, 4:1, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−6.70 (complex signals, 36H, aromatic protons); 4.94 (m, 2H, 2xH-1); 3.98−3.96 (m, 2H, 2xH-6_a); 3.84−3.70 {overlapped signals, 18H, 4xN[CH(CH_3)$_2$]$_2$, 2xH-6_b and OCH_3 of the *DMTr group*}; 3.67−3.26 [overlapped signals, 20H, 2x(O-CH_2-CH_2-CN), 4x(CH_2-O-sugar), 2xH-4, 2xH-5, 2xH-2 and 2xH-3]; 2.64 and 2.53 [two t's, 2H each, 2x(-O-CH_2-CH_2-CN)]; 1.62−1.24 [complex signals, 64H, 2x(-CH_2-)$_8$]; 1.20−1.05 {complex signals, 24H, 4xN[CH(CH_3)$_2$]$_2$}; 0.90, 0.88 and 0.86 [s's, 12H, 4x(CH_3)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 130.1, 129.3, 128.2, 127.6, 126.5, 122.3, 116.7 and 112.9 (aromatic carbons); 101.3 (C-1); 84.5 (quaternary C of the *DMTr group*); 82.0 (C-5); 81.8 [2x(CH_2-CH_2-O-sugar)]; 75.4 and 75.3 (C-4); 73.4 and 73.1 (C-3); 72.5 (C-2); 63.9 (C-6); 60.7 (-O-CH_2-CH_2-CN); 55.0 (OCH_3 of the *DMTr group*); 43.0 {N[CH(CH_3)$_2$]$_2$}; 31.8, 30.3, 29.6, 29.3 and 26.1 [2x(-CH_2-)$_8$]; 24.3 {N[CH(CH_3)$_2$]$_2$}; 22.6 [2x(CH_2-CH_3)]; 14.0 [2x(CH_3) and -O-CH_2-CH_2-CN]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ 151.4 and 150.2. ESI-MS (positive ions): calcd for $C_{64}H_{95}N_2O_9P$, 1066.678; *m/z*, found 1067.84 ($M + H^+$); 1105.61 ($M + K^+$); 1168.74 ($M + Et_3NH^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{64}H_{95}N_2O_9PNa$ 1089.6673; found 1089.6684 ($M + Na^+$).

Synthesis of 2,3-Di-*O*-undecyl-phenyl-β-D-glucopyranoside-4-*O*-(2-chlorophenylphosphate), 9a. 2-Chlorophenyl-dichlorophosphate (715 μL, 4.4 mmol, 4 equiv) was added dropwise to a stirred solution of compound **8a** (1.0 g, 1.1 mmol, 1 equiv), 1,2,4-triazole (607 mg, 8.8 mmol, 8 equiv), and triethylamine (1.2 mL, 8.8 mmol, 8 equiv) in anhydrous pyridine (11 mL) at 0 °C. The mixture was then allowed to warm to room temperature. After 3 h the reaction was concentrated under reduced pressure. The crude was then diluted with $CHCl_3$, transferred into a separatory funnel, washed three times with water, concentrated under reduced pressure, and purified by column chromatography eluted with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%) in the presence of a few drops of TFA, affording pure **9a** (785 mg, 1.0 mmol) in 95% yield: white amorphous powder, $R_f = 0.3$ (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.60−6.96 (complex signals, 9H, aromatic protons); 5.00 (d, $J = 7.6$ Hz, 1H, H-1); 4.35 (m, 1H, H-4); 3.96−3.92 [overlapped signals, 3H, H_2-6 and 1x(CH_2-CH-O-sugar)]; 3.77−3.58 [overlapped signals, 3H, 3x(CH_2-CH-O-sugar)]; 3.54−3.46 (overlapped signals, 2H, H-3 and H-5); 3.34 (t, 1H, H-2); 1.60−1.52 [m, 4H, 2x(CH_2-CH_2-O-sugar)]; 1.37−1.18 [overlapped signals, 36H, 2x(-CH_2-)$_8$]; 0.90−0.88 [m, 6H, 2x(CH_3)]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.5, 148.5, 146.8, 129.9, 129.4, 127.6, 123.9, 122.7, 121.2 and 116.6 (aromatic carbons); 102.2 (C-1); 83.4 [2x(CH_2-CH_2-O-sugar)]; 81.4 (C-5); 75.2 (C-4); 74.0 (C-3); 73.1 (C-2); 60.6 (C-6); 31.8, 30.3, 29.5, 29.4, 25.9 and 25.7 [2x(-CH_2-)$_8$]; 22.6 [2x(CH_2-CH_3)]; 13.9 [2x(CH_3)]. ^{31}P NMR (CD_3OD, 161.98 MHz): δ −6.5. ESI-MS (negative ions): calcd for $C_{40}H_{64}ClO_9P$, 754.398; *m/z*, found 753.18 ($M - H)^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{40}H_{63}ClO_9P$ 753.3898; found 753.3945 $(M-H)^-$.

Synthesis of Linear Precursor 11a. Derivative **9a** (150 mg, 0.198 mmol, 1 equiv) and compound **10a** (255 mg, 0.240 mmol, 1.2 equiv), previously dried by repeated coevaporations with anhydrous CH_3CN and kept under reduced pressure, were reacted with a 0.45 M tetrazole solution in anhydrous CH_3CN (5.0 mL). The reaction was left under stirring at room temperature and monitored by TLC in the eluent system CH_2Cl_2/CH_3OH, 95:5 (v/v). After 2.0 h, a 5.5 M *tert*-butylhydroperoxide (*t*-BuOOH) solution in decane (1.0 mL) was added to the mixture and left under stirring at room temperature. After 30 min the reaction mixture was diluted with $CHCl_3$, transferred into a separatory funnel, washed three times with water, concentrated under reduced pressure, and purified by column chromatography eluted with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%) in the presence of a few drops of TFA, affording pure **11a** (225 mg, 0.158 mmol) in 80% yield: white amorphous powder, $R_f = 0.4$ (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58−6.80 (complex signals, 14H, aromatic protons); 4.92 (d, $J = 7.6$ Hz, 1H, H-1); 4.81 (d, $J = 7.6$ Hz, 1H, H-1′); 4.45−4.22 [overlapped signals, 13H, H_2-6-O-P, (-O-CH_2-CH_2-CN), 1xH-4 and 4x(CH_2-CH_2-O-sugar)]; 3.92−3.32 [overlapped signals, 9H, H_2-6-OH, 1xH-4, 2xH-2, 2xH-5 and 2xH-3]; 2.57−2.51 [m, 2H, (-O-CH_2-CH_2-CN)]; 1.60−1.54 [m, 8H, 4x(CH_2-CH_2-O-sugar)]; 1.34−1.26 [overlapped signals, 64H, 4x(-CH_2-)$_8$]; 0.87 [t, 12H, 4x(CH_3)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −2.7 and −8.5. ESI-MS (negative ions): calcd for $C_{77}H_{126}ClNO_{17}P_2$, 1433.819; *m/z*, found 1433.56 ($M - H)^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{77}H_{125}ClNO_{17}P_2$ 1432.8116; found 1432.8139 $(M - H)^-$.

