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Glycoside-Clustering Round Calixarenes toward the Development of Multivalent Carbohydrate Ligands. Synthesis and Conformational Analysis of Calix[4]arene *O*- and *C*-Glycoconjugates

Alessandro Dondoni,*[,†] Martin Kleban,[†] Xubo Hu,[†] Alberto Marra,[†] and Harold D. Banks*[,‡]

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, 44100 Ferrara, Italy and U. S. Army Edgewood Chemical Biological Center APG Maryland 21010-5424

adn@dns.unife.it

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Bis- and tetra-*O*- and *C*-glycosyl calixarenes (calixsugars) have been prepared by tethering carbohydrate moieties to a tetrapropoxycalix[4]arene scaffold through alkyl chains. Two methodologies have been employed. One consisted of the stereoselective multiple glycosylation of upper rim calix[4]arene polyols leading to calix-*O*-glycosides; the other involved a multiple Wittig olefination of upper rim calix[4]arene-derived polyaldehydes by the use of sugar phosphoranes and reduction of the alkene double bonds affording calix-*C*-glycosides. The NMR spectra and NOE experiments of bis-glycosylated products indicate that compounds bearing sugar-protected residues exist preferentially in solution in a flattened cone arrangement (*far* conformation) whereas deprotected derivatives adopt a *close* conformation. Calculations by molecular mechanics of the latter compounds point to a *close* conformation as well in gas phase.

Introduction

The ease of preparation in large scale quantities and variable size of the cavity, tunable conformation, and selective and multiple derivatization are the main features responsible for raising calixarenes to the level of popularity of crown ethers and cyclodextrins as selective receptors for charged polar species, mainly cations.[1] On the other hand, the use of calixarenes as a platform for the implantation of biologically active molecules that can bind complementary neutral species has attracted much less attention. We addressed this issue in some instances over the last years by considering the synthesis of upper and lower rim calix[4]arene-based glycoconjugates (calixsugars).[2] Extensive *O*-glycosylation with four-carbohydrate units transformed intrinsically lipophilic calixarene scaffolds into water-soluble chiral systems. In particular they can be regarded as clusters of glycosides anchored to a structurally well-defined scaffold and therefore can serve as multivalent agents for molecular recognition. It is well established that interaction between cell-surface oligosaccharides and their receptor, lectins, that occurs, for example, in the adhesion of bacteria and viruses to the surface of cells, is important in various intercellular communication and signal transduction events.[3] However, since the affinity of carbohydrates for their protein receptors is almost inevitably weak,[3,4] the hypothesis was formulated several years ago that efficient carbohydrate−protein adhesion results from a multiplicity of simultaneous binding events, i.e., multivalency or glycoside cluster effect, which compensates for weak individual interactions.[3,5] Following the pioneering work of Lee and co-workers in the early 1980s,[5] several research groups have recently reported the synthesis of various collections of densely glycosylated systems[6] wherein the carbohydrate moieties are (a) tethered to the backbone of polymers[7] or peptides,[8] (b) distributed on the periphery of dendrimers or assembled in fully carbohydrate dendrimers,[9,10] (c) introduced in rigid scaffolds such as calix[4]arenes,[2,11] calix[4]resorcarenes,[12] azamacrocycles,[13] cyclodextrins,[14] (d) joined to the headgroups of molecules

† Università di Ferrara.

‡ U. S. Army Edgewood Research. To whom computational chemistry questions should be addressed.

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in liposomes,[15] and (e) linked noncovalently to metal complexes.[16] These and other[17] spectacular results have led to a general acceptance of the cluster glycoside effect as a leading concept in the development of inhibitors of carbohydrate-mediated biological recognition.[18]

We report in this paper an advancement of our previous work on calix[4]arene-based glycoside clusters.[2] We will describe the synthesis of new bis- and tetra-glycosylated calix[4]arenes (calixsugars) wherein scaffolding of carbohydrate moieties occurs by oxygen and carbon linkages of various length. Two methodologies will be illustrated, one consisting of the stereoselective multiple glycosylation of upper rim calix[4]arene polyols leading to calix-*O*-glycosides, the other involving multiple Wittig olefination of upper rim calix[4]arene-derived polyaldehydes by the use of sugar phosphoranes and reduction of the resulting alkene double bonds affording calix-*C*-glycosides (Figure 1). The effect of the glycosylation on the conformation of the calix[4]arene scaffold and the consequential organization of the carbohydrate moieties will also be discussed based on ^{1}H NMR analysis and molecular mechanics calculations. Hence, our work on calixarene derivatization with carbohydrate ligands for the recognition of complementary species[19] follows a different and much less explored line with respect to that employing calixarene derivatives as selective receptors for ions.[1] In a similar context to ours, Roy and co-workers reported the synthesis of a tetravalent α-sialoside[20] and an α-D-GalNAc adorned dendrimer[9k] wherein the carbohydrate moieties are attached to the phenoxy groups at the lower rim of the calix[4]arene core through long polyamidic arms.[21] However, small glycoclusters with much simpler structures as the calixsugars presented below may give rise to a better preorganization of the carbo-

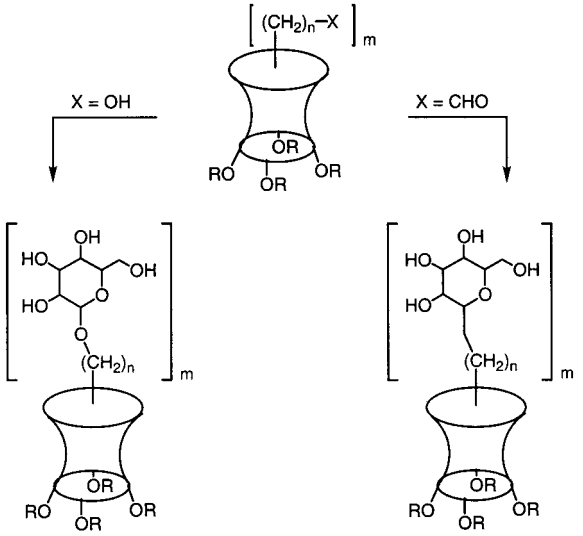

FIGURE 1. Schematic structures of *O*- and *C*-glycosyl calix[4]arenes prepared (m = 2 or 4).

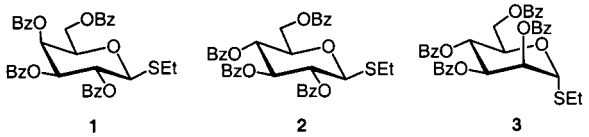

FIGURE 2. Model ethylthio glycosides employed as glycosyl donors.

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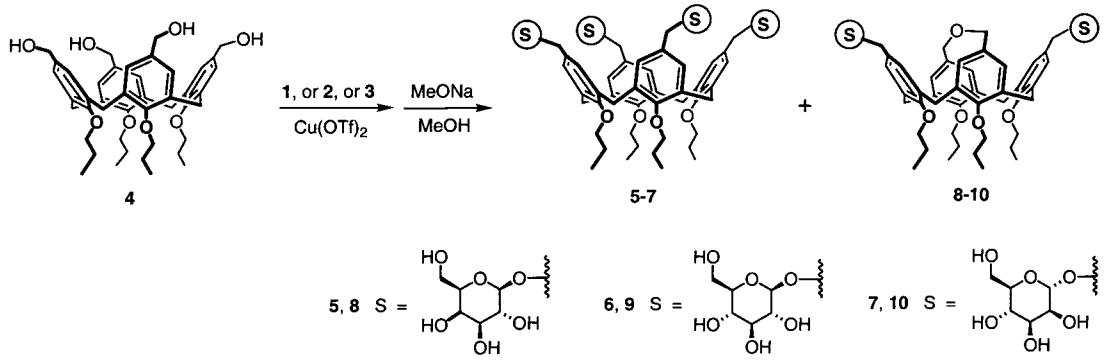
SCHEME 1

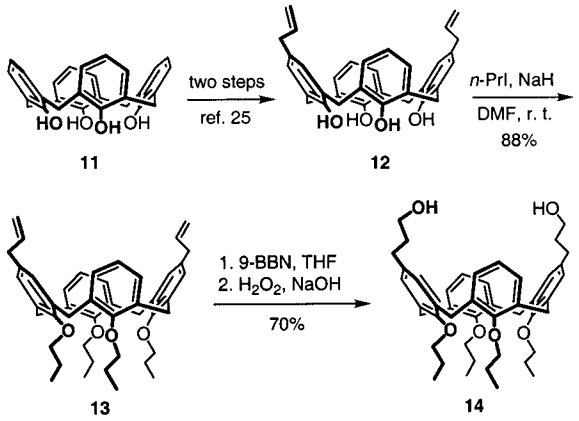


hydrate moieties due to the short spacer arms as well as provide a higher potential for guest inclusion by taking advantage of the proximity of the calixarene cavity.

Results and Discussion

Synthesis of *O*-Glycosyl Calix[4]arenes. Despite the intellectual appeal of glycoside-clustering round calix[4]arenes, the introduction of carbohydrate moieties at the upper rim via multiple *O*-glycosylation reaction of short arm calix[4]arene polyols was undeniably a nontrivial task.[2a,c] Having solved the problem regarding the glycosyl donor system by the use of copper(II) triflate-activated *O*-benzoyl thioglycosides in MeCN−CH_2Cl_2 (2:1) as a solvent[22] to achieve enough reactivity and high level of 1,2-trans selectivity, a remaining concern was about the intramolecular reaction between the 1,3-distal hydroxy groups leading to ether-bridged side products. We reported that the coupling between excess ethylthio tetrabenzoyl-β-D-galactopyranoside **1** shown in Figure 2 and the cone tetrapropoxy-calix[4]arene **4**, afforded the β-linked tetra-*O*-galactosyl calix[4]arene derivative **5** (60%) (Scheme 1), while the capped bis-glycosyl derivative **8** was formed in very small amount (3%).[2c] On the other hand, the more complex thioethyl lactoside donor afforded exclusively the corresponding ether-bridged bis-*O*-lactosyl calix[4]arene.[2c] Apparently in this case the sluggish glycosylation reaction was amply surpassed by the competing intramolecular ether formation. The ease of this coupling reaction is very likely due to the strongly acidic conditions inducing the formation of a benzylic-type carbocation, which gives rise to an intramolecular coupling with the opposite hydroxy group. We have now confirmed that this side reaction quite seriously hampers the extensive glycosylation of the tetrol **4** by the thioethyl glucopyranoside **2** and mannopyranoside **3** as glycosyl donors. In both cases the multiple glycosylation reactions were accompanied by substantial intramolecular ether formation giving rise to mixtures of tetra-*O*-glycosylcalix[4]arene and the corresponding capped calixsugar (**6** and **9**; **7** and **10**) in comparable yet low yields (25−35%). Nevertheless, these multiple *O*-glycosidation reactions also occurred on the single multiantennary substrate **4** with total 1,2-trans stereoselectivity since all glucopyranose moieties in **6** featured the β-*O*-glycosidic linkage[23] whereas the mannopyranose residues in **7** were α-linked.[24]

SCHEME 2



Given the intrinsic difficult access to *O*-glycoconjugates of the short spacer arm calix[4]arene tetrol **4** in satisfactory yields, we decided to examine the glycosylation reactions of calix[4]arene polyol derivatives with longer arms. At first we considered the synthesis of bis-glycosyl derivatives as a preliminary approach to the more complex perglycosylated products. To this aim, a multigram scale preparation of the symmetrical dihydroxypropyl tetrapropoxy-calix[4]arene **14** was carried out starting from the known 5,17-di-*O*-allyl-calix[4]arene[25] **12** by *O*-propylation of the phenolic oxygens to give **13** and hydroboration−oxidation of the latter (Scheme 2).

