Calixsugars:† Preparation of Upper Rim *O*-Ketopyranosyl Calix[4]arenes†

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Calixarenes[1] are quite popular macrocyclic oligomers arising from the phenol−formaldehyde polymerization and are currently of increasing interest. They provide the basic architectural array for the construction of larger molecular systems with defined structures and properties.[2] Numerous potential applications of calixarene derivatives as specific ligands for cations, anions, and neutral molecules have been foreseen.[3] The *para*-substituted tetramer calix[4]arenes have attracted most of the attention because their formation can be favored by adopting suitable condensation conditions[4] and their conformational mobility can be controlled by placing appropriate substituents in the phenyl rings.[5] Among the complex molecular fragments which have been installed at either rim of these macrocycles,[6] those arising from natural sugars may offer various opportunities for molecular recognition in water of chiral highly polar organic molecules. To this aim we and others have recently described the preparation of calix[4]arenes substituted at the lower and upper rims with *O*-glycosyl groups derived from aldofuranoses and aldopyranoses.[7] Given the ready preparation of various thiazolyl ketols[8] and the role of their acetates to serve as efficient glycosyl donors,[9] it appeared quite interesting to us to extend to these ketoses the glycosylation of calixarenes. Various synthetic elaborations of the resulting calixsugars were foreseen via the facile transformation of the thiazole ring into a readily manipulatable functionality such as the formyl group.[10] This synthetic equivalence plays a pivotal role in this chemistry too. First of all the aldehyde releasing from the thiazole ring is compatible with the presence of the most common hydroxyl protective groups such as the benzyl, isopropylidene, and silyl.[11] Second, the modest electron-withdrawing character of the thiazole ring appears to affect much less dramatically than others groups the glycosylation reaction via an oxycarbenium ion intermediate.[12]

As a ketosyl donor we chose the readily available[8] D-*galacto* derivative **1** whose reactions with trimethylsilyl azide[13] and sugar alcohols[9] were already demonstrated. Hence a model glycosylation reaction between **1** (1.5 equiv for each OH group) and the symmetrical bis-(hydroxymethyl)-substituted calix[4]arene[7,14] **2** (Scheme 1) was generated under the same conditions, *i.e.*, in CH_2Cl_2 at room temperature in the presence of trimethylsilyl triflate (TMSOTf; 1.5 equiv for each OH group) and 4-Å molecular sieves. The slow addition of the Lewis acid by a syringe pump to the solution of **1** and **2** was employed in order to avoid tethering in the latter by intramolecular ether linkage formation (see Experimental Section). Under these conditions the α-linked di-*O*-galactosyl calixarene **4** was isolated by flash chromatography in 60% yield.[15] While the fixed cone conformation of the calixarene moiety in **4** was apparent from the chemical shifts and multiplicity patterns[16] of the proton signals of the methylene bridges in its ^{1}H NMR spectrum, the stereochemistry at the anomeric center of the two sugar moieties was established by ^{13}C NMR analysis of a product derived from it (see below). The high level and sense of stereoselectivity observed in this reaction of the galactoketose acetate **1** are very much in line with the results of earlier glycosylation reactions of this substrate.[9]

† The trivial name calixsugars refers to calixarene derivatives wherein one or more mono- or oligosaccharide moieties are bounded at either the upper or lower rim by an *O*- or *C*-glycosidic bond. The term has been created in analogy to that used for calixarene−crown ether coupled systems (Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075), which were later referred to as calixcrowns (see: (a) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567. (b) Yamamoto, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1994**, 469).

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(1) (a) Gutsche, C. D. In *Calixarenes, Monograph in Supramolecular Chemistry*, Vol. 1; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, 1991.

(2) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.

(3) For recent reviews, see: (a) Takeshita, M.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088. (b) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 3. (c) Lhoták, P.; Shinkai, S. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 963.

(4) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234.