Synthesis of Cyclic Dimer 12a. Derivative **11a** (35 mg, 0.024 mmol, 1 equiv), previously dried by several coevaporations with anhydrous pyridine, and MSNT (213 mg, 0.72 mmol, 30 equiv) were dissolved in anhydrous pyridine (24 mL) and left overnight under stirring at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with CH_2Cl_2, transferred into a separatory funnel, washed three times with water, concentrated under reduced pressure, and purified by column chromatography. Elution with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%) afforded pure **12a** (25 mg, 0.018 mmol) in 75% yield: white amorphous powder, $R_f = 0.5$ (CH_2Cl_2/CH_3OH, 97:3, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35−6.53 (complex signals, 14H, aromatic protons); 5.02 (d, $J = 7.0$ Hz, 1H, H-1); 4.81 (d, $J = 7.0$ Hz, 1H, H-1′); 4.70 (m, 1H, H-4); 4.58 (m, 1H, H-4′); 4.46−4.16 [overlapped signals, 6H, H_2-6, (-O-CH_2-CH_2-CN), H-3 and H-3′]; 3.98−3.85 (overlapped signals, 2H, H_2-6′); 3.77 [(t, 8H, 4x(-CH_2-CH_2-O-sugar)]; 3.68 (m, 1H, H-5); 3.54 (overlapped signals, 2H, H-5′ and H-2); 3.42 (m, 1H, H-2′); 2.70−2.61 [m, 2H, (-O-CH_2-CH_2-CN)]; 1.63−1.57 [m, 8H, 4x(CH_2-CH_2-O-sugar)]; 1.38−1.17 [overlapped signals, 64H, 4x(-CH_2-)$_8$]; 0.90−0.85 [m, 12H, 4x(CH_3)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 131.7, 131.7, 130.5, 129.7, 129.4, 127.6, 126.3, 123.0, 122.7, 122.1, 116.6 and 116.3 (aromatic carbons); 117.1 (CN); 101.3 and 101.3 (C-1 and C-1′); 82.0 and 81.7 (C-5 and C-5′); 81.4 [4x(CH_2-CH_2-O-sugar)]; 74.6 and 74.5 (C-4 and C-4′); 73.6 and 73.5 (C-2 and

C-2′); 72.4 and 72.1 (C-3 and C-3′); 66.1 and 65.4 (C-6 and C-6′); 62.2 (-O-*C*H$_2$-CH$_2$-CN); 31.8, 30.2, 30.0, 29.5, 29.5 and 29.2 [4x(-CH$_2$-)$_8$]; 22.6 [4x(*C*H$_2$-CH$_2$-O-sugar)]; 19.1 (-O-CH$_2$-*C*H$_2$-CN); 14.0 [4x(CH$_3$)]. ^{31}P NMR (CDCl$_3$, 161.98 MHz): δ −4.9 and −9.4. ESI-MS (positive ions): calcd for $C_{77}H_{124}ClNO_{16}P_2$, 1415.808; *m/z*, found 1438.60 (M + Na$^+$), 1454.61 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{77}H_{124}ClNO_{16}P_2Na$ 1438.7982; found 1438.8019 (M + Na$^+$).

Compound **12a** (25 mg, 0.018 mmol), coevaporated several times with anhydrous pyridine and dried under reduced pressure, was treated with Et$_3$N/pyridine (3 mL, 1:1, v/v) to selectively remove the 2-cyanoethyl group and left overnight under stirring at 50 °C. The reaction mixture was quenched by *in vacuo* removal of the solvent. The crude was purified by column chromatography, eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%), affording pure **13a** (23 mg, 0.018 mmol) in an almost quantitative yield: white amorphous powder, R_f = 0.3 (CH_2Cl_2/CH_3OH, 97:3, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70−6.83 (complex signals, 14H, aromatic protons); 4.96 (d, J = 7.5 Hz, 1H, H-1); 4.81 (d, J = 7.5 Hz, 1H, H-1′); 4.75 (m, 1H, H-4); 4.45−4.02 (overlapped signals, 5H, H$_2$-6, H-4′, H-3 and H-3′); 3.94−3.50 (overlapped signals, 11H, 4x(-CH$_2$-C*H*$_2$-O-sugar), H$_2$-6′ and H-5); 3.48−3.23 (overlapped signals, 3H, H-5′, H-2 and H-2′); 1.67−1.55 [m, 8H, 4x(C*H*$_2$-CH$_2$-O-sugar)]; 1.40−1.09 [overlapped signals, 64H, 4x(-C*H*$_2$-)$_8$]; 0.87 [m, 12H, 4x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −2.5 and −9.9. ESI-MS (negative ions): calcd for $C_{74}H_{121}ClO_{16}P_2$, 1362.781; *m/z*, found 1361.92 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{74}H_{120}ClO_{16}P_2$ 1361.7740; found 1361.7865 (M − H)$^-$.

Compound **13a** (23 mg, 0.013 mmol), dissolved in dioxane (200 μL), was reacted with 1 mL of a saturated aqueous LiOH solution, and the resulting mixture was left overnight under vigorous stirring at 50 °C. Then the reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2, transferred into a separatory funnel, and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography. Eluting the column with CH_2Cl_2 containing growing amounts of CH_3OH (from 0 to 15%) gave pure cyclic dimer **1a** (22 mg, 0.013 mmol) in an almost quantitative yield: white amorphous powder, R_f = 0.5 (CH_2Cl_2/CH_3OH 9:1 v/v). ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K, 14 mM): δ 7.30−6.93 (complex signals, 10H, aromatic protons); 4.91 (d, J = 7.6 Hz, 1H, H-1); 4.83 (d, J = 7.6 Hz, 1H, H-1′); 4.61−4.33 (m, 2H, H-4 and H-4′); 4.20−4.09 (m, 4H, H$_2$-6 and H$_2$-6′); 4.03−3.98 [overlapped signals, 8H, 4x(-CH$_2$-C*H*$_2$-O-sugar)]; 3.90−3.40 (overlapped signals, 6H, H-3 and H-3′, H-5 and H-5′, H-2 and H-2′); 1.66−1.53 [m, 8H, 4x(C*H*$_2$-CH$_2$-O-sugar)]; 1.34−1.09 [overlapped signals, 64H, 4x(-C*H*$_2$-)$_8$]; 0.87 [m, 12H, 4x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz, 298 K, 14 mM): δ 0.3 and −0.3. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K, 1.7 mM): δ 7.32−6.98 (complex signals, 10H, aromatic protons); 4.94 (d, J = 7.0 Hz, 2H, 2xH-1); 4.60−4.40 (overlapped signals, 6H, 2xH-4 and 2xH$_2$-6); 4.00−3.74 (overlapped signals, 10H, 2xH-3 and 4x(-CH$_2$-C*H*$_2$-O-sugar); 3.51−3.45 (overlapped signals, 4H, 2xH-5 and 2xH-2); 1.86−1.50 [m, 8H, 4x(C*H*$_2$-CH$_2$-O-sugar)]; 1.34−1.07 [overlapped signals, 64H, 4x(-C*H*$_2$-)$_8$]; 0.91-[m, 12H, 4x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz, 298 K, 1.7 mM): δ −0.4. ESI-MS (negative ions): calcd for $C_{68}H_{118}O_{16}P_2$, 1252.789 *m/z*, found 1251.97 (M − H)$^-$, 625.21 (M − 2H)$^{2-}$. HRMS (MALDI-TOF): *m/z* calcd for $C_{68}H_{117}O_{16}P_2$ 1251.7817; found 1251.7885 (M − H)$^-$.