Coupling reactions of **14** were carried out with *galacto*, *gluco*, and *manno* thioglycosides **1**−**3** to verify their efficiency as glycosyl donors toward the calixarene-scaffolded hydroxypropyl group. The reactions performed under the same standard conditions described above (Cu(OTf)$_2$, MeCN−CH_2Cl_2, room temperature), afforded the corresponding bis-*O*-glycosyl calix[4]arenes **15**−**17** in very good isolated yields (76−83%) (Figure 3). As expected, the NMR analysis of these *O*-glycosides confirmed

(22) Although the solvent of choice for a fast glycosidation reaction is MeCN (see: Marra, A.; Gauffeny, F.; Sinaÿ, P. *Tetrahedron*, **1991**, *47*, 5149) the use of CH_2Cl_2 as a cosolvent was necessary because some batches of highly crystalline **4** were only partially soluble in pure MeCN at room temperature.

(23) The ^{1}H NMR spectra of *O*-calixsugars **6**, **9Ac**, **15**, **16**, **18**, **22**, and **23** showed $J_{1,2}$ values in the 7.3−7.9 Hz range (9.5 Hz for the *C*-calixsugar **35Ac**) as expected for transdiaxial H-1 and H-2 protons of pyranose units in a $^4C_1$ conformation (β-D configuration).

(24) The α-D configuration of **7**, **10Ac**, **17**, and **24Ac** was demonstrated by NOE difference experiments. Irradiation of H-1 or H-5 did not show 1,3-diaxial NOE interactions between H-1 and H-3 or H-5.

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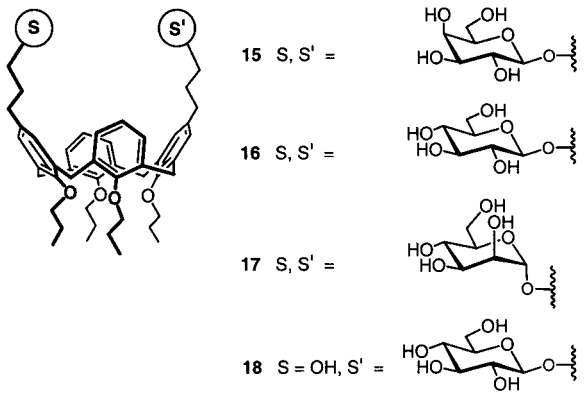
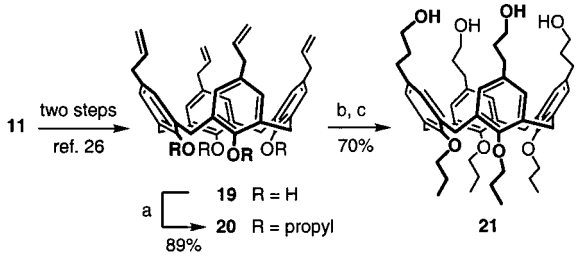


FIGURE 3. Mono- and bis-*O*-calixsugars prepared from the calix[4]arene diol **14**.

the anomeric β-linkage[23] for the gluco- and galactopyranose residues in **15** and **16** and the α-linkage[24] for the mannopyranose moieties in **17**. The ether-bridged products arising from the intramolecular coupling of the two alcoholic functions were not observed in the crude reaction mixtures. The only byproducts which were observed in variable amounts were the corresponding mono-*O*-glycosyl calix[4]arenes. The gluco derivative **18** which was isolated and duly characterized[23] represents one of these products.

Encouraged by the above results, we proceeded to the construction of more densely glycosylated architectures. The calix[4]arene tetrol **21** designed as the tetravalent glycosyl acceptor was prepared from the known[26] tetraallyl calix[4]arene **19** (Scheme 3) via a reaction sequence identical to that which was followed for the preparation of the calix[4]arene diol **14**. Scaffolding of four carbohydrate residues in the tetrol **21** was readily carried out by multiple glycosylation using the ethylthio glycoside donors **1**−**3** and activation by $Cu(OTf)_2$ under the above standard conditions. In all cases the coupling reaction between the activated glycoside and the alcohol proceeded smoothly and cleanly afforded the corresponding tetra-*O*-glycosyl calix[4]arene in a preparatively significant isolated yield (galactosyl **22**, 75%; glucosyl **23**, 62%; mannosyl **24**, 58%) (Figure 4). The β- and α-linkages at the anomeric center of these *O*-glycosides as shown in the corresponding structures were substantiated by their NMR spectra.[23,24] In no instances were capped products arising from the intramolecular ether bridge formation observed. Instead, mixtures of partially glycosylated products were obtained which appeared by NMR and MS analyses to consist of tris-*O*-glycosyl derivatives.

SCHEME 3



[a] Key: (a) *n*-PrI, NaH, DMF, rt; (b) 9-BBN, THF, 0 °C; (c) H_2O_2, NaOH, 40 °C.

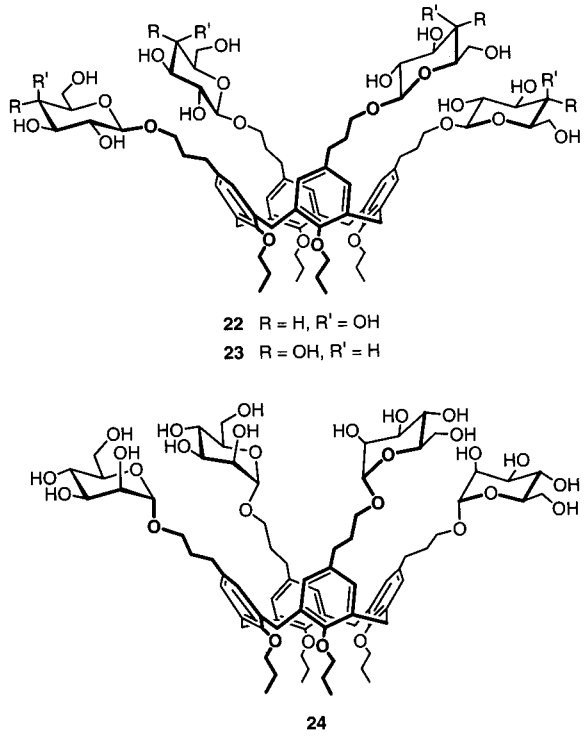


FIGURE 4. Tetra-*O*-calixsugars prepared from the calix[4]-arene tetrol **21**.

Synthesis of *C*-Glycosyl Calix[4]arenes. In the evolution of our program in this area, we were led to consider the scaffolding of carbohydrate moieties in calix[4]arenes through all carbon tethers. We planned to obtain a collection of these neoglycoconjugates which could be used as multivalent glycoside assemblies under conditions which were not tolerated by the oxygen-linked analogues because of their acid-sensitive anomeric acetal linkage. Guided by our rather extensive experience in *C*-glycoside synthesis via Wittig coupling of suitable aldehyde and phosphorus ylide partners,[27] we focused on this venerable carbon−carbon bond forming reaction for the introduction of various carbohydrate residues at the upper rim of the calix[4]arene skeleton. It was anticipated some molecular diversity by carbohydrate variation could be introduced using the readily available[27a] sugar phosphorane precursors **25**−**27** (Figure 5).

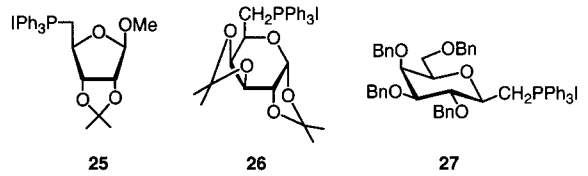


FIGURE 5. Phosphonium iodide precursors of sugar phosphoranes.

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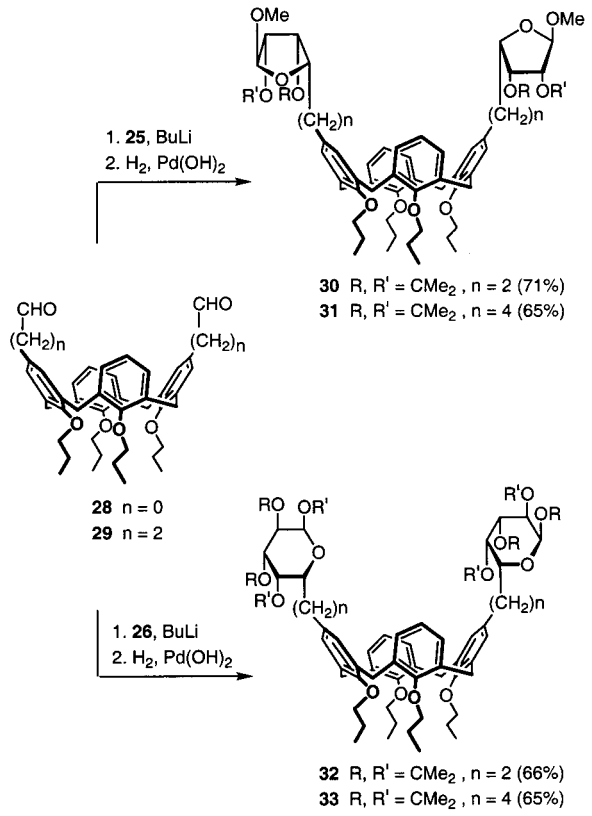
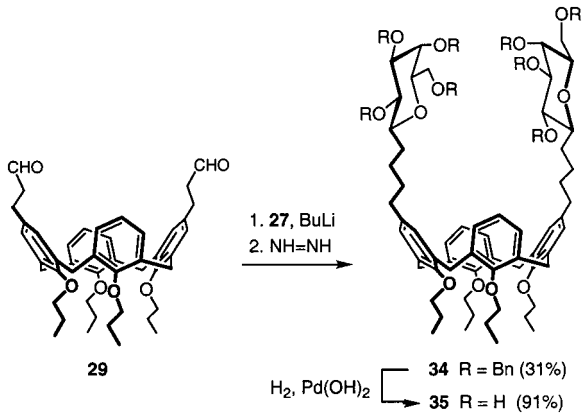
SCHEME 4



It was first considered the Wittig olefination of the known calix[4]arene dialdehyde **28**[19a] with the ribofuranose and galactopyranose phosphoranes derived from the phosphonium iodides **25** and **26**. The generation of the ylides in situ under the optimized conditions established in our laboratory[27a] (BuLi, THF−HMPA, 4-Å molecular sieves, −50 °C) followed by the reaction with **28** at low temperature afforded mixtures of *E* and *Z* alkenes (Scheme 4). These mixtures were liberated from the unreacted dialdehyde, triphenylphosphine oxide, and the sugar diphenylphosphine oxide and then hydrogenated ($Pd(OH)_2$ on carbon) to give the nonanomeric carbon-linked calixsugars **30** and **32** in good yield (66−71%). It is worth noting that the assigned α-L-*lyxo* configuration[28] of the furanose rings in **30** is consistent with the well-known inversion of configuration[27a] at C-4 in the ylide derived from the *β*-D-*ribo*-configured phosphonium salt **25**. A similar inversion of configuration did not occur at C-5 of the pyranose ring of the ylide derived from **26**, and consequently the two sugar moieties in the *C*-calixsugar **32** featured the original α-D-*galacto* configuration.[29] The olefination−reduction sequence was repeated using the same ylides from **25** and **26** and the calix[4]arene bispropanal **29.** This new derivatized calixarene was easily prepared in 60% yield by oxidation of the diol **14** (see Scheme 2) with pyridinium chlorochromate in CH_2Cl_2.

SCHEME 5



Both reactions afforded the corresponding carbon-linked calixsugars **31** and **33** in essentially the same isolated yields (65%).

Given the satisfactory reactivity of the calix[4]arene dialdehydes **28** and **29** with the phosphorus ylides from **25** and **26**, we considered the reaction of these aldehydes with the sterically more demanding *O*-benzyl-protected sugar ylide derived from the phosphonium salt **27**. This ylide was unreactive with the aromatic dialdehyde **28** while it afforded the coupling product with the long arm calix[4]arene dialdehyde **29** to give after reduction of the two alkene double bonds, the *C*-glycosyl calix[4]arene **34** in modest yield (31%) (Scheme 5). Finally, the removal of the *O*-benzyl protective groups from **34** afforded the *C*-calixsugar **35**,[23] the methylene isostere of the *O*-calixsugar **15**.

