Synthesis and Properties of *O*-Glycosyl Calix[4]arenes (Calixsugars)**

Alessandro Dondoni,* Alberto Marra, Marie-Christine Scherrmann, Alessandro Casnati, Francesco Sansone, and Rocco Ungaro

Abstract: Model *O*-glycosylation reactions at either rim of calix[4]arenes are described with the aim of providing access to a new family of carbohydrate-containing calixarene derivatives named calixsugars. One or two sugar moieties (D-mannofuranose and D-glucopyranose) were introduced at the lower rim of the parent calix[4]arene by glycosylation of the phenolic hydroxyl groups by means of a Mitsunobu reaction. Tetrapropoxy calix[4]-arenes bearing two or four hydroxymethyl groups at the upper rim were coupled with perbenzoylated thioethyl D-galactoside and D-lactoside in the presence of the thiophilic promoter copper(II) triflate. In this way β-linked bis- and tetrakis-*O*-galactosyl calix[4]arenes were obtained in good yield, the latter showing some solubility in water. For the *O*-lactosyl derivatives only the bis-substituted compound could be obtained because of the competing formation of an intramolecular ether linkage between 1,3-hydroxymethyl groups. Preliminary binding studies showed some affinity of the galactose-containing calixsugars toward charged carbohydrates and dihydrogen phosphate anion.

Keywords
calixarenes · carbohydrates · glycosylations · host–guest chemistry · Mitsunobu reaction

Introduction

Following cyclodextrins and crown ethers, calixarenes and their derivatives[1] are enjoying a burgeoning role in host–guest chemistry.[2] In particular calix[4]arenes provide a versatile platform of well-defined shape for the construction of more sophisticated structures, which in turn can be used as receptors of ions and neutral organic molecules.[3] Thus, calix[4]arene moieties have been assembled into multiple systems,[4] or connected to porphyrins,[5] crown ethers,[6] fullerenes,[7] cyclodextrins,[8] and amino acids.[9] Quite often, the elaborated receptor systems have enhanced binding ability or show new properties with respect to the original calixarene. Surprisingly, carbohydrate-linked calixarenes have not been described. The presence of polyhydroxylated chiral substituents such as mono- or disaccharides at one or both the calixarene rims may induce water solubility and therefore create the conditions for applications of these compounds as enzyme mimics and molecular receptors in aqueous solutions. Furthermore the presence of the hydrophilic chiral domain determined by the sugar moieties and the adjacent hydrophobic cavity of the calixarene may result in enhanced binding properties particularly toward polar organic molecules. Given the relevance of hydrogen bonding in molecular recognition processes,[10] the numerous binding sites offered by the carbohydrates should allow strong interactions with similar molecules. Since sugars play significant roles in biological systems, including cellular recognition and adhesion, and cell growth and differentiation,[11] carbohydrate recognition is a subject of increasing importance.[12] To address these issues, we have considered the synthesis of *O*-glycosyl calix[4]arene derivatives (calixsugars) and explored conditions for the introduction of one or more furanose and pyranose moieties at the lower and upper rims. Following earlier reports on this synthetic work,[13] we would like to describe here the results of a more extensive research project together with the initial study of the receptor properties of this new class of calixarene derivatives.

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[**] This trivial name refers to calixarene derivatives in which one or more mono- or oligosaccharide moieties are bound to either the upper or lower rim by *O*- or *C*-glycosidic bond.

Results and Discussion

Glycosylation at the Lower Rim: Given the ready availability of the calix[4]arene[14] **1a** and the *p-tert*-butyl calix[4]arene **1b**, we first examined the glycosylation at the lower rim of these compounds, taking advantage of the phenolic hydroxyl groups. Various methods are known for the synthesis of *O*-aryl glycosides,[15] however, the low nucleophilicity of the phenolic hydroxyl group requires very reactive glycosyl donors or acti-

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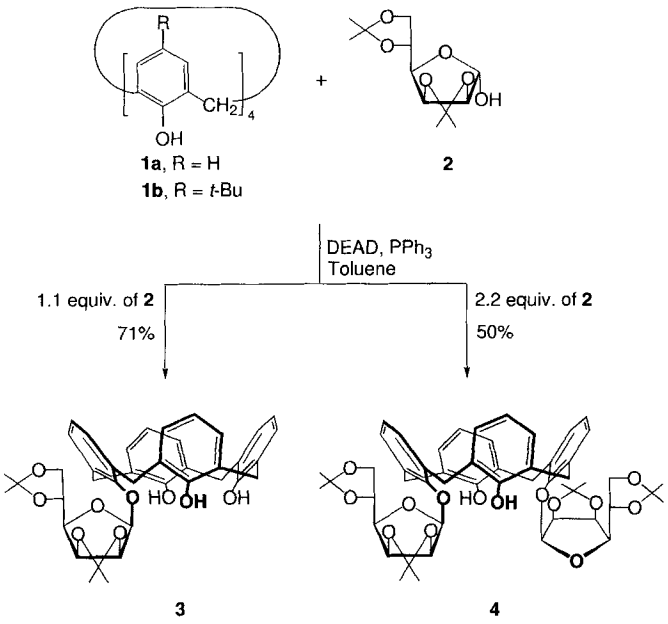
vated glycosyl acceptors (e.g. silylated or stannylated phenol derivatives). The need for prior activation of the reactants can be avoided by use of Mitsunobu conditions,[16] that is, by condensation of a phenol and a carbohydrate unprotected at the anomeric position in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine.[17] This method was tested for the glycosylation of **1a** with the configurationally stable α-D-mannofuranose diacetonide[18] **2** (Scheme 1). Successful coupling of these compounds was carried out in the presence of DEAD and PPh_3 in toluene at 70 °C to give the monoglycosylated calixarene **3** (71 %) after purification by column chromatography on silica gel. The insertion of only one sugar unit in the reaction to give **3** may be due to the higher acidity of one calix[4]arene hydroxyl group with respect to the others.[19] The use



Scheme 1.

Abstract in Italian: *Le reazioni di O-glicosilazione al bordo inferiore o superiore di calix[4]areni hanno permesso di sintetizzare alcuni calixareni contenenti carboidrati, denominati calixzuccheri. L'introduzione di una o due unità di D-mannofuranosio o D-glucopiranosio al bordo inferiore è stata effettuata mediante reazione di Mitsunobu tra lo zucchero in forma emiacetalica e gli ossidrili fenolici. La glicosilazione di tetrapropossi-calix[4]areni aventi due o quattro gruppi idrossimetilici al bordo superiore è stata realizzata impiegando il tioetil D-galattoside e il tioetil D-lattoside perbenzoilati come glicosil donatori e il triflato di rame(II) come attivatore tiofilico. In questo modo si sono ottenuti, stereoselettivamente e in buona resa, sia il bis- che il tetrakis-O-galattosil-calix[4]arene solubile in acqua. D'altra parte si sono potuti sintetizzare solo bis-O-lattosil-calix[4]areni a causa di una reazione intramolecolare competitiva che porta alla formazione di un legame etereo. Gli studi preliminari di riconoscimento molecolare hanno mostrato che i D-galattosil-calix[4]areni possiedono proprietà complessanti nei confronti di carboidrati dotati di carica e dell' anione diidrogenofosfato.*

of 4.4 equiv of **2** produced a complex mixture of compounds apparently devoid of glycosylated calixarene derivatives. Instead a substantial amount of *N*-mannofuranosyl hydrazide derivative $EtO_2CN(R)\text{-}NHCO_2Et$ (R = mannofuranosyl) was isolated. However, when calix[4]arene **1a** was first sonicated in the presence of DEAD (3 equiv) and PPh_3 (3 equiv) to allow the formation of the Mitsunobu adduct, and subsequently treated with the hemiacetal **2** (2.2 equiv), the bisglycosylated calixarene **4** was obtained in 50% yield.

Both the mono- and bisglycosylation reactions appeared to be β-selective as expected for nucleophilic displacement by the phenoxide ion on the glycosyloxyphosphonium intermediate. The glycosyl linkages in calixsugars **3** and **4** were established to be β by means of the coupling constant values of the anomeric protons in the ^1H NMR spectra[20] ($J_{1,2}$ = 3.0 and 3.6 Hz, respectively) and the enhancement between H-1 and H-4 observed in NOE experiments. Moreover the cone conformation of the calixarene moiety in both compounds was substantiated by the chemical shifts of the protons and the multiplicity pattern of their signals,[21] along with the chemical shifts of the carbon atoms of the methylene bridges.[22] Calixsugars **3** and **4** appeared to be fixed in the cone conformation since the ^1H NMR spectra showed these characteristic features over a wide range of temperatures (from −80 to 160 °C).[23]

Unfortunately, attempted deacetonization of glycosides **3** and **4** failed since only one *O*-isopropylidene group was removed in $AcOH/H_2O$ (4:1) at room temperature, while substantial decomposition took place at higher temperature. Therefore the corresponding unprotected compounds could not be prepared.