Synthesis of BnO-TEG-OH (I). Tetra(ethylene glycol) (TEG, Scheme 3) (2.82 g, 14.5 mmol, 1 equiv), dissolved in anhydrous THF (8 mL), was reacted with sodium hydride (208 mg, 8.7 mmol, 1.6 equiv). The mixture was left under stirring for 10 min, and then benzylbromide (1.5 mL, 8.7 mmol, 1.6 equiv) was added to the stirred mixture, which was left 12 h at room temperature. The reaction mixture was quenched by addition of CH_3OH, filtered on celite, and purified by column chromatography. Eluting the column with ethyl acetate, target compound **I** was recovered in a pure form in 65% yield (2.69 g, 9.47 mmol): oil, R_f = 0.5 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35−7.32 (m, 5H, aromatic protons); 4.56 [s, 2H, (-C*H*$_2$-Ph)]; 3.75−3.62 [overlapped signals, 14H, 3x (-O-C*H*$_2$-C*H*$_2$-O-) and (-O-C*H*$_2$-CH$_2$-OH)]; 3.59 (t, J = 4.5 and 4.5 Hz, 2H, -C*H*$_2$OH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.1, 128.2, 127.6 and 127.4 (aromatic carbons); 73.1 (-*C*H$_2$-Ph); 72.4, 70.5, 70.2 and 69.3 [(-O-CH$_2$-CH$_2$-O-)]; 61.6 (O-CH$_2$-CH$_2$-OH). ESI-MS (positive ions): calcd for $C_{15}H_{23}O_5$, 283.154; *m/z*, found 306.69 (M + Na$^+$), 322.65 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{15}H_{23}O_5Na$ 306.1443; found 306.1460 (M + Na$^+$).

Synthesis of BnO-TEG-OMs (II). To 2.69 g of compound **I** (9.47 mmol, 1 equiv), dissolved in 22 mL of anhydrous CH_2Cl_2 were sequentially added DIPEA (3.3 mL, 18.9 mmol, 2 equiv) and mesylchloride (MsCl) (875 μL, 11.4 mmol, 1.2 equiv), and the resulting mixture was left overnight at room temperature. The reaction mixture was then concentrated under reduced pressure, transferred into a separatory funnel, and washed twice with a saturated NaCl solution. The organic phase, dried over anhydrous Na_2SO_4, was filtered, concentrated under reduced pressure, and then chromatographed on a silica gel column. Eluting with ethyl acetate/*n*-hexane 9:1 (v/v) containing growing amounts of ethyl acetate (from 90% to 100%), gave product **II** (3.26 g, 9.00 mmol) in 95% yield: oil, R_f = 0.6 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.22 (m, 5H, aromatic protons); 4.56 [s, 2H, (-C*H*$_2$-Ph)]; 4.36 [t, J = 4.5 and 5.0 Hz, 2H, (-CH$_2$-C*H*$_2$-O-Ms)]; 3.75 [t, J = 4.5 and 4.0 Hz, 2H, (-CH$_2$-C*H*$_2$-O-CH$_2$Ph)]; 3.67−3.61 [overlapped signals, 12H, 3x (-O-CH$_2$-CH$_2$-O-)]; 3.05 [s, 3H, (−SO$_2$− C*H*$_3$)]. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.1, 128.2, 127.6 and 127.5 (aromatic carbons); 73.1 (*C*H$_2$-Ph); 70.5, 70.4, 69.3 [3x(-O-*C*H$_2$-*C*H$_2$-O-)]; 69.1 (-O-*C*H$_2$-CH$_2$-O-Ms); 68.9 (-O-CH$_2$-*C*H$_2$-O-Ms); 37.5 (−SO$_2$-*C*H$_3$). ESI-MS (positive ions): calcd for $C_{16}H_{26}O_7S$, 362.140; *m/z*, found 385.69 (M + Na$^+$), 401.65 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{16}H_{26}O_7SNa$ 385.1297; found 385.1401 (M + Na$^+$).

Synthesis of 6b. Compound **5** (774 mg, 2.25 mmol, 1 equiv) dissolved in anhydrous *N*,*N*-dimethylformamide (15.0 mL) was reacted with sodium hydride (162 mg, 6.75 mmol, 3 equiv). The mixture was left under stirring for 10 min, and then 2.45 g of compound **II** (6.75 mmol, 3 equiv) was added under stirring at room temperature. After 4 h, the reaction mixture was quenched by addition of CH_3OH and concentrated under reduced pressure. The crude was then diluted with $CHCl_3$, transferred into a separatory funnel and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography. Eluting the column with ethyl acetate/*n*-hexane 85/15 (v/v) gave pure **6b** (1.59 g, 1.80 mmol) in 80% yield: white amorphous powder, R_f = 0.5 (ethyl acetate/*n*-hexane, 85:15, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50−7.03 (complex signals, 20H, aromatic protons); 5.54 (s, 1H, Ph-C*H*); 5.03 (d, J = 7.5 Hz, 1H, H-1); 4.56 [s, 4H, (-C*H*$_2$-Ph)]; 4.36 (dd, J = 5.0 and 5.0 Hz, 1H, H-4); 4.08−4.04 [m, 2H, (-C*H*$_2$-O-C-2)]; 4.02−3.83 (overlapped signals, 3H, C*H*$_2$-O-C-3 and H-6$_a$); 3.78 (t, J = 10.4 and 10.4 Hz, 1H, H-3); 3.69−3.56 [overlapped signals, 29H, 7x (O-C*H*$_2$-C*H*$_2$-O) and H-6$_b$)]; 3.52 (t, J = 9.0 and 8.0 Hz, 1H, H-2); 3.49−3.44 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 138.3, 137.2, 129.4, 128.9, 128.2, 128.1, 127.6, 127.5, 127.5, 126.0, 122.9, 117.1 and 116.6 (aromatic carbons); 101.9 (Ph-*C*H); 101.2 (C-1); 82.5 and 81.7 [(*C*H$_2$-O-CH$_2$-Ph)]; 80.7 (C-5); 73.1 [2x(-*C*H$_2$-Ph)]; 72.5 and 72.4 (2x*C*H$_2$-O-sugar); 70.5 [12x (O-CH$_2$ *TEG*)], 69.4 (C-3); 68.6 (C-4); 66.3 (C-2); 62.5 (C-6). ESI-MS (positive ions): calcd for $C_{49}H_{64}O_{14}$, 876.430; *m/z*, found 898.98 (M + Na$^+$), 914.95 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{49}H_{64}O_{14}Na$ 899.4194; found 899.4248 (M + Na$^+$).

