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o-Xylylene Protecting Group in Carbohydrate Chemistry: Application to the Regioselective Protection of a Single *vic*-Diol Segment in Cyclodextrins

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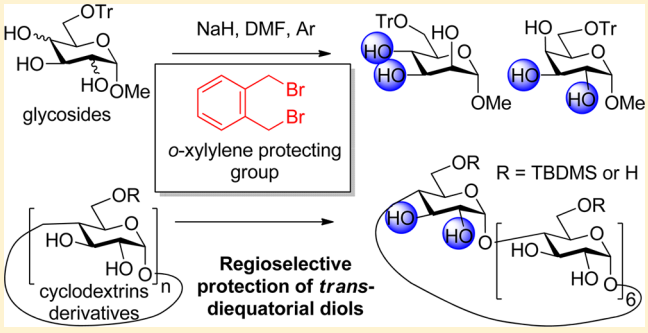
Supporting Information

ABSTRACT: A systematic study of the suitability of α,α'-dibromo-*o*-xylene as a reagent for cyclic *o*-xylylene protection of *vic*-diols in different monosaccharide substrates is reported. The installation of this protecting group, formally equivalent to a di-*O*-benzylation reaction, proceeds with good regioselectivity toward 1,2-*trans*-diequatorial diol systems in pyranose and furanose rings. Initially, the benzyl ether-type derivative of the more acidic hydroxyl is preferentially formed. Subsequent intramolecular etherification toward the equatorial-oriented vicinal OH is kinetically favored. The methodology has been implemented for the simultaneous protection of the secondary O-2 and O-3 positions of a single D-glucopyranosyl unit in cyclic oligosaccharides of the cyclodextrin (CD) family (cyclomaltohexa-, -hepta-, and -octaose; α, β, and γCD).



INTRODUCTION

Protecting group strategies are incorporated into most approaches toward the synthesis of natural products and other molecule targets.[1,2] The choice of appropriate protecting group strategies is especially delicate in the design and execution of complex multifunctional molecules in order to minimize the manipulation steps. The need for selective protection of hydroxyl groups for the synthetic production of carbohydrates represents a paradigmatic example in this sense.[3−5] Among the battery of hydroxyl protecting groups currently employed in organic chemistry, benzyl ethers have proven very useful.[1] They can withstand a wide range of reaction conditions used during manipulation of other protecting groups such as esters, silyl ethers, carbamates, or acetals and can be removed under mild conditions.[1,6] However, *O*-benzylation of polyols systems generally proceeds with low regioselectivity, which is a quite serious drawback frequently encountered in carbohydrate chemistry.

Full benzylation of carbohydrate hydroxyl groups is generally trivial, although it may face some difficulties and require optimized conditions in the case of relatively large oligosaccharides.[7] Regioselective partial benzylation is, however, much less evident and requires ingenious strategies. For example, regioselective reductive ring opening of the 4,6-di-*O*-benzylidene group,[8−10] transient protection with silyl ether,[11] and metal complex (e.g., tin, copper and silver) mediated benzylation[12−16] are methods developed for selective benzyl protection. Alternatively, regioselective debenzylation of highly *O*-benzylated carbohydrates can be used for the preparation of partially benzylated sugars in specific cases. It has been effected with stoichiometric amounts of strong, sensitive Lewis acids such as $SnCl_4$ or $TiCl_4$,[17] excess alumanes (DIBAL or TRIBAL) at high temperatures[18−20] or under microwave activation,[21] BCl_3 or I_2/Et_3SiH at low temperature,[22,23] and excess $CrCl_2$ and LiI at high temperature.[24] None of these methods rely on the differential reactivity of the benzylating or debenzylating reagent toward 1,2-diol moieties, a goal that generally requires the formation of cyclic derivatives.[1] Considering the versatility of *O*-benzyl protection and the frequent need for selectively blocking *vic*-diol segments in carbohydrate chemistry, the implementation of a methodology for the installation of a cyclic benzyl ether-type protecting group was highly desired.

The use of di-*O*-*o*-xylylene structural elements for the cyclic protection of 1,2- and 1,3-diols was first published in 1989 by Poss and Smyth.[25] This masking device can be introduced under basic conditions by using α,α'-dibromo-*o*-xylene as precursor and removed by hydrogenolysis (Scheme 1).

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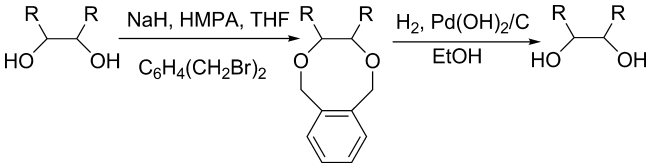
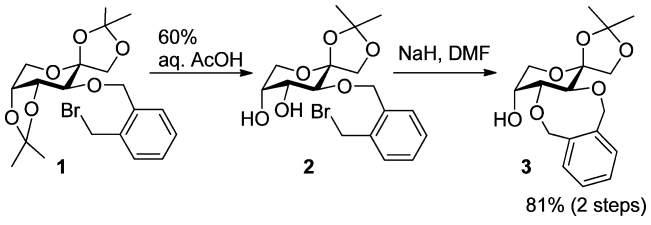
Scheme 1. Protection and Deprotection of a *vic*-Diol by an *o*-Xylylene Group



Protection of a vicinal diol segment by a cyclic xylylene group, instead of two independent benzyl ethers, results in a considerable efficiency improvement in terms of atom economy.[26]

Inspired by the concept of intramolecular delivery of vicinal functionality,[27] we considered the use of the cyclic *o*-xylylene group for benzyl-type protection of *vic*-diols in carbohydrate chemistry. We hypothesized that differences in the acidity of the hydroxyl groups might trigger preferential benzyl-type protection at specific positions.[28] Intramolecular etherification should then be kinetically favored over intermolecular ether bridging reactions. Moreover, regioselectivity might arise due to configurational and conformational bias. In an early work, this strategy was successfully applied to the multistep synthesis of D-fructose derivative **3**, a key intermediate in the high-yielding synthesis of glycosidase inhibitors of the polyhydroxylated pyrrolidine family (DMDP and DGDP), from precursor **1** (Scheme 2).[29] Direct *o*-xylylenation of β-D-fructopyranose or

Scheme 2. Synthesis of 3 *via* Intramolecular Ring Closing of Xylylenation



-fructofuranose[30−32] and β-D-arabinose[33] *vic*-diol derivatives has further been accomplished, which found application in the synthesis of complex oligosaccharides.

In the above commented diol examples, the regioselectivity of the initial benzylation step and the preferred sense of the cyclization reaction was irrelevant. Nevertheless, geometrical considerations suggested that the *o*-xylylene tether would provide the appropriate distance restriction to favor 1,2- versus 1,3-*O*-(*o*-xylylene) protection in more complex polyol systems. Additionally, the diequatorial disposition of the oxygen atoms at the eight-membered dioxacyclooctene-type ring must be favored as compared to the diaxial orientation (Figure 1).

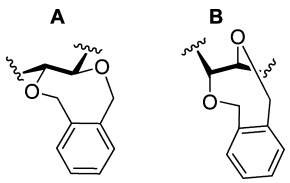


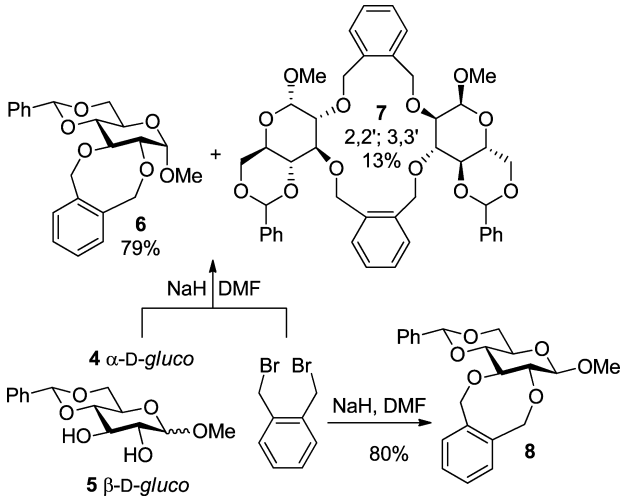
Figure 1. *trans*-Diequatorial (A) and *trans*-diaxial (B) dispositions of oxygens on a cyclic *o*-xylylene group.

Such difference should result in preferred cyclic *o*-xylylenation patterns, significantly broadening the utility of the reaction in carbohydrate chemistry. To explore the potential of the cyclic *o*-xylylene group for regioselective protection, a systematic study on different monosaccharide substrates differing in the number and orientation of hydroxyl groups has now been undertaken. The methodology has been further applied to the regioselective functionalization of the secondary rim of cyclodextrins (CDs), a family of cyclic torus-shaped oligosaccharides composed of α-(1→4)-linked glucopyranosyl units that are widely used as host moieties and nanometric platforms in supramolecular chemistry.[34] A preliminary communication of this aspect was already published[35] and demonstrated application in the construction of fluorescently active self-assembling systems.[36−38] A full account of the scope and limitations of the strategy is now presented.

RESULTS AND DISCUSSION

Evaluation of the Cyclic *o*-Xylylene Group for Protection of Vicinal Diols in Monosaccharides. *Protection of 1,2-Diols in Pyranose Derivatives.* First, we have examined the cyclic diether protection of the *trans*-diequatorial vicinal hydroxy groups 2-OH and 3-OH in methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides **4** and **5**[39] by treatment with 1,2-bis(bromomethyl)benzene (1.1 equiv) in the presence of sodium hydride (5 equiv; Scheme 3). In the

Scheme 3. Xylylenation of Benzylidene Glucopyranoside Derivatives 4 and 5



case of α-D-glucopyranoside **4**, the monomeric cyclic diether derivative **6** and the dimeric macrocyclic derivative **7** (92% altogether) were obtained in 6:1 relative proportion, whereas the monomeric *o*-xylylene derivative **8** (80% yield) was the only product isolated from the β-anomer **5**. MS, ^{1}H and ^{13}C NMR, and 1D NOESY experiments supported the symmetric structure of dimer **7**, with two monosaccharide units connected through their O-2 and O-3 positions by two *o*-xylylene bridges. 1D NOESY experiments confirmed that the *o*-xylylene segments connected identical positions at both glucopyranoside units.

When the xylylenation reaction was conducted on the α-D-*galacto* derivative **9**,[39] intramolecular cyclization reaction leading to the *trans*-diequatorial cyclic diether **10** (42%) was

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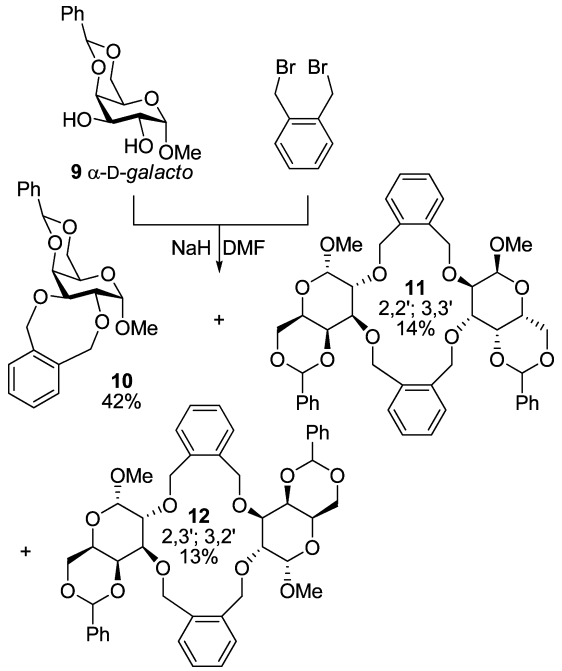
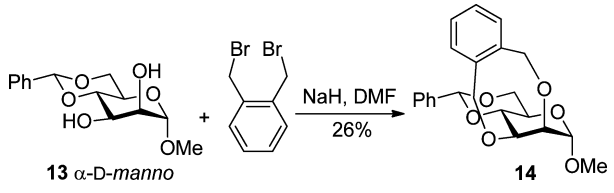
also favored over intermolecular bridging (27%). This dimer fraction consisted of a 1:1 mixture of two bicyclic structures, **11** and **12**, that could be separated and characterized in pure form. MS and NMR data and 1D NOESY experiments confirmed that compounds **11** and **12** corresponded to dimeric and symmetric structures in which two *o*-xylylene bridges connect identical (C-2—C-2′ and C-3—C-3′) or different positions (C-2—C-3′ and C-3—C-2′) at both sugar rings, respectively. No side products arising from higher cyclic or linear oligomers were observed (Scheme 4).

Scheme 4. Xylylenation of the Benzylidene Galactopyranoside Derivative 9



The above reaction conditions were next applied to methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**13**),[40] having a *cis*-axial/equatorial disposition of the reacting hydroxyls (Scheme 5). The corresponding 2,3-*O*-(*o*-xylylene) derivative **14** was

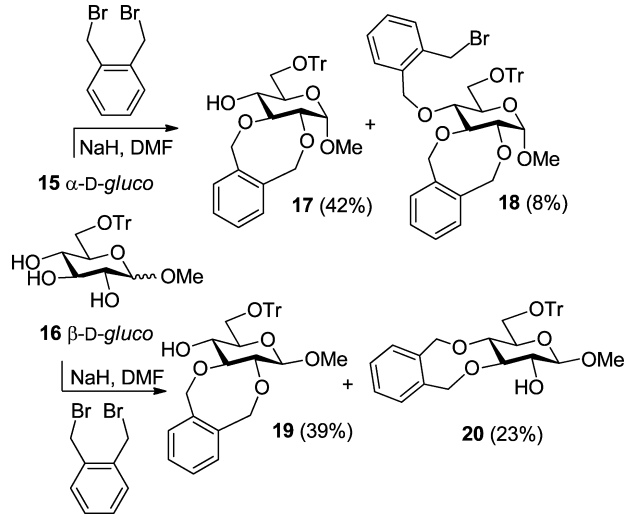
Scheme 5. Xylylenation of the Benzylidene Mannopyranoside Derivative 13



obtained as the only isolable product, but in a modest 26% yield. Most probably, formation of oligomers through intermolecular etherification competes in this case with the intermolecular process leading to the cyclic diether, which likely reflects a more favorable conformational arrangement of the condensed dioxaoctene-type ring for *trans*-diaxial as compared to *cis*-axial/equatorial relative orientations of the vicinal oxygens. It is worth noting that in all the benzylidene derivatives included in this study the phenyl group adopts the equatorial disposition, so that the difference in reactivity between the α-D-*gluco* **4** and α-D-*manno* epimer **13** has to be ascribed to the configurational shift at C-2 position.

In order to evaluate the potential for regioselective *o*-xylylenation, triol systems were next assayed. Methyl 6-*O*-trityl glycopyranosides with α-D-*gluco* (**15**),[41] β-D-*gluco* (**16**),[41] α-D-*manno* (**21**),[42] and α-D-*galacto* (**22**)[43] configurations were used as model pyranoid substrates for this purpose. Reactions were carried out in DMF using 2.6 equiv of sodium hydride and 1.3 equiv of 1,2-bis(bromomethyl)benzene. The α-D-*gluco* derivative **15** afforded the ether-type protected adducts **17** and **18** in 5.25:1 relative proportion (50% global yield). In both compounds the cyclic diether segment connects O-2 and O-3 positions. In the case of the β-anomer **16**, the 2,3-*O*-(*o*-xylylene) derivative (**19**, 39%) was also the major reaction product, but a significant proportion of the 3,4-*O*-regioisomer **20** was also formed (Scheme 6).

Scheme 6. Xylylenation of 6-*O*-Trityl Glucopyranoside Derivatives 15 and 16



The regioselectivity of the cyclic protection was reversed for the α-D-*manno* derivative **21**. Thus, a mixture of compounds **23** and **24**, both incorporating the cyclic xylylene segment at positions O-3 and O-4, was now obtained, with no trace of 2,3-*o*-xylylene protected isomers. This result confirms the preference for *trans*-1,2-diol segments of cyclic *o*-xylylene protection over *cis*-(axial/equatorial) dispositions, overcoming even the unfavorable steric effect that may exert the trityl group at O-6. Finally, direct *o*-xylylenation of the substrate with α-D-*galacto* configuration **22** led preferentially to the *trans*-diequatorial cyclic diether derivatives **25** and **26**. A very small proportion of the fully protected derivative **27** involving the axial 4-OH in the cyclic groups was also isolated (Scheme 7).