The glycosylation of **1a** by Mitsunobu coupling with 1.1 equiv of tetraacetyl-α,β-D-glucopyranose[24] (**5**) (Scheme 2) produced a complex mixtures of diastereomeric mono- and bisglycosides. Column chromatography on silica gel afforded a 3:1 mixture of α- and β-monoglycosides[25] (≈60%) and a 1:1 mixture of α,α- and α,β-bisglycosides (≈20%). Attempts to isolate the individual monoglycosides were unsuccessful even by HPLC.[26] On the other hand, the reaction of **1a** with 2.2 equiv of **5** afforded an approximately 1:1 mixture of α,α-bisglycoside **6** and α,β-isomer **7** in approximately 45% overall yield. Since the α-anomer of **5** is significantly favored over the β-isomer (3:1 ratio),[27] the α-selectivity in these Mitsunobu couplings might be explained by assuming a higher concentration of the glycosyloxyphosphonium intermediate derived from the β rather than from the α-anomer of **5**.[28] The bisglycosides **6** and **7**, separated by HPLC and purified by crystallization, were recovered in 16% and 14% yield, respectively.

The configurations at the anomeric positions in **6** and **7** could be clearly established from the ^1H NMR spectra since $J_{1,2}$ values of around 3.5 and 8.0 Hz were observed, as expected for α-D-aldopyranosides and β-D-aldopyranosides in $^4C_1$ conformations having dihedral angles H-1/C-1/C-2/H-2 of nearly 60 and 180°, respectively. The cone conformation of the macrocycle was assigned also in this case from ^1H and ^{13}C NMR spectra as discussed above.[21, 22] The symmetrical substitution in **6** was easily deduced from the presence of only two types of diastereotopic carbons for the four methylene bridges in the ^{13}C NMR spectrum. The symmetrical substitution of the intrinsically unsymmetrical compound **7** could not be established in the same way. However, this problem was solved by a simple chem-

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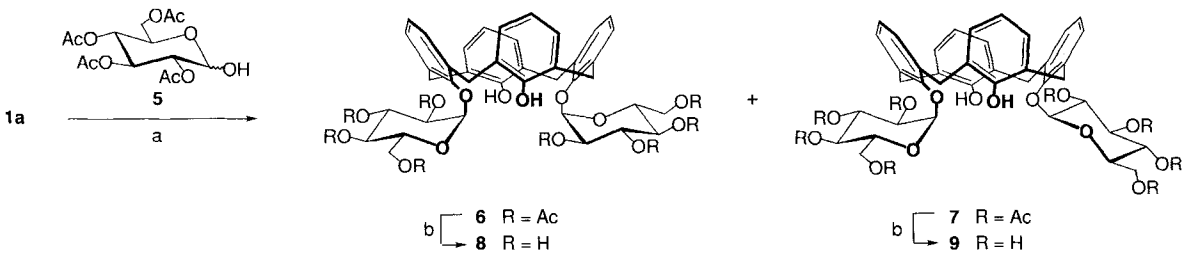
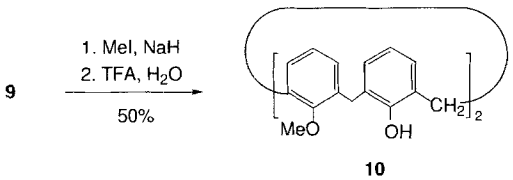


Scheme 2. Reagents: a) DEAD, PPh_3, toluene; b) MeOH, Et_3N, H_2O.

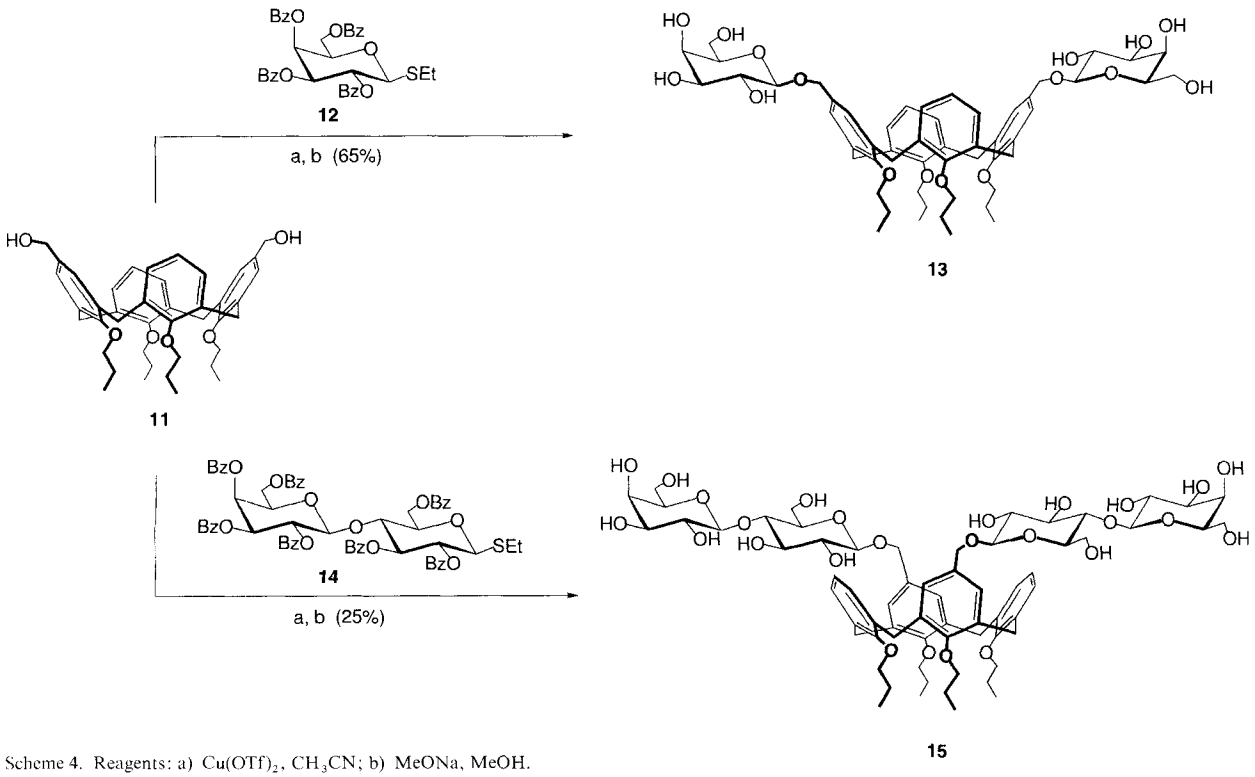
ical correlation. Upon deacetylation with $CH_3OH/Et_3N/H_2O$, compound **7** was converted into the unprotected bis-*O*-glucosyl calix[4]arene **9**, which was sequentially permethylated and deglycosylated to give the known[29] 1,3-dimethoxy-calix[4]arene **10** (Scheme 3). Unfortunately, the calixsugar **9** as well the isomer **8**, which was obtained in the same way from the octaacetyl derivative **6**, proved to be insoluble in water.



Scheme 3.

Having set up the conditions for a satisfactory Mitsunobu coupling of the model furanose **2** and pyranose **5** with calix[4]arene **1a**, we attempted to apply the same method to the *p-tert*-butyl calix[4]arene **1b**. We were able to observe that this calixarene also reacted with **5** in the presence of DEAD and PPh_3 in refluxing toluene. However, we did not isolate the condensation products, because their separation by crystallization was inefficient and chromatographic purification was problematic due to the low solubility in the majority of common solvents.

Glycosylation at the Upper Rim: The symmetrical 1,3-dihydroxymethyl calix[4]arene[30] **11**, whose cone conformation is blocked by the four *O*-propyl groups at the lower rim, was considered to be a suitable substrate for the introduction of two carbohydrate moieties at the upper rim. The numerous methods available for stereocontrolled glycoside synthesis[31] offered us a wide choice for this reaction. Since thioglycosides are stable and readily available molecules, which can act as efficient donors upon direct activation by various thiophilic catalysts,[32] thioethyl tetrabenzoyl-β-D-galactopyranoside **12** was selected as model glycosyl donor. The benzoyl substituent at C-2 is known to be superior to acetyl for the stereoselective synthesis of 1,2-*trans* glycosides.[33] Copper(II) triflate [$Cu(OTf)_2$] was considered as a convenient promoter[34] of the glycosylation reaction, since it is a stable, commercially available, nontoxic, and yet very efficient reagent. Thus the coupling between the calixarene **11** and 2.4 equiv of the pyranoside **12** in the presence of $Cu(OTf)_2$ and acetonitrile proceeded rapidly (45 min) at room temperature (Scheme 4). In contrast, the reaction carried out in



Scheme 4. Reagents: a) $Cu(OTf)_2$, CH_3CN; b) MeONa, MeOH.