Synthesis of 7b. Compound **6b** (1.60 g, 1.80 mmol, 1 equiv) was reacted with 5 mL of a TFA/CH_2Cl_2/H_2O (1:10:0.5, v/v/v) solution at 0 °C. After 4 h, the reaction mixture was diluted with

CH_2Cl_2, and the resulting solution was washed twice with water and then concentrated under reduced pressure. The crude was purified by column chromatography. Eluting the column with ethyl acetate, containing growing amounts of CH_3OH (from 10 to 20%) gave pure **7b** (1.40 g, 1.80 mmol) in almost quantitative yield: white amorphous powder, $R_f = 0.2$ (ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−6.94 (complex signals, 15H, aromatic protons); 4.91 (d, $J = 7.2$ Hz, 1H, H-1); 4.52 and 4.51 (s′s, 2H each, two C*H*$_2$-Ph); 4.10−3.92 [m, 4H, 2x(-C*H*$_2$-O-sugar)]; 3.86−3.68 (overlapped signals, 7H, H-4, H$_2$-6 and 2x(C*H*$_2$-O-CH$_2$-Ph)]; 3.62−3.49 [overlapped signals, 25H, H-3 and O-CH$_2$-CH$_2$-O *TEG*]; 3.42−3.36 (m, 1H, H-5); 3.34 (t, $J = 6.0$ and 7.2 Hz, 1H, H-2); 2.24 (t, 1H, CH$_2$O*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 139.0, 129.4, 128.2, 127.6, 127.5, 122.6 and 116.5 (aromatic carbons); 101.1 (C-1); 85.8 [2x(*C*H$_2$-O-CH$_2$-Ph)]; 82.0 (C-5); 75.3 (C-4); 73.1 [2x(-*C*H$_2$-Ph)]; 72.3 (C-3); 71.9 (C-2); 70.8 and 70.5 [overlapped signals, 6x(O-CH$_2$-CH$_2$-O *TEG*)]; 69.3 (2x*C*H$_2$-O-sugar); 62.9 (C-6). ESI-MS (positive ions): calcd for $C_{42}H_{60}O_{14}$, 788.398; *m/z*, found 811.49 (M + Na$^+$), 827.50 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{42}H_{60}O_{14}Na$ 811.3881; found 811.3899 (M + Na$^+$).

Synthesis of 8b. Compound **7b** (1.40 g, 1.80 mmol, 1 equiv), dissolved in anhydrous pyridine (5.4 mL), was reacted with DMTrCl (731 mg, 2.16 mmol, 1.3 equiv). The reaction mixture, left at room temperature overnight under stirring, was then diluted with CH_3OH and concentrated under reduced pressure. The crude was next purified on a silica gel column. Elution with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 5%) in the presence of a few drops of pyridine gave pure **8b** (2.00 g, 1.80 mmol) in 98% yield: glassy compound, mp dec > 90 °C. $R_f = 0.7$ ($CHCl_3/CH_3OH$, 98:2, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−6.82 (complex signals, 28H, aromatic protons); 5.06 (d, $J = 8.0$ Hz, 1H, H-1); 4.67 and 4.63 (s′s, 2H each, two C*H*$_2$-Ph); 4.30−4.20 [overlapped signals, 3H, 1x(CH$_2$-O-sugar) and H-6$_a$]; 4.02−3.90 [overlapped signals, 3H, 1x(CH$_2$-O-sugar) and H-6$_b$]; 3.85−3.82 [m, 5H, 2x(C*H*$_2$-O-CH$_2$-Ph) and H-4]; 3.80−3.60 [overlapped signals, 32H, H-3, H-5, O-CH$_2$-CH$_2$-O *TEG* and 2x(OCH$_3$) of the *DMTr group*]; 3.54 (m, 1H, H-2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 149.7, 145.0, 138.2, 135.8, 130.0, 129.3, 128.2, 127.6, 126.4, 123.6, 122.4, 116.9, 114.7 and 112.9 (aromatic carbons); 101.2 (C-1); 86.1 (quaternary C of the *DMTr group*); 84.9 [2x(*C*H$_2$-O-CH$_2$-Ph)]; 82.1 (C-5); 75.3 (C-4); 73.1 [2x(-*C*H$_2$-Ph)]; 72.3 (C-3); 71.8 (C-2); 70.5 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 (2x*C*H$_2$-O-sugar); 64.0 (C-6); 55.0 (OCH$_3$ of the *DMTr group*). ESI-MS (positive ions): calcd for $C_{63}H_{78}O_{16}$, 1090.529; *m/z*, found 1113.58 (M + Na$^+$), 1129.58 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{63}H_{78}O_{16}Na$ 1113.5188; found 1113.5233 (M + Na$^+$).