It can be postulated that the observed differences in regioselectivity depend, besides the already mentioned higher preference for *trans*-diequatorial diol orientations, on the relative acidity of the secondary hydroxyl groups and the nucleophilicity of the resulting alkoxide. The acidity depends on the solvent used and is modulated by intramolecular H-bonds while steric effects control the nucleophilicity. The involvement of OH-2 in H-bonding with O-1 in α-D-glucopyranosides[44] renders this hydroxyl group the most acidic in compound **15**, favoring initial benzylation at this position.[45] The next intramolecular etherification at O-3 is then kinetically

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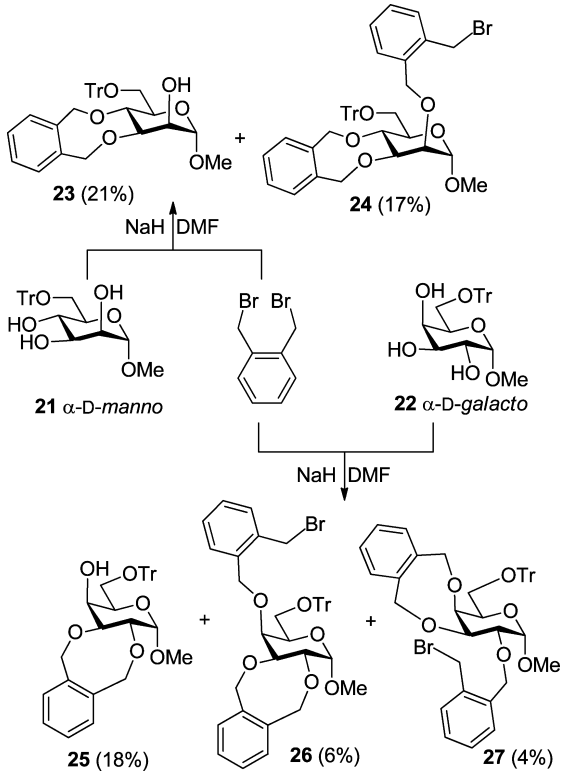
Scheme 7. Xylylenation of 6-*O*-Trityl Manno- and Galacto-Pyranoside Derivatives 21 and 22

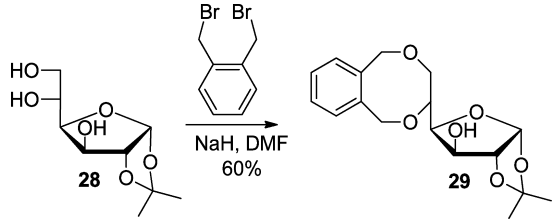


favored over intermolecular reactions. Differences in acidity are less pronounced in the case of the *β-gluco* anomer **16**, leading to a lower selectivity, whereas it is reversed in favor of OH-3 for the *α-manno* epimer. In the α-D-galactopyranoside, both OH-2- and OH-3 hydroxyls have similar chemical reactivity as both are involved in *cis*-H-bonds with vicinal oxygens.[45] Although cyclization through OH-2 must be favored after initial alkylation at O-3, a small proportion of the O-3,O-4 cyclic diether is also formed.

Even though the yields on the selectively *o*-xylylenated derivatives **17**, **19**, **20**, **23**, and **25** are far from optimal, they are remarkable considering that classical benzylation with benzyl chloride under identical reaction conditions led to very complex mixtures of no synthetic utility. Moreover, the starting substrates are initial building blocks of low synthetic cost. Alternative regioselective differentiation of the three hydroxyls is not trivial and would require elaborated multistep syntheses, often involving tedious purification steps that handicap the overall yield. As an example, compound **23**, with selectively protected OH-3 and OH-4 and differentiated OH-2 and OH-6 positions, is a suitable precursor for the construction of the high mannose oligosaccharides involved in viral and bacterial infection, characterized by α(1−2) and α(1−6) linkages,[46−49] that was obtained in just two steps from commercial methyl α-D-mannopyranoside.

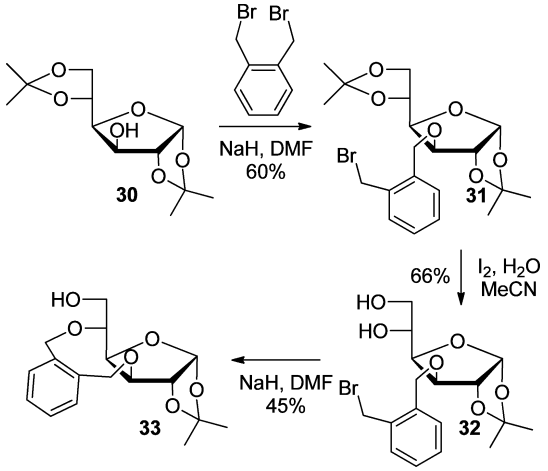
Regioselective Protection of 1,2- and 1,3-Diols in Furanose Derivatives. Furanose substrates are very well suited to test the relative propensity of the cyclic *o*-xylylenation reaction to afford either 1,2- or 1,3-diether derivatives. Xylylenation of commercially available 1,2-*O*-isopropylidene-α-D-glucofuranose **28** under the above conditions afforded preferentially the 5,6-di-*O*-cyclic diether **29** in 60% yield (Scheme 8). No trace of 3,5- or 3,6-di-*O*-cyclic diethers was observed.

Scheme 8. Xylylenation of Isopropylidene Glucofuranoside Derivative 28



To explore the utility of the xylylenation approach for the protection of 1,3-diol segments of carbohydrates, a stepwise strategy was explored. Our synthetic route started from 3-*O*-(*o*-bromomethylbenzyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**31**), prepared from commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**30**). Selective hydrolysis of the 5,6-*O*-isopropylidene group in MeCN with aqueous iodine[50] provided diol **32**. Formation of the nine-membered diether ring involving OH-5 readily took place when **32** was subjected to benzylation conditions, affording compound **33** in moderate yield (45%, Scheme 9).

Scheme 9. Synthesis of the 1,3-Cyclic Diether 33 by Stepwise *o*-Xylylenation



Application of the *o*-Xylylenation Reaction to the Regioselective Functionalization of Cyclodextrins at Their Secondary Rim. Position-selective functionalization of cyclodextrins is critical for the development of applications as sensors,[51,52] catalysts,[53−55] artificial enzymes,[56,57] or drug delivery systems[58] among others. Most reported methods are limited to primary hydroxyls.[19,59−65] Only a few examples of the preparation of mono- and bifunctionalized CDs at the secondary rim have recently been reported.[35,66−74] In view of the results obtained on monosaccharide substrates, and considering that OH-2 is significantly more acidic than OH-3 and OH-6 and that the hydroxyls at the secondary CD rim are arranged in *trans*-diequatorial diol segments, the possibility of statistic *o*-xylylenation to access selectively O-2^{I},O-3^{I}-differentiated derivatives of the commercially available cyclomaltohexa- (αCD), -hepta- (βCD), and -octaose (γCD) seemed very appealing.

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Protection of Secondary Hydroxyls in CD Derivatives Selectively Protected at the Primary Rim. A concern when considering selective cyclic protection at O-2 and O-3 within the same glucopyranoside subunit of the CD macroring was that it could compete with the formation of the regioisomer involving O-2 and O-3 in two consecutive monosaccharide subunits, since the respective interatomic distances are practically identical (Figure 2). This question was first

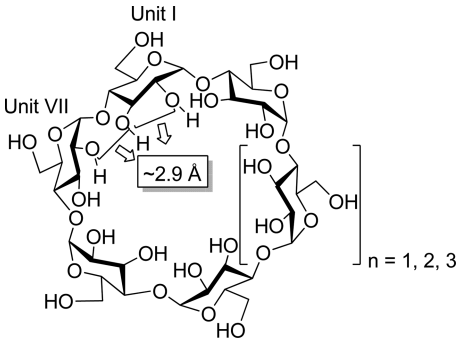


Figure 2. Interatomic distances between O-2 and O-3 in two consecutive monosaccharide subunits in α, β, and γCDs (n = 1, 2, and 3, respectively).

addressed using per-6-*O*-(*tert*-butyldimethylsilyl)-cyclomaltoheptaose **34**[75] as a model compound in order to limit the possibilities for positional isomerism. In principle, the formation of the first ether connection on one of the secondary hydroxyls (OH-2 or OH-3)[76] should kinetically favor subsequent intramolecular etherification. The intermolecular reaction must be much more strongly disfavored now as compared with monosaccharide substrates due to steric reasons.

Several reaction conditions for *o*-xylylenation of **34** with 1,2-dibromomethylbenzene, including the use of *N*,*N*-dimethylformamide (DMF) or dichloromethane as solvents and sodium hydride (NaH), NaH/15-crown-5-ether, or a mixture of BaO/$Ba(OH)_2$ as bases, were assayed (Table 1).

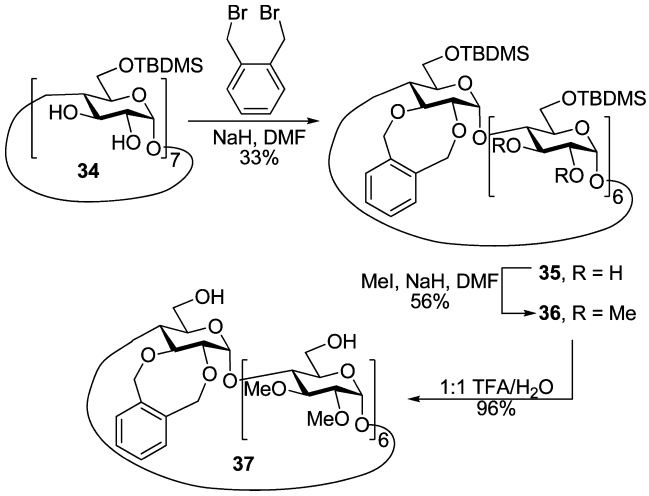
It was concluded that reaction with 1,2-dibromomethylbenzene (3 equiv) and NaH (6 equiv) in DMF for 15 min were the optimal conditions, leading to compound **35** in 33% yield (Scheme 10), with 55% of the starting material **34** being recovered (73% yield referred to the converted product). The location of the xylylene protecting group at the secondary

Table 1. Xylylenation Assays of the βCD Derivative 34[a]

base/CD (molar ratio)	solvent	$t_{reaction}$ (h)	yield of **35** (%)
NaH (2.5/1)	DMF	6	3
NaH (16/1)	DMF	1.5	<3[b]
NaH (3.6/1)	DMF	1.5	7
NaH (1.4/1)	DMF	5	<3[b]
NaH (6/1)	DMF	0.25	30
NaH + 1:4 BaO-$Ba(OH)_2{\cdot}8H_2O$ (2.7/1)	DMF	24	<3[b]
NaH + 4:1 BaO-$Ba(OH)_2{\cdot}8H_2O$ (2.7/1)	DMF	24	<3[b]
NaH + 15-crown-5 (2.5/1)	DCM	24	7
NaH + 15-crown-5 (1.9/1)	DCM	24	<3[b]

[a]All assays were carried out at room temperature. [b]Detected by ESMS but not isolated.

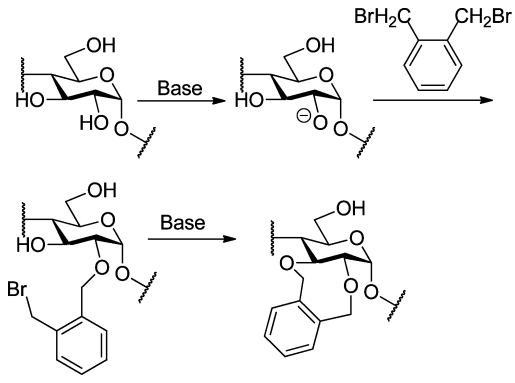
Scheme 10. Synthesis of the Mono-*o*-xylylene βCD Derivative 37



hydroxyls of the same glucopyranosyl unit in **35** was confirmed by a combination of TOCSY and NOESY experiments after full O-methylation of the remaining hydroxyls (→ **36**) and removal of the silyl ether groups (→ **37**). The 1D NOESY spectrum showed NOE contacts between the pair of signals corresponding to the benzyl-type protons and the signals for H-2 and H-3 located on the carbons that support the ether functionalities. On the other hand, the COSY spectrum confirmed that these signals belong to the same spin system, indicating that they are located at the same D-glucopyranose residue. This remarkable result represents the first described procedure to distinguish two hydroxyls at a single glucose unit in cyclodextrins.

Direct Xylylenation of Native Cyclodextrins. Taking into account the differences in the acidity of the hydroxyl groups in native CDs (OH-2 > OH-6 > OH-3),[77] pH modulation could favor mono-2-O-alkylation in the first step of the reaction leading to cyclic *o*-xylylenation, then allowing direct (O-2^I,O^I-3)-regioselective protection with no need of prior face-selective differentiation. (Scheme 11).

Scheme 11. General Strategy To Obtain 2,3-*O*-(*o*-Xylylene) Derivatives on Cyclodextrins



It is worth pointing out that differences in OH acidities are very sensitive to the solvent and need to be carefully adjusted for a given reaction. In our case, the use of equimolecular LDA in DMSO was found to provide the optimal conditions for the target transformation.[35] α, β, and γCDs were thus transformed into the corresponding 2^I,3^I-*O*-(*o*-xylylene) derivatives **38**, **44**,

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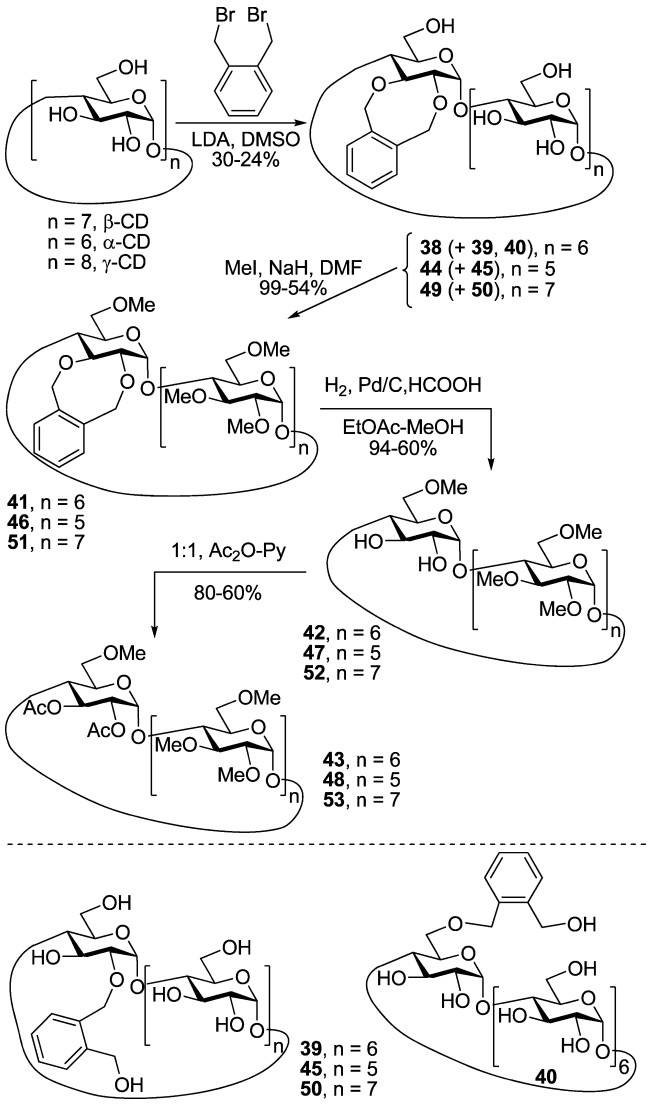
and **49** in 24−30% yields. The use of DMF instead of DMSO, different proportions of LDA (from 0.5 to 2.0 equiv), or other bases (NaOEt, NaH) was found detrimental for the yield of monoxylylenated product. The utility of this strategy for transient protection was confirmed after methylation (→ **41**, **46**, and **51**), a transformation that is known to preserve the water solubility and inclusion capabilities of the CDs. The *o*-xylylene cyclic ether could then be removed by hydrogenolysis in the presence of formic acid to give the corresponding diols **42**, **47**, and **52** in good yields (60−94%). The availablility of the diol system for further chemical manipulation was confirmed by acetylation (→ **43**, **48**, and **53**; Scheme 12). Their ^{1}H NMR spectra showed the expected chemical shifts of the H-2^I (4.76−4.72 ppm) and H-3^I (5.61−5.51 ppm). The results demonstrated the versatility of the monoxylylenation protection to obtain CD derivatives with facial differentiation at the secondary rim of one glucose unit.

Scheme 12. Direct Xylylenation Reactions of Cyclodextrins and Synthesis the of Di-2^I,3^I-*O*-acetylated Derivatives 43, 48, and 53



Although the number of regioisomers for di-O-protection of *α*, *β*, and *γ*CDs, including di-O-benzylation, in the absence of intramolecularly favored processes are 27, 33, and 36, respectively, only the 2^I,3^I-cyclic ether regioisomer (**38**, **44**, and **49**) was obtained in the three cases using the above protocol, and no dimerization product was detected. However, mass spectrometry analysis of the reaction mixture unraveled the presence of small proportions of monoalkylated derivatives (**39**, **40**, **45**, and **50**) that were isolated by semipreparative HPLC using a C-18 column as stationary phase and MeCN/H_2O mixtures as mobile phase. The ^{13}C NMR spectra of derivatives **39**, **45**, and **50** showed a significant shield of the C-3^I signal (72.1−72.5 ppm) in comparison with the corresponding diprotected derivatives **38**, **44**, and **49** (78.4−81.7). However, the C-2^I signals of derivatives **39**, **45**, and **50** did not display remarkable changes. This fact is in agreement with the absence of the ether connection at O-3^I and its presence at O-2^I. In the case of compound **40**, both O-3^I and O-2^I signals were shielded, in agreement with the presence of the ether substituent at the primary O-6^I position.

■ CONCLUSIONS

In summary, a systematic study of the suitability of the cyclic *o*-xylylene group for protection of diols in different monosaccharide substrates has been conducted. It is particularly noteworthy that the new methodology provides alternative opportunities for selective 1,2- or 1,3-diol protection in pyranose and furanose derivatives. *o*-Xylylenation of 1,2-diols is kinetically favored, allowing regioselective protection in polyol systems. Moreover, 1,2-*trans*-diequetorial diols react preferentially over 1,2-*cis*-(axial/equatorial) diols. Further selectivity can be achieved by taking into consideration the difference in the acidity of the available OH groups. Application of these conclusions to the selective protection of a single *vic*-diol system at the secondary rim of native cyclodextrins illustrates the potential of this approach. Given the general character of the strategies here reported, further applications in oligosaccharide synthetic schemes, leading to an improved atom economy, are expected. Work in that direction is currently sought in our laboratories.

