JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Toward a Molecular Lego Approach for the Diversity-Oriented Synthesis of Cyclodextrin Analogues Designed as Scaffolds for Multivalent Systems

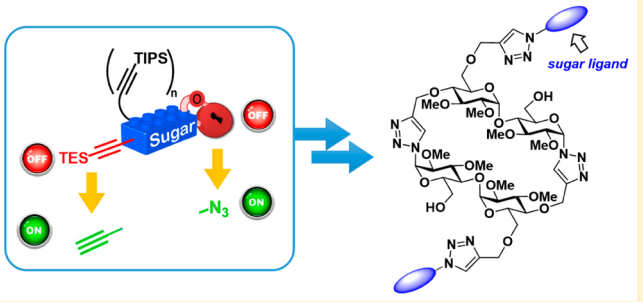
Mathieu L. Lepage,[†] Jérémy P. Schneider,[†] Anne Bodlenner,[†] and Philippe Compain*[,†,‡]

[†]Laboratoire de Synthèse Organique et Molécules Bioactives, Université de Strasbourg/CNRS (UMR 7509), Ecole Européenne de Chimie, Polymères et Matériaux, 25 rue Becquerel, 67087 Strasbourg, France

[‡]Institut Universitaire de France, 103 Bd Saint-Michel, 75005 Paris, France

Supporting Information

ABSTRACT: A modular strategy has been developed to access a diversity of cyclic and acyclic oligosaccharide analogues designed as prefunctionalized scaffolds for the synthesis of multivalent ligands. This convergent approach is based on bifunctional sugar building blocks with two temporarily masked functionalities that can be orthogonally activated to perform Cu(I)-catalyzed azide−alkyne cycloaddition reactions (CuAAC). The reducing end is activated as a glycosyl azide and masked as a 1,6-anhydro sugar, while the nonreducing end is activated as a free alkyne and masked as a triethylsilyl-alkyne. Following a cyclooligomerization approach, the first examples of close analogues of cyclodextrins composed of D-glucose residues and triazole units bound together through α-(1,4) linkages were obtained. The cycloglucopyranoside analogue containing four sugar units was used as a template to prepare multivalent systems displaying a protected D-mannose derivative or an iminosugar by way of CuAAC. On the other hand, the modular approach led to acyclic alkyne-functionalized scaffolds of a controlled size that were used to synthesize multivalent iminosugars.



INTRODUCTION

The multivalent concept represents an appealing strategy for designing ligands and drugs that modulate a biological response.[1] Multivalency is, for example, of paramount importance in numerous intercellular recognition events based on the recognition of carbohydrates by multivalent carbohydrate-binding proteins (lectins).[2] In this case, the cumulative use of individually weak carbohydrate epitope−lectin interactions can lead to highly specific binding, a phenomenon referred to as the cluster or multivalent effect.[3] By harnessing the power of multivalency, chemists have been able to disclose synthetic glycoclusters exhibiting impressive affinity enhancements up to 6 orders of magnitude over the corresponding monovalent lectin ligands.[4,5] Recently, the interest of multivalent design was further extended to carbohydrate-processing enzymes.[6−8] It was thus shown, rather counterintuitively, that strong inhibitory multivalent effects could be obtained with glycosidases even though they usually display a single substrate-binding site.[7,8] Indeed, the major mechanism underlying the "intrinsic" multivalent effect, the chelate effect, involves the binding of multivalent ligands with oligomeric receptors.[9] In spite of the impressive progress made in the past decades, the design of multivalent ligands with optimized biological properties still remains a difficult challenge considering, *inter alia*, the complexity of the multivalent ligand−receptor binding mechanisms and the possible lack of three-dimensional data for the targeted proteins. In the absence of decisive structural design criteria, a diversity-oriented strategy based on the screening of cluster libraries may represent a valuable approach.[10] Such a method depends, however, on the possibility to easily access a large diversity of clickable scaffolds. The central scaffold is indeed at the core of the design of a multimeric ligand as it defines its size, shape, and flexibility, as well as the number, the presentation, and the density of binding epitopes. Despite its apparent structural diversity, from aromatic molecules to macrocycles and dendrimers,[11] the pool of scaffolds available to construct well-defined multivalent systems is intrinsically limited. Additional issues have also to be faced if one considers readily synthetic accessibility and the challenge raised by the selective functionalization of polysubstituted scaffold precursors. A typical example is found with cyclodextrins (CDs) that are cyclic oligosaccharides made of five or more α-D-glucopyranoside units bound to each other through $\alpha(1\rightarrow4)$ glycosidic bonds, creating a cone-shaped structure. CDs hold many advantages as biocompatible cores to build multivalent constructs.[12,13] For example, regioselective functionalization of the hydroxyl groups present on their primary and secondary faces offers unique opportunities to probe the influence of binding epitope spatial orientation on biological activity. One of the main drawbacks associated with such scaffolds is the limited number of possible combinations considering that very few CDs are

Received: August 19, 2015
Published: October 6, 2015

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

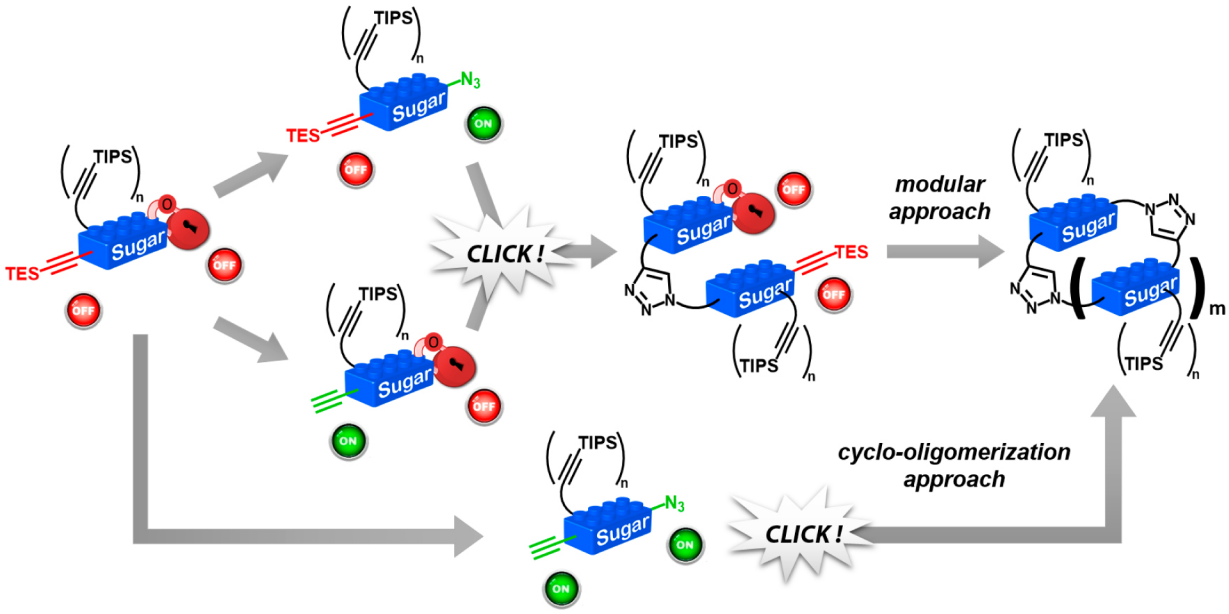


Figure 1. Overview of the modular synthetic approach to prefunctionalized scaffolds.

commercially available and that selective functionalization of a scaffold bearing several identical functional groups is always a difficult challenge.[14,15] In connection with our recent studies on the multivalent effect in glycosidase inhibition,[7,16] we have designed a convergent access to a diversity of cores having the structural advantages of CDs within the context of multivalency. Following a molecular Lego approach, key prefunctionalized carbohydrate building blocks are used as modules to construct linear or cyclic scaffolds (Figure 1). One of the main advantages of this approach is that the scaffolds are easily functionalized—for future ligand attachment—at the stage of more simple mono- or disaccharide blocks according to well-mastered synthetic procedures. Key structural elements including fluorescent probes, recognition markers, or cell-penetrating agents may thus be easily added to the multivalent systems at different stages of the synthesis. To overcome lengthy synthetic pathways based on classical glycosylation chemistry, Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC)[17−19] has been chosen to link the building blocks. This methodology indeed circumvents the problems of iterative stereoselectivity in oligosaccharide synthesis and the fine-tuning of reaction conditions for every individual glycosylation step.[20] The efficiency of the CuAAC process is also exploited for the simultaneous introduction of the azido-armed ligands at the end of the cluster synthesis. Herein, we report the preliminary studies of the feasibility of the above-described convergent strategy using representative building blocks and following either a direct approach (cyclooligomerization) or a more controlled sequential linear oligomerization process, followed by a macrocyclization. All the key steps of the cyclooligomerization approach and the controlled building of linear oligomers have been validated on a model disaccharide building block, leading to the first examples of a new class of glycoclusters.

RESULTS AND DISCUSSION

Synthetic Design. Our strategy is based on the synthesis of bifunctional sugar building blocks with temporarily masked functionalities that can be orthogonally activated to perform CuAAC reactions (Figure 1). At one end, the "anomeric" position will be activated as an α-glycosyl azide ("**ON**") and masked as a 1,6-anhydro sugar ("**OFF**"). This reaction, recently developed in our group having in mind the herein presented Lego strategy,[21] has the advantage of releasing a differentiated primary hydroxyl group at C-6 in a late stage of the synthesis for post-functionalization purposes. The other end at C-4 will be activated as a terminal free alkyne ("**ON**") and masked as a TES (triethylsilyl)-alkyne ("**OFF**").

Once synthesized, these prefunctionalized modules could be regioselectively turned **ON** at one of their extremities to give two "ready-to-click" units in a divergent manner. Through CuAAC coupling, they would combine into a new deactivated entity which could undergo successive activations, iterative couplings—with an activated unit module or an activated oligomer—and finally a macrocylization. In this way, the careful control of the oligomerization would lead to tailored *neo*-CDs of the desired size, and also to the corresponding acyclic analogues. In a second approach, direct access to symmetrical *neo*-CDs could be obtained via cyclooligomerization by simultaneously turning **ON** both extremities of the sugar module.

To mimic the CD structure, an analogue should possess two different polyhydroxylated faces and be strictly composed of D-*gluco* saccharides and triazole units, bound together through α-(1,4) linkages. Several groups have already described macrocycles incorporating both carbohydrate and triazole moieties.[22] Furthermore, results published by the groups of Crich[23] and Dondoni[24] suggest that the replacement of a carbohydrate unit by a triazole moiety preserves the orientation and the overall length of oligosaccharide chains. The most widely used strategy consists of the cyclooligomerization of bifunctional blocks, i.e., bearing both an azide and a terminal alkyne. Following this approach, the closest structure to a CD was obtained by the group of Gin,[25] although in a D-*manno* configuration. In a general manner, the cyclooligomerization process appears to be very substrate-dependent and affords mixtures of (cyclo)oligomers of different sizes, whose purification remains tricky. Alternatively, the group of Dondoni and Marra[26] reported an iterative, more controlled, step-by-step synthesis of α-(1,6) bound cyclooligosaccharides. Having in mind the idea of building *neo*-CDs from bifunctional modules having two extremities able to be

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

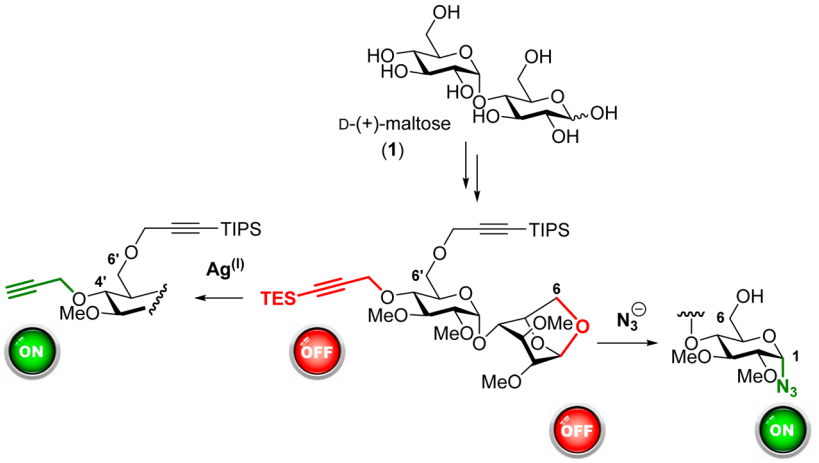


Figure 2. Key activation steps of the modular synthetic approach to prefunctionalized scaffolds.

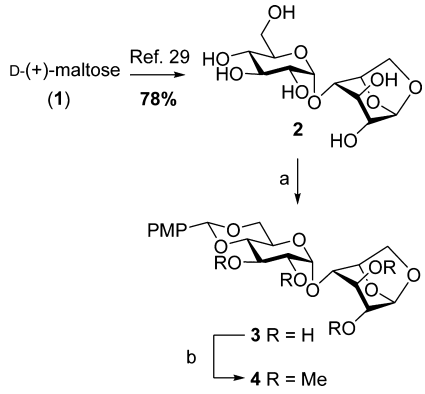
orthogonally turned **ON**, we have designed a joint strategy that could proceed either through cyclooligomerization or through iterative coupling, followed by macrocyclization. We chose to work first with the inexpensive disaccharide D-(+)-maltose (Figure 2), which presents the advantage of being reasonably easy to differentiate while allowing us to quickly reach the size of native CDs. This maltose unit should bear an α-azide at its reducing end (C-1) and a propargyl group at its nonreducing extremity (C-4′, Figure 2). In a first phase of our study, we decided to limit the prefunctionalization of the *neo*-CD and the "secondary face" was thus blocked by methoxy groups to decrease the polarity of the modules.

Beyond the inter- and intramolecular CuAAC reactions, two of the key steps of our strategy lie in the selective activation of both ends of the bifunctional building blocks (Figure 2). One of the crucial points is, in particular, to differentiate the different alkynes present in the prefunctionalized sugar building blocks. These functional groups have indeed to be activated independently for the two types of CuAAC reactions: the ones used to construct the scaffold, and the ones used to introduce the azido-armed ligands. This requirement could be achieved by using TES (triethylsilyl)- and TIPS (triisopropylsilyl)-protected propargyl ethers. The groups of Pale[27] and Aucagne[28] have indeed shown that TMS- and TES-alkynes could be deprotected in the presence of terminal TIPS-alkyne groups using silver(I) salts. By analogy with classical oligosaccharide synthetic strategies, the TIPS groups act as permanent protecting groups that are unmasked before the late introduction of the azido ligands by CuAAC reactions.

Scaffold Synthesis. Maltosan **2** was synthesized from D-(+)-maltose (**1**) following conditions adapted from those of Shoda et al.[29] The *p*-methoxyphenyl benzylidene **3** was prepared under harsh conditions by refluxing under vacuum a slightly acidic mixture of maltosan **2** and *p*-methoxybenzaldehyde dimethyl acetal in DMF. The remaining hydroxyl groups were then blocked by a quantitative methylation to give **4** (Scheme 1).

The reductive opening of the benzylidene acetal was at first carried out under conditions reported by Vásquez et al.[30] A commercial solution of DIBAL-H was added dropwise onto a solution of **4** in CH_2Cl_2 (Scheme 2). The reaction was found to proceed in high yields but with unsatisfactory regioselectivity, even at low temperature (−78 °C) and with careful addition. Furthermore, the ratio between the two regioisomers, which were not separable by silica gel chromatography in our hands,

Scheme 1[a]



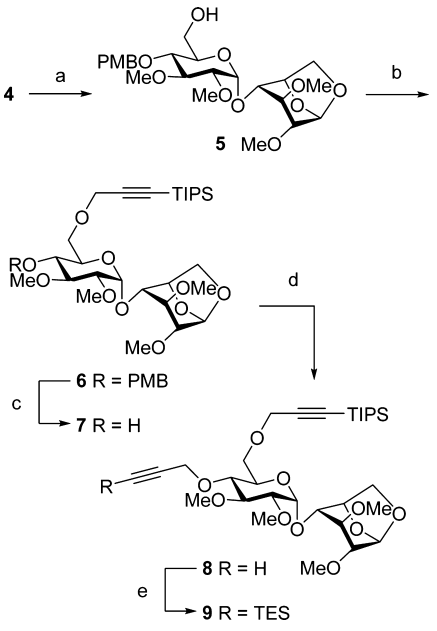
[a]Reagents and conditions: (a) PMP-CH(OMe)$_2$ (1.5 equiv), Amberlite IR-120 (H^+), DMF, 70 °C, 0.05 bar, 88%; (b) NaH (6 equiv), MeI (6 equiv), DMF, −10 to 15 °C, 99%.

was not reproducible. As a successful alternative, the reverse addition at room temperature of a solution of **4** in CH_2Cl_2 onto an excess of DIBAL-H afforded the 6′-hydroxyl regioisomer **5** in high yield and with complete regioselectivity. The primary alcohol **5** was then quantitatively alkylated with TIPS-propargyl bromide, and the PMB ether **6** was smoothly deprotected with DDQ to give the secondary alcohol **7** in good yield. Propargylation of compound **7** under Williamson conditions to give **8** proved difficult on a 1 g scale. After optimization studies, we found, fortuitously, that the reaction required the addition of a catalytic amount of methanol (10 mol %) since no conversion was observed in its absence, even after prolonged reaction times. Finally, the terminal alkyne was quantitatively protected with a triethylsilyl group under strong basic conditions to afford **9**. This synthetic sequence provided the first prefunctionalized building-block models: compound **9**, deactivated at both ends (**OFF-OFF**), and compound **8**, deactivated at the reducing end (**ON-OFF**).