Synthesis of 6-*O*-(4,4′-Dimethoxytriphenylmethyl)-2,3-di-*O*-TEG-phenyl-β-D-glucopyranoside-4-*O*-(2-cyanoethyl-*N*,*N*-diisopropyl)phosphoramidite, 10b. To a solution of compound **8b** (1.0 g, 0.91 mmol, 1 equiv), dissolved in anhydrous CH_2Cl_2 (7 mL) were sequentially added DIPEA (630 μL, 3.6 mmol, 4 equiv) and 2-cyanoethyl-*N*,*N*-diisopropylchlorophosphoramidite (400 μL, 1.82 mmol, 2 equiv) under stirring at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure. The crude was then chromatographed on a silica gel column, eluting with *n*-hexane containing growing amounts of ethyl acetate (from 20% to 50%) in the presence of a few drops of triethylamine, furnishing desired compound **10b** (993 mg, 0.77 mmol) in 85% yield: oil, as a mixture of diastereomers, $R_f = 0.2$ (CH_2Cl_2/CH_3OH, 98:2, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46−6.81 (complex signals, 56H, aromatic protons); 5.07 (m, 2H, 2xH-1); 4.66 [s, 8H, 4x(-C*H*$_2$-Ph)]; 4.14−3.91 [overlapped signals, 14H, 2x(-O-C*H*$_2$-CH$_2$-CN), 4x(-C*H*$_2$-O-sugar) and 2xH-6$_a$]; 3.87−3.83 (overlapped signals, 10H, 4x(C*H*$_2$-O-CH$_2$Ph) and 2xH-4); 3.79−3.71 [overlapped signals, 64H, 2xH-6$_b$, 2xH-3, (O-CH$_2$-CH$_2$-O *TEG*) and 4x(OCH$_3$) *DMTr group*]; 3.68−3.46 [overlapped signals, 4H, 2xH-2 and 2xH-5]; 3.40−3.29 {m, 4H, 2xN[C*H*(CH$_3$)$_2$]$_2$}; 2.48−2.35 [m, 4H, 2x(-O-CH$_2$-C*H*$_2$-CN)]; 1.18, 1.17, 1.16, 1.15, 1.11, 1.10, 0.96 and 0.95 {s′s, 3H each, 24H, 4xN[CH(C*H*$_3$)$_2$]$_2$}. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 157.3, 138.3, 136.2, 130.1, 129.3, 128.2, 127.6, 126.5, 122.4, 116.9 and 112.9 (aromatic carbons); 117.2 (CN); 101.1 (C-1); 86.0 (quaternary C of the *DMTr group*); 85.0 and 84.6 [2x(*C*H$_2$-O-CH$_2$-Ph)]; 82.5 (C-5); 75.3 (C-4); 73.1 [2x(-*C*H$_2$-Ph)]; 72.3 (C-3); 72.0 (C-2); 70.5 (O-CH$_2$-CH$_2$-O *TEG*); 69.4 (2x*C*H$_2$-O-sugar); 63.8 (C-6); 60.2 (-O-*C*H$_2$-CH$_2$-CN); 55.0 (OCH$_3$ of the *DMTr group*); 43.0 {N[*C*H(CH$_3$)$_2$]$_2$}; 24.4 {N-[CH(*C*H$_3$)$_2$]$_2$}; 14.1 (-O-CH$_2$-*C*H$_2$-CN). ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ 151.1 and 150.5. ESI-MS (positive ions): calcd for $C_{72}H_{95}N_2O_{17}P$, 1290.637; *m/z*, found 1292.68 (M + H$^+$), 1392.73 (M + Et$_3$NH$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{72}H_{95}N_2O_{17}PNa$ 1313.6266; found 1313.6296 (M + Na$^+$).

Synthesis of 2,3-Di-*O*-TEG-phenyl-β-D-glucopyranoside-4-*O*-(2-chlorophenylphosphate), 9b. 2-Chlorophenyl-dichlorophosphate (590 μL, 3.64 mmol, 4 equiv) was added dropwise to a stirred solution of compound **8b** (1.0 g, 0.91 mmol, 1 equiv), 1,2,4-triazole (503 mg, 7.28 mmol, 8 equiv), and triethylamine (1.0 mL, 7.28 mmol, 8 equiv) in anhydrous pyridine (8.8 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 3 h the reaction mixture was concentrated under reduced pressure. The crude was then diluted with $CHCl_3$, transferred into a separatory funnel and washed three times with water, then concentrated under reduced pressure and purified by column chromatography. Elution with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%), with the addition of a few drops of TFA, afforded pure **9b** (810 mg, 0.84 mmol) in 92% yield: white amorphous powder, $R_f = 0.3$ (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31−6.93 (complex signals, 19H, aromatic protons); 4.88 (d, $J = 7.6$ Hz, 1H, H-1); 4.55−4.51 [m, 4H, 2x(-C*H*$_2$-Ph)]; 4.02−3.88 [overlapped signals, 11H, 2x (-C*H*$_2$-O-CH$_2$Ph), 2x(C*H*$_2$-O-sugar), H-4 and H$_2$-6]; 3.74−3.47 [overlapped signals, 27H, H-3, H-2, H-5 and (O-CH$_2$-CH$_2$-O *TEG*)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 156.6, 148.2, 141.9, 137.6, 137.2, 129.8, 129.2, 128.1, 127.4, 124.9, 124.2, 122.5, 121.7 and 116.2 (aromatic carbons); 100.8 (C-1); 85.6 and 83.8 [2x(*C*H$_2$-O-CH$_2$-Ph)]; 81.3 (C-5); 74.7 (C-4); 72.8 and 72.5 [2x(-*C*H$_2$-Ph)]; 72.4 (C-2); 71.4 (C-3); 70.0, 69.8, 69.6, 69.3 and 68.8 [(O-CH$_2$-CH$_2$-O *TEG*), 2x(CH$_2$-*C*H$_2$-O-sugar)]; 67.9 (C-6). ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −4.5. ESI-MS (negative ions): calcd for $C_{48}H_{63}ClO_{17}P$, 977.349; *m/z*, found 976.84 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{48}H_{62}ClO_{17}P$ 976.3413; found 976.3480 (M − H)$^-$.

Synthesis of Linear Precursor 11b. Derivative **9b** (150 mg, 0.153 mmol, 1 equiv) and compound **10b** (237 mg, 0.184 mmol, 1.2 equiv), previously dried by repeated coevaporations with anhydrous CH_3CN and kept under reduced pressure, were reacted with a 0.25 M DCI solution in anhydrous CH_3CN (5.0 mL). The reaction was left under stirring at 40 °C and monitored by TLC in the eluent system CH_2Cl_2/CH_3OH 94/6 (v/v). After 2.0 h, a 5.5 M *t*-BuOOH solution in *n*-decane (1.0 mL) was added to the mixture and left under stirring at room temperature. After 30 min the reaction mixture was diluted with $CHCl_3$, transferred into a separatory funnel and washed three times with water. The organic phase, concentrated under reduced pressure, was then purified by column chromatography. Elution with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%) in the presence of a few drops of TFA afforded pure **11b** (215 mg, 0.115 mmol) in 75% yield: white amorphous powder, $R_f = 0.4$ (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−6.92 (complex signals, 34H, aromatic protons); 4.91 (d, $J = 7.5$ Hz, 1H, H-1); 4.83 (d, $J = 7.5$ Hz, 1H, H-1′); 4.66−4.33 [overlapped signals, 18H, H$_2$-6-O-P, 4x(-C*H*$_2$-O-sugar) and 4x(-C*H*$_2$-Ph)]; 4.24−4.15 (m, 2H, O-C*H*$_2$-CH$_2$-CN); 4.06−3.54 [overlapped signals, 62H, (O-CH$_2$-CH$_2$-O *TEG*), 4x(C*H*$_2$-O-CH$_2$Ph), 2xH-3, 2xH-4 and H$_2$-6-OH]; 3.50−3.30 (partially submerged, overlapped signals, 4H, 2xH-2 and 2xH-5); 2.69−2.57 (m, 2H, O-CH$_2$-C*H*$_2$-CN). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.1, 156.8, 149.1, 138.1, 137.9, 137.8, 129.8, 129.6, 129.3, 128.4, 128.3, 128.2, 127.6, 127.4, 124.8, 123.4, 122.9, 122.5, 121.3, 116.7, 116.6 and 116.4 (aromatic carbons); 117.3 (CN); 101.5 (C-1 and C-1′); 84.4 and 82.7 [4x(*C*H$_2$-O-CH$_2$-Ph)]; 82.1 and 81.9 (C-5 and