■ EXPERIMENTAL SECTION

General Chemical Reagents and Methods. Reagents and solvents were purchased from commercial sources and used without further purification. Methyl 4,6-*O*-benzylidene-D-gluco- and -galacto-pyranosides **4**, **5**, and **9** were prepared by treatment of the corresponding methyl glycoside precursors with benzaldehyde in presence of $ZnCl_2$ using the reported route method.[39] The corresponding *α*-D-*manno* derivative **13** was prepared from methyl *α*-D-mannopyranoside by reaction with benzaldehyde dimethyl acetal under catalysis with camphorsulfonic acid.[40] Methyl 6-*O*-triphenylmethyl-D-glycopyranosides with *α*-D-*gluco* **15**,[41] *β*-D-*gluco***16**,[41] *α*-D-*manno* **21**,[42] and *α*-D-*galacto* **22**[43] configurations and per-6-*O*-(*tert*-butyldimethylsilyl)cyclomaltoheptaose **34**[74] were obtained according to literature procedures. 1,2-*O*-Isopropylidene-*α*-D-glucofuranose **28** and 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose **30** were commercially available compounds. Optical rotations were measured with a polarimeter, using a sodium lamp (λ = 589 nm) at 22 °C in 1 cm or 1 dm tubes. IR spectra were recorded on a FTIR instrument. NMR experiments were performed at 300 (75.5), 400 (100.6), and 500 (125.7) MHz. 1D TOCSY as well as 2D COSY and HMQC experiments were carried out to assist in signal assignment. In the FABMS spectra, the primary beam consisted of Xe atoms with maximun energy of 8 keV. The samples were dissolved in *m*-nitrobenzyl alcohol or thioglycerol as the matrices, and the positive ions were separated and accelerated over a potencial of 7 keV. NaI was added as cationizing agent. In the CIMS spectra, isobutane was used as the reactive gas (500 mA, 8 kV). MALDI-TOF mass spectra were

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acquired on a spectrometer operating in the positive-ion mode with an accelerating voltage of 28 keV. Samples were dissolved in MeCN at mM concentration and mixed with a standard solution of α-cyano-4-hydroxycinnamic acid (α-cyano; 20 mg mL^{-1} in 25:25:1 MeOH/H_2O/AcOH, 2 μL); 1 μL of the mixture was loaded onto the target plate and then allowed to air-dry at room temperature. For ESI mass spectra, 0.1 pM sample concentrations were used, the mobile phase consisting of 50% aq MeCN at 0.1 mL min^{-1}. HRMS spectra were recorded in a QTRAP mass spectrometer (hybrid triple quadrupole/linear ion trap mass spectrometer). Thin-layer chromatography was performed on precoated TLC plates, silica gel 30F-245, with visualization by UV light and by carrying with 10% H_2SO_4 or 0.2% w/v cerium(IV) suphate-5% ammonium molybdate in 2 M H_2SO_4. Column chromatography was performed on chromagel (silice 60 AC.C 70−200 μm). An analytical HPLC system equipped with a pump and an ELSD detector was used. The separation was performed at room temperature on an analytical column of ES 5μ (5 μm particle size, 250 mm × 4.6 mm). The mobile phase consisted of water (solvent A) and MeCN (solvent B). The composition of the mobile phase varied during the run according to a linear gradient as follows: A−B: 0 min (0:100, v/v), 0−50 min (50:50, v/v) at a flow rate of 1.0 mL/min. Data acquisition and processing were performed with the instrument software. A preparative HPLC system equipped with a LC4000 pump and an ELSD detector was used. The separation was performed at room temperature on a column of ES 5μ (5 μm particle size, 250 mm × 10 mm). The mobile phase consisted of water (solvent A) and MeCN (solvent B). The composition of the mobile phase varied during the run according to a linear gradient as follows: A−B, 0 min (0:100, v/v), 0−50 min (50:50, v/v) at a flow rate of 4.7 mL/min. Data acquisition and processing were performed with the instrument software. Elemental analyses were performed with a microanalysis measuring apparatus.

General Procedure for *o*-Xylylene Protection of Methyl 4,6-*O*-Benzylidene-D-Glycopyranosides (6−8, 10−12, and 14). To a solution of the corresponding methyl 4,6-*O*-benzylidene-D-glycopyranoside **4**, **5**, **9**, and **13** (0.1 g, 0.35 mmol) in dry DMF (6 mL) was added NaH (60% in mineral oil, 70 mg, 1.75 mmol), and the suspension was stirred at room temperature for 15 min. 1,2-Dibromomethylbenzene (102 mg, 0.385 mmol) was then added, and the reaction mixture was further stirred for 30 min at room temperature. After quenching with MeOH (5 mL), the solvent was removed under reduced pressure. H_2O (10 mL) and 1:1 toluene/Et_2O (15 mL) were added, and the organic layer was separated, washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography using 1:2 EtOAc/petroleum ether as eluent.

*Methyl 4,6-O-Benzylidene-2,3-O-(o-xylylene)-α-D-glucopyranoside (**6**).* Amorphous solid. Yield: 108 mg (79%); R_f 0.46 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +109.5 (*c* 1.0, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53−7.14 (m, 9 H, Ph), 5.53 (s, 1 H, C*H*Ph), 5.15, 5.00 (2 d, 2 H, $^2J_{H,H}$ = 14.0 Hz, C*H*Ph), 5.08 (s, 2 H, CH_2Ph), 4.87 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.28 (dd, 1 H, $J_{6a,6b}$ = 10.5 Hz, $J_{5,6a}$ = 5.0 Hz, H-6a), 4.02 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.84 (ddd, 1 H, $J_{5,6b}$ = 10.5 Hz, $J_{4,5}$ = 9.0 Hz, H-5), 3.71 (t, 1 H, H-6b), 3.63 (dd, 1 H, H-2), 3.53 (t, 1 H, H-4), 3.44 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.3−126.4 (Ph), 101.9 (CHPh), 99.1 (C-1), 80.5 (C-4), 80.3 (C-2), 78.1 (C-3), 73.6, 73.1 (CH_2Ph), 69.0 (C-6), 62.1 (C-5), 55.2 (OMe); CIMS *m*/*z* 385 (30%, $[M + H]^+$), 384 (55%, $[M]^+$), 353 (20%, $[M - OMe]^+$). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.72; H, 6.56.

*Cyclobis[methyl 4,6-O-benzylidene-α-D-glucopyranoside]-2^I,2^{II}:3^I,3^{II}-di-O-(o-xylylene) (**7**).* Amorphous solid. Yield: 35 mg (13%); R_f 0.32 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +53.8 (*c* 0.8, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.12 (m, 18 H, Ph), 5.56 (s, 2 H, C*H*Ph), 5.02, 4.78 (2 d, 4 H, $^2J_{H,H}$ = 11.5 Hz, C*H*Ph), 4.95, 4.67 (2 d, 4 H, $^2J_{H,H}$ = 12.0 Hz, C*H*Ph), 4.86 (d, 2 H, $J_{1,2}$ = 3.5 Hz, H-1), 4.31 (dd, 2 H, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ = 5.0 Hz, H-6a), 4.07 (t, 2 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.86 (ddd, 2 H, $J_{5,6b}$ = 10.0 Hz, $J_{4,5}$ = 9.0 Hz, H-5), 3.74 (t, 2 H, H-6b), 3.64 (t, 2 H, H-4), 3.62 (dd, 2 H, H-2), 3.45 (s, 6 H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.4−126.1 (Ph), 101.3 (CHPh), 99.2 (C-1), 82.0 (C-4), 79.5 (C-2), 79.3 (C-3), 72.9, 71.2 (CH_2Ph), 69.3 (C-6), 62.4 (C-5), 55.4 (OMe); FABMS *m*/*z* 791 (10%, $[M + Na]^+$). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.63; H, 6.06.

*Methyl 4,6-O-Benzylidene-2,3-O-(o-xylylene)-β-D-glucopyranoside (**8**).* Amorphous solid. Yield: 109 mg (80%); R_f 0.82 (1:2 EtOAc/cyclohexane); $[\alpha]_D$ −10.5 (*c* 1.0, DCM); UV (DCM) 248 nm (ε_{mM} 10.3); IR (ATR) 3053, 2923, 1453, 1363, 1085, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.17 (m, 9 H, Ph), 5.52 (s, 1 H, C*H*Ph), 5.15, 5.13 (2 d, 2 H, $^2J_{H,H}$ = 13.8 Hz, C*H*Ph), 5.03, 4.95 (2 d, 2 H, CH_2Ph), 4.37 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 4.33 (dd, 1 H, $J_{6a,6b}$ = 10.5 Hz, $J_{5,6a}$ = 5.1 Hz, H-6a), 3.78 (t, 1 H, $J_{5,6b}$ = 9.3 Hz, H-6b), 4.02 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3), 3.55 (t, 1 H, $J_{4,5}$ = 9.3 Hz, H-4), 3.45 (dd, 1 H, H-2), 3.39 (td, 1 H, H-5), 3.44 (s, 3 H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.2−126.3 (Ph), 103.9 (CHPh), 101.7 (C-1), 80.9 (C-4), 79.8.3 (C-2,3), 72.8, 72.6 (CH_2Ph), 68.7 (C-6), 66.0 (C-5), 57.5 (OMe); ESIMS *m*/*z* 407 $[M + Na]^+$. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.70; H, 6.35.

*Methyl 4,6-O-Benzylidene-2,3-O-(o-xylylene)-α-D-galactopyranoside (**10**).* Amorphous solid. Yield: 58 mg (42%); R_f 0.31 (1:1 EtOAc/petroleum ether); $[\alpha]_D$ +193.5 (*c* 1.0, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.09 (m, 9 H, Ph), 5.57 (s, 1 H, C*H*Ph), 5.14, 5.11 (2 d, 2 H, $^2J_{H,H}$ = 8.0 Hz, C*H*Ph), 5.05 (s, 2 H, CH_2Ph), 5.02 (d, 1 H, $J_{1,2}$ = 2.5 Hz, H-1), 4.39 (d, 1 H, $J_{3,4}$ = 3.5 Hz, H-4), 4.26 (dd, 1 H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 1.5 Hz, H-6a), 4.14 (dd, 1 H, $J_{2,3}$ = 10.5 Hz, H-2), 4.09 (t, 1 H, $J_{5,6b}$ = 1.5 Hz, H-6b), 4.04 (dd, 1 H, H-3), 3.87 (bs, 1 H, H-5), 3.45 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.0−126.4 (Ph), 101.0 (CHPh), 99.7 (C-1), 77.3 (C-2), 77.0 (C-3), 76.1 (C-4), 74.6, 73.8 (CH_2Ph), 69.3 (C-6), 62.8 (C-5), 55.5 (OMe); CIMS *m*/*z* 385 (5%, $[M + H]^+$), 384 (15%, $[M]^+$), 353 (30%, $[M - OMe]^+$). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.47; H, 6.23.

*Cyclobis[methyl 4,6-O-benzylidene-α-D-galactopyranoside]-2^I,2^{II}:3^I,3^{II}-di-O-(o-xylylene) (**11**).* Amorphous solid. Yield: 38 mg (14%); R_f 0.51 (2:1 EtOAc/petroleum ether); $[\alpha]_D$ +117.4 (*c* 1.2, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.17 (m, 18 H, Ph), 5.52 (s, 2 H, C*H*Ph), 4.99 (d, 2 H, $J_{1,2}$ = 3.0 Hz, H-1), 4.98, 4.94 (2 d, 4 H, $^2J_{H,H}$ = 11.5 Hz, C*H*Ph), 4.60, 4.58 (2 d, 4 H, $^2J_{H,H}$ = 7.0 Hz, C*H*Ph), 4.28 (d, 2 H, $J_{3,4}$ = 3.5 Hz, H-4), 4.24 (bd, 2 H, $J_{6a,6b}$ = 11.5 Hz, H-6a), 4.09 (dd, 2 H, $J_{2,3}$ = 10.0 Hz, H-2), 4.04 (bd, 2 H, H-6b), 3.98 (t, 2 H, H-3), 3.53 (bs, 2 H, H-5), 3.41 (s, 6 H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.1−126.3 (Ph), 100.9 (CHPh), 99.3 (C-1), 75.8 (C-2,3), 74.2 (C-4), 71.2 (CH_2Ph), 69.5 (C-6), 69.3 (CH_2Ph), 62.4 (C-5), 55.5 (OMe); FABMS *m*/*z* 791 (100%, $[M + Na]^+$). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.49; H, 6.18.

*Cyclobis[methyl 4,6-O-benzylidene-α-D-galactopyranoside]-2^I,3^{II}:3^I,2^{II}-di-O-(o-xylylene) (**12**).* Amorphous solid. Yield: 35 mg (13%); R_f 0.30 (2:1 EtOAc/petroleum ether); $[\alpha]_D$ +64.9 (*c* 1.0, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.15 (m, 18 H, Ph), 5.50 (s, 2 H, C*H*Ph), 5.03, 4.52 (2 d, 4 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 4.93, 4.62 (2 d, 4 H, $^2J_{H,H}$ = 11.9 Hz, C*H*Ph), 4.90 (d, 2 H, $J_{1,2}$ = 3.3 Hz, H-1), 4.35 (d, 2 H, $J_{3,4}$ = 2.8 Hz, H-4), 4.27 (d, 2 H, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.07 (m, 4 H, H-2, H-6b), 3.98 (dd, 2 H, $J_{2,3}$ = 10.0 Hz, H-3), 3.64 (bs, 2 H, H-5), 3.38 (s, 6 H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.9−126.3 (Ph), 101.1 (CHPh), 99.2 (C-1), 75.9 (C-2), 75.6 (C-3), 74.5 (C-4), 71.1, 69.6 (CH_2Ph), 69.5 (C-6), 62.5 (C-5), 55.5 (OMe); FABMS *m*/*z* 791 (5%, $[M + Na]^+$). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.79; H, 6.01.

*Methyl 4,6-O-Benzylidene-2,3-O-(o-xylylene)-α-D-mannopyranoside (**14**).* Amorphous solid. Yield: 35 mg (26%); R_f 0.58 (1:2 EtOAc/cyclohexane); $[\alpha]_D$ +50.6.5 (*c* 1.0, DCM); UV (DCM) 228 nm (ε_{mM} 3.2); IR (ATR) 2914, 1459, 1376, 1089, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57−7.11 (m, 9 H, Ph), 5.90 (2 d, 2 H, $^2J_{H,H}$ = 11.5 Hz, C*H*Ph), 5.68 (s, 1 H, C*H*Ph), 5.43, 4.72 (2 d, 2 H, $^2J_{H,H}$ = 15.9 Hz, C*H*Ph), 4.66 (s, 1 H, H-1), 4.32−4.24 (m, 2 H, H-6a, H-4), 4.08 (dd, 1 H, $J_{2,3}$ =3.0 Hz, $J_{3,4}$ = 9.9 Hz, H-3), 3.94 (t, 1 H, $J_{6a,6b}$ = $J_{5,6b}$ = 10.5 Hz, H-6b), 3.91−3.85 (m, 2 H, H-2, H-5), 3.25 (s, 3 H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.3−126.2 (Ph), 102.4 (CHPh), 101.4 (C-1), 78.8 (C-3), 77.3 (C-4), 71.7 (CH_2Ph), 71.6 (C-2), 70.9 (CH_2Ph), 68.9 (C-6), 63.7 (C-5), 54.9 (OMe); ESIMS *m*/*z* 407 [M +

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Na]$^+$. HREIMS calcd for $C_{22}H_{24}O_6$ 385.1651, found 385.1641. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.91; H, 6.40.

General Procedure for *o*-Xylylene Protection of Methyl 6-*O*-Triphenylmethyl-D-glycopyranosides (17−20 and 23−27). To a solution of methyl 6-*O*-triphenylmethyl-D-glycopyranoside **15**, **16**, **21**, and **22** (50 mg, 0.115 mmol) in dry DMF (2.3 mL) at 0 °C under Ar atmosphere was added NaH (60% in mineral oil, 12 mg, 0.3 mmol), and the suspension was stirred at room temperature for 15 min. Then, a solution of 1,2-dibromomethylbenzene (39.5 mg, 0.15 mmol) in dry DMF (1 mL) was added dropwise, and the mixture was stirred for 1 h at room temperature. Further treatment as described for **6**−**8** and column chromatography using 1:4 → 1:2 EtOAc/petroleum ether containing 0.5% of Et_3N as eluent gave **17**−**20** and **23**−**27**.

*Methyl 6-O-Triphenylmethyl-2,3-O-(o-xylylene)-α-D-glucopyranoside (**17**).* Amorphous solid. Yield: 26 mg (42%); R_f 0.41 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +37.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.07 (m, 19 H, Ph), 5.21, 4.88 (2 d, 2 H, $^2J_{H,H}$ = 13.5 Hz, C*H*Ph), 5.14, 4.96 (2 d, 2 H, $^2J_{H,H}$ = 15.0 Hz, C*H*Ph), 4.83 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 3.78 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 3.70 (m, 1 H, H-5), 3.51 (t, 1 H, $J_{4,5}$ = 9.1 Hz, H-4), 3.50 (dd, 1 H, H-2), 3.42 (s, 3 H, OMe), 3.35 (dd, 1 H, $J_{6a,6b}$ = 9.9 Hz, $J_{5,6a}$ = 4.1 Hz, H-6a), 3.33 (dd, 1 H, $J_{5,6b}$ = 5.1 Hz, H-6b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.8−126.9 (Ph), 98.4 (C-1), 87.0 (*C*Ph_3), 81.1 (C-3), 80.0 (C-2), 73.8, 73.1 (*C*H_2Ph), 71.3 (C-4), 69.4 (C-5), 64.1 (C-6), 55.1 (OMe); FABMS *m*/*z* 538 (10%, [M]$^+$). Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.73; H, 6.15.

