Synthesis of Cyclodextrin-Based Carbohydrate Clusters by Photoaddition Reactions

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The syntheses of homogeneous cyclodextrin-based carbohydrate clusters, persubstituted with β-D-thioglucosyl or D-thiolactosyl residues on either (a) the *primary* face, (b) the *secondary* face, or (c) *both* the primary and the secondary faces of their cyclodextrin tori, are described. The key step in the synthetic methodology, namely the attachment of the carbohydrate residues to the cyclodextrin torus, proceeds in moderate-good yields (42−70%) by the photoaddition of thiol groups, positioned at the anomeric centers of the carbohydrate residues, to allyl ether functions on the cyclodextrins. Facile removal of protecting groups then affords the free cluster compounds. Extensive 1-D and 2-D NMR spectroscopic investigations were performed on these compounds to determine their structures and establish their homogeneities, and a brief computer molecular modeling study allowed estimates of the dimensions of the clusters to be determined.

Introduction

Contemporary carbohydrate research has been driven largely by the realization that cell surface protein−carbohydrate interactions play crucial roles in many biological processes, as well as by the understanding that nature compensates for the low intrinsic affinities of carbohydrates for proteins through the cooperative binding of multiple copies of ligands and receptors, the so-called "multivalent" and "glycoside-cluster effect".[1] Of the many molecular scaffolds that have been used to display carbohydrate ligands in multivalent arrays, those that also possess the intrinsic potential to act as hosts for the complexation of guest molecules may prove to be the most useful in the development of "intelligent" drug delivery systems.[2] At a basic level, the synthetic strategy used for the construction of such cluster compounds is straightforward. It involves attachment of carbohydrate residues onto an appropriately functionalized macrocycle that is known to complex with certain guest molecules. For example, research groups headed by Dondoni[3] and Roy[4] have reported the attachment of carbohydrate residues onto calixarene scaffolds. Aoyama and co-workers[5] have reported their findings on the synthesis and properties of calix[4]resorcarene-based carbohydrate cluster compounds and have outlined how these hosts can be used to deliver guest molecules to surfaces[5a] and to lectins.[5d] More recently, the Japanese group has shown[5f] how saccharide units can be used to "mask" the hydrophobicity of the macrocyclic core of calix[4]resorcarene- and porphyrin-based carbohydrate clusters, thus preventing nonspecific hydrophobic interactions between the cluster compounds and the cells. By utilizing fluorescence microscopy, they have also shown that galactoside clusters exhibit a remarkable selectivity for hepatocytes versus the analogous glucoside clusters and that this interaction is solely a consequence of carbohydrate−receptor interactions.

The cyclodextrins[6] (CDs) are naturally occurring cyclic oligosaccharides that display a promiscuous appetite for guest inclusion which has already been exploited[7] in drug formulations. It is possible that CD-based glycoclusters could prove more useful for receptor-mediated drug delivery than those based on calixarenes or resorcarenes

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from a perspective of biocompatability and H_2O solubility. Since Driguez and co-workers[8] reported the synthesis of perthioglucosylated derivatives of β-CD in 1994, several other groups[9] have recently described alternative synthetic strategies for the perfunctionalization of CDs, *but on their primary faces only*, with carbohydrate appendages. In at least one instance,[9c] the ability of compounds of this type to interact with plant lectins has been demonstrated.

In the course of our ongoing research[10] on glycodendrimers, we became interested in developing efficient methods for derivatizing CDs with saccharide residues on (1) *the secondary, as well as the primary faces* of CDs and then extending this strategy to the perfunctionalization of (2) *both the primary and the secondary faces* of CDs, simultaneously. Perfunctionalization of the secondary face of CDs with carbohydrate residues could result in cluster compounds that have several advantages over their primary face-substituted counterparts. It is generally accepted that the principal mode of CD-guest binding is via the secondary face of the CD.

We reported recently[11] the results of our preliminary investigations concerning the synthesis of CD-based carbohydrate cluster compounds. Here, we describe in detail the efficient synthesis of some β-CD-based carbohydrate cluster compounds and their complete characterization.

Results and Discussion

Synthetic Strategy. The precise and clean perfunctionalization of CDs is notoriously difficult to accomplish.[12] We sought a synthetic strategy which would allow us to perfunctionalize *either* or *both* the primary and the secondary faces of cyclodextrins with carbohydrate appendages. Our chosen strategy had to recognize the fact that the attachment of carbohydrate units onto the CD core is the most crucial step in the synthesis of CD-based cluster molecules. With this thought in mind, it is worth noting some important considerations that arise in the quest for a successful synthetic strategy. First, the functionalities X and Y (Figure 1) should be easy to introduce onto the carbohydrate appendages and the CD cores, respectively, to ensure the rapid synthesis of the building blocks. Second, the reaction chosen for the attachment of the carbohydrate units onto the CD core has to be inherently a very high yielding one since it must be performed six or more times on the same molecule.[13] Third, the attachment of carbohydrate residues onto the CD core should be performed as late as possible in the synthetic scheme. This consideration arises because any further synthetic manipulations on large CD-based molecules results inevitably in the loss of precious compound, in addition to being almost certainly nontrivial to implement.

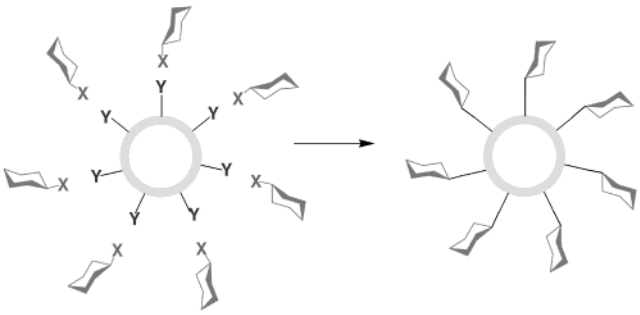

Figure 1. Graphical representation of the key synthetic step (involving the simultaneous reaction of seven carbohydrate units with the CD core) in the synthesis of CD-based carbohydrate cluster compounds.

Previous synthetic methods for the attachment of carbohydrate units onto CDs include nucleophilic displacements with thiolate anions,[9c–e] as well as amide[2a–d,9h] and thiourea[2e,9b] bond formations. Although all these synthetic methods do lead to the attachment of carbohydrate residues to CD cores, they suffer from a lack of synthetic flexibility, viz., it is not straightforward to extend these methods for the attachment of carbohydrate residues to either the secondary or *both* faces of CDs. After a preliminary survey of possible reactions, we focused our attention on the well-known[14] anti-Markovnikov photoaddition of thiols to allyl ethers to yield thioethers as the key step in the attachment of carbohydrate appendages to CD cores. This reaction has a proven record in both carbohydrate[15] and CD[16] chemistry, with an example described by Lindhorst et al.[15b] being a particularly encouraging one since it involves the successful occurrence of five photoadditions per molecule. Additionally, these photoadditions are performed under mild conditions and are tolerant of a range of functionalities. Moreover, the ease of introduction of (1) allyl ether

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(12) Perfunctionalization of α-, β-, or γ-CD is an inherently divergent process that may demand up to 18, 21, or 24 reactions to be performed on each molecule. Chemical reactions that are performed on CDs must therefore be highly efficient to avoid the formation of undersubstituted products that usually prove to be chromatographically similar to the target compounds and also lack the high axial symmetry of fully substituted CDs that is necessary to allow easy and definitive characterization by NMR spectroscopy.

(13) The consequences of a reaction's yield when performed several times simultaneously on a molecule such as β-CD are important. For example, a reaction with a yield of 80% would afford a derivative in $(0.8)^7 = 21\%$ yield when performed seven times on β-CD.

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(15) For examples, see: (a) Lee, R. T.; Lee, Y. C. *Carbohydr. Res.* **1974**, *37*, 193−196. (b) Kieburg, C.; Dubber, M.; Lindhorst, T. K. *Synlett* **1997**, 1447−1449.

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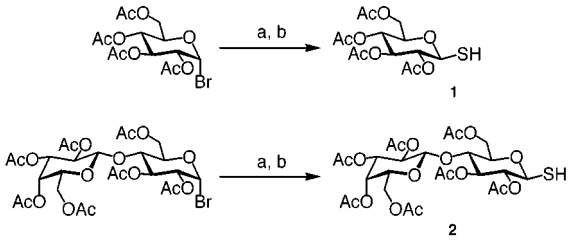
Scheme 1. Synthesis of Thioglycosides 1 and 2[a]



[a] Reagents and conditions: (a) thiourea, acetone, reflux; (b) $K_2S_2O_5$, H_2O, $CHCl_3$, reflux, **1**, 40%, **2**, 77%.

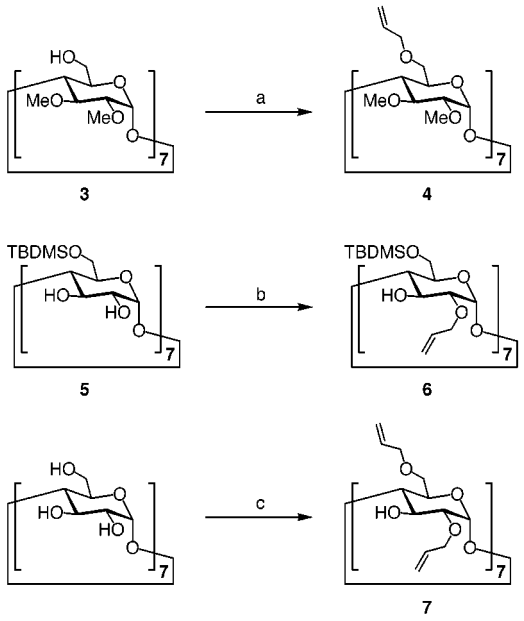
functions onto the CD torus and (2) thiol groups onto the anomeric centers of saccharides makes this photoaddition an appealing choice of reaction to use in the key step.

Synthesis of Building Blocks. We chose as the thiol components, β-D-thioglucose (**1**) and β-D-thiolactose (**2**), both of which are easily prepared (Scheme 1) from their corresponding glycosyl bromides. Stereospecific nucleophilic displacement of peracetyl-α-D-bromoglucose and α-D-bromolactose with thiourea, followed by treatment of the isothiouronium intermediates with aqueous potassium bisulfite in a biphasic reaction, afforded[17] the thiols **1** and **2** in 40% and 77% yields, respectively.[18]

We chose to prepare three different allyl ether-substituted β-CD cores, one of which was perfunctionalized with allyl ethers on (1) the primary face of β-CD, another on (2) the secondary face of β-CD, and yet another on (3) both faces of β-CD. Thus, reaction (Scheme 2) of **3**[19] with sodium hydride and allylbromide in DMF afforded (32%) **4**, a compound which is persubstituted on the primary face of the CD torus with seven allyl ether functions. The synthesis of a β-CD derivative persubstituted on its secondary face with allyl ether functions was accomplished using a known procedure[20] by reaction of **5**[21] with sodium hydride and allylbromide in DMF to afford **6** in 26% yield. Finally, reaction[22] of β-CD with allylbromide in the presence of BaO and $Ba(OH)_2 \cdot 8H_2O$ in a mixture of DMF and DMSO gave, in only 17% yield, a β-CD derivative **7**, persubstituted with seven allyl ether functions on *each* face of its CD torus.