C-5′); 75.0 and 74.7 (C-4 and C-4′); 73.1 [4x(-*C*H$_2$-Ph)]; 72.7 and 72.1 (C-2 and C-2′); 72.0 and 71.9 (C-3 and C-3′); 70.8, 70.7, 70.6, 70.5, 70.4, 70.2 and 70.0 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 68.8 (C-6-O-P); 62.0 (C-6-OH); 60.2 (-O-*C*H$_2$-CH$_2$-CN); 19.1 (-O-CH$_2$-*C*H$_2$-CN). ^{31}P NMR (CDCl$_3$, 161.98 MHz): δ −3.1 and −7.4. ESI-MS (negative ions): calcd for $C_{93}H_{126}ClNO_{33}P_2$, 1881.738; *m/z*, found 1881.35 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{93}H_{125}ClNO_{33}P_2$ 1880.7298; found 1880.7320 (M − H)$^-$.

Synthesis of Cyclic Dimer 12b. Derivative **11b** (35 mg, 0.018 mmol, 1 equiv), previously dried by repeated coevaporations with anhydrous pyridine, and MSNT (160 mg, 0.54 mmol, 30 equiv) were dissolved in anhydrous pyridine (18 mL) and left overnight under stirring at room temperature. The reaction mixture was then concentrated under reduced pressure, dissolved in CH_2Cl_2, transferred into a separatory funnel, and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography, eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1% to 10%), affording pure **12b** (25 mg, 0.013 mmol) in 75% yield: white amorphous powder, R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−6.53 (complex signals, 34H, aromatic protons); 5.04 (d, J = 7.5 Hz, 1H, H-1); 4.86 (d, J = 7.0 Hz, 1H, H-1′); 4.72 (m, 1H, H-4); 4.55−4.46 [overlapped signals, 10H, 4x(-C*H*$_2$-Ph) and 2xH-6$_a$]; 4.42 (m, 1H, H-4′); 4.39−4.35 [m, 2H, (-O-C*H*$_2$-CH$_2$-CN)]; 4.33−4.24 [overlapped signals, 2H, 2xH-6$_b$); 4.14−3.93 [overlapped signals, 16H, 4x(CH$_2$-C*H*$_2$-O-sugar) and 4x(C*H*$_2$-O-CH$_2$Ph)]; 3.90−3.75 (m, 2H, 2xH-3); 3.69−3.52 [overlapped signals, 49H, (O-CH$_2$-CH$_2$-O *TEG*) and H-2]; 3.50−3.45 [overlapped signals, 3H, H-2′ and 2xH-5]; 2.68 [t, 2H, (-O-CH$_2$-C*H*$_2$-CN)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.8, 145.2, 138.1, 130.6, 129.5, 128.3, 128.1, 128.1, 128.0, 127.6, 127.5, 126.0, 123.1, 122.9, 121.4, 116.8 and 116.6 (aromatic carbons); 117.0 (CN); 101.1 (C-1); 100.6 (C-1′); 82.2 and 82.0 (C-5 and C-5′); 75.4 (C-4 and C-4′); 73.1 [4x(-*C*H$_2$-Ph)]; 72.9 and 72.4 (C-2 and C-2′); 72.1 (C-3 and C-3′); 70.5 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 66.0 (C-6 and C-6′); 62.4 (-O-*C*H$_2$-CH$_2$-CN); 19.1 (-O-CH$_2$-*C*H$_2$-CN). ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −4.9 and −9.5. ESI-MS (positive ions): calcd for $C_{93}H_{124}ClNO_{32}P_2$, 1863.727; *m/z*, found 1886.04 (M + Na$^+$), 1906.06 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{93}H_{124}ClNO_{32}P_2Na$ 1886.7168; found 1886.7196 (M + Na$^+$).

Compound **12b** (25 mg, 0.013 mmol), coevaporated several times with anhydrous pyridine and then dried under reduced pressure, was treated with Et_3N/pyridine (3 mL, 1:1, v/v), and the resulting mixture left overnight under stirring at 50 °C. The reaction was quenched by in vacuo removal of the solvent. The crude was then purified by column chromatography eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1% to 10%), affording pure **13b** (23 mg, 0.013 mmol) in an almost quantitative yield: white amorphous powder, R_f = 0.2 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44−6.81 (complex signals, 34H, aromatic protons); 4.92 (d, J = 7.5 Hz, 1H, H-1); 4.81 (d, J = 7.0 Hz, 1H, H-1′); 4.74 (m, 1H, H-4); 4.55 [s, 8H, 4x(O-C*H*$_2$-Ph)]; 4.42 (m, 2H, 2xH-6$_a$); 4.15 (m, 1H, H-4′); 4.08−3.90 [overlapped signals, 18H, 2xH-6$_b$, 4x(CH$_2$-C*H*$_2$-O-sugar) and 4x(C*H*$_2$-O-CH$_2$Ph)]; 3.70−3.51 [overlapped signals, 54H, (O-CH$_2$-CH$_2$-O *TEG*), 2xH-2, 2xH-3 and 2xH-5]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 138.1, 130.5, 129.4, 128.2, 127.6, 127.5, 126.7, 126.2, 123.2, 122.9, 122.5, 122.0, 120.2, 117.1 and 116.8 (aromatic carbons); 101.1 (C-1); 99.5 (C-1′); 82.3 and 81.9 (C-5 and C-5′); 75.9 and 75.8 (C-4 and C-4′); 73.1 [4x(O-CH$_2$-Ph)]; 72.7 and 72.3 (C-2 and C-2′); 72.2 and 72.0 (C-3 and C-3′); 70.5 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 65.4 and 64.4 (C-6 and C-6′). ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −2.8 and −9.8. ESI-MS (negative ions): calcd for $C_{90}H_{121}ClO_{32}P_2$, 1810.700; *m/z*, found 1809.63 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{90}H_{120}ClO_{32}P_2$ 1809.6926; found 1809.7000 (M − H)$^-$.