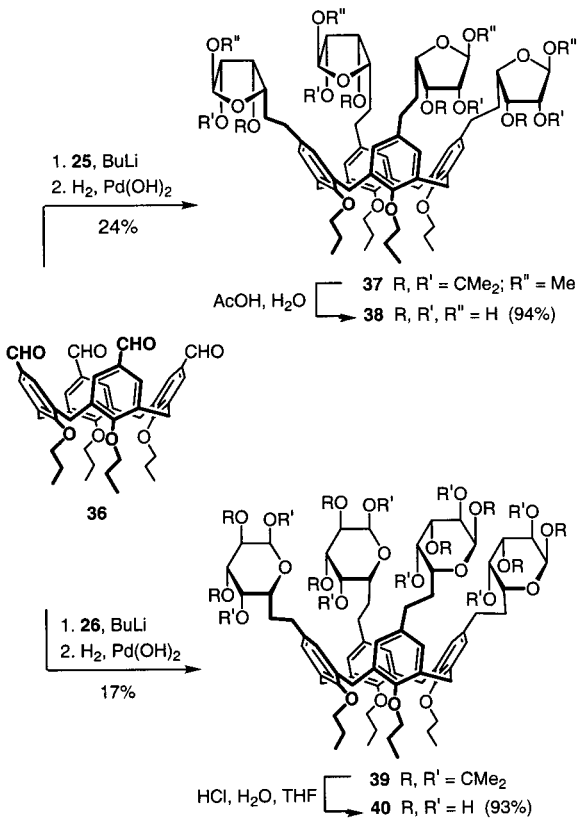
We next explored the introduction of more than two sugar moieties via multiple olefination of the known[2c] calix[4]arene tetraaldehyde **36** with the ylides derived from **25** and **26**. These reactions afforded quite complex mixtures of alkenes as judged by NMR analysis. Therefore, these mixtures were subjected to hydrogenolysis in the presence of $Pd(OH)_2$ on carbon. The main products isolated in modest yields were the carbon-linked calixsugars **37** (24%) and **39** (17%) featuring four carbohydrate residues joined to the calix[4]arene skeleton by ethylene bridges (Scheme 6). The α-L-*lyxo* configuration of the furanose rings in **37** and the α-D-*galacto* of the pyranose rings in **39** were assigned on the basis of their NMR spectra.[28,29] Finally, the removal of the *O*-isopropylidene protecting groups from the carbohydrate moieties of these compounds was carried out by acid hydrolysis. The unprotected *C*-calixsugar **38** and **40** were obtained as mixtures of α- and *β*-anomers (only one isomer is shown in Scheme 6) in almost quantitative yields. Quite deceptively, these compounds also proved to be soluble in methanol but insoluble in water. Given the lack of reactivity of the ylide derived from the phosphonium salt **27** with the calix[4]arene dialdehyde **28**, no attempts were made to react the same ylide with the tetraaldehyde **36.** Unfortunately, despite several attempts we failed to prepare a long arm calix[4]arene tetraaldehyde. Hence, no further efforts were made for the preparation of densely glycosylated carbon-linked calixarenes based on the Wittig olefination approach.

Conformational Studies. Calix[4]arenes are conformationally mobile systems for which the cone, partial

(28) This assignment was based on the very small coupling constant value ($J_{3,4}$ < 0.5 Hz) of the furanose ring of the phosphonium salt **25** compared with the higher value ($J_{3,4}$ = 3.2 Hz) of the carbohydrate residues in the calixsugar **30**. See: (a) Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem*. **1966**, *3*, 485. (b) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547.

(29) Similar values af all coupling constants, particularly that between H-4 and H-5, were found in the phosphonium salt **26** ($J_{4,5}$ = 2.0 Hz) and in the calixsugar **32** ($J_{4,5}$ = 1.7 Hz).

SCHEME 6



cone, 1,2-alternate, and 1,3-alternate conformers are possible.[1e] In the cone conformation, all aryl rings are above the best plane drawn through the methylene bridges. Calix[4]arenes can be fixed in the cone conformation by the installation at the lower rim of suitable groups (*O*-propyl or larger) which inhibit the oxygen-through-the-annulus rotation.[30] However, most calix[4]-arenes do not exist in the higher symmetry C_4 point group conformation but rather as two rapidly interchanging flattened cone conformations.[31] Usually, the 5,17-bis-substituted calix[4]arenes adopt the flattened cone conformation with the substituted phenyl rings pointing away from each other (*far* conformation). This can be deduced by the chemical shifts of the relevant aromatic protons in their ^{1}H NMR spectra. In fact, the protons of the rings that are parallel (unsubstituted) are magnetically shielded by the opposite rings (substituted), leading to an upfield shift of ca. 0.5−1 ppm.[32] Accordingly, we observed large $\Delta\delta$ values between the protons of substituted and unsubstituted phenyl rings for calixsugars **30**−**33**, the compounds bearing the most sterically demanding sugar units[33] (Table 1). On the other hand, the products **15**−**17** and **35** carrying deprotected and consequently less bulky sugar residues showed $\Delta\delta$ values below 0.15 ppm which suggests a modest preference for the *far* conformation in solution. However, in these complex molecules some unpredictable anisotropy effects could influence the chemical shifts of the aromatic protons, and therefore the conformational assignments derived therefrom can be uncorrect. Thus, the average conformation in solution at room temperature was additionally ascertained by NOE difference experiments.[32] Upon irradiation of the equatorial protons (H_{eq}) of the methylene bridges connecting the four aryl rings in **30**−**33**, strong NOEs were observed for the aromatic protons of the substituted rings (Table 1). The analogous effects for the corresponding protons of the unsubstituted rings were significantly weaker. These findings indicated a marked preference for the *far* conformation, since in this spatial arrangement the H_{eq} protons are closer to the substituted aryl rings. The NOE experiments performed for the other calixsugars revealed variable conformational arrangements (see Table 1). In fact, compound **15** showed a slight preference for the *far* conformation, **16** appeared to have equal concentrations of each flattened cone, while **17** and **35** adopted a *close* conformation. The behavior of the latter compounds suggests the presence of intramolecular hydrogen bonds between the two sugar units which are not disrupted by the deuterated methanol used as a solvent.

TABLE 1. NMR Data of the Bis-Substituted Calixsugars

compd	solvent	$\Delta\delta$ (ppm)[a]	NOE H_{subst} (%)[b]	NOE $H_{unsubst}$ (%)[b]
15	CD_3OD	0.15	7.8	7.2
16	CD_3OD	0.13	6.9	6.9
17	CD_3OD	−0.08	6.5	8.2
30	$CDCl_3$	0.50	8.8	5.4
31	$CDCl_3$	0.40	8.6	6.2
32	$CDCl_3$	0.60	7.8	5.3
33	$CDCl_3$	0.51	8.6	5.8
35	CD_3OD	0.10	5.4	6.0

[a] Difference between the chemical shifts of the protons of the substituted (H_{subst}) and unsubstituted ($H_{unsubst}$) aryl rings. [b]Observed upon irradiation of the equatorial protons of the methylene bridges.

Given the prodigious number of possible conformational isomers for each calixsugar, interpretation of the ^{1}H NMR experiments in terms of fundamental principles would be difficult without a knowledge of the extent to which each conformer is preferred. Such questions can be addressed computationally. Due to the size of the molecules under consideration, the level of theory was confined to molecular mechanics in the absence of solvent. It should be noted that while the reported computational results are not directly comparable to the ^{1}H NMR solution results, gas-phase calculations are meritorious in that they allow study of this series compounds in terms of their intrinsic properties, free of intermolecular interactions.[34] The probable qualitative effects of the polar, hydrogen bonding solvent, deuterated methanol, on the gas-phase structures were then considered in order to make a comparison with the experimental results. This approach has been applied successfully to the study of calix[4]arenes.[35]

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(31) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454.

(32) Krebs, F. C.; Larsen, M.; Jørgensen, M.; Jensen, P. R.; Bielecki, M.; Schaumburg, K. *J. Org. Chem.* **1998**, *63*, 9872.

(33) Large $\Delta\delta$ values between the protons of substituted and unsubstituted phenyl rings have been also observed for short arm bis-glycosylated calix[4]arenes reported in ref 2c (see compounds **13** and **15**).

(34) (a) For a review of the use of force fields in molecular mechanics calculations applied to oligosaccharides, see: Imberty, A.; Pérez, S. *Chem. Rev.* **2000**, *100*, 4567. (b) For a recent discussion of the difficulties of studying these complex molecules at higher levels of theory, see: Callam, C. S.; Singer, S. J.; Lowary, T. L.; Hadad, C. M. *J. Am. Chem. Soc.* **2001**, *123*, 11743.

TABLE 2. Relative Energies, Dipole Moments, and Hydrogen Bonding of Calixsugars.

compd	$E_{far} - E_{close}$[a] (kcal mol^{-1})	dipole moment[b] (Debyes)	transannular[c] hydrogen bonds	angles[d]
5			2	81.1, 145.3
6			4 (+ 1 intra)	94.0, 138.4
7			6 (+ 1 intra)	92.5, 140.7
8			1 (to ether bridge)	70.5, 153.4
close-**15**	6.99	1.61	1	82.6, 146.6
far-**15**		3.10	0	84.2, 138.6
close-**16**	8.42	5.70	0	81.6, 147.8
far-**16**		4.59	0	87.7, 142.2
close-**17**	2.19	8.63	1	86.9, 144.3
far-**17**		4.02	0	87.4, 138.2
close-**18**	6.97	4.79	1	92.6, 137.3
far-**18**		3.58	0	93.8, 135.5
22			3	108.4, 130.6
23			4 (+ 1 intra)	89.6, 141.6
24			4	87.2, 144.6
close-**30**	1.84	2.22	N/A	79.1, 147.8
far-**30**		2.66	N/A	101.5, 131.3
close-**31**	7.94	2.35	N/A	85.9, 145.9
far-**31**		1.68	N/A	81.9, 147.8
close-**35**	4.40	1.41	2	87.2, 144.6
far-**35**		5.06	0	109.3, 130.2

[a] Calculated using the mole fractions of each contributing conformation (see text). [b]Calculated for the global minimum using the AM1 semiempirical method. [c]A hydrogen−oxygen distance of 2.5 Å or less and angular default values were used. [d]Dihedral angles of the planes of the aryl groups with a plane perpendicular to the C_2 axis of the calixarene.

Table 2 provides the calculated[36] energy differences between the *far* and *close* for **15**−**18** and **35** from the energy distributions derived from the conformational search as well as the number and nature of hydrogen bonds and the dipole moments calculated semiempirically by the AM1 method. All compounds are predicted to adopt mainly a *close* conformation. Even for the smallest energy difference in the case of **17**, if the reasonable assumption is made that entropy differences are relatively small, only 3% of the molecules are in the *far* conformation at 25 °C. In the gas phase for the bis-substituted calixsugars, preference for one flattened cone conformation over the other is the result of the interaction of several energy terms. First of all, given the plethora of hydroxyl groups, both inter- and intrasugar hydrogen bonding are possible. Second, nonbonding interactions of the substituents with themselves and with unsubstituted aryl groups of the calixarene core must be considered. Finally, in the absence of the stabilizing influences of neighboring calixsugars or solvent, any conformation that minimizes the dipole moment of the molecule will be favored.

