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Novel Cyclic Phosphate-Linked Oligosaccharides (CyPLOSs) Covalently Immobilized on Solid Supports for Potential Cation Scavenging

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For potential cation scavenging both from water and from organic solvents, here we propose a synthetic procedure for functionalization of a Tentagel solid support with novel cyclic phosphate-linked oligosaccharide (CyPLOS) analogues. To establish the feasibility of the synthetic strategy, the cyclic dimer was the model compound selected to be incorporated onto the solid support. This functionalization was achieved through a stepwise solid-phase synthesis of the linear dimer, obtained by standard phosphoramidite protocols, followed by a synthesis of the cyclic molecule on the resin. The key intermediate in our synthetic strategy was a suitably derivatized sugar phosphoramidite building block, with the secondary hydroxy functions masked as TBDMS ethers. This proved to be an orthogonal protection with respect to the DMT ether, fully compatible with the phosphoramidite and the phosphotriester chemistry used for the oligomerization and the cyclization process onto the solid support, respectively. Conditions for the total unmasking of the hydroxy groups of the cyclic dimer, not affecting the integrity of the cyclic structure nor its linkage with the solid matrix, have been optimized. Gel-phase ^{31}P NMR spectroscopy has been used extensively here to monitor the efficiency of the reactions carried out on the solid support.

Introduction

Cyclodextrins exhibit remarkable inclusion properties towards a large number of chemically different compounds, due to their characteristic toroidal structure, and for this reason are among the most studied macrocyclic systems in supramolecular chemistry.[1] A notable advantage of cyclodextrins over other interesting host molecules such as, for instance, calyx[4]arenes, is their intrinsic high water solubility, in conjunction with the hydrophobic nature of the internal cavity. This allows specific recognition in aqueous solutions, which is of the utmost importance in mimicking biological processes or in the development of novel biosensors. Being polyfunctional molecules, cyclodextrins are useful scaffolds that, suitably elaborated, can provide artificial receptors capable of specifically binding a variety of different ions or neutral molecules in water.[2] Additional interest in cyclodextrins arises from their potential as efficient scavengers of environmentally hazardous compounds from water.[3] Among other uses, per(3,6-anhydro)-cyclodextrins have emerged as good complexing agents for metals,[4] with potential applications in cleaning of biological solutions and also for the transport of radioactive metals for diagnostic or therapeutic purposes.[5] Insertion of single carboxylate functions on these modified cyclodextrins has resulted in enhanced affinity towards heavy metals, suggesting that immobilization of these macrocycles on suitable insoluble supports may produce new materials useful for the elimination or concentration of toxic cations from aqueous solutions and especially from biological fluids.[6]

Upon suitable modification, cyclodextrins can also be converted into lipophilic tools, thus extending their use also to organic solvents. Particularly interesting are amphiphilic cyclodextrins, displaying acceptable solubility in a wide range of solvents.[7] Typical examples of amphiphilic cyclodextrins reported in the literature include preformed oligosaccharide macrocycles with covalently attached hydrophobic moieties such as cholesterol,[8] or cyclodextrins peralkylated at their primary or secondary faces with long aliphatic chains, connected through stable ether linkages.[9]

The preparation of modified cyclic oligosaccharides starting from preformed cyclodextrins, which is still the most commonly followed route, has a valid, though more laborious, alternative in the total synthesis approach. This involves the stepwise synthesis of the linear oligomer, followed by appropriate circularization, and points to a higher degree of molecular diversity in the construction of the macrocycle, allowing, for instance, the insertion of com-

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pletely unusual monomeric residues[10] or the replacement of the natural *O*-(1,4)-glycosidic linkages with alternative, more stable chemical bonds.[11]

Aiming at specific cation recognition, we recently described novel cyclic oligosaccharides, 4,6-linked through chemically and enzymatically stable phosphodiester bonds (**1**–**3**, Figure 1), that we have named CyPLOSs (Cyclic Phosphate-Linked OligoSaccharide analogues).[12] These molecules were synthesized starting from an appropriate 4-phosphoramidite derivative of phenyl-β-D-glucopyranoside (**4**, Figure 1). The assembly of the linear precursor was carried out on a DNA synthesizer by standard phosphoramidite protocols. The solid support used was engineered to allow an on-resin circularization procedure, which upon a mild basic treatment released exclusively the cyclic molecule into solution.[13] The systematic evaluation of the cation-binding abilities of these cyclic oligomers is currently underway and will be published in due course. It can be noted here that the cation-scavenging potential of this class of cyclic saccharide surrogates, combining some constitutive elements of small cyclodextrins and crown ethers, and exhibiting phosphodiester bonds within the oligosaccharide core as a distinct structural motif, should a priori be widely modulatable by ad hoc selection of the nature, stereochemistry and number of the monomeric building blocks.

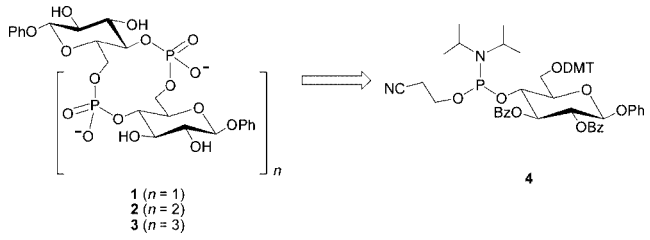
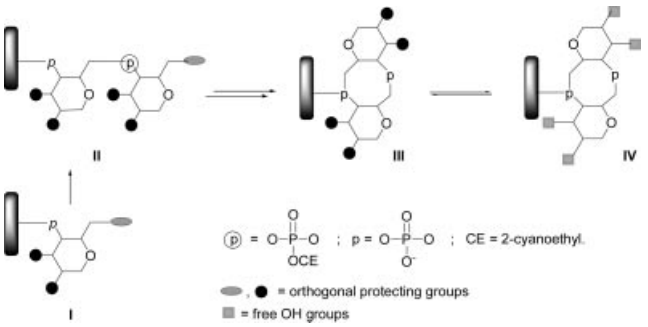


Figure 1. Dimeric, trimeric and tetrameric CyPLOS (**1**–**3**) and building block **4**.

Our goal is indeed to develop a general synthetic platform for the preparation of solid supports functionalized with lipophilic cyclic glycomimetics that, upon a single treatment, will be easily convertible into highly hydrophilic macrocycles, allowing us to sequester cations from both aqueous and organic solutions. As a model for potential cation scavenging, here we describe the synthesis of resin-bound cyclic phosphate-linked disaccharide compounds with their secondary hydroxy functions decorated with bulky TBDMS groups. This solid matrix, as depicted in Scheme 1, can switch from an "off-recognition" state, anchoring a predominantly lipophilic system, with all the four hydroxy groups per grafted cycle blocked in the form of silyl ethers, to an "on-recognition" state, exposing highly hydrophilic macrocycles to the solvent. To our convenience, both kinds of cyclic derivatives, the TBDMS-protected or the fully deprotected compounds, can be detached from the solid matrix and recovered in a pure form after simple gel filtration chromatography.