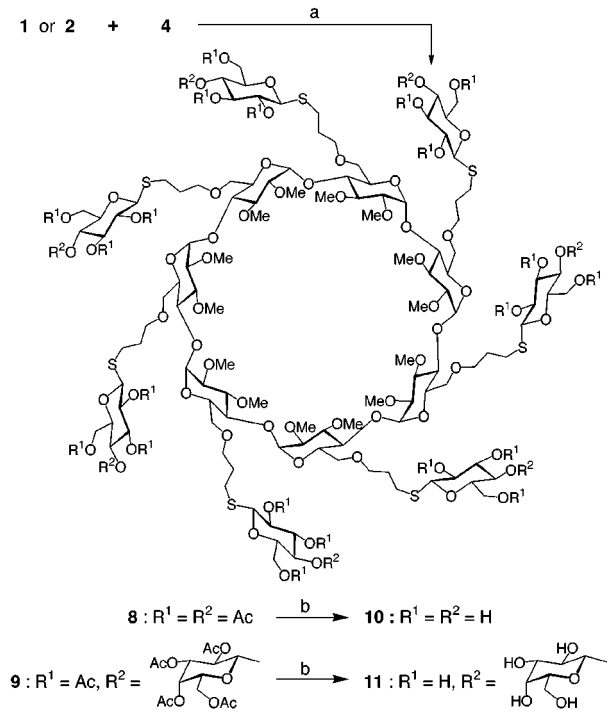
Synthesis of Primary Face-Substituted Clusters. The primary face modification of β-CD with seven carbohydrate appendages was achieved efficiently (Scheme 3) when a methanolic solution of a mixture of **1** (21 equiv) and **4** was irradiated with UV light from an Hg lamp. After 5 h, TLC indicated an almost quantitative conversion to **8** when the concentration of **2** in the reaction mixture was ca. 5 mM. At lower concentrations, undersubstitution of **2** occurs; if the concentration of the reactants is too high, then the major product of the reaction is the disulfide formed by dimerization of two molecules of **1**. Purification of the crude product from the photochemical reaction by silica gel column chromatography afforded a pure compound in 67% yield.[23] Matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) mass spectrometry of this compound revealed a

Scheme 2. Synthesis of Allyl Ether β-CD Cores[a]



[a] Reagents and conditions: (a) allyl bromide, NaH (60%), DMF, 32%; (b) allyl bromide, NaH (95%), DMF, 26%; (c) allyl bromide, BaO, $Ba(OH)_2 \cdot 8H_2O$, DMF/DMSO (1:1), 17%.

Scheme 3. Synthesis of the Glucose and Lactose Series of Cluster Compounds Substituted on Their Primary Faces[a]



[a] Reagents and conditions: (a) *hν*, MeOH, 5 h, **8**, 67%, **9**, 58%; (b) NaOMe, MeOH, 5 h, **10**, 99%, **11**, 96%.

(17) Stanek, J.; Sindlerova, M.; Cerny, M. *Collect. Czech. Chem. Commun.* **1965**, *30*, 297−302.

(18) By carefully following the procedure described in ref 17, it was observed that substantial amounts of hemiacetal were formed in the nucleophilic displacement with thiourea, lowering the yield of thiol **1**. Thus, for the synthesis of thiol **2**, all reagents were dried overnight over P_2O_5 in a drying pistol under high vacuum, and acetone was distilled from anhydrous calcium sulfate. By taking these precautions, the procedure resulted in a substantially higher yield of **2**.

(19) Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203−221.

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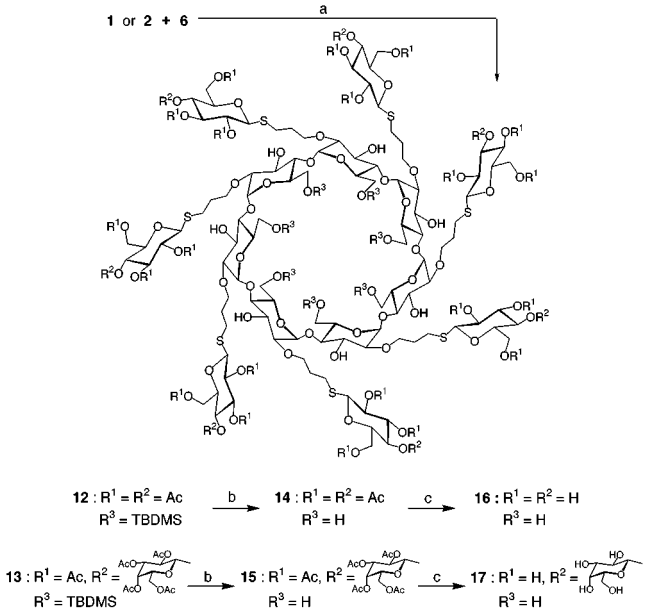
(23) The reported yields have not been optimized.

Scheme 4. Synthesis of the Glucose and Lactose Series of Cluster Compounds Substituted on Their Secondary Faces[a]

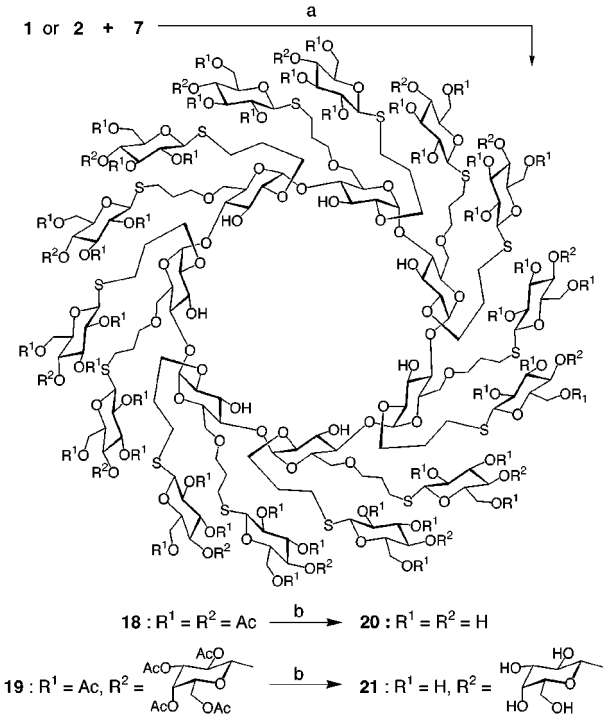


[a]Reagents and conditions: (a) *hν*, MeOH, C_6H_6, 5 h, **12**, 42%, **13**, 84%; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 4 h, **14**, 74%, **15**, 75%; (c) NaOMe, MeOH, 1−2 d, 16, 99%, **17**, 90%.

peak at *m*/*z* 4185 $[M + Na]^+$ corresponding to *β*-CD derivative **8**, fully adorned with seven *β*-D-thioglucose residues. The identity of **8** was established unequivocally from close inspection of its ^1H and ^{13}C NMR spectra. Deprotection (NaOMe/MeOH) of **8** yielded (99%) **10**, which was also fully characterized by ^1H and ^{13}C NMR spectroscopies. The lactose analogue of **10** was prepared in an almost identical manner. Reaction of **2** with **4** afforded a crude reaction mixture which was more conveniently purified by gel filtration chromatography[24] to give the acetylated lactose cluster compound **9**. Deacetylation (NaOMe/MeOH) of **9** afforded the free lactose cluster compound **11** in almost quantitative yield. Again, both the acetylated cluster compound **9** and the free cluster compound **11** were fully characterized by ^1H and ^{13}C NMR spectroscopies and MALDI-TOF mass spectrometry.

Synthesis of Secondary Face-Substituted Clusters. The same synthetic strategy was followed to prepare *β*-CD derivatives perfunctionalized on their secondary faces with seven carbohydrate appendages. Reaction (Scheme 4) of the thiols **1** or **2** with **6**, under essentially the same conditions as those described above for the synthesis of **10** and **11**, gave the fully substituted glucose and lactose cluster compounds, namely **12** and **13** in 42% and 84% yields, respectively. *O*-Desilylation[25] of **12** and **13** with $BF_3{\cdot}OEt_2$ afforded the glucose (**14**) and lactose (**15**) intermediates,[26] which, after deprotection (NaOMe/MeOH), furnished the fully deprotected glucose and lactose cluster compounds **16** and **17**, respectively.

Scheme 5. Synthesis of Glucose and Lactose Series of Cluster Compounds Substituted with Carbohydrate Units on Both Their Primary and Secondary Faces[a]



[a] Reagents and conditions: (a) *hν*, MeOH, C_6H_6, 5 h, **18**, 70%, **19**, 66%; (b) NaOMe, MeOH, 1−2 d, then NaOH, **20**, 99%, **21**, 99%.

Synthesis of Clusters Substituted on Both Faces. The next obvious question was could this photochemical approach be used to modify entirely *both* the primary and the secondary faces of a *β*-CD derivative by means of a reaction that would involve the formation of no less than 14 thioether bonds per molecule? Reaction (Scheme 5) of per-2,6-diallyl-*β*-CD (**7**) with **1** or **2** in MeOH/C_6H_6 gave the desired protected glucose and lactose cluster compounds, namely **18** and **19** in 70% and 66% yields, respectively. Deprotection of **18** and **19** afforded the free cluster compounds **20** and **21**, respectively, which were fully characterized by both ^1H and ^{13}C NMR spectroscopies. It is worth noting that compounds **20** and **21** contain a total of 21 and 35 pyranoside residues, respectively, demonstrating that large, well-defined carbohydrate clusters can be prepared in very few synthetic steps using this particular synthetic methodology.

Structural Characterization. The purified products obtained from the photochemical additions were thoroughly analyzed by spectroscopic techniques to establish (1) that the product was homogeneous and contained no under-"substituted" products and (2) that the product was of a satisfactory purity.

^{1}H NMR Spectroscopy. A common feature of the ^1H NMR spectra of the acetylated compounds **8**, **9**, **12**−**15**, **18**, and **19** is that they display broadened signals[27] arising from their CD protons, while the signals for the

(24) The glucose series of compounds was purified by column chromatography (SiO_2, EtOAc/hexanes). However, this technique often resulted in "band-broadening", probably as a consequence of the relatively large molecular mass of the compounds in question and, consequently, low yields of pure compounds. Therefore, the lactose series of compounds was purified by gel filtration chromatography (LH-20), a technique which was found to be far superior for the purification of these compounds.

(25) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295−299.