In closing this section, it is worthwhile to discuss differences between the gas-phase calculation results which predict preference for the *close* conformations for the unprotected bis-substituted calixsugars and those obtained from ^{1}H NMR studies in deuterated methanol. In solution, it is reasonable to presume that methanol molecules cluster about the polar unprotected sugar moieties, effectively increasing the bulk and making the likely preferred conformations for both *close* and *far* those in which the tethered functions are directed outward, away from the cavity. Since unfavorable nonbonding interaction differences are minimized in these conformations, it is not surprising that the small energy differences found experimentally for **15**−**17** and **35** would diverge from the conclusions derived from gas-phase molecular mechanics calculations.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent[37] and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) and copper(II) triflate (white powder, 98% pure) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography[38] was performed on silica gel 60 (230−400 mesh). Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. In the ^{1}H NMR spectra reported below, the *n* and *m* values quoted in geminal or vicinal proton−proton coupling constants $J_{n,m}$ refer to the number of the corresponding sugar protons. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. High resolution (8500−9000) mass spectra were acquired in the mass range *m*/*z* 100−1500 using a Qstar instrument (Applied Biosystem) with electrospray ionization in positive ion TOF mode. The internal standard used for calibration was a mixture of cesium iodide and a known peptide producing two peaks at *m*/*z* 132.9054 and 829.5398. Since the elemental analyses of calixarenes are very often uncorrected[2b,c,39] (found carbon values considerably lower than the calculated ones), the identity of the following new compounds were established by MS and NMR analyses. Ethylthio glucopyranoside **2**[40] and mannopyranoside **3**[41] were synthesized as described for the preparation of the galactoside **1**.[2c] Calixarene derivatives **4**[2c], **12**,[25] **19**,[26] **28**,[19a] **36**[2c] and phosphonium salts **25**,[42] **26**,[43] **27**[44] were prepared as reported. The synthesis of calixsugars **5** and **8** has been already described by us.[2c]

5,11,17,23-Tetrakis-[(β-D-glucopyranosyl)oxymethyl]-25,26,27,28-tetrapropoxy-calix[4]arene (6). A solution of

(35) (a) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165. (b) Botta, B.; Di Giovanni, M. C.; Delle Monache, G.; De Rosa, M. C.; Gacs-Baitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, *59*, 1532. (c) Botta, B.; Delle Monache, G.; Salvatore, P.; Gasparrini, F.; Villani, C.; Botta, M.; Corelli, F.; Tafi, A.; Gacs-Baitz, E.; Santini, A.; Carvalho, C. F.; Misiti, D. *J. Org. Chem.* **1997**, *62*, 932. (d) Botta, B.; Delle Monache, G.; De Rosa, M. C.; Seri, C.; Benedetti, E.; Iacovino, R.; Botta, M.; Corelli, F.; Masignani, V.; Tafi, A.; Gacs-Baitz, E.; Santini, A.; Misiti, D. *J. Org. Chem.* **1997**, *62*, 1788. (e) Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511. (f) Banks, H. D.; Dondoni, A.; Kleban, M.; Marra, A. *Chirality* **2002**, *14*, 173.

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(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(39) (a) Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790. (b) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.

(40) Wetgand, F.; Ziemann, H. *Justus Liebigs Ann. Chem.* **1962**, *657*, 179.

(41) Sarbania, S.; Roy, N. *Ind. J. Chem. B* **1998**, *37*, 252.

(42) Secrist III, J. A.; Wu, S.-R. *J. Org. Chem.* **1977**, *42*, 4084.

(43) Secrist III, J. A.; Wu, S.-R. *J. Org. Chem.* **1979**, *44*, 1434.

(44) Dondoni, A.; Marra, A.; Massi. A. *Tetrahedron* **1998**, *54*, 2827.

tetrol **4** (427 mg, 0.60 mmol) and thioglycoside **2** (770 mg, 1.20 mmol) in anhydrous CH_2Cl_2 (10 mL) was slowly diluted with anhydrous CH_3CN (20 mL) at room temperature and then treated with activated 4-Å powdered molecular sieves (1.20 g) and, after 15 min, copper(II) triflate (430 mg, 1.20 mmol). Two portions of both thioglycoside **2** and copper(II) triflate (1.20 mmol each) were added to the reaction mixture after 30 and 60 min. Stirring was continued at room temperature for an additional 60 min, and then the mixture was diluted with an excess of Et_3N and CH_2Cl_2, filtered through a pad of Celite, and concentrated. The residue was eluted from a short column (4 × 10 cm) of silica gel with 2:1 cyclohexane−AcOEt to remove the copper salts and unreacted **4**. The crude mixture was treated with freshly prepared 0.1 M solution of CH_3ONa in CH_3OH (50 mL) at room-temperature overnight and then neutralized with acetic acid and concentrated. The residue was eluted from a column of Sephadex LH-20 (3 × 90 cm) with 1:1 CH_2Cl_2−CH_3OH to give first **9** (154 mg, 25%) slightly contaminated by uncharacterized byproducts. An analytical sample of the corresponding peracetate **9Ac** was obtained by acetylation (1:1 acetic anhydride−pyridine) and column chromatography on silica gel (1:1 cyclohexane−AcOEt): $[\alpha]_D$ −25 (*c* 1.1, $CHCl_3$). ^{1}H NMR (CD_2Cl_4, 120 °C): δ 0.94 and 1.18 (2 t, J = 7.3 Hz, 12 H, 4 $OCH_2CH_2CH_3$), 1.84−1.94 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.02, 2.06, and 2.13 (3 s, 24 H, 8 Ac), 3.15 (d, 4 H, J = 13.2 Hz, 4 H_{eq} of $ArCH_2Ar$), 3.74 (t, 4 H, J = 6.5 Hz, 2 $OCH_2CH_2CH_3$), 3.83 (ddd, 2 H, $J_{4,5}$ = 9.5, $J_{5,6a}$ = 2.8, $J_{5,6b}$ = 5.0 Hz, 2 H-5), 3.99−4.04 (m, 4 H, 2 $OCH_2CH_2CH_3$), 4.11 and 4.20 (2 d, 4 H, J = 12.5 Hz, $ArCH_2OCH_2Ar$), 4.26 (dd, 2 H, $J_{6a,6b}$ = 12.0 Hz, 2 H-6a), 4.34 (dd, 2 H, 2 H-6b), 4.51 (d, 2 H, J = 13.2 Hz, 2 H_{ax} of $ArCH_2Ar$), 4.52 (d, 2 H, J = 13.2 Hz, 2 H_{ax} of $ArCH_2Ar$), 4.77 and 4.96 (2 d, 4 H, J = 11.7 Hz, 2 $ArCH_2O$), 4.78 (d, 2 H, $J_{1,2}$ = 7.9 Hz, 2 H-1), 5.12 (dd, 2 H, $J_{3,4}$ = 9.5 Hz, 2 H-4), 5.13 (dd, 2 H, $J_{2,3}$ = 9.3 Hz, 2 H-2), 5.37 (dd, 2 H, 2 H-3), 5.82 and 5.85 (2 d, 4 H, J = 2.0 Hz, Ar), 7.11 and 7.15 (2 d, 4 H, J = 2.0 Hz, Ar). MALDI-TOF MS (1355.5): 1378.3 (M + Na), 1394.5 (M + K).

Eluted second was **6** (285 mg, 35%) as a syrup ca. 95% pure by ^{1}H NMR analysis. An analytical sample of **6** was obtained by acetylation (1:1 acetic anhydride−pyridine), column chromatography on silica gel (2:1 AcOEt−cyclohexane), and transesterification (CH_3ONa−CH_3OH): $[\alpha]_D$ −47 (*c* 0.5, CH_3OH). ^{1}H NMR (CD_3OD) selected data: δ 1.01 (t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.90−1.97 (m, 8 H, 4 $OCH_2CH_2CH_3$), 3.15 and 4.44 (2 d, 8 H, J = 13.4 Hz, 4 $ArCH_2Ar$), 4.27 (d, 4 H, $J_{1,2}$ = 7.7 Hz, 4 H-1), 6.72 (s, 8 H, Ar). ^{1}H NMR (DMSO-d_6) selected data: δ 0.96 (t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 3.16 and 4.33 (2 d, 8 H, J = 13.2 Hz, 4 $ArCH_2Ar$), 3.48 (dd, 4 H, $J_{5,6a}$ = 4.7, $J_{6a,6b}$ = 11.5 Hz, 4 H-6a), 3.66 (dd, 4 H, $J_{5,6b}$ = 1.0 Hz, 4 H-6b), 3.79 (t, 8 H, J = 7.4 Hz, 4 $OCH_2CH_2CH_3$), 4.12 (d, 4 H, $J_{1,2}$ = 7.8 Hz, 4 H-1), 4.16 and 4.46 (2 d, 8 H, J = 11.2 Hz, 4 $ArCH_2O$), 6.66 and 6.67 (2 s, 8 H, Ar). ^{13}C NMR (DMSO-d_6): δ 9.8 ($OCH_2CH_2CH_3$), 23.4 ($OCH_2CH_2CH_3$), 30.9 ($ArCH_2Ar$), 61.9 (C-6), 70.8, 74.1, 77.0 ($OCH_2CH_2CH_3$), 101.5 (C-1), 129.1, 130.9, 135.1, 156.7. ESI-TOF HRMS. Calcd for $C_{136}H_{193}KO_{56}$ (M_2 + H^+ + K^+): *m*/*z* 700.29016; found: *m*/*z* 700.2933.

5,11,17,23-Tetrakis-[(α-D-mannopyranosyl)oxymethyl]-25,26,27,28-tetrapropoxy-calix[4]arene (7). Tetrol **4** (285 mg, 0.40 mmol) was glycosylated with **3** as described for the preparation of **6** to give, after column chromatography on Sephadex LH-20 (1:1 CH_2Cl_2−CH_3OH), first **10** (115 mg, 28%) slightly contaminated by uncharacterized byproducts. An analytical sample of the corresponding peracetate **10Ac** was obtained by acetylation (1:1 acetic anhydride−pyridine) and column chromatography on silica gel (1:1 cyclohexane−AcOEt): $[\alpha]_D$ +31 (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 0.85 and 1.12 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.77−1.91 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.00, 2.06, 2.16, and 2.17 (4 s, 24 H, 8 Ac), 3.12 and 4.43 (2 d, 8 H, J = 13.4 Hz, 4 $ArCH_2Ar$), 3.64 (t, 4 H, J = 6.6 Hz, 2 $OCH_2CH_2CH_3$), 3.90−3.96 (m, 4 H, 2 $OCH_2CH_2CH_3$), 4.10−4.15 (m, 4 H), 4.34−4.35 (m, 6 H), 4.68 and 4.83 (2 d, 4 H, J = 11.7 Hz, 2 $ArCH_2O$), 5.03 (d, 2 H, $J_{1,2}$ = 1.6 Hz, 2 H-1), 5.33 (dd, 2 H, $J_{3,4}$ = 10.0, $J_{4,5}$ = 9.5 Hz, 2 H-4), 5.39 (dd, 2 H, $J_{2,3}$ = 3.5 Hz, 2 H-2), 5.49 (dd, 2 H, 2 H-3), 5.50−5.72 and 5.80−6.03 (m, 4 H, Ar), 7.09 and 7.13 (2 d, 4 H, J = 1.7 Hz, Ar). ^{13}C NMR: δ 9.8 and 10.9 ($OCH_2CH_2CH_3$), 20.7, 20.8, 20.9, 23.0, and 23.5 ($OCH_2CH_2CH_3$), 31.0 ($ArCH_2Ar$), 62.5 (C-6), 66.3, 68.6, 69.3, 69.7, 76.3 ($OCH_2CH_2CH_3$), 96.3 (C-1), 127.4, 128.8, 129.6, 133.3, 137.7, 154.7, 169.8, 169.9, 170.1, 170.7. MALDI-TOF MS (1355.5): 1377.9 (M + Na), 1394.2 (M + K).