Access to bifunctional module **10** activated at C-1 (**OFF-ON**) was then performed by $TMSN_3$ ring-opening of 1,6-anhydro sugar **9** mediated by TMSOTf according to a methodology recently reported by our group[21] (Scheme 3). However, under typical experimental conditions,[21] only glycosyl azides **11** resulting from the cleavage of the internal glycosidic linkage in **9** could be isolated in 70% yield. This glycosidic bond was found to be far

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 2[a]



[a]Reagents and conditions: (a) reverse addition on DIBAL-H (3 equiv), CH_2Cl_2, rt, 99%; (b) NaH (1.5 equiv), (triisopropylsilyl)propargyl bromide (2 equiv), THF, rt, 99%; (c) DDQ (1.25 equiv), CH_2Cl_2/H_2O 10:1, rt, 77%; (d) NaH (5 equiv), propargyl bromide (5 equiv), MeOH (10 mol %), THF, rt, 99%; (e) LiHMDS (2.5 equiv), TESCl (1.5 equiv), THF, 0 °C, 99%.

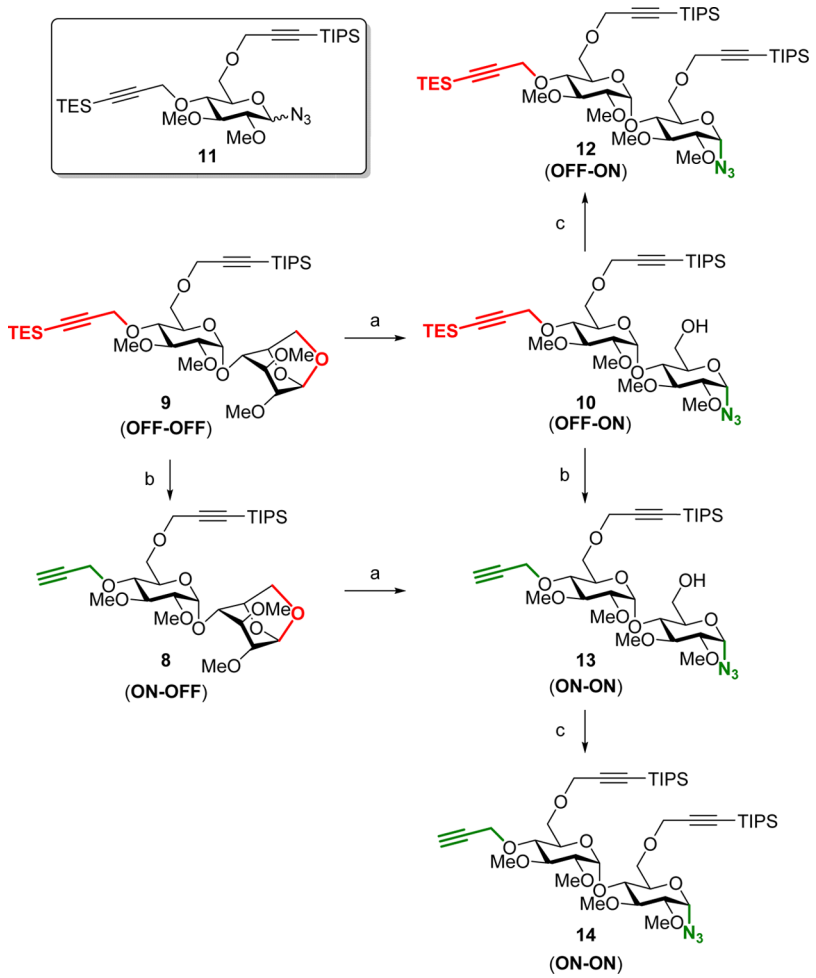
less labile in a much sterically hindered environment, as shown by the good yield obtained from the per-*O*-benzyl maltosan substrate.[21] To avoid this unwanted side reaction, a substoichiometric amount of triethylamine was used to buffer the acidity of the reaction medium. The quantity of base had to be finely tuned to prevent the degradation of the starting material without inhibiting the $TMSN_3$ ring-opening reaction. The optimum reaction conditions were obtained with the use of 0.3 equiv of triethylamine in solution in acetonitrile, with α-glycoside azide **10** being isolated in 77% yield after separation of the two anomers by flash chromatography on silica gel. It is important to note that the use of a slightly higher amount of base (0.4 equiv) led to no conversion at all, whereas the use of 0.25 equiv led to the formation of the monosaccharide **11** resulting from the internal glycosidic bond cleavage in **9**.

The crucial activation of the nonreducing end of α-glycosyl azide **10**, i.e., the selective deprotection of the TES-alkyne in the presence of the TIPS-alkyne group using $AgNO_3$,[27,28] was then evaluated (Scheme 3). To our delight, the silver(I)-promoted deprotection of TES-alkyne **10** proceeded in good yield to provide the desired disaccharide building block **13**, activated at both ends and prefunctionalized for the future installation of the ligand moieties by CuAAC. This compound could be also obtained in high yield following the reverse reaction order from 1,6-anhydro sugar **9**; the silver(I)-catalyzed deprotection provided terminal alkyne **8**, which was reacted under our optimized nucleophilic ring-opening conditions, affording building block **13** after separation of the two anomers by flash chromatography on silica gel. The primary hydroxyl group obtained after the TMSOTf-mediated azidation reaction can be easily functionalized, as shown by the propargylation of alcohols **10** and **13** providing the difunctionalized TIPS-protected alkyne modules **12** (activated at C-1) and **14** (diactivated), respectively (Scheme 3). Having in hand the model disaccharide building blocks **8**, **10**, and **12**−**14** displaying all possible combinations of activation, i.e., activated or not for click chemistry at one or both ends, we turned our attention to the construction of the scaffold architecture by CuAAC. Following a modular approach, the coupling step between the corresponding monoactivated modules, the α-glycosyl azides **10** or **12** and the terminal alkyne **8**, was performed under typical CuAAC reaction conditions (copper sulfate and sodium ascorbate system) to afford the *neo*-tetrasaccharides **15** and **16** in 60% and 82% yield, respectively (Scheme 4). As a prelude to a second intermolecular CuAAC reaction, the 1,6-anhydro sugars **15** and **16** have to be converted into the corresponding α-glycosyl azides. Unfortunately, under our typical azidation conditions and after many attempts, the TMSOTf-mediated opening of the anhydro bridge in **15** and **16** resulted either in no conversion of the starting material or in its degradation mainly via glycosidic cleavage when increasing the amounts of reagents. As described above, the decisive influence of the amount of triethylamine during the $TMSN_3$ ring-opening of 1,6-anhydro **9** suggests that the presence of a weakly basic triazole moiety in **15** and **16** could be sufficient to inhibit the reaction. Attempts to overcome this difficulty by protonation of the triazole ring using a diethyl ether solution saturated with $HCl_{(g)}$ prior to the azidation reaction had no success. While the triazole ring generated by CuAAC has numerous advantages in the context of click chemistry and bioconjugation, such as stability or low toxicity, the results obtained with compounds **15** and **16** indicate that, in some cases, its weak basicity may be a decisive issue for Lewis acid mediated reactions. The modular approach was nevertheless evaluated to access, by way of click ligation at the nonreducing extremity of the growing oligosaccharide analogues, prefunctionalized acyclic scaffolds of a controlled size. To this purpose, the *neo*-tetrasaccharide **16** was reacted with $AgNO_3$ to provide terminal alkyne **17**, which was obtained in 83% yield (Scheme 4). The elongation via CuAAC reaction between this compound and α-glycosyl azide **12** was found to be successful and afforded the expected hexasaccharide analogue **18**, showing the feasibility of the modular approach to access acyclic scaffolds functionalized with several protected alkyne groups. Removal of all silyl protecting groups with 12 equiv of TBAF afforded the linear *neo*-oligogosaccharide **19** bearing six alkynes available for further coupling via CuAAC.

To validate the final steps of our strategy and obtain the first "ready-to-be-grafted" cyclic scaffolds, we turned our attention to the cyclooligomerization approach starting from disaccharide **13** activated at both ends (Scheme 5). In the first place, several attempts using a mixture of copper iodide and DBU[25b] in a diluted solution of **13** in toluene did not allow isolation of the expected *neo*-CD **20**. The use of sodium ascorbate and copper sulfate were found to yield no improvements, leading to unwanted polymerization reactions. *Neo*-CDs were nevertheless obtained by adopting a reverse addition strategy. Careful dropwise addition of a diluted solution of **13** in THF/H_2O onto a concentrated solution of $CuSO_4$/sodium ascorbate provided, after a careful purification by flash chromatography on silica gel, the cyclodimerization product **20** along with the cyclotrimerization product **21** in 42% and 9% yield, respectively (Scheme 5). The formation of oligomers of higher molecular weight (cyclic or acyclic) seemed to be minimal, as suggested by TLC and ^1H NMR spectroscopy performed on the crude residue. The moderate yields observed may be partly explained by the high amounts of $CuSO_4$ and sodium ascorbate required for the process to be selective for the di- and trimeric species. This led to

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 3[a]



[a]Reagents and conditions: (a) $TMSN_3$ (10 equiv), TMSOTf (0.5 equiv), NEt_3 (0.3 equiv), CH_3CN, rt, 94% for **10** (from **9**) and ratio α/β = 4.5:1; 97% for **13** (from **8**) and ratio α/β = 4.1:1; (b) $AgNO_3$ (5 or 3 equiv), CH_2Cl_2/MeOH/water 7:4:1, rt, 89% for **8** (from **9**), 74% for **13** (from **10**); (c) NaH (3 equiv), (triisopropylsilyl)propargyl bromide (3 equiv), THF, rt, 71% for **12** (from **10**), 89% for **14** (from **13**).

precipitation of copper species during the reaction and further complicated the treatment of the workup process.

Extensive NMR analysis including HSQC, HMBC, and DOSY as well as high-resolution mass spectrometry were necessary to determine the structure of the compounds isolated after column chromatography. All cyclic oligomers indeed have different, but close, NMR spectra due to the presence of a symmetry axis (Figure 3) but can be distinguished from their exact mass and size. Linear oligomers and cyclic oligomers of the same number of building blocks have the same exact mass, but can be distinguished from NMR and/or IR analyses showing or not the presence of a terminal alkyne and an azide function. The high-resolution mass spectra ESI-HRMS are consistent with the target structures, as attested by the detection of major ions such as $[M + H]^+$ or $[M + Na]^+$ (see the Supporting Information). Since the fact that electrospray nebulization is a soft method of ionization producing intact molecular ions with minimal fragmentation and that higher masses were not detected, it can be concluded that the observed ions are the molecular ions from compounds **20** and **21**, respectively, and do not stem from heavier oligomers fragmentation. In addition to the presence of the protons and carbons of the triazoles identified by NMR, the analysis of the ^1H NMR spectra of pseudo CDs **20** and **21** shows an important downfield shift of the proton signals in the vicinity of the triazole ring (Figure 3). The absence of a residual signal around 2.4 ppm—as expected for acetylenic protons—and of the strong stretching vibration band of the azide function around 2100 cm^{-1} discards the corresponding acyclic isomers, which would have the same exact mass.

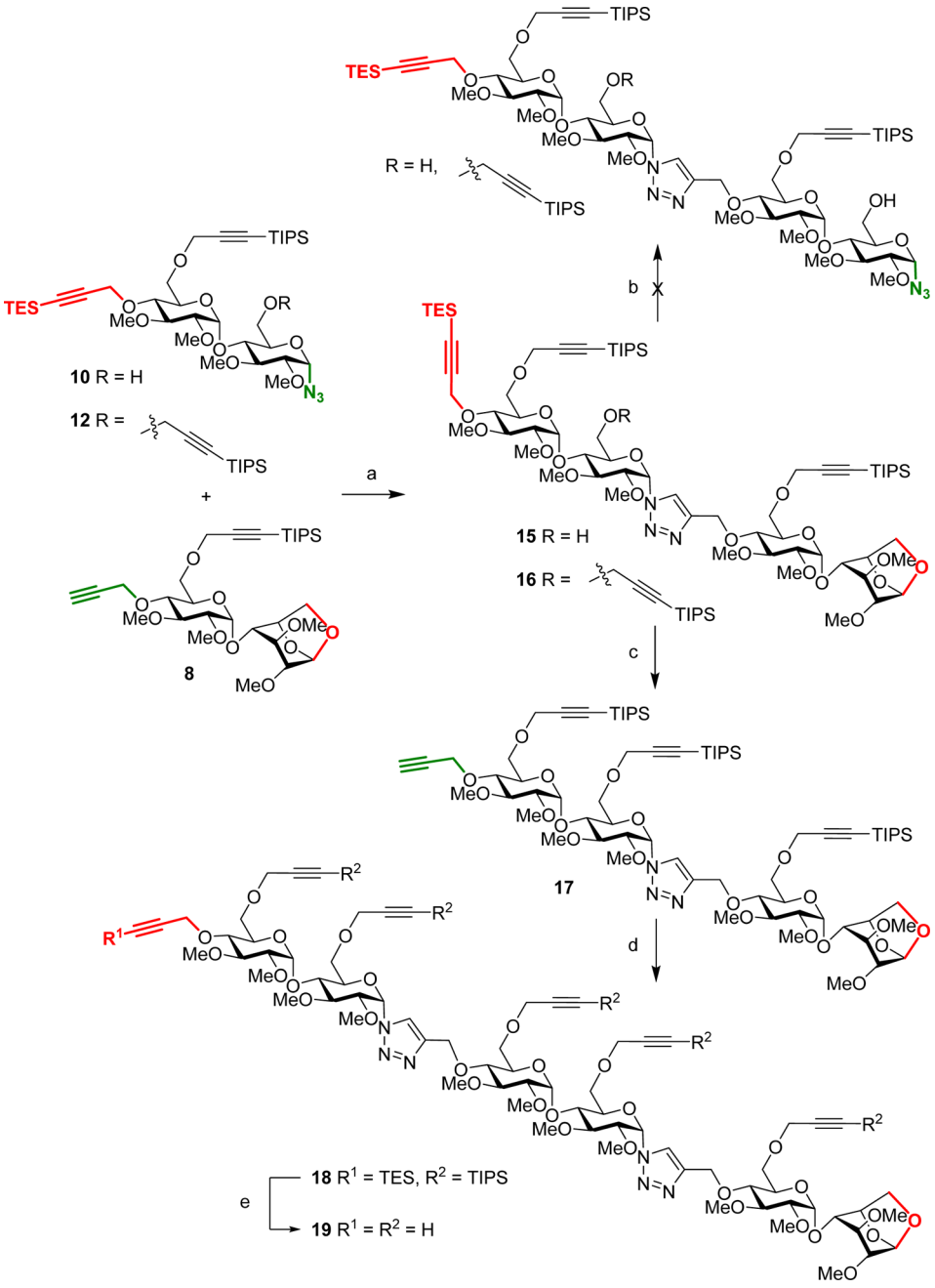
Furthermore, a DOSY-type NMR analysis enabled us to estimate the hydrodynamic diameter of cyclodimer **20**. The computation indicates a diameter ranging around 1 nm, which is consistent with values reported in the literature (1.46−1.75 nm for common CDs).[31]

To access "clickable" scaffolds, the TIPS protecting groups in **20** had then to be efficiently removed. The reaction of 4 equiv of silver fluoride[32] with **20** afforded terminal alkyne **22** in 75% yield (Scheme 5).

Cluster Synthesis. The final key step of our strategy that involved the grafting of azido-armed ligands onto the synthesized polyalkyne scaffolds by CuAAC was performed first with the orthogonally protected α-azidomannose **23**[21] (Scheme 6). D-Mannose and derivatives are indeed important ligands to target mannose-binding lectins, which play an important immune role by binding to carbohydrates on the surface of a wide range of pathogens such as viruses and bacteria.[33] In the presence of $CuSO_4$/sodium ascorbate, the microwave-mediated CuAAC proceeded smoothly in DMF/H_2O (1/1) and provided the

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 4[a]



[a]Reagents and conditions: (a) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, 60% (**15**), 82% (**16**); (b) (i) $HCl{\cdot}Et_2O$ (0 or 1 equiv), (ii) $TMSN_3$ (20 or 50 equiv), TMSOTf (0.4−10 equiv), CH_3CN, 20−100°C; (c) $AgNO_3$ (5 equiv), CH_2Cl_2/MeOH/H_2O 10:4:1, rt, 83%; (d) **12** (1.7 equiv), $CuSO_4{\cdot}5H_2O$ (0.5 equiv), sodium ascorbate (1 equiv), THF/H_2O 1:1, 40°C, 82%; (e) TBAF (12 equiv), THF, rt, 74%.

expected divalent mannose derivative **24** in 70% yield (Scheme 6). The two-step preparation of the more challenging divalent iminosugar cluster **26** was then performed from scaffold **22** and *N*-azidononyl-deoxynojirimycin derivative **25**.[16b] Based on a robust process developed in our group,[16] attachment of peracetylated iminosugar **25** on **22** via CuAAC reaction, followed by de-*O*-acetylation using an anion exchange resin, afforded the divalent iminosugar **27** (Scheme 6). It is noteworthy that the two primary OH groups in **20**−**22**, **24**, or **26** represent an opportunity to introduce additional structural elements of interest such as a fluorescent probe or a recognition marker.