(26) Deprotection with tetrabutylammonium fluoride (TBAF) in THF consistently failed to deprotect compound **12** efficiently. We hypothesize that TBAF is basic enough to cause partial deacetylation of the carbohydrate appendages.

protons on the carbohydrate appendages are sharp. This phenomenon is revealed also in the ^{13}C NMR spectra, where the signals corresponding to the CD carbons are much weaker and broader than those arising from the carbons in the glucose appendages. The reason for this signal broadening is most likely the expression of a dynamic phenomenon; the glucose appendages cause the CD glucose residues to move on a time scale approaching that of the NMR time scale, hence inducing the line widths of the CD signals to increase. This signal broadening could be alleviated to some extent by heating the sample, and so in some cases, NMR spectra were recorded in $(CD_3)_2NCDO$, which allowed the samples to be warmed to 360−370 K.

The ^1H NMR spectra of the purified compounds, that is, **8**, **9**, **12**, **13**, **18**, and **19**, obtained from the photoadditions, did not reveal any signals corresponding to the allyl ether protons of the CD starting materials. Instead, signals corresponding to $-(CH_2)_3-$ units were present, displaying the expected chemical shifts and integrations and thus supporting the hypothesis that all the allyl ether functions on the CD torus had reacted with a thiol group. Further useful structural information was gained from the ^1H NMR signal for the H-2 proton of the CD torus.[28] In nearly all cases, this signal was evident as the expected doublet of doublets; in others, signal broadening decreased its resolution to that of a partially resolved doublet of doublets. The ^1H NMR spectra of the protected glucose cluster compounds **8**, **12**, and **18** are shown in Figure 2. Broadening of the H-2 signal is most severe in the spectrum (Figure 2c) of **18**, while **8** and **12** give spectra (Figure 2a,b) with better resolution of this H-2 signal. Other signals corresponding to the protons on the CD torus of **18** are also significantly broadened.[29] The fact that **18** is adorned on both faces of the CD torus with glucose units can also be inferred from its ^1H NMR spectrum. Since the glucose units on the primary face of the CD torus occupy a different constitutional environment to the corresponding glucose units on the secondary faces, the resonances associated with each appended glucose unit appear at slightly different chemical shifts. For example, the anomeric protons corresponding to the appended glucose residues appear as two partially overlapping doublets centered at δ 4.54 and 4.57. However, some signals corresponding to the glucose appendages resonate at essentially the same chemical shifts. This fact is well demonstrated (Figure 2c) for the H-2′ and H-3′ protons of the glucose appendages, which overlap so well with their H-2″ and H-3″ counterparts that each effectively appears as a single "triplet". It was not possible to assign unambiguously the protons of the glucose appendages as being associated with either the glucose units on the primary face or those on the secondary face. High-quality and informative 2-D spectra, however, could

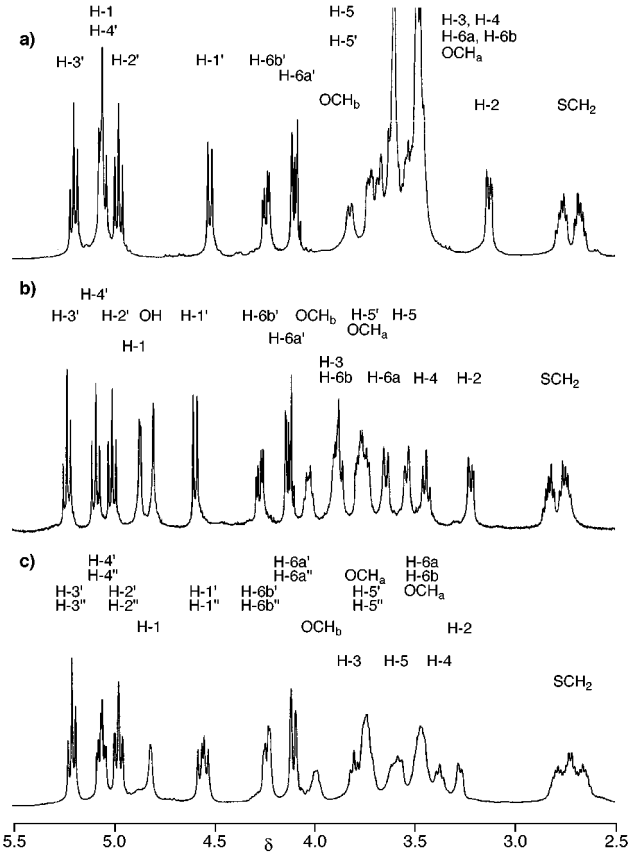


Figure 2. The "carbohydrate region" of the ^1H NMR (500 MHz, $CDCl_3$) spectra of the *O*-acetylated glucose series (a) **8**, (b) **12**, and (c) **18**. Note that the presence of an appended carbohydrate residue at C-2 results in a small upfield shift for H-1.

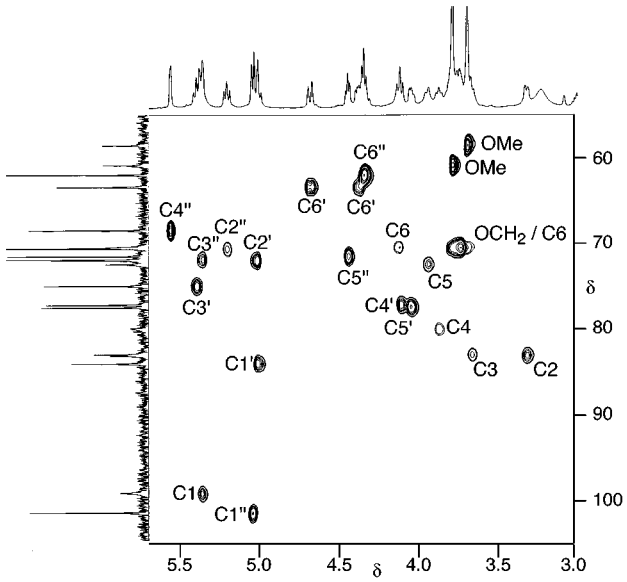


Figure 3. The partial HMQC (500 MHz, $(CD_3)_2NCDO$, 370 K) spectrum of the *O*-acetylated lactose cluster **9**.

be obtained for all the acetylated compounds, as illustrated by the fully assigned heteronuclear multiple-quantum coherence (HMQC) spectrum (Figure 3) of **9**, despite signal broadening problems. By using a combination of 2-D-COSY and HMQC experiments, it was possible to assign fully the ^1H NMR spectra for all the acetylated glucose and lactose cluster compounds.

(27) Broadening of the ^1H NMR signals was most severe for the series which are persubstituted on both faces of the CD torus with carbohydrate appendages. This signal broadening was least severe for the series which are persubstituted on only their primary faces with carbohydrate appendages.

(28) Although the ^1H NMR signal corresponding to the H-1 proton of the CD torus is generally the most useful and diagnostic probe signal for the CD torus, for many of these compounds, this signal was "hidden" beneath signals arising from protons in the carbohydrate appendages. Fortunately, the signal for H-2 could always be observed, and thus it was often the most diagnostic for the CD torus.

(29) Presumably, having two glucose units appended to each CD residue leads to more pronounced signal-broadening than when only one glucose unit is attached to each CD residue.

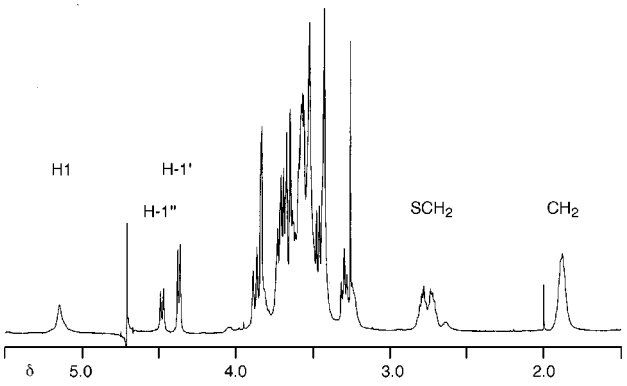


Figure 4. The ^{1}H NMR (500 MHz, D_2O) spectrum of the lactose cluster **11**. The water signal has been presaturated for clarity.

The ^{1}H NMR spectra of the final deacetylated compounds **10**, **11**, **16**, **17**, **20**, and **21**, reveal that, apart from the anomeric protons, all other carbohydrate protons resonate in the region $\delta \approx 3.0-4.0$, and so not many peaks in these spectra can be assigned. For most of these deacetylated compounds, the resonances associated with the anomeric protons in the CD torus reveal themselves to be broadened singlets, whereas the resonances associated with the anomeric proton(s) of the carbohydrate appendages appear as their expected doublets. Importantly, the integrations of the signals corresponding to the anomeric protons of the CD torus and the signals corresponding to the anomeric proton(s) of the appendage carbohydrate units have essentially the same value. These features can be observed in the ^{1}H NMR spectrum (Figure 4) of **11**.

^{13}C NMR Spectroscopy. Analysis of the ^{13}C NMR spectra of the acetylated compounds **8**, **9**, **12, 13**, **18**, and **19** revealed no signals corresponding to those carbons associated with the allyl ether functions of compounds **4**, **6**, and **7**. Instead, signals corresponding to the $-(CH_2)_3-$ linker between the CD and the appended carbohydrate unit were evident in the spectrum. By using the ^{13}C 135-DEPT pulse sequence, it was possible to assign easily all the carbon atoms in the $-(CH_2)_3-$ linker, as well as all C-6 carbon atoms on account of the negative phasing of these signals. By utilizing HMQC and DEPT experiments, it was possible to assign unambiguously the carbon resonances in the spectra of all the acetylated compounds.

Further proof that compounds **18** and **19** are completely substituted on both the primary and the secondary faces of their CD tori comes from the analyses of their ^{13}C DEPT NMR spectra. Analysis of the carbohydrate region of the ^{13}C DEPT NMR spectrum (Figure 5) of **18** reveals signals corresponding to all the carbon atoms in the glucose appendages on the primary and secondary faces of the cyclodextrin torus. The signals corresponding to the carbon atoms on both the primary and the secondary face glucose appendages appear at more or less identical chemical shifts. As in the case of the ^{1}H NMR spectra of these compounds, however, it was not possible to assign unambiguously carbon signals to the carbohydrate units on a particular face of the CD torus.

Although the decetylated cluster compounds also afforded good quality ^{13}C NMR spectra, like their ^{1}H NMR counterparts, these spectra defied unambiguous assignment of signals to carbon atoms.