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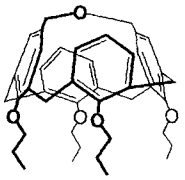
dichloromethane was sluggish and did not afford appreciable amounts of product. The isolation of the benzoylated calixsugar that was formed in the reaction in acetonitrile was quite troublesome, because of the presence of unreacted calixarene **11**, galactoside **12**, and products derived from the hydrolysis of the latter. The removal of the benzoyl protecting groups by a transesterification reaction with sodium methoxide in methanol allowed the isolation by chromatography of the expected β-linked[35] bis-*O*-galactosyl calixarene **13** in pure form and satisfactory yield (65%). This compound also proved to be insoluble in water. The ether-bridged calixarene **16** was also isolated in very low yield (2%). Evidently this compound was formed through intramolecular acid-catalyzed coupling of the two hydroxymethyl groups. In agreement with ^{1}H NMR data of other calixarenes bridged at the upper rim,[36] compound **16** showed a set of broad signals at unusually high field ($\delta \approx 5$) corresponding to the aromatic protons of the two ether-linked phenyl rings. The considerable flattening of the macrocycle due to the bridging subjects these protons to the anisotropic effect of the other aromatic rings.



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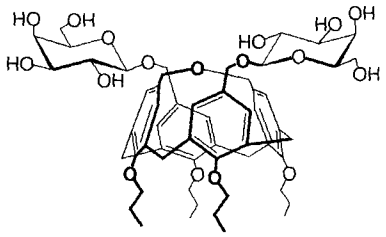
The diol **11** was also subjected to glycosylation with thioethyl heptabenzoyl-β-D-lactoside **14**, to investigate whether the method would allow the insertion of a disaccharide moiety. It was hoped that the extension of the hydrophilic domain with longer carbohydrate chains could provide some water solubility to the system. The coupling between **11** and **14** (2.4 equiv) under the above conditions ($Cu(OTf)_2$, CH_3CN, RT), followed by treatment of the crude reaction mixture with sodium methoxide, afforded the β-linked[35] bis-*O*-lactosyl calixarene **15** in only 25% isolated yield. In this case the sluggish glycosylation reaction was surpassed by the competing intramolecular coupling of the two hydroxymethyl groups of **11** to give the capped calixarene **16** as major product (50% yield). No attempts were made to improve the yield of **15** since this calixsugar also turned out to be insoluble in water.

We therefore turned our attention to increasing the number of carbohydrate moieties at the upper rim of the macrocycle by the introduction of four sugar moieties, one for each aromatic ring. To this end the tetrahydroxymethylated calix[4]arene **20** was prepared from **1a** via the tetrapropoxy derivative **18** and the tetraaldehyde **19** (Scheme 5). The glycosylation of **20** with 6 equiv of the thioethyl galactoside **12** in the presence of $Cu(OTf)_2$ and CH_3CN followed by methanolysis afforded a rewarding 60% yield of the *water-soluble* (up to 5 mM),[37] all β-linked[30] tetrakis-*O*-galactosyl calixarene **21** (Scheme 6). The by-product in this reaction was the ether-bridged bis-*O*-galactosyl calixarene[35] **17**, which



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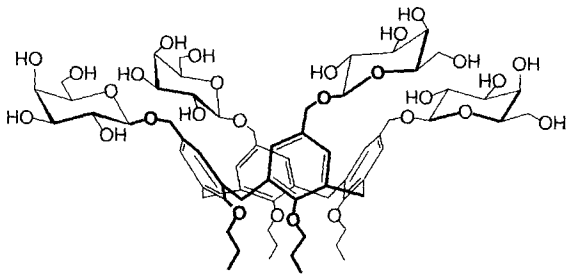
was isolated in very small amounts (3%). In the coupling of the tetrol **20** with the thioethyl lactoside **14**, a similar compound, namely, the capped calixsugar[35] **22** (Scheme 6) was the only product obtained in low yield (25%). In this case the formation of the intramolecular ether bridge is favored over the introduction of the third bulky carbohydrate moiety.



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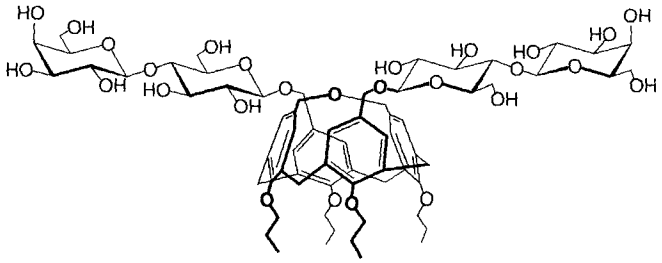

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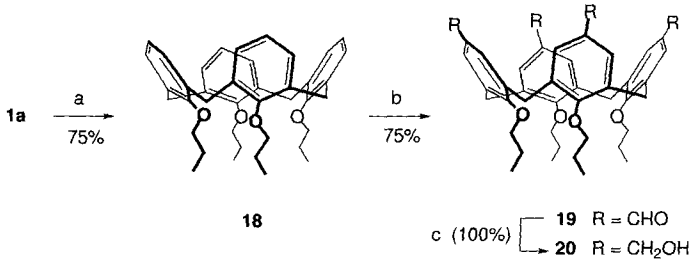
Scheme 6. Reagents: a) $Cu(OTf)_2$, CH_3CN; b) MeONa, MeOH.



Scheme 5. Reagents: a) *n*PrI, NaH; b) $(CH_2)_6N_4$, TFA; c) $NaBH_4$.

Binding Studies: The bis- and tetrakis-β-D-*O*-galactosyl calix[4]arenes **13** and **21** were used for an exploratory investigation into the ability of calixsugars in recognizing neutral and charged molecules. Preliminary complexation studies were carried out by ^{1}H NMR titration[38] with monosaccharides, amino acids, and other compounds, which are expected to interact with carbohydrates. Because of the low solubility of **13** and **21** in convenient solvents for investigating host–guest chemistry operating through hydrogen bonding[39] ($CDCl_3$) and hydrophobic inter-

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actions[12b] (H_2O), the measurements were carried out in highly competitive solvents such as [D_4]MeOH or [D_6]DMSO. Various neutral carbohydrates and *N*-protected amino acids did not appear to be complexed.[40] On the other hand, complexation occurred between **21** and charged guests such as D-glucosamine hydrochloride and tetrabutylammonium dihydrogen phosphate. In the first case significant changes in the chemical shifts of the guest signals were observed, but the quantitative analysis of the data in terms of binding constants was complicated by the simultaneous presence of both 1:1 and 2:1 host–guest complexes.

In the case of dihydrogen phosphate anion ($H_2PO_4^-$) there was good evidence for 1:1 complexation.[41] The titration curve (Figure 1) gave a good fit between the experimental and theoretical data by the use of three signals as probes. A mean stability constant value of $31 \pm 4\ M^{-1}$ was obtained. It is known that phosphonate groups can interact with diols and alkyl glycosides giving association constants of the order of 10^2–10^3 in acetonitrile.[42] The much lower stability constant obtained for $H_2PO_4^-$ and **21** is probably due to the highly competitive solvent [D_6]DMSO employed in this case. Nevertheless this result is very promising and indicates the potential of this and other calixsugars as receptors of phosphate- or phosphonate-bearing molecules of biological relevance.[43]

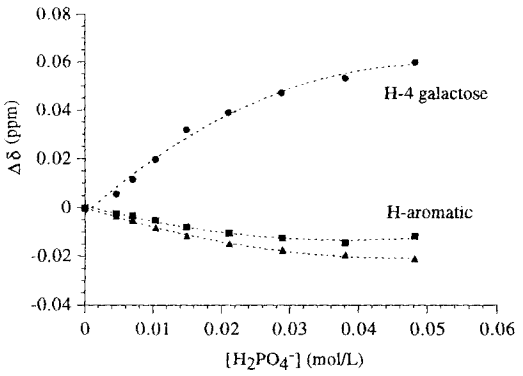

Figure 1. Plots of complexation-induced shifts ($\Delta\delta$) for H-4 of the galactose moiety and two aromatic protons in the ^{1}H NMR spectra ([D_6]DMSO) of host **21** as a function of concentration of $H_2PO_4^-$.