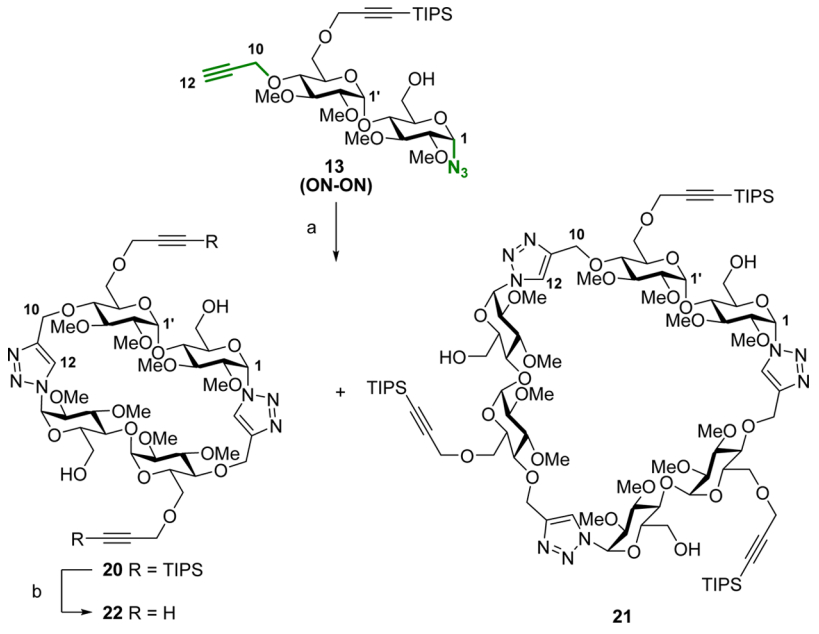
Similarly, linear polyalkyne *neo*-oligosaccharide **19** was used as a scaffold to afford hexavalent iminosugars cluster **28** (Scheme 7) by CuAAC using azidononyl-deoxynojirimycin **25**,[16b] validating thus our growth-controlled strategy for the synthesis of tunable linear multivalent systems.

CONCLUSION

In conclusion, we have reported the first preliminary study of the feasibility of a modular approach toward tailored prefunctionalized cyclodextrin analogues based on bifunctional carbohydrate building blocks that could be orthogonally activated at both ends for CuAAC. The two key steps involved in the preparation of the

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 5[a]



[a]Reagents and conditions: (a) $CuSO_4 \cdot 5H_2O$ (10 equiv), sodium ascorbate (20 equiv), THF/H_2O 1:1, rt, 42% (**20**), 9% (**21**); (b) AgF (4 equiv), CH_3CN, rt, 75%.

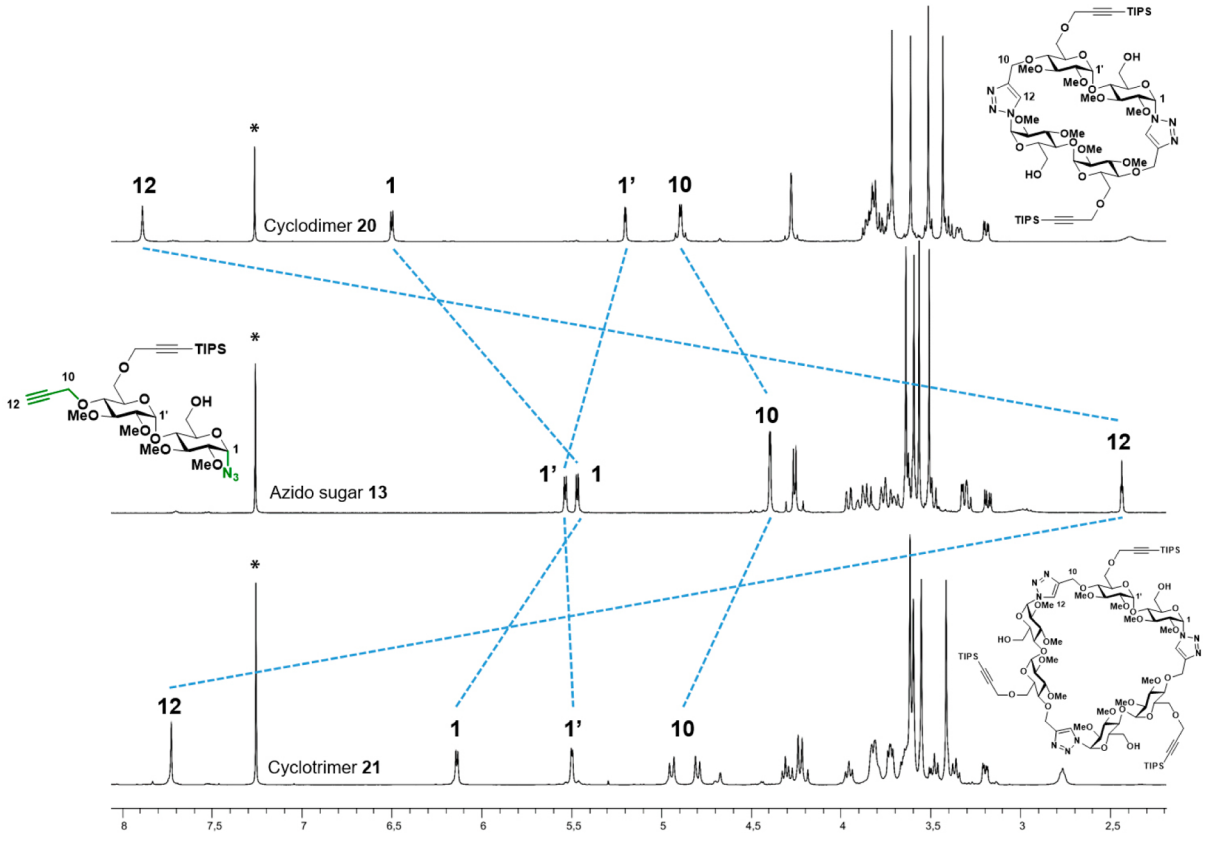
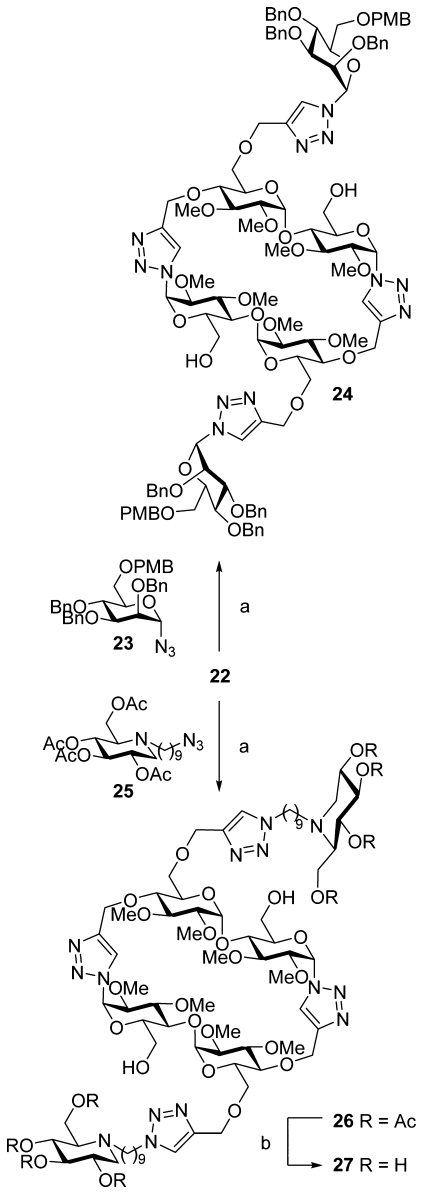


Figure 3. ^1H NMR spectra (400 MHz, $CDCl_3$) of bifunctional module **13**, cyclodimer **20**, and cyclotrimer **21** (* indicates residual chloroform peak).

disaccharide modules, i.e., anomeric position azidation and selective TES-alkyne group deprotection, were found to be successful. Indeed, all the desired model disaccharide modules activated at each one or at both ends were obtained. The next anomeric activation reaction involved in the step-by-step modular approach proved more difficult at the stage of the *neo*-tetrasaccharide analogues obtained by the combination of the appropriate monoactivated disaccharide modules. So far, the low basicity of the internal triazole moiety prevented further activation by TMSOTf-mediated opening of the 1,6-anhydro ring and, consequently, the access to CD analogues. The modular approach was shown to be nevertheless useful to access acyclic

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 6[a]



[a]Reagents and conditions: (a) **23** or **25** (excess), $CuSO_4{\cdot}5H_2O$ (0.25 equiv), sodium ascorbate (0.5 equiv), DMF/H_2O 4:1, MW 80 °C, 70% (**24**), 73% (**26**); (b) Amberlite IRA-400 (OH^-), MeOH/H_2O 1:1, 40 °C, 89%.

alkyne-functionalized scaffolds of a controlled size by click ligation at the nonreducing extremity of the growing oligosaccharide analogues. On the other hand, the cyclo-oligomerization approach led to the first examples of close analogues of CDs composed of D-*gluco* disaccharides and triazole units bound together through α-(1,4) linkages. Prefunctionalized *neo*-CDs prepared in nine steps from D-(+)-maltose and containing four or six glucose units were thus obtained in 21% and 4% overall yield, respectively. The successful grafting by CuAAC of azide-armed ligands onto the cyclic or linear scaffolds built through the Lego approach validated the last synthetic stages of our strategy. Beyond their interest for the multivalent design of bioactive systems, prefunctionalized *neo*-CDs may also find interesting applications[34] in transition-metal chemistry by providing tailored cavity-shaped ligands. Exploring the potential of the modular Lego approach in the fields of multivalent design and metalated cavitands is an ongoing effort in our laboratory.

EXPERIMENTAL SECTION

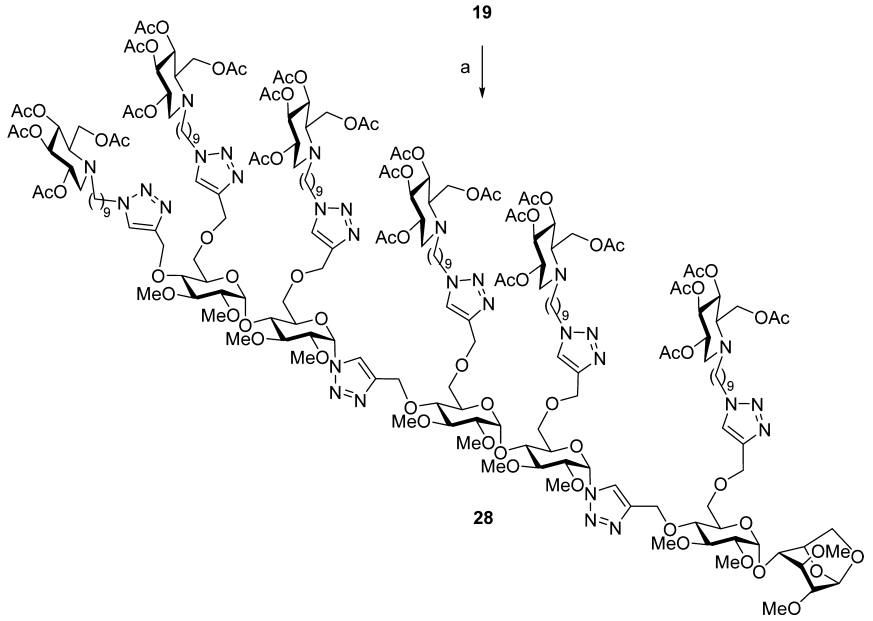
General Methods and Remarks. Commercially available starting materials were purchased from commercial suppliers and were used without further purification. When specified, anhydrous solvents were required. Tetrahydrofuran (THF) was distilled over sodium/benzophenone under argon or dried by passage through an activated alumina column under argon. Dimethylformamide (DMF) and acetonitrile were purchased anhydrous over molecular sieves. Triethylamine and pyridine were distilled over KOH and were stored over KOH under argon. All the reactions were carried out in standard glassware or in vials adapted to a Biotage Initiator microwave reactor. Most of the crude mixtures were purified by flash chromatography on silica gel 60 (230−400 mesh, 0.040−0.063 mm). Automated flash chromatography was performed using a system equipped with UV/vis and ELSD detectors. Reaction monitoring and primary characterization of products were achieved by thin layer chromatography (TLC) on aluminum sheets coated with silica gel 60 F254. Eluted TLCs were revealed under UV (254 nm) and with chemicals. Nuclear magnetic resonance (NMR) spectra were recorded on 300, 400, or 500 MHz spectrometers with solvent peaks as reference. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. ^1H and ^{13}C signals were assigned by correlation spectroscopy (COSY), heteronuclear single quantum correlation (HSQC), and heteronuclear multiple-bond correlation spectroscopy (HMBC). Infrared (IR) spectra (cm^{-1}) were recorded neat. ESI-TOF high-resolution mass spectra (HRMS) were carried out on a MicroTOF spectrometer. Specific rotations were determined on a polarimeter with a sodium lamp (λ = 589 nm).

Maltosan 2. (Adapted from ref 29). To a solution of D-(+)-maltose monohydrate (1 equiv, 18 g, 49.9 mmol) in water (1 L) were added successively triethylamine (9 equiv, 45.4 g, 62.4 mL, 449 mmol) and 2-chloro-1,3-dimethylimidazolium chloride (3 equiv, 25 g, 150 mmol). The mixture was stirred for 15 h at room temperature. The aqueous mixture was washed with CH_2Cl_2 (3 × 200 mL), concentrated under reduced pressure, and then coevaporated with toluene. The crude thick residue was then acetylated by adding successively pyridine (200 mL) and Ac_2O (60 mL). After stirring for 3 h at room temperature, the solution was then concentrated under reduced pressure and coevaporated with toluene. The crude residue was triturated with EtOAc and filtered to afford $NEt_3{\cdot}HCl$ as the solid and a filtrate containing acetylated maltosan,[35] which was concentrated. The residue was then recrystallized from boiling MeOH (ca. 150 mL). The white powder was then deacetylated by adding metallic sodium (0.09 equiv, 100 mg, 4.3 mmol) at 0 °C to a suspension of acetylated maltosan in MeOH (200 mL). The suspension was stirred for 20 h, while it progressively became clear and then milky. The milky mixture was treated with DOWEX X8 (H^+ form) resin (10 g), and then stirred for 3 h 30. Another portion of DOWEX resin (10 g) was added, and the solution became clear and colorless in 20 min. The mixture was then filtered and concentrated, to afford pure maltosan **2** (12.6 g, 78%). Spectroscopic data (^1H NMR and ^{13}C NMR) matched those reported in the literature.[29a] R_f maltosan (**2**) 0.40 (CH_3CN/water/30 wt %-NH_4OH 6:2:2); R_f peracetylated maltosan 0.52 (EtOAc/PE 75:25).

Compound 3. A solution of **2** (1 equiv, 10 g, 30.8 mmol) and paramethoxybenzaldehyde dimethyl acetal (1.5 equiv, 8.43 g, 7.89 mL, 46.3 mmol) with Amberlite IR-120 (H^+) (4 g) in DMF (50 mL) was heated at 70 °C under 0.05 bar for 16 h, using a condenser to avoid evaporation of DMF and acetal. The reaction mixture was allowed to cool to room temperature and was filtered to remove acidic resin. The filtrate was strongly concentrated under reduced pressure. A mixture of CH_2Cl_2 (100 mL) and H_2O (20 mL) was added to the crude residue, causing a white precipitate. The suspension was filtered twice to afford pure **3** (12 g, 88%) as a white solid. R_f 0.76 (CH_3CN/water 9:1); mp 233 °C; $[\alpha]_D^{20}$ = +49.5 (*c* 0.5, MeOH/H_2O); ^1H NMR (CD_3OD, 400 MHz) δ 7.44 (d, *J* = 8.7 Hz, 2H; H-9), 6.91 (d, *J* = 8.7 Hz, 2H; H-10), 5.53 (s, 1H; H-7), 5.32 (s, 1H; H-1), 5.06 (d, *J* = 4.0 Hz, 1H; H-1′),

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

Scheme 7[a]



[a]Reagents and conditions: (a) **25** (excess), $CuSO_4 \cdot 5H_2O$ (1 equiv), sodium ascorbate (2 equiv), DMF/H_2O 4:1, MW 80 °C, 79%.

4.65 (d, J = 5.4 Hz, 1H; H-5), 4.22 (dd, J = 10.4, 5.1 Hz, 1H; H-6′a), 4.12 (d, J = 7.4 Hz, 1H; H-6a), 3.98−3.87 (m, 2H; H-3′ and H-5′), 3.79 (s, 3H; MeO), 3.79−3.66 (m, 3H; H-3, H-6b and H-6′b), 3.60 (s, 1H; H-4), 3.51 (dd, J = 9.5, 4.0 Hz, 1H; H-2′), 3.46 (t, J = 9.3 Hz, 1H; H-4′), 3.42 ppm (s, 1H; H-2); ^{13}C NMR (CD_3OD, 100 MHz) δ 161.7 (C-11), 131.6 (C-8), 129.0 (C-9), 114.5 (C-10), 103.5 (C-1), 103.2 (C-7), 100.4 (C-1′), 82.9 (C-4′), 78.3 (C-4), 76.9 (C-5), 74.4 (C-2′), 72.1 (C-2 and C-3′), 71.7 (C-3), 70.0 (C-6′), 66.5 (C-6), 64.7 (C-5′), 55.8 ppm (MeO); IR (neat) ν = 3305 cm^{-1} (broad, O-H); HRMS (ESI) m/z calcd for $C_{20}H_{26}O_{11}Na$ $[M + Na]^+$ 465.1367; found 465.1353.