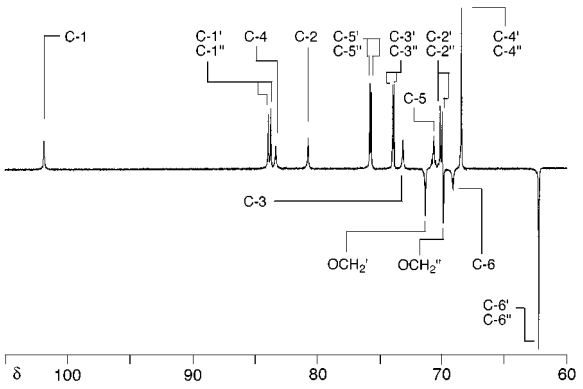


Figure 5. The ^{13}C DEPT NMR (125 MHz, $CDCl_3$) spectrum of *O*-acetylated glucose cluster **18** showing the carbohydrate region.

Table 1. Approximate Molecular Dimensions of Deprotected Carbohydrate Cluster Compounds as Estimated from Computer Molecular Modeling

carbohydrate cluster	molecular width (Å)[a]	molecular height (Å)[b]
10	23	17
11	34	18
16	31	13
17	36	21
20	31	31
21	43	43

[a] Approximate molecular width is defined as the diameter of the molecule when viewed along the CD toroidal axis. [b] Approximate molecular height is defined as the height of the molecule when viewed perpendicular to the CD toroidal axis.

MALDI-TOF Mass Spectrometry. MALDI-TOF mass spectrometry proved to be a useful technique for characterizing the acetylated cluster compounds. The expected mass ions, which did not give rise to any fragmentation, were observed for all of these acetylated compounds. However, their deacetylated analogues gave very weak mass ions. As no fragmentation was observed for the acetylated cluster compounds, MALDI-TOF mass spectrometry also served as a useful check of the homogeneities of compounds. Any under-substituted compounds present as impurities should also reveal peaks corresponding to one or more carbohydrate appendages less than the expected mass ion. However, no peaks corresponding to under-substituted compounds were observed in any of the MALDI-TOF mass spectra of the acetylated cluster compounds.

Molecular Modeling. In an attempt to gain some insight into the nature of the three-dimensional structure of the carbohydrate cluster compounds, we performed a molecular dynamics study using the Macromodel[30] program. This modeling allowed us to visualize several feasible low-energy conformations of the clusters, predict any significant intramolecular noncovalent interactions which could affect the compounds' potential performance as delivery vehicles, and estimate the molecular dimensions of each cluster (Table 1). Even though these models do not give an accurate representation of the "time-averaged" conformations of the highly flexible cluster molecules, they do nevertheless provide a useful "snapshot" of their structures.

(30) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

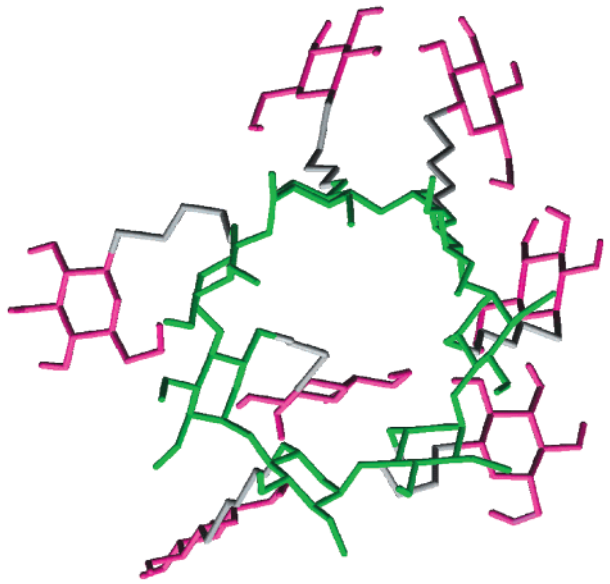


Figure 6. View of the three-dimensional structure of the glucose-7-mer **10** as determined by computer molecular modeling, looking through the CD torus from the secondary face of the CD. The CD torus is depicted in light gray, and the glucose appendages are depicted in dark gray.

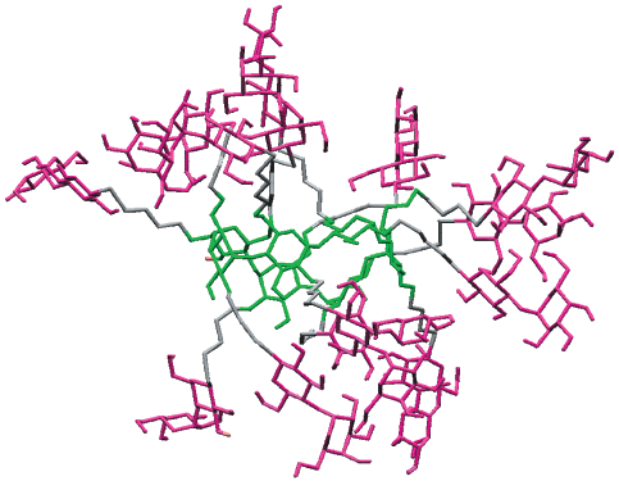


Figure 7. A side-on view of the three-dimensional structure of the lactose-14-mer **21** as determined by computer molecular modeling. The CD core is depicted in light gray, and the glucose appendages are depicted in dark gray.

Modeling indicated that, in the case of all compounds, the glucosyl residues in their CD tori would adopt their preferred $^4C_1$ chair conformations. There were no unusual interglycosidic torsion angles, which indicated that in all cases, there was not a significant deviation from C_7 symmetry. Compounds **16** and **17** are slightly wider than their primary face-substituted counterparts **10** (Figure 6) and **11**. Compounds **20** and **21** (Figure 7) adopt a more globular appearance, with their height and widths being of similar lengths.

There are several reported examples[31] of hydrophobic alkyl chains, which are covalently attached to a CD, including themselves within the CD cavity. For all cluster compounds, that is, **10**, **11**, **16**, **17**, **20**, and **21**, our modeling indicated no inclusion, or indeed even partial inclusion, of either the hydrophobic $-(CH_2)_3-$ spacer arms or their carbohydrate appendages. Inspection of space-filling Covey−Pauling−Koultun (CPK) molecular models indicated that the spacer arms attached to both the primary and the secondary faces were unlikely to even partially include themselves in the hydrophobic cavity of the CD, principally because the spacer arms are too short to form a complementary fit with the CD cavity. Additionally, analysis of CPK models indicate that the spacer arms on the primary face are further discouraged from being included through the primary face on account of the narrower diameter of this face.[32] However, it is not unreasonable to assume that longer alkyl spacer arms could become included within the CD cavity, especially spacer arms present on the secondary face.

The computer-generated models also indicate that, although each carbohydrate appendage has a significant degree of conformational freedom, they are situated close enough to each other that a certain amount of interresidual H-bonding is almost certain to occur.

Conclusions

We have described a novel synthetic strategy for the permodification of *either* or *both* faces of β-CD with carbohydrate residues in good yields. This strategy relies on the photoaddition of thiols to allyl ethers, a reaction that has proven to be a surprisingly good candidate for the key synthetic step, namely, the attachment of carbohydrate residues to CD cores, in the synthesis of carbohydrate cluster compounds. As it is relatively easy to prepare saccharides with thiol functions at their anomeric centers, this strategy could probably be extended easily to the attachment of more complicated oligosaccharides onto CD cores. In fact, given the high efficiency of this photoaddition reaction, it may be of considerable general utility in the preparation of a vast range of multivalent conjugates.

Experimental Section

General Methods. Chemicals were purchased from commercial suppliers and used as received. All solvents were used as purchased with the exception of CH_2Cl_2 (distilled from CaH_2) and MeOH (distilled from Mg turnings). All photoadditions were performed in borosilicate glass vials. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F. The plates were developed by charring with 5% H_2SO_4 in EtOH. Column chromatography was carried out using silica gel 60 F (230−400 mesh). Gel filtration chromatography was performed using either (1) a column packed with Sephadex LH-20 (3 cm × 90 cm) eluting with MeOH at 1 mL min^{-1} or (2) a column packed with Biogel P-6 (3 cm × 93 cm) eluting with H_2O at 1 mL min^{-1}. In both cases, the eluant was monitored with a refractive index detector. Fast atom bombardment mass spectra (FAB-MS) were obtained from a mass spectrometer, using *m*-nitrobenzyl alcohol as matrix. Matrix-assisted laser desorption ionization-time-of-flight mass spectra (MALDI-TOF-MS) were recorded on an instrument using a *trans*-indole acrylic acid matrix and an average of 50 laser shots per sample. ^{1}H NMR spectra were recorded on either a 400 or 500 MHz spectrometer with either the residual solvent or the external TMS as calibrants. ^{13}C

(31) For examples, see: (a) Impellizzeri, G.; Pappelardo, G.; D'Alessandro, F.; Rizzarelli, E.; Saviano, M.; Iacovino, R.; Benedetti, E.; Pedone, C. *Eur. J. Org. Chem.* **2000**, 1065−1076. (b) Tanabe, T.; Usui, S.; Nakamura, A.; Ueno, A. *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *36*, 79−93. (c) Nelissen, H. F. M.; Venema, F.; Uittenbogaard, R. M.; Feiters, M. C.; Nolte, R. J. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2045−2053. (d) Berthault, P.; Duchesne, D. D.; Desvaux, H.; Gilquin, B. *Carbohydr. Res.* **1995**, *276*, 267−87.

(32) Parrot-Lopez and co-workers reported[2a] a β-CD derivative with a C_7 alkyl spacer arm terminated with an *N*-glyucosyl residue. On the basis of NMR evidence, they concluded that the C_7 alkyl spacer arm did not self-include within the CD cavity.

NMR spectra were recorded at either 100 or 125 MHz. Chemical shifts are expressed in ppm, and the coupling constants in the case of ^{1}H NMR spectra are quoted in Hertz (Hz) and are within an error range of ca. ±0.5 Hz. The following abbreviations are used to explain the multiplicities: s, singlet; bs, broad singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-1-thioglucopyranosyl (1). Thiourea (1.91 g, 25.1 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (10.3 g, 25.1 mmol) in Me_2CO (11.0 mL), and the suspension was heated under reflux until all the thiourea dissolved. Following the formation of a white precipitate (∼10 min), further Me_2CO was added, and the resulting slurry was heated under reflux for a further 20 min, after which time TLC indicated the disappearance of the bromide. Solvents were removed in vacuo, and H_2O (10 mL) and CH_2Cl_2 (10 mL) were added to the reaction mixture. Potassium persulfite (4.23 g) was added, and the biphasic solution was brought to reflux. After 12 h, the reaction was allowed to cool, and H_2O (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The product was purified by column chromatography (SiO_2:EtOAc/hexanes 2:5) to afford **1** as a white solid (3.63 g, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00, 2.02, 2.08, 2.09 (12H, 4s, 4 × Ac), 2.31 (1H, d, J = 10.0 Hz, SH), 3.70−3.74 (1H, m, H-5), 4.12 (1H, dd, $^3J_{5,6a}$ = 2.2 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 4.24 (1H, dd, $^3J_{5,6b}$ = 4.6 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 4.54 (1H, t, $^3J_{1,2} \approx {}^3J_{1,SH}$ = 10.0 Hz, H-1), 4.97 (1H, t, $^3J_{1,2} \approx {}^3J_{2,3}$ = 10.0 Hz, H-2), 5.10 (1H, t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.4 Hz, H-4), 5.21 (1H, t = $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.4 Hz, H-3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.68, 20.71, 20.85, 20.88, 62.1, 68.2, 73.64, 73.67, 76.4, 78.8, 169.5, 169.7, 170.2, 170.8. FAB-ms m/z: 323 $[M + H]^+$. Anal. Calcd for $C_{14}H_{20}O_9S$: C, 46.15; H, 5.53. Found: C, 46.23; H, 5.35.