Scheme 1. General synthetic platform for the functionalization of Tentagel resin with cyclic disaccharide analogues.

Results and Discussion

Here we propose a simple and versatile protocol for the functionalization of standard Tentagel supports with novel cyclic CyPLOS analogues, based on the initial construction of the linear counterpart and subsequent on-resin cyclization. The crucial issue in our synthetic plan was the suitable selection of the solid support, of the linker and of the functional group protection strategy.

Tentagel resin (0.29 mequiv. per g of primary amino groups), widely adopted for the solid-phase synthesis of oligonucleotides, peptides and related analogues, was the support of choice for its compatibility with standard automated phosphoramidite protocols and also for its suitability for applications in water, in view of direct tests of resin-bound compounds in aqueous environments. In addition, given the high flexibility of PEG chains attached to the polystyrene backbone on Tentagel support, it is generally assumed that the conformational mobility of substrates immobilized onto this copolymer is not substantially altered, so their complexation abilities should also not be hampered. The bifunctional linker 2-(3-chloro-4-hydroxyphenyl)acetic acid was directly introduced onto the solid support, thus affording a phenolic OH resin, useful for the covalent attachment of a tailored phosphoramidite saccharide derivative. In this synthetic context, the previously described building block **4** (Figure 1) was of no use, having its 2- and 3-OH groups protected in the form of benzoic esters, typically removed under basic conditions, under which phosphotriester functions would definitely not survive. Therefore, an alternative protection strategy was necessary in our synthetic scheme in order to achieve fully deprotected cyclic molecules still anchored to the solid support (**IV**, Scheme 1).

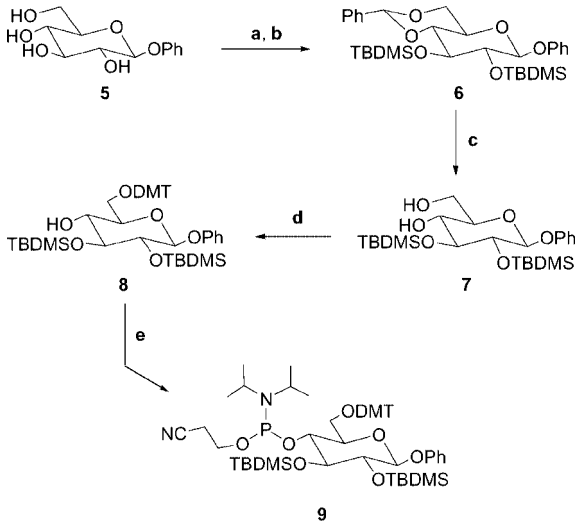
In the literature, the TBDMS group has been widely used to mask the primary hydroxy groups of cyclodextrins,[14] conferring a high degree of lipophilicity on the final oligosaccharides. Here this protecting group was chosen as the appendage to cap the glucoside 2- and 3-hydroxy functions in **I** in a transient manner, since it satisfies the following prerequisites: i) it can easily be installed, by standard and high-fidelity reactions, ii) it is orthogonal both to 4,4′-dimethoxytriphenylmethyl (DMT) and 2-cyanoethyl groups, typically used for the transient protection of primary hy-

droxy and phosphate diester groups, respectively, iii) it can be selectively detached by a standard fluoride treatment, expected not to affect the integrity of the circular structure nor the stability of the phenyl glucoside moieties, iv) it is highly hydrophobic, able to affect the solubility properties of the cyclic molecule in organic media significantly, and v) it is stable to the mild basic treatments required to detach the phosphodiester-linked cyclic molecule, in case its release in solution is desired. For our specific purposes, we optimized the conditions for its complete removal in the solid phase while not affecting the more labile phosphotriester function linking the cyclic molecule to the solid matrix. As a further advantage, in the case of experiments carried out in solution, the treatment with fluoride for TBDMS removal does not involve troublesome purification steps; in fact, due to the net increase in hydrophilicity, the resulting macrocycle is typically water-soluble, so that either washing with organic solvents or a simple gel filtration chromatography allow the target molecule to be easily isolated from the reaction mixture in a very pure form.

Phosphoramidite **9**, obtained in five easy and high-yielding reaction steps depicted in Scheme 2, was therefore chosen as the key intermediate in our synthetic strategy. This building block shows the following features: 1) anomeric position blocked in the form of a phenyl glucoside, stable to the various treatments required in the synthesis and furnishing a UV/Vis tag attached to the sugar building block, 2) 6-OH protected in the form of a DMT ether, 3) 4-OH derivatized with 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite, and 4) protected at both the 2- and the 3-positions as a TBDMS ether. Phosphoramidite **9** was prepared starting from commercially available phenyl β-D-glucopyranoside (**5**), which was first converted in almost quantitative yield into the corresponding 4,6-benzylidene derivative, by treatment with α,α-dimethoxytoluene in the presence of catalytic amounts of PTSA. Next, the hydroxy functions at the 2- and 3-positions were treated with TBDMSCl in DMF in the presence of imidazole, thus furnishing derivative **6** in 87% yield.

After removal of the benzylidene group, achieved in 82% yield by treatment with TFA in DCM, the 6-OH of **7** was selectively protected in the form of an acid-labile DMT ether by addition of DMTCl in pyridine, yielding derivative **8** in 92% yield. Successive phosphitylation at the 4-OH position by treatment with 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite in the presence of DIEA gave target compound **9** in 90% yield. The overall yield for the synthesis of **9** starting from compound **5** was 60% for the five steps. In all cases, the intermediate compounds and final derivative **9** were purified by silica gel chromatography and were then fully characterized by NMR (^{1}H, ^{13}C and also ^{31}P in the case of **9**) and ESI-MS data.