Compound 4. To a solution of **3** (1 equiv, 1 g, 2.26 mmol) in anhydrous DMF (15 mL) was added sodium hydride (60 wt % in oil, 6 equiv, 0.542 g, 13.6 mmol) at −10 °C. The mixture was stirred for 10 min, and MeI (6 equiv, 1.92 g, 0.844 mL, 13.6 mmol) was added at −10 °C. The mixture was stirred for 20 h, allowing the temperature to slowly rise to 15 °C. The reaction was quenched by addition of MeOH. Then, a saturated solution of NH_4Cl (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated. The crude residue was recrystallized from boiling MeOH (ca. 50 mL) to afford **4** (1.11 g, 99%). R_f 0.77 (CH_2Cl_2/MeOH 8:2); mp 136.0 °C; $[\alpha]_D^{26}$ = +45.8 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 8.7 Hz, 2H; H-9), 6.89 (d, J = 8.7 Hz, 2H; H-10), 5.50 (s, 1H; H-7), 5.44 (s, 1H; H-1), 5.18 (d, J = 3.8 Hz, 1H; H-1′), 4.58 (d, J = 5.4 Hz, 1H; H-5), 4.21 (dd, J = 10.3, 4.9 Hz, 1H; H-6′a), 3.93 (td, J = 9.9, 4.6 Hz, 1H; H-5′), 3.86 (d, J = 7.3 Hz, 1H; H-6a), 3.80 (s, 3H; MeO), 3.78 (t, J = 9.4 Hz, 1H; H-3′), 3.69 (dd, J = 7.3, 5.5 Hz, 1H; H-6b), 3.69 (dd, J = 10.3, 9.9 Hz, 1H; H-6′b), 3.63 (s, 3H; MeO), 3.57−3.49 (m, 5H; H-4, H-4′ and MeO), 3.47 (s, 3H; MeO), 3.46 (s, 3H; MeO), 3.40 (t, J = 3.5 Hz, 1H; H-3), 3.31 (dd, J = 9.4, 3.8 Hz, 1H; H-2′), 3.09 ppm (d, J = 3.3 Hz, 1H; H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2 (C-11), 129.9 (C-8), 127.5 (C-9), 113.7 (C-10), 101.5 (C-7), 100.5 (C-1), 97.7 (C-1′), 82.4 (C-4′), 81.0 (C-2′), 80.5 (C-2), 79.3 (C-3), 79.1 (C-3′), 77.4 (C-4), 75.8 (C-5), 69.0 (C-6′), 66.5 (C-6), 63.1 (C-5′), 61.1 (MeO), 58.5 (two MeO), 57.6 (MeO), 55.4 ppm (MeO); IR (neat) 2926 cm^{-1} (broad, C-H st), 1088 cm^{-1} (broad, C-O st); HRMS (ESI) m/z calcd for $C_{24}H_{34}O_{11}Na$ $[M + Na]^+$ 521.1993; found 521.2035.

Compound 5. To a solution of DIBAL-H (1.0 M in hexanes, 3 equiv, 11.1 mL, 11.1 mmol), diluted with CH_2Cl_2 (10 mL), was added compound **4** (1 equiv, 1.85 g, 3.71 mmol) in CH_2Cl_2 (10 mL) in one portion at 20 °C. The mixture was stirred for 5 min at 20 °C. TLC control showed total conversion of the starting material. The reaction was carefully quenched with MeOH at room temperature until the end of the gas release. Then, a solution of HCl (1 M, 150 mL) was added to the mixture, which was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (150 mL), dried with Na_2SO_4, filtered, and concentrated to afford pure **5** (1.84 g, 99%). R_f 0.29 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +57.1 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J = 8.6 Hz, 2H; H-9), 6.89 (d, J = 8.6 Hz, 2H; H-10), 5.41 (s, 1H; H-1), 5.17 (d, J = 3.7 Hz, 1H; H-1′), 4.80 (d, J = 10.6 Hz, 1H; H-7a), 4.57 (d, J = 5.3 Hz, 1H; H-5), 4.57 (d, J = 10.6 Hz, 1H; H-7b), 3.84 (d, J = 7.3 Hz, 1H; H-6a), 3.80 (s, 3H; MeO), 3.81−3.72 (m, 2H; H-5′ and H-6′a), 3.70−3.62 (m, 3H; H-3′, H-6b and H-6′b), 3.66 (s, 3H; MeO), 3.51 (d, J = 3.4 Hz, 1H; H-4), 3.51 (s, 3H; MeO), 3.47 (s, 3H; MeO), 3.45 (s, 3H; MeO), 3.39 (t, J = 3.4 Hz, 1H; H-3), 3.38 (dd, J = 9.7, 8.9 Hz, 1H; H-4′), 3.22 (dd, J = 9.7, 3.7 Hz, 1H; H-2′), 3.07 ppm (d, J = 3.4 Hz, 1H; H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5 (C-11), 130.4 (C-8), 129.9 (C-9), 114.0 (C-10), 100.4 (C-1), 96.4 (C-1′), 83.1 (C-3′), 81.8 (C-2′), 80.6 (C-2), 79.5 (C-3), 77.3 (C-4′), 77.1 (C-4), 75.6 (C-5), 74.6 (C-7), 71.5 (C-5′), 66.5 (C-6), 62.1 (C-6′), 61.1, 58.5, 58.3, 57.5, 55.4 ppm (MeO); IR (neat) 3474 cm^{-1} (broad, O-H); HRMS (ESI) m/z calcd for $C_{24}H_{36}O_{11}Na$ $[M + Na]^+$ 523.2150; found 523.2157.

Compound 6. To a solution of **5** (1 equiv, 3.10 g, 6.19 mmol) and (triisopropylsilyl)propargyl bromide (2 equiv, 3.41 g, 3.12 mL, 12.4 mmol) in anhydrous THF (40 mL) was added sodium hydride (60 wt % in oil, 1.5 equiv, 372 mg, 9.29 mmol) at 20 °C. The mixture was stirred for 40 h at 20 °C. The reaction was quenched with MeOH (until the precipitate dissolved), and the mixture was concentrated under reduced pressure. Then, a saturated solution of NH_4Cl (250 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water (250 mL), dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to afford **6** (4.34 g, 99%). R_f 0.52 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +50.0 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, J = 8.7 Hz, 2H; H-9), 6.87 (d, J = 8.7 Hz, 2H; H-10), 5.40 (s, 1H; H-1), 5.16 (d, J = 3.7 Hz, 1H; H-1′), 4.76 (d, J = 10.7 Hz, 1H; H-7a), 4.57 (d, J = 10.7 Hz, 1H; H-7b), 4.57 (d, J = 5.4 Hz, 1H; H-5), 4.24 (d, J = 16.0 Hz, 1H; H-7′a), 4.17 (d, J = 16.0 Hz, 1H; H-7′b), 3.86 (ddd, J = 10.1, 4.2, 1.9 Hz, 1H; H-5′), 3.83 (d, J = 7.3 Hz, 1H; H-6a), 3.80 (s, 3H; MeO), 3.75 (dd, J = 10.3, 1.9 Hz, 1H; H-6′a), 3.69 (dd, J = 10.4, 4.3 Hz, 1H; H-6′b), 3.64 (dd, J = 9.7, 8.8 Hz, 1H; H-3′), 3.64 (dd, J = 7.3, 5.5 Hz, 1H; H-6b), 3.62 (s, 3H; MeO), 3.51 (dd, J = 4.1,

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

1.6 Hz, 1H; H-4), 3.48 (s, 3H; MeO), 3.46 (s, 3H; MeO), 3.45 (dd, J = 10.1, 8.8 Hz, 1H; H-4′), 3.45 (s, 3H; MeO), 3.38 (t, J = 3.9 Hz, 1H; H-3), 3.25 (dd, J = 9.7, 3.7 Hz, 1H; H-2′), 3.06 (d, J = 3.8 Hz, 1H; H-2), 1.04 ppm (s, 21H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4 (C-8), 130.7 (C-11), 129.7 (C-9), 113.9 (C-10), 103.0 (C-8′), 100.6 (C-1), 97.0 (C-1′), 88.1 (C-9′), 83.1 (C-3), 81.7 (C-2′), 81.1 (C-2), 79.6 (C-3′), 77.8 (C-4), 77.5 (C-4′), 75.9 (C-5), 74.7 (C-7), 70.7 (C-5′), 68.4 (C-6′), 66.7 (C-6), 61.1 (MeO), 59.6 (C-7′), 58.7 (MeO), 58.2 (MeO), 57.6 (MeO), 55.4 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 2178 cm^{-1} (very weak, C≡CSiR$_3$); HRMS (ESI) m/z calcd for $C_{36}H_{58}O_{11}SiNa$ [M + Na] $^+$ 717.3641; found 717.3542.

Compound 7. To a solution of **6** (1 equiv, 4.34 g, 6.24 mmol) in a mixture of CH_2Cl_2/H_2O (10:1, 1.5 mL) was added DDQ (1.25 equiv, 1.81 g, 7.81 mmol) at 20 °C. The mixture was stirred for 45 min at 20 °C. A saturated solution of $NaHCO_3$ (300 mL) was added, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water (350 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1 to 98:2) to afford **7** (2.77 g, 77%). R_f 0.26 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +46.0 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.41 (s, 1H; H-1), 5.17 (d, J = 3.8 Hz, 1H; H-1′), 4.62 (d, J = 5.1 Hz, 1H; H-5), 4.23 (s, 2H; H-7′), 3.88 (m, 1H; H-5′), 3.86 (d, J = 7.1 Hz, 1H; H-6a), 3.80 (dd, J = 10.2, 2.6 Hz, 1H; H-6′a), 3.75 (dd, J = 10.2, 5.0 Hz, 1H; H-6′b), 3.66 (dd, J = 7.1, 5.5 Hz, 1H; H-6b), 3.63 (s, 3H; MeO), 3.56−3.49 (m, 3H; H-4, H-3′ and H-4′), 3.469 (s, 3H; MeO), 3.465 (s, 3H; MeO), 3.457 (s, 3H; MeO), 3.39 (t, J = 3.7 Hz, 1H; H-3), 3.26 (m, 1H; H-2′), 3.07 (d, J = 3.6 Hz, 1H; H-2), 1.06 ppm (s, 21H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.0 (C-8′), 100.6 (C-1), 97.1 (C-1′), 88.2 (C-9′), 82.3 (C-3′), 81.4 (C-2′), 81.0 (C-2), 79.5 (C-3), 78.0 (C-4), 75.9 (C-5), 70.8 (C-5′), 70.6 (C-4′), 68.7 (C-6′), 66.7 (C-6), 61.1 (MeO), 59.7 (C-7′), 58.7 (MeO), 57.8 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3460 (broad, O-H), 2178 cm^{-1} (very weak, C≡CSiR$_3$); HRMS (ESI) m/z calcd for $C_{28}H_{50}O_{10}SiNa$ [M + Na]$^+$ 597.3065; found 597.3058.

Compound 8. *From 7:* To a solution of **7** (1 equiv, 930 mg, 1.62 mmol), propargyl bromide (80 wt % in toluene, 5 equiv, 1.20 g, 0.870 mL, 8.09 mmol), and MeOH (0.1 equiv, 4.7 mg, 6 μL, 0.16 mmol) in anhydrous THF (25 mL) was added sodium hydride (60 wt % in oil, 5 equiv, 324 mg, 8.09 mmol) at 20 °C. The mixture was stirred for 21 h at 20 °C. The reaction was quenched with MeOH and concentrated. A saturated solution of NH_4Cl (150 mL) was added, and the aqueous mixture was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to afford **8** (1.02 g, 99%). *From 9:* To a solution of **9** (1 equiv, 50.4 mg, 0.0693 mmol) in a mixture of CH_2Cl_2/MeOH/water (7:4:1, 3.4 mL) was added $AgNO_3$ (4.96 equiv, 58.4 mg, 0.344 mmol). The mixture was stirred at room temperature for 18 h. The reaction was quenched with NH_4Cl (30 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was washed with a saturated solution of NH_4Cl (2 × 30 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to afford **8** (37.7 mg, 89%). R_f 0.52 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{24}$ = +56.0 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.40 (s, 1H; H-1), 5.15 (d, J = 3.2 Hz, 1H; H-1′), 4.58 (d, J = 5.1 Hz, 1H; H-5), 4.39 (s, 2H; H-10), 4.24 (s, 2H; H-7′), 3.84 (d, J = 7.1 Hz, 1H; H-6a), 3.82 (m, 1H; H-5′), 3.80 (d, J = 10.2 Hz, 1H; H-6′a), 3.72 (dd, J = 10.2, 4.6 Hz, 1H; H-6′b), 3.64 (dd, J = 7.1, 5.1 Hz, 1H; H-6b), 3.62 (s, 3H; MeO), 3.62 (t, J = 9.7 Hz, 1H; H-3′), 3.51 (d, J = 3.3 Hz, 1H; H-4), 3.47 (s, 3H; MeO), 3.45 (s, 6H; two MeO), 3.42 (t, J = 9.8 Hz, 1H; H-4′), 3.37 (t, J = 3.3 Hz, 1H; H-3), 3.23 (dd, J = 9.6, 3.3 Hz, 1H; H-2′), 3.06 (d, J = 2.9 Hz, 1H; H-2), 2.43 (s, 1H; H-12), 1.06 ppm (s, 21H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.9 (C-8′), 100.6 (C-1), 96.8 (C-1′), 88.2 (C-9′), 83.0 (C-3′), 81.6 (C-2′), 81.0 (C-2), 80.1 (C-11), 79.5 (C-3), 77.7 (C-4), 77.0 (C-4′), 75.8 (C-5), 74.4 (C-12), 70.3 (C-5′), 68.3 (C-6′), 66.7 (C-6), 61.1 (MeO), 59.8 (C-7′), 59.5 (C-10), 58.6 (MeO), 58.2 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3264 (weak, CC-H), 2178 (very weak, C≡CSiR$_3$), 2118 cm^{-1} (very weak, C≡CH); HRMS (ESI) m/z calcd for $C_{31}H_{52}O_{10}SiNa$ [M + Na]$^+$ 635.3222; found 635.3240.

Compound 9. To a solution of **8** (1 equiv, 1.25 g, 2.04 mmol) in anhydrous THF (20 mL) was added dropwise a solution of LiHMDS in THF (2.5 equiv, 1 M, 5.11 mL, 5.11 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C, and then chlorotriethylsilane (1.5 equiv, 0.472 g, 0.525 mL, 3.07 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C. TLC showed complete conversion. The reaction was quenched by the addition of a saturated solution of NH_4Cl (100 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (100 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/PE 15:85 to 50:50) to afford **9** (1.48 g, quantitative). R_f 0.59 (EtOAc/PE 1:1); $[\alpha]_D^{20}$ = +51.9 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.40 (s, 1H: H-1), 5.15 (d, J = 3.8 Hz, 1H; H-1′), 4.59 (d, J = 5.2 Hz, 1H; H-5), 4.41 (s, 2H; H-10), 4.22 (s, 2H; H-7′), 3.85 (dd, J = 10.2, 1.7 Hz, 1H; H-6′a), 3.85 (d, J = 7.1 Hz, 1H; H-6a), 3.84 (ddd, J = 9.1, 5.5, 1.7 Hz, 1H; H-5′), 3.67 (dd, J = 10.1, 5.5 Hz, 1H; H-6′b), 3.65 (dd, J = 7.1, 5.2 Hz, 1H; H-6b), 3.62 (s, 3H; MeO), 3.61 (dd, J = 9.6, 9.1 Hz, 1H; H-3′), 3.52 (d, J = 4.1 Hz, 1H; H-4), 3.47 (s, 3H; MeO), 3.46 (s, 3H; MeO), 3.45 (s, 3H; MeO), 3.39 (t, J = 9.1 Hz, 1H; H-4′), 3.38 (dd, J = 4.1, 3.8 Hz, 1H; H-3), 3.22 (dd, J = 9.6, 3.8 Hz, 1H; H-2′), 3.05 (d, J = 3.8 Hz, 1H; H-2), 1.07 (s, 21H; TIPS), 0.99 (t, J = 7.9 Hz, 9H; CH_3 TES), 0.60 ppm (q, J = 7.9 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.0 (C-11 and C-8′), 100.7 (C-1), 97.0 (C-1′), 88.7 (C-12 or C-9′), 88.0 (C-12 or C-9′), 83.1 (C-3′), 81.6 (C-2′), 81.4 (C-2), 79.7 (C-3), 78.0 (C-4), 77.3 (C-4′), 76.0 (C-5), 70.4 (C-5′), 68.8 (C-6′), 66.9 (C-6), 61.0 (MeO), 60.8 (C-7′), 59.5 (C-10), 58.7 (MeO), 58.2 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.6 (CH_3 TES), 4.4 ppm (CH_2 TES); IR (neat) 2177 cm^{-1} (weak, C≡CSiR$_3$); HRMS (ESI) m/z calcd for $C_{37}H_{66}O_{10}Si_2Na$ [M + Na]$^+$ 749.4087; found 749.4060.