Eluted second was **7** (170 mg, 31%) as a syrup ca. 95% pure by ^{1}H NMR analysis. An analytical sample of **7** was obtained by acetylation (1:1 acetic anhydride−pyridine), column chromatography on silica gel (2:1 AcOEt−cyclohexane), and transesterification (CH_3ONa−CH_3OH): $[\alpha]_D$ +44 (*c* 0.5, CH_3OH). ^{1}H NMR (CD_3OD): δ 1.05 (t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.91−2.03 (m, 8 H, 4 $OCH_2CH_2CH_3$), 3.18 and 4.48 (2 d, 8 H, J = 13.4 Hz, 4 $ArCH_2Ar$), 3.56 (ddd, 4 H, $J_{4,5}$ = 9.5, $J_{5,6a}$ = 5.5, $J_{5,6b}$ = 2.0 Hz, 4 H-5), 3.62 (dd, 4 H, $J_{3,4}$ = 9.5 Hz, 4 H-4), 3.72 (dd, 4 H, $J_{2,3}$ = 3.4 Hz, 4 H-3), 3.73 (dd, 4 H, $J_{6a,6b}$ = 12.4 Hz, 4 H-6a), 3.80 (dd, $J_{1,2}$ = 1.7 Hz, 4 H-2), 3.87 (dd, 4 H, 4 H-6b), 3.88 (t, 8 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 4.24 and 4.43 (2 d, 8 H, J = 11.7 Hz, 4 $ArCH_2O$), 4.74 (d, 4 H, 4 H-1), 6.63 and 6.69 (2 d, 8 H, J = 1.7 Hz, Ar). ^{13}C NMR (CD_3OD): δ 9.8 ($OCH_2CH_2CH_3$), 23.4 ($OCH_2CH_2CH_3$), 30.8 ($ArCH_2Ar$), 61.8 (C-6), 67.6, 68.8, 71.2, 71.6, 73.7, 77.0, 99.2 (C-1), 128.3, 131.2, 135.0, 156.5. ESI-TOF HRMS. Calcd for $C_{136}H_{193}KO_{56}$ (M_2 + H^+ + K^+): *m*/*z* 700.29016; found: *m*/*z* 700.2904.

5,17-Diallyl-25,26,27,28-tetrapropoxy-calix[4]arene (13). To a stirred solution of tetrol **12** (2.52 g, 5.0 mmol) in DMF (50 mL) were added NaH (1.60 g, 40.0 mmol, of a 60% dispersion in oil) and, after 10 min, 1-iodopropane (3.91 mL, 40.0 mmol). The mixture was stirred at room-temperature overnight and then diluted with CH_3OH (2 mL), and, after 30 min, 1 M HCl (50 mL) was added to precipitate crude **13**. The solid was filtered, washed with H_2O and pentane, and dried. The residue was crystallized with CH_2Cl_2−CH_3OH to give **13** (2.96 g, 88%) as a white solid; mp 154−155 °C (CH_2Cl_2−CH_3OH); ^{1}H NMR: δ 0.96 and 1.06 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.86−2.02 (m, 8 H, 4 $OCH_2CH_2CH_3$), 3.13 and 4.44 (2 d, 8 H, J = 13.1 Hz, 4 $ArCH_2Ar$), 3.22 (ddd, 8 H, J = 1.4, 1.7, 6.8 Hz, 4 $CH_2CH{=}CH_2$), 3.79 (t, 4 H, J = 7.3 Hz, 2 $OCH_2CH_2CH_3$), 3.88−3.94 (m, 4 H, 2 $OCH_2CH_2CH_3$), 4.99−5.06 (m, 4 H, 2 $CH_2CH{=}CH_2$), 5.87−6.01 (m, 2 H, 2 $CH_2CH{=}CH_2$), 6.38−6.48 (m, 6 H, Ar), 6.67 (s, 4 H, Ar). ^{13}C NMR: δ 10.3, 23.2, 31.0, 31.5, 34.2, 62.6, 76.8, 121.9, 128.0, 128.2, 134.7, 134.8, 135.0, 154.8, 156.4. MALDI-TOF MS (673.0): 696.1 (M + Na), 711.9 (M + K).

5,17-Bis(3-hydroxypropyl)-25,26,27,28-tetrapropoxy-calix[4]arene (14). To a cooled (0 °C), stirred solution of **13** (2.02 g, 3.0 mmol) in anhydrous THF (30 mL) was added dropwise 9-boracyclo[3.3.1]nonane (48 mL, 24.0 mmol, of a 0.5 M solution in hexane). The solution was allowed to reach room temperature in 30 min and then cooled to 0 °C and slowly diluted with 10 M NaOH (3.0 mL) and 30% H_2O_2 (9.0 mL). The mixture was stirred at room temperature for 30 min and then warmed to 40 °C. Stirring was continued for an additional 2 h, and then the mixture was cooled to room temperature, diluted with 1 M phosphate buffer at pH 7 (30 mL), concentrated to remove the organic solvents, and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 15:1 CH_2Cl_2−acetone to give **14** (1.49 g, 70%) as a white solid; mp 133−135 °C (CH_3OH); ^{1}H NMR: δ 0.98 and 1.00 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.57−1.70 (m, 4 H, 2 $CH_2CH_2CH_2OH$), 1.88−1.96 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.40 (t, 4 H, J = 7.8 Hz, 2 $CH_2CH_2CH_2OH$), 3.10 and 4.42 (2 d, 8 H, J = 13.2 Hz, 4 $ArCH_2Ar$), 3.57−3.62 (m, 4 H, 2 $CH_2CH_2CH_2OH$), 3.82 and 3.84 (2 t, 8 H, J = 7.1 Hz, 4 $OCH_2CH_2CH_3$), 6.45−6.60 (m, 6 H, Ar), 6.52 (s, 4 H, Ar). ^{13}C NMR: δ 10.3, 23.2, 31.0, 31.5, 34.2, 62.6, 76.8, 121.9, 128.0,

128.2, 134.7, 134.8, 135.0, 154.8, 156.4. MALDI-TOF MS (709.0): 732.0 (M + Na), 748.3 (M + K).

5,17-Bis[3-(β-D-galactopyranosyloxy)propyl]-25,26,27,-28-tetrapropoxy-calix[4]arene (15). A solution of diol **14** (212 mg, 0.30 mmol) and thioglycoside **1** (577 mg, 0.90 mmol) in anhydrous CH_2Cl_2 (10 mL) was slowly diluted with anhydrous CH_3CN (20 mL) at room temperature and then treated with activated 4-Å powdered molecular sieves (0.60 g) and, after 15 min, copper(II) triflate (326 mg, 0.90 mmol). Stirring was continued at room temperature for an additional 2 h, and then the mixture was diluted with an excess of Et_3N and CH_2Cl_2, filtered through a pad of Celite, and concentrated. The residue was eluted from a short column (2 × 10 cm) of silica gel with 2:1 cyclohexane−AcOEt to remove the copper salts. The crude mixture was treated with freshly prepared 0.1 M solution of CH_3ONa in CH_3OH (30 mL) at room-temperature overnight and then neutralized with acetic acid and concentrated. The residue was eluted from a column of Sephadex LH-20 (2 × 80 cm) with 1:1 CH_2Cl_2−CH_3OH to give **15** (257 mg, 83%) as an amorphous solid; $[\alpha]_D$ −5.5 (*c* 0.8, CH_3OH). ^1H NMR (CD_3OD): δ 1.04 and 1.09 (2 t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.75−1.85 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 1.92−2.06 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.48 (t, 4 H, *J* = 7.5 Hz, 2 $ArCH_2CH_2CH_2CH_2$), 3.12 and 4.48 (2 d, 8 H, *J* = 13.0 Hz, 4 $ArCH_2Ar$), 3.48−3.61 (m, 8 H), 3.78−3.94 (m, 16 H), 4.24 (d, 2 H, $J_{1,2}$ = 7.3 Hz, 2 H-1), 6.47−6.55 (m, 6 H, Ar), 6.64 (s, 4 H, Ar). ^{13}C NMR (CD_3OD): δ 10.7, 10.9, 24.1, 24.2, 31.8, 32.3, 32.6, 62.0, 69.9, 70.2, 72.3, 74.6, 76.0, 77.6, 104.7, 122.8, 128.8, 129.2, 135.6, 136.0, 156.0, 157.1. ESI-TOF HRMS. Calcd for $C_{58}H_{81}O_{16}$ (M + H^+): *m*/*z* 1033.55250; found: *m*/*z* 1033.5537.

5,17-Bis[3-(β-D-glucopyranosyloxy)propyl]-25,26,27,28-tetrapropoxy-calix[4]arene (16). Diol **14** (284 mg, 0.40 mmol) was glycosylated with **2** and debenzoylated as described for the preparation of **15**. The crude product was eluted from a column of Sephadex LH-20 (2 × 80 cm) with 1:1 CH_2Cl_2−CH_3OH to give first **18** (52 mg, 15%) as a white solid; mp 181−182 °C (CH_3OH-H_2O); $[\alpha]_D$ −8 (*c* 1.0, CH_3OH). ^1H NMR (CD_3OD): δ 1.63−1.85 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 1.87−2.08 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.37−2.56 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 3.12 and 4.45 (2 d, 8 H, *J* = 13.0 Hz, 4 $ArCH_2Ar$), 3.21 (dd, 1 H, $J_{1,2}$ = 7.7, $J_{2,3}$ = 9.1 Hz, H-2), 3.26−3.43 (m, 3 H, H-3, H-4, H-5), 3.44−3.58 (m, 3 H), 3.70 (dd, 1 H, $J_{5,6a}$ = 5.2, $J_{6a,6b}$ = 11.8 Hz, H-6b), 3.79−3.95 (m, 10 H), 4.26 (d, 1 H, H-1), 6.42−6.64 (m, 10 H, Ar). ^{13}C NMR (CD_3OD): δ 10.7, 11.0, 24.4, 24.5, 31.9, 32.5, 32.9, 35.7, 62.4, 62.7, 70.2, 71.6, 75.1, 77.8, 78.1, 104.5, 123.0, 129.0, 129.4, 135.8, 136.3, 136.4, 156.2, 157.4. ESI-TOF HRMS. Calcd for $C_{52}H_{70}KO_{11}$ (M + K^+): *m*/*z* 909.45551; found: *m*/*z* 909.4571.

Eluted second was **16** (330 mg, 80%) as a white solid; mp 167−169 °C (CH_3OH-H_2O); $[\alpha]_D$ −11.7 (*c* 1.0, CH_3OH). ^1H NMR (CD_3OD): δ 1.02 and 1.07 (2 t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.72−1.84 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 1.89−2.06 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.46 (t, 4 H, *J* = 7.5 Hz, 2 $ArCH_2CH_2CH_2CH_2$), 3.11 and 4.46 (2 d, 8 H, *J* = 13.0 Hz, 4 $ArCH_2Ar$), 3.22 (dd, 2 H, $J_{1,2}$ = 7.8, $J_{2,3}$ = 8.8 Hz, 2 H-2), 3.26−3.43 (m, 6 H, 2 H-3, 2 H-4, 2 H-5), 3.45−3.56 (m, 2 H, $ArCH_2CH_2CH_2CH_2$), 3.70 (dd, 2 H, $J_{5,6a}$ = 5.0, $J_{6a,6b}$ = 11.7 Hz, 2 H-6b), 3.79−3.95 (m, 12 H), 4.27 (d, 2 H, 2 H-1), 6.45−6.56 (m, 6 H, Ar), 6.64 (s, 4 H, Ar). ^{13}C NMR (CD_3OD): δ 10.8, 24.4, 31.9, 32.6, 32.9, 62.8, 70.2, 71.7, 75.1, 77.9, 78.1, 104.5, 123.0, 129.0, 129.5, 135.8, 136.3, 136.5, 156.3, 157.4. ESI-TOF HRMS. Calcd for $C_{58}H_{80}NaO_{16}$ (M + Na^+): *m*/*z* 1055.53442; found: *m*/*z* 1055.5339.