(5) Unmodified calix[4]arenes are conformationally mobile macrocycles which adopt a cone conformation because of strong hydrogen bonds among the hydroxy groups. The *n*-propylation of these groups inhibits the oxygen-through-the-annulus rotation and allows the isolation of the blocked cone conformational isomer (see: (a) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955).

(6) Besides the crown ether moieties, also porphyrin (Nagasaki, T.; Fujishima, H.; Shinkai, S. *Chem. Lett.* **1994**, 989) and β-cyclodextrin (D′ Alessandro, F.; Gulino, F. G.; Impellizzeri, G.; Pappalardo, G.; Rizzarelli, E.; Sciotto, D.; Vecchio, G. *Tetrahedron Lett.* **1994**, *35*, 629. van Dienst, E.; Snellink, B. H. M.; von Piekartz, I.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 1151) have been covalently linked to calix[4]arenes.

(7) Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479.

(8) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404.

(9) Dondoni, A.; Marra, A.; Rojo, I.; Scherrmann, M.-C. *Tetrahedron* **1996**, *52*, 3057.

(10) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992, pp 377−437. Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo, and VCH: Weinheim, 1992; pp 105−128.

(11) This feature favors the use of thiazole instead of furan since the cleavage of the furan ring to carboxyl group requires strong oxidative conditions which are not tolerated by the above protective groups (Dondoni, A.; Marra, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323 and references cited therein). However, due to the electron-donor character of the furan ring, the glycosylation reaction should be favored by the presence of this heterocycle at the anomeric position (see: (a) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280. (b) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929).

(12) Although this matter has been already discussed in our previous paper (see ref 9), it may be recalled here that *O*-glycosidations of sugar bearing at C-1 an alkoxymethyl (*i.e.*, ketoses) or an alkoxycarbonyl group (*i.e.*, ulosonic acids) can be efficiently carried out only if highly reactive leaving groups are present at the anomeric position (*e.g.*, -SR, -SC(S)OEt, $-OP(OR)_2$). For recent articles, see: (a) Lönn, H.; Stenvall, K. *Tetrahedron Lett.* **1992**, *33*, 115. (b) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763. (c) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen, H.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 864. (d) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 5657.

(13) Dondoni, A.; Scherrmann, M.-C.; Marra, A.; Delépine, J.-L. *J. Org. Chem.* **1994**, *59*, 7517.