Conclusions

The model *O*-glycosylation reactions described above allowed the regio- and stereoselective introduction of sugar moieties at either rim of calixarenes. These routes should pave the way for the synthesis of appropriately designed host systems. The final aim of this research topic was to provide an entry into the molecular recognition of polar chiral substrates, especially carbohydrates, both in water and in organic solvents. The preliminary binding studies, showing some affinity of calixsugars for charged molecules, indicate a direction for further development of this chemistry.[50]

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere in oven-dried glassware. Anhydrous solvents were prepared according to standard procedures[44] and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (50 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[45] 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. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at RT for $CDCl_3$ solutions, 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. FAB and MALDI-TOF mass spectra were acquired by using 3-nitrobenzyl alcohol and α-cyano-4-hydroxycinnamic acid, respectively, as the matrix. Since the elemental analyses of calixarenes are very often uncorrected[46] (found carbon values considerably lower than the calculated ones), the identity of the following new compounds were established by MS and NMR analyses.

25-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl)oxy-26,27,28-trihydroxy-calix[4]arene (3): Diethyl azodicarboxylate (118 μL, 0.75 mmol) was added to a vigorously stirred mixture of calixarene **1a** (212 mg, 0.50 mmol), hemiacetal **2** (143 mg, 0.55 mmol), triphenylphosphine (198 mg, 0.75 mmol), and anhydrous toluene (10 mL). Stirring was continued at 70 °C for an additional hour; then the mixture was cooled to RT and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane/AcOEt to give **3** (236 mg, 71%) as a colorless foam: $[\alpha]_D = -43.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: $\delta = 9.91, 9.42, 8.65$ (3s, 3H; 3OH), 7.20 (dd, 1H, $J = 1.6, 7.5$ Hz; Ar), 7.08–6.91 (m, 8H; Ar), 6.68, 6.67, 6.61 (3t, 3H, $J = 7.5$ Hz; Ar), 5.38–5.33 (m, 2H; H-1, H-2), 4.90–4.85 (m, 1H; H-3), 4.65 (d, 1H, $J = 13.8$ Hz; H_{ax} of ArCH_2Ar), 4.56 (d, 1H, $J = 13.0$ Hz; H_{ax} of ArCH_2Ar), 4.55 (dt, 1H, $J_{4,5} = 6.3$, $J_{5,6} = 5.8$ Hz; H-5), 4.34 (d, 1H, $J = 13.4$ Hz; H_{ax} of ArCH_2Ar), 4.23 (d, 1H, $J = 13.7$ Hz; H_{ax} of ArCH_2Ar), 4.14 (d, 2H; 2H-6), 3.68 (dd, 1H, $J_{3,4} = 3.8$ Hz; H-4), 3.47, 3.46, 3.43, 3.39 (4d, 4H; 4H_{eq} of ArCH_2Ar), 1.84, 1.57, 1.43, 1.39 (4s, 12H; 4CH_3). ^{1}H NMR ([D_6]DMSO): $\delta = 9.61, 9.35, 8.30$ (3s, 3H; 3OH), 7.34 (dd, 1H, $J = 1.6, 7.6$ Hz; Ar), 7.21 (dd, 1H, $J = 1.6, 7.6$ Hz; Ar), 7.17–7.08 (m, 5H; Ar), 6.97 (dd, 1H, $J = 1.6, 7.6$ Hz; Ar), 6.93 (t, 1H, $J = 7.6$ Hz; Ar), 6.64 (t, 1H, $J = 7.6$ Hz; Ar), 6.54 (t, 1H, $J = 7.6$ Hz; Ar), 5.48 (d, 1H, $J_{1,2} = 3.0$ Hz; H-1), 5.25 (dd, 1H, $J_{2,3} = 6.0$ Hz; H-2), 4.83 (dd, 1H, $J_{3,4} = 3.7$ Hz; H-3), 4.55 (d, 1H, $J = 13.3$ Hz; H_{ax} of ArCH_2Ar), 4.44 (d, 1H, $J = 12.5$ Hz; H_{ax} of ArCH_2Ar), 4.40 (ddd, 1H, $J_{4,5} = 4.5$, $J_{5,6a} = J_{5,6b} = 6.5$ Hz; H-5), 4.11 (d, 1H, $J = 13.0$ Hz; H_{ax} of ArCH_2Ar), 4.05 (d, 1H, $J = 13.3$ Hz; H_{ax} of ArCH_2Ar), 4.04 (d, 2H; 2H-6), 3.85 (dd, 1H; H-4), 3.52, 3.51, 3.43 (3d, 4H; 4H_{eq} of ArCH_2Ar), 1.71, 1.46, 1.29, 1.26 (4s, 12H; 4CH_3). ^{13}C NMR: $\delta = 151.1, 150.8, 150.3, 149.4, 134.9, 134.7, 130.0–126.7, 121.5, 121.4, 120.9$ (Ar), 113.4, 109.1 (2O-C-O), 106.4 (C-1), 79.1 (C-2), 78.5 (C-3), 76.9 (C-4), 73.2 (C-5), 66.4 (C-6), 32.0 (ArCH_2Ar), 31.8 (2ArCH_2Ar), 30.9 (ArCH_2Ar), 26.7 (CH_3), 25.3 (2CH_3), 24.2 (CH_3). FAB-HRMS. Calcd for $C_{40}H_{43}O_9$ [$M^+ + H$]: 667.2907; found: 667.2916.

25,27-Bis[(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)oxy]-26,28-dihydroxy-calix[4]arene (4): Diethyl azodicarboxylate (111 μL, 0.70 mmol) was added to a stirred solution of **1a** (100 mg, 0.24 mmol) and triphenylphosphine (185 mg, 0.70 mmol) in anhydrous toluene (3 mL). The biphasic mixture was sonicated in an ultrasonic cleaning bath at RT until a suspension was formed (≈10 min), before **2** (135 mg, 0.52 mmol) was added. Stirring was continued at RT for an additional 30 min, and the mixture was then concentrated. The residue was eluted from a column of silica gel with 20:1 $CHCl_3$/THF to give **4** (107 mg, 50%) as a white solid: m.p. > 350 °C; $[\alpha]_D = -24.7$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: $\delta = 7.08$ (d, 4H, $J = 7.4$ Hz; Ar), 6.73–6.57 (m, 8H; Ar), 6.51 (s, 2H; 2OH), 5.04 (d, 2H, $J_{1,2} = 3.6$ Hz; 2H-1), 4.90 (dd, 2H, $J_{2,3} = 3.7$ Hz; 2H-2), 4.80 (dd, 2H, $J_{3,4} = 3.5$ Hz; 2H-3), 4.70, 3.27 (2d, 4H, $J = 13.8$ Hz; 2ArCH_2Ar), 4.52 (ddd, 2H, $J_{4,5} = 7.4$, $J_{5,6a} = J_{5,6b} = 5.1$ Hz; 2H-5), 4.38, 3.33 (2d, 4H, $J = 13.3$ Hz; 2ArCH_2Ar), 4.11–4.06 (m, 4H; 2H-6), 3.57 (dd, 2H; 2H-4), 1.72, 1.45, 1.41, 1.38 (4s, 24H; 8CH_3). ^{13}C NMR: $\delta = 153.3, 151.4, 133.9, 131.9, 128.7, 128.6, 128.5, 128.3, 128.1, 124.9, 118.4$ (Ar), 113.9, 109.1 (4O-C-O), 106.1 (2C-1), 79.2, 79.1 (2C-2, 2C-3), 76.8 (2C-4), 73.1 (2C-5), 66.7 (2C-6), 31.4, 30.8 (4ArCH_2Ar), 26.8, 26.2, 25.5, 25.3 (8CH_3). FAB-HRMS. Calcd for $C_{52}H_{61}O_{14}$ [$M^+ + H$]: 909.4061; found: 909.4120.

When the same reaction was performed at 70 °C similar results were obtained. The use of tributylphosphine instead of triphenylphosphine led to lower yields of bisglycoside **4**.