*Methyl 6-O-Triphenylmethyl-4-O-(o-bromomethylbenzyl)-2,3-O-(o-xylylene)-α-D-glucopyranoside (**18**).* Amorphous solid. Yield: 7 mg (8%); R_f 0.61 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +53.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−6.79 (m, 23 H, Ph), 5.21, 4.94 (2 d, 2 H, $^2J_{H,H}$ = 13.2 Hz, C*H*Ph), 5.19, 5.02 (2 d, 2 H, $^2J_{H,H}$ = 14.8 Hz, C*H*Ph), 4.98, 4.31 (2 d, 2 H, $^2J_{H,H}$ = 10.7 Hz, C*H*Ph), 4.94 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.73, 4.37 (2 d, 2 H, $^2J_{H,H}$ = 10.1 Hz, CHBr), 3.95 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 3.77 (ddd, 1 H, $J_{4,5}$ = 9.1 Hz, $J_{5,6b}$ = 3.3 Hz, $J_{5,6a}$ = 1.6 Hz, H-5), 3.62 (dd, 1 H, H-2), 3.56 (t, 1 H, H-4), 3.44 (s, 3 H, OMe), 3.42 (dd, 1 H, $J_{6a,6b}$ = 10.2 Hz, H-6a), 3.16 (dd, 1 H, H-6b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.9−126.9 (Ph), 98.3 (C-1), 86.4 (*C*Ph_3), 82.3 (C-3), 81.2 (C-2), 77.1 (C-4), 74.2, 73.3, 71.9 (*C*H_2Ph), 69.9 (C-5), 62.8 (C-6), 54.9 (OMe), 30.8 (*C*H_2Br); FABMS *m*/*z* 745, 743 (90%, 75%, [M + Na]$^+$). Anal. Calcd for $C_{42}H_{41}BrO_6$: C, 69.90; H, 5.73. Found: C, 69.69; H, 5.64.

*Methyl 6-O-Triphenylmethyl-2,3-O-(o-xylylene)-β-D-glucopyranoside (**19**).* Amorphous solid. Yield: 24 mg (39%); R_f 0.58 (1:2 EtOAc/cyclohexane); $[\alpha]_D$ +37.2 (*c* 1.0, $CHCl_3$); UV (DCM) 248 nm (ε_{mM} 10.3); IR (ATR) 2924, 1488, 1447, 1068, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.12 (m, 19 H, Ph), 5.22, 4.90 (2 d, 2 H, $^2J_{H,H}$ = 13.2 Hz, C*H*Ph), 5.10, 5.05 (2 d, 2 H, $^2J_{H,H}$ = 14.8 Hz, C*H*Ph), 4.27 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 3.58 (m, 1 H, H-4), 3.57 (s, 3 H, OMe), 3.51 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.8 Hz, H-3), 3.42−3.35 (m, 3 H, H-5, H-6ab), 3.34 (dd, 1 H, H-2), 2.86 (d, 1 H, $J_{4,OH}$ = 2.0 Hz, OH-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.5−127.1 (Ph), 103.2 (C-1), 87.1 (*C*Ph_3), 83.2 (C-3), 80.3 (C-2), 73.4 (C-5), 72.9, 72.7 (*C*H_2Ph), 71.6 (C-4), 64.3 (C-6), 56.9 (OMe); ESIMS *m*/*z* 561 [M + Na]$^+$. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.67; H, 6.29.

*Methyl 6-O-Triphenylmethyl-3,4-O-(o-xylylene)-β-D-glucopyranoside (**20**).* Amorphous solid. Yield: (0.25 g of starting material) 14 mg (23%); R_f 0.23 (1:2 EtOAc/cyclohexane); $[\alpha]_D$ +37.2 (*c* 1.0, $CHCl_3$); UV (DCM) 248 nm (ε_{mM} 10.3); IR (ATR) 3430, 2969, 2925, 1456, 1375, 1084, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.12 (m, 19 H, Ph), 5.23, 4.82 (2 d, 2 H, $^2J_{H,H}$ = 12.8 Hz, C*H*Ph), 4.79, 4.65 (2 d, 2 H, $^2J_{H,H}$ = 14.8 Hz, C*H*Ph), 4.25 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 3.58 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.59 (s, 3 H, OMe), 3.57−3.50 (m, 2 H, H-3, H-6a), 3.46 (dd, 1 H, $J_{2,3}$ = 9.6 Hz, H-2), 3.38 (bd, 1 H, H-5), 3.21 (dd, 1 H, $J_{6a,6b}$ = 9.6 Hz, $J_{5,6b}$ = 3.2 Hz, H-6b), 2.53 (bs, 1 H, OH-2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.8−127.0 (Ph), 103.3 (C-1), 86.3 (*C*Ph_3), 82.8 (C-3), 76.4 (C-4), 74.6 (C-5), 73.1 (C-2), 72.5, 72.2 (*C*H_2Ph), 62.1 (C-6), 56.5 (OMe); ESIMS *m*/*z* 561 [M + Na]$^+$. HREIMS calcd for $C_{34}H_{34}O_6$ 538.2355, found 538.2357.

*Methyl 6-O-Triphenylmethyl-3,4-O-(o-xylylene)-α-D-mannopyranoside (**23**).* Amorphous solid. Yield: 13 mg (21%); R_f 0.71 (1:4 EtOAc/petroleum ether); $[\alpha]_D$ +23.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.11 (m, 19 H, Ph), 5.74, 4.57 (2 d, 2 H, $^2J_{H,H}$ = 12.1 Hz, C*H*Ph), 5.42, 4.68 (2 d, 2 H, $^2J_{H,H}$ = 15.4 Hz, C*H*Ph), 4.63 (d, 1 H, $J_{1,2}$ = 1.5 Hz, H-1), 4.02 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ =9.4 Hz, H-4), 3.79 (m, 3 H, H-2, H-3, H-5), 3.48 (d, 2 H, $J_{5,6}$ = 5.2 Hz, H-6), 3.35 (s, 3 H, OMe), 2.96 (s, 1 H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.6−126.5 (Ph), 100.3 (C-1), 87.1 (*C*Ph_3), 81.3 (C-2), 71.4 (*C*H_2Ph), 70.8 (C-5), 70.4 (*C*H_2Ph), 70.3 (C-3), 68.2 (C-4), 65.2 (C-6), 54.6 (OMe); FABMS *m*/*z* 561 (20%, [M + Na]$^+$). Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.79; H, 6.20.

*Methyl 2-O-(o-Bromomethylbenzyl)-6-O-triphenylmethyl-3,4-O-(o-xylylene)-α-D-mannopyranoside (**24**).* Amorphous solid. Yield: 14 mg (17%); R_f 0.46 (1:4 EtOAc/petroleum ether); $[\alpha]_D$ +60.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.13 (m, 23 H, Ph), 5.83, 4.63 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, C*H*Ph), 5.47, 4.70 (2 d, 2 H, $^2J_{H,H}$ = 15.2 Hz, C*H*Ph), 4.94, 4.39 (2 d, 2 H, $^2J_{H,H}$ = 10.4 Hz, C*H*Ph), 4.75, 4.36 (2 d, 21 H, $^2J_{H,H}$ = 10.1 Hz, CHBr), 4.69 (d, 1 H, $J_{1,2}$ = 1.2 Hz, H-1), 3.95 (dd, 1 H, $J_{3,4}$ = 9.1 Hz, $J_{2,3}$ = 2.8 Hz, H-3), 3.90 (t, 1 H, $J_{3,4}$ = 9.4 Hz, H-4), 3.83 (m, 2 H, H-2, H-5), 3.44 (dd, 1 H, $J_{6a,6b}$ = 9.7 Hz, $J_{5,6a}$ = 1.2 Hz, H-6a), 3.38 (s, 3 H, OMe), 3.28 (dd, 1 H, $J_{5,6b}$ = 6.1 Hz, H-6b); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.1−126.8 (Ph), 100.1 (C-1), 86.4 (*C*Ph_3), 82.1 (C-3), 73.8 (C-4), 72.0, 71.7, 70.5 (*C*H_2Ph), 71.8 (C-2), 71.3 (C-5), 63.5 (C-6), 54.5 (OMe), 31.0 (*C*H_2Br); FABMS *m*/*z* 745, 743 (40%, 30%, [M + Na]$^+$). Anal. Calcd for $C_{42}H_{41}BrO_6$: C, 69.90; H, 5.73. Found: C, 70.04; H, 5.87.

*Methyl 6-O-Triphenylmethyl-2,3-O-(o-xylylene)-α-D-galactopyranoside (**25**).* Amorphous solid. Yield: 11 mg (18%); R_f 0.45 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +102.9 (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.05 (m, 19 H, Ph), 5.26, 4.77 (2 d, 2 H, $^2J_{H,H}$ = 13.2 Hz, C*H*Ph), 5.14, 4.91 (2 d, 2 H, $^2J_{H,H}$ = 14.8 Hz, C*H*Ph), 4.86 (d, 1 H, $J_{1,2}$ = 3.1 Hz, H-1), 4.04 (bs, 1 H, H-4), 3.84 (m, 3 H, H-2, H-3, H-5), 3.44 (s, 3 H, OMe), 3.39 (dd, 1 H, $J_{6a,6b}$ = 9.7 Hz, $J_{5,6a}$ = 6.6 Hz, H-6a), 3.30 (dd, 1 H, $J_{5,6b}$ = 5.5 Hz, H-6b), 2.30 (s, 1 H, OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.9−127.0 (Ph), 98.5 (C-1), 86.7 (*C*Ph_3), 76.7 (C-2), 76.4 (C-3), 73.6, 72.0 (*C*H_2Ph), 69.1 (C-4), 68.9 (C-5), 66.0 (C-6), 55.2 (OMe); FABMS *m*/*z* 561 (10%, [M + Na]$^+$). Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.72; H, 6.13.

*Methyl 4-O-(o-Bromomethylbenzyl)-6-O-triphenylmethyl-2,3-O-(o-xylylene)-α-D-galactopyranoside (**26**).* Yield: 7 mg (6%); R_f 0.59 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +28.5 (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−6.71 (m, 23 H, Ph), 5.28, 4.82 (2 d, 2 H, $^2J_{H,H}$ = 13.0 Hz, C*H*Ph), 5.15, 4.83 (2 d, 2 H, $^2J_{H,H}$ = 15.2 Hz, C*H*Ph), 4.86, 4.36 (2 d, 2 H, $^2J_{H,H}$ = 10.3 Hz, C*H*Ph), 4.77 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 4.45, 3.93 (2 d, 2 H, $^2J_{H,H}$ = 10.0 Hz, CHBr), 4.02 (bd, 1 H, $J_{3,4}$ = 2.7 Hz, H-4), 3.96 (dd, 1 H, $J_{2,3}$ = 9.6 Hz, H-3), 3.85 (dd, 1 H, H-2), 3.80 (bt, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5), 3.42 (dd, 1 H, $J_{6a,6b}$ = 9.5 Hz, H-6a), 3.36 (s, 3 H, OMe), 3.24 (dd, 1 H, H-6b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.9−127.1 (Ph), 98.7 (C-1), 87.1 (*C*Ph_3), 78.1 (C-2), 77.6 (C-3), 76.2 (C-4), 74.0, 72.6, 72.2 (*C*H_2Ph), 69.3 (C-5), 62.5 (C-6), 55.2 (OMe), 31.5 (*C*H_2Br); FABMS *m*/*z* 745, 743 (20%, 15%, [M + Na]$^+$). Anal. Calcd for $C_{42}H_{41}BrO_6$: C, 69.90; H, 5.73. Found: C, 69.98; H, 5.68.

*Methyl 2-O-(o-Bromomethylbenzyl)-6-O-triphenylmethyl-3,4-O-(o-xylylene)-α-D-galactopyranoside (**27**).* Yield: 3 mg (4%); R_f 0.63 (1:2 EtOAc/petroleum ether); $[\alpha]_D$ +16.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.02 (m, 23 H, Ph), 5.46, 4.54 (2 d, 2 H, $^2J_{H,H}$ = 12.8 Hz, C*H*Ph), 5.40, 4.56 (2 d, 2 H, $^2J_{H,H}$ = 14.5 Hz, C*H*Ph), 4.91, 4.81 (2 d, 2 H, $^2J_{H,H}$ = 11.7 Hz, C*H*Ph), 4.81, 4.73 (2 d, 2 H, $^2J_{H,H}$ = 10.2 Hz, CHBr), 4.77 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 4.10 (bs, 1 H, H-4), 4.03 (dd, 1 H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.00 (dd, 1 H, H-2), 3.70 (bt, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 7.2 Hz, H-5), 3.26 (s, 3 H, OMe), 3.25 (m, 2 H, H-6a, H-6b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.9−127.1 (Ph), 98.5 (C-1), 86.8 (*C*Ph_3), 78.1 (C-2), 74.0 (C-3), 71.8 (C-4), 72.1, 71.1, 69.1 (*C*H_2Ph), 68.5 (C-5), 61.2 (C-6), 55.3 (OMe), 33.7 (*C*H_2Br); FABMS *m*/*z* 745, 743 (20%, 15%, [M + Na]$^+$). Anal. Calcd for $C_{42}H_{41}BrO_6$: C, 69.90; H, 5.73. Found: C, 69.93; H, 5.72.

Preparation of 1,2-*O*-Isopropylidene-5,6-*O*-(*o*-xylylene)-α-D-glucofuranose (29). Compound **29** was prepared from the

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commercial 1,2-*O*-isopropylidene-α-D-glucofuranose **28** (100 mg, 0.454 mmol) following the procedure above-described for derivatives **6**–**8**. Column chromatography, eluent 2:3 EtOAc/petroleum ether. Amorphous solid. Yield: 88 mg (60%); R_f 0.50 (1:1 EtOAc/petroleum ether); $[\alpha]_D$ −50.5 (*c* 1.0, DCM); IR (ATR) ν_{max} 3297, 2918, 1456, 1067, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.23 (m, 4 H, Ph), 5.94 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 5.08, 4.70 (2 d, 2 H, $^2J_{H,H}$ = 13.0 Hz, C*H*Ph), 5.00, 4.89 (2 d, 2 H, $^2J_{H,H}$ = 12.5 Hz, C*H*Ph), 4.60 (d, 1 H, H-2), 4.19 (dd, 1 H, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.03 (d, 1 H, H-3), 3.91 (dd, 1 H, $J_{5,6a}$ = 3.5 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.74 (ddd, 1 H, $J_{5,6b}$ = 5.5 Hz, H-5), 3.66 (dd, 1 H, H-6b), 2.60 (bs, 1 H, OH), 1.45, 1.32 (2 s, 6 H, 2 CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.4−128.7 (Ph), 111.8 (*C*Me_2), 105.9 (C-1), 83.5 (C-2), 81.8 (C-3), 80.3 (C-4), 79.0 (C-5), 74.2, 72.8 (CH_2Ph), 63.3 (C-6), 26.8, 26.3 (*C*Me_2); ESIMS *m*/*z* 345 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.41; H, 6.95.

Preparation of 1,2-*O*-Isopropylidene-3,5-*O*-(*o*-xylylene)-α-D-glucofuranose (33). *3-O-(2-Bromomethyl)benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**31**).* To a solution of commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **30** (0.5 g, 1.92 mmol) in dry DMF (20 mL) at 0 °C under Ar atmosphere was added NaH (60% in mineral oil, 192 mg, 4.80 mmol), and the suspension was stirred at room temperature for 15 min. Then, a solution of 1,2-dibromomethylbenzene (1.26 g, 4.80 mmol) in dry DMF (15 mL) was added dropwise, and the mixture was stirred for 1 h at room temperature. Further treatment as described for **6**–**8** and column chromatography using 1:6 EtOAc/petroleum ether as eluent gave **31**. Amorphous solid. Yield: 0.51 g (60%); R_f 0.44 (1:4 EtOAc/petroleum ether); $[\alpha]_D$ −129.5 (*c* 1.1, DCM); IR (ATR) ν_{max} 2985, 1456, 1071, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 4 H, Ph), 5.83 (d, 1 H, $J_{1,2}$ = 6.0 Hz, H-1), 4.75, 4.68 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, C*H*Ph), 4.61, 4.52 (2 d, 2 H, $^2J_{H,H}$ = 9.0 Hz, CH_2Br), 4.57 (d, 1 H, H-2), 4.25 (dt, 1 H, $J_{4,5}$ = 9.0 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 6.0 Hz, H-5), 4.03 (dd, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.01 (dd, 1 H, $J_{6a,6b}$ = 9.0 Hz, H-6a), 3.98 (d, 1 H, H-3), 3.91 (dd, 1 H, H-6b), 1.42, 1.34, 1.29, 1.25 (4 s, 12 H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.4−128.7 (Ph), 111.8, 109.1 (*C*Me_2), 105.3 (C-1), 82.5 (C-2), 81.8 (C-3), 81.4 (C-4), 72.3 (C-5), 69.7 (CH_2Ph), 67.6 (C-6), 39.9 (CH_2Br), 26.8, 26.7, 26.2, 25.3 (*C*Me_2); ESIMS *m*/*z* 465, 467 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{27}O_6Br$: C, 54.18; H, 6.14. Found: C, 54.30; H, 6.18.