5,17-Bis[3-(α-D-mannopyranosyloxy)propyl]-25,26,27,-28-tetrapropoxy-calix[4]arene (17). Diol **14** (212 mg, 0.30 mmol) was glycosylated with **3** and debenzoylated as described for the preparation of **15** to give **17** (235 mg, 76%) as a white solid; mp 220−221 °C (CH_3OH-H_2O); $[\alpha]_D$ +34.7 (*c* 1.0, CH_3OH). ^1H NMR (CD_3OD): δ 1.06 and 1.08 (2 t, 8 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.68−1.77 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 1.92−2.06 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.35−2.46 (m, 4 H, 2 $ArCH_2CH_2CH_2CH_2$), 3.13 and 4.47 (2 d, 8 H, *J* = 12.5 Hz, 4 $ArCH_2Ar$), 3.56 (ddd, 2 H, $J_{4,5}$ = 9.3, $J_{5,6a}$ = 5.4, $J_{5,6b}$ = 2.6 Hz, 2 H-5), 3.65 (dd, 2 H, $J_{3,4}$ = 9.5 Hz, 2 H-4), 3.74 (dd, 2 H, $J_{6a,6b}$ = 11.7 Hz, 2 H-6a), 3.75 (dd, 2 H, $J_{2,3}$ = 3.3 Hz, 2 H-3), 3.83 (dd, 2 H, 2 H-6b), 3.84 (dd, 2 H, $J_{1,2}$ = 1.7 Hz, 2 H-2), 4.73 (d, 2 H, 2 H-1), 6.52 (s, 4 H, Ar), 6.55−6.62 (m, 6 H, Ar). ^{13}C NMR (CD_3OD): δ 10.9, 24.5, 31.9, 32.6, 32.7, 62.9, 67.7, 68.5, 72.3, 72.7, 74.5, 77.8, 77.9, 101.7, 123.1, 129.2, 129.3, 136.0, 136.1, 156.1, 157.7. ESI-TOF HRMS. Calcd for $C_{58}H_{80}NaO_{16}$ (M + Na^+): *m*/*z* 1055.53442; found: *m*/*z* 1055.5337.

5,11,17,23-Tetraallyl-25,26,27,28-tetrapropoxy-calix[4]-arene (20). To a stirred solution of tetrol **19** (1.75 g, 3.0 mmol) in DMF (30 mL) were added NaH (0.96 g, 24.0 mmol, of a 60% dispersion in oil) and, after 10 min, 1-iodopropane (2.34 mL, 24.0 mmol). The mixture was stirred at room-temperature overnight and then diluted with CH_3OH (2 mL) and, after 30 min, concentrated. The residue was diluted with 1 M phosphate buffer at pH 7 (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 9:1 cyclohexane−AcOEt to give **20** (2.01 g, 89%) as a white solid; mp 125−126 °C (CH_2Cl_2−CH_3OH). ^1H NMR: δ 1.01 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.90−2.02 (m, 8 H, 4 $OCH_2CH_2CH_3$), 3.09 (ddd, 8 H, *J* = 1.5, 1.8, 6.5 Hz, 4 $CH_2CH{=}CH_2$), 3.10 and 4.42 (2 d, 8 H, *J* = 13.0 Hz, $ArCH_2Ar$), 3.81−3.87 (m, 8 H, 4 $OCH_2CH_2CH_3$), 4.93 (ddt, 4 H, *J* = 1.8, 1.8, 17.2 Hz, H_{trans} of $CH_2CH{=}CH_2$), 4.99 (ddt, 4 H, *J* = 1.5, 1.8, 10.2 Hz, H_{cis} of $CH_2CH{=}CH_2$), 5.84 (ddt, 4 H, *J* = 6.5, 10.2, 17.2 Hz, 4 $CH_2CH{=}CH_2$), 6.50 (s, 8 H, Ar). ^{13}C NMR: δ 10.3, 23.2, 30.9, 39.4, 76.8, 114.8, 128.2, 132.8, 134.7, 138.3, 154.8. MALDI-TOF MS (753.1): 776.3 (M + Na), 792.1 (M + K).

5,11,17,23-Tetrakis(3-hydroxypropyl)-25,26,27,28-tetrapropoxy-calix[4]arene (21). The tetraallyl derivative **20** (1.51 g, 2.0 mmol) was treated with 9-BBN (64 mL, 32.0 mmol) as described for the preparation of **14**. The crude product was crystallized from CH_3CN to give **21** (1.16 g, 70%) as a white solid; mp 175−176 °C (CH_3CN); ^1H NMR: δ 1.02 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.67−1.77 (m, 8 H, 4 $CH_2CH_2CH_2OH$), 1.93−2.06 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.41 (t, 8 H, *J* = 7.5 Hz, 4 $CH_2CH_2CH_2OH$), 2.82 (s, 4 H, 4 OH), 3.10 and 4.42 (2 d, 8 H, *J* = 13.0 Hz, $ArCH_2Ar$), 3.56 (t, 8 H, *J* = 6.8 Hz, 4 $CH_2CH_2CH_2OH$), 3.80−3.86 (m, 8 H, 4 $OCH_2CH_2CH_3$), 6.56 (s, 8 H, Ar). ^{13}C NMR: δ 10.3, 23.2, 30.7, 31.3, 33.9, 62.2, 77.0, 127.9, 134.7, 134.8, 154.4. MALDI-TOF MS (825.1): 848.4 (M + Na), 864.2 (M + K).

5,11,17,23-Tetrakis[3-(β-D-galactopyranosyloxy)propyl]-25,26,27,28-tetrapropoxy-calix[4]arene (22). A solution of tetrol **21** (165 mg, 0.20 mmol) and thioglycoside **1** (384 mg, 0.60 mmol) in anhydrous CH_2Cl_2 (5 mL) was slowly diluted with anhydrous CH_3CN (10 mL) at room temperature and then treated with activated 4-Å powdered molecular sieves (0.80 g) and, after 15 min, copper(II) triflate (218 mg, 0.60 mmol). The mixture was stirred at room temperature for 1 h, and then thioglycoside **1** (0.60 mmol) and copper(II) triflate (0.60 mmol) were added. Stirring was continued for an additional 1 h, and then the mixture was diluted with an excess of Et_3N and CH_2Cl_2, filtered through a pad of Celite, and concentrated. The residue was eluted from a short column (2 × 10 cm) of silica gel with 2:1 cyclohexane−AcOEt to remove the copper salts. The crude mixture was treated with freshly prepared 0.1 M solution of CH_3ONa in CH_3OH (20 mL) at room-temperature overnight and then neutralized with acetic acid and concentrated. The residue was eluted from a column of Sephadex LH-20 (2 × 80 cm) with 1:1 CH_2Cl_2−CH_3OH to give **22** (220 mg, 75%) as an amorphous solid; $[\alpha]_D$ −10 (*c* 0.6, CH_3OH). ^1H NMR (CD_3OD): δ 1.02 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.66−1.76 (m, 8 H, 4 $ArCH_2CH_2CH_2CH_2$), 1.88−2.01 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.37 (t, 8 H, *J* = 7.5 Hz, 4 $ArCH_2CH_2CH_2CH_2$), 3.05 and 4.40 (2 d, 8 H, *J* = 13.0 Hz, $ArCH_2Ar$), 3.45−3.57 and 3.72−3.88 (2 m, 40 H), 4.21 (d, 4 H, $J_{1,2}$ = 7.3 Hz, 4 H-1), 6.50 (s, 8 H, Ar). ESI-TOF HRMS. Calcd for $C_{152}H_{225}KO_{56}$ (M_2 + H^+ + K^+): *m*/*z* 756.35275; found: *m*/*z* 756.3501.

5,11,17,23-Tetrakis[3-(β-D-glucopyranosyloxy)propyl]-25,26,27,28-tetrapropoxy-calix[4]arene (23). The tetrol **21** (165 mg, 0.20 mmol) was glycosylated with **2** and debenzoylated as described for the preparation of **22** to give **23** (183 mg, 62%) as a white solid; mp 167 °C (softening), 205 °C (dec); $[\alpha]_D$ −13.7 (*c* 1.6, CH_3OH). ^1H NMR (CD_3OD): δ 1.04 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.68−1.80 (m, 8 H, 4 $ArCH_2CH_2CH_2$), 1.91−2.04 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.40 (t, 8 H, *J* = 7.5 Hz, 4 $ArCH_2CH_2CH_2$), 3.08 and 4.43 (2 d, 8 H, *J* = 12.9 Hz, $ArCH_2Ar$), 3.23 (dd, 4 H, $J_{1,2}$ = 7.8, $J_{2,3}$ = 9.2 Hz, 4 H-2), 3.28−3.44 (m, 12 H, 4 H-3, 4 H-4, 4 H-5), 3.46−3.57 (m, 4 H, $ArCH_2CH_2CH_2$), 3.71 (dd, 4 H, $J_{5,6a}$ = 5.1, $J_{6a,6b}$ = 6.9 Hz, 4 H-6a), 3.80−3.94 (m, 16 H), 4.28 (d, 4 H, 4 H-1), 6.58 (s, 8 H, Ar). ^{13}C NMR (CD_3OD): δ 10.9, 24.5, 31.9, 32.7, 32.9, 62.8, 70.2, 71.6, 75.1, 77.9, 78.1, 104.4, 129.3, 135.9, 136.4, 155.9. ESI-TOF HRMS. Calcd for $C_{152}H_{225}KO_{56}$ ($M_2 + H^+ + K^+$): *m*/*z* 756.35275; found: *m*/*z* 756.3531.

5,11,17,23-Tetrakis[3-(α-D-mannopyranosyloxy)propyl]-25,26,27,28-tetrapropoxy-calix[4]arene (24). The tetrol **21** (165 mg, 0.20 mmol) was glycosylated with **3** and debenzoylated as described for the preparation of **22** to give **24** (171 mg, 58%) as a white solid; mp 205 °C (dec); $[\alpha]_D$ +16.8 (*c* 1.0, CH_3OH). ^1H NMR (CD_3OD): δ 1.05 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.65−1.78 (m, 8 H, 4 $ArCH_2CH_2CH_2$), 1.90−2.05 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.31−2.42 (m, 8 H, 4 $ArCH_2CH_2CH_2$), 3.10 and 4.44 (2 d, 8 H, *J* = 12.8 Hz, $ArCH_2Ar$), 3.30−3.40 (m, 4 H), 3.52−3.90 (m, 36 H), 4.76 (d, 4 H, $J_{1,2}$ = 1.8 Hz, 4 H-1), 6.56 (s, 8 H, Ar). ^{13}C NMR (CD_3OD): δ 10.9, 24.2, 24.4, 31.9, 32.8, 62.8, 67.8, 68.5, 72.2, 72.7, 74.5, 77.9, 101.6, 129.2, 135.9, 136.1, 155.9. ESI-TOF HRMS. Calcd for $C_{152}H_{225}KO_{56}$ ($M_2 + H^+ + K^+$): *m*/*z* 756.35275; found: *m*/*z* 756.3526.

5,11,17,23-Tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)propyl]-25,26,27,28-tetrapropoxy-calix[4]arene (24Ac). For NMR studies a sample of **24** was acetylated at room temperature in 1:1 acetic anhydride−pyridine, concentrated, and used without further purifications. ^1H NMR selected data: δ 1.00 (t, 12 H, *J* = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 2.02, 2.08, 2.10, and 2.18 (4 s, 48 H, 16 Ac), 3.06 and 4.40 (2 d, 8 H, *J* = 13.0 Hz, $ArCH_2Ar$), 3.98 (dd, 4 H, $J_{4,5}$ = 9.5, $J_{5,6a}$ = 2.4, $J_{5,6b}$ = 5.0 Hz, 4 H-5), 4.07 (dd, 4 H, $J_{6a,6b}$ = 12.2 Hz, 4 H-6a), 4.30 (dd, 4 H, 4 H-6b), 4.80 (d, 4 H, $J_{1,2}$ = 1.8 Hz, 4 H-1), 5.25 (dd, 4 H, $J_{2,3}$ = 3.2 Hz, 4 H-2), 5.30 (dd, 4 H, $J_{3,4}$ = 10.0 Hz, 4 H-4), 5.36 (dd, 4 H, 4 H-3), 6.44 (s, 8 H, Ar).