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25,27-Dihydroxy-26,28-bis[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)oxy]-calix[4]arene (6) and **25,27-dihydroxy-26-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)oxy-28-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy-calix[4]arene (7)**: Diethyl azodicarboxylate (236 μL, 1.50 mmol) was added to a stirred solution of calixarene **1a** (212 mg, 0.50 mmol), hemiacetal **5** (383 mg, 1.10 mmol), and triphenylphosphine (393 mg, 1.50 mmol) in anhydrous toluene (5 mL). Stirring was continued at RT for an additional hour, and the suspension was then filtered through a pad of Celite and concentrated. The residue was eluted from a column of silica gel with 4:1 Et_2O/cyclohexane to give crude **6** and **7** together with unreacted **5** and other by-products (0.40 g). The mixture was purified by HPLC (25 × 200 mm silica gel column, 60 Å, 6 μm, 72:28 cyclohexane/AcOEt, 28 mL min^{-1}, detection at 280 nm) to give, first, **6** contaminated by **5** (145 mg). Crystallization from Et_2O afforded pure **6** (87 mg, 16%): m.p. 223 °C (softening at 132 °C); $[\alpha]_D = +94.5$ ($c = 0.9$, $CHCl_3$). ^1H NMR: $\delta = 7.16-7.09$ (m, 4H; Ar), 6.79 (t, 2H, $J = 7.5$ Hz; Ar), 6.70–6.63 (m, 4H; Ar), 6.59 (t, 2H, $J = 7.5$ Hz; Ar), 5.85 (dd, 2H, $J_{2,3} = 10.3$, $J_{3,4} = 9.5$ Hz; 2H-3), 5.49 (d, 2H, $J_{1,2} = 3.7$ Hz; 2H-1), 5.40 (s, 2H; 2OH), 5.26 (dd, 2H, $J_{4,5} = 10.4$ Hz; 2H-4), 5.20 (dd, 2H; 2H-2), 4.70 (ddd, 2H, $J_{5,6a} = 4.8$, $J_{5,6b} = 2.0$ Hz; 2H-5), 4.54, 3.40 (2d, 8H, $J = 14.0$ Hz; 4ArCH_2Ar), 4.49 (dd, 2H, $J_{6a,6b} = 12.4$ Hz; 2H-6a), 4.14 (dd, 2H; 2H-6b), 2.08, 2.04, 2.02, 1.88 (4s, 24H; 8CH_3CO). ^{13}C NMR: $\delta = 170.9$ (2CH_3CO), 170.1 (4CH_3CO), 169.9 (2CH_3CO), 152.7, 152.0, 131.6, 131.4, 129.7, 129.0–128.5, 125.1, 119.8 (Ar), 100.6 (2C-1), 71.3 (2C-2), 70.1 (2C-3), 69.9 (2C-5), 68.0 (2C-4), 61.7 (2C-6), 31.3, 30.8 (4ArCH_2Ar), 20.5–20.2 (8CH_3CO). FAB-MS for $C_{56}H_{60}O_{22}$ (1085.10): $m/z = 1086$ [$M^+ + H$].

Compound **7** eluted second contaminated by uncharacterized by-products (125 mg). Crystallization from Et_2O gave pure **7** (76 mg, 14%): m.p. 242–244 °C; $[\alpha]_D = +29.3$ ($c = 0.9$, $CHCl_3$). ^1H NMR: $\delta = 7.17-7.04$, 6.82–6.50 (2m, 12H; Ar), 5.88 (dd, 1H, $J_{2,3} = 10.5$, $J_{3,4} = 9.5$ Hz; H-3α), 5.70, 5.28 (2s, 2H; 2OH), 5.55 (dd, 1H, $J_{1,2} = 8.2$, $J_{2,3} = 9.4$ Hz; H-2β), 5.42 (d, 1H, $J_{1,2} = 3.5$ Hz; H-1α), 5.34 (dd, 1H, $J_{3,4} = 9.5$ Hz; H-3β), 5.30 (dd, 1H, $J_{4,5} = 10.6$ Hz; H-4α), 5.26 (dd, 1H, $J_{4,5} = 9.8$ Hz; H-4β), 5.14 (dd, 1H; H-2α), 5.07 (ddd, 1H, $J_{5,6a} = 3.8$, $J_{5,6b} = 1.6$ Hz; H-5α), 4.87 (d, 1H; H-1β), 4.70–4.61 (m, 3H, H-6aα, 2H_{ax} of ArCH_2Ar), 4.49 (d, 1H, $J = 14.5$ Hz; H_{ax} of ArCH_2Ar), 4.40 (d, 1H, $J = 13.2$ Hz; H_{ax} of ArCH_2Ar), 4.33 (dd, 1H, $J_{6a,6b} = 12.6$ Hz; H-6bα), 4.25 (dd, 1H, $J_{5,6a} = 4.4$, $J_{6a,6b} = 12.4$ Hz; H-6aβ), 4.11 (dd, 1H, $J_{5,6b} = 2.5$ Hz; H-6bβ), 3.60 (ddd, 1H; H-5β), 3.39–3.28 (m, 4H; 4H_{eq} of ArCH_2Ar), 2.14, 2.04, 1.86 (3s, 24H; 8CH_3CO).^{13}C NMR: $\delta = 171.1$, 170.7, 170.4, 170.2, 169.8, 169.7, 169.5, 169.3 (8CH_3CO), 153.0, 152.9, 152.6, 149.1, 134.4, 131.8, 131.7, 131.2, 130.3, 129.3–128.0, 126.0, 124.7, 119.8, 119.2 (Ar), 103.4 (C-1β), 101.0 (C-1α), 72.6 (C-3β), 72.0 (C-5β), 71.9 (C-2α), 70.6 (C-2β), 70.0 (C-3α), 69.4 (C-5α), 68.4 (C-4β), 68.0 (C-4α), 62.0 (C-6α), 61.3 (C-6β), 31.6, 31.3, 31.0, 30.3 (4ArCH_2Ar), 20.6–20.1 (8CH_3CO). FAB-MS for $C_{56}H_{60}O_{22}$ (1085.10): $m/z = 1086$ [$M^+ + H$].

25,27-Bis[(α-D-glucopyranosyl)oxy]-26,28-dihydroxy-calix[4]arene (8): A solution of **6** (108 mg, 0.10 mmol) in 8:1:1 $CH_3OH/Et_3N/H_2O$ (2 mL) was kept ar RT overnight, and then concentrated. The residue was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give **8** (66 mg, 88%) as a white solid: m.p. 194–197 °C (from MeOH/AcOEt); $[\alpha]_D = +143$ ($c = 0.8$, CH_3OH). ^1H NMR (CD_3OD): $\delta = 7.10-7.04$, 6.96–6.91 (2m, 8H; Ar), 6.71, 6.63 (2t, 4H, $J = 7.5$ Hz; Ar), 5.41 (d, 2H, $J_{1,2} = 3.9$ Hz; 2H-1), 5.00, 3.36 (2d, 4H, $J = 13.5$ Hz; 2ArCH_2Ar), 4.67, 3.35 (2d, 4H, $J = 13.0$ Hz; 2ArCH_2Ar), 4.48 (ddd, 2H, $J_{4,5} = 9.9$, $J_{5,6a} = J_{5,6b} = 3.3$ Hz; 2H-5) 4.24 (dd, 2H, $J_{2,3} = 9.9$, $J_{3,4} = 9.5$ Hz; 2H-3), 3.89–3.82 (m, 4H; 4H-6), 3.79 (dd, 2H; 2H-2), 3.57 (dd, 2H; 2H-4). ^{13}C NMR (CD_3OD): $\delta = 154.2$, 153.3, 135.7, 134.3, 131.1, 130.3, 130.1, 129.9, 129.8, 129.6, 126.4, 120.8 (Ar), 106.6 (2C-1), 77.1 (2C-5), 74.5 (2C-3), 74.1 (2C-2), 71.1 (2C-4), 62.3 (2C-6), 32.8, 32.6 (4ArCH_2Ar). FAB-HRMS. Calcd for $C_{40}H_{44}NaO_{14}$ [$M^+ + Na$]: 771.2629; found: 771.2631.