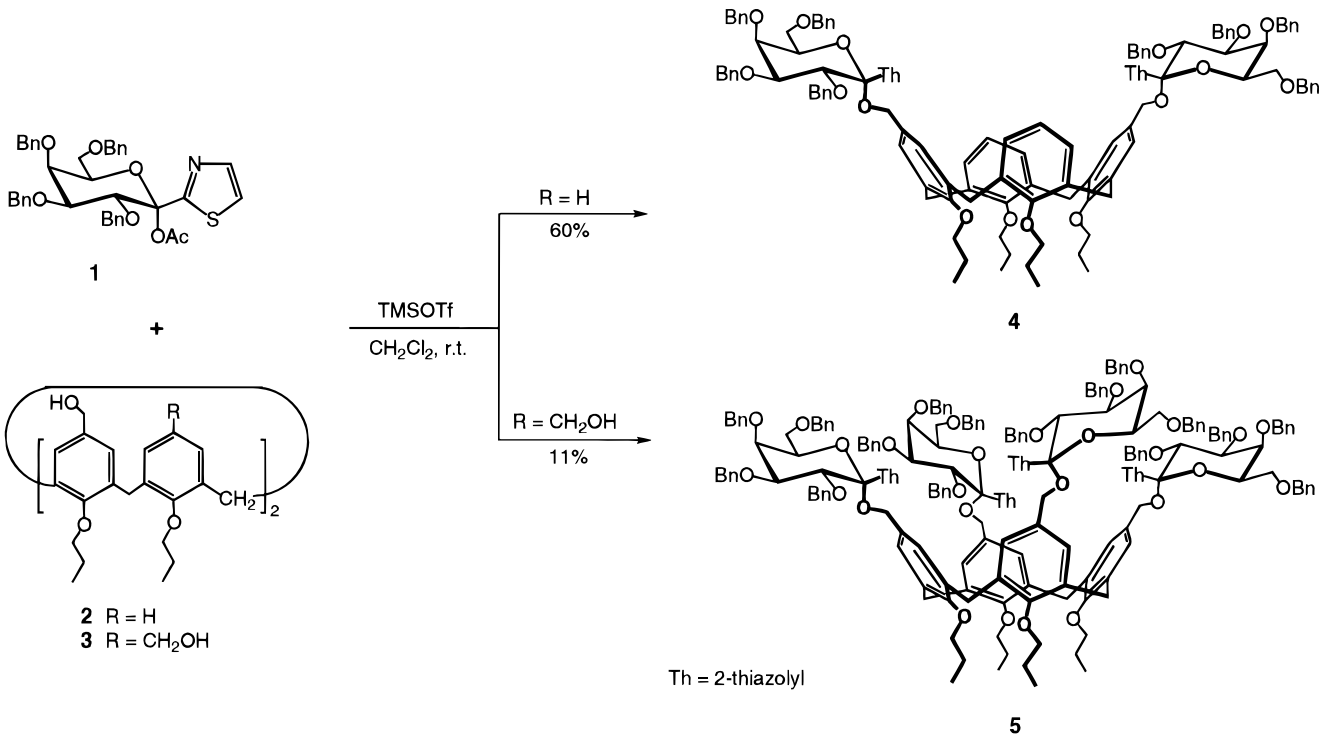
(14) Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.; Reinhoudt, D. N. *Gazz. Chim. Ital.* **1996**, *126*, 99.

(15) Also isolated was unreacted thiazolyl ketol acetate **1** in 32% yield.

(16) Calix[4]arenes having a cone conformation display the signals for the equatorial and axial protons of the methylene bridges as well resolved doublets at $\delta \sim 3$ and $\delta \sim 4$, respectively (see ref 1a, pp 108−111).

S0022-3263(96)00417-3 CCC: $12.00

Scheme 1



Accordingly, an identical explanation can be advanced, *i.e.*, the formation of a chairlike transition state[17] derived from an axial attack of the hydroxyl group of the acceptor **2** to the less hindered face of the oxycarbenium ion intermediate (generated from **1** by the TMSOTf-promoted removal of the acetoxy group) existing in a half-chair conformation and bearing a nonparticipating group at C-2.