Compound **13b** (23 mg, 0.013 mmol), dissolved in dioxane (200 μL), was reacted with 1 mL of a saturated aqueous LiOH solution, and the resulting mixture was left overnight under stirring at 50 °C. Then the reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2, transferred into a separatory funnel, and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography. Eluting the column with CH_2Cl_2 containing growing amounts of CH_3OH (from 0 to 15%) gave pure cyclic dimer **1b** (22 mg, 0.013 mmol) in an almost quantitative yield: oil, R_f = 0.5 (CH_2Cl_2/CH_3OH 9:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.00 (complex signals, 30H, aromatic protons); 4.81 (broad signal, 2H, H-1 and H-1′); 4.55−4.49 [complex, broad signals, 8H, 4x(C*H*$_2$-Ph)]; 4.25−3.83 [broad, overlapped signals, 14H, 2xH$_2$-6, 2xH-4 and 4x(CH$_2$-C*H*$_2$-O-sugar)]; 3.72−3.46 [overlapped signals, 62H, 4x(C*H*$_2$-O-CH$_2$Ph), (O-CH$_2$-CH$_2$-O *TEG*), 2xH-2, 2xH-3 and 2xH-5]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 138.1, 130.4, 129.4, 128.2, 127.6, 127.5, 126.7, 126.2, 123.2, 122.9, 122.5, 122.0, 120.2, 117.1 and 116.7 (aromatic carbons); 101.2 (C-1 and C-1′); 82.3 (C-5 and C-5′); 75.8 (C-4 and C-4′); 73.1 [4x(O-*C*H$_2$-Ph)]; 72.7 (C-2 and C-2′); 72.2 (C-3 and C-3′); 70.4 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 59.4 (C-6 and C-6′). ^{31}P NMR ($CDCl_3$, 161.98 MHz, 9 mM): very broad signal, centered at δ −2.8. ^{31}P NMR ($CDCl_3$, 161.98 MHz, 1.7 mM): sharp signal at δ −2.7. ESI-MS (negative ions): calcd for $C_{84}H_{116}O_{32}P_2$, 1698.692; *m/z*, found 1698.01 (M − H)$^-$; 849.62 (M − 2H)$^{2-}$. HRMS (MALDI-TOF): *m/z* calcd for $C_{84}H_{115}O_{32}P_2$ 1697.6847; found 1697.6891 (M − H)$^-$.

Synthesis of Linear Precursor 11c. Derivative **9b** (150 mg, 0.153 mmol, 1 equiv) and compound **10a** (265 mg, 0.184 mmol, 1.2 equiv), previously dried by repeated coevaporations with anhydrous CH_3CN and kept under reduced pressure, were reacted with a 0.25 M DCI solution in anhydrous CH_3CN (5.0 mL). The reaction was left under stirring at 40 °C and monitored by TLC in the eluent system CH_2Cl_2/CH_3OH 96/4 (v/v). After 2.0 h, a 5.5 M *t*-BuOOH solution in *n*-decane (1.0 mL) was added to the mixture and left under stirring at room temperature. After 30 min the reaction mixture was diluted with $CHCl_3$, transferred into a separatory funnel and washed three times with water. The organic phase, concentrated under reduced pressure, was then purified by column chromatography eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%) in the presence of a few drops of TFA, affording pure **11c** (190 mg, 0.115 mmol) in 75% yield: white amorphous powder, R_f = 0.4 (CH_2Cl_2/CH_3OH, 96/4, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−6.92 (complex signals, 24H, aromatic protons); 4.95−4.75 (overlapped signals, 3H, 2xH-1 and H-4); 4.55−3.14 [overlapped signals, 53H, 2xH$_2$-6, O-C*H*$_2$-CH$_2$-CN, 4x(-C*H*$_2$-O-sugar), 2x(-C*H*$_2$-Ph), 2xH-3, H-4′, (O-CH$_2$-CH$_2$-O *TEG*), 2x(C*H*$_2$-O-CH$_2$Ph), 2xH-2 and 2xH-5]; 2.55−2.40 (broad signals, 2H, O-CH$_2$-C*H*$_2$-CN); 1.58 [m, 4H, 2x(C*H*$_2$-CH$_2$-O-sugar)]; 1.37−1.07 [overlapped signals, 32H, 2x(-C*H*$_2$-)$_8$]; 0.88 [t, 6H, 2x-(CH$_3$)]. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.2, 156.8, 149.3, 138.2, 137.7, 131.1, 129.5, 129.3, 129.2, 129.0, 128.6, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4, 124.8, 123.8, 123.4, 123.2, 122.7, 122.4, 121.7, 121.5, 116.6 and 116.3 (aromatic carbons); 117.8 (CN); 101.9 and 101.7 (C-1 and C-1′); 84.7 and 84.3 [4x(*C*H$_2$-O-CH$_2$-Ph)]; 82.2 and 81.6 (C-5 and C-5′); 73.9 and 73.5 (C-4 and C-4′); 73.0 [2x-(-*C*H$_2$-Ph)]; 72.7 and 72.4 (C-2 and C-2′); 71.9 (C-3 and C-3′); 70.4, 70.3 and 70.2 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 66.7 and 66.0 (C-6-O-P); 63.9 and 63.0 (C-6-OH); 61.9 and 61.4 (-O-*C*H$_2$-CH$_2$-CN); 31.8, 30.2, 29.5 and 29.2 [2x(-CH$_2$-)$_8$]; 22.5 [2x(*C*H$_2$-CH$_2$-O-sugar)]; 19.0 (-O-CH$_2$-*C*H$_2$-CN); 13.9 [4x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −1.1, −4.5 and −6.9. ESI-MS (negative ions): calcd for $C_{85}H_{125}ClNO_{25}P_2$, 1656.770; *m/z*, found 1657.88 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{85}H_{124}ClNO_{25}P_2$ 1655.7626; found 1655.7811 (M − H)$^-$.

Synthesis of Cyclic Dimer 12c. Derivative **11c** (35 mg, 0.021 mmol, 1 equiv), previously dried by repeated coevaporations with anhydrous pyridine, 4-dimethylaminopyridine (DMAP) (2.6 mg,