2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-*β*-D-1-thioglucopyranosyl (2). Thiourea (338 mg, 4.45 mmol) was added to a solution of 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-α-D-glucopyranosyl bromide (3.09 g, 4.43 mmol) in Me_2CO (5.0 mL), and the suspension was heated under reflux for 1 h, during which time all the thiourea dissolved. Solvents were removed in vacuo, and the residue was dissolved in H_2O (5 mL) and CCl_4 (10 mL). Potassium persulfite (1.67 g) was added, and the biphasic solution was brought to reflux. After 75 min, the reaction was allowed to cool, and H_2O (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The product was purified by column chromatography (SiO_2:EtOAc/hexanes 1:1) to afford **2** as a white solid (1.84 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.96, 2.041, 2.044, 2.06, 2.07, 2.13, 2.15 (21H, 7s, 7 × Ac), 2.27 (1H, d, J = 7.9 Hz, S*H*), 3.61−3.65 (1H, m), 3.80 (1H, t, J = 9.5 Hz), 3.87 (1H, t, J = 7.0 Hz), 4.05−4.17 (3H, m), 4.45 (1H, dd, J = 1.9, 12.1 Hz), 4.47 (1H, d, J = 7.9 Hz), 4.52 (1H, t, J = 9.7 Hz), 4.88 (1H, t, J = 9.6 Hz), 4.94 (1H, dd, J = 3.4, 10.4 Hz), 5.09 (1H, dd, J = 7.9 Hz, 10.4 Hz), 5.18 (1H, t, J = 9.2 Hz), 5.34 (1H, d, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.46, 20.59, 20.61, 20.71, 20.74, 20.84, 60.8, 62.2, 66.5, 69.0, 70.7, 70.9, 73.4, 73.8, 76.0, 77.1, 78.4, 101.1. FAB-ms m/z: 653 $[M + H]^+$. Anal. Calcd for $C_{26}H_{36}O_{17}S$: C, 47.85; H, 5.52. Found: C, 47.97; H, 5.72.

Per-6-*O*-allyl-per-2,3-dimethyl-*β*-cyclodextrin (4). NaH (60 wt % in oil, 197 mg, 4.92 mmol) was weighed into a reaction vessel. Hexane (5 mL) was added and stirred for 1 min. The suspension was allowed to settle, and the hexane was decanted off. This hexane washing procedure was repeated two more times to obtain oil-free NaH. DMF was added, and the suspension was stirred under a N_2 atmosphere at 0 °C. A solution of per-2,3-dimethyl-*β*-cyclodextrin (**3**) (299 mg, 0.225 mmol) in DMF (5 mL) was added dropwise, and the reaction was then allowed to stir at 0 °C for 1 h. Allyl bromide (0.7 mL, 8.1 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for a further 2 h, then subsequently it was stirred at room temperature for 42 h. MeOH (5 mL) was then added to the reaction mixture and, after stirring for 5 min, the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (10 mL) and aqueous saturated NaCl solution (10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to yield a pale yellow oil (408 mg). This oil was purified by column chromatography (SiO_2, 1% MeOH/$CHCl_3$) to afford pure **4** as a white foam (114 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.17 (7H, dd, $^3J_{1,2}$ = 3.5 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 3.46−3.52 (7H, m, H-3), 3.49 (21H, s, MeO), 3.59−3.66 (14H, m, H-4, H-5), 3.64 (21H, s, MeO), 3.77−3.87 (14H, m, H6a, H6b), 3.94−4.07 (14H, m, OC*H*$_2$CH=CH$_2$), 5.12−5.16 (7H, m, H-1, CH=C*H*H cis), 5.24 (7H, dd, $^2J_{gem}$ = 1.5 Hz, $^3J_{vic}$ = 17.0 Hz, CH=C*H*H trans), 5.82−5.95 (7H, m, C*H*=CH$_2$), proton assignments were confirmed by COSY experiments. ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.4, 61.4 (2-OMe, 3-OMe), 68.9 (C-6), 70.8 (C-5), 72.1 (O*C*H$_2$-CH=CH$_2$), 80.2, 81.7, 98.7 (C-2, C-3, C-4), 98.7 (C-1), 116.6 (OCH$_2$CH=*C*H$_2$), 134.8 (OCH$_2$*C*H=CH$_2$). MALDI-TOF-MS m/z: 1633 $[M + Na]^+$. Anal. Calcd for $C_{77}H_{126}O_{35}$: C, 57.39; H, 7.83. Found: C, 57.50; H, 8.00.

Per-6-*tert*-butyldimethylsilyl-per-2-allyl-*β*-cyclodextrin (6). A solution of per-6-*tert*-butyldimethylsilyl-*β*-cyclodextrin (**5**) (5.09 g, 2.63 mmol) in DMF (240 mL) under an atmosphere of Ar was cooled to 0 °C, and NaH powder (95%, 0.50 g, 20.83 mmol) was added portionwise. The reaction was allowed to stir at 0 °C for 1.5 h and then overnight at room temperature. The reaction vessel was cooled to 0 °C, and allyl bromide (1.64 mL, 18.95 mmol) was added dropwise. The reaction was then allowed to stir at 0 °C for 1 h and finally overnight at room temperature. The reaction was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (250 mL) and washed with brine (200 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford a white foam. Purification by column chromatography (SiO_2, 15% EtOAc/hexane to 20% EtOAc/hexanes) afforded pure **6** as a white foam (1.48 g, 26%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.03 (21H, s, SiC*H*$_3$), 0.04 (21H, s, SiC*H*$_3$), 0.88 (63H, s, C(C*H*$_3$)), 3.31 (7H, dd, $^3J_{1,2}$ = 3.5 Hz, $^3J_{2,3}$ = 9.6 Hz, H-2), 3.50 (7H, t, $^3J_{3,4} \approx {}^3J_{4,5}$ = H-4), 3.57 (7H, d, J = 9.4 Hz, H-5), 3.66 (7H, d, $^2J_{6a,6b}$ = 10.4 Hz, H-6a), 3.92 (7H, dd, $^3J_{5,6a}$ = 2.9 Hz, $^2J_{6a,6b}$ = 10.4 Hz, H-6b), 3.96 (7H, t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.3 Hz, H-3), 4.23 (7H, dd, J = 6.8 Hz, J = 12.5 Hz, OC*H*$_a$), 4.48 (7H, dd, J = 5.3 Hz, J = 12.5 Hz, OC*H*$_b$), 4.90 (7H, d, $^2J_{1,2}$ = 3.5 Hz, H-1), 5.21 (7H, d, J = 10.3 Hz, CH=C*H*$_2$ cis), 5.31 (7H, dd, $^2J_{gem}$ = 1.4 Hz, $^3J_{vic}$ = 17.2 Hz, CH=C*H*$_2$ trans), 5.92−5.99 (7H, m, C*H*=CH$_2$), proton assignments were confirmed by COSY experiments. ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.2 (Si*C*H$_3$), −5.1 (Si*C*H$_3$), 18.3 (*C*(CH$_3$)$_3$), 25.9 (C(*C*H$_3$)$_3$), 61.7 (C-6), 71.6, 79.5, 82.0 (C-2, C-3, C-4, C-5), 73.2 (O*C*H$_2$), 101.1 (C-1), 118.2 (*C*H$_2$=CH), 134.3 (CH$_2$=*C*H). MALDI-TOF m/z: 2238 $[M + Na]^+$. Anal. Calcd for $C_{105}H_{196}O_{35}Si$: C, 56.93; H, 8.92. Found: C, 57.06; H, 9.04.

Per-2,6-diallyl-*β*-cyclodextrin (7). *β*-Cyclodextrin (3.0 g, 2.6 mmol) was added portionwise to a stirred suspension of BaO (15.0 g, 97.8 mmol), $Ba(OH)_2 \cdot 8H_2O$ (15.0 g, 47.5 mmol), and allyl bromide (21.2 g, 175.2 mmol) in DMF/DMSO (1:1, 150 mL). The reaction vessel was covered with foil to protect it from light and set aside to stir under an Ar atmosphere for 20 h. NH_4OH solution (28%) was added, and the reaction mixture was stirred for 30 min before being poured into $CHCl_3$ (500 mL). Hexane (500 mL) was added to help precipitate inorganic material. The mixture was filtered through a sintered funnel, and the filtrate was washed with H_2O (3 × 400 mL) and then dried ($MgSO_4$). The organic layer was then filtered and evaporated to dryness to give an off-white foam. Purification by column chromatography (SiO_2, 20% EtOAc/$CHCl_3$) afforded **7** as a white foam (722 mg, 17%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.42−3.48 (14H, m), 3.65 (14H, m), 3.75 (7H, dd, J = 3.3, 9.8 Hz), 3.94 (7H, t, J = 9.2 Hz), 3.98 (7H, dd, J = 6.0, 12.8 Hz), 4.07 (7H, dd, J = 5.3, 12.8 Hz), 4.22 (7H, dd, J = 7.0, 12.5 Hz), 4.46 (7H, dd, J = 5.3, 12.5 Hz), 4.90 (7H, d, J = 3.7 Hz), 5.16 (7H, dd, J = 1.3, 10.4 Hz), 5.21 (7H, d, J = 10.3 Hz), 5.26 (71H, dd, J = 1.3, 17.0 Hz), 5.29 (7H, dd, J = 1.3, 18.4 Hz), 5.88−5.95 (14H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 68.8, 70.5, 72.5, 73.6, 79.3, 83.8, 102.1, 117.2, 118.9, 134.4, 135.1. FAB-ms m/z: 1827 $[M + Cs]^+$. Anal. Calcd for $C_{84}H_{18}O_{35}$: C, 59.43; H, 7.43. Found: C, 59.49; H, 7.40.