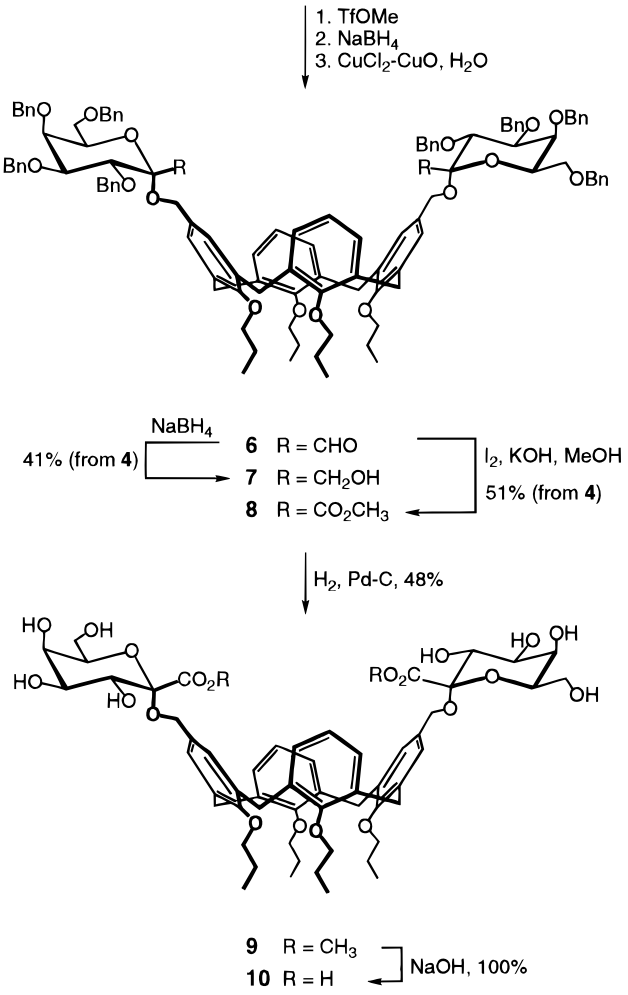
The glycosylation reaction of the same ketosyl donor **1** (1.5 equiv for each OH group) with the tetrakis(hydroxymethyl) calix[4]arene[7] **3** under similar conditions as above (CH_2Cl_2, rt, 1.5 equiv of TMSOTf for each OH group) produced a complex mixture of di-, tri-, and tetraadducts from which the tetrasubstituted calixsugar **5** (Scheme 1) was isolated by flash chromatography in only 11% yield. Individual minor products were not isolated. The poor yield of **5** is very likely due to the restricted cone conformation of the macrocycle and the increasing congestion of the system by the sequential insertion of the bulky ketosyl fragments. Nevertheless, calixsugar **5** appeared to be the product of stereoselective glycosylation as well, since all the four sugar moieties were installed through an α-glycosyl linkage. This stereochemistry was assigned on the basis of strict similarities between the ^{1}H NMR spectrum of **5** and that of the disubstituted calixsugar **4**. To the best of our knowledge, there are no precedents of polyol multiglycosylation with a ketose.

Model synthetic elaborations were generated by the cleavage of the two thiazole rings of the disubstituted calixsugar **4** (Scheme 2) employing the usual one-pot protocol constituted by three sequential and high-yield reactions, *i.e.*, *N*-methylation, reduction, and hydrolysis.[18] The concomitant application of this procedure to two thiazole rings belonging to the same substrate has no precedents. Quite happily, successful unmasking took place to give the dialdehyde **6** which, without purification, was either reduced with sodium borohydride to the diol **7** (41% isolated yield) or oxidized[19] with iodine in methanolic KOH to the diester **8** (51% isolated yield). The anomeric configuration of **8** was assigned on the basis of the vicinal coupling constants between the carboxyl carbon C-1 and the axial proton H-3 (ulosonic acid numbering) following a rule established for sialic acid derivatives.[20] The ^{13}C NMR spectrum, recorded with selective decoupling of the methyl ester protons, showed the C-1 signal as a singlet ($^3J_{C-1,\,H-3} < 1$ Hz), as expected for an α-D-ulosonate derivative in a $^4C_1$ conformation having nearly 60° dihedral angle C-1–C-2–C-3–H-3.[21] The stereochemistry assigned to diester **8** was assumed for its precursors as well.

Quite unexpectedly, the removal of the benzyl protective groups from the diol **7** proved unsuccessful by repeated attempts of hydrogenolysis in the presence of various catalysts (Pd−C, Rh−C, $Pd(OH)_2$). Instead, substantial decomposition of this compound occurred to give complex mixtures of products containing sugar molecules arising from the cleavage of the anomeric benzylic bond. On the other hand, satisfactory debenzylation of the diester **8** to compound **9** (48% isolated yield) was carried out by reduction with hydrogen over Pd−C at 4 bar. The saponification of **9** led to the totally unprotected heptulosonic acid moieties shown in the calixsugar **10**. The same reaction sequence was unsuccessful with the tetrathiazolyl derivative **5**. The thiazolyl-to-formyl unmasking protocol with this compound

(17) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.
(18) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.
(19) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.
(20) (a) Haverkamp, J.; Spoormaker, T.; Dorland, L.; Vliegenthart, J. F. G.; Schauer, R. *J. Am. Chem. Soc.* **1979**, *101*, 4851. (b) Hori, H.; Nakajima, T. Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317. (c) Prytulla, S.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Carbohydr. Res.* **1991**, *215*, 345.
(21) The β-D-anomer having a nearly 180° dihedral angle should display the C-1 signal as a doublet ($^3J_{C-1,H-3} \approx 4.0$ Hz).