5,17-Bis(2-formylethyl)-25,26,27,28-tetrapropoxy-calix[4]arene (29). A mixture of diol **14** (1.42 g, 2.0 mmol), activated 4-Å powdered molecular sieves (2.0 g), and anhydrous CH_2Cl_2 (50 mL) was stirred at room temperature for 15 min, and then pyridinium chlorochromate (1.08 g, 5.0 mmol) was added. The suspension was stirred for 1 h, diluted with Et_2O (100 mL), stirred for an additional 10 min, filtered through a pad of silica gel (6 × 3 cm, d × h), and concentrated. The residue was eluted from a column of silica gel with 6:3:1 cyclohexane−CH_2Cl_2−Et_2O to give **29** (0.85 g, 60%) as a white solid; mp 187−188 °C (CH_2Cl_2-Et_2O). ^1H NMR: δ 0.98 and 1.00 (2 t, 12 H, *J* = 7.6 Hz, 4 $OCH_2CH_2CH_3$), 1.88−1.97 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.54−2.59 and 2.64−2.66 (2 m, 8 H, 2 $ArCH_2CH_2CHO$), 3.10 and 4.42 (2 d, 8 H, *J* = 13.2 Hz, $ArCH_2Ar$), 3.83 (t, 8 H, *J* = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 6.51 (s, 4 H, Ar), 6.53−6.56 (m, 6 H, Ar), 9.73 (s, 2 H, CHO). ^{13}C NMR: δ 10.2, 10.3, 23.2, 27.6, 30.9, 45.5, 76.7, 122.0, 127.9, 128.0, 133.1, 134.7, 135.2, 155.2, 156.3, 202.3. MALDI-TOF MS (705.0): 728.1 (M + Na), 744.0 (M + K).

5,17-Bis(methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-1,4-hexofuranosid-6-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (30). To a cooled (−50 °C), stirred mixture of **25** (690 mg, 1.20 mmol) and activated 4-Å powdered molecular sieves (1.2 g) in anhydrous THF (4 mL) and HMPA (2 mL) was added *n*-BuLi (750 μL, 1.20 mmol, of a 1.6 M solution in hexane) and, after 5 min, a solution of **28** (195 mg, 0.30 mmol) in anhydrous THF (2 mL). The mixture was allowed to reach −20 °C in 3 h and then was diluted with Et_2O (150 mL), filtered through a pad of Celite, washed with 1 M phosphate buffer at pH 7 (30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 1:1:1 cyclohexane−CH_2Cl_2−Et_2O (containing 0.3% of triethylamine) to give a *E*,*Z*-mixture of unsaturated calixsugars. A vigorously stirred mixture of the residue, 20% palladium hydroxide on carbon (100 mg), and AcOEt (10 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a positive pressure of hydrogen (4 bar) and then filtered through a plug of cotton and concentrated to give **30** (212 mg, 71%) as a white solid; mp 163−165 °C (acetone−H_2O); $[\alpha]_D$ −17 (*c* 1.2, $CHCl_3$). ^1H NMR: δ 0.94 and 1.08 (2 t, 12 H, *J* = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 1.35 and 1.50 (2 s, 12 H, $(CH_3)_2C$), 1.86−2.10 (m, 12 H, 4 H-5, 4 $OCH_2CH_2CH_3$), 2.58−2.71 (m, 4 H, 4 H-6), 3.10 and 4.43 (2 d, 8 H, *J* = 13.2 Hz, $ArCH_2Ar$), 3.35 (s, 6 H, 2 OCH_3), 3.74 (t, 4 H, *J* = 6.9 Hz, 2 $OCH_2CH_2CH_3$), 3.88−3.98 (m, 6 H, 2 $OCH_2CH_2CH_3$, 2 H-4), 4.56 (d, 2 H, $J_{2,3}$ = 5.9 Hz, 2 H-2), 4.64 (dd, 2 H, $J_{3,4}$ = 3.2 Hz, 2 H-3), 4.90 (s, 2 H, 2 H-1), 6.25−6.35 (m, 6 H, Ar), 6.80 (s, 4 H, Ar). ^{13}C NMR: δ 10.0 and 10.6 ($OCH_2CH_2CH_3$), 23.0 and 23.4 ($OCH_2CH_2CH_3$), 25.0 and 26.1 (Me_2C), 30.3, 31.0, and 31.1 ($ArCH_2Ar$, C-5, C-6), 54.4 (OCH_3), 76.5 and 76.8 ($OCH_2CH_2CH_3$), 79.1, 80.4, 85.2 (C-2, C-3, C-4), 106.9 (C-1), 112.3 (Me_2C), 121.9, 127.5, 128.4, 128.6, 133.8, 134.7, 135.9, 155.6, and 155.7 (Ar). MALDI-TOF MS (993.3): 1016.4 (M + Na), 1032.6 (M + K).

5,17-Bis(methyl 5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-1,4-octofuranosid-8-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (31). Dialdehyde **29** (141 mg, 0.20 mmol) was treated with **25** (460 mg, 0.80 mmol) and hydrogenated as described for the preparation of **30** to give **31** (136 mg, 65%) as a white solid; mp 162−163 °C (EtOH); $[\alpha]_D$ −21 (*c* 1.2, $CHCl_3$). ^1H NMR: δ 0.92 and 1.05 (2 t, 12 H, *J* = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 1.33 and 1.48 (2 s, 12 H, 2 $(CH_3)_2C$), 1.48−1.67 (m, 8 H, 4 H-6, 4 H-7), 1.73−1.81 (m, 4 H, 4 H-5), 1.86−1.98 (m, 8 H, 4 $OCH_2CH_2CH_3$), 2.49 (t, 4 H, *J* = 7.5 Hz, 4 H-8), 3.09 and 4.41 (2 d, 8 H, *J* = 13.2 Hz, $ArCH_2Ar$), 3.32 (s, 6 H, 2 OCH_3), 3.73 (t, 4 H, *J* = 7.0 Hz, 2 $OCH_2CH_2CH_3$), 3.85−3.94 (m, 6 H, 2 $OCH_2CH_2CH_3$, 2 H-4), 4.55 (d, 2 H, $J_{2,3}$ = 5.9 Hz, 2 H-2), 4.62 (dd, 2 H, $J_{3,4}$ = 3.3 Hz, 2 H-3), 4.86 (s, 2 H, 2 H-1), 6.27−6.38 (m, 6 H, Ar), 6.71 (s, 4 H, Ar). ^{13}C NMR: δ 10.0 and 10.6 ($OCH_2CH_2CH_3$), 23.0 and 23.4 ($OCH_2CH_2CH_3$), 25.1 and 26.2 (Me_2C), 26.0, 28.2, 31.8, and 35.2 (C-5, C-6, C-7, C-8), 31.0 ($ArCH_2Ar$), 54.4 (OCH_3), 76.5 and 76.7 ($OCH_2CH_2CH_3$), 79.9, 80.3, 85.2 (C-2, C-3, C-4), 106.9 (C-1), 112.2 (Me_2C), 127.5, 128.4, 134.0, 135.6, 135.7, 155.6, 155.7 (Ar). MALDI-TOF MS (1049.4): 1072.4 (M + Na), 1088.5 (M + K).

5,17-Bis(6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,5-heptopyranosid-7-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (32). Dialdehyde **28** (130 mg, 0.20 mmol) was treated with **26** (505 mg, 0.80 mmol) and hydrogenated as described for the preparation of **30** to give **32** (146 mg, 66%) as a white solid; mp 174−176 °C (CH_2Cl_2−CH_3OH); $[\alpha]_D$ −40 (*c* 1.2, $CHCl_3$). ^1H NMR: δ 0.89 and 1.06 (2 t, 12 H, *J* = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 1.33, 1.37, 1.42, and 1.50 (4 s, 24 H, 4 $(CH_3)_2C$), 1.84−2.11 (m, 12 H, 4 H-6, 4 $OCH_2CH_2CH_3$), 2.56−2.78 (m, 4 H, 4 H-7), 3.07 and 4.39 (2 d, 8 H, *J* = 13.2 Hz, $ArCH_2Ar$), 3.68−3.76 (m, 6 H, 2 $OCH_2CH_2CH_3$, 2 H-5), 3.89 (t, *J* = 8.0 Hz, 4 H, 2 $OCH_2CH_2CH_3$), 4.17 (dd, 2 H, $J_{3,4}$ = 7.9, $J_{4,5}$ = 1.7 Hz, 2 H-4), 4.30 (dd, 2 H, $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.2 Hz, 2 H-2), 4.60 (dd, 2 H, 2 H-3), 5.57 (d, 2 H, 2 H-1), 6.23−6.30 (m, 6 H, Ar), 6.78 and 6.83 (2 d, 4 H, *J* = 1.6 Hz, Ar). ^{13}C NMR: δ 9.9 and 10.7 ($OCH_2CH_2CH_3$), 23.0 and 23.4 ($OCH_2CH_2CH_3$), 24.4, 25.0, 25.8, and 26.1 (Me_2C), 31.0, 31.8 ($ArCH_2Ar$, C-6, C-7), 66.7, 70.6, 71.0, 72.8 (C-2, C-3, C-4, C-5), 76.4 and 76.8 ($OCH_2CH_2CH_3$), 96.3 (C-1), 108.3 and 109.0 (Me_2C), 122.0, 127.5, 127.6, 128.4, 129.0, 133.7, 134.7, 136.0, 155.5, and 155.7 (Ar). MALDI-TOF MS (1105.4): 1128.3 (M + Na), 1144.5 (M + K).

5,17-Bis(6,7,8,9-tetradeoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,5-nonopyranosid-9-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (33). Dialdehyde **29** (141 mg, 0.20 mmol) was treated with **26** (505 mg, 0.80 mmol) and hydrogenated as described for the preparation of **30** to give **33** (150 mg, 65%) as a white solid; mp 114−116 °C (CH_2Cl_2−CH_3OH); $[\alpha]_D$ −37.6 (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 0.92 and 1.08 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.35, 1.38, 1.50, and 1.54 (4 s, 24 H, 4 $(CH_3)_2C$), 1.55−2.02 (m, 20 H), 2.52 (t, 4 H, J = 7.5 Hz, 4 H-9), 3.10 and 4.42 (2 d, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.67−3.81 (m, 6 H, 2 $OCH_2CH_2CH_3$, 2 H-5), 3.91−3.96 (m, 4 H, 2 $OCH_2CH_2CH_3$), 4.17 (dd, 2 H, $J_{3,4}$ = 7.8, $J_{4,5}$ = 1.8 Hz, 2 H-4), 4.32 (dd, 2 H, $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.3 Hz, 2 H-2), 4.62 (dd, 2 H, 2 H-3), 5.57 (d, 2 H, 2 H-1), 6.23−6.26 (m, 4 H, Ar), 6.34 (dd, 2 H, J = 6.3, 8.5 Hz, Ar), 6.75 (s, 4 H, Ar). ^{13}C NMR: δ 9.9 and 10.6 ($OCH_2CH_2CH_3$), 23.4 and 24.4 ($OCH_2CH_2CH_3$), 24.9, 25.3, and 26.1 (Me_2C), 26.0, 29.9, 30.9, 31.6, and 35.2 ($ArCH_2Ar$, C-6, C-7, C-8, C-9), 67.2, 70.5, 70.9, and 72.8 (C-2, C-3, C-4, C-5), 76.4 and 76.7 ($OCH_2CH_2CH_3$), 96.6 (C-1), 108.2 and 108.9 (Me_2C), 121.9, 127.4, 128.4, 133.8, 135.7, 135.9, 155.4, and 155.5 (Ar). ESI-TOF HRMS. Calcd for $C_{70}H_{97}O_{14}$ ($M + H^+$): *m*/*z* 1161.68787; found: *m*/*z* 1161.6819.