Compound 10. To a solution of **9** (1 equiv, 493 mg, 0.678 mmol) and $TMSN_3$ (10 equiv, 822 mg, 0.948 mL, 6.78 mmol) in anhydrous CH_3CN (15 mL) was added a solution of TMSOTf (0.5 equiv, 76.9 mg, 0.0626 mL, 0.339 mmol) and NEt_3 (0.3 equiv, 20.6 mg, 0.0283 mL, 0.203 mmol) in CH_3CN (1.5 mL). The mixture was stirred for 4 h 30 at 20 °C. TLC control showed complete conversion of the starting material. The reaction was quenched with a saturated solution of $NaHCO_3$ (150 mL). EtOAc was added (150 mL), and the layers were separated. The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 150 mL). Conc. HCl (1 mL) was added along with MeOH (10 mL). After a brief shaking, the mixture was washed with water (150 mL) and brine (150 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/PE 10:90 to 40:60) to afford **10** (403 mg, 77%) and the corresponding β-anomer (87 mg, 17%). **Data for 10**: R_f 0.33 (EtOAc/PE 35:65); $[\alpha]_D^{20}$ = +119.6 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.52 (d, J = 4.1 Hz, 1H; H-1′), 5.47 (d, J = 4.0 Hz, 1H; H-1), 4.43 (d, J = 15.9 Hz, 1H; H-10a), 4.38 (d, J = 15.9 Hz, 1H; H-10b), 4.26 (d, J = 16.3 Hz, 1H; H-7′a), 4.19 (d, J = 16.3 Hz, 1H; H-7′b), 4.01 (dd, J = 10.0, 1.1 Hz, 1H; H-6′a), 3.91 (dd, J = 12.9, 2.5 Hz, 1H; H-6a), 3.86 (dd, J = 10.0, 8.6 Hz, 1H; H-4), 3.76 (ddd, J = 10.0, 2.5, 1.9 Hz, 1H; H-5), 3.73 (dd, J = 12.9, 1.9 Hz, 1H; H-6b), 3.70 (ddd, J = 10.0, 7.4, 1.1 Hz, 1H; H-5′), 3.63 (s, 3H; MeO), 3.62 (dd, J = 9.5, 8.6 Hz, 1H; H-3), 3.59 (s, 3H; MeO), 3.58 (dd, J = 10.2, 7.4 Hz, 1H; H-6′b), 3.56 (s, 3H; MeO), 3.51 (s, 3H; MeO), 3.49 (dd, J = 9.9, 9.0 Hz, 1H; H-3′), 3.32 (dd, J = 9.5, 4.1 Hz, 1H; H-2), 3.29 (dd, J = 10.0, 9.0 Hz, 1H; H-4′), 3.17 (dd, J = 9.9, 4.2 Hz, 1H; H-2′), 1.07 (s, 21H; TIPS), 0.99 (t, J = 7.9 Hz, 9H; CH_3 TES), 0.61 ppm (q, J = 7.9 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.7 (C-11 or C-8′), 102.5 (C-11 or C-8′), 97.8 (C-1′), 89.1 (C-12 or C-9′), 88.6 (C-12 or C-9′), 87.1 (C-1), 83.9 (C-3′), 83.2 (C-3), 82.3 (C-2), 82.0 (C-2′), 77.0 (C-4′), 73.1 (C-4), 72.6 (C-5′), 71.2 (C-5), 69.3 (C-6′), 61.0 (MeO), 60.7 (MeO), 60.6 (C-10), 60.5 (C-6), 60.1 (MeO), 59.5 (C-7′), 59.1 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.6 (CH_3 TES), 4.4 ppm (CH_2 TES); IR (neat) 3498 (broad, O-H), 2178 (very weak, C≡CSiR$_3$), 2113 cm^{-1} (sharp, N_3); HRMS (ESI) m/z calcd for $C_{37}H_{67}N_3O_{10}Si_2Na$ [M + Na]$^+$ 792.4257; found 792.4230. **Data for the corresponding β-anomer of**

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

10: R_f 0.53 (EtOAc/PE 35:65); $[\alpha]_D^{20}$ = +33.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.51 (d, *J* = 4.1 Hz, 1H; H-1′), 4.49 (d, *J* = 8.7 Hz, 1H; H-1), 4.40 (s, 2H; H-10), 4.26 (d, *J* = 16.2 Hz, 1H; H-7′a), 4.20 (d, *J* = 16.2 Hz, 1H; H-7′b), 3.94 (d, *J* = 9.5 Hz, 1H; H-6′a), 3.89−3.79 (m, 3H; H-4 and H-6), 3.69 (dd, *J* = 9.5, 6.5 Hz, 1H; H-5′), 3.63 (m, 1H; H-6′b), 3.63 (s, 3H; MeO), 3.60 (s, 3H; MeO), 3.58 (s, 3H; MeO), 3.56 (s, 3H; MeO), 3.47 (dd, *J* = 9.8, 8.9 Hz, 1H; H-3′), 3.44−3.37 (m, 2H; H-3 and H-5), 3.32 (dd, *J* = 9.5, 8.9 Hz, 1H; H-4′), 3.17 (dd, *J* = 9.8, 4.1 Hz, 1H; H-2′), 2.97 (t, *J* = 8.8 Hz, 1H; H-2), 2.82 (br s, 1H; O−H), 1.07 (s, 21H; TIPS), 0.99 (t, *J* = 7.9 Hz, 9H; CH_3 TES), 0.61 ppm (q, *J* = 7.9 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.8 (C-11 or C-8′), 102.7 (C-11 or C-8′), 97.5 (C-1′), 90.0 (C-1), 89.0 (C-12 or C-9′), 88.5 (C-12 or C-9′), 86.8 (C-3), 84.2 (C-2), 83.8 (C-3′), 81.9 (C-2′), 77.2 (C-5 or C-4′), 77.1 (C-5 or C-4′), 72.5 (C-4), 71.1 (C-5′), 68.9 (C-6′), 61.02 (MeO), 60.99 (C-6), 60.8 (C-10), 60.6 (MeO), 60.4 (MeO), 60.1 (MeO), 59.5 (C-7′), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.6 (CH_3 TES), 4.4 ppm (CH_2 TES); IR (neat) 3453 (broad, O-H), 2178 (very weak, C≡CSiR$_3$), 2114 cm^{-1} (sharp, N_3); HRMS (ESI) *m*/*z* calcd for $C_{37}H_{67}N_3O_{10}Si_2Na$ $[M + Na]^+$ 792.4257; found 792.4283.

Compound 12. To a solution of **10** (1 equiv, 11.8 mg, 0.0153 mmol) and (triisopropylsilyl)propargyl bromide (3 equiv, 12.7 mg, 12 μL, 0.046 mmol) in anhydrous THF (0.5 mL) was added sodium hydride (60 wt % in oil, 3 equiv, 1.8 mg, 0.046 mmol) at 20 °C. The mixture was stirred for 20 h at 20 °C. The reaction was quenched with MeOH and concentrated under reduced pressure. Then, a saturated solution of NH_4Cl (20 mL) was added and the aqueous mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/PE 10:90 to 20:80) to afford **12** (10.5 mg, 71%). R_f 0.72 (EtOAc/PE 30:70); $[\alpha]_D^{20}$ = +89.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.58 (d, *J* = 3.6 Hz, 1H; H-1′), 5.45 (d, *J* = 4.1 Hz, 1H; H-1), 4.41 (s, 2H; H-10), 4.33 (d, *J* = 16.2 Hz, 1H; H-7a), 4.25 (s, 2H; H-7′), 4.11 (d, *J* = 16.2 Hz, 1H; H-7b), 3.92 (dd, *J* = 11.3, 1.3 Hz, 1H; H-6a), 3.90 (ddd, *J* = 10.2, 3.1, 1.3 Hz, 1H; H-5), 3.84 (dd, *J* = 10.2, 8.6 Hz, 1H; H-4), 3.79 (dd, *J* = 10.3, 1.7 Hz, 1H; H-6′a), 3.72 (dd, *J* = 10.3, 4.4 Hz, 1H; H-6′b), 3.70 (dd, *J* = 11.3, 3.1 Hz, 1H; H-6b), 3.64 (ddd, *J* = 9.4, 3.1, 1.7 Hz, 1H; H-5′), 3.63 (s, 3H; MeO), 3.57 (dd, *J* = 9.5, 8.6 Hz, 1H; H-3), 3.56 (s, 3H; MeO), 3.53 (s, 3H; MeO), 3.50 (s, 3H; MeO), 3.48 (t, *J* = 9.4 Hz, 1H; H-3′), 3.41 (t, *J* = 9.4 Hz, 1H; H-4′), 3.33 (dd, *J* = 9.5, 4.1 Hz, 1H; H-2), 3.16 (dd, *J* = 9.5, 3.7 Hz, 1H; H-2′), 1.07 (s, 42H; two TIPS), 0.99 (t, *J* = 7.9 Hz, 9H; CH_3 TES), 0.60 ppm (q, *J* = 7.9 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.3 (C-8, C-8′ or C-11), 103.1 (C-8, C-8′ or C-11), 103.0 (C-8, C-8′ or C-11), 96.7 (C-1′), 88.5 (C-9, C-9′ or C-12), 88.3 (C-9, C-9′ or C-12), 88.0 (C-9, C-9′ or C-12), 87.1 (C-1), 83.4 (C-3 or C-3′), 83.3 (C-3 or C-3′), 82.0 (C-2 or C-2′), 81.8 (C-2 or C-2′), 77.5 (C-4′), 72.1 (C-4), 71.8 (C-5), 70.7 (C-5′), 68.5 (C-6′), 67.1 (C-6), 61.0 (MeO), 60.9 (C-10), 60.5 (MeO), 59.5 (C-7′), 59.4 (MeO), 59.3 (C-7), 59.1 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.5 (CH_3 TES), 4.4 ppm (CH_2 TES); IR (neat) 2168 (weak, C≡CSiR$_3$), 2113 cm^{-1} (strong, N_3); HRMS (ESI) *m*/*z* calcd for $C_{49}H_{89}N_3O_{10}Si_3Na$ $[M + Na]^+$ 986.5748; found 986.5652.

Compound 13. *From* ***8***: To a solution of **8** (1 equiv, 146 mg, 0.239 mmol) and $TMSN_3$ (10 equiv, 289 mg, 0.333 mL, 2.39 mmol) in anhydrous CH_3CN (5 mL) was added a solution of TMSOTf (0.5 equiv, 27.1 mg, 0.022 mL, 0.119 mmol) and triethylamine (0.3 equiv, 7.24 mg, 0.01 mL, 0.0716 mmol) in CH_3CN (0.4 mL). The mixture was stirred for 4 h 30 at 20 °C. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL). EtOAc was added (30 mL), and the layers were separated. The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 30 mL). A few drops of conc. HCl were added along with MeOH (ca. 2 mL). After a brief shaking, the mixture was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/PE 20:80 to 60:40) to afford **13** (122 mg, 78%) and the corresponding β-anomer (29 mg, 19%). *From* ***10***: To a solution of **10** (1 equiv, 369.4 mg, 0.480 mmol) in a mixture of CH_2Cl_2 /MeOH/water (7:4:1, 6 mL) was added $AgNO_3$ (3 equiv, 244.4 mg, 1.439 mmol). The mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated solution of NH_4Cl (50 mL) and water (50 mL), and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to afford **13** (232.4 g, 74%). **Data for 13**: R_f 0.40 (EtOAc/PE 1:1); $[\alpha]_D^{21}$ = +128.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (d, *J* = 4.2 Hz, 1H; H-1′), 5.47 (d, *J* = 4.0 Hz, 1H; H-1), 4.39 (d, *J* = 2.4 Hz, 2H; H-10), 4.29 (d, *J* = 16.3 Hz, 1H; H-7′a), 4.23 (d, *J* = 16.3 Hz, 1H; H-7′b), 3.96 (dd, *J* = 9.9, 1.3 Hz, 1H; H-6′a), 3.89 (dd, *J* = 13.1, 2.7 Hz, 1H; H-6a), 3.86 (dd, *J* = 9.8, 8.6 Hz, 1H; H-4), 3.76 (ddd, *J* = 9.8, 2.7, 1.7 Hz, 1H; H-5), 3.74 (dd, *J* = 13.1, 1.7 Hz, 1H; H-6b), 3.70 (ddd, *J* = 9.9, 6.8, 1.3 Hz, 1H; H-5′), 3.64 (s, 3H; MeO), 3.62 (dd, *J* = 9.4, 8.6 Hz, 1H; H-3), 3.62 (dd, *J* = 9.9, 6.8 Hz, 1H; H-6′b), 3.60 (s, 3H; MeO), 3.57 (s, 3H; MeO), 3.51 (s, 3H; MeO), 3.49 (dd, *J* = 9.9, 8.9 Hz, 1H; H-3′), 3.31 (dd, *J* = 9.4, 4.0 Hz, 1H; H-2), 3.30 (dd, *J* = 9.9, 8.9 Hz, 1H; H-4′), 3.18 (dd, *J* = 9.9, 4.2 Hz, 1H; H-2′), 2.44 (t, *J* = 2.4 Hz, 1H; H-12), 1.07 ppm (s, 21H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.4 (C-8′), 97.6 (C-1′), 88.7 (C-9′), 87.1 (C-1), 83.8 (C-3′), 83.2 (C-3), 82.4 (C-2′), 82.0 (C-2), 79.9 (C-11), 77.0 (C-4′), 74.7 (C-12), 73.0 (C-5), 72.5 (C-4), 71.0 (C-5′), 68.9 (C-6′), 61.1 (MeO), 60.7 (MeO), 60.6 (C-6), 60.1 (MeO), 59.7 (C-10), 59.6 (C-7′), 59.1 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3490 (broad, O-H), 3311 (weak, CC-H), 2112 cm^{-1} (strong, N_3); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{53}N_3O_{10}SiNa$ $[M + Na]^+$ 678.3392; found 678.3430. **Data for the corresponding β-anomer of 13**: R_f 0.59 (EtOAc/PE 1:1); $[\alpha]_D^{20}$ = +53.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (d, *J* = 4.1 Hz, 1H; H-1′), 4.49 (d, *J* = 8.8 Hz, 1H; H-1), 4.39 (s, 2H; H-10), 4.26 (s, 2H; H-7′), 3.89 (dd, *J* = 8.6, 3.9 Hz, 1H; H-6′a), 3.84 (d, *J* = 9.6 Hz, 1H; H-5), 3.82 (s, 2H; H-6), 3.71−3.54 (m, 2H; H-5′, H-6′b), 3.63 (s, 3H; MeO), 3.60 (s, 3H; MeO), 3.58 (s, 3H; MeO), 3.56 (s, 3H; MeO), 3.47 (dd, *J* = 9.8, 8.9 Hz, 1H; H-3′), 3.45−3.38 (m, 2H; H-3 and H-4), 3.35 (dd, *J* = 9.6, 8.9 Hz, 1H; H-4′), 3.19 (dd, *J* = 9.8, 4.1 Hz, 1H; H-2′), 2.96 (t, *J* = 8.8 Hz, 1H; H-2), 2.44 (t, *J* = 2.2 Hz, 1H; H-12), 1.07 ppm (s, 21H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.6 (C-8′), 97.4 (C-1′), 90.0 (C-1), 88.6 (C-9′), 86.7 (C-3), 84.2 (C-2), 83.8 (C-3′), 82.0 (C-2′), 80.0 (C-11), 77.08, 77.02 (C-4 and C-4′), 74.6 (C-12), 72.3 (C-5), 70.9 (C-5′), 68.6 (C-6′), 61.08 (MeO), 61.06 (C-6), 60.6 (MeO), 60.5 (MeO), 60.1 (MeO), 59.8 (C-10), 59.6 (C-7′), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3493 (broad, O-H), 3308 (weak, CC-H), 2115 cm^{-1} (strong, N_3); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{53}N_3O_{10}SiNa$ $[M + Na]^+$ 678.3392; found 678.3383.

Compound 14. To a solution of **13** (1 equiv, 47.5 mg, 0.0724 mmol) and (triisopropylsilyl)propargyl bromide (3 equiv, 59.8 mg, 0.0549 mL, 0.217 mmol) in anhydrous THF (2 mL) was added sodium hydride (3 equiv, 8.69 mg, 0.217 mmol) at 20 °C. The mixture was stirred for 16 h at 20 °C. The reaction was quenched with a saturated solution of saturated NH_4Cl (10 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/pentane 20:80 to 30:70) to afford **14** (54.8 mg, 89%). R_f 0.79 (EtOAc/PE 4:6); $[\alpha]_D^{20}$ = +113.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.58 (d, *J* = 3.7 Hz, 1H; H-1′), 5.44 (d, *J* = 4.2 Hz, 1H; H-1), 4.38 (d, *J* = 2.4 Hz, 1H; H-10), 4.31 (d, *J* = 16.1 Hz, 1H; H-7a), 4.28 (d, *J* = 16.2 Hz, 1H; H-7′a), 4.21 (d, *J* = 16.2 Hz, 1H; H-7′b), 4.07 (d, *J* = 16.1 Hz, 1H; H-7b), 3.94−3.80 (m, 3H; H-4, H-5 and H-6a), 3.80−3.65 (m, 3H; H-6b and H-6′), 3.65−3.38 (m, 4H; H-3, H-3′, H-4′ and H-5′), 3.62 (s, 3H; MeO), 3.55 (s, 3H; MeO), 3.52 (s, 3H; MeO), 3.48 (s, 3H; MeO), 3.31 (dd, *J* = 9.5, 4.2 Hz, 2H; H-2), 3.17 (dd, *J* = 9.6, 3.7 Hz, 1H; H-2′), 2.41 (t, *J* = 2.4 Hz, 1H; H-12), 1.06 ppm (s, 42H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.1, 102.9 (C-8 and C-8′), 96.7 (C-1′), 88.4, 88.1 (C-9 and C-9′), 87.0 (C-1), 83.4 (two C, C-3 and C-3′), 82.0 (C-2′), 81.9 (C-2), 80.2 (C-11), 77.1 (C-4′), 74.3 (C-12), 72.0 (C-4), 71.8 (C-5), 70.5 (C-5′), 68.1 (C-6′), 67.1 (C-6), 61.0 (MeO), 60.5 (MeO), 59.9 (C-10), 59.5 (C-7′), 59.4 (MeO), 59.3 (C-7), 59.1 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3311 (weak, CC-H), 2171 (weak, C≡CSiR$_3$), 2112 cm^{-1} (strong, N_3); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{75}N_3O_{10}Si_2Na$ $[M + Na]^+$ 872.4883; found 872.4871.