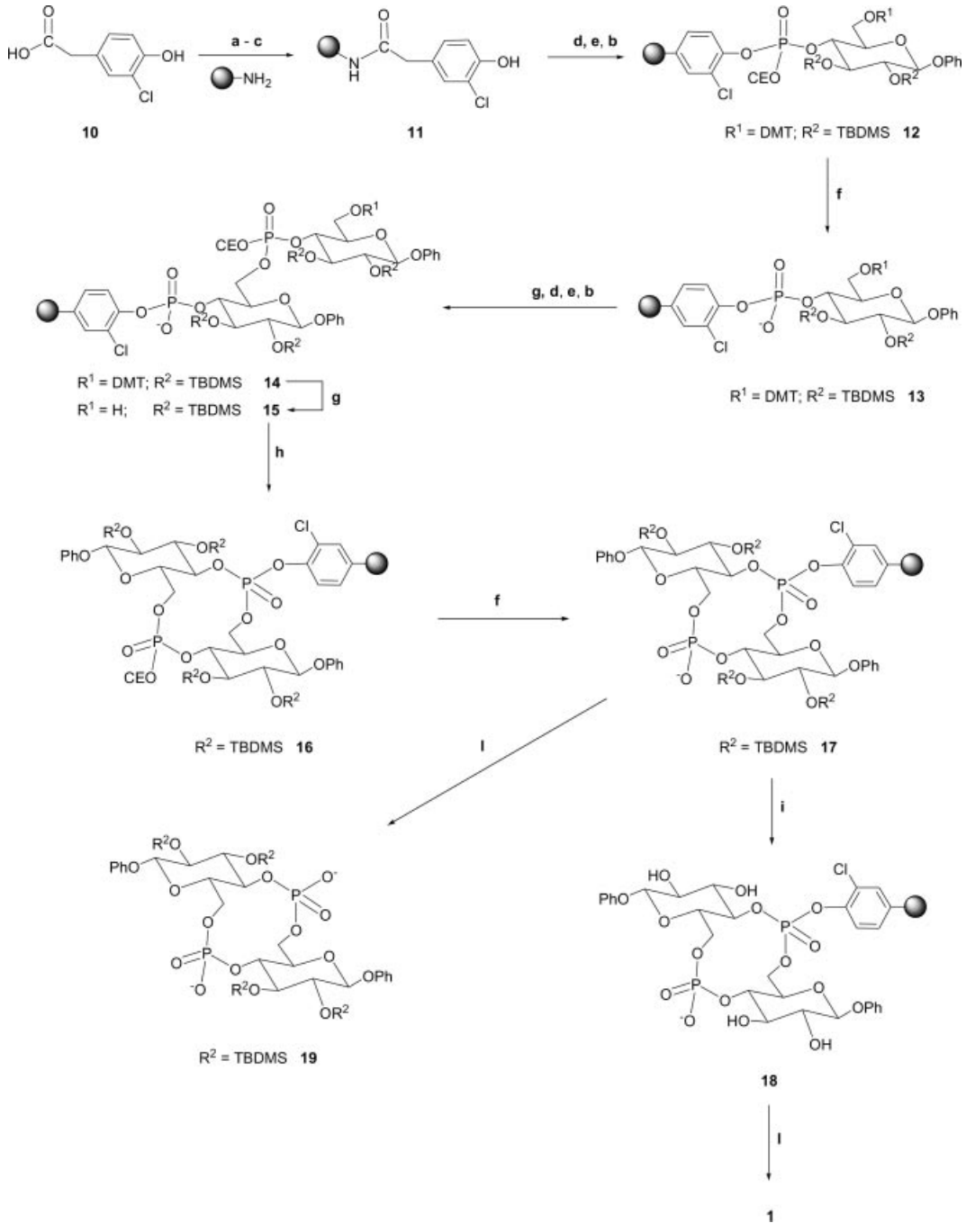
The functionalization of the solid support was achieved by treatment of building block **9** with TentaGel-NH_2 resin (0.29 mequiv. g^{-1}) previously derivatized with 2-(3-chloro-4-hydroxyphenyl)acetic acid (**10**), in the presence of DIC, HOBt and DIEA, as shown in Scheme 3.[15] The first sugar building block was anchored to resin **11** by standard phos-



Scheme 2. a) α,α-Dimethoxytoluene, PTSA cat., DMF, 12 h, 50 °C (100%); b) TBDMSCl, imidazole 48 h, DMF, room temp. (87%); c) TFA/DCM/H_2O (1:10:0.5, v/v/v), 4 h, 0 °C (82%); d) DMTCl, pyridine, 12 h, room temp. (92%); e) 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite, DIEA, DCM, 1 h, room temp. (90%).

phoramidite chemistry, involving tetrazole activation, oxidation and capping, to afford support **12** with a loading of 0.16 mequiv. g^{-1}, as calculated by the DMT test. Successively, treatment with triethylamine in pyridine allowed the removal, by a β-elimination mechanism, of the 2-cyanoethyl group, thus converting the phosphotriester into the more stable phosphodiester function and furnishing support **13**.

From resin **13**, the oligosaccharide chain was grown by exploiting a standard phosphoramidite protocol, well optimized for the solid-phase synthesis of oligonucleotides.[16] The synthetic procedure involved the following steps: a) removal of the DMT group from the 6-OH function on functionalized support **13** by treatment with DCA in DCM (2%), b) coupling with the addition monomer **9**, in the presence of tetrazole, c) oxidation of the phosphite triester to phosphate triester, by treatment with an iodine solution (0.1 M) in THF/H_2O/pyridine to give the support **14**, d) capping with acetic anhydride in pyridine to block unreacted hydroxy functions, and e) removal of the DMT group from the 6-OH function of the second added monomer, to afford support **15**. The efficiency of the coupling reaction was evaluated by spectrophotometric DMT tests, in all cases showing incorporation yields very close to 100%. Once the linear precursor on support **15** had been achieved, the following cyclization step was carried out by exploiting classical phosphotriester chemistry protocols in the solid phase. The linear oligomer was treated with the condensing agent MSNT in pyridine, to afford support **16**. This was then treated with triethylamine, to induce selective removal of the 2-cyanoethyl group from the phosphodiester interglucoside linkages, giving support **17**. All the crucial steps on the solid phase, from the functionalization of the support to the cyclization and deprotection of the dimer were monitored: i) directly on the solid phase, by ^{31}P NMR spectroscopy performed on the resin suspended in $CDCl_3$, and ii) indi-



Scheme 3. a) DIC, HOBt, DIEA, pyridine, 12 h, room temp.; b) Ac_2O/pyridine (1:1, v/v), 1 h, room temp.; c) 18 M NH_4OH, 1 h, 50 °C; d) coupling with **9**, 0.45 M tetrazole in CH_3CN, 1 h, room temp.; e) 0.1 M I_2 in THF/H_2O/pyridine, 3 treatments, 5 min each, room temp.; f) Et_3N/pyridine (1:1, v/v), 3 treatments, 6 h each, room temp.; g) 2% DCA in DCM, 5 treatments, 3 min each, room temp.; h) MSNT, pyridine, 3 treatments, 6 h each, room temp.; i) $Et_3N{\cdot}3\,HF$/THF (3:1, v/v), 12 h, 50 °C; l) 0.2 M 1,1,3,3-tetramethylguanidinium 2-nitrobenzaldoximate in H_2O/dioxane (1:1, v/v), 12 h, room temp.

rectly, by detachment, after each step, of samples of the glycomimetics grown onto the solid support and analysis of the released material by ^1H and ^{31}P NMR spectroscopy and ESI-MS spectrometry.