1°-Glucose-7-mer Cluster (8). The thiol **1** (489 mg, 1.34 mmol, 21 equiv) and the CD **4** (103 mg, 64 μmol) were dissolved in distilled MeOH (concentration of **4** = 5 mM). A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following removal of solvent, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes) to afford the product as a white foam (182 mg, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.85−1.89 (14H, m, SCH_2CH_2), 1.98, 2.00, 2.04, 2.06 (84H, 4s, 4 x Ac), 2.64−2.73 (7H, m, SCH_a), 2.76−2.83 (7H, m, SCH_b), 3.12 (7H, dd, $^3J_{1,2}$ = 3.0 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 3.46−3.64 (35H, m, H-3, H-4, H-6a, H-6b, OCH_a), 3.49 (21H, s, OCH_3), 3.60 (21H, s, OCH_3), 3.66−3.69 (7H, m, H-5), 3.71−3.81 (7H, m, H-5′), 3.80−3.84 (7H, m, OCH_b), 4.09−4.12 (7H, m, H-6a′), 4.24 (7H, dd, $^3J_{5',6b'}$ = 4.6 Hz, $^2J_{6a',6b'}$ = 12.4 Hz, H-6b′), 4.53 (7H, d, $^3J_{1',2'}$ = 10.0 Hz, H-1′), 4.98 (7H, t, $^3J_{1',2'} \approx {}^3J_{2',3'}$ = 9.8 Hz, H-2′), 5.04−5.08 (14H, m, H-1, H-4′), 5.21 (7H, t, $^3J_{2',3'} \approx {}^3J_{3',4'}$ = 9.4 Hz, H-3′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.76, 20.79, 20.92, 20.96 (4 x CH_3CO), 27.3 (SCH_2), 30.4 (SCH_2CH_2), 58.8 (CH_3O), 61.5 (CH_3O), 62.3 (C-6′), 68.5 (C-4′), 69.7 (OCH_2), 70.0 (C-6), 70.1 (C-2′), 71.5 (C-5), 74.0 (C-3′), 75.9 (C-5′), 80.1 (C-3), 81.8 (C-4), 82.3 (C-2), 83.9 (C-1′), 99.1 (C-1), 169.5, 169.6, 170.3, 170.7 (4 x CH_3CO). MALDI-TOF *m/z*: 4185 $[M + Na]^+$. Anal. Calcd for $C_{175}H_{266}O_{98}S_7 \cdot 2H_2O$: C, 50.06; H, 6.48. Found: C, 50.12; H, 6.46.

1°-Lactose-7-mer Cluster (9). The thiol **2** (556 mg, 0.85 mmol, 21 equiv) and CD **4** (64 mg, 40 μmol) were dissolved in distilled MeOH (concentration of **4** = 5 mM). A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following removal of solvent, the residue was purified by gel filtration chromatography (LH-20, MeOH, 1 mL min^{-1}) to afford the product as a white foam (143 mg, 58%). ^{1}H NMR ($(CD_3)_2NCDO$, 360K, 500 MHz): δ 2.06−2.14 (14H, m, SCH_2CH_2), 2.12, 2.23, 2.24, 2.25, 2.26, 2.31 (147H, 6s, 7 x Ac), 2.91−3.04 (14H, m, SCH_2), 3.32 (7H, dd, $^3J_{1,2}$ = 3.2 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 3.67 (7H, t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 8.7 Hz, H-3), 3.70 (21H, s, OCH_3), 3.71−3.82 (21H, m, OCH_2, H-6a), 3.79 (21H, s, OCH_3), 3.87 (7H, t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.0 Hz, H-4), 3.90−3.97 (7H, m, H-5), 4.00−4.09 (7H, m, H-5′), 4.10−4.14 (14H, m, H-4′, H-6b), 4.32−4.03 (21H, m, H-6a′, H-6a″, H-6b″), 4.65 (7H, t, *J* = 7.0 Hz, H-5″), 5.01−5.06 (21H, m, H-1′, H-2′, H-1″), 5.21 (7H, dd, $^3J_{1',2'}$ = 8.0 Hz, $^3J_{2',3'}$ = 10.0 Hz, H-2′), 5.37 (7H, dd, $^3J_{3'',4''}$ = 3.4 Hz, $^3J_{2'',3''}$ = 10.0 Hz, H-3″), 5.38−5.49 (14H, m, H-1, H-3′), 5.56 (7H, d, *J* = 3.5 Hz, H-4″). ^{13}C NMR ($(CD_3)_2NCDO$, 370K, 125 MHz): δ 20.18, 20.22, 20.38, 20.49, 20.67, 20.72, 20.75 (7s, CH_3CO), 27.9 (SCH_2CH_2), 58.5 (CH_3O), 60.8 (CH_3O), 61.9 (C-6″), 63.3 (C-6′), 68.4 (C-4″), 70.2 (C-6, OCH_2), 70.5 (C-2′), 71.4 (C-5′), 71.8 (C-3″), 71.9 (C-2′), 72.3 (C-5), 74.9 (C-3′), 77.1 (C-4′), 77.4 (C-5′), 79.9 (C-4), 82.9 (C-3), 83.0 (C-2), 83.9 (C-1′), 98.9 (C-1), 101.3 (C-1″), 169.6, 169.8, 169.9, 170.0, 170.4, 170.5, 170.7 (CH_3CO). MALDI-TOF *m/z*: 6203 $[M + Na]^+$. Anal. Calcd for $C_{259}H_{378}O_{154}S_7 \cdot 3H_2O$: C, 49.89; H, 6.20. Found: C, 50.03; H, 6.41.

1°-Glucose-7-mer Cluster (10). Methanolic NaOMe (1 M) (0.25 mL) was added to a stirred solution of **8** (172 mg, 41 μmol) in dry MeOH (20 mL), and the reaction was allowed to stand at room temperature. After TLC indicated completion (5 h), the reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo. The resultant glass was dissolved in H_2O and freeze-dried to afford **10** as a white fluff (122 mg, 99%). Selected NMR data. ^{1}H NMR (D_2O, 500 MHz): δ 1.91−2.04 (14H, m, CH_2), 2.81−2.93 (14H, m, SCH_2), 3.21 (7H, dd, *J* = 2.9 Hz, *J* = 9.6 Hz, H-2), 3.54 (21H, s, OCH_3), 3.64 (21H, s, OCH_3), 4.43 (7H, d, *J* = 9.6 Hz, H-1′), 5.20 (7H, d, *J* = 2.9 Hz, H-1). ^{13}C NMR (CD_3OD, 125 MHz): δ 28.7, 32.1, 59.9, 62.6, 63.8, 71.6, 71.9, 72.3, 73.5, 75.2, 80.4, 81.4, 82.7, 83.9, 84.3, 88.1, 100.4. MALDI-TOF *m/z*: 2121 $[M]^+$.

1°-Lactose-7-mer Cluster (11). Methanolic NaOMe (1 M) (1.0 mL) was added to a stirred solution of **9** (143 mg, 23 μmol) in dry MeOH (20 mL), and the reaction was allowed to stand at room temperature. After TLC indicated completion (5 h), the reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo. The resultant glass was dissolved in H_2O and freeze-dried to afford **11** as a white fluff (92 mg, 96%). Selected NMR data. ^{1}H NMR (D_2O, 500 MHz): δ 1.86−1.96 (14H, m, CH_2), 2.70−2.85 (14H, m, SCH_2), 3.29 (7H, t, *J* = 7.0 Hz), 3.30 (21H, s, OCH_3), 3.52 (21H, s, OCH_3), 4.37 (7H, d, *J* = 7.7 Hz, H-1″), 4.48 (7H, d, *J* = 9.9 Hz, H-1′), 5.15 (7H, bs, H-1). ^{13}C NMR (D_2O, 125 MHz): δ 27.3, 30.1, 58.6, 61.0, 61.2, 61.4, 69.1, 70.3, 71.5, 72.9, 73.3, 75.8, 76.5, 81.0, 81.4, 81.9, 85.9, 100.1, 103.5. MALDI-TOF *m/z*: 4127 $[M]^+$.

2°-Glucose-7-mer (12). To thiol **1** (239 mg, 0.66 mmol, 21 eq.) and CD **7** (68 mg, 31 μmol, concentration CD = 5 mM) was added distilled MeOH. C_6H_6 was then added dropwise until the CD was completely dissolved. A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following the removal of solvents, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes, gradient elution, 60: 40 to 90:10) to afford the product as a white foam (62 mg, 42%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.029 (21H, s, $SiCH_3$), 0.037 (21H, s, $SiCH_3$), 0.879 (63H, s, $C(CH_3)$), 1.92−1.94 (14H, m, SCH_2CH_2), 2.02, 2.04, 2.07, 2.10 (84H, 4s, 4 x Ac), 2.77−2.91 (14H, m, SCH_2), 3.25 (7H, dd, $^3J_{1,2}$ = 3.1 Hz, $^3J_{2,3}$ = 9.6 Hz, H-2), 3.48 (7H, t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.0 Hz, H-4), 3.54 (7H, d, $^3J_{5,6a}$ = 9.6 Hz, H-5), 3.68 (7H, d, $^2J_{6a,6b}$ = 10.8 Hz, H-6a), 3.77−3.83 (14H, m, H-5′, OCH_a), 3.90−3.94 (14H, m, H-3, H-6b), 4.04−4.10 (7H, m, OCH_b), 4.17 (7H, dd, $^3J_{5',6a'}$ = 2.3 Hz, $^2J_{6a',6b'}$ = 12.0 Hz, H-6a′), 4.31 (7H, dd, $^3J_{5',6b'}$ = 4.8 Hz, $^2J_{6a',6b'}$ = 12.0 Hz, H-6b′), 4.64 (7H, d, $^3J_{1',2'}$ = 10.1 Hz, H-1′), 4.91 Hz (7H, d, $^3J_{1,2}$ = 3.1 Hz, H-1), 5.05 (7H, t, $^3J_{1',2'} \approx {}^3J_{2',3'}$ = 10.1 Hz, H-2′), 5.13 (7H, $^3J_{3',4'} \approx {}^3J_{4',5'}$ = 9.8 Hz, H-4′), 5.28 (7H, t, $^3J_{2',3'} \approx {}^3J_{3',4'}$ = 9.4 Hz, H-3′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ −4.9, −4.8 ($Si(CH_3)_2$), 18.5 ($SiC(CH_3)_3$), 20.8, 21.1 (CH_3CO), 26.1 ($SiC(CH_3)_3$), 27.6 (SCH_2CH_2), 30.5 (SCH_2), 61.9 (C-6), 62.4 (C-6′), 68.6 (C-3′), 70.3 (C-2′), 71.3 (OCH_2), 71.9 (C-5), 73.3 (C-3), 74.2 (C-3′), 75.9 (C-4′), 81.2 (C-2), 82.4 (C-4), 84.3 (C-1′), 101.4 (C-1), 169.6, 169.7, 170.4, 170.8 (4 x CH_3CO). MALDI-TOF *m/z*: 4789 $[M + Na]^+$. Anal. Calcd for $C_{203}H_{336}O_{98}S_7Si_7$: C, 51.16; H, 7.11. Found: C, 50.90; H, 7.08.