*3-O-(o-Bromomethylbenzyl)-1,2-O-isopropylidene-α-D-glucofuranose (**32**).* To a solution of **31** (0.45 g, 1.01 mmol) in MeCN (20 mL) were added iodine (50 mg, 0.196 mmol) and H_2O (21 μL, 1.16 mmol). The mixture was stirred for 4 h at room temperature. The reaction was neutralized by addition of saturated aqueous $NaHCO_3$, and then EtOAc (10 mL) was added. The excess of iodine was removed by addition of 10% $Na_2S_2O_3$ solution until decoloration of the organic layer. The organic layer was separated, washed with H_2O (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography using 1:1 EtOAc/petroleum ether as eluent. Amorphous solid. Yield: 0.27 g (66%); R_f 0.20 (1:1 EtOAc/petroleum ether); $[\alpha]_D$ −311.9 (*c* 1.0, DCM); IR (ATR) ν_{max} 3413, 2933, 1454, 1072, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.19 (m, 4 H, Ph), 5.86 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.81, 4.64 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, C*H*Ph), 4.61 (d, 1 H, H-2), 4.53 (s, 2 H, CH_2Br), 4.08 (m, 2 H, H-3, H-4), 3.93 (m, 1 H, H-5), 3.76 (dd, 1 H, $J_{6a,6b}$ = 11.4 Hz, $J_{5,6a}$ = 3.0 Hz, H-6a), 3.64 (dd, 1 H, $J_{5,6b}$ = 8.5.0 Hz, H-6b), 1.42, 1.26 (2 s, 6 H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.0−128.7 (Ph), 111.8 (*C*Me_2), 105.1 (C-1), 82.3 (C-3), 81.9 (C-2), 79.9 (C-4), 69.4 (CH_2Ph), 68.9 (C-5), 64.3 (C-6), 30.8 (CH_2Br), 26.7, 26.1 (*C*Me_2); ESIMS *m*/*z* 425, 427 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{23}O_6Br$: C, 50.63; H, 5.75. Found: C, 50.27; H, 5.32.

*1,2-O-Isopropylidene-3,5-O-(o-xylylene)-α-D-glucofuranose (**33**).* To a solution of **32** (264 mg, 0.654 mmol) in dry DMF (25 mL) at room temperature under Ar atmosphere was added NaH (60% in mineral oil, 47 mg, 1.18 mmol), and the suspension was stirred at room temperature for 4 h. The reaction was quenched by addition of Et_2O (30 mL) and H_2O (15 mL), and the organic layer was separated, washed with H_2O (5 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography using 1:1 EtOAc/petroleum ether as eluent. Amorphous solid. Yield: 95 mg (45%); R_f 0.30 (1:1 EtOAc/petroleum ether); $[\alpha]_D$ −298.5 (*c* 1.0, DCM); IR (ATR) ν_{max} 3290, 2917, 1456, 1067, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.13 (m, 4 H, Ph), 5.86 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 5.00, 4.61 (2 d, 2 H, $^2J_{H,H}$ = 12.9 Hz, C*H*Ph), 4.91, 4.80 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, C*H*Ph), 4.52 (d, 1 H, H-2), 4.09 (dd, 1 H, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.94 (d, 1 H, H-3), 3.83 (dd, 1 H, $J_{6a,6b}$ = 11.4 Hz, $J_{5,6a}$ = 3.0 Hz, H-6a), 3.67 (ddd, 1 H, $J_{5,6b}$ = 6.0 Hz, H-5), 3.57 (dd, 1 H, H-6b), 1.92 (bs, 1 H, OH), 1.36, 1.23 (2 s, 6 H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.4−128.7 (Ph), 111.8 (*C*Me_2), 105.9 (C-1), 83.5 (C-2), 81.8 (C-3), 80.4 (C-4), 79.1 (C-5), 74.3, 72.8 (CH_2Ph), 63.4 (C-6), 26.8, 26.3 (*C*Me_2); ESIMS *m*/*z* 345 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.40; H, 7.12.

Preparation of 2^I,3^I-*O*-(*o*-Xylylene)cyclomaltoheptaose Derivatives (35–37). *Heptakis(6-O-tert-butyldimethylsilyl)-2^I,3^I-O-(o-xylylene)cyclomaltoheptaose (**35**).* To a solution of **34** (894 mg, 0.46 mmol) in dry DMF (90 mL) at 0 °C under Ar was added NaH (60% in mineral oil, 111 mg, 2.77 mmol). The reaction mixture was stirred for 15 min, and then a solution of 1,2-dibromomethylbenzene (366 mg, 1.39 mmol) in dry DMF (10 mL) was dropwise added. The reaction mixture was stirred at 0 °C under Ar atmosphere for 30 min and then was left to reach room temperature for 24 h. Further treatment as described for **6**–**8** and column chromatography using 60:1 → 6:1 DCM/MeOH containing 0.5% of Et_3N as eluent gave **35**. Amorphous solid. Yield: 309 mg (33%); R_f = 0.34 (9:1 DCM/MeOH); $[\alpha]_D$ = +133.8 (*c* 0.73, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ 7.29−7.156 (m, 4 H, Ph), 5.28, 4.99 (2 d, 2 H, $^2J_{H,H}$ = 14.1 Hz, C*H*Ph), 5.12, 5.07 (2 d, 2 H, $^2J_{H,H}$ = 14.7 Hz, C*H*Ph), 5.12 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^I), 5.01−4.94 (m, 6 H, H-1^{II-VII}), 4.11−3.91 (m, 8 H, H-6a^{I-VII}, H-3^I), 3.90−3.82 (m, 6 H, H-3^{II-VII}), 3.79−3.73 (m, 7 H, H-6b^{I-VII}), 3.69−3.64 (m, 8 H, H-5^{I-VII}, H-4^I), 3.59−3.52 (m, 7 H, H-4^{II-VII}, H-2^I), 3.44−3.36 (m, 6 H, H-2^{II-VII}), 0.89 (s, 63 H, Me_3C), 0.02 (s, 42 H, Me_2Si); 1D TOCSY (H-1^I irradiation) δ 4.11 (bd, 1 H, $J_{6a,6b}$ = 11.5 Hz, H-6a^I), 3.97 (m, 1 H, H-3^I), 3.76 (m, 1 H, H-6b^I), 3.69 (m, 2 H, H-4^I, H-5^I), 3.54 (dd, 1 H, $J_{2,3}$ = 8.8 Hz, H-2^I); ^{13}C NMR (125.7 MHz, CD_3OD) δ 136.3−127.8 (Ph), 102.4, 102.3, 102.2, 101.9, 101.6 (C-1^{II-VII}), 100.7 (C-1^I), 81.7, 81.0, 80.9, 80.8, 80.7 (C-4^{II-VII}), 80.8 (C-2^I), 80.4 (C-3^I), 78.4 (C-4^I), 73.7, 73.6, 73.4, 73.3, 73.2 (C-3^{II-VII}), 73.2 (CH_2Ph), 73.1, 73.0, 72.9 (C-2^{II-VII}), 72.9 (CH_2Ph), 72.7, 72.5, 72.4 (C-5^{II-VII}), 72.1 (C-5^I), 62.2, 62.1, 61.9 (C6^{II-VII}), 61.8 (C-6^I), 25.2 (*Me*$_3$C), 17.9 (Me_3C); FABMS *m*/*z* 2059 $[M + Na]^+$. Anal. Calcd for $C_{92}H_{174}O_{35}Si_7$: C, 54.25; H, 8.61. Found: C, 53.98; H, 8.36.

*Heptakis(6-O-tert-butyldimethylsilyl)-2^{II-VII},3^{II-VII}-dodeca-O-methyl-2^I,3^I-O-(o-xylylene)cyclomaltoheptaose (**36**).* To a solution of **35** (114 mg, 0.06 mmol) in dry DMF (4.5 mL) at 0 °C under Ar atmosphere were added NaH (60% in mineral oil, 134 mg, 3.36 mmol) and MeI (209 mL, 3.36 mmol), and the reaction mixture was stirred at room temperature for 2 h. Further treatment as described for **6**–**8** and column chromatography using 1:4 → 1:3 EtOAc/petroleum ether as eluent gave **36**. Amorphous solid. Yield: 69 mg (56%); R_f = 0.34 (1:3 EtOAc/petroleum ether); $[\alpha]_D$ = +96.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.05 (m, 4 H, Ph), 5.26, 4.73 (2 d, 2 H, $^2J_{H,H}$ = 12.7 Hz, C*H*Ph), 5.18, 5.12 (2 d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 5.19−5.12 (m, 7 H, H-1^{I-VII}), 4.10−4.01 (m, 7 H, H-6a^{I-VII}), 3.79 (m, 1 H, H-3^I), 3.79−3.61 (m, 6 H, H-4^{II-VII}), 3.61−3.47 (m, 8 H, H-6b^{I-VII}, H-4^I), 3.59−3.35 (m, 14 H, H-5^{I-VII}, H-3^{II-VII}, H-2^I), 3.11−3.00 (m, 6 H, H-2^{II-VII}), 3.75, 3.70, 3.64, 3.62, 3.57, 3.56, 3.52, 3.50, 3.49, 3.47, 3.43, 3.25 (12 s, 36 H, Me), 0.85 (s, 63 H, Me_3C), 0.01 (s, 42 H, Me_2Si); 1D TOCSY (H-3^I irradiation) δ 5.15 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^I), 4.10 (d, 1 H, $J_{6a,6b}$ = 12.2 Hz, H-6a^I), 3.61 (d, 1 H, H-6b^I), 3.56 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4^I), 3.53 (m, 1 H, H-5^I), 3.41 (dd, 1 H, $J_{2,3}$ = 9.0 Hz, H-2^I); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.4−126.8 (Ph), 99.8 (C-1^I), 98.6, 98.2, 98.1, 98.0, 97.9 (C-1^{II-VII}), 82.3, 82.2, 82.0, 81.8 (C-2^{II-VII}, C-3^{II-VII}), 82.0 (C-2^I), 80.2, 79.2, 78.8, 78.7, 78.6, 78.5, 78.2 (C-4^{I-VII}), 79.0 (C-3^I), 74.8 (CH_2Ph), 72.4 (CH_2Ph), 72.3 (C-5^I), 72.3, 72.2, 72.0, 71.9 (C-5^{II-VII}), 62.6, 62.3, 62.2, 61.7, 61.5, 61.4, 61.3, 58.8, 58.7, 58.6, 58.5 (C-6^{I-VII}, Me), 26.0

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(Me_3C), 18.5 (Me_3C); MALDI-TOFMS m/z 2226.2 $[M + Na]^+$. Anal. Calcd for $C_{104}H_{198}O_{35}Si_7$: C, 56.62; H, 8.78. Found: C, 56.64; H, 9.05.

$2^{II-VII},3^{II-VII}$-Dodeca-O-methyl-$2^I,3^I$-O-(o-xylylene)-cyclomaltoheptaose (37). A solution of **36** (170 mg, 0.08 mmol) in TFA/H_2O (1:1, 10 mL) was stirred at 45 °C for 2 h. The solution was concentrated and co-evaporated several times with water to eliminate traces of the acid. The resulting residue was dissolved in water and freeze-dried to give **37** as an amorphous solid. Yield: 108 mg (96%); R_f = 0.47 (10:1:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +108.7 (c 1.0, H_2O); UV (MeOH) 220 nm (ε_{mM} 10.7); IR (ATR) ν_{max} 3391, 2926, 1675, 1454, 1132, 1084, 1017 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.35−7.14 (m, 4 H, Ph), 5.25 (d, 1 H, $J_{1,2}$ = 3.4 Hz, H-1^I), 5.35−5.19 (m, 6 H, H-1^{II-VII}), 5.09, 4.98 (2 d, 2 H, $^2J_{H,H}$ = 14.7 Hz, C*H*Ph), 4.85 (bs, 2 H, CH_2Ph), 3.92−3.76 (m, 7 H, H-$6a^{I-VII}$), 3.79−3.68 (m, 7 H, H-$6b^{I-VII}$), 3.79−3.62 (m, 7 H, H-5^{I-VII}), 3.78−3.38 (m, 7 H, H-3^{I-VII}), 3.67−3.52 (m, 7 H, H-4^{I-VII}), 3.39−3.21 (m, 7 H, H-2^{I-VII}), 3.60 (× 2), 3.55, 3.52, 3.50, 3.49, 3.42, 3.41, 3.27 (× 4) (7 s, 36 H, 12 Me); 1D TOCSY (H-1^I irradiation) δ 3.90 (m, 1 H, H-$6a^I$), 3.78 (m, 2 H, H-3^I, H-5^I), 3.74 (m, 1 H, H-$6b^I$), 3.62 (m, 1 H, H-4^I), 3.39 (dd, 1 H, H-2^I); ^{13}C NMR (125.7 MHz, D_2O) δ 136.8−128.0 (Ph), 98.1, 97.9, 97.6, 96.7, 96.0 (C-1^{II-VII}), 97.8 (C-1^I), 81.9, 81.8, 81.4, 81.2, 80.9 (C-3^{II-VII}), 80.8, 80.5, 80.4, 80.3, 80.2 (C-2^{II-VII}), 80.2 (C-2^I), 79.9 (C-3^I), 78.6, 78.3, 76.8, 75.4, 75.0 (C-4^{I-VII}), 73.3, 73.0 (CH_2Ph), 70.2, 71.9, 71.8, 71.6, 70.5 (C-5^{I-VII}), 60.7, 60.6, 60.5, 60.4, 60.3, 60.2, 59.6, 58.4, 58.1 (C-6^{I-VII}, Me); FABMS m/z 1428 (100%, $[M + Na]^+$). Anal. Calcd for $C_{62}H_{100}O_{35}$: C, 52.98; H, 7.17. Found: C, 52.77; H, 7.15.

General Procedure for Synthesis of $2^I,3^I$-Di-*O*-xylylenated Cyclodextrin Derivatives 38, 44, and 49. To a solution of dry cyclodextrin (α, β or γ) (0.88 mmol) in dry DMSO (40 mL) at 0 °C under Ar atmosphere was added LDA (2 M in THF/*n*-heptane, 441 μL, 0.88 mmol). The reaction mixture was stirred for 16 h, and then a solution of 1,2-dibromomethylbenzene (232 mg, 0.88 mmol) in dry DMSO (5 mL) was dropwise added. The reaction mixture was stirred at room temperature for 7 h and concentrated. The resulting residue was purified by column chromatography using 10:1:1 → 6:3:1 MeCN/H_2O/NH_4OH as eluent to yield the corresponding $2^I,3^I$-*O*-xylylenated derivative as major compound (**38**, **44**, and **49**) and minor amounts of monosubstituted derivatives (**39**, **40**, **45**, and **50**).

$2^I,3^I$-O-(o-Xylylene)cyclomaltoheptaose (38). $2^I,3^I$-*O*-Xylylenation of β-cyclodextrin yielded **38** as an amorphous solid. Yield: 326 mg (30%); R_f = 0.42 (6:3:1 MeCN/H_2O/NH_4OH); HPLC (t_R 36.9 min); $[\alpha]_D$ = +124.2 (c 1.0, DMSO); ^1H NMR (500 MHz, DMSO) δ 7.26−7.12 (m, 4 H, Ph), 5.73−5.61 (m, 7 H, OH-6), 5.14, 4.88 (2 d, 2 H, $^2J_{H,H}$ = 14.3 Hz, C*H*Ph), 5.06 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^I), 5.05, 4.94 (2 d, 2 H, $^2J_{H,H}$ = 14.3 Hz, C*H*Ph), 4.83−4.78 (m, 6 H, H-1^{II-VII}), 4.57−4.32 (m, 14 H, OH-2, OH-3), 3.80 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.9 Hz, H-3^I), 3.68 (m, 1 H, H-$6a^I$), 3.64−3.48 (m, 23 H, H-$6b^I$, H-5^I,H-4^I, H-2^I, H-3 $^{II-VII}$, H-5^{II-VII}, H-$6a^{I-VII}$), 3.35−3.21 (m, 18 H, H-4^{II-VII}, H-$6b^{II-VII}$, H-2^{II-VII}); 1D TOCSY (H-3^I irradiation) δ 5.06 (d, 1 H, H-1^I), 4.50 (m, 2 H, OH-2, OH-3), 3.68 (m, 1 H, H-$6a^I$), 3.58 (m, 1 H, H-$6b^I$), 3.54 (m, 1 H, H-5^I), 3.52 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4^I), 3.49 (dd, 1 H, $J_{2,3}$ = 8.9 Hz, H-2^I); ^{13}C NMR (125.7 MHz, DMSO) δ = 137.1−128.3 (Ph), 102.4, 102.3, 102.1 (C-1^{II-VII}), 100.6 (C-1^I), 82.5, 82.1, 81.8, 81.7 (C-4^{II-VII}), 81.7 (C-3^I), 81.0 (C-2^I), 79.1 (C-4^I), 73.8, 73.7, 73.6, 73.4 (C-3^{II-VII}), 73.7 (CH_2Ph), 73.2 (C-5^I), 73.1 (CH_2Ph), 73.0, 72.9, 72.8, 72.7, (C-2^{II-VII}), 72.6, 72.5, 72.1 (C-5^{II-VII}), 60.6, 60.5, 60.3 (C-6^{II-VII}), 60.1 (C-6^I). FABMS m/z 1259 (100%, $[M + Na]^+$). Anal. Calcd for $C_{50}H_{76}O_{35}$: C, 48.54; H, 6.19. Found: C, 48.38; H, 5.96.