Scheme 2



followed by the reduction or oxidation of the crude mixture as described above did not produce any isolable product.

In conclusion, the preparation of calixsugars bearing interesting functional groups in the sugar unit has been shown here. This and previous work[7] open the route for the installation of various types of glycosidic fragments at the lower and upper rims of calixarenes. The application of these methodologies to designed structures and the exploration of their physicochemical properties now become of interest.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[22] and freshly distilled prior to use. Commercially available powdered 4-Å molecular sieves (50 μm average particle size) were used without further activation. Flash column chromatography[23] was performed on silica gel 60 (230−400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at rt for $CDCl_3$ solutions, unless otherwise specified. Assigments were aided by decoupling and/or homo- and heteronuclear two-dimensional experiments. FAB mass spectra were acquired using 3-nitrobenzyl alcohol as the matrix. Since the elemental analyses of calixarenes are very often uncorrected[24] (found carbon values considerably lower than the calculated ones), the identity and purity of the following new compounds were established by MS and NMR analyses.

25,26,27,28-Tetrapropoxy-5,17-bis[[[2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α-D-galactopyranosyl]oxy]methyl]calix[4]arene (4). A mixture of calix[4]arene **2** (130 mg, 0.2 mmol), acetate **1** (400 mg, 0.6 mmol), activated 4-Å powdered molecular sieves (0.60 g), and anhydrous CH_2Cl_2 (6 mL) was stirred at rt for 15 min; then a solution of trimethylsilyl triflate (108 μL, 0.6 mmol) in anhydrous CH_2Cl_2 (1 mL) was added during 30 min by means of a syringe pump apparatus equipped with a gas-tight syringe. After an additional 15 min at rt, the mixture was treated with an excess of Et_3N, diluted with CH_2Cl_2, filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (5:1, then 2:1) to afford first **4** (224 mg, 60%) as a syrup: $[\alpha]_D = +16.5$ (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.85 and 7.36 (2 d, 4 H, J = 3.5 Hz, 2 Th), 7.35−7.18 (m, 40 H, 8 Ph), 7.09 and 6.93 (2 d, 4 H, J = 1.5 Hz, Ar), 6.25 (t, 2 H, J = 7.5 Hz, Ar), 6.20 and 6.13 (2 dd, 4 H, J = 2.0, 7.5 Hz, Ar), 4.99 and 4.65 (2 d, 4 H, J = 11.8 Hz, 2 PhCH_2), 4.77 and 4.73 (2 d, 4 H, J = 11.5 Hz, 2 PhCH_2), 4.66 and 4.37 (2 d, 4 H, J = 11.0 Hz, 2 PhCH_2), 4.54 and 4.47 (2 d, 4 H, J = 11.7 Hz, 2 PhCH_2), 4.53 and 4.40 (2 d, 4 H, J = 11.3 Hz, 2 ArCH_2O), 4.41 (d, 2 H, J = 13.0 Hz, 2 Hax of ArCH_2Ar), 4.39 (d, 2 H, J = 13.0 Hz, 2 Hax of ArCH_2Ar), 4.24 (dd, 2 H, $J_{2,3}$ = 10.0, $J_{3,4}$ = 2.2 Hz, 2 H-3), 4.16 (d, 2 H, 2 H-2), 4.09−4.04 (m, 4 H, 2 H-4, 2 H-5), 3.90−3.20 (m, 4 H, 2 $CH_3CH_2CH_2$O), 3.82−3.73 (m, 4 H, 4 H-6), 3.71 (t, 4 H, 2 $CH_3CH_2CH_2$O), 3.09 (d, 2 H, 2 Heq of ArCH_2-Ar), 3.08 (d, 2 H, 2 Heq of ArCH_2Ar), 2.00−1.83 (m, 8 H, 4 $CH_3CH_2CH_2$O), 1.09 (t, 6 H, J = 7.0 Hz, 2 $CH_3CH_2CH_2$O), 0.89 (t, 6 H, J = 7.0 Hz, 2 $CH_3CH_2CH_2$O). FAB-MS for $C_{116}H_{122}N_2O_{16}S_2$: m/z 1865.3 (M + H$^+$). Eluted second was unreacted **1** (128 mg, 32%).