Compound 15. To a 5 mL microwave vial containing **10** (1 equiv, 14.2 mg, 0.0184 mmol) and **8** (1.17 equiv, 13.2 mg, 0.0215 mmol) in

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

DMF (0.5 mL) was added a bright yellow solution of $CuSO_4{\cdot}5H_2O$ (0.2 equiv, 0.921 mg, 0.00369 mmol) and sodium ascorbate (0.4 equiv, 1.46 mg, 0.00738 mmol) in water (0.1 mL). The mixture was stirred and heated under microwave irradiation at 90 °C for 3 h. The mixture was transferred in a flask with MeOH and concentrated under reduced pressure. The residue was then diluted in a 9:1 (v/v) mixture of CH_3CN/30 wt %-NH_4OH and filtered on a pad of silica gel, using the same mixture as eluent (25 mL). The filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1 to 96:4) to afford **15** (15.4 mg, 60%). R_f 0.39 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +71.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H; H-12), 6.15 (d, *J* = 5.6 Hz, 1H; H-1″), 5.49 (d, *J* = 4.2 Hz, 1H; H-1‴), 5.40 (s, 1H; H-1), 5.16 (d, *J* = 3.6 Hz, 1H; H-1′), 4.98 (d, *J* = 11.9 Hz, 1H; H-10a), 4.82 (d, *J* = 11.9 Hz, 1H; H-10b), 4.58 (d, *J* = 5.4 Hz, 1H; H-5), 4.46−4.34 (m, 2H; H-10′), 4.34−4.14 (m, 5H; H-3″, H-7′ and H-7‴), 4.03−3.93 (m, 2H; H-4″ and H-6‴a), 3.90−3.43 (m, 36H; H-2″, H-3′, H-3‴, H-4, H-4′, H-5′, H-5″, H-5‴, H-6, H-6′, H-6″, H-6‴b and seven MeO), 3.41 (s, 3H; MeO), 3.38 (t, *J* = 3.6 Hz, 1H; H-3), 3.33−3.29 (m, 1H; H-4‴), 3.26 (dd, *J* = 9.8, 3.6 Hz, 1H; H-2′), 3.16 (dd, *J* = 9.8, 4.2 Hz, 1H; H-2‴), 3.06 (d, *J* = 3.6 Hz, 1H; H-2), 1.09−1.03 (m, 42H; two TIPS), 0.99 (t, *J* = 7.9 Hz, 9H; CH_3 TES), 0.61 ppm (q, *J* = 7.8 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7 (C-11), 124.3 (C-12), 103.0, 102.8, 102.6 (C-8′, C-8‴ and C-11′), 100.6 (C-1), 98.1 (C-1‴), 97.1 (C-1′), 89.0, 88.5, 88.2 (C-9′, C-9‴ and C-12′), 83.7 (C-3‴), 83.26, 83.22 (C-1″ and C-3″), 82.9 (C-3′), 82.0 (C-2‴), 81.7, 81.6 (C-2′ and C-2″), 80.9 (C-2), 79.5 (C-3), 78.1, 77.8 (C-4 and C-4′), 77.0 (C-4‴), 75.8 (C-5), 74.4 (C-5″), 73.7 (C-4″), 71.3 (C-5‴), 70.6 (C-5′), 69.3 (C-6‴), 68.1 (C-6′), 66.6 (C-6), 66.2 (C-10), 61.1 (MeO), 60.0 (MeO), 60.6 (C-6″ or C-10′), 60.54 (MeO), 60.49 (C-6″ or C-10′), 59.9 (MeO), 59.7, 59.5 (C-7′ and C-7‴), 59.4 (MeO), 58.6 (MeO), 58.2 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.6 (CH_3 TES), 4.4 ppm (CH_2 TIPS); IR (neat) 3477 (broad, O-H), 2186 cm^{-1} (very weak, C≡CSiR$_3$); HRMS (ESI) *m*/*z* calcd for $C_{68}H_{119}N_3O_{20}Si_3Na$ $[M + Na]^+$ 1404.7587; found 1404.7491.

Compound 16. To a solution of **12** (1 equiv, 200 mg, 0.207 mmol) and **8** (1 equiv, 127 mg, 0.207 mmol) in THF (3 mL) was added a bright yellow suspension of $CuSO_4{\cdot}5H_2O$ (0.5 equiv, 25.9 mg, 0.104 mmol) and sodium ascorbate (1 equiv, 41.1 mg, 0.207 mmol) in water (3 mL) at 20 °C. The mixture was stirred for 21 h at 50 °C., while it slowly darkened. The reaction mixture was diluted with a mixture of CH_3CN/EtOAc/30 wt %-NH_4OH (3:1:1) and was filtered over a pad of silica gel (2 cm thick) using the same mixture as eluent (50 mL). The filtrate was concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1 to 98:2) to afford **16** (267 mg, 82%). R_f 0.46 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +54.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (s, 1H; H-12), 6.12 (d, *J* = 5.4 Hz, 1H; H-1″), 5.51 (d, *J* = 3.4 Hz, 1H; H-1‴), 5.40 (s, 1H; H-1), 5.16 (d, *J* = 3.5 Hz, 1H; H-1′), 4.98 (d, *J* = 12.0 Hz, 1H; H-10a), 4.82 (d, *J* = 12.0 Hz, 1H; H-10b), 4.58 (d, *J* = 5.1 Hz, 1H; H-5), 4.40 (s, 2H; H-10′), 4.30 (d, *J* = 16.0 Hz, 1H; H-7″a), 4.33−4.16 (m, 5H; H-3″, H-7′ and H-7‴), 4.10 (d, *J* = 16.0 Hz, 1H; H-7″b), 3.99−3.92 (m, 2H; H-4″ and H-5″), 3.91−3.56 (m, 21H; H-2″, H-3′, H-5′, H-5‴, H-6, H-6′, H-6″, H-6‴ and three MeO), 3.56−3.33 (m, 20H; H-3, H-3‴, H-4, H-4′, H-4‴ and five MeO), 3.27 (dd, *J* = 9.4, 3.6 Hz, 1H; H-2′), 3.17 (dd, *J* = 9.7, 3.4 Hz, 1H; H-2‴), 3.60 (d, *J* = 3.1 Hz, 1H; H-2), 1.13−1.02 (m, 63H; three TIPS), 0.98 (t, *J* = 7.9 Hz, 9H; CH_3 TES), 0.60 ppm (q, *J* = 7.9 Hz, 6H; CH_2 TES); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7 (C-11), 124.2 (C-12), 103.22 (C-8′, C-8″, C-8‴ or C-11′), 103.15 (C-8′, C-8″, C-8‴ or C-11′), 103.05 (C-8′, C-8″, C-8‴ or C-11′), 103.00 (C-8′, C-8″, C-8‴ or C-11′), 100.6 (C-1), 96.97 (C-1′ or C-1‴), 96.94 (C-1′ or C-1‴), 88.4 (C-9′, C-9″, C-9‴ or C-12′), 88.1 (C-9′, C-9″, C-9‴ or C-12′), 88.00 (C-9′, C-9″, C-9‴ or C-12′), 87.96 (C-9′, C-9″, C-9‴ or C-12′), 83.2 (C-3‴), 83.1 (C-1″), 83.0 (C-3″), 82.9 (C-3′), 81.9 (C-2‴), 81.5 (C-2′), 81.2 (C-2″), 80.8 (C-2), 79.3 (C-3), 78.1 (C-4 or C-4‴), 77.9 (C-4 or C-4′), 77.4 (C-4‴), 75.8 (C-5), 73.4 (C-4″ or C-5″), 73.3 (C-4″ or C-5″), 70.7 (C-5′ or C-5‴), 70.5 (C-5′ or C-5‴), 68.5 (C-6′ or C-6‴), 68.1 (C-6′ or C-6‴), 67.3 (C-6″), 68.6 (C-6), 66.3 (C-10), 61.1 (MeO), 61.0 (MeO), 60.9 (C-10′), 60.3 (MeO), 59.7 (C-7′ and C-7‴), 59.5 (MeO), 59.4 (C-7″), 59.2 (MeO), 58.6 (MeO), 58.3 (MeO), 57.7 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.5 (CH_3 TES), 4.4 ppm (CH_2 TES); IR (neat) 2174 cm^{-1} (weak, C≡CSiR$_3$); HRMS (ESI) *m*/*z* calcd for $C_{80}H_{141}N_3O_{20}Si_4Na$ $[M + Na]^+$ 1598.9078; found 1598.8971.

Compound 17. To a solution of **16** (1 equiv, 57 mg, 0.036 mmol) in a 10:4:1 (v/v/v) mixture of CH_2Cl_2/MeOH/H_2O was added $AgNO_3$ (5 equiv, 31.5 mg, 0.18 mmol) at 20 °C. The mixture was stirred for 17 h at 20 °C. A saturated solution of NH_4Cl (10 mL) was added to the mixture, which was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 95:5) to afford **17** (44 mg, 0.030 mmol, 83%) as a colorless oil. R_f 0.43 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +74° (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H; H-12′), 6.12 (d, *J* = 5.9 Hz, 1H; H-1″), 5.53 (d, *J* = 3.4 Hz, 1H; H-1‴), 5.40 (s, 1H; H-1), 5.16 (d, *J* = 3.9 Hz, 1H; H-1′), 4.97 (d, *J* = 12.2 Hz, 1H; H-10′a), 4.82 (d, *J* = 12.2 Hz, 1H; H-10′b), 4.58 (d, *J* = 5.9 Hz, 1H; H-5), 4.39 (d, *J* = 2.4 Hz, 2H; H-10‴), 4.29 (d, *J* = 16.1 Hz, 1H; H-7″a), 4.33−4.16 (m, 5H; H-3″, H-7′ and H-7‴), 4.09 (d, *J* = 16.1 Hz, 1H; H-7″b), 3.99−3.92 (m, 2H; H-4″ and H-5″), 3.91−3.56 (m, 21H; H-2″, H-3′, H-5′, H-5‴, H-6, H-6′, H-6″, H-6‴ and three MeO), 3.56−3.33 (m, 20H; H-3, H-3‴, H-4, H-4′, H-4‴ and five MeO), 3.26 (dd, *J* = 9.3, 3.6 Hz, 1H; H-2′), 3.18 (dd, *J* = 9.3, 3.3 Hz, 1H; H-2‴), 3.06 (d, *J* = 3.6 Hz, 1H; H-2), 2.41 (t, *J* = 2.4 Hz, 1H, H-12‴), 1.13−1.02 (m, 63H; three TIPS) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7 (C-11′), 124.2 (C-12′), 103.16, 103.03, 103.98 (C-8′, C-8″, C-8‴), 100.6 (C-1), 97.06, 96.91 (C-1′ and C-1‴), 88.14, 88.11, 88.07 (C-9′, C-9″, C-9‴), 83.2 (C-3‴), 83.1 (C-1″), 83.0 (C-3″), 82.9, (C-3′), 82.1 (C-2‴), 81.6 (C-2′), 81.2 (C-2″), 80.9 (C-2), 80.2 (C-11‴), 79.5 (C-3), 78.2, 77.8 (C-4 and C-4′), 77.4 (C-4‴), 75.8 (C-5), 74.3 (C-12‴), 73.4 (C-4″ and C-5″), 70.61, 70.57 (C-5′ and C-5‴), 68.2, 68.1 (C-6′ and C-6‴), 67.3 (C-6″), 66.6 (C-6), 66.3 (C-10′), 61.1 (MeO), 61.0 (MeO), 60.3 (MeO), 59.81 (C-10‴), 59.7, 59.54 (C-7′ and C-7‴), 59.48 (MeO), 59.42 (C-7″), 59.2 (MeO), 58.6 (MeO), 58.2 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS) ppm; IR (neat) 2172 (weak, C≡CSiR$_3$) cm^{-1} ; MS (ESI) *m*/*z* calcd for $C_{74}H_{128}N_3O_{20}Si_3$ $[M + H]^+$ 1462.8393; found 1462.8372.

Compound 18. To a solution of **12** (1.72 equiv, 50 mg, 0.052 mmol) and **17** (1 equiv, 44.1 mg, 0.030 mmol) in THF (2.5 mL) was added a bright yellow suspension of $CuSO_4{\cdot}5H_2O$ (3.76 mg, 0.0151 mmol, 0.5 equiv) and sodium ascorbate (5.97 mg, 0.0301 mmol, 1 equiv) in H_2O (2.5 mL). The mixture was stirred at 40 °C for 18 h. The mixture was concentrated, diluted in a mixture of MeCN/water/30 wt %-NH_4OH (9:1:1), and filtered with the same eluent on a small pad of SiO_2 (typically 1 cm thick). The filtrate was evaporated under reduced pressure, and NMR analysis showed incomplete conversion. The crude product was dissolved in THF (2.5 mL), and a bright yellow suspension of $CuSO_4{\cdot}5H_2O$ (3.76 mg, 0.0151 mmol, 0.5 equiv) and sodium ascorbate (5.97 mg, 0.0301 mmol, 1 equiv) in H_2O (2.5 mL) was added. The mixture was heated at 40 °C for 18 h. The mixture was evaporated under reduced pressure, diluted in a mixture of MeCN/water/30 wt %-NH_4OH (9:1:1), and filtered with the same eluent on a small pad of SiO_2 (typically 1 cm thick). The filtrate was evaporated under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 90:10) to afford **18** (60.2 mg, 0.025 mmol, 82%) as a colorless oil. R_f 0.43 (DCM/MeOH 95:5); $[\alpha]_D^{20}$ = +71° (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H; H-12′ or H-12‴), 7.69 (s, 1H; H-12‴ or H-12′), 6.11 (d, *J* = 5.8 Hz, 2H; H-1″ and H-X1), 5.52 (d, *J* = 4.1 Hz, 2H; H-1‴ and H-Y1), 5.40 (s, 1H; H-1), 5.16 (d, *J* = 3.8 Hz, 1H; H-1′), 4.97 (d, *J* = 11.9 Hz, 1H; H-10′a), 4.93 (d, *J* = 12.2 Hz, 1H; H-10‴a), 4.86 (d, *J* = 12.2 Hz, 1H; H-10‴b), 4.81 (d, *J* = 11.9 Hz, 1H; H-10′b), 4.58 (d, *J* = 6.2 Hz, 1H; H-5), 4.41 (s, 2H; H-Y10), 4.32−4.16 (m, 10H, H-7″a, H-X7a, H-3″, H-7′, H-7‴, H-X3 and H-Y7), 4.10 (d, *J* = 16.1 Hz, 1H; H-7″b), 4.07 (d, *J* = 15.9 Hz, 1H; H-X7b), 4.00−3.90 (m, 4H; H-4″, H-5″, H-X4 and H-X5), 3.91−3.33 (m, 61H; H-2″, H-3′, H-5′, H-5‴, H-6, H-6′, H-6″, H-6‴, H-X2, H-Y5, H-X6, H-Y6, H-3, H-3‴, H-4, H-4′, H-4‴, H-Y3, H-Y4 and 18 MeO), 3.26 (dd, *J* = 9.9, 3.8 Hz, 1H; H-2′), 3.20 (dd, *J* = 9.3, 3.3 Hz, 1H; H-Y2 or H-2‴), 3.16 (dd, *J* = 9.3, 3.3 Hz, 1H; H-2‴ or H-Y2), 3.06 (d, *J* = 3.2 Hz, 1H; H-2), 1.11−1.02 (m, 105H; five TIPS), 0.98 (t, *J* = 7.7 Hz, 9H; CH_3-CH_2-TES), 0.60 (q, *J* = 7.7 Hz, 6H; CH_3-CH_2-TES ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7 (C-11′ and

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

C-11‴), 124.3, 124.2 (C-12′ and C-12‴), 103.28, 103.22, 103.1, 103.03, 103.01 (C-8′, C-8″, C-8‴, C-X8, C-Y8 and C-Y11), 100.6 (C-1), 97.11, 97.07, 96.96 (C-1′, C-1‴ and C-Y1), 88.4, 88.15, 88.07, 88.04, 87.96, 87.94 (C-9′, C-9″, C-9‴, C-X9, C-Y9 and C-Y12), 83.2 (C-Y3), 83.1 (C-1″ and C-X1), 83.03, 83.01 (C-3″ and C-X3), 82.89, 82.86 (C-3′ and C-3‴), 82.1 (C-2‴), 82.0 (C-Y2), 81.6, 81.3 (C-2″ and C-X2), 81.2 (C-2′), 80.9 (C-2), 79.5 (C-3), 78.2, 77.85, 77.80, 77.4 (C-4, C-4′, C-4‴, C-Y4), 75.8 (C-5), 73.8, 73.5, 73.44, 73.40 (C-4″, C-5″, C-X4 and C-X5), 71.0, 70.61, 70.57 (C-5′, C-5‴ and C-Y5), 68.6 (C-Y6 or C-X6), 68.2, 68.1 (C-6′ and C-6‴), 67.3 (C-6″ and C-X6 or C-Y6), 66.6 (C-6), 66.3, 66.2 (C-10′ and C-10‴), 61.08 (MeO), 61.03 (MeO), 60.97 (MeO), 60.8 (C-Y10), 60.38 (MeO), 60.37 (MeO), 59.71, 59.70, 59.68 (C-7′, C-7‴ and C-Y7), 59.51 (MeO), 59.46 (MeO), 59.50, 59.42 (C-7″, C-X7), 59.3 (MeO), 59.2 (MeO), 58.6 (MeO), 58.2 (MeO), 57.6 (MeO), 18.7 (CH_3 TIPS), 11.3 (CH TIPS), 7.5 (CH_3-CH_2-TES), 4.4 (CH_3-CH_2-TES) ppm; IR (neat) 2169 (weak, C≡CSiR_3) cm^{-1} ; MS (ESI) *m*/*z* calcd for $C_{123}H_{218}N_6O_{30}Si_6$ $[M + 2H]^{2+}$ 1213.7161; found 1213.7120.