25-(α-D-Glucopyranosyl)oxy-27-(β-D-glucopyranosyl)oxy-26,28-dihydroxy-calix[4]arene (9): The bisglucoside **7** (108 mg, 0.10 mmol) was deacetilated as described for the preparation of **8** to afford **9** (67 mg, 90%) as a white solid: m.p. 210–212 °C (from MeOH/AcOEt); $[\alpha]_D = +29.4$ ($c = 0.8$, CH_3OH). ^1H NMR (CD_3OD): $\delta = 7.13-6.95$ (m, 8H; Ar), 6.81, 6.74, 6.64, 6.61 (4t, 4H, $J = 7.5$ Hz; Ar), 5.32 (d, 1H, $J_{1,2} = 3.8$ Hz; H-1α), 5.12 (d, 1H, $J = 13.8$ Hz; H_{ax} of ArCH_2Ar), 4.91 (d, 1H, $J_{1,2} = 7.8$ Hz; H-1β), 4.69 (d, 2H, $J = 13.2$ Hz; 2H_{ax} of ArCH_2Ar), 4.61 (d, 1H, $J = 13.4$ Hz; H_{ax} of ArCH_2Ar), 4.59 (ddd, 1H, $J_{4,5} = 9.9$, $J_{5,6a} = J_{5,6b} = 3.2$ Hz; H-5α), 4.19 (dd, 1H, $J_{2,3} = 10.0$, $J_{3,4} = 9.2$ Hz; H-3α), 3.91 (dd, 1H, $J_{2,3} = 9.2$ Hz; H-2β), 3.87 (d, 2H; 2H-6α), 3.84 (dd, 1H, $J_{5,6a} = 2.3$, $J_{6a,6b} = 11.9$ Hz; H-6aβ), 3.77 (dd, 1H; H-2α), 3.73 (dd, 1H, $J_{5,6b} = 5.2$ Hz; H-6bβ), 3.62 (dd, 1H; H-4α), 3.61 (dd, 1H, $J_{3,4} = 9.0$ Hz; H-3β), 3.55 (dd, 1H, $J_{4,5} = 9.3$ Hz; H-4β), 3.45–3.31 (m, 4H; 4H_{eq} of ArCH_2Ar), 3.28 (ddd, 1H; H-5β). ^{13}C NMR (CD_3OD): $\delta = 154.3$, 153.7, 153.3, 150.5, 137.1, 136.4, 134.8, 134.7, 130.9–129.0, 127.4, 126.5, 121.3, 120.7 (Ar), 107.5 (C-1β), 106.8 (C-1α), 70.6 (C-5β), 77.8 (C-3β), 76.7 (C-5α), 76.1 (C-2β), 74.7 (C-3α), 74.0 (C-2α), 71.4 (C-4β), 71.0 (C-4α), 62.6, 62.2 (C-6α, C-6β), 33.4, 32.8, 32.6, 31.9 (4ArCH_2Ar). FAB-HRMS. Calcd for $C_{40}H_{44}NaO_{14}$ [$M^+ + Na$]: 771.2629; found: 771.2617.

25,27-Dihydroxy-26,28-dimethoxy-calix[4]arene (10): NaH (23 mg, 0.568 mmol, of a 60% dispersion in oil) and then CH_3I (57 μL, 0.908 mmol) were added to a stirred, cooled (0 °C) solution of **9** (17 mg, 0.023 mmol) in DMF (2 mL). The mixture was stirred at 0 °C for an additional 2 h, then diluted with aqueous 1 M HCl (2 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. A solution of the crude product in 1:4 water/trifluoroacetic acid (2 mL) was stirred at 100 °C for 15 min, then cooled to RT, and concentrated. The residue was submitted to preparative TLC (silica gel 60 F_{254}, 0.5 mm layer, 2:1 cyclohexane/AcOEt) to give known[29] **10** (5 mg, 50%). The structure of **10** was confirmed by MS and NMR analyses.

Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (12): A solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (7.03 g, 18.0 mmol) and ethanethiol (1.46 mL, 19.8 mmol) in anhydrous CH_2Cl_2 (120 mL) was treated with $BF_3 \cdot Et_2O$ (2.26 mL, 18.0 mmol) at RT for 2 h, diluted with Et_3N (2 mL), and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane/AcOEt to afford ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (5.65 g). A solution of the product in freshly prepared ≈0.5 M solution of CH_3ONa in CH_3OH (60 mL) was kept at RT overnight, then neutralized with Amberlite IR 120 (H^+ form), and concentrated. Freshly distilled benzoyl chloride (8.70 mL, 75.0 mmol) was slowly added to a stirred solution of the crude ethyl 1-thio-β-D-galactopyranoside in pyridine (40 mL). The mixture was stirred at RT for an additional 2 h, then diluted with CH_3OH (5 mL), and concentrated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with H_2O (40 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with cyclohexane/AcOEt (from 6:1 to 2:1) to give **12** (8.19 g, 71%) as a colorless foam: $[\alpha]_D = +106$ ($c = 1.0$, $CHCl_3$); ref. [47] +145 ($c = 2.1$, $CHCl_3$). ^1H NMR: $\delta = 8.10-7.22$ (m, 20H; 4Ph), 6.04 (dd, 1H, $J_{3,4} = 3.3$, $J_{4,5} = 0.8$ Hz; H-4), 5.85 (dd, 1H, $J_{1,2} = 9.8$, $J_{2,3} = 10.0$ Hz; H-2), 5.65 (dd, 1H; H-3), 4.88 (d, 1H; H-1), 4.68 (dd, 1H, $J_{5,6a} = 5.7$, $J_{6a,6b} = 10.3$ Hz; H-6a), 4.41 (dd, 1H, $J_{5,6b} = 6.5$ Hz; H-6b), 4.36 (ddd, 1H; H-5), 2.87, 2.81 (2dq, 2H, $J = 7.4$, 12.2 Hz; CH_2CH_3), 1.33 (t, 3H, $J = 7.4$ Hz; CH_2CH_3). ^{13}C NMR: $\delta = 166.0$ (C=O), 165.5 (2C=O), 165.3 (C=O), 133.6–133.3, 129.9–128.3 (Ph), 84.3 (C-1), 75.0 (C-5), 72.7 (C-3), 68.3 (C-4), 68.2 (C-2), 62.2 (C-6), 24.5 (CH_2CH_3), 15.0 (CH_2CH_3). Anal. calcd for $C_{36}H_{32}O_9S$: C, 67.48; H, 5.03; S, 5.00. Found: C, 67.49; H, 5.11; S, 4.80.

5,17-Bis[(β-D-galactopyranosyl)oxymethyl]-25,26,27,28-tetrapropoxy-calix[4]arene (13): A mixture of diol **11** (130 mg, 0.20 mmol), thioglycoside **12** (102 mg, 0.16 mmol), and anhydrous CH_3CN (10 mL) was stirred at 50 °C until a clear solution was obtained, and was then cooled to RT and treated with activated 4 Å powdered molecular sieves (0.80 g) and, after 15 min, with copper(II) triflate (58 mg, 0.16 mmol). Two portions of both thioglycoside **12** and copper(II) triflate (0.16 mmol each) were added to the reaction mixture after 15 and 30 min. Stirring was continued at RT for an additional 15 min. The mixture was then 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 × 7 cm) of silica gel with 3:1 cyclohexane/AcOEt in order to remove the copper salts. The crude mixture was treated with freshly prepared ≈0.1 M solution of CH_3ONa in CH_3OH (10 mL) at RT overnight, then neutralized with AcOH, and concentrated. The residue was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give, first, **16** (3 mg, ≈2%) contaminated by an uncharacterized by-product. ^1H NMR: $\delta = 7.16$ (d, 4H, $J = 7.4$ Hz; Ar), 6.98 (t, 2H, $J = 7.4$ Hz; Ar), 6.00–5.60 (m, 4H; Ar), 4.44, 3.13 (2d, 8H, $J = 14.0$ Hz; 4ArCH_2Ar), 3.93 (t, 4H, $J = 7.5$ Hz; 2$CH_3CH_2CH_2$), 3.65 (t, 4H, $J = 6.5$ Hz; 2$CH_3CH_2CH_2$), 1.90–1.78 (m, 8H; 4$CH_3CH_2CH_2$), 1.12 (t, 6H, $J = 7.3$ Hz; 2$CH_3CH_2CH_2$), 0.85 (t, 6H, $J = 7.5$ Hz; 2$CH_3CH_2CH_2$). ^{13}C NMR: $\delta = 154.6$, 137.5, 133.1, 129.0, 127.2, 121.5 (Ar), 76.5, 76.2, 75.8 (4$CH_3CH_2CH_2$, 2ArCH_2O), 30.9 (4ArCH_2Ar), 23.4, 22.9

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($4CH_3CH_2CH_2$), 10.7, 9.7 ($4CH_3CH_2CH_2$). CI-MS (CH_4) for $C_{42}H_{50}O_5$ (634.86): $m/z = 635$ [$M^+ + H$].