5,17-Bis(5,9-anhydro-6,7,8,10-tetra-*O*-benzyl-1,2,3,4-tetradeoxy-D-*glycero*-L-*manno*-decitol-1-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (34). To a cooled (−50 °C), stirred mixture of **27** (278 mg, 0.30 mmol) and activated 4-Å powdered molecular sieves (0.6 g) in anhydrous THF (2 mL) and HMPA (1 mL) were added *n*-BuLi (190 μL, 0.30 mmol, of a 1.6 M solution in hexane) and, after 5 min, a solution of **29** (106 mg, 0.15 mmol) in anhydrous THF (1 mL). The mixture was allowed to reach −20 °C in 3 h and then was diluted with Et_2O (100 mL), filtered through a pad of Celite, washed with 1 M phosphate buffer at pH 7 (20 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 1:1:1 cyclohexane−CH_2Cl_2−Et_2O to give a *E*,*Z*-mixture of unsaturated calixsugars. To a warmed (85 °C), stirred solution of the residue and freshly recrystallized *p*-toluenesulfonhydrazide (56 mg, 0.30 mmol) in dimethoxyethane (6 mL) was added 1 M aqueous sodium acetate (300 μL) in six portions during 3 h. After an additional 2 h at 85 °C, the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 6:3:1 cyclohexane−CH_2Cl_2−Et_2O to give **34** (81 mg, 31%) as a syrup; $[\alpha]_D$ −2.9 (*c* 0.4, $CHCl_3$). ^{1}H NMR selected data: δ 0.88 and 1.07 (2 t, 12 H, J = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 3.07 and 4.42 (2 d, 8 H, J = 13.5 Hz, $ArCH_2Ar$), 3.72 (t, 4 H, J = 7.0 Hz, 2 $OCH_2CH_2CH_3$), 3.92 (t, 4 H, J = 7.8 Hz, 2 $OCH_2CH_2CH_3$), 4.44 and 4.50 (2 d, 4 H, J = 10.8 Hz, $PhCH_2$), 4.95 and 4.96 (2 d, 4 H, J = 11.0 Hz, $PhCH_2$), 6.19−6.30 (m, 6 H, Ar), 6.76 (s, 4 H, Ar), 7.23−7.39 (m, 40 H, 8 Ph). MALDI-TOF MS (1750.3): 1773.4 (M + Na), 1789.6 (M + K).

5,17-Bis(5,9-anhydro-1,2,3,4-tetradeoxy-D-*glycero*-L-*manno*-decitol-1-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (35). A vigorously stirred mixture of **34** (87 mg, 0.05 mmol), 20% palladium hydroxide on carbon (90 mg), and 1:1 CH_3OH−AcOEt (10 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a positive pressure of hydrogen (4 bar) and then filtered through a plug of cotton and concentrated to give **35** (46 mg, 91%) as an amorphous solid; $[\alpha]_D$ −2.7 (*c* 0.3, CH_3OH). ^{1}H NMR (CD_3OD): δ 1.02 and 1.08 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 1.33−1.67 and 1.86−2.04 (2 m, 20 H), 2.36 (t, J = 7.0 Hz, $ArCH_2(CH_2)_3$), 3.05−3.12 (m, 2 H, 2 H-5), 3.09 and 4.45 (2 d, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.38−3.46 (m, 6 H, 2 H-6, 2 H-7, 2 H-9), 3.68 (dd, 2 H, $J_{9,10a}$ = 5.8, $J_{10a,10b}$ = 11.2 Hz, 2 H-10a), 3.73 (dd, 2 H, $J_{9,10b}$ = 6.6 Hz, 2 H-10b), 3.82 and 3.88 (2 t, 8 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 3.99 (dd, 2 H, $J_{7,8}$ = 4.0, $J_{8,9}$ = 1.0 Hz, 2 H-8), 6.44−6.51 (m, 6 H, Ar), 6.57 (s, 4 H, Ar). ^{13}C NMR (CD_3OD): δ 10.7, 11.0, 24.4, 24.5, 26.5, 31.9, 32.7, 33.1, 36.5, 62.7, 70.8, 72.8, 76.5, 77.8, 77.9, 80.0, 81.6, 123.0, 129.4, 135.8, 136.2, 137.2, 156.2, 157.4. ESI-TOF HRMS. Calcd for $C_{120}H_{169}KO_{28}$ ($M_2 + H^+ + K^+$): *m*/*z* 534.27880; found: *m*/*z* 534.2770.

5,17-Bis(6,7,8,10-tetra-*O*-acetyl-5,9-anhydro-1,2,3,4-tetradeoxy-D-*glycero*-L-*manno*-decitol-1-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (35Ac). For NMR studies, a sample of **35** was acetylated at room temperature in 1:1 acetic anhydride−pyridine, concentrated, and used without further purifications. ^{1}H NMR selected data: δ 0.96 and 1.07 (2 t, 12 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 3.10 and 4.45 (2 d, 8 H, J = 13.4 Hz, $ArCH_2Ar$), 3.37−3.44 (m, 2 H, 2 H-5), 3.87 (dd, 2 H, $J_{8,9}$ = 0.7, $J_{9,10a}$ = 6.5, $J_{9,10b}$ = 6.7 Hz, 2 H-9), 4.09 (dd, 2 H, $J_{10a,10b}$ = 11.1 Hz, 2 H-10a), 4.18 (dd, 2 H, 2 H-10b), 5.03 (dd, 2 H, $J_{6,7}$ = 10.0, $J_{7,8}$ = 3.4 Hz, 2 H-7), 5.12 (dd, 2 H, $J_{5,6}$ = 9.5 Hz, 2 H-6), 5.44 (dd, 2 H, 2 H-8), 6.23−6.38 (m, 6 H, Ar), 6.76 (s, 4 H, Ar).

5,11,17,23-Tetrakis(methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-1,4-hexofuranosid-6-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (37). To a cooled (−50 °C), stirred mixture of **25** (1.383 g, 2.40 mmol) and activated 4-Å powdered molecular sieves (1.2 g) in anhydrous THF (8 mL) and HMPA (4 mL) were added *n*-BuLi (1.50 mL, 2.40 mmol, of a 1.6 M solution in hexane) and, after 5 min, a solution of **36** (211 mg, 0.30 mmol) in anhydrous THF (2 mL). The mixture was allowed to reach −20 °C in 3 h and then was diluted with Et_2O (150 mL), filtered through a pad of Celite, washed with 1 M phosphate buffer at pH 7 (30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane−AcOEt (containing 0.3% of triethylamine) to give a *E*,*Z*-mixture of unsaturated calixsugars. A vigorously stirred mixture of the residue, 20% palladium hydroxide on carbon (100 mg), CH_3OH (5 mL), and AcOEt (5 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a positive pressure of hydrogen (4 bar) and then filtered through a plug of cotton and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 5:1 to 2:1, containing 0.3% of triethylamine) to give **37** (90 mg, 24%) as an amorphous solid; $[\alpha]_D$ −38 (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 0.98 (t, 12 H, J = 7.4 Hz, 4 $OCH_2CH_2CH_3$), 1.31 and 1.45 (2 s, 24 H, 4 $(CH_3)_2C$), 1.76−1.86 (m, 8 H, 8 H-5), 1.91 (sext, 8 H, J = 7.4 Hz, 4 $OCH_2CH_2CH_3$), 2.31−2.56 (m, 8 H, 8 H-6), 3.03 and 4.38 (2 d, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.32 (s, 12 H, 4 OCH_3), 3.78−3.85 (m, 4 H, 4 H-4), 3.81 (t, 8 H, J = 7.5 Hz, 4 $OCH_2CH_2CH_3$), 4.52 (d, 4 H, $J_{2,3}$ = 5.9 Hz, 4 H-2), 4.55 (dd, 4 H, $J_{3,4}$ = 3.2 Hz, 4 H-3), 4.85 (s, 4 H, 4 H-1), 6.43 and 6.44 (2 s, 8 H, Ar). ^{13}C NMR: δ 9.4 ($OCH_2CH_2CH_3$), 22.2 ($OCH_2CH_2CH_3$), 24.1 and 25.2 (Me_2C), 29.3, 30.1, and 30.8 ($ArCH_2Ar$, C-5, C-6), 53.5 (OCH_3), 76.1, 78.1 and 79.5 (C-2, C-3, C-4), 84.2 ($OCH_2CH_2CH_3$), 105.9 (C-1), 111.2 (Me_2C), 126.9, 127.1, 133.6, and 153.8 (Ar). MALDI-TOF MS (1249.6): 1272.4 (M + Na), 1288.5 (M + K).

5,11,17,23-Tetrakis(5,6-dideoxy-α,β-L-*lyxo*-1,4-hexos-6-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (38). To a warmed (100 °C), stirred solution of **37** (63 mg, 0.05 mmol) in acetic acid (20 mL) was added dropwise H_2O (5 mL). The solution was refluxed for 16 h and then concentrated. The residue was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 2:1 CH_3OH−CH_2Cl_2 to give **38** (55 mg, 94%) as mixtures of anomers. MALDI-TOF MS (1177.4): 1200.7 (M + Na), 1216.3 (M + K).

5,11,17,23-Tetrakis(6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,5-heptopyranosid-7-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (39). The tetra-aldehyde **36** (211 mg, 0.30 mmol) was treated with **26** (1.518 g, 2.40 mmol) and hydrogenated as described for the preparation of **37** to give **39** (82 mg, 17%) as a syrup; $[\alpha]_D$ −64 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 0.95 (t, 12 H, J = 7.3 Hz, 4 $OCH_2CH_2CH_3$), 1.32, 1.33, 1.35, and 1.48 (4 s, 48 H, 8 $(CH_3)_2C$), 1.73−1.93 (m, 16 H, 4 $OCH_2CH_2CH_3$, 8 H-6), 2.33−2.51 (m, 8 H, 8 H-7), 2.99 and

4.32 (2 d, 8 H, J = 13.2 Hz, 4 ArCH_2Ar), 3.59 (ddd, 4 H, $J_{4,5}$ = 1.7, $J_{5,6a}$ = $J_{5,6b}$ = 7.5 Hz, 4 H-5), 3.74 (t, 8 H, J = 7.5 Hz, 4 OCH_2CH$_2$CH$_3$), 4.11 (dd, 4 H, $J_{3,4}$ = 8.0 Hz, 4 H-4), 4.26 (dd, 4 H, $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.3 Hz, 4 H-2), 4.56 (dd, 4 H, 4 H-3), 5.52 (d, 4 H, 4 H-1), 6.41 and 6.47 (2 d, 8 H, J = 1.5 Hz, Ar). ^{13}C NMR: δ 10.3 (OCH$_2$CH$_2$*C*H$_3$), 23.1 (OCH$_2$*C*H$_2$CH$_3$), 24.5, 25.0, 25.7, and 26.0 (*Me*$_2$C), 30.7, 31.0, and 31.5 (ArCH$_2$Ar, C-6, C-7), 66.3, 70.5, 70.9, 72.7 (C-2, C-3, C-4, C-5), 76.6 (O*C*H$_2$CH$_2$CH$_3$), 96.6 (C-1), 108.2 and 108.9 (Me$_2$*C*), 127.8, 128.3, 134.4, 134.5, and 154.6 (Ar). MALDI-TOF MS (1618.0): 1641.3 (M + Na), 1657.1 (M + K).

5,11,17,23-Tetrakis(6,7-dideoxy-α,β-D-*galacto*-1,5-heptos-7-yl)-25,26,27,28-tetrapropoxy-calix[4]arene (40). To a warmed (60 °C), stirred solution of **39** (81 mg, 0.05 mmol) in distilled THF (20 mL) was added dropwise 1 M HCl (1 mL). The solution was refluxed for 12 h and then concentrated. The residue was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 2:1 $CH_3OH-CH_2Cl_2$ to give **40** (61 mg, 93%) as mixtures of anomers. MALDI-TOF MS (1297.5): 1320.5 (M + Na), 1336.7 (M + K).

Computational Methodology. All calculations were performed on an SGI Octane or Indigo 2 workstation. Monte Carlo conformational searches were performed using MacroModel V.6.0[45] with the Amber* force field in the absence of solvent. Since the Monte Carlo randomization permitted the chemically forbidden interconversion of the flattened cone and partial cone forms of these calixarenes, it was necessary either to constrain distances between opposing upper rim positions, or torsions within the annulus. Typically 5000 steps were performed. The search was repeated until no new low energy conformers were identified. The average conformational search produced over 100 conformers, several of which were found within 2.0 kcal mol^{-1} of the energy of the global minimum. Each of these conformations was separately minimized, so that the global minimum could be established. The energy of each conformation was used to calculate its mole fraction.[36] For bis-substituted derivatives, it was found that inclusion of contributions from conformers other than the global minimum did not change the interpretation of the results. Only the global minimum geometry is reported. Semiempirical calculations at the AM1 level were obtained using Spartan V. 5.5.1.[46]

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Supporting Information Available: Detailed discussion on conformational studies by molecular mechanics. ^{1}H NMR spectra of new compounds as evidence of the degree of purity. This material is available free of charge via the Internet at http://pubs.acs.org.

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