2^I-O-(2-Hydroxymethylbenzyl)cyclomaltoheptaose (39). Compound **39** was purifed by semipreparative HPLC (t_R 40.0 min). Amorphous solid. Yield: 55 mg (5%); R_f = 0.43 (6:3:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +94.4 (c 1.0, DMSO); ^1H NMR (500 MHz, DMSO-d_6) δ 7.45−7.24 (m, 4 H, Ph), 5.01 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^I), 4.87−4.81 (m, 8 H, H-1^{II-VII}, CH_2Ph), 4.63, 4.60 (2 d, 2 H, $^2J_{H,H}$ = 14.0 Hz, C*H*Ph), 3.87 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3^I), 3.75−3.46 (m, 27 H, H-3^{II-VII}, H-5^{I-VII}, H-$6a^{I-VII}$, H-$6b^{I-VII}$), 3.45−3.25 (m, 14 H, H-4^{I-VII}, H-2^{I-VII}); 1D TOCSY (H-1^I irradiation) δ 3.87 (t, 1 H, H-3^I), 3.65 (m, 1 H, H-$6a^I$), 3.57 (m, 2 H, H-5^I, H-$6b^I$), 3.41 (m, 1 H, H-4^I), 3.33 (m, 1 H, H-2^I); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 141.5−127.1 (Ph), 102.5, 102.4, 102.2 (C-1^{II-VII}), 100.4 (C-1^I), 82.6, 82.3, 82.0, 81.9 (C-4^{I-VII}), 79.8 (C-2^I), 73.5, 73.4, 73.3, 73.1, 72.9, 72.5, 72.3, 72.2 (C-3^{I-VII}, C-2^{II-VII}, C-5^{I-VII}), 73.8, 72.8, 72.7, 72.5 (C-5^{II-VI}), 70.9 (CH_2Ph), 60.7 (CH_2Ph), 60.4 (C-6^{I-VII}); ESIMS m/z 1277.2 $[M + Na]^+$, 1293.2 $[M + K]^+$. Anal. Calcd for $C_{50}H_{78}O_{36}$: C, 47.85; H, 6.26. Found: C, 47.49; H, 6.02.

6^I-O-(2-Hydroxymethylbenzyl)cyclomaltoheptaose (40). Compound **40** was purified by semipreparative HPLC (t_R 41.7 min). Amorphous solid. Yield: 33 mg (3%); R_f = 0.40 (6:3:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +81.3 (c 1.0, DMSO); UV (MeOH) 212 nm (ε_{mM} 7.7); IR (ATR) ν_{max} 3305, 2927, 1653, 1540, 1152, 1020 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.43−7.21 (m, 4 H, Ph), 4.88−4.80 (m, 7 H, H-1^{I-VII}), 4.57, 4.51 (2 d, 2 H, $^2J_{H,H}$ = 12.1 Hz, C*H*Ph), 4.55 (bs, 2 H, CH_2Ph), 3.84−3.44 (m, 28 H, H-$6a^{I-VII}$, H-$6b^{I-VII}$, H-3^{I-VII}, H-5^{I-VII}), 3.45−3.27 (m, 14 H, H-4^{I-VII}, H-2^{I-VII}); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 140.6−127.0 (Ph), 102.5 (C-1^{II-VII}), 100.4 (C-1^I), 82.7, 82.1, 82.0, 81.9 (C-4^{I-VII}), 73.7, 73.5, 72.9, 72.8, 72.6, 72.5 (C-3^{I-VII}, C-2^{I-VII}, C-5^{I-VII}), 70.3 (CH_2Ph), 60.7 (CH_2Ph), 60.4 (C-6^{I-VII}); ESIMS m/z 1277.2 $[M + Na]^+$, 1293.2 $[M + K]^+$. Anal. Calcd for $C_{50}H_{78}O_{36}$: C, 47.85; H, 6.26. Found: C, 47.61; H, 6.10.

$2^I,3^I$-O-(o-Xylylene)cyclomaltohexaose (44). $2^I,3^I$-*O*-Xylylenation of α-cyclodextrin following the general procedure above-described yielded **44** as an amorphous solid after precipitation from water as major compound and minor amounts of **45**. Yield: 230 mg (24%); R_f = 0.54 (6:3:1 MeCN/H_2O/NH_4OH); HPLC (t_R 35.4 min); $[\alpha]_D$ = +152.2 (c 1.0, DMSO); UV (MeOH) 214 nm (ε_{mM} 7.3); IR (ATR) ν_{max} 3334, 2927, 1645, 1409, 1151, 1078, 1027 $cm^{-1}$$^1H$ NMR (500 MHz, D_2O, 333 K) δ 7.70−7.63 (m, 4 H, Ph), 5.48 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^I), 5.46, 5.40 (2 d, 2 H, $^2J_{H,H}$ = 14.6 Hz, C*H*Ph), 5.43, 5.30 (2 d, 2 H, $^2J_{H,H}$ = 13.7 Hz, C*H*Ph), 5.37−5.28 (m, 5 H, H-1^{II-VI}), 4.41−3.98 (m, 26 H, H-3^{I-VI}, H-$6a^{I-VI}$, H-$6b^{I-VI}$, H-5^{I-VI}, H-2^I, H-4^I), 3.98−3.88 (m, 5 H, H-2^{II-VI}), 3.91−3.78 (m, 5 H, H-4^{II-VI}); 1D TOCSY (H-1^I irradiation) δ 4.29 (d, 1 H, $J_{6a,6b}$ = 12.5 Hz, H-$6a^I$), 4.25 (dd, 1 H, $J_{5,6b}$ = 3.0 Hz, H-$6b^I$), 4.21 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^I), 4.14 (m, 1 H, H-5^I), 4.05 (dd, 1 H, H-2^I), 4.03 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4^I); ^{13}C NMR (125.7 MHz, D_2O, 333 K) δ 136.9−128.6 (Ph), 102.0, 101.9, 101.8, 101.7, 101.6 (C-1^{II-VI}), 100.9 (C-1^I), 82.5, 82.0, 81.9, 81.8 (C-4^{II-VI}), 80.8 (C-3^I), 80.4 (C-4^I), 79.5 (C-2^I), 74.2, 74.0, 73.8, 73.6 (C-3^{II-VI}), 73.8 (CH_2Ph), 72.8, 72.7, 72.5 (C-5^{II-VI}), 72.7 (CH_2Ph), 72.3, 72.2, 72.1, 71.9 (C-2^{II-VI}), 61.0 (C-6^{I-VI}); ESIMS m/z 1113.2 $[M + K]^+$. Anal. Calcd for $C_{44}H_{66}O_{30}$: C, 49.16; H, 6.19. Found: C, 48.99; H, 5.95

2^I-O-(2-Hydroxymethylbenzyl)cyclomaltohexaose (45). Compound **45** was purified by semipreparative HPLC (t_R 37.4 min). Amorphous solid. Yield: 29 mg (3%); R_f = 0.54 (6:3:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +65.6 (c 1.0, DMSO); ^1H NMR (500 MHz, D_2O) δ 7.46−7.36 (m, 4 H, Ph), 5.16 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^I), 5.00−4.95 (m, 5 H, H-1^{II-VI}), 4.84, 4.82 (2 d, 2 H, $^2J_{H,H}$ = 11.4 Hz, C*H*Ph), 4.74, 4.71 (2 d, 2 H, $^2J_{H,H}$ = 13.3 Hz, C*H*Ph), 4.04 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3^I), 3.93−3.73 (m, 23 H, H-3^{II-VI}, H-5^{I-VI}, H-$6a^{I-VI}$, H-$6b^{I-VI}$), 3.59−3.47 (m, 12 H, H-4^{I-VI}, H-2^{I-VI}); 1D TOCSY (H-3^I irradiation) δ 5.16 (d, 1 H, H-1^I), 3.82 (d, 1 H, $J_{6a,6b}$ = 12.0 Hz, H-$6a^I$), 3.77 (m, 2 H, H-5^I, H-$6b^I$), 3.55 (m, 2 H, H-2^I, H-4^I); ^{13}C NMR (125.7 MHz, D_2O) δ 139.0−128.2 (Ph), 101.6, 101.4, 101.3 (C-1^{II-VI}), 99.2 (C-1^I), 81.6, 81.5, 81.3, 81.2, 81.1 (C-4^{I-VI}), 79.0 (C-2^I), 73.3 (C-3^{II-VI}), 72.5 (C-3^I), 72.0 (C-5^{I-VI}), 71.6, 71.4 (C-2^{I-VI}), 70.8 (CH_2Ph), 61.2 (CH_2Ph), 60.4 (C-6^{I-VI}); ESIMS m/z 1115.3 $[M + Na]^+$. Anal. Calcd for $C_{44}H_{68}O_{31}$: C, 48.35; H, 6.27. Found: C, 48.07; H, 6.12.

$2^I,3^I$-O-(o-Xylylene)cyclomaltooctaose (49). Amorphous solid. Yield: 408 mg (29%); R_f = 0.52 (MeCN/H_2O/NH_4OH 6:3:1); HPLC (t_R 37.0 min); $[\alpha]_D$ = +154.8 (c 0.91, H_2O). UV (MeOH) 212 nm (ε_{mM} 6.3); IR (ATR) ν_{max} 3350, 2926, 1645, 1414, 1155, 1081, 1025 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.10−6.96 (m, 4 H, Ph), 5.28 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^I), 5.20, 4.73 (2 d, 2 H, $^2J_{H,H}$ = 13.4 Hz, C*H*Ph), 5.16, 5.09 (2 d, 2 H, $^2J_{H,H}$ = 14.0 Hz, C*H*Ph), 5.12−4.98 (m, 7 H, H-$1^{II-VIII}$), 4.13−4.03 (m, 7 H, H-$5^{II-VIII}$), 3.97−3.62 (m, 27 H, H-3^{I-VIII}, H-$6a^{I-VIII}$, H-$6b^{I-VIII}$, H-5^I, H-4^I, H-2^I), 3.63−3.47 (m, 14 H, H-$2^{II-VIII}$, H-$4^{II-VIII}$); 1D TOCSY (H-1^I irradiation) δ 3.93 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.3 Hz, H-3^I), 3.92 (m, 2 H, H-$6a^I$, H-5^I), 3.89 (d, 1 H, $J_{6a,6b}$ = 11.5 Hz, H-$6b^I$), 3.79 (m, 1 H, H-2^I), 3.75 (m, 1 H, H-4^I); ^{13}C NMR (125.7 MHz, D_2O) δ 136.2−128.0 (Ph), 102.3, 102.2, 102.0, 101.7,

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101.6, 101.0 (C-$1^{II-VIII}$), 100.3 (C-1^{I}), 81.7, 81.1, 80.5, 80.0, 79.8, 79.6, 79.2, 79.1 (C-4^{I-VIII}), 79.1 (C-2^{I}), 78.4 (C-3^{I}), 73.8 (CH_2Ph), 73.7, 73.5, 73.2, 72.9, 72.8, 72.7, 72.6, 72.5, 72.3, 72.1, 72.0, 71.9, 71.8, 71.7 (C-$2^{II-VIII}$, C-$3^{II-VIII}$, C-5^{I-VIII}), 60.5, 60.3, 60.1, 59.9 (C-6^{I-VIII}); ESIMS m/z 1421.3 $[M + Na]^+$, 719.1 $[M + 2K]^{2+}$. Anal. Calcd for $C_{56}H_{86}O_{40}$: C, 48.07; H 6.19. Found: C, 47.95; H, 6.06.

*2^{I}-O-(2-Hydroxymethylbenzyl)cyclomaltooctaose (**50**).* Compound **50** was purified by semipreparative HPLC (t_R 40.0 min). Amorphous solid. Yield: 99 mg (7%); R_f = 0.37 (6:3:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +119.0 (c 0.5 in MeOH); UV (MeOH) 212 nm (ε_{mM} 11.0); IR (ATR) ν_{max} 3350, 2923, 1663, 1413, 1156, 1080, 1025 cm^{-1}; 1H NMR (500 MHz, D_2O) δ 7.40–7.29 (m, 4 H, Ph), 5.19 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^{I}), 5.02–4.98 (m, 7 H, H-$1^{II-VIII}$), 4.82, 4.80 (2 d, 2 H, $^2J_{H,H}$ = 12.4 Hz, C*H*Ph), 4.70, 4.66 (2 d, 2 H, $^2J_{H,H}$ = 12.8 Hz, C*H*Ph), 3.96 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{I}), 3.82–3.72 (m, 31 H, H-$3^{II-VIII}$, H-5^{I-VIII}, H-6a^{I-VIII}, H-6b^{I-VII}), 3.56–3.44 (m, 16 H, H-4^{I-VIII}, H-2^{I-VIII}); 1D TOCSY (H-1^{I} irradiation) δ 3.96 (d, 1 H, H-3^{I}), 3.74 (m, 3 H, H-5^{I}, H-6a^{I}, H-6b^{I}), 3.52 (m, 2 H, H-2^{I}, H-4^{I}); ^{13}C NMR (125.7 MHz, D_2O) δ 139.1–128.3 (Ph), 101.6, 101.5, 101.3, 101.1 (C-2^{I}, C-$1^{II-VIII}$), 99.1 (C-1^{I}), 80.4, 80.2, 80.0, 79.5, 79.4 (C-4^{I-VIII}), 72.9 (C-$3^{II-VIII}$), 72.3 (C-$2^{II-VIII}$), 72.1 (C-3^{I}), 71.8, 71.6, 71.4 (C-5^{I-VIII}), 71.6, 71.2 (CH_2Ph), 61.3 (CH_2Ph), 60.2 (C-6^{I-VIII}); ESIMS m/z 728.1 $[M + K + H]^{2+}$. Anal. Calcd for $C_{56}H_{88}O_{41}$: C, 47.46; H, 6.26. Found: C, 47.33; H, 6.46.

General Procedure for Synthesis of Permethylated Cyclodextrin Derivatives 41, 46, and 51. To a solution of monoxylylenated cyclodextrin derivatives **38**, **44**, or **49** (0.16 mmol) in dry DMF (12 mL) at 0 °C under Ar atmosphere were added NaH (60% in mineral oil, 589 mg, 14.73 mmol) and MeI (917 μL, 14.73 mmol), and the mixture was stirred at room temperature for 12 h. Then, the reaction mixture was quenched with water (15 mL) and extracted with Et_2O (4 × 15 mL). The combined organic layer was washed with water (3 × 10 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography using 20:1 DCM/MeOH as eluent to yield the corresponding methylated compounds **41**, **46**, and **51**.

*2^{II-VII},3^{II-VII},6^{I-VII}-Nonadeca-O-methyl-2^{I},3^{I}-O-(o-xylylene)-cyclomaltoheptaose (**41**).* Amorphous solid. Yield: 243 mg (99%); R_f = 0.23 (20:1 DCM/MeOH); $[\alpha]_D$ = +164.3 (c 1.0, $CHCl_3$); UV (MeOH) 216 nm (ε_{mM} 6.9); IR (ATR) ν_{max} 2927, 1457, 1135, 1033 cm^{-1}; 1H NMR (500 MHz, D_2O) δ 7.25–7.13 (m, 4 H, Ph), 5.26–5.14 (m, 7 H, H-1^{I-VII}), 4.98, 4.91 (2 d, 2 H, $^2J_{H,H}$ = 14.6 Hz, C*H*Ph), 4.95, 4.92 (2 d, 2 H, $^2J_{H,H}$ = 14.5 Hz, C*H*Ph), 3.85 (m, 1 H, H-6a^{I}), 3.79–3.67 (m, 6 H, H-6a^{II-VII}), 3.68–3.52 (m, 7 H, H-4^{I-VII}), 3.66–3.43 (m, 7 H, H-6b^{I-VII}), 3.64–3.43 (m, 8 H, H-3^{I-VII}, H-2^{I}), 3.58–3.40 (m, 7 H, H-5^{I-VII}), 3.28–3.17 (m, 6 H, H-2^{II-VII}), 3.57, 3.53, 3.48, 3.47, 3.44, 3.43, 3.41, 3.38 (× 2), 3.36, 3.27 (× 3), 3.26 (× 3), 3.25, 3.23, 3.17 (15 s, 57 H, Me); 1D TOCSY (H-6a^{I} irradiation) δ 5.17 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1^{I}), 3.78 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{I}), 3.67 (dd, 1 H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 4.0 Hz, H-6b^{I}), 3.60 (t, 1 H, $J_{4,5}$ = 10.5 Hz, H-4^{I}), 3.57 (m, 1 H, H-5^{I}), 3.44 (dd, 1 H, H-2^{I}); ^{13}C NMR (125.7 MHz, D_2O) δ 136.7–128.1 (Ph), 98.1 (C-1^{I}), 97.7, 97.6, 97.5, 97.3, 96.7, 96.2 (C-1^{II-VII}), 81.6, 81.5, 81.2, 81.0 (C-3^{II-VII}), 80.5, 80.3, 80.2 (C-2^{II-VII}), 79.9 (C-3^{I}), 79.2 (C-2^{I}), 77.9, 77.8, 77.7, 76.9, 76.0, 75.6 (C-4^{I-VII}), 73.3 (CH_2Ph), 72.4 (CH_2Ph), 70.6, 70.5 (C-5^{I-VII}), 70.9, 70.8, 70.6, 70.5, 70.4 (C-6^{II-VII}), 69.5 (C-6^{I}), 60.2, 60.6, 60.0, 59.7, 58.5, 58.4, 58.3, 58.2, 58.0 (Me); FABMS m/z 1526 (100%, $[M + Na]^+$). Anal. Calcd for $C_{69}H_{114}O_{35}$: C, 55.12; H 7.64. Found: C, 54.93; H, 7.46.