Compound **13** was eluted second (127 mg, 65%). This compound proved to be >95% pure by ^1H NMR analysis. An analytical sample was obtained by preparative HPLC (25 × 100 mm C18 column, 60 Å, 6 μm, 85:15 CH_3OH/H_2O, 13 mL min^{-1}, detection at 280 nm): m.p. 227–228 °C (from CH_3OH-H_2O); $[\alpha]_D = -24.8$ ($c = 0.9$, CH_3OH). ^1H NMR (CD_3OD): $\delta = 6.85$ (s, 4H; Ar), 6.47–6.36 (m, 6H; Ar), 4.68, 4.40 (2d, 4H, $J = 11.0$ Hz; $2ArCH_2O$), 4.44, 3.13 (2d, 8H, $J = 13.3$ Hz; $4ArCH_2Ar$), 4.26 (d, 2H, $J_{1,2} = 7.7$ Hz; 2H-1), 3.91, 3.77 (2t, 8H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$), 3.82 (dd, 2H, $J_{3,4} = 3.3$, $J_{4,5} = 0.8$ Hz; 2H-4), 3.78 (dd, 2H, $J_{5,6a} = 4.6$, $J_{6a,6b} = 11.3$ Hz; 2H-6a), 3.73 (dd, 2H, $J_{5,6b} = 5.3$ Hz; 2H-6b), 3.55 (dd, 2H, $J_{2,3} = 9.6$ Hz; 2H-2), 3.49 (ddd, 2H; 2H-5), 3.44 (dd, 2H; 2H-3), 2.02–1.86 (m, 8H; $4CH_3CH_2CH_2$), 1.05, 0.98 (2t, 12H, $J = 7.4$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR (CD_3OD): $\delta = 158.3$, 157.5, 137.0, 136.9, 135.6, 132.2, 130.2, 129.4, 129.3, 123.2 (Ar), 103.7 (2C-1), 78.0, 77.9 ($4CH_3CH_2CH_2$), 76.8 (2C-5), 75.1 (2C-3), 72.6 (2C-2), 72.0 ($2ArCH_2O$), 70.4 (2C-4), 62.6 (2C-6), 31.9 ($4ArCH_2Ar$), 24.5, 24.3 ($4CH_3CH_2CH_2$), 11.0, 10.6 ($4CH_3CH_2CH_2$). FAB-HRMS. Calcd for $C_{54}H_{72}NaO_{16}$ [$M^+ + Na$]: 999.4718; found: 999.4769.

When the glycosylation reaction was carried out in CH_2Cl_2 instead of CH_3CN as the solvent, only trace amounts of glycosylated calix[4]arenes were detected.

Ethyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (14): Freshly distilled benzoyl chloride (790 μL, 6.80 mmol) was slowly added to a stirred solution of ethyl 4-*O*-(β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside[48] (250 mg, 0.65 mmol) in pyridine (5 mL). The mixture was stirred at RT for an additional 6 h, then diluted with methanol (1 mL), and concentrated. The residue was eluted from a column of silica gel with 15:1 toluene/ethyl acetate to give **14** (541 mg, 75%) as an amorphous solid: $[\alpha]_D = +49.8$ ($c = 1.0$, $CHCl_3$). ^1H NMR: $\delta = 8.05$–7.11 (m, 35H; 7 Ph), 5.83 (dd, 1H, $J_{2,3} = 9.5$, $J_{3,4} = 9.3$ Hz; H-3), 5.73 (dd, 1H, $J_{3',4'} = 3.4$, $J_{4',5'} = 0.8$ Hz; H-4'), 5.72 (dd, 1H, $J_{1',2'} = 7.9$, $J_{2',3'} = 10.3$ Hz; H-2'), 5.48 (dd, 1H, $J_{1,2} = 9.8$ Hz; H-2), 5.37 (dd, 1H; H-3'), 4.87 (d, 1H; H-1'), 4.73 (d, 1H; H-1), 4.60 (dd, 1H, $J_{5,6a} = 1.8$, $J_{6a,6b} = 12.2$ Hz; H-6a), 4.48 (dd, 1H, $J_{5,6b} = 4.7$ Hz; H-6b), 4.23 (dd, 1H, $J_{4,5} = 9.5$ Hz; H-4), 3.91 (ddd, 1H, $J_{5',6'a} = J_{5',6'b} = 6.5$ Hz; H-5'), 3.87 (ddd, 1H; H-5), 3.75–3.70 (m, 2H; H-6'), 2.75–2.62 (m, 2H; CH_3CH_2), 1.20 (t, 3H, $J = 7.5$ Hz; CH_3CH_2). ^{13}C NMR: $\delta = 165.8$–164.7 (C=O), 133.5–133.2, 129.9–128.2 (Ar), 100.9 (C-1'), 83.7 (C-1), 77.0 (C-5), 75.9 (C-4), 74.0 (C-3), 71.7 (C-3'), 71.3 (C-5'), 70.5 (C-2), 69.8 (C-2'), 67.4 (C-4'), 62.6 (C-6), 61.0 (C-6'), 24.4 (CH_2CH_3), 14.8 (CH_2CH_3). Anal. calcd for $C_{63}H_{54}O_{17}S$: C, 67.85; H, 4.88. Found: C, 68.07; H, 4.96.

5,17-Bis[(4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosyl)oxymethyl]-25,26,27,28-tetrapropoxy-calix[4]arene (15): The diol **11** (33 mg, 0.05 mmol) was glycosylated with thioglycoside **14** (134 mg, 0.12 mmol) in the presence of copper(II) triflate (43 mg, 0.12 mmol), as described for the preparation of **13**. After debenzoylation the crude mixture was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give, first, **16** (16 mg, ≈50%) contaminated by uncharacterized by-products. Eluted second was **15** (16 mg, 25%): m.p. 214–216 °C (from CH_3OH-H_2O); $[\alpha]_D = -19.5$ ($c = 0.4$, CH_3OH). ^1H NMR (CD_3OD) selected data: $\delta = 6.82$ (s, 4H; Ar), 6.51–6.39 (m, 6H; Ar), 4.64, 4.40 (2d, 4H, $J = 11.0$ Hz; $2ArCH_2O$), 4.45, 3.13 (2d, 8H, $J = 14.0$ Hz; $4ArCH_2Ar$), 4.37 (d, 2H, $J_{1,2} = 7.4$ Hz; 2H-1), 4.31 (d, 2H, $J_{1',2'} = 7.9$ Hz; 2H-1'), 2.00–1.88 (m, 8H; $4CH_3CH_2CH_2$), 1.05, 0.99 (2t, 12H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR (CD_3OD) selected data: $\delta = 158.1$, 157.3, 136.8, 135.5, 131.8, 130.2, 130.1, 129.3, 129.2, 123.1 (Ar), 105.1, 102.5 (2C-1, 2C-1'), 62.5, 61.9 (2C-6, 2C-6'), 31.9 ($4ArCH_2Ar$), 24.5, 24.4 ($4CH_3CH_2CH_2$), 11.0, 10.7 ($4CH_3CH_2CH_2$). FAB-HRMS. Calcd for $C_{66}H_{92}NaO_{26}$ [$M^+ + Na$]: 1323.5775; found: 1323.5826.

25,26,27,28-Tetrapropoxy-calix[4]arene (18): A mixture of calix[4]arene **1a** (2.00 g, 4.7 mmol), NaH (2.26 g, 47.1 mmol, of a 50% dispersion in oil), propyl iodide (4.6 mL, 47.1 mmol), and DMF (30 mL) was stirred at RT overnight, and then slowly poured into aqueous 1 M HCl (100 mL) to precipitate crude **18**. The solid was recovered by filtration, dried, and triturated with CH_3OH to give pure **18** (2.09 g, 75%): m.p. 197–199 °C; ref. [49] 197–199 °C. ^1H NMR: $\delta = 6.61$–6.55 (m, 12H; Ar), 4.44, 3.14 (2d, 8H, $J = 13.3$ Hz; $4ArCH_2Ar$), 3.84 (t, 8H, $J = 7.4$ Hz; $4CH_3CH_2CH_2$), 1.91 (ψ-sext, $J = 7.4$ Hz; $4CH_3CH_2CH_2$), 0.98 (t, 12H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR: $\delta = 156.6$, 135.1, 128.1, 121.9 (Ar), 76.7 ($CH_3CH_2CH_2$), 31.0 ($ArCH_2Ar$), 23.2 ($CH_3CH_2CH_2$), 10.3 ($CH_3CH_2CH_2$). CI-MS (CH_4) for $C_{40}H_{48}O_4$ (592.82): $m/z = 593$[$M^+ + H$].

5,11,17,23-Tetraformyl-25,26,27,28-tetrapropoxy-calix[4]arene (19): A mixture of calixarene **18** (570 mg, 0.96 mmol), hexamethylenetetramine (4.04 g, 28.84 mmol), and trifluoroacetic acid (20 mL) was stirred at 125 °C for 4 h in a screw-capped vial, then cooled to RT, diluted with aqueous 1 M HCl (50 mL) and CH_2Cl_2 (50 mL), and vigorously stirred at RT for 3 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (50 mL), dried (Na_2SO_4), and concentrated. Crystallization of the residue from CH_3OH afforded **19** (590 mg, 87%) as a white solid: m.p. 289–290 °C. ^1H NMR: $\delta = 9.58$ (s, 4H; 4CHO), 7.15 (s, 8H; Ar), 4.51, 3.35 (2d, 8H, $J = 13.8$ Hz; $4ArCH_2Ar$), 3.94 (t, 8H, $J = 7.4$ Hz; $4CH_3CH_2CH_2$), 1.90 (ψ-sext, $J = 7.4$ Hz; $4CH_3CH_2CH_2$), 1.01 (t, 12H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR: $\delta = 191.1$ (CHO), 161.7, 135.4, 131.3, 130.1 (Ar), 76.4 ($CH_3CH_2CH_2$), 30.8 ($ArCH_2Ar$), 23.2 ($CH_3CH_2CH_2$), 10.1 ($CH_3CH_2CH_2$). CI-MS (CH_4) for $C_{44}H_{48}O_8$ (704.87): $m/z = 705$ [$M^+ + H$].