25,26,27,28-Tetrapropoxy-5,11,17,23-tetrakis[[[2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α-D-galactopyranosyl]oxy]-methyl]calix[4]arene (5). A mixture of calix[4]arene **3** (71 mg, 0.1 mmol), acetate **1** (400 mg, 0.6 mmol), activated 4-Å powdered molecular sieves (0.60 g), and anhydrous CH_2Cl_2 (6 mL) was stirred at rt for 15 min; then a solution of trimethylsilyl triflate (108 μL, 0.6 mmol) in anhydrous CH_2Cl_2 (1 mL) was added during 50 min by means of a syringe pump apparatus equipped with a gas-tight syringe. At the end of the addition, the mixture was treated with an excess of Et_3N, diluted with CH_2Cl_2, filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane−AcOEt to give **5** together with uncharacterized byproducts. Column chromatography (12:1 CH_2Cl_2−Et_2O) of this mixture afforded pure **5** (35 mg, 11%) as a syrup: $[\alpha]_D = +12.3$ (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 7.69 (d, 4 H, $J_{4,5}$ = 3.2 Hz, H-4 of 4 Th), 7.31−7.20 (m, 84 H, 16 Ph, H-5 of 4 Th), 6.71−6.52 (2 d, 8 H, J = 2.0 Hz, 4 Ar), 4.90 and 4.57 (2 d, 8 H, J = 11.7 Hz, 4 PhCH_2), 4.66 and 4.61 (2 d, 8 H, J = 12.0 Hz, 4 PhCH_2), 4.52 and 4.20 (2 d, 8 H, J = 11.0 Hz, 4 PhCH_2), 4.43 and 4.33 (2 d, 8 H, J = 11.6 Hz, 4 PhCH_2), 4.33 and 3.00 (2 d, 8 H, J = 13.2 Hz, 4 ArCH_2Ar), 4.16 and 3.93 (2 d, 8 H, J = 11.7 Hz, 4 ArCH_2O), 4.07−4.00 (m, 8 H, 4 H-2, 4 H-3), 3.98 (m, 4 H, 4 H-4), 3.82−3.68 (m, 16 H, 4 $CH_3CH_2CH_2$O, 4 H-5, 4 H-6a), 3.54 (dd, 4 H, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 8.1 Hz, 4 H-6b), 1.91−1.78 (m, 8 H, 4 $CH_3CH_2CH_2$O), 0.92 (t, 12 H, J = 7.4 Hz, 4 $CH_3CH_2CH_2$O). Electrospray-MS for $C_{192}H_{196}N_4O_{28}S_4$: m/z 3135.83 ± 1.21 (M + H$^+$).