*2^{II-VI},3^{II-VI},6^{I-VI}-Hexadeca-O-methyl-2^{I},3^{I}-O-(o-xylylene)-cyclomaltohexaose (**46**).* Amorphous solid. Yield: 185 mg (89%); R_f = 0.28 (20:1 DCM/MeOH); $[\alpha]_D$ = +162.6 (c 1.0, $CHCl_3$); UV (MeOH) 214 nm (ε_{mM} 7.3); IR (ATR) ν_{max} 2931, 1457, 1365, 1139, 1026 cm^{-1}; 1H NMR (500 MHz, D_2O) δ 7.20–7.09 (m, 4 H, Ph), 5.26, 4.94 (2 d, 2 H, $^2J_{H,H}$ = 15.6 Hz, C*H*Ph), 5.16–4.92 (m, 6 H, H-1^{I-VI}), 4.91, 4.59 (2 d, 2 H, $^2J_{H,H}$ = 12.9 Hz, C*H*Ph), 3.92 (dd, 1 H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 3.9 Hz, H-6a^{I}), 3.80–3.60 (m, 13 H, H-6a^{II-VI}, H-6b^{I-VI}, H-5^{I}, H-3^{I}), 3.59–2.56 (m, 17 H, H-3^{II-VI}, H-4^{I-VI}, H-5^{I-VI}, H-2^{I}), 3.24–2.94 (m, 5 H, H-2^{II-VI}), 3.77, 3.53, 3.48, 3.42, 3.40, 3.37, 3.32, 3.29, 3.28, 3.26, 3.25, 3.09 (12 s, 48 H, Me); 1D TOCSY (H-6a^{I} irradiation) δ 5.01 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1^{I}), 3.80 (m, 1 H, H-5^{I}), 3.72 (d, 1 H, $J_{6a,6b}$ = 12.5 Hz, H-6b^{I}), 3.60 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^{I}), 3.42 (m, 1 H, H-2^{I}), 3.29 (m, 1 H, H-4^{I}); ^{13}C NMR (125.7 MHz, D_2O) δ 137.6–126.8 (Ph), 100.7 (C-1^{I}), 99.2, 99.0, 98.8, 98.7, 98.6 (C-1^{II-VI}), 84.1 (C-3^{I}), 82.2, 81.6, 81.3, 81.2, 81.1, 81.0, 80.7, 80.6, 80.1 (C-2^{II-VI}, C-3^{II-VI}, C-4^{I-VI}), 78.6 (C-2^{I}), 75.6 (CH_2Ph), 73.1 (CH_2Ph), 71.0, 70.9, 70.8, 70.7, 70.6 (C-5^{I-VI}, C-6^{I-VI}), 61.9, 61.6, 61.3, 60.4, 58.3, 57.9, 57.8, 57.6, 57.5, 57.1 (Me); ESIMS m/z 1321.4 $[M + Na]^+$, 1337.3 $[M + K]^+$. Anal. Calcd for $C_{60}H_{98}O_{30}$: C, 55.46; H 7.60. Found: C, 55.37; H, 7.55.

*$2^{II-VIII}$,$3^{II-VIII}$,6^{I-VIII}-Docosa-O-methyl-2^{I},3^{I}-O-(o-xylylene)-cyclomaltooctaose (**51**).* Amorphous solid. Yield: 147 mg (54%); R_f = 0.24 (20:1 DCM/MeOH); $[\alpha]_D$ = +177.7 (c 1.0, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 7.24–6.98 (m, 4 H, Ph), 5.22, 4.75 (2 d, 2 H, $^2J_{H,H}$ = 12.7 Hz, C*H*Ph), 5.08 (bs, 2 H, CH_2Ph), 5.06 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1^{I}), 5.30–5.08 (m, 7 H, H-$1^{II-VIII}$), 4.91, 4.59 (2 d, 2 H, $^2J_{H,H}$ = 12.9 Hz, C*H*Ph), 3.87–3.70 (m, 9 H, H-6a^{I-VIII}, H-3^{I}), 3.70–3.62 (m, 24 H, H-$3^{II-VIII}$, H-5^{I-VIII}, H-6b^{I-VIII}, H-2^{I}), 3.27–3.11 (m, 7 H, H-$2^{II-VIII}$), 3.66, 3.63, 3.62, 3.58, 3.53, 3.51, 3.50, 3.49, 3.46, 3.45, 3.44, 3.43, 3.42, 3.32, 3.31 (18 s, 66 H, Me); 1D TOCSY (H-1^{I} irradiation) δ 3.82 (d, 1 H, $J_{5,6a}$ = 2.4 Hz, $J_{6a,6b}$ = 8.9 Hz, H-6a^{I}), 3.79 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, H-4^{I}), 3.71 (t, 1 H, $J_{2,3}$ = 9.0 Hz, H-3^{I}), 3.68 (m, 2 H, H-5^{I}, H-6b^{I}), 3.54 (dd, 1 H, $J_{1,2}$ = 3.0 Hz, H-2^{I}); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.0–127.0 (Ph), 99.6 (C-1^{I}), 98.5, 98.2, 98.1, 98.0, 97.8, 97.7 (C-$1^{II-VIII}$), 82.4, 82.3, 82.2, 82.1, 82.0, 81.9, 81.8, 81.7, 81.6 (C-2^{I-VIII}, C-$3^{II-VIII}$), 81.4 (C-3^{I}), 80.0, 79.8, 79.4, 79.2, 79.1, 77.8, 77.2, 77.0 (C-4^{I-VIII}), 74.4 (CH_2Ph), 72.6 (CH_2Ph), 71.4, 71.3, 71.1, 71.0, 70.8, 70.7 (C-5^{I-VIII}, C-6^{I-VIII}), 61.8, 61.4, 61.3, 61.1, 61.0, 59.2, 59.1, 59.0, 58.7, 58.6, 58.4 (Me); ESIMS m/z 1729.8 $[M + Na]^+$, 1745.8 $[M + K]^+$. Anal. Calcd for $C_{78}H_{130}O_{40}$: C, 54.85; H 7.67. Found: C, 54.85; H, 7.70.

General Procedure for Synthesis of Cyclodextrin Derivatives 42, 47, and 52. To a solution of methylated derivatives **41**, **46**, or **51** (0.16 mmol) in 1:1 EtOAc/MeOH (10 mL) and aqueous HCOOH (10%, 1.6 mL) was added 10% Pd/C (80 mg). The resulting suspension was hydrogenated at 1 atm for 16 h, then filtered through Celite, and concentrated. The residue was purified by column chromatography using the eluent indicated in each case to afford the corresponding methylated derivatives **42**, **47**, and **52**.

*2^{II-VII},3^{II-VII},6^{I-VII}-Nonadeca-O-methylcyclomaltoheptaose (**42**).* Column chromatography, eluent 10:1:0 → 10:1:0.5 MeCN/H_2O/NH_4OH) gave **42** as an amorphous solid. Yield: 137 mg (60%); R_f = 0.42 (10:1:0.5 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +158.7 (c 1.0, $CHCl_3$); IR (ATR) ν_{max} 3443, 2929, 1454, 1143, 1034 cm^{-1}; 1H NMR (500 MHz, D_2O) δ 5.18–5.14 (m, 6 H, H-1^{II-VII}), 4.94 (d, 1 H, $J_{1,2}$ = 3.6, H-1^{I}), 3.80–3.64 (m, 8 H, H-6a^{I-VII}, H-3^{I}), 3.66–3.63 (m, 6 H, H-4^{II-VII}), 3.66–3.43 (m, 10 H, H-6b^{I-VII}, H-4^{I}, H-5^{I}, H-2^{I}), 3.62–3.53 (m, 12 H, H-3^{II-VII}, H-5^{II-VII}), 3.29–3.21 (m, 6 H, H-2^{II-VII}), 3.52, 3.49, 3.43, 3.40, 3.27, 3.26 (7 s, 57 H, Me); 1D TOCSY (H-1^{I} irradiation) δ 3.79 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{I}), 3.64 (dd, 1 H, $J_{6a,6b}$ = 11.5 Hz, H-6a^{I}), 3.57 (m, 1 H, H-6b^{I}), 3.50 (m, 2 H, $J_{4,5}$ = 9.5 Hz, H-4^{I}, H-5^{I}), 3.45 (dd, 1 H, H-2^{I}); ^{13}C NMR (125.7 MHz, D_2O) δ 100.3 (C-1^{I}), 98.2, 97.6, 97.4, 97.1, 96.9, 96.8 (C-1^{II-VII}), 81.5, 81.2, 81.1, 80.9, 80.7, 80.4, 80.2, 80.0 (C-2^{II-VII}, C-3^{II-VII}), 77.8, 77.3, 77.0, 76.6 (C-4^{I-VII}), 73.0 (C-3^{I}), 71.8 (C-2^{I}), 70.8, 70.7, 70.6, 70.5, 70.4, 70.3, 70.2 (C-5^{I-VII}, C-6^{I-VII}), 60.3, 59.8, 59.7, 59.5, 59.4, 58.9, 58.4, 58.2, 58.1, 58.0 (Me); ESIMS m/z 1423 $[M + Na]^+$. Anal. Calcd for $C_{61}H_{108}O_{35}$: C, 52.28; H; 7.77. Found: C, 52.32; H, 7.78.

*2^{II-VI},3^{II-VI},6^{I-VI}-Hexadeca-O-methylcyclomaltohexaose (**47**).* Column chromatography, eluent 10:1:0 → 10:1:0.5 MeCN/H_2O/NH_4OH) gave **47** as an amorphous solid. Yield: 180 mg (94%); R_f = 0.50 (10:1:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +166.7 (c 1.0, $CHCl_3$); IR (ATR) ν_{max} 3447, 2935, 1454, 1032 cm^{-1}; 1H NMR (500 MHz, D_2O) δ 5.11–5.08 (m, 5 H, H-1^{II-VI}), 4.89 (d, 1 H, $J_{1,2}$ = 3.9, H-1^{I}), 3.83 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3^{I}), 3.80–3.55 (m, 28 H, H-4^{II-VI}, H-3^{II-VI}, H-5^{I-VI}, H-6a^{I-VI}, H-6b^{I-VI}), 3.47 (m, 1 H, H-4^{I}), 3.45 (m, 1 H, H-2^{I}), 3.28–3.13 (m, 5 H, H-2^{II-VI}), 3.52, 3.50, 3.49, 3.44, 3.38, 3.28 (7 s, 58 H, Me); 1D TOCSY (H-3^{I} irradiation) δ 4.90 (d, 1 H, H-1^{I}), 3.80 (m, 1 H, H-5^{I}), 3.62 (m, 2 H, H-6a^{I}, H-6b^{I}), 3.47 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 10.5 Hz, H-4^{I}), 3.45 (dd, 1 H, H-2^{I}); ^{13}C NMR (125.7 MHz,

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D_2O) δ 101.1 (C-1^{I}), 99.8, 98.5, 98.4, 98.1 (C-1^{II-VI}), 81.8 (C-2^{I}), 81.6, 81.4, 80.9, 80.2, 80.1, 79.7, 78.7 (C-2^{II-VI}, C-3^{II-VI}, C-4^{I-VI}), 73.2 (C-3^{I}), 71.4, 71.1, 71.0, 70.9, 70.8, 70.7, 70.4 (C-5^{I-VI}, C-6^{I-VI}), 60.9, 60.4, 60.2, 58.9, 58.4, 58.3, 57.7, 57.5, 57.4 (Me); ESIMS m/z 1219.4 $[M + Na]^+$; 1235.4 $[M + K]^+$. Anal. Calcd for $C_{52}H_{92}O_{30}$: C, 52.17; H 7.75. Found: C, 52.01; H, 7.40.

*$2^{II-VIII},3^{II-VIII},6^{I-VIII}$-Docosa-O-methylcyclomaltooctaose (**52**).* Column chromatography, eluent 10:1:0 → 10:1:1 MeCN/H_2O/NH_4OH gave **52** as an amorphous solid. Yield: 180 mg (70%); R_f = 0.44 (10:1:1 MeCN/H_2O/NH_4OH); $[\alpha]_D$ = +167.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, D_2O) δ 5.32−5.25 (m, 7 H, H-$1^{II-VIII}$), 5.05 (d, 1 H, $J_{1,2}$ = 3.6, H-1^{I}), 3.93−3.74 (m, 16 H, H-$6a^{II-VIII}$, H-$4^{II-VIII}$, H-5^{I}, H-3^{I}), 3.71−3.52 (m, 16 H, H-$5^{II-VIII}$, H-$6a^{I}$, H-$6b^{I-VIII}$), 3.53 (m, 1 H,, H-4^{I}), 3.41 (dd, 1H, $J_{2,3}$ = 10.1, H-2^{I}), 3.32−3.25 (m, 7 H,, H-2^{I-VIII}), 3.48, 3.47, 3.45, 3.44, 3.43, 3.29, 3.28 (7 s, 48 H, Me); 1D TOCSY (H-1^{I} irradiation) δ 3.88 (m, 1 H, H-5^{I}), 3.82 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{I}), 3.62 (m, 1 H, H-$6a^{I}$), 3.58 (m, 1 H, H-$6b^{I}$), 3.53 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4^{I}), 3.30 (dd, 1 H, H-2^{I}); ^{13}C NMR (125.7 MHz, D_2O) δ 99.4 (C-1^{I}), 96.4, 96.2, 95.8, 95.6, 95.2, 95.1 (C-$1^{II-VIII}$), 81.2, 81.0, 80.9, 80.7, 80.6, 80.4, 80.3, 80.1 (C-$2^{II-VIII}$, C-$3^{II-VIII}$), 77.8, 75.5, 75.0,74.6, 74.5, 74.2, 73.3, 73.1 (8 C, C-4^{I-VIII}), 72.4 (C-3^{I}), 71.7 (C-2^{I}), 70.9, 70.8, 70.7, 70.6, 70.5, 60.9, 69.8, 69.7, 69.4 (C-5^{I-VIII}, C-6^{I-VIII}), 58.9, 58.8, 58.6, 58.5, 58.4, 58.3, 58.2, 58.1, 57.9, 57.6 (Me); ESIMS m/z 1627.7 $[M + Na]^+$; 1643.7 $[M + K]^+$. Anal. Calcd for $C_{70}H_{124}O_{40}$: C, 52.36; H 7.78. Found: C, 52.31; H, 7.83.

General Procedure for Synthesis of $2^{I},3^{I}$-Di-*O*-acetylated Cyclodextrin Derivatives 43, 48, and 53. The $2^{I},3^{I}$-unprotected derivative **42**, **47**, or **52** (0.06 mmol) was dissolved in Ac_2O/pyridine (1:1, 1 mL) and stirred at 45 °C for 4 days. Then, water (10 mL) was added, and the mixture was extracted with DCM (4 × 5 mL). The combined organic layer was washed with H_2SO_4 (2 N, 35 mL) and saturated aqueous $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography using 20:1 DCM/MeOH as eluent to give the corresponding diacetylated derivatives **43**, **48**, and **53**.

*$2^{I},3^{I}$-Di-O-acetyl-$2^{II-VII},3^{II-VII},6^{I-VII}$-nonadeca-O-methylcyclomaltoheptaose (**43**).* Amorphous solid. Yield: 53 mg (60%); R_f = 0.18 (20:1 DCM/MeOH); $[\alpha]_D$ = +145.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (dd, 1 H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 9.4 Hz, H-3^{I}), 5.21 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1^{I}), 5.15−4.93 (m, 6 H, H-1^{II-VII}), 4.76 (dd, 1 H, H-2^{I}), 3.98 (dd, 1 H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 3.5 Hz, H-$6a^{I}$), 3.87−3.71 (m, 14 H, H-4^{I-VII}, H-$6a^{II-VII}$, H-5^{I}), 3.60−3.44 (m, 13 H, H-5^{II-VII}, H-$6b^{I-VII}$), 3.53−3.48 (m, 6 H, H-3^{II-VII}), 3.63, 3.62, 3.60, 3.58, 3.55, 3.53, 3.48, 3.46, 3.42, 3.37, 3.35 (12 s, 57 H, Me), 3.17−3.05 (m, 6 H, H-2^{II-VII}), 2.06 (s, 6 H, MeCO); 1D TOCSY (H-1^{I} irradiation) δ 5.51 (dd, 1 H, H-3^{I}), 4.76 (dd, 1 H, H-2^{I}), 3.98 (dd, 1 H, H-$6a^{I}$), 3.86 (m, 1 H, H-5^{I}), 3.75 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4^{I}), 3.55 (d, 1 H, H-$6b^{I}$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.7, 170.2 (CO), 99.5, 99.3, 98.9 (C-1^{II-VII}), 98.2 (C-1^{I}), 82.7, 82.4, 82.1, 82.0, 81.9, 81.8 (C-2^{II-VII}), 81.7, 81.5, 81.2 (6 C, C-3^{II-VII}), 80.7, 80.6, 80.4, 79.6 (C-4^{II-VII}), 78.6 (C-4^{I}), 71.8, 71.6, 71.5, 71.4, 71.3, 71.2, 71.0, 70.9, 70.8 (C-5^{II-VII}, C-6^{II-VII}), 71.4 (C-2^{I}), 70.6 (C-6^{I}), 69.7 (C-3^{I}), 61.6 (C-5^{I}), 61.5, 61.4, 61.2, 60.3, 59.1, 59.0, 58.9, 58.7, 58.6, 58.3 (Me), 21.0, 20.8 (*Me*CO); ESIMS m/z 1507.7 $[M + Na]^+$, 1523.7 $[M + K]^+$. Anal. Calcd for $C_{65}H_{112}O_{37}$: C, 52.55; H, 7.60. Found: C, 52.46; H, 7.71.