5,11,17,23-Tetra(hydroxymethyl)-25,26,27,28-tetrapropoxy-calix[4]arene (20): A suspension of **19** (1.00 g, 1.4 mmol) in 5:1 EtOH/THF (25 mL) was stirred with $NaBH_4$ (161 mg, 4.26 mmol) at RT for 1 h, and then concentrated. The residue was treated with aqueous 1 M HCl (30 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was separated, washed with H_2O (2 × 15 mL), dried ($MgSO_4$), and concentrated to give **20** (1.01 g, 100%) as a white solid: m.p. 271–272 °C (from CH_3OH). ^1H NMR: $\delta = 6.69$ (s, 8H; Ar), 4.42, 3.15 (2d, 8H, $J = 13.0$ Hz; $4ArCH_2Ar$), 4.34 (s, 8H; $4CH_2OH$), 3.84 (t, 8H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$), 1.94 (ψ-sext, $J = 7.5$ Hz; $4CH_3CH_2CH_2$), 0.99 (t, 12H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR: $\delta = 155.9$, 134.8, 134.6, 127.0 (Ar), 76.9 ($CH_3CH_2CH_2$), 64.7 (CH_2OH), 31.0 ($ArCH_2Ar$), 23.3 ($CH_3CH_2CH_2$), 10.3 ($CH_3CH_2CH_2$). CI-MS (CH_4) for $C_{44}H_{56}O_8$ (712.93): $m/z = 712.6$ [$M^+ + H$].

5,11,17,23-Tetrakis[(β-D-galactopyranosyl)oxymethyl]-25,26,27,28-tetrapropoxy-calix[4]arene (21): A mixture of tetrol **20** (213 mg, 0.30 mmol), thioglycoside **12** (384 mg, 0.60 mmol), and anhydrous CH_3CN (15 mL) was stirred at 50 °C until a clear solution was obtained. It was then cooled to RT and treated with activated 4 Å powdered molecular sieves (1.20 g) and, after 15 min, with copper(II) triflate (217 mg, 0.60 mmol). Two portions of both thioglycoside **12** and copper(II) triflate (0.60 mmol each) were added to the reaction mixture after 15 and 30 min. Stirring was continued ar RT for an additional 15 min. The mixture was then 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 (3 × 8 cm) of silica gel with 2:1 cyclohexane/AcOEt in order to remove the copper salts. The crude mixture was treated with freshly prepared ≈0.1 M solution of CH_3ONa in CH_3OH (10 mL) at RT overnight, then neutralized with AcOH, and concentrated. The residue was eluted from a column of Sephadex LH-20 (2.5 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give, first, **17** (10 mg, ≈3%) slightly contaminated by uncharacterized by-products. ^1H NMR (CD_3OD) selected data: $\delta = 7.27$, 7.21 (2s, 4H, Ar), 5.93, 5.67 (2bs, 4H, Ar), 4.93, 4.75 (2d, 4H, $J = 11.7$ Hz; $2ArCH_2O$-sugar), 4.42, 3.11 (2d, 8H, $J = 13.7$ Hz; $4ArCH_2Ar$), 4.41 (d, 2H, $J_{1,2} = 7.7$ Hz; 2H-1), 1.87–1.77 (m, 8H, 4 $CH_3CH_2CH_2$), 1.15, 0.86 (2t, 12H, $J = 7.3$ Hz; $4CH_3CH_2CH_2$). MALDI-TOF MS for $C_{56}H_{74}O_{17}$ (1019.21): $m/z = 1041.9$ [$M^+ + Na$].

Compound **21** eluted second (245 mg, 60%) as an amorphous solid and proved to be >95% pure by ^1H NMR analysis. An analytical sample was obtained by preparative HPLC (25 × 100 mm C18 column, 60 Å, 6 μm, 80:20 CH_3OH/H_2O, 13 mL min^{-1}, detection at 280 nm): $[\alpha]_D = -33.4$ ($c = 0.4$, CH_3OH). ^1H NMR (CD_3OD): $\delta = 6.70$ (s, 8H; Ar), 4.55, 4.33 (2d, 8H, $J = 11.3$ Hz; $4ArCH_2O$), 4.44, 3.14 (2d, 8H, $J = 13.1$ Hz; $4ArCH_2Ar$), 4.21 (d, 4H, $J_{1,2} = 7.5$ Hz; 4H-1), 3.84 (t, 8H, $J = 7.4$ Hz; $4CH_3CH_2CH_2$), 3.81 (dd, 4H, $J_{3,4} = 3.3$, $J_{4,5} = 0.7$ Hz; 4H-4), 3.79 (dd, 4H, $J_{5,6a} = 7.0$, $J_{6a,6b} = 11.4$ Hz; 4H-6a), 3.72 (dd, 4H, $J_{5,6b} = 5.3$ Hz; 4H-6b), 3.54 (dd, 4H, $J_{2,3} = 9.7$ Hz; 4H-2), 3.47 (ddd, 4H; 4H-5), 3.46 (dd, 4H; 4H-3), 2.00–1.88 (m, 8H; $4CH_3CH_2CH_2$), 1.02 (t, 12H, $J = 7.5$ Hz; $4CH_3CH_2CH_2$). ^{13}C NMR (CD_3OD): $\delta = 157.8$, 136.2, 132.2, 130.2, 130.1 (Ar), 103.3 (C-1), 78.0 ($CH_3CH_2CH_2$), 76.8 (C-5), 75.0 (C-3), 72.5 (C-2), 71.7 ($ArCH_2O$), 70.4 (C-4), 62.6 (C-6), 31.9 ($ArCH_2Ar$), 24.4

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($CH_3CH_2CH_2$), 10.8 ($CH_3CH_2CH_2$). FAB-HRMS. Calcd for $C_{68}H_{96}NaO_{28}$ [M^+ + Na]: 1383.5986; found: 1383.6040.

Since some batches of crystalline **20** proved to be partially soluble in CH_3CN at room temperature, the glycosylation reaction was also carried out in 1:1 CH_3CN/CH_2Cl_2 with similar results. However, when the reaction was performed in pure CH_2Cl_2 as the solvent, only trace amounts of glycosylated calix[4]arenes were detected.

Bis(β-D-lactosyl)calix[4]arene derivative 22: Tetrol **20** (29 mg, 0.04 mmol) was glycosylated with thioglycoside **14** (268 mg, 0.24 mmol) in the presence of copper(II) triflate (87 mg, 0.24 mmol), as described for the preparation of **21**. After debenzoylation the crude mixture was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give a mixture of **22** and several by-products. This mixture was submitted to preparative TLC (silica gel $60F_{254}$, 0.5 mm layer, 5:3:2 AcOEt/*i*PrOH/H_2O) to afford **22** (13 mg, ≈25%) slightly contaminated by an uncharacterized by-product. ^{1}H NMR (CD_3OD) selected data: δ = 7.28, 7.21 (2d, 4H, J = 2.0 Hz; Ar), 6.00–5.50 (m, 4H; Ar), 4.92, 4.76 (2d, 4H, J = 11.5 Hz; 2 ArCH_2O-sugar), 4.50 (d, 2H, $J_{1',2'}$ = 7.9 Hz; 2H-1'), 4.42 (d, 4H, J = 13.8 Hz; 4H_{ax} of ArCH_2Ar), 4.37 (d, 2H, $J_{1,2}$ = 7.5 Hz; 2H-1), 3.12, 3.11 (2d, 4H; 4H_{eq} of ArCH_2Ar). MALDI-TOF MS for $C_{68}H_{94}O_{27}$ (1343.50): m/z = 1365.2 [M^+ + Na], 1381.6 [M^+ + K].

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[26] The mixture of monoglucosides was eluted at 13 mL min^{-1} from a 25 × 100 mm silica gel column (60 Å, 6 μm) with 82:18 cyclohexane:AcOEt (detection at 280 nm).

[27] The ^{1}H NMR spectra recorded at room temperature for ≈0.2 M solutions of hemiacetal **5** in $CDCl_3$ or C_6D_6 showed a constant α/β ratio of 3:1 even in the presence of calixarene **1a**.

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