Accordingly, all the reactions involving the phosphorus centre (i.e., the oxidation of the phosphite triester to phosphate triester in **12**, the subsequent deprotection to give the desired phosphate diester in **13**, as well as the growing of the saccharide chain in **14**, the following cyclization to give **16** and phosphate deprotection to give **17**) were directly followed in the solid phase by ^{31}P NMR spectroscopy. Typically, on oxidation of the P^{III} atoms to the P^V state, a large upfield shift is observed, with the two signals centred at δ = 140 ppm coalescing into a broad resonance shifted at –4 ppm. This signal, upon removal of the 2-cyanoethyl group, is characteristically shifted downfield by ca. 2 ppm.

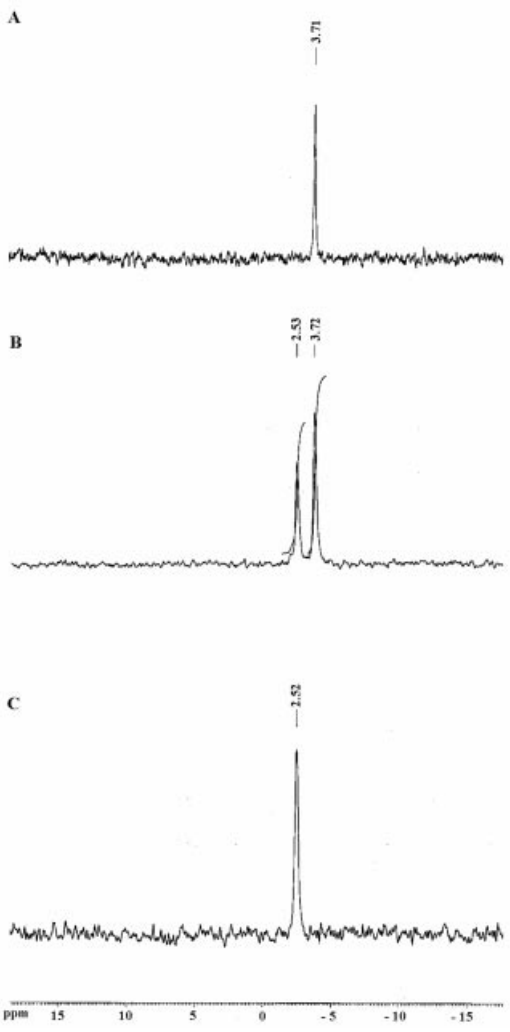


Figure 2. ^{31}P NMR spectra (161.98 MHz) of resin **12** suspended in $CDCl_3$ (panel A), after the first 6 h treatment with Et_3N/pyridine (panel B), and after the third and last 6 h treatment with Et_3N/pyridine (panel C), showing the complete conversion of resin **12** into **13**.

An example of ^{31}P NMR spectroscopic monitoring of the 2-cyanoethyl removal from phosphodiester function to obtain support **13** is shown in Figure 2.

Critically, the efficiency of the cyclization reactions in giving functionalized support **16** was ascertained through the following data: a) total disappearance of the signal at δ = –2.52 ppm in the ^{31}P NMR spectrum, attributed to the phosphodiester function in support **15**, with the emergence of a new, broad signal at δ = –4.17 ppm, consistent with the desired phosphotriester function (see Figure 3), and b) recovery, after detachment with benzaldoximate ions, of the fully protected cyclic dimer **19**, in a pure form (see Figure 4) and in the expected amounts. By combining these data, it was concluded that the cyclization yields with the solid-phase method were in all cases (within the detection limits of the NMR technique) close, if not superior, to 95%. The detachment of cyclic dimer **19** from the insoluble matrix was achieved by treatment of solid support **17** with a 1,1,3,3-tetramethylguanidinium 2-nitrobenzaldoximate solution in H_2O/dioxane (0.2 M), selectively cleaving the 2-chlorophenate group from a dialkyl-phosphodiester function. Following this procedure, the cyclic compound is released into solution exclusively, whereas the unreacted lin-

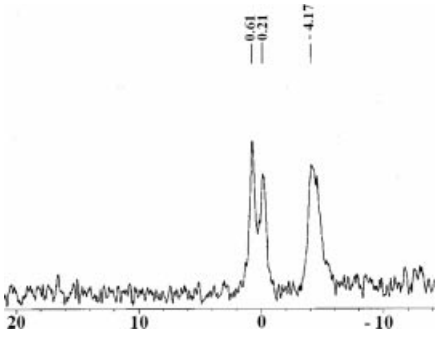


Figure 3. ^{31}P NMR spectrum (161.98 MHz) of resin **16** suspended in $CDCl_3$.

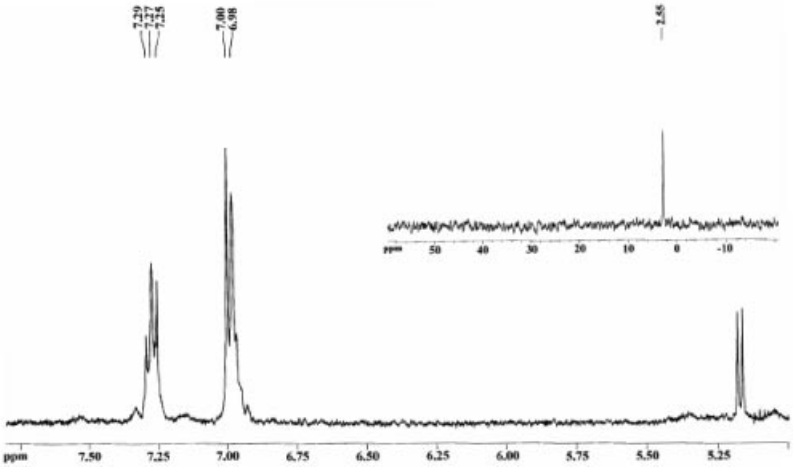


Figure 4. Low-field region of the ^1H NMR spectrum (400 MHz, $CDCl_3$) of cyclic dimer **19**. In the inset, its ^{31}P NMR spectrum (161.98 MHz, $CDCl_3$).

ear molecules or polymeric chains formed in the solid phase by undesired intramolecular reactions – if any – are not affected by this treatment and therefore remain on the solid support.[13]