25,26,27,28-Tetrapropoxy-5,17-bis[[(3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranosyl)oxy]methyl]calix[4]-arene (7). A mixture of thiazolyl ketoside **4** (186 mg, 0.1 mmol), activated 4-Å powdered molecular sieves (0.2 g), anhydrous CH_2Cl_2 (0.5 mL), and anhydrous CH_3CN (1 mL) was stirred at rt for 10 min; then methyl triflate (28 μL, 0.26 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness. The crude bis(*N*-methylthiazolium) salt was suspended in 1:1 MeOH−Et_2O (2 mL) and treated with $NaBH_4$ (15 mg, 0.4 mmol). The mixture was stirred at rt for an

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(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(24) The issue regarding these discrepancies in elemental analyses has been addressed by authoritative researchers in calixarene chemistry. See: (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.

additional 5 min; diluted with acetone (1 mL), and concentrated. The residue was suspended in CH_2Cl_2, filtered through Celite, and concentrated. A solution of the crude thiazolidines in CH_2Cl_2 (0.5 mL) was diluted with CH_3CN (1 mL) and H_2O (0.1 mL), and then treated with CuO (127 mg, 1.6 mmol) and $CuCl_2 \cdot 2H_2O$ (34 mg, 0.2 mmol). The mixture was sonicated at rt for 10 min in an ultrasonic cleaning bath and then concentrated to dryness (temperature not exceeding 40 °C). The brown solid was triturated with Et_2O (4 × 3 mL), and the liquid phase was pipetted and filtered through Celite. The solution was concentrated to afford the dialdehyde **6** as a brown syrup which was used in the next step without further purification. To a stirred solution of crude **6** in Et_2O (1 mL) and MeOH (0.5 mL) was added $NaBH_4$ (15 mg, 0.4 mmol). Stirring was continued at rt for 10 min; then acetone (1 mL) was added and the mixture was concentrated. A solution of the crude diol in CH_2Cl_2 (30 mL) was washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated. Column chromatography (5:1 cyclohexane−AcOEt) of the residue afforded **7** (72 mg, 41%) as a syrup: $[\alpha]_D = +21.9$ (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.40−7.22 (m, 40 H, 8 Ph), 6.83 and 6.76 (2 d, 4 H, $J = 2.0$ Hz, Ar), 6.36−6.26 (m, 6 H, Ar), 4.99 and 4.78 (2 d, 4 H, $J = 11.1$ Hz, 2 PhCH_2), 4.95 and 4.58 (2 d, 4 H, $J = 11.3$ Hz, 2 PhCH_2), 4.73 (s, 4 H, 2 PhCH_2), 4.51 and 4.41 (2 d, 4 H, $J = 11.8$ Hz, 2 PhCH_2), 4.49 and 4.42 (2 d, 4 H, $J = 12.0$ Hz, 2 ArCH_2O), 4.40 (d, 2 H, $J = 13.2$ Hz, 2 Hax of ArCH_2Ar), 4.39 (d, 2 H, $J = 13.2$ Hz, 2 Hax of ArCH_2Ar), 4.25 (d, 2 H, $J_{3,4} = 10.0$ Hz, 2 H-3), 4.11 (dd, 2 H, $J_{4,5} = 2.6$ Hz, 2 H-4), 4.01 (d, 1 H, $J_{5,6} = 1.0$ Hz, 2 H-5), 3.94 (ddd, 2 H, $J_{6,7a} = J_{6,7b} = 6.5$ Hz, 2 H-6), 3.91−3.85 (m, 4 H, 2 $CH_3CH_2CH_2O$), 3.75 (t, 4 H, $J = 7.0$ Hz, 2 $CH_3CH_2CH_2O$), 3.66 (dd, 2 H, $J_{1a,1b} = 11.8$, $J_{1a,OH} = 9.2$ Hz, 2 H-1a), 3.62−3.59 (m, 4 H, 4 H-7), 3.57 (dd, 2 H, $J_{1b,OH} = 3.5$ Hz, 2 H-1b), 3.06 (d, 4 H, 4 Heq of ArCH_2Ar), 2.38 (dd, 2 H, 2 OH), 1.98−1.83 (m, 8 H, 4 $CH_3CH_2CH_2O$), 1.04 (t, 6 H, $J = 7.3$ Hz, 2 $CH_3CH_2CH_2O$), 0.92 (t, 6 H, $J = 7.3$ Hz, 2 $CH_3CH_2CH_2O$). FAB-MS for $C_{112}H_{124}O_{18}$: *m*/*z* 1781.3 ($M + Na^+$).