Compound 19. To a solution of **18** (1 equiv, 60.2 mg, 0.025 mmol) in THF (2 mL) was added a solution of TBAF in THF (1 M, 12 equiv, 87 μL, 0.3 mmol) at 0 °C under argon. After stirring for 18 h at room temperature, the mixture was evaporated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 95:5) to afford a mixture of the product and TBAF. Purification by a second flash chromatography (CH_2Cl_2/MeOH 100:0 to 97:3) afforded **19** (28.2 mg, 0.018 mmol, 74%) as a colorless oil. R_f 0.43 (DCM/MeOH 95:5); $[\alpha]_D^{20}$ = +100° (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (s, 1H; H-12′ and H-12‴), 6.149 (d, *J* = 5.5 Hz, 1H; H-1″ or H-X1), 6.146 (d, *J* = 5.3 Hz, 1H; H-1″ or H-X1), 5.55 (d, *J* = 3.6 Hz, 1H; H-1‴ or H-Y1), 5.52 (d, *J* = 3.7 Hz, 1H; H-1‴ or H-Y1), 5.40 (s, 1H; H-1), 5.15 (d, *J* = 3.7 Hz, 1H; H-1′), 5.01 (d, *J* = 11.9 Hz, 1H; H-10′a), 5.0 (d, *J* = 12.2 Hz, 1H; H-10‴a), 4.834 (d, *J* = 11.9 Hz, 1H; H-10′b), 4.826 (d, *J* = 12.0 Hz, 1H; H-10‴b), 4.58 (d, *J* = 5.4 Hz, 1H; H-5), 4.39 (d, *J* = 11.8 Hz, 2H; H-Y10), 4.30−4.09 (m, 12H, H-3″, H-X3, H-7′, H-7″, H-7‴, H-X7 and H-Y7), 4.00−3.90 (m, 4H; H-4″, H-5″, H-X4 and H-X5), 3.91−3.55 (m, 33H; H-2″, H-3′, H-5′, H-5‴, H-6, H-6′, H-6″, H-6‴, H-X2, H-Y5, H-X6, H-Y6 and five MeO), 3.55−3.33 (m, 28H; H-3, H-3‴, H-4, H-4′, H-4‴, H-Y3, H-Y4 and seven MeO), 3.25 (dd, *J* = 9.7, 3.7 Hz, 1H; H-2′), 3.22 (dd, *J* = 9.7, 3.8 Hz, 1H; H-Y2 or H-2‴), 3.18 (dd, *J* = 9.5, 3.6 Hz, 1H; H-2‴ or H-Y2), 3.06 (d, *J* = 3.3 Hz, 1H; H-2), 2.44 (m, 3.5H, H-9′, H-9″, H-9‴, H-X9, H-Y9 and H-Y12) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.85, 144.80 (C-11′ and C-11‴), 124.3 (C-12′ and C-12‴), 100.6 (C-1), 97.0 (C-1′), 96.90, 96.87 (C-1‴ and C-Y1), 83.23, 83.22, 83.02, 82.98, 82.94, 82.90, 82.8 (C-1″, C-3′, C-3″, C-3‴, C-X1, C-X3, C-Y3), 82.02, 82.00, 81.6 (C-2′, C-2‴, C-Y2), 81.08, 81.03 (C-2″ and C-X2), 80.7 (C-2), 79.6, 79.5, 79.21, 79.18 (C-8′, C-8″, C-8‴, C-X8, C-Y8), 79.53 (C-Y12), 79.4 (C-3), 77.9, 77.8, 77.4, 77.1 (C-4, C-4′, C-4‴ and C-Y4), 75.7 (C-5), 75.6, 75.5, 75.33, 75.26, 74.9 (C-9′, C-9″, C-9‴, C-X9, C-Y9), 74.18 (C-Y11), 73.16, 73.14, 73.11, 73.0 (C-4″, C-X4, C-5″ and C-X5), 70.7, 70.53, 70.49 (C-5′, C-5‴ and C-Y5), 68.3, 68.2, 68.16, 68.14 (C-6′, C-6″, C-6‴, C-X6, and C-Y6), 66.5 (C-6), 66.3 (C-10′), 66.2 (C-10‴), 61.06 (MeOx2), 61.01 (MeO), 60.25 (MeO), 60.21 (MeO), 59.95 (C-Y10), 59.47 (MeO), 59.44 (MeO), 59.31 (MeO), 59.27 (MeO), 58.77, 58.75, 58.73, 58.71, 58.69 (C-7′, C-7″, C-7‴, C-X7, C-Y7), 58.6 (MeO), 58.3 (MeO), 57.6 (MeO) ppm; IR (neat): 3283 (weak CC-H), 2112 (weak, C≡CH) cm^{-1} ; MS (ESI) *m*/*z* calcd for C_{72} H_{102} D_2 N_6 O_{30} $[M + H]^+$ 1533.6870; found 1533.6892.

Compounds 20 and 21. To a vigorously stirred bright yellow suspension of $CuSO_4$·$5H_2O$ (10 equiv, 694.8 mg, 2.78 mmol) and sodium ascorbate (20 equiv, 1.10 g, 5.56 mmol) in a mixture of H_2O/THF (1:1, 10 mL) at 20 °C was added dropwise (drops of 7 μL, over 3 h) a solution of **13** (1 equiv, 182.5 mg, 0.278 mmol) in a mixture of H_2O/THF (1:1, 60 mL). TLC showed complete conversion. The reaction mixture was diluted with a mixture of CH_3CN/EtOAc/30 wt %-NH_4OH (2:2:1, 50 mL) and was filtered over a pad of silica gel (2 cm thick) using the same mixture as eluent (50 mL). The filtrate was concentrated. Then, CH_2Cl_2 (30 mL) and water (30 mL) were added and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was carefully purified by flash chromatography (CH_2Cl_2/MeOH 99:1 to 88:12) to afford **20** (74.9 mg, 42%) and **21** (15.0 mg, 9%). **Data for cyclodimer 20**: R_f 0.74 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = +63.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 2H; H-12), 6.50 (d, *J* = 5.2 Hz, 2H; H-1), 5.20 (d, *J* = 3.4 Hz, 2H; H-1′), 4.92 (d, *J* = 11.4 Hz, 2H; H-10a), 4.88 (d, *J* = 11.4 Hz, 2H; H-10b), 4.28 (s, 4H; H-7′), 3.90−3.68 (m, 16H; H-2, H-3, H-4, H-6, H-5′ and H-6′), 3.71 (s, 6H; MeO), 3.61 (s, 6H; MeO), 3.52 (dd, *J* = 9.8, 8.7 Hz, 2H; H-3′), 3.52 (s, 6H; MeO), 3.43 (s, 6H; MeO), 3.40 (dd, *J* = 9.7, 8.7 Hz, 2H; H-4′), 3.36 (ddd, *J* = 10.6, 3.8, 1.9 Hz, 2H; H-5), 3.19 (dd, *J* = 9.8, 3.4 Hz, 2H; H-2′), 1.05 ppm (s, 42H; TIPS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.8 (C-11), 123.7 (C-12), 102.4 (C-8′), 99.5 (C-1′), 88.8 (C-9′), 83.5 (C-3′), 83.1 (C-1), 82.6 (C-3), 82.4 (C-2′), 80.4 (C-2), 78.2 (C-4′), 77.5 (C-4), 73.7 (C-5), 71.0 (C-5′), 68.8 (C-6′), 66.8 (C-10), 62.0 (C-6), 61.6 (MeO), 60.8 (MeO), 59.8 (C-7′), 59.2 (MeO), 58.6 (MeO), 18.7 (CH_3 TIPS), 11.2 ppm (CH TIPS); IR (neat) 3457 cm^{-1} (broad, O-H); HRMS (ESI) *m*/*z* calcd for $C_{62}H_{106}N_6O_{20}Si_2Na$ $[M + Na]^+$ 1333.6893; found 1333.6889. **Data for cyclotrimer 21**: R_f 0.70 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = +98.2 (*c* 0. 5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (s, 3H; H-12), 6.21 (d, *J* = 5.6 Hz, 3H; H-1), 5.47 (d, *J* = 4.1 Hz, 3H; H-1′), 5.04 (d, *J* = 10.9 Hz, 3H, H-10a), 4.64 (d, *J* = 12.2 Hz, 3H; H-10b), 4.30 (t, *J* = 8.5 Hz, 3H; H-3), 4.28 (s, 6H; H-7′), 3.98 (dd, *J* = 9.7, 8.6 Hz, 3H; H-4), 3.90−3.30 (m, 51H; H-2, H-5, H-6, H-3′, H-5′, H-6′ and 3 × MeO), 3.38 (s, 9H, MeO), 3.34 (dd, 3H, *J* = 9 Hz; H-4′), 3.20 (dd, *J* = 10.0, 4.1 Hz, 3H; H-2′), 2.85 (br s, 3H; OH), 1.05 ppm (s, 63H; TIPS); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2 (C-11), 124.3 (C-12), 102.6 (C-8′), 98.3 (C-1′), 88.6 (C-9′), 83.7 (C-3′), 83.4 (C-3), 83.2 (C-1), 82.0 (C-2′), 81.5 (C-2), 79.0 (C-4′), 73.8 (C-5), 73.6 (C-4), 71.2 (C-5′), 69.0 (C-6′), 65.9 (C-10), 61.5 (MeO), 60.8 (C-6), 60.5 (MeO), 60.1 (MeO), 59.8 (C-7′), 59.3 (MeO), 18.7 (CH_3 TIPS), 11.3 ppm (CH TIPS); IR (neat) 3469 (broad, O-H), 2173 cm^{-1} (weak, C≡CSiR_3); HRMS (ESI) *m*/*z* calcd for $C_{93}H_{160}N_9O_{30}Si_3$ $[M + H]^+$ 1967.0573; found 1967.0705. HRMS (ESI) *m*/*z* calcd for $C_{93}H_{161}N_9O_{30}Si_3$ $[M + 2H]^{2+}$ 984.0323; found 984.0410.

Compound 22. To a solution of **20** (1 equiv, 50.8 mg, 0.0387 mmol) in anhydrous CH_3CN (1.33 mL) was added AgF (4 equiv, 19.7 mg, 0.155 mmol) under argon and in the dark. The mixture was stirred for 20 h in the dark at room temperature. A solution of HCl (1 M, 1 mL, 1 mmol) was added, and the mixture was further stirred for 5 min. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 90:10) to afford pure **22** (29.1 mg, 75%) as a colorless oil. R_f 0.21 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +96.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 2H; H-12), 6.47 (d, *J* = 4.6 Hz, 2H; H-1), 5.18 (d, *J* = 3.3 Hz, 2H; H-1′), 4.94 (d, *J* = 11.2 Hz, 2H; H-10a), 4.87 (d, *J* = 11.2 Hz, 2H; H-10b), 4.24 (dd, *J* = 15.9, 2.2 Hz, 2H; H-7′a), 4.17 (dd, *J* = 15.9, 2.2 Hz, 2H; H-7′b), 3.88−3.67 (m, 22H; H-2, H-3, H-4, H-6, H-5′, H-6′ and MeO), 3.61 (s, 6H; MeO), 3.53 (dd, *J* = 9.7, 8.7 Hz, 2H; H-3′), 3.51 (s, 6H; MeO), 3.43 (s, 6H; MeO), 3.42 (t, *J* = 9.2 Hz, 2H; H-4′), 3.34 (m, 2H; H-5), 3.19 (dd, *J* = 9.7, 3.3 Hz, 2H; H-2′), 2.49 ppm (t, *J* = 2.2 Hz, 2H; H-9′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.7 (C-11), 123.7 (C-12), 99.5 (C-1′), 83.4 (C-3′), 83.0 (C-1), 82.33, 82.29 (C-2′ and C-3), 80.1 (C-2), 79.2 (C-8′), 78.1 (C-4′), 77.7 (C-4), 75.6 (C-9′), 74.0 (C-5), 71.0 (C-5′), 68.8 (C-6′), 66.6 (C-10), 62.0 (C-6), 61.4 (MeO), 60.7 (MeO), 59.1 (MeO), 58.9 (C-7′), 58.7 ppm (MeO); IR (neat) 3452 (broad, O-H), 3270 (weak, CC-H), 2115 cm^{-1} (very weak, C≡CH); HRMS (ESI) *m*/*z* calcd for $C_{44}H_{67}N_6O_{20}$ $[M + H]^+$ 999.4405; found 999.4365. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{66}N_6O_{20}Na$ $[M + Na]^+$ 1021.4224; found 1021.4193. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{66}N_6O_{20}Na_2$ $[M + 2Na]^+$ 522.2058; found 522.2074.

Cluster 24. To a solution of **22** (1 equiv, 10.8 mg, 0.0108 mmol) and **23**[21] (6.83 equiv, 44 mg, 0.0739 mmol) in DMF (1 mL) was added a bright yellow solution of $CuSO_4$·$5H_2O$ (0.25 equiv, 0.675 mg, 0.0027 mmol) and sodium ascorbate (0.5 equiv, 1.07 mg, 0.00541 mmol) in H_2O (0.25 mL). The mixture was stirred and heated under microwave irradiation at 80 °C for 1 h. The mixture was diluted with a mixture of CH_3CN/EtOAc/30 wt %-NH_4OH (2:2:1) and filtered through a pad of

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

silica gel (2 cm thick), using the same mixture as eluent (25 mL). The filtrate was concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 90:10) to afford pure **24** (16.5 mg, 70%) as a colorless oil. R_f 0.30 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +68.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (s, 2H; H-12), 7.81 (s, 2H; H-9′), 7.40−7.00 (m, 30H; ArH Bn), 7.20 (d, *J* = 8.6 Hz, 4H; ArH PMB), 6.81 (d, *J* = 8.6 Hz, 4H; ArH PMB), 6.34 (d, *J* = 5.1 Hz, 2H; H-1), 5.99 (d, *J* = 3.1 Hz, 2H; H-1*), 5.15 (d, *J* = 3.4 Hz, 2H; H-1′), 4.96 (d, *J* = 11.3 Hz, 2H; H-10a), 4.81 (dd, *J* = 3.1, 2.8 Hz, 2H; H-2*), 4.76−4.37 (m, 22H; 3 × CH_2 Bn, CH_2 PMB, H-10b and H-7′), 4.04 (dd, *J* = 8.0, 2.8 Hz, 2H; H-3*), 3.96 (dd, *J* = 8.7, 8.0 Hz, 2H; H-4*), 3.89−3.47 (m, 24H; H-2, H-3, H-4, H-6, H-3′, H-5′, H-6′, H-5* and H-6*), 3.77 (s, 6H; MeO), 3.70 (s, 6H; MeO), 3.58 (s, 6H; MeO), 3.51 (s, 6H; MeO), 3.42(m, 2H; H-5), 3.39 (s, 6H; MeO), 3.33 (t, *J* = 9.2 Hz, 2H; H-4′), 3.17 ppm (dd, *J* = 9.9, 3.4 Hz, 2H; H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3 (Ar), 145.6, 145.0 (C-11 and C-8′), 138.3, 138.2, 137.9, 130.2, 129.6, 129.0−127.5 (Ar), 123.5, 122.7 (C-12 and C-9′), 113.9 (Ar), 99.4 (C-1′), 85.2 (C-1*), 83.4 (C-3′), 83.0 (C-1), 82.3 (C-2′), 82.0 (C-3), 79.9 (C-2), 78.6 (C-3* and C-4′), 77.8 (C-4), 74.8 (C-5*), 74.5 (CH_2 Bn/PMB), 74.4 (C-5), 74.3 (C-4*), 74.0 (C-2*), 73.4, 73.1, 72.6 (CH_2 Bn/PMB), 71.0 (C-5′), 70.1 (C-6′), 68.5 (C-6*), 66.7 (C-10), 64.9 (C-7′), 61.5 (C-6), 61.3, 60.5, 59.1, 58.6, 55.4 (5 × MeO); IR (neat) 3468 cm^{-1} (broad, O-H); HRMS (ESI) *m*/*z* calcd for $C_{114}H_{142}N_{12}O_{32}$ $[M + 2H]^{2+}$ 1095.4921; found 1095.4842.

Cluster 26. To a solution of **22** (1 equiv, 8.3 mg, 0.00831 mmol) and **25**[16b] (4 equiv, 15.7 mg, 0.0332 mmol) in DMF (1 mL) was added a bright yellow solution of $CuSO_4{\cdot}5H_2O$ (0.25 equiv, 0.519 mg, 0.00208 mmol) and sodium ascorbate (0.5 equiv, 0.823 mg, 0.00415 mmol) in H_2O (0.2 mL). The mixture was stirred and heated under microwave irradiation at 80 °C for 1 h. The mixture was diluted with a mixture of CH_3CN/EtOAc/30 wt %-NH_4OH (2:2:1) and filtered through a pad of silica gel (2 cm thick), using the same mixture as eluent (25 mL). The filtrate was concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 90:10) to afford pure **26** (12.1 mg, 73%) as a colorless oil. R_f 0.30 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +57.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (s, 2H; H-12), 7.55 (s, 2H; H-9′), 6.41 (d, *J* = 3.8 Hz, 2H; H-1), 5.13 (d, *J* = 3.3 Hz, 2H; H-1′), 5.07 (t, *J* = 8.9 Hz, 2H; H-4*), 5.03 (dd, *J* = 9.2, 8.9 Hz, 2H; H-3*), 4.98 (d, *J* = 11.6 Hz, 2H; H-10a), 4.96 (ddd, *J* = 10.2, 9.2, 5.3 Hz, 2H; H-2*), 4.67 (d, *J* = 11.6 Hz, 2H; H-10b), 4.66 (d, *J* = 12.4 Hz, 2H; H-7′a), 4.59 (d, *J* = 12.4 Hz, 2H; H-7′b), 4.29 (t, *J* = 7.3 Hz, 4H; H-15*), 4.15 (d, *J* = 2.2 Hz, 4H; H-6*), 3.90−3.62 (m, 16H; H-2, H-3, H-4, H-6, H-5′ and H-6′), 3.69 (s, 6H; MeO), 3.59 (s, 6H; MeO), 3.58 (m, 4H; H-3′ and H-5), 3.51 (s, 6H; MeO), 3.41 (s, 6H; MeO), 3.35 (t, *J* = 9.4 Hz, 2H; H-4′), 3.18 (dd, *J* = 11.3, 5.3 Hz, 2H; H-1*a), 3.17 (dd, *J* = 9.8, 3.3 Hz, 2H; H-2′), 2.71 (m, 2H; H-7*a), 2.63 (dt, *J* = 8.9, 2.2 Hz, 2H; H-5*), 2.55 (m, 2H; H-7*b), 2.32 (dd, *J* = 11.3, 10.2 Hz, 2H; H-1*b), 2.10−1.97 (several s, 24H; Ac), 1.85 (m, 4H; H-14*), 1.48−1.20 ppm (m, 24H; H-8* to H-13*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.5, 170.2, 169.9 (C═O acetate), 145.68, 145.67 (C-8′ and C-11), 123.4 (C-12), 122.7 (C-9′), 99.4 (C-1′), 83.4 (C-3′), 83.0 (C-1), 82.3 (C-2′), 81.4 (C-3), 79.5 (C-2), 78.6 (C-4′), 77.8 (C-4), 75.0 (C-5), 74.9 (C-3*), 71.0 (C-5′), 69.8 (C-6′), 69.7, 69.6 (C-2* and C-4*), 66.7 (C-10), 64.9 (C-7′), 61.8 (C-6), 61.6 (C-5*), 61.2 (MeO), 60.3 (MeO), 59.7 (C-6*), 59.0 (MeO), 58.7 (MeO), 53.1 (C-1*), 51.9 (C-7*), 50.5 (C-15*), 30.3, 29.5, 29.1, 27.4, 27.3, 26.6, 24.8 (C-8* to C-14*), 21.1−20.6 ppm (CH_3 acetate); IR (neat) 3467 (broad, O-H), 1746 cm^{-1} (strong, C═O acetate); HRMS (ESI) *m*/*z* calcd for $C_{90}H_{142}N_{14}O_{36}Na$ $[M + Na]^+$ 2017.9603; found 2017.9490.