Once the cyclization conditions had been optimized, special attention was devoted to the desilylation reaction on solid support **17**. The complete deprotection of the hydroxy groups – under conditions not affecting the stability of the phosphotriester bond linking the macrocycle to the solid resin – was achieved by addition of fluoride; particularly, the $Et_3N{\cdot}3HF$ complex was found to be preferable to the more aggressive TBAF, NH_4F or $BF_3{\cdot}Et_2O$, though their use is widely documented for TBDMS removal in per-*O*-silylated cyclodextrins. Several tests were carried out to optimize this reaction, by varying the excess, solvent and temperature conditions. Checking for optimal conditions was carried out: 1) once the desilylation procedure had been completed, by detaching the glycomimetics from weighed samples of the solid support by treatment with benzaldoximate ions and evaluating, by ^1H NMR and ESI-MS analysis of the material released in solution, the effective deprotection, and 2) during the desilylation treatments, by direct analysis, through ESI-MS techniques, of the combined eluates and washings of the solid support obtained for each $Et_3N{\cdot}3HF$ treatment, so to ensure that no precious dimeric material is cleaved, even in traces, as an undesired side reaction of the desilylation procedure. Full removal of the TBDMS groups in the solid phase, without concomitant detrimental loss of functionalization on the support, thus affording the target solid support **18**, was finally achieved by adopting $Et_3N{\cdot}3HF$ in anhydrous THF (1:1, v/v) and carrying out the reaction at 50 °C for 12 h. In all our experiments, the treatment with $Et_3N{\cdot}3HF$ at 50 °C, even if prolonged for 48 h on the functionalized resin, did not lead to any detectable side reaction; particularly, no detachment of saccharidic material from the Tentagel support was observed. Interestingly, only the experiments carried out at high temperature proved to be successful. On the contrary, when the reactions were carried out at room temperature, only partial TBDMS deprotection occurred, as shown by the presence in the eluates, after treatment with oximate ions on the solid phase, of all the possible TBDMS derivatives of cyclic dimer **1**, bearing from zero to four TBDMS groups, in different ratios.

The possibility of releasing both kinds of cyclic oligosaccharide derivatives (i.e., lipophilic **19** and the fully deprotected, hydrophilic **1**) from the solid support was then investigated. Starting from support **18**, an overnight treatment with oximate ions at room temp. provided cyclic dimer **1**, which proved to be identical to an authentic, previously synthesized sample, in the expected high purity and yields. Similar results were obtained when resin **17** was exposed to the same treatment, yielding the lipophilic cyclic oligosaccharide derivative **19** as the sole compound, as ascertained by RP-HPLC analysis of the detached material. The latter experiments further demonstrated the complete orthogonality of aryl-phosphotriester functions with respect to TBDMS ether groups (Figure 4).

From the perspective of developing resins for cation exchange that can be kept either in the "off-recognition" (i.e., in the protected form) or in the "on-recognition" (i.e., in a totally deprotected form) states, the TBDMS ether can therefore also be regarded as a useful protection system for secondary hydroxy groups in the solid phase. In principle, the liberated OH groups in support **18** are easily amenable to subsequent reprotection, either with TBDMS or with other protecting groups, if required, so to yield a switchable motif, crucial for potential cation recognition.

Further studies are now in progress to evaluate the potential of these Tentagel solid supports functionalized with saccharide-based macrocycles for analytical applications in different solvent systems or also at the interface between water and immiscible organic solvents, in analogy with recent investigations carried out on ion-exchange resins,[17] chemically modified silica gels[18] or polystyrene.[19] Applications to chiral discrimination are also being examined.

Conclusions

In principle, grafting of a specific host molecule onto a solid support may significantly affect its behaviour and binding properties. However, given the specific features of Tentagel resin, a polystyrene matrix copolymerized with highly flexible and hydrophilic PEG chains, macrocycles immobilized on such a solid support can be assumed to exhibit almost unaltered complexation abilities. Within this scenario, we have developed a synthetic protocol to obtain Tentagel resins functionalized with novel cyclic oligosaccharide analogues (CyPLOS) bearing phosphodiester linkages as the interglycosidic bonds, here proposed as synthetic platforms for potential cation scavenging. Stepwise solid-phase synthesis was adopted here to build the macrocycle, by growing the linear dimer first and then cyclizing it onto the solid support. The key point in our synthetic strategy was the selection of suitably derivatized sugar phosphoramidite building blocks, with the secondary hydroxy functions masked as TBDMS ethers. This proved to be an orthogonal protection with respect to the DMT ether, fully compatible with phosphoramidite and phosphotriester chemistry, used for the oligomerization and the cyclization process onto the solid support, respectively. Gel-phase ^{31}P NMR spectroscopy has been extensively used here to monitor the efficiency of the reactions carried out on the solid support. Interestingly, after the crucial cyclization reaction, ^{31}P NMR signals diagnostic of the P^V atom in an aryl-phosphodiester function (centered at ca. –2 ppm) were absent, with the concomitant appearance of two new signals at $\delta \approx$ –4 ppm, attributable to a chiral P^V atom in an aryl-phosphotriester bond. The obtained results point at nearly quantitative yields for the circularization of the linear disaccharide mimic, within the detection limit of the NMR technique. It was thus demonstrated that the presence of bulky, lipophilic appendages on the secondary 2- and 3-OH groups of the glucose monomer had no adverse effects on the final outcome of the crucial cyclization step. Sub-

sequently, optimization for the full deprotection of the macrocycle in the solid phase was carried out, to provide the desired solid support, functionalized with the cyclic oligosaccharide analogues. Where desired, either the fully deprotected or the TBDMS-protected cyclic molecules can be detached from the solid support.

Experimental Section

Abbreviations

Ac_2O = acetic anhydride; AcOEt = ethyl acetate; *t*BuOOH = *tert*-butyl hydroperoxide; DCA = dichloroacetic acid; DCM = dichloromethane; DCCI = *N*,*N*-dicyclohexylcarbodiimide; DIC = *N*,*N*-diisopropylcarbodiimide; DIEA = diisopropylethylamine; DMF = *N*,*N*-dimethylformamide; DMT = 4,4′-dimethoxytriphenylmethyl; Et_3SiH = triethylsilane; Et_3N = triethylamine; EtOH = ethanol; Fmoc = fluorenylmethoxycarbonyl; HOBt = *N*-hydroxybenzotriazole. MSNT = 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole; PTSA = *p*-toluenesulfonic acid; TBDMS = *tert*-butyldimethylsilyl; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

Materials and Methods: TLC analyses were carried out on silica gel plates from Merck (60, F254). Reaction products on TLC plates were viewed under UV light and then by treatment with a 10% $Ce(SO_4)_2/H_2SO_4$ aqueous solution. For column chromatography, silica gel from Merck (Kieselgel 40, 0.063–0.200 mm) was used. Tentagel® NH_2 (0.29 mmol g^{-1} of primary amino groups) was purchased from NovaBiochem. The solid support functionalizations were carried out in a short glass column (5 cm length, 1 cm i.d.) fitted with a sintered glass filter, a stopcock and a cap. The linear oligosaccharide chains were assembled on an Expedite Perseptive Biosystems DNA synthesizer, using phosphoramidite **9** as the building block.