2°-Lactose-7-mer Cluster (13). To thiol **2** (557 mg, 0.85 mmol, 21 equiv) and CD **6** (106 mg, 49 μmol, concentration CD = 5 mM) was added distilled MeOH. C_6H_6 was added dropwise until the CD was completely dissolved. A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following the removal of solvents, the residue was purified by gel filtration chromatography (LH-20, MeOH, 1 mL min^{-1}) to afford the product as a white foam (536 mg, 84%). ^{1}H NMR ($(CD_3)_2NCDO$, 370K, 500 MHz): δ 0.12 (42H, s, $Si(CH_3)_2$), 0.95 (63H, s, $SiC(CH_3)_3$), 1.93−1.97 (14H, m, SCH_2CH_2), 1.94, 2.00, 2.04, 2.05, 2.07, 2.12, 2.13 (147H, 7s, 7 x CH_3CO), 2.73−2.89 (14H, m, SCH_2), 3.32 (7H, d, *J* = 9.2 Hz, H-2), 3.59 (7H, t, *J* = 9.0 Hz, H-4), 3.70−3.75 (7H, m, H-5), 3.81−3.88 (21H, m, H-6a, OCH_a, H-5′), 3.94 (14H, t, *J* = 9.0 Hz, H-3, H-4′), 4.03−4.12 (14H, m, H-6b, OCH_b), 4.13−4.21 (21H, m, H-6a′, H-6a″, H-6b″), 4.27 (7H, t, *J* = 6.4 Hz, H-5″), 4.75 (7H, s, O*H*), 4.81−4.87 (21H, m, H-1′, H-2′, H-1″), 5.03 (7H, d, *J* = 10.0 Hz, H-2″), 5.06 (7H, s, H-1), 5.19 (7H, dd, *J* = 3.1, 10.0 Hz, H-3″), 5.22 (7H, t, *J* = 8.5 Hz, H-3′), 5.38 (7H, d, *J* = 3.1 Hz, H-4″). ^{13}C NMR ($(CD_3)_2NCDO$, 370K, 125 MHz): δ −4.7, −4.6 ($Si(CH_3)_2$), 18.7 ($SiC(CH_3)_3$), 20.20, 20.25, 20.40, 20.50, 20.67, 20.70, 20.77 (7 x CH_3CO), 26.4 ($SiC(CH_3)_3$), 27.7 (SCH_2CH_2), 31.0 (SCH_2), 61.9 (C-6″), 62.8 (C-6), 63.4 (C-6′), 68.4 (C-4′), 70.5 (C-2″), 71.4 (C-5″), 71.6 (OCH_2), 71.8 (C-3″), 71.9 (C-2′), 72.7 (C-5), 73.8 (C-3), 74.9 (C-3′), 77.1 (C-4′), 77.4 (C-5′), 82.0 (C-2), 82.8 (C-4), 84.0 (C-1′), 101.3 (C-1″), 101.7 (C-1), 169.6, 169.8, 169.9, 170.0, 170.4, 170.5, 170.6 (7 x CH_3CO). MALDI-TOF *m/z*: 6350 $[M + Na]^+$. Anal. Calcd for $C_{249}H_{448}O_{154}S_7Si_7$: C, 47.00; H, 7.16. Found: C, 46.81; H, 7.08.

2°-Glucose-7-mer Cluster (14). $BF_3 \cdot OEt_2$ (145 μL) was added dropwise via a micropipet to a stirred solution of **12** (389 mg, 82 μmol) in CH_2Cl_2 (10.0 mL). The reaction was

stirred at room temperature under an Ar atmosphere. After 4 h, TLC indicated that the reaction had gone to completion. H_2O (5 mL) was added, and the resulting mixture was stirred for a further 30 min. CH_2Cl_2 (100 mL) and H_2O (100 mL) were added, and the organic layer was washed with brine (100 mL) and then dried ($MgSO_4$) and filtered. The solvents were removed in vacuo, and the residue was purified by column chromatography (SiO_2, EtOAc/hexanes, gradient elution, 50: 50 to 70:30) to afford the product as a white foam (237 mg, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.89−1.98 (14H, m, SCH_2CH_2), 2.00, 2.02, 2.06, 2.08 (84H, 4s, 4 x Ac), 2.67−2.76 (14H, m, SCH_a), 2.78−2.85 (14H, m, SCH_b), 3.18−3.26 (7H, m, H-4), 3.32 (7H, d, $^3J_{2,3}$ = 8.6 Hz, H-2), 3.65−3.82 (35H, m, H-6a, 6-OH, H-5, OCH_a, H-5′), 3.87 (7H, t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 8.6 Hz, H-3), 3.92−3.98 (7H, m, H-6b), 3.98−4.10 (7H, m, OCH_a), 4.12 (7H, d, $^2J_{6a',6b'}$ = 12.0 Hz, H-6a′), 4.25 (7H, dd, $^3J_{5',6b'}$ = 4.6 Hz, $^2J_{6a',6b'}$ = 12.4 Hz, H-6b′), 4.56 (7H, d, $^3J_{1',2'}$ = 10.0 Hz, H-1′), 4.70 (7H, s, OH-3), 4.81 (7H, s, H-1), 5.00 (7H, t, $^3J_{1',2'} \approx {}^3J_{2',3'}$ = 9.6 Hz, H-2′), 5.08 (7H, $^3J_{3',4'} \approx {}^3J_{4',5'}$ = 9.6 Hz, H-4′), 5.22 (7H, t, $^3J_{2',3'} \approx {}^3J_{3',4'}$ = 9.4 Hz, H-3′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.84, 20.99, 21.03 (CH_3CO), 27.2 (SCH_2CH_2), 30.3 (SCH_2), 61.8 (C-6), 62.5 (C-6′), 68.6 (C-4′), 70.2 (C-2′), 71.4 (OCH_2), 72.1 (C-5), 73.5 (C-3), 74.1 (C-3′), 75.9 (C-5′), 80.7 (C-2), 84.0 (C-1′), 84.3 (C-4), 101.9 (C-1), 169.6, 169.7, 170.4, 171.0 (4 x CH_3CO). MALDI-TOF *m*/*z*: 3966 $[M]^+$. Anal. Calcd for $C_{161}H_{238}O_{98}S_7 \cdot 3H_2O$: C, 48.10; H, 5.96. Found: C, 47.89; H, 6.09.

2°-Lactose-7-mer Cluster (15). $BF_3 \cdot OEt_2$ (142 μL) was added dropwise via a micropipet to a stirred solution of **13** (368 mg, 55 μmol) in CH_2Cl_2 (15 mL). The reaction was stirred at room temperature under an Ar atmosphere. After 4 h, TLC indicated that the reaction had gone to completion. H_2O (7 mL) was added, and the resulting mixture was stirred for a further 30 min. CH_2Cl_2 (50 mL) and H_2O (50 mL) were added, and the organic layer was washed with brine (50 mL) and then dried ($MgSO_4$) and filtered. The solvents were removed in vacuo, and the residue was purified by gel filtration chromatography (LH-20, MeOH, 1 mL min^{-1}) to afford the product as a white foam (241 mg, 75%). ^{1}H NMR ($(CD_3)_2NCDO$, 370K, 500 MHz): δ 1.90−1.95 (14H, m), 1.92, 2.02, 2.03, 2.042, 2.045, 2.11 (147H, 6s), 2.75−2.78 (7H, m), 2.82−2.87 (7H, m), 3.35 (7H, dd, J = 3.3, 9.4 Hz), 3.45 (7H, t, J = 9.3 Hz), 3.73 (7H, d, J = 8.1 Hz), 3.76−3.97 (42H, m), 3.98−4.01 (7H, m), 4.10−4.20 (21H, m), 4.23 (7H, t, J = 6.7 Hz), 4.49 (7H, d, J = 11.8 Hz), 4.74 (7H, s), 4.80−4.85 (21H, m), 4.97−5.03 (14H, m), 5.06 (7H, s, H-1), 5.17 (7H, dd, J = 3.4, 10.2 Hz), 5.18−5.20 (7H, m), 5.36 (7H, d, J = 3.4 Hz). ^{13}C NMR (125 MHz, $(CD_3)_2NCDO$, 370 K): δ 20.2, 20.3, 20.4, 20.5, 20.70, 20.73, 20.8, 27.8, 31.8, 61.7, 62.0, 63.4, 68.5, 70.5, 71.5, 71.6, 71.9, 72.0, 73.0, 74.1, 74.9, 77.2, 77.4, 81.9, 84.0, 84.2, 101.3, 102.0, 169.7, 169.88, 169.95, 170.01, 170.49, 170.52, 170.7. MALDI-TOF *m*/*z*: 5984 $[M]^+$. Anal. Calcd for $C_{245}H_{350}O_{154}S_7 \cdot 3H_2O$: C, 48.74; H, 5.94. Found: C, 48.57; H, 5.73.

2°-Glucose-7-mer Cluster (16). Methanolic NaOMe (1 M) (0.4 mL) was added to a stirred solution of **14** (95 mg, 25 μmol) in dry MeOH (5.0 mL), and the reaction was left at room temperature. After TLC indicated completion (2 d), H_2O (10 mL) was added to dissolve precipitates, and the reaction was left to stir for a further 1 h, during which time the precipitate dissolved. The reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo, and the resultant glass was dissolved in H_2O and freeze-dried to afford **16** as a white fluff (67 mg, 99%). Selected NMR data. ^{1}H NMR (D_2O, 500 MHz): δ 1.85−1.92 (14H, m, CH_2), 2.71−2.77 (7H, m, SCH_a), 2.80−2.86 (7H, m, SCH_b), 3.25 (7H, t, J = 9.8 Hz, H-2′), 3.37 (7H, dd, J = 2.0 Hz, J = 5.7 Hz, H-2), 3.41 (7H, t, J = 9.0 Hz, H-3′), 4.45 (7H, d, J = 9.8 Hz, H-1′), 5.12, (7H, s, H-1). ^{13}C NMR (D_2O, 125 MHz): δ 26.3, 29.4, 60.0, 60.8, 69.4, 70.4, 71.1, 72.1, 73.5, 79.7, 80.9, 85.2, 99.6. MALDI-TOF *m*/*z*: 2789 $[M]^+$.