Cluster 27. To a solution of **22** (1 equiv, 12.1 mg, 0.00606 mmol) in a mixture of MeOH/water (1:1 4 mL) was added Amberlite IRA-400 (OH^-) (300 mg) at room temperature. The mixture was stirred at 40 °C for 16 h. The mixture was filtered (rinsing with MeOH, water and mixture thereof). The filtrate was concentrated to afford pure **27** (9.0 mg, 89%) as a colorless viscous oil. $[\alpha]_D^{20}$ = +61.3 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.11 (s, 2H; H-12), 7.98 (s, 2H; H-9′), 6.44 (d, *J* = 4.8 Hz, 2H; H-1), 5.16 (d, *J* = 3.3 Hz, 2H; H-1′), 5.00 (d, *J* = 11.4 Hz, 2H; H-10a), 4.67 (d, *J* = 12.4 Hz, 2H; H-7′a), 4.61 (d, *J* = 11.4 Hz, 2H; H-10b), 4.58 (d, *J* = 12.4 Hz, 2H; H-7′b), 4.35 (t, *J* = 7.0 Hz, 4H; H-15*), 4.00 (dd, *J* = 7.1, 5.1 Hz, 2H; H-3), 3.97−3.80 (m, 8H; H-2, H-5′ and H-6*), 3.80−3.50 (m, 34H; H-4, H-5, H-6, H-3′, H-6′, H-2* and 3 × MeO), 3.50−3.38 (m, 10H; H-3*, H-4* and MeO), 3.26−3.10 (m, 6H; H-2′, H-4′ and H-1*a), 2.99 (m, 2H; H-7*a), 2.80 (m, 2H; H-7*b), 2.54−2.39 (m, 4H; H-1*b and H-5*), 1.86 (m, 4H; H-14*), 1.58 (m, 4H; H-8*), 1.31 ppm (m, 20H; H-9* to H-13*); ^{13}C NMR (CD_3OD, 100 MHz) δ 146.6, 145.8 (C-8′ and C-11), 125.3 (C-9′), 125.0 (C-12), 100.6 (C-1′), 84.8 (C-3′), 84.6 (C-1), 83.5 (C-2′), 81.6 (C-3), 80.0 (C-2), 79.9 (C-4′), 79.3, 79.2 (C-4 and C-3*), 77.2 (C-5), 72.3 (C-5′), 71.1 (C-4*), 70.6 (C-6′), 69.8 (C-2*), 67.6 (C-5*), 67.2 (C-10), 65.4 (C-7′), 62.5 (C-6), 61.4, 60.6, 59.1, 59.0 (4 × MeO), 58.1 (C-6*), 56.8 (C-1*), 54.0 (C-7*), 51.5 (C-15*), 31.3, 30.5, 30.4, 30.0, 28.3, 27.5, 25.0 ppm (C-8* to C-14*); IR (neat) 3356 cm^{-1} (broad, O-H); HRMS (ESI) *m*/*z* calcd for $C_{74}H_{127}N_{14}O_{28}$ $[M + H]^+$ 1659.8939; found 1659.8814. HRMS (ESI) *m*/*z* calcd for $C_{74}H_{128}N_{14}O_{28}$ $[M + 2H]^{2+}$ 830.4506; found 830.4431.

Cluster 28. To a solution of **19** (1 equiv, 25.1 mg, 0.016 mmol) and **25**[16b] (10.5 equiv, 85.8 mg, 0.172 mmol) in DMF (4 mL) was added a bright yellow suspension of $CuSO_4{\cdot}5H_2O$ (1 equiv, 4 mg, 0.016 mmol) and sodium ascorbate (2 equiv, 6.5 mg, 0.033 mmol) in H_2O (1 mL). The mixture was heated at 80 °C for 1 h under microwave irradiation. The mixture was evaporated under reduced pressure, diluted in a mixture of MeCN/water/30 wt %-NH_4OH (9:1:1), and filtered with the same eluent on a small pad of SiO_2 (typically 1 cm thick). The solvents were evaporated under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 to 95:5) to afford **28** (58.9 mg, 0.013 mmol, 79%) as a colorless oil. R_f 0.41 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +58.1° (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.88 (s, 1H), 7.78 (s, 1H), 7.61 (s, 2H), 7.60 (s, 1H), 7.56 (m, 3H) (H-12′, H-12‴, H-9′, H-9″, H-9‴, H-X9, H-Y9, H-Y12), 6.18 (d, *J* = 5.6 Hz, 1H; H-1″ or H-X1), 6.16 (d, *J* = 5.6 Hz, 1H; H-1″ or H-X1), 5.53 (d, *J* = 3.4 Hz, 1H; H-1‴ or H-Y1),), 5.50 (d, *J* = 3.6 Hz, 1H; H-1‴ or H-Y1), 5.36 (s, 1H; H-1), 5.12 (d, *J* = 3.6 Hz, 1H; H-1′), 5.08−4.97(m, 12H, H-Z3 and H-Z4), 4.97−4.89 (m, 8H, H-10′a, H-10‴a and H-Z2), 4.74−4.43 (m, 15H, H-5, H-7′, H-7″, H-7‴, H-X7, H-Y7, H-10′b, H-10‴b and H-Y10), 4.33−4.22 (m, 14H, H-3″, H-X3 and H-Z15), 4.16−4.08 (m, 12H, H-Z6), 3.99−3.88 (m, 4H, H-4″, H-X4, H-5″, H-X5), 3.36 (m, 60H,H-2″, H-X2, H-3′, H-3‴, H-Y3, H-4, H-4′, H-4‴, H-Y4, H-5′, H-5‴, H-Y5, H-6, H-6′, H-6″, H-6‴, H-X6, H-Y6 and 12 MeO), 3.34 (t, *J* = 3.3 Hz, 1H, H-3), 3.22 (dd, *J* = 9.5 and 3.3 Hz, 1H, H-2′), 3.20−3.12 (m, 8H, H-2‴, H-Y2 and H-Z1), 3.03 (d, *J* = 3.3 Hz, 1H; H-2), 2.74−2.64 (m, 6H, H-Z7a), 2.64−2.58 (m, 6H, H-Z5), 2.58−2.48 (m, 6H, H-Z7b), 2.3 (t, 6H, *J* = 11.1 Hz, H-Z1b), 2.04 (s, 18H, OAc), 1.99 (s, 36H, OAc), 1.98 (s, 18H, OAc), 1.90−1.80 (m, 12H, H-Z14), 1.46−1.13 (m, 72H, from H-Z8 to H-Z13) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 70000 scans) δ 171.0, 170.4, 170.1, 169.8 (C═O acetate), 145.3, 145.1, 144.77, 144.73, 144.67, 144.64, 144.55, 144.4 (C-8′, C-8″, C-8‴, C-X8, C-Y8, C-11′, C-11‴ and C-Y11), 124.9, 124.6, 124.5, 122.9, 122.6 (C-9′, C-9″, C-9‴, C-X9, C-Y9, C-12′, C-12‴ and C-Y12), 100.5 (C-1), 97.0 (C-1′), 96.7, 96.6, (C-1‴ and C-Y1), 83.2, 83.02, 82.92, 82.88, 82.77 (C-1″, C-X1, C-3′, C-3″, C-3‴, C-X3 and C-Y3), 82.0 (C-2‴ and C-Y2), 81.6 (C-2′), 81.3, 81.2 (C-2″ and C-X2), 80.6 (C-2), 79.4 (C-3), 77.96, 77.87, 77.78, 77.70 (C-4, C-4′, C-4‴, C-Y4), 75.6 (C-5), 74.8 (C-Z3), 73.3, 73.2, 73.1, 72.9 (C-4″, C-X4, C-5″ and C-X5), 70.8, 70.7, 70.5 (C-5′, C-5‴ and C-Y5), 69.6 (C-Z4), 69.5 (C-Z2), 69.0, 68.8, 68.7, 68.6 (C-6′, C-6″, C-6‴, C-X6 and C-Y6), 66.5 (C-6), 66.2 (C-10′), 66.1 (C-10‴), 65.2, 64.9 (C-7′, C-7″, C-7‴, C-X7, C-Y7, and C-Y10), 61.5 (C-Z5), 61.03, 60.99, 60.96, 60.33, 60.29 (OMe), 59.6 (C-Z6), 59.44, 59.41, 59.22, 59.18, 58.5, 58.2, 57.6 (OMe), 53.5 (C-Z1), 51.9 (C-Z7), 50.4 (C-Z15), 30.52−30.31 (C-Z14), 29.0, 27.2, 26.6 (from C-Z9 to Z-13), 24.7 (C-Z8), 20.96, 20.93, 20.83, 20.77 ($\underline{C}H_3$-C═O), ppm; IR (neat): 1744 (strong C═O) cm^{-1} ; MS (ESI) *m*/*z* calcd for $C_{210}H_{333}N_{30}O_{78}$ $[M + 3H]^{3+}$ 1507.7666; found 1507.7685.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01938.

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733

AUTHOR INFORMATION

Corresponding Author

*E-mail: philippe.compain@unistra.fr. Tel: (+33) 3-6885-2792. Fax: (+33) 3-6885-2754.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the CNRS, the University of Strasbourg, the Centre International de Recherche aux Frontières de la Chimie (FRC), and the Institut Universitaire de France (IUF). M.L.L. thanks the French Ministry of Research for a fellowship. The authors express their gratitude to David Augros for assistance with synthetic work and to Michel Schmitt and Bruno Vincent for NMR studies.

REFERENCES

(1) Choi, S.-K. *Synthetic Multivalent Molecules: Concepts and Biomedical Applications*; Wiley-Interscience: Hoboken, N.J, 2004.

(2) (a) Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555−578. (b) Ambrosi, M.; Cameron, N. R.; Davis, B. G. *Org. Biomol. Chem.* **2005**, *3*, 1593−1608. (c) Kiessling, L. L.; Gestwicki, J. E.; Strong, L. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2348−2368.

(3) (a) Lee, R. T.; Ichikawa, Y.; Kawasaki, T.; Drickamer, K.; Lee, Y. C. *Arch. Biochem. Biophys.* **1992**, *299*, 129−136. (b) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637−674. (c) Dam, T. K.; Brewer, C. F. *Adv. Carbohydr. Chem. Biochem.* **2010**, *63*, 139−164. (d) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321−327.

(4) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669.

(5) (a) Conte, M. L.; Staderini, S.; Chambery, A.; Berthet, N.; Dumy, P.; Renaudet, O.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2012**, *10*, 3269−3277.

(6) Durka, M.; Buffet, K.; Iehl, J.; Holler, M.; Nierengarten, J.-F.; Vincent, S. P. *Chem. - Eur. J.* **2012**, *18*, 641−651.

(7) Compain, P.; Bodlenner, A. *ChemBioChem* **2014**, *15*, 1239−1251.

(8) (a) Gouin, S. *Chem. - Eur. J.* **2014**, *20*, 11616−11628. (b) Zelli, R.; Longevial, J.-F.; Dumy, P.; Marra, A. *New J. Chem.* **2015**, *39*, 5050−5074.

(9) (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754−2794. (b) Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922−14933. (c) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U. S. A.* **1971**, *68*, 1678−1683. (d) Wittmann, V.; Pieters, R. J. *Chem. Soc. Rev.* **2013**, *42*, 4492−4503.

(10) (a) Schwefel, D.; Maierhofer, C.; Beck, J. G.; Seeberger, D. S.; Diederichs, K.; Möller, H. M.; Welte, W.; Wittmann, V. *J. Am. Chem. Soc.* **2010**, *132*, 8704−8719. (b) Wittmann, V.; Seeberger, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4348−4352.

(11) For recent reviews, see: (a) Lahmann, M. *Top. Curr. Chem.* **2009**, *288*, 17−65. (b) Deniaud, D.; Julienne, K.; Gouin, S. G. *Org. Biomol. Chem.* **2011**, *9*, 966−979. (c) Pieters, R. J. *Org. Biomol. Chem.* **2009**, *7*, 2013−2025. (d) Hartmann, M.; Lindhorst, T. K. *Eur. J. Org. Chem.* **2011**, 3583−3609. (e) Jayaraman, N. *Chem. Soc. Rev.* **2009**, *38*, 3463−3483. (f) Martínez, A.; Ortiz Mellet, C.; Garcia Fernández, J. M. *Chem. Soc. Rev.* **2013**, *42*, 4746−4773. (g) Chabre, Y. M.; Roy, R. *Adv. Carbohydr. Chem. Biochem.* **2010**, *63*, 165−393. (h) Chabre, Y. M.; Roy, R. *Chem. Soc. Rev.* **2013**, *42*, 4657−4708.

(12) Faugeras, P.-A.; Boëns, B.; Elchinger, P.-H.; Brouillette, F.; Montplaisir, D.; Zerrouki, R.; Lucas, R. *Eur. J. Org. Chem.* **2012**, 4087−4105.

(13) Martínez, Á.; Ortiz Mellet, C.; Garcia Fernández, J. M. *Chem. Soc. Rev.* **2013**, *42*, 4746−4773.

(14) Jouffroy, M.; Armspach, D.; Matt, D.; Toupet, L. *Org. Biomol. Chem.* **2013**, *11*, 3699−3705.

(15) Sollogoub, M. *Synlett* **2013**, *24*, 2629−2640.

(16) See, for examples: (a) Compain, P.; Decroocq, C.; Iehl, J.; Holler, M.; Hazelard, D.; Mena Barragán, T.; Ortiz Mellet, C.; Nierengarten, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 5753−5756. (b) Decroocq, C.; Rodríguez-Lucena, D.; Russo, V.; Mena Barragán, T.; Ortiz Mellet, C.; Compain, P. *Chem. - Eur. J.* **2011**, *17*, 13825−13831. (c) Compain, P.; Decroocq, C.; Joosten, A.; de Sousa, J.; Rodriguez-Lucena, D.; Butters, T. D.; Bertrand, J.; Clément, R.; Boinot, C.; Becq, F.; Norez, C. *ChemBioChem* **2013**, *14*, 2050−2058. (d) Bonduelle, C.; Huang, J.; Mena-Barragán, T.; Ortiz Mellet, C.; Decroocq, C.; Etamé, E.; Heise, A.; Compain, P.; Lecommandoux, S. *Chem. Commun.* **2014**, *50*, 3350−3352.

(17) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(18) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(19) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015.

(20) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1919−1958.

(21) Lepage, M. L.; Bodlenner, A.; Compain, P. *Eur. J. Org. Chem.* **2013**, 1963−1972.

(22) Santoyo-González, F.; Hernández-Mateo, F. In *Heterocycles from Carbohydrate Precursors*; Ashry, E. S. H., Ed.; Springer: Berlin, 2007; Vol. 7, pp 133−177.

(23) Crich, D.; Yang, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8896−8899.

(24) Lo Conte, M.; Marra, A.; Chambery, A.; Gurcha, S. S.; Besra, G. S.; Dondoni, A. *J. Org. Chem.* **2010**, *75*, 6326−6336.

(25) (a) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638−1639. (b) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *Org. Lett.* **2005**, *7*, 4479−4482.

(26) Conte, M. L.; Grotto, D.; Chambery, A.; Dondoni, A.; Marra, A. *Chem. Commun.* **2011**, *47*, 1240−1242.

(27) Orsini, A.; Vitérisi, A.; Bodlenner, A.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2005**, *46* (13), 2259−2262.

(28) Valverde, I. E.; Delmas, A. F.; Aucagne, V. *Tetrahedron* **2009**, *65*, 7597−7602.

(29) (a) Tanaka, T.; Huang, W. C.; Noguchi, M.; Kobayashi, A.; Shoda, S. *Tetrahedron Lett.* **2009**, *50*, 2154−2157. (b) Noteworthy, an acetylation−recrystallization−deacetylation sequence was necessary to isolate the polar, water-soluble product in high purity with 74% yield. In our hands, an excess of triethylamine was used as proton scavenger and the resulting ammonium salts defeated our attempts of purification on a 10 g scale.

(30) Roën, A.; Mayato, C.; Padrón, J. I.; Vázquez, J. T. *J. Org. Chem.* **2008**, *73*, 7266−7279.

(31) Szejtli, J. *Chem. Rev.* **1998**, *98* (5), 1743−1754.

(32) Kim, S.; Kim, B.; In, J. *Synthesis* **2009**, 1963−1968.

(33) Ip, W. K. E.; Takahashi, K.; Ezekowitz, R. A.; Stuart, L. M. *Immunol. Rev.* **2009**, *230*, 9−21.

(34) (a) For a review on the applications of carbohydrate-derived macrocycles, see: Xie, J.; Bogliotti, N. *Chem. Rev.* **2014**, *114*, 7678−7739. (b) For a review dealing with CD-based metalated cavitands, see: Gramage-Doria, R.; Armspach, D.; Matt, D. *Coord. Chem. Rev.* **2013**, *257*, 776−816.

(35) Fujimaki, I.; Ichikawa, Y.; Kuzuhara, H. *Carbohydr. Res.* **1982**, *101*, 148−151.

DOI: 10.1021/acs.joc.5b01938
J. Org. Chem. 2015, 80, 10719−10733