HPLC analyses and purifications were performed on a Beckman System Gold instrument fitted with a UV detector module 166 and a Shimadzu Chromatopac C-R6A integrator. By HPLC analysis on a Nucleosil 100–5 C18 Supelco analytical column (250 × 4.6 mm, 5 μm), eluted with a linear gradient from 0 to 100% of CH_3CN in H_2O over 30 min, flow: 0.8 mL min^{-1}, detection at λ = 264 nm, all the synthesised compounds proved to be more than 98% pure. For the ESI MS analyses, a Waters Micromass ZQ instrument – fitted with an Electrospray source – was used in the positive and/or negative mode. NMR spectra were recorded on Bruker WM-400 or Varian Gemini 300 spectrometers. All the chemical shifts are expressed in ppm with respect to the residual solvent signal; *J* values are in Hz. The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = double doublet. ^{31}P NMR spectra have been registered using 85% H_3PO_4 as the external reference.

UV measurements were carried out on a Jasco V-530 UV spectrophotometer equipped with a Jasco ETC-505T temperature controller unit. The temperature was kept constant with a thermoelectrically controlled cell holder (JASCO PTC-348).

Synthesis of Phenyl 4-*O*-[(2-Cyanoethoxy)(diisopropylamino)phosphanyl]-6-*O*-(4,4′-dimethoxytriphenylmethyl)-2,3-di-*O*-(*tert*-butyldimethylsilyl)-β-D-glucopyranoside (9)

Synthesis of Derivative 6: Phenyl 4,6-benzylidene-β-D-glucopyranoside (1.4 g, 4 mmol), prepared in almost quantitative yields as previously reported,[12] was repeatedly coevaporated with anhydrous pyridine, dried under reduced pressure, dissolved in anhydrous DMF (10 mL) and treated with *tert*-butyldimethylsilyl chloride (3.0 g, 5 equiv.) and imidazole (1.8 g, 6.8 equiv.). The mixture was left whilst stirring at room temp. and monitored by TLC with $CHCl_3/CH_3OH$ 98:2 (v/v) as the eluent system. After 48 h the reaction mixture was diluted with $CHCl_3$, the organic phase was washed three times with $NaHCO_3$ (5%), filtered and concentrated under reduced pressure. The resulting crude product was purified on a silica gel column eluted with benzene/petroleum ether 9:1 (v/v), which gave 1.98 g of target compound **6** (87% yields).

Compound 6: White amorphous solid. R_f = 0.8 [benzene/AcOEt 98:2 (v/v)]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46–6.97 (complex signals, 10 H, aromatic H), 5.44 (s, 1 H, Ph–CH), 5.12 (d, *J* = 9.5 Hz, 1 H, 1-H), 4.31 (dd, *J* = 3.0 and 12 Hz, 1 H, 4-H), 3.92–3.55 (overlapped signals, 5 H, 2-H, 3-H, 5-H and 6-H_2), 0.88 and 0.82 (2 s, 9 H each, 2× *tert*-butyl groups of the two TBDMS moieties), 0.19, 0.14, 0.046 and 0.005 (4 s, 3 H each, 2× methyl groups of the two TBDMS moieties) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.6, 137.3, 129.5, 129.2, 128.2, 126.6, 122.3 and 116.2 (aromatic C), 102.5 (Ph-CH), 100.2 (C-1), 81.7 (C-5), 76.0 (C-4), 69.1 (C-2 and C-3), 66.0 (C-6), 26.2 (CH_3 of the *tert*-butyl groups), 18.4 and 18.2 (quaternary C of the *tert*-butyl groups), –3.0 and –3.7 (2× methyl groups of the TBDMS groups) ppm. ESI-MS (positive ions): calculated for $C_{31}H_{48}O_6Si_2$: 572.884; found: 573.59 $[M + H]^+$, 595.45 $[M + Na]^+$, 611.40 $(M + K]^+$.

Synthesis of Derivative 7: Compound **6** (1.6 g, 2.8 mmol) was treated with a TFA/DCM/H_2O solution [1:10:0.5 (v/v/v), 3 mL]. The reaction was left at 0 °C and monitored by TLC using benzene/AcOEt 98:2 (v/v) as the eluent system. After 4 h, the reaction mixture was diluted with DCM and the organic phase was washed twice with water, filtered and concentrated. The resulting crude product was purified on a silica gel column, eluted with benzene containing growing volumes of AcOEt (from 0 to 20%), which gave 1.1 g of pure **7** (82% yields).

Compound 7: White amorphous solid. R_f = 0.4 [benzene/AcOEt 95:5 (v/v)]. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35–6.96 (complex signals, 5 H, aromatic H), 5.08 (d, *J* = 6.0 Hz, 1 H, 1-H), 3.82 (m, 2 H, 6-H_2), 3.71 (overlapped signals, 2 H, 2-H and 3-H), 3.57 (overlapped signals, 2 H, 4-H and 5-H), 2.49 (d, *J* = 4.0 Hz, 1 H, 4-OH), 1.93 (t, 1 H, 6-OH), 0.99 and 0.87 (2 s, 9 H each, 2× *tert*-butyl groups of the two TBDMS moieties), 0.20, 0.16, 0.13 and 0.010 (4 s, 3 H each, 2× methyl groups of the two TBDMS moieties) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.3, 129.5, 122.1, 115.6 (aromatic C), 99.1 (C-1), 77.0 (C-5), 75.9 (C-3), 74.2 (C-2), 70.9 (C-4), 62.7 (C-6), 26.1 (CH_3 of the *tert*-butyl groups), 18.2 and 18.1 (quaternary C of the *tert*-butyl groups), –3.2, –3.3, –3.8 and –3.9 (2 methyl groups of the TBDMS groups) ppm. ESI-MS (positive ions): calculated for $C_{24}H_{44}O_6Si_2$: 484.268; found: 507.39 $[M + Na]^+$, 523.48 $[M + K]^+$.

Synthesis of Derivative 8: Compound **7** (1.0 g, 2.06 mmol), dissolved in anhydrous pyridine (9 mL), was treated with DMTCl (850 mg, 1.2 equiv.). The reaction, left whilst stirring overnight at room temp., was then quenched by addition of CH_3OH and concentrated under reduced pressure. The crude reaction product was diluted with $CHCl_3$ and the organic phase was washed twice with water, filtered and concentrated. The crude product was then purified on a silica gel column eluting with cyclohexane, treated with a few drops of pyridine, containing increasing amounts of AcOEt (from 2 to 20%), to yield 1.5 g of pure target compound **8** (92% yields).