*$2^{I},3^{I}$-Di-O-acetyl-$2^{II-VI},3^{II-VI},6^{I-VI}$-hexadeca-O-methylcyclomaltohexaose (**48**).* Amorphous solid. Yield: 46 mg (60%); R_f = 0.30 (20:1 DCM/MeOH); $[\alpha]_D$ = +148.8 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (dd, 1 H, $J_{2,3}$ = 10.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3^{I}), 5.11 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1^{I}), 5.11−4.92 (m, 6 H, H-1^{II-VI}), 4.76 (dd, 1 H, H-2^{I}), 3.95 (dd, 1 H, $J_{6a,6b}$ = 10.8 Hz, $J_{5,6a}$ = 3.5 Hz, H-$6a^{I}$), 3.89−3.67 (m, 7 H, H-$6a^{II-VI}$, H-4^{I}, H-5^{I}), 3.66−3.42 (m, 21 H, H-3^{II-VI}, H-4^{II-VI}, H-5^{II-VI}, H-$6b^{I-VI}$), 3.64, 3.60, 3.58, 3.57, 3.52, 3.47, 3.45, 3.44, 3.43, 3.38, 3.37, 3.36 (12 s, 48 H, Me), 3.16−3.04 (m, 5 H, H-2^{II-VI}), 2.07, 2.06 (2 s, 6 H, MeCO); 1D TOCSY (H-3^{I} irradiation) δ 5.11 (d, 1 H, H-1^{I}), 4.76 (dd, 1 H, H-2^{I}), 3.94 (dd, 1 H, H-$6a^{I}$), 3.85 (m, 1 H, H-5^{I}), 3.79 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4^{I}), 3.60 (d, 1 H, H-$6b^{I}$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.7, 170.5 (CO), 100.4, 100.3, 100.0 (C-1^{II-VI}), 99.8 (C-1^{I}), 82.7, 82.5 (C-3^{II-VI}), 82.4, 82.3, 82.2, 81.5 (C-2^{II-VI}), 81.1, 81.2, 81.0, 80.8, 80.2 (C-4^{II-VI}), 79.7 (C-4^{I}), 71.7, 71.6, 71.5, 71.4, 71.3, 71.2, 71.1 (C-5^{II-VI}, C-6^{II-VI}), 71.2 (C-2^{I}), 70.8 (C-6^{I}), 69.3 (C-3^{I}), 62.1 (C-5^{I}), 61.8, 61.7, 60.3, 59.1, 59.0, 58.9, 57.9, 57.8, 57.7, 57.6 (Me), 21.1, 20.9 (*Me*CO); ESIMS m/z 1303.5 $([M + Na]^+)$; 1319.5 $([M + K]^+)$. Anal. Calcd for $C_{56}H_{96}O_{32}$: C, 52.49; H, 7.55. Found: C, 52.42; H, 7.68

*$2^{I},3^{I}$-Di-O-acetyl-$2^{II-VIII},3^{II-VIII},6^{I-VIII}$-docosa-O-methylcyclomaltooctaose (**53**).* Amorphous solid. Yield: 81 mg (80%); R_f = 0.23 (20:1 DCM/MeOH); $[\alpha]_D$ = +142.7 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (dd, 1 H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 9.0 Hz, H-3^{I}), 5.34−4.95 (m, 7 H, H-$1^{II-VIII}$), 5.24 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1^{I}), 4.72 (dd, 1 H, H-2^{I}), 3.94 (dd, 1 H, $J_{6a,6b}$ = 10.8 Hz, $J_{5,6a}$ = 3.4 Hz, H-$6a^{I}$), 3.91−3.78 (m, 9 H, H-$6a^{II-VIII}$, H-5^{I}), 3.78−3.60 (m, 8 H, H-4^{I-VIII}), 3.60−3.45 (m, 7 H, H-$3^{II-VIII}$), 3.56−3.45 (m, 15 H, H-$5^{II-VIII}$, H-$6b^{I-VIII}$), 3.69, 3.68, 3.63, 3,62, 3.56, 3.52, 3.51, 3.50, 3.49, 3.47, 3.45, 3.41 (14 s, 66 H, Me), 3.21−3.08 (m, 7 H, H-$2^{II-VIII}$), 2.06, 2.03 (2 s, 6 H, MeCO); 1D TOCSY (H-2^{I} irradiation) δ 5.53 (dd, 1 H, H-3^{I}), 5.24 (d, 1 H, H-1^{I}), 3.95 (dd, 1 H, H-$6a^{I}$), 3.81 (m, 1 H, H-5^{I}), 3.76 (t, 1 H, $J_{4,5}$ = 9.2 Hz, H-4^{I}), 3.49 (d, 1 H, H-$6b^{I}$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.1, 170.0 (CO), 98.6, 98.0, 97.8, 97.7, 97.6, 97.4 (C-$1^{II-VIII}$), 98.0 (C-1^{I}), 82.6, 82.5, 82.3, 82.0, 81.9, 81.8, 81.6, 81.5 (C-$2^{II-VIII}$, C-$3^{II-VIII}$), 80.3, 80.2, 79.5, 78.1, 77.1, 76.8, 76.6, 76.0 (C-4^{I-VIII}), 71.7 (C-2^{I}), 71.4, 71.3, 71.2, 71.1, 71.0, 70.9, 70.6 (C-5^{I-VIII}, C-6^{I-VIII}), 69.8 (C-3^{I}), 62.1, 62.0, 61.8, 61.5, 61.3, 61.1, 60.9, 59.2, 59.1, 59.0, 58.8, 58.6, 58.5, 58.1 (Me), 21.1, 20.7 (*Me*CO); ESIMS m/z 1711.8 $[M + Na]^+$; 1728.7 $[M + K]^+$. Anal. Calcd for $C_{74}H_{128}O_{42}$: C, 52.60; H, 7.64. Found: C, 52.46; H, 7.52.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of newly synthesized compounds and HPLC chromatograms of compounds **38**−**40**, **44**, **45**, **49**, and **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Greene, T. W., Ed.; Wiley-VCH: New York, 2006.

(2) Clarke, P. A.; Martin, W. H. C. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2003**, *99*, 84−103.

(3) Fraser-Reid, B.; Jayaprakash, K. N.; López, J. C.; Gómez, A. M.; Uriel, C. *ACS Symp. Ser.* **2007**, *960*, 91−117.

(4) Guo, J.; Ye, X. *Molecules* **2010**, *15*, 7235−7265.

(5) Codee, J. D. C.; Ali, A.; Overkleeft, H. S.; van der Marel, G. A. *C. R. Chim.* **2011**, *14*, 178−193.

(6) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056−2083.

(7) (a) Glaudemans, C. P. J.; Fletcher, H. G., Jr. *Methods Carbohydr. Chem.* **1963**, *6*, 373−376. (b) Oscarson, S. Protective Groups Strategies. In *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC Press: Boca Raton, 2005; Chapter 3.

(8) Shie, C. R.; Tzeng, Z. H.; Kulkarni, S. S.; Uang, B. J.; Hsu, C. Y.; Hung, S. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665−1668.

(9) Hernández-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206−7211.

(10) Balakumar, V.; Aravind, A.; Baskaran, S. *Synlett* **2004**, 647−650.
(11) Lee, J.-C.; Chang, S.-W.; Liao, C.-C.; Chi, F.-C.; Chen, C.-S.; Wen, Y.-S.; Wang, C.-C.; Kulkarni, S. S.; Puranik, R.; Liu, Y.-H.; Hung, S.-C. *Chem.—Eur. J.* **2004**, *10*, 399−415.
(12) Halila, S.; Benazza, M.; Demailly, G. *J. Carbohydr. Chem.* **2001**, *20*, 467−483.
(13) Cubero Izquierdo, I.; López-Espinosa, M.-T. P.; Robles Díaz, R.; Franco Montalbán, F. *Carbohydr. Res.* **2001**, *330*, 401−408.
(14) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 12−15.
(15) Eby, R.; Webster, K. T.; Schuerche, C. *Carbohydr. Res.* **1984**, *129*, 111−120.
(16) Malik, S.; Dixit, V.-A.; Bharatam, P. V.; Kartha, K. P. *Carbohydr. Res.* **2010**, *345*, 559−564.
(17) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346−1353.
(18) Jia, C.; Zhang, Y.; Zhang, L.-H.; Sinaÿ, P.; Sollogoub, M. *Carbohydr. Res.* **2006**, *341*, 2135−2144.
(19) Lecourt, T.; Herault, A.; Pearce, J.; Sollogoub, M.; Sinaÿ, P. *Chem.—Eur. J.* **2004**, *10*, 2960−2971.
(20) Roizel, B. C.; Cabianca, E.; Rollin, P.; Sinaÿ, P. *Tetrahedron* **2002**, *58*, 9579−9583.
(21) Zaborova, E.; Bleriot, Y.; Sollogoub, M. *Tetrahedron Lett.* **2010**, *51*, 1254−1256.
(22) Xie, J.; Menand, M.; Valery, J.-M. *Carbohydr. Res.* **2005**, *340*, 481−487.
(23) Pastore, A.; Valerio, S.; Adinolfi, M.; Iadonisi, A. *Chem.—Eur. J.* **2011**, *17*, 5881−5889.
(24) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963−966.
(25) Poss, A. J.; Smyth, M. S. *Synth. Commun.* **1989**, *19*, 3363−3366.
(26) Trost, B. M. *Science* **1991**, *254*, 1471−1477.
(27) Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61−72.
(28) For seminal works on regioselective alkylation of carbohydrates, see: (a) Garegg, P. J.; Iversen, T.; Oscarson, S. *Carbohydr. Res.* **1976**, *50*, C12−C14. (b) Dasgupta, F.; Garegg, P. J. *Synthesis* **1994**, 1121−1123. (c) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem.* **2011**, 5860−5878.
(29) García-Moreno, M. I.; Aguilar, M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **2006**, *8*, 297−299.
(30) Balbuena, P.; Rubio, E. M.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Commun.* **2006**, 2610−2612.
(31) Méndez-Ardoy, A.; Suárez-Pereira, E.; Balbuena Oliva, P.; Jiménez Blanco, J. L.; Ortiz Mellet, C.; García Fernández, J. M. *Eur. J. Org. Chem.* **2011**, 517−528.
(32) (a) Ortiz Mellet, C.; García Fernández, J. M. *Top. Curr. Chem.* **2010**, *294*, 49−77. (b) García-Moreno, M. I.; Benito, J. M.; Ortiz Mellet, C.; García Fernández, J. M. *Molecules* **2008**, *13*, 1640−1670.
(33) Imamura, A.; Lowary, T. L. *Org. Lett.* **2010**, *12*, 3686−3689.
(34) (a) *Cyclodextrins and Their Complexes*, 1st ed.; Dodziuk, H., Ed.; Wiley-VCH: Weinheim, 2006. (b) Benito, J. M.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Soc. Rev.* **2011**, *40*, 1586−1608. (c) Jiménez Blanco, J. L.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Soc. Rev.* **2013**, DOI: 10.1039/C2CS35219B. (d) Martínez, A.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Soc. Rev.* **2013**, DOI: 10.1039/C2CS35424A.
(35) Balbuena, P.; Lesur, D.; González Alvárez, M. J.; Mendicuti, F.; Ortiz Mellet, C.; García Fernández, J. M. *Chem Commun.* **2007**, 3270−3272.
(36) (a) González-Alvarez, M. J.; Balbuena, P.; Ortiz Mellet, C.; García Fernández, J. M.; Mendicuti, F. *J. Phys. Chem. B* **2008**, *112*, 13717−13729. (b) Gonzalez-Alvarez, M. J.; Vicente, J.; Ortiz Mellet, C.; García Fernández, J. M.; Mendicuti, F. *J. Fluoresc.* **2009**, *19*, 975−988.
(37) González-Alvarez, M. J.; Méndez-Ardoy, A.; Benito, J. M.; García Fernández, J. M.; Mendicuti, F. *J. Photochem. Photobiol. A: Chem.* **2011**, *223*, 25−36.
(38) González-Álvarez, M. J.; Mayordomo, N.; Gallego-Yerga, L.; Ortiz Mellet, C.; Mendicuti, F. *Tetrahedron* **2012**, *68*, 2961−2972.
(39) Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem.—Eur. J.* **1999**, *5*, 2722−2729.
(40) Kumar, V.; Gauniyar, H. M.; Shaw, A. K. *Tetrahedron: Asymmetry* **2007**, *18*, 2069−2078.
(41) Chaudhary, S. K.; Hernández, O. *Tetrahedron Lett.* **1979**, *2*, 95−98.
(42) Tennant-Eyles, R. J.; Davis, B. G.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2000**, *11*, 231−243.
(43) Barone, G.; Bedini, E.; Iadonisi, A.; Manzo, E.; Parrilli, M. *Synlett* **2002**, 1645−1648.
(44) (a) Hu, G. X.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 4369−4391. (b) Moitessier, M.; Chapleur, Y. *Tetrahedron Lett.* **2003**, *44*, 1731−1733.
(45) Ness, K. A.; Migaud, M. E. *Beilstein J. Org. Chem.* **2007**, *3*, no. 26.
(46) *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: New York, 1999.
(47) Wittman, V. In *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2008; p 1735.
(48) van Vliet, S. J.; Grün, C.; van Kooyk, Y. In *Protein-Carbohydrate Interactions in Infectious Diseases*; Bewley, C. A., Ed.; RSC Publishing: Oxford, U.K., 2006; p 106.
(49) Epstein, J.; Eichbaum, Q.; Sheriff, S.; Ezekowitz, R. A. B. *Curr. Opin. Immunol.* **1996**, *8*, 29−35.
(50) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsaiah, E. *Tetrahedron Lett.* **2005**, *46*, 8745−8748.
(51) Becuwe, M.; Landy, D.; Delattre, F.; Cazier, F.; Fourmentin, S. *Sensors* **2008**, *8*, 3689−3705.
(52) Surpateanu, G.; Fourmentin, S.; Landy, D.; Surpateanu, G. G.; Decock, P. *Trends Heterocycl. Chem.* **2006**, *11*, 63−79.
(53) Cintas, P.; Cravotto, G.; Calcio Gaudino, E.; Orio, L.; Boffa, L. *Catal. Sci. Technol.* **2012**, *2*, 85−87.
(54) Mojr, V.; Buděšínský, M.; R. Cibulka, R.; Kraus, T.; Mojr, V. *Org. Biomol. Chem.* **2011**, *9*, 7318−7326.
(55) Jeunesse, C.; Armspach, D.; Matt, D. *Chem. Commun.* **2005**, 5603−5614.
(56) Fenger, T. H.; Bols, M. *J. Incl. Phenom. Macrocycl. Chem.* **2011**, *69*, 397−402.
(57) Bjerre, J.; Rousseau, C.; Marinescu, L.; Bols, M. *Appl. Microbiol. Biotechnol.* **2008**, *81*, 1−11.
(58) Benito, J. M.; Gómez-García, M.; Ortiz Mellet, C.; Baussanne, I.; Defaye, J.; García Fernández, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10355−10363.
(59) Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78−80.
(60) Xue, W.; Zhang, L. *Synthesis.* **2011**, *22*, 3612−14.
(61) Chmurski, K.; Defaye, J. *Supramol. Chem.* **2000**, *12*, 221−224.
(62) García Fernández, J. M.; Ortiz Mellet, C.; Jiménez Blanco, J. L.; Fuentes Mota, J.; Gadelle, A.; Coste-Sarguet, A.; Defaye, J. *Carbohydr. Res.* **1995**, *268*, 57−71.
(63) Guieu, S.; Sollogoub, M. *J. Org. Chem.* **2008**, *73*, 2819−2828.
(64) Ghosh, R.; Zhang, P.; Wang, A.; Ling, C.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1548−52.
(65) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977−1996.
(66) Teranishi, K. *Tetrahedron* **2003**, *59*, 2519−2538.
(67) Popielarski, S. R.; Mishra, S.; Davis, M. E. *Bioconjugate Chem.* **2003**, *14*, 672−678.
(68) Fukudome, M.; Okabe, Y.; Sakaguchi, M.; Morikawa, H.; Fujioka, T.; Yuan, D.; Fujita, K. *Tetrahedron Lett.* **2004**, *45*, 9045−9048.
(69) Xiao, Y.; Wu, Q.; Wang, N.; Lin, X. *Carbohydr. Res.* **2004**, *339*, 1279−1283.
(70) Wang, N.; Wu, Q.; Xiao, Y. M.; Chen, C. X.; Lin, X. F. *Bioorg. Med. Chem.* **2005**, *13*, 3667−3671.
(71) Mamba, B. B.; Krause, R. W.; Malefetse, T. J.; Nxumalo, E. N. *Environ. Chem. Lett.* **2007**, *5*, 79−84.

(72) Guitet, M.; Beaumais, S. A. d.; Bleriot, Y.; Vauzeilles, B.; Zhang, Y.; Menand, M.; Sollogoub, M. *Carbohydr. Res.* **2012**, *356*, 278−281.
(73) Masurier, N.; Estour, F.; Lefevre, B.; Brasme, B.; Masson, P.; Lafont, O. *Carbohydr. Res.* **2006**, *341*, 935−940.
(74) Masurier, N.; Lafont, O.; Le Provost, R.; Lesur, D.; Masson, P.; Djedaïni-Pilard, F.; Estour, F. *Chem. Commun.* **2009**, 589−591.
(75) Fügedi, P. *Carbohydr. Res.* **1989**, *192*, 366−369.
(76) For selected examples of O-2 monoalkylation of CDs, see: (a) Hanessian, S.; Benalil, A.; C. Laferrière, C. *J. Org. Chem.* **1995**, *60*, 4786−4797. (b) Casas-Solvas, J. M.; Ortiz-Salmerón, E.; Fernández, I.; García-Fuentes, L.; Santoyo-González, F.; Vargas-Berenguel, A. *Chem.—Eur. J.* **2009**, *15*, 8146−8162.
(77) van Dienst, E.; Snellink, B. H. M.; von Piekartz, I.; Grote Gansey, M. H. B.; Venema, F.; Feiters, M. C.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6537−6545.