0.021 mmol, 1 equiv) and MSNT (190 mg, 0.63 mmol, 30 equiv) were dissolved in anhydrous pyridine (20 mL) and left overnight under stirring at room temperature. The reaction mixture was then concentrated under reduced pressure, dissolved in CH_2Cl_2, transferred into a separatory funnel, and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1 to 10%), affording pure **12c** (26 mg, 0.016 mmol) in 75% yield: white amorphous powder, R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−6.95 (complex signals, 24H, aromatic protons); 5.01−4.86 (overlapped signals, 2H, 2xH-1); 4.68 (m, 1H, H-4); 4.56−4.49 [overlapped signals, 6H, 2x(-C*H*$_2$-Ph) and 2xH-6$_a$]; 4.42 (m, 1H, H-4′); 4.35−4.14 [overlapped signals, 4H, (-O-C*H*$_2$-CH$_2$-CN) and 2xH-6$_b$); 4.09−3.70 [overlapped signals, 14H, 2xH-3, 4x(CH$_2$-C*H*$_2$-O-sugar) and 2x(C*H*$_2$-O-CH$_2$Ph)]; 3.70−3.54 [overlapped signals, 24H, (O-CH$_2$-CH$_2$-O *TEG*)]; 3.53−3.35 [overlapped signals, 4H, 2xH-2 and 2xH-5]; 2.67 [t, 2H, (-O-CH$_2$-C*H*$_2$-CN)]; 1.65−1.54 [m, 4H, 2x(C*H*$_2$-CH$_2$-O-sugar)]; 1.42−1.17 [overlapped signals, 32H, 2x(-C*H*$_2$-)$_8$]; 0.89 [t, 6H, 2x(CH$_3$)]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9, 153.5, 146.4, 145.9, 143.9, 141.6, 138.1, 132.8, 132.5, 132.2, 130.6, 129.6, 129.5, 128.2, 128.0, 127.8, 127.6, 126.0, 123.1, 121.4, 117.0 and 116.9 (aromatic carbons); 116.2 (CN); 101.9 (C-1); 101.4 (C-1′); 82.2 and 81.9 [2x(*C*H$_2$-O-CH$_2$-Ph)]; 81.6 and 81.3 (C-5 and C-5′); 75.3 (C-4 and C-4′); 73.9 and 73.6 (C-2 and C-2′); 73.1 [2x(-*C*H$_2$-Ph)]; 72.3 and 72.1 (C-3 and C-3′); 70.5 (O-CH$_2$-CH$_2$-O *TEG*); 69.3 [4x(CH$_2$-*C*H$_2$-O-sugar)]; 68.1 and 66.7 (C-6 and C-6′); 61.9 (-O-*C*H$_2$-CH$_2$-CN); 31.8, 30.1, 29.5 and 29.2 [2x(-CH$_2$-)$_8$]; 22.5 [2x(*C*H$_2$-CH$_2$-O-sugar)]; 18.4 (-O-CH$_2$-*C*H$_2$-CN); 14.0 [4x-(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −2.1, −4.8, −7.4 and −10.5. ESI-MS (positive ions): calcd for $C_{85}H_{124}ClNO_{24}P_2$, 1639.768; *m/z*, found 1663.80 (M + Na$^+$), 1680.74 (M + K$^+$). HRMS (MALDI-TOF): *m/z* calcd for $C_{85}H_{124}ClNO_{24}P_2Na$ 1662.7575; found 1662.7610 (M + Na$^+$).

Compound **12c** (25 mg, 0.015 mmol), coevaporated several times with anhydrous pyridine and then dried under reduced pressure, was treated with piperidine/DMF (3 mL, 1:5, v/v), and the resulting mixture left overnight under stirring at 70 °C. The reaction was quenched by *in vacuo* removal of the solvent. The crude was then purified by column chromatography eluting with CH_2Cl_2 containing growing amounts of CH_3OH (from 1% to 10%), affording pure **13c** (23 mg, 0.014 mmol) in 96% yield: white amorphous powder, R_f = 0.2 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−6.80 (complex signals, 24H, aromatic protons); 4.92−4.67 (broad signals, 3H, 2xH-1 and H-4); 4.53 [s, 4H, 2x-(O-C*H*$_2$-Ph)]; 4.43 (m, 2H, 2xH-6$_a$); 4.23−3.90 [overlapped, broad signals, 19H, 2xH-6$_b$, H-4′, 4x(CH$_2$-C*H*$_2$-O-sugar) and 4x(C*H*$_2$-O-CH$_2$Ph)]; 3.70−3.44 [overlapped, broad signals, 54H, (O-CH$_2$-CH$_2$-O *TEG*), 2xH-2, 2xH-3 and 2xH-5]; 1.65−1.48 [broad signals, 4H, 2x(C*H*$_2$-CH$_2$-O-sugar)]; 1.40−1.16 [overlapped signals, 32H, 2x(-C*H*$_2$-)$_8$]; 0.87 [t, 6H, 2x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ −2.1 and −10.0. ESI-MS (negative ions): calcd for $C_{82}H_{121}ClO_{24}P_2$, 1586.741; *m/z*, found 1585.63 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{82}H_{120}ClO_{24}P_2$ 1585.7333; found 1585.7379 (M − H)$^-$.

Compound **13c** (23 mg, 0.014 mmol), dissolved in dioxane (200 μL), was reacted with 1 mL of a saturated aqueous LiOH solution, and the resulting mixture was left overnight under stirring at 50 °C. Then the reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2, transferred into a separatory funnel and washed three times with water. The organic phase was concentrated under reduced pressure and purified by column chromatography. Eluting the column with CH_2Cl_2 containing growing amounts of CH_3OH (from 0 to 15%) gave pure cyclic dimer **1c** (22 mg, 0.013 mmol) in 93% yield: oil, R_f = 0.5 (CH_2Cl_2/CH_3OH 9:1 v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39−6.80 (complex signals, 20H, aromatic protons); 4.98−4.62 (broad signals, 3H, 2xH-1 and H-4); 4.54 and 4.53 [two s′s, 2H each, 2x(O-C*H*$_2$-Ph)]; 4.43 (m, 2H, 2xH-6$_a$); 4.30−3.75 [broad, overlapped signals, 11H, 2xH-6$_b$, H-4′ and 4x(CH$_2$-C*H*$_2$-O-sugar)]; 3.72−3.30 [overlapped signals, 34H, (O-CH$_2$-CH$_2$-O *TEG*), 2xH-2, 2xH-3 and 2xH-5]; 1.69−1.55 [broad signals, 4H, 2x(C*H*$_2$-CH$_2$-O-sugar)]; 1.40−1.08 [overlapped signals, 32H, 2x(-C*H*$_2$-)$_8$]; 0.88 [t, 6H, 2x(CH$_3$)]. ^{31}P NMR ($CDCl_3$, 161.98 MHz, 298 K, 10 mM): a large set of resonances is present between δ 0.7 and −7.1. ^{31}P NMR ($CDCl_3$, 161.98 MHz, 298 K, 100 μM): sharp signal at δ 1.6. MALDI-TOF (negative ions): calcd for $C_{76}H_{116}O_{24}P_2$, 1474.733; *m/z*, found 1472.86 (M − H)$^-$. HRMS (MALDI-TOF): *m/z* calcd for $C_{76}H_{115}O_{24}P_2$ 1473.7253; found 1473.7303 (M − H)$^-$.

Acknowledgment. We thank Centro di Metodologie Chimico-Fisiche (CIMCF), Università di Napoli "Federico II", for the MS and NMR facilities.

Supporting Information Available: General Information, copies of ^{1}H, ^{13}C and, where present, ^{31}P NMR spectra for the synthesized compounds. VT-NMR spectra for **1a**, **1b**, and **1c** and ^{31}P NMR spectra registered at different concentrations for **1b** and **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7017087