Compound 8: White amorphous solid. R_f = 0.5 [cyclohexane/AcOEt 9:1 (v/v)]. ^1H NMR (C_6D_6, 400 MHz): δ = 7.77–6.76 (complex signals, 18 H, aromatic H), 5.02 (d, *J* = 7.5 Hz, 1 H, 1-H), 3.99 (dd,

J = 7.5 and 8.0 Hz, 1 H, 2-H), 3.76 (m, 1 H, 5-H), 3.66 (m, 2 H, 6-H_2), 3.58 (overlapped signals, 2 H, 3-H and 4-H), 3.38 and 3.37 (2 s, 3 H each, 2× OCH_3 of DMT group), 1.16 and 1.15 (2 s, 9 H each, 2× *tert*-butyl groups of the two TBDMS moieties), 0.45, 0.39, 0.37 and 0.36 (4 s, 3 H each, 4× methyl groups of the two TBDMS moieties) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.3, 144.8, 135.9, 130.0, 129.3, 128.3, 128.1, 127.3, 126.7, 121.8, 116.1 and 113.0 (aromatic C), 99.4 (C-1), 86.2 (quaternary C of the DMT group), 78.2 (C-5), 74.8 and 74.7 (C-2 and C-3), 72.1 (C-4), 64.1 (C-6), 55.1 (OCH_3 of the DMT group), 26.2 (CH_3 of the *tert*-butyl group), 18.3 and 18.4 (quaternary C of the *tert*-butyl groups), –3.0 and –3.5 (CH_3 groups directly linked to Si in the TBDMS moieties) ppm. ESI-MS (positive ions): calculated for $C_{45}H_{62}O_8Si_2$: 786.398; found 809.56 $[M + Na]^+$, 826.51 $[M + K]^+$.

Synthesis of Derivative 9: DIEA (940 μL, 5.34 mmol) and 2-cyanoethyl *N*,*N*-diisopropyl-chlorophosphoramidite (640 μL, 2.94 mmol, 3.2 equiv.) were sequentially added to compound **8** (700 mg, 0.89 mmol), dissolved in anhydrous DCM (6 mL). The reaction, monitored by TLC using cyclohexane/AcOEt 9:1 (v/v) as the eluent system, was left 1 h at room temperature. Then the mixture was diluted with AcOEt and the organic phase was washed with a saturated NaCl aq. solution, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified on a silica gel column, eluted with cyclohexane (with a few drops of triethylamine) containing increasing volumes of AcOEt (from 3 to 10%), which provided 780 mg (0.79 mmol) of pure **9** (90% yields).

Compound 9 (as a diastereomeric mixture): White amorphous solid. R_f = 0.4 [cyclohexane/AcOEt 9:1 (v/v)]. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46–6.74 (complex signals, 36 H, aromatic H), 5.31 and 5.30 (2 d, J = 7.0 and 7.0 Hz, 2 H, 2× 1-H), 4.02 (m, 2 H, 2× 2-H), 3.90 (m, 4 H, 2× 4-H and 2× 5-H), 3.88 (m, 2 H, 2× 3-H), 3.77 (s, 12 H, 2× OCH_3 of the DMT group), 3.84–3.67 (m, 4 H, OCH_2CH_2CN), 3.60–3.50 [m, 4 H, $CH(CH_3)_2$], 3.35–3.23 (m, 4 H, 6-H_2), 2.57–2.41 (m, 4 H, OCH_2CH_2CN), 1.19–1.12 [overlapped signals, 24 H, $CH(CH_3)_2$], 0.88 and 0.80 (2 s, 18 H each, 2× *tert*-butyl groups of the two TBDMS moieties), 0.17, 0.15, 0.12, 0.09, 0.08, 0.07, –0.05 and –0.06 (4 s, 24 H, 4× methyl groups of the two TBDMS moieties) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.3, 157.1, 145.0, 136.2, 136.1, 123.0, 129.2, 128.2, 128.1, 127.6, 126.8, 126.5, 121.7, 121.6, 116.1 and 112.9 (aromatic C), 117.5 and 117.4 (CN), 100.1 (C-1), 86.0 (quaternary C of the DMT group), 79.2 and 79.0 (C-4), 77.5 and 77.4 (C-5), 75.6, 75.4, 70.7 and 70.6 (C-2 and C-3), 64.8 (C-6), 58.6, 58.4, 58.1 and 58.0 (OCH_2CH_2CN), 55.0 (OCH_3 of the DMT group), 43.15, 43.07, 43.06 and 42.95 $[CH(CH_3)_2]$; 25.9, 25.8, 25.7 and 24.4 [CH_3 of the *tert*-butyl group and $CH(CH_3)_2$], 20.1, 20.0, 18.8 and 18.7 (quaternary C of the *tert*-butyl group and OCH_2CH_2CN), –4.1, –4.2, –4.4, –4.6 and –4.9 (CH_3 groups of the TBDMS moieties) ppm. ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ = 152.4 and 150.6 ppm. ESI-MS (positive ions): calculated for $C_{54}H_{79}N_2O_9PSi_2$: 986.506; found: 987.66 $[M + H]^+$, 1009.79 $[M + Na]^+$, 1025.70 $[M + K]^+$.

Synthesis of Solid Support 18. Functionalization of the Solid Support with Phosphoramidite Derivative 9

Synthesis of Support 11: TentaGel-NH_2 resin (500 mg, 0.14 mmol), swollen in anhydrous DCM, was treated with 2-(3-chloro-4-hydroxyphenyl)acetic acid (**10**, 270 mg, 1.45 mmol), DIC (220 μL, 1.45 mmol), DIEA (250 μL, 1.45 mmol) and HOBt (200 mg, 1.45 mmol) in anhydrous pyridine (4 mL). The reaction was left overnight at room temp. whilst stirring. The obtained support was then repeatedly washed with pyridine, DCM, MeOH and CH_3CN, treated with Ac_2O/pyridine 1:1 (v/v), 400 μL total volume, for 1 h at r.t. and then with aq. ammonia for 1 h at 50 °C and finally exhaustively washed with solvents and dried under reduced pressure.

Synthesis of Functionalized Support 13: Phosphoramidite **9** (280 mg, 0.29 mmol), dissolved in a tetrazole solution (0.45 M, 300 μL), was added to support **11** (200 mg). The reaction was left for 1 h at room temp. whilst stirring and, after repeated washings with CH_3CN, the resin was oxidized with an iodine solution in THF/H_2O/pyridine (0.1 M, 3 treatments of 300 μL, 5 min each), furnishing support **12**. The efficiency of incorporation of the first saccharide residue was spectrophotometrically evaluated by UV measurements of the DMT cation at λ = 498 nm (ε = 71700 cm^{-1} M^{-1}), released by acidic treatment ($HClO_4$/EtOH 3:2, v/v) of weighed aliquots of the dried resin. The obtained functionalization was 0.16 mequiv. g^{-1} on average, corresponding to 65% incorporation of derivative **9**. Subsequently, the support was capped by treatment with Ac_2O in pyridine (1:1, v/v, 400 μL total volume, 1 h). Next, support **12** was treated with Et_3N/pyridine (1:1, v/v, 400 μL total volume, 3 treatments, 6 h each) at room temp. in order to remove the 2-cyanoethyl group, to afford the desired **13**. Spectrophotometric tests were then carried out to check that no losses in functionalization had occurred due to this treatment. After repeated washings, the resin was dried under reduced pressure, suspended in $CDCl_3$ and analysed by ^{31}P NMR spectroscopy, which confirmed the complete conversion of the phosphotriester into phosphodiester function.