2°-Lactose-7-mer Cluster (17). Methanolic NaOMe (1 M) (1.5 mL) was added to a stirred solution of **15** (189 mg, 31 μmol) in dry MeOH (5.0 mL), and the reaction was allowed to stand at room temperature. After TLC indicated completion (1 d) of the reaction, H_2O (10 mL) was added to dissolve precipitates, and the reaction was left to stir for a further 1 h, during which time the precipitate dissolved. The reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo, and the resultant glass was dissolved in H_2O and freeze-dried to afford **17** as a white fluff (138 mg, 90%). Selected NMR data. ^{1}H NMR (D_2O, 500 MHz): δ 1.84−1.90 (14H, m, CH_2), 2.68−2.74 (7H, m, SCH_a), 2.78−2.83 (7H, m, SCH_b), 3.21 (7H, t, J = 9.3 Hz), 4.35 (7H, d, J = 7.8 Hz, H-1″), 4.47 (7H, d, J = 9.9 Hz, H-1′), 5.11 (7H, s, H-1). ^{13}C NMR (D_2O, 125 MHz): δ 26.3, 29.4, 60.15, 60.9, 68.4, 70.5, 70.8, 71.2, 71.9, 72.1, 72.4, 75.2, 75.6, 78.1, 78.5, 79.8, 81.1, 85.1, 99.7, 102.7. MALDI-TOF *m*/*z*: 3924 $[M]^+$.

1°,2°-Glucose-14-mer Cluster (18). To thiol **1** (1.58 g, 4.31 mmol, 42 equiv) and the CD **7** (173 mg, 0.10 mmol, concentration CD = 5 mM) was added distilled MeOH. C_6H_6 was added dropwise until the CD was completely dissolved. A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following the removal of solvents, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes, gradient elution, 60: 40 to 100:0) to afford the product as a white foam (488 mg, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.82−1.90 (28H, m, SCH_2CH_2), 1.99, 2.00, 2.04, 2.06, 2.07 (168H, 5s, Ac), 2.56−2.85 (28H, m, SCH_2), 3.27 (7H, d, $^3J_{2,3}$ = 9.2 Hz, H-2), 3.39 (7H, t, J = 9.0 Hz, H-4), 3.45−3.54 (28H, m, H-6a, H-6b, OCH_2), 3.56−3.68 (7H, m, H-5), 3.70−3.78 (21H, m, H-5′, OCH_a), 3.81 (7H, t, $^3J_{2,3}$ = 9.0 Hz, H-3), 3.97−4.04 (7H, m, OCH_b), 4.11 (14H, d, $^2J_{6a',6b'}$ = 10.9 Hz, H-6a′), 4.24 (14H, dd, $^3J_{5',6b'}$ = 3.5 Hz, $^2J_{6a',6b'}$ = 11.5 Hz, H-6b′), 4.54 (7H, d, $^3J_{1',2'}$ = 10.0 Hz, H-1′), 4.57 (7H, d, $^3J_{1',2'}$ = 10.0 Hz, H-1′), 4.82 (7H, bs, H-1), 4.98 (14H, t, $^3J_{2',3'}$ = 9.2 Hz, H-2′), 5.06 (7H, t, $^3J_{3',4'}$ = 9.7 Hz, H-4′), 5.07 (7H, t, $^3J_{3',4'}$ = 9.7 Hz, H-4′), 5.22 (7H, t, $^3J_{3',4'}$ = 9.3 Hz, H-3′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4, 20.66 (CH_3CO), 26.9, 27.0 (SCH_2CH_2), 29.5, 30.0 (SCH_2), 62.2 (C-6′), 68.4 (C-4′), 69.1 (C-6), 69.9 (OCH_2), 70.0, 70.1 (C-2′), 70.6 (C-5), 71.3 (OCH_2), 73.1 (C-3), 73.9, 74.0 (C-3′), 75.7, 75.8 (C-5′), 80.7 (C-2), 83.3 (C-4), 83.7, 83.9 (C-1′), 101.9 (C-1), 169.20, 169.23, 169.29, 169.77, 169.96, 170.02, 170.37, 170.47 (8 x CH_3CO). MALDI-TOF *m*/*z*: 6820 $[M + Na]^+$. Anal. Calcd for $C_{280}H_{406}O_{161}S_{14} \cdot 4H_2O$: C, 48.96; H, 6.07. Found: C, 48.73; H, 5.76.

1°,2°-Lactose-14-mer Cluster (19). To thiol **2** (540 mg, 828 μmol, 28 equiv) and CD **7** (50 mg, 30 μmol, concentration CD = 5 mM) was added distilled MeOH. C_6H_6 was added dropwise until the CD was completely dissolved. A stream of Ar was bubbled through the solution for 20 min to thoroughly degas it. The solution, kept under an atmosphere of Ar, was placed in front of an Hg lamp and stirred for 5 h. Following the removal of solvents, the residue was purified by gel filtration chromatography (LH-20, 20% $CHCl_3$/MeOH, 1 mL min^{-1}) to afford the product as a white foam (212 mg, 66%). ^{1}H NMR ($(CD_3)_2NCDO$, 380K, 500 MHz): δ 1.91−1.98 (28H, m, SCH_2CH_2), 1.95, 2.05, 2.06, 2.07, 2.08, 2.09, 2.14 (294H, 7s, 7 x AcO), 2.72−2.91 (28H, m, SCH_2), 3.36 (14H, d, J = 9.0 Hz, H-2), 3.51 (7H, t, J = 8.7 Hz, H-4), 3.55−3.63 (21H, m, H-6a, OCH_2), 3.76−3.78 (7H, m, H-5), 3.82−3.91 (21H, m, H-5′, OCH_a), 3.93−3.97 (28H, m, H-3, H-4′), 4.01−4.06 (14H, m, H-6b, OCH_b), 4.14−4.22 (42H, m, H-6a′, H-6a″, H-6b″), 4.25 (14H, t, J = 6.5 Hz, H-5″), 4.52 (14H, d, J = 11.0 Hz, H-6b′), 4.80−4.88 (42H, m, H-1′, H-2′, H-1″), 5.02 (7H, bs, H-1), 5.04 (7H, t, J = 8.1 Hz, H-2″), 5.18−5.24 (28H, m, H-3′, H-3″), 5.39 (14H, d, J = 3.3 Hz, H-4″). ^{13}C NMR ($(CD_3)_2NCDO$, 370K, 125 MHz): δ 20.7, 20.8, 20.9, 21.04, 21.08, 21.3, (6 x CH_3CO), 28.28, 28.38 (SCH_2CH_2), 31.56, 31.66 (SCH_2), 62.5 (C-6″), 63.9 (C-6′), 68.9 (C-4′), 70.5 (C-6), 71.0 (OCH_2), 71.1 (C-2″), 72.0 (C-5″), 72.2 (OCH_2), 72.4 (C-3″,C-5), 72.5 (C-2′), 74.4 (C-3), 75.5 (C-3′), 77.6 (C-4′), 78.0 (C-5′), 80.0 (C-2), 82.4 (C-4), 84.4 (C-1′), 84.5 (C-1′), 101.8 (C-1″), 102.8 (C-1), 170.1, 170.3, 170.45, 170.55, 170.9, 171.9 (6 x CH_3CO). MALDI-TOF *m*/*z*: 10833 $[M]^+$. Anal. Calcd for $C_{448}H_{630}O_{273}S_{14} \cdot 6H_2O$: C, 49.18; H, 5.91. Found: C, 49.23; H, 5.89.

1°,2°-Glucose-14-mer Cluster (20). Methanolic NaOMe (1 M) (4.0 mL) was added to a stirred solution of **18** (372 mg, 55 μmol) in dry MeOH (20 mL), and the reaction was allowed to

stand at room temperature. After TLC had indicated completion (1 d) of the reaction, 1 M NaOH (2 mL) was added to dissolve precipitates, and the reaction was left to stir for a further 1 d, during which time the precipitate dissolved. The reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo, and the resultant glass was dissolved in H_2O and freeze-dried to afford **20** as a white fluff (307 mg, 99%). An analytical sample was prepared by gel filtration chromatography (Biogel P-6, H_2O, 1 mL min^{-1}). Selected NMR data. ^1H NMR (D_2O, 360 K, 500 MHz): δ 2.33−2.41 (28H, m, CH_2), 3.19−3.35 (28H, m, SCH_2), 4.91 (7H, d, J = 9.9 Hz, H-1′), 4.93 (7H, d, J = 9.9 Hz, H-1″), 5.56 (7H, d, J = 3.0 Hz, H-1). ^{13}C NMR (D_2O, 345 K, 125 MHz): δ 23.7, 26.9, 27.1, 29.9, 30.1, 61.59, 61.66, 69.4, 70.1, 70.3, 70.9, 71.3, 71.6, 72.89, 72.97, 77.82, 77.89, 80.30, 80.35, 81.96, 85.81, 85.88, 100.4. MALDI-TOF m/z: 4381 $[M]^+$.

1°,2°-Lactose-14-mer Cluster (21). Methanolic NaOMe (1 M) (0.5 mL) was added to a stirred solution of **19** (305 mg, 28 μmol) in dry MeOH (10 mL) and THF (4 mL). Within 1 min, a suspension appeared which dissolved upon the addition of H_2O (10 mL). The reaction was left to stir at room temperature, and 1 M methanolic NaOMe was added (0.3 mL) if the pH dropped below 9. After the pH remained constant (pH = 9) for 4 h, the reaction was neutralized with Amberlite IR-120 (H^+ form) ion-exchange resin and filtered. The solvents were removed in vacuo, and the resultant glass was dissolved in H_2O and freeze-dried to afford **21** as a white fluff (189 mg, 99%). An analytical sample was prepared by gel filtration chromatography (Biogel P-6, H_2O, 1 mL min^{-1}). Selected NMR data. ^1H NMR (D_2O, 300 K, 500 MHz): δ 1.77−1.89 (28H, m, CH_2), 2.61−2.87 (28H, m, SCH_2), 4.32 (14H, d, J = 7.7 Hz, H-1″), 4.44 (14H, d, J = 9.8 Hz, H-1′), 5.02 (7H, bs, H-1). ^{13}C NMR (D_2O, 300 K, 125 MHz): δ 26.9, 27.1, 29.9, 30.1, 61.0, 61.3, 69.0, 70.3, 70.9, 71.3, 71.4, 72.8, 73.1, 75.7, 76.3, 76.4, 79.0, 80.4, 82.2, 85.7, 100.7, 103.3. MALDI-TOF m/z: 6713 $[M]^+$.

Molecular Modeling. Molecular modeling was carried out using the Amber* force field as implemented in Macromodel[30] (V 5.0). The assembly was built within the INPUT submode, and the geometry optimization was carried out by first fully minimizing the initial structure (final gradient < 0.05 kJ $Å^{-1}$) using the Polak Ribière Conjugate Gradient (PRCG) algorithm[33] with extended nonbonded cutoffs (4 Å for hydrogen bonding, 8 Å for van der Waals, and 20 Å for electrostatic interactions). The assembly was then subjected to a molecular dynamics simulation (10 ps, 1.5 fs time step, 300 K, Amber*, extended cutoffs) to afford a system conformationally dissimilar to the initial structure. The structure of the supermolecule was then fully minimized again (PRCG, Amber*, extended cutoffs, final gradient < 0.05 kJ $Å^{-1}$) to afford the conformation displayed. For all steps, solvent effects were considered in the form of the GB/SA[34] solvation model for H_2O.

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