Solid Support 12: ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ = –3.98 ppm.

Solid Support 13: ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ = –2.52 ppm.

Synthesis of Linear Precursor 15: Solid support **13** (200 mg, 0.02 mequiv.), swollen in anhydrous DCM, was treated with DCA in CH_2Cl_2 (2%, 5 treatments of 300 μL each, 3 min). Subsequently, the resin was exhaustively washed with pyridine, DCM and anhydrous CH_3CN and treated with phosphoramidite **9** (60 mg, 3 equiv.), dissolved in a tetrazole solution in anhydrous CH_3CN (0.45 M, 500 μL). The support, left for 1.5 h at room temp., was then washed with CH_3CN, and then treated with an I_2 solution in pyridine/H_2O/THF (0.1 M, 3 treatments of 300 μL, 5 min each). The support, repeatedly washed with CH_3CN, was dried under reduced pressure. The efficiency of incorporation of the second glycosidic residue in the solid phase, monitored by UV measurements at λ = 498 nm (ε = 71700 cm^{-1} M^{-1}) of the DMT cation released by acidic treatments [$HClO_4$/EtOH 6:4 (v/v)] on weighed amounts of the resin, was 0.10 mequiv. g^{-1}, corresponding to almost quantitative incorporation of derivative **9**. After a capping treatment with Ac_2O in pyridine (1:1, v/v, 1 h at room temp.), the resulting support **14** was detritylated by the procedure reported above for **13** and then exhaustively washed with DCM and CH_3CN, giving support **15**.

Synthesis of Support 17: Three treatments with MSNT (150 mg each, 0.51 mmol, 25 equiv., 3× 6 h) dissolved in pyridine (1.5 mL) were performed at room temp. on support **15** (100 mg), previously swollen in anhydrous pyridine, whilst stirring, to afford support **16**. After repeated washings with pyridine and CH_3CN, the resin was then treated with Et_3N/Py (1:1, v/v) for 3 h whilst stirring, yielding desired support **17**. After repeated washings with solvents the resin was dried, suspended in $CDCl_3$ and analysed by ^{31}P NMR spectroscopy, which confirmed that the reaction had gone to completion.

Solid Support 16: ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ = 0.61, –0.21, –4.17 and –4.32 ppm.

Solid Support 17: ^{31}P NMR ($CDCl_3$, 161.98 MHz): δ = 2.08, 0.61, –3.52 and –4.36 ppm.

Synthesis of Support 18: Resin **17**, bearing the protected cyclic dimer, was then subjected to several tests to optimize the full removal of the TBDMS groups in the solid phase, varying the solvent, temperature, excess and nature of the desilylating agent. In order to test the efficiency of the adopted desilylating systems, after each test, samples (30 mg) of the resins were treated with 1,1,3,3-tetramethylguanidinium 2-nitrobenzaldoximate solution (0.2 M, 500 μL) in H_2O/dioxane (1:1, v/v) for 12 h at room temp., and the obtained eluates were then analysed by ^1H NMR and ESI-MS data. Full TBDMS removal was achieved by suspending the resin in THF (100 μL) and $Et_3N{\cdot}3HF$ (300 μL, 1.8 mmol, 1200 equiv.) and leaving it for 12 h at 50 °C. Under these conditions, the cyclic dimer **1**[12] was exclusively detached from the solid support by benzaldoximate treatment and was found to be identical to an authentic, independently synthesized sample.

Synthesis of TBDMS-Protected Cyclic Dimer 19: A sample (30 mg) of functionalized resin **17** was treated with a solution of 1,1,3,3-tetramethylguanidinium 2-nitrobenzaldoximate (0.2 M, 500 μL) in H_2O/dioxane (1:1, v/v) for 12 h at room temp. The detached material, after gel filtration chromatography on a Sephadex G25 column eluted with H_2O/EtOH 1:1 (v/v), was then analysed by HPLC on an analytical RP18 column (Nucleosil 100–5 C18 Supelco, 4.6 × 250 mm, 5 μm). By using a gradient from 30% to 100% of CH_3CN in TEAB (0.1 M, pH 7.0) over 15 min, flow: 0.8 mL min^{-1}, detection at λ = 265 nm, a unique main peak was observed in the mixture, accounting for more than 90% of the total integrated area, with retention time 17.46 min. This, collected, gave 2 mg (40% overall yields calculated from support **13**) of pure target compound **19**.

Compound 19, Triethylammonium Salt: ^1H NMR (CD_3OD, 400 MHz): δ = 7.29–6.97 (complex signals, 5 H, aromatic H), 5.17 (d, J = 8.0 Hz, 1 H, 1-H), 4.17–3.98 (overlapped signals, 3 H, 4-H and 6-H_2), 3.85 (t, J = 8.0 and 8.0 Hz, 1 H, 3-H), 3.75 (m, 1 H, 5-H), 3.69 (t, J = 8.0 and 8.0 Hz, 1 H, 2-H), 3.21 [q, 6 H, $(CH_3CH_2)_3NH]^+$, 1.32 [t, 9 H, $(CH_3CH_2)_3NH]^+$, 0.97 and 0.87 (2 s, 9 H each, *tert*-butyl groups of the TBDMS moieties), 0.23, 0.19, 0.17 and 0.15 (4 s, 3 H each, methyl groups of the TBDMS moieties) ppm. ^{31}P NMR (CD_3OD, 161.98 MHz): δ = 2.66 ppm. UV (CH_3OH): λ_{max} = 267 nm. ESI-MS (negative ions): calculated for $C_{48}H_{86}O_{16}Si_4P_2$: 1093.480; found 545.42 $(M - 2H)^{2-}$; 1092.84 $[M - H]^-$.

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[15] In our previous paper, we first coupled the bifunctional linker 2-(3-chloro-4-hydroxyphenyl)acetic acid (**10**) with the 4-phosphoramidite sugar building block in solution, and then treated the resulting adduct with the TentaGel-NH_2 solid support. Here this procedure was simplified by directly attaching bifunctional linker **10** to the resin by classical peptide coupling proto-

cols, as also reported in ref.[13a], and by then treating phenolic resin **11** with sugar building block **9**. On comparing the two routes for the synthesis of cyclic dimer **1**, no significant differences were found either in yields or in purity of the released material.

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