25,26,27,28-Tetrapropoxy-5,17-bis[[(methyl 3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranosylonate)oxy]methyl]-calix[4]arene (8). The thiazolyl ketoside **4** (186 mg, 0.1 mmol) was converted into the dialdehyde **6** as described for the preparation of **7**. To a vigorously stirred solution of crude **6** in Et_2O (1 mL) and MeOH (1 mL) were added, dropwise and simultaneously, a 1 M solution of KOH in MeOH and a 0.5 M solution of I_2 in MeOH until the intermediate methyl hemiacetals formed *in situ* had disappeared (TLC analysis); then the mixture was neutralized with AcOH and concentrated. The crude diester was diluted with CH_2Cl_2 (30 mL), washed with aqueous 10% $Na_2S_2O_3 \cdot 5H_2O$ (2 × 5 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 6:1 cyclohexane−AcOEt to give **8** (92 mg, 51%) as a syrup: $[\alpha]_D = -3.8$ (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 7.38−7.21 (m, 40 H, 8 Ph), 7.07 and 6.95 (2 d, 4 H, $J = 1.8$ Hz, Ar), 6.28−6.15 (m, 6 H, Ar), 4.97 and 4.66 (2 d, 4 H, $J = 11.8$ Hz, 2 PhCH_2), 4.87 and 4.70 (2 d, 4 H, $J = 11.5$ Hz, 2 PhCH_2), 4.85 and 4.47 (2 d, 4 H, $J = 11.4$ Hz, 2 ArCH_2O), 4.73 (s, 4 H, 2 PhCH_2), 4.50 and 4.40 (2 d, 4 H, $J = 11.5$ Hz, 2 PhCH_2), 4.41 (d, 2 H, $J = 13.5$ Hz, 2 Hax of ArCH_2Ar), 4.39 (d, 2 H, $J = 13.5$ Hz, 2 Hax of ArCH_2Ar), 4.37 (d, 2 H, $J_{3,4} = 10.0$ Hz, 2 H-3), 4.10 (dd, 2 H, $J_{4,5} = 2.7$ Hz, 2 H-4), 3.99 (dd, 2 H, $J_{5,6} = 1.0$ Hz, 2 H-5), 3.96−3.91 (m, 4 H, 2 $CH_3CH_2CH_2O$), 3.87 (ddd, 2 H, $J_{6,7a} = J_{6,7b} = 6.5$ Hz, 2 H-6), 3.70 (t, 4 H, $J = 7.0$ Hz, 2 $CH_3CH_2CH_2O$), 3.65−3.61 (m, 4 H, 4 H-7), 3.58 (s, 6 H, 2 $COCH_3$), 3.07 (d, 4 H, 4 Heq of ArCH_2-Ar), 2.00−1.82 (m, 8 H, 4 $CH_3CH_2CH_2O$), 1.08 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$), 0.88 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$). ^{13}C NMR (selected data): δ 167.83 (2 CO_2CH_3), 100.44 (2 C-2), 52.42 (2 CO_2CH_3), 31.00 (4 ArCH_2Ar), 23.45 and 23.01 (4 $CH_3CH_2CH_2O$), 10.73 and 9.92 (4 $CH_3CH_2CH_2O$). FAB-MS for $C_{114}H_{124}O_{20}$: *m*/*z* 1837.5 ($M + Na^+$).

25,26,27,28-Tetrapropoxy-5,17-bis[[(methyl α-D-*galacto*-heptulopyranosylonate)oxy]methyl]calix[4]arene (9). A vigorously stirred mixture of **8** (91 mg, 0.05 mmol) and 10% palladium on activated carbon (45 mg) in 2:1 MeOH-AcOEt (10 mL) was degassed under vacuum and saturated with hydrogen three times. The suspension was stirred for an additional 4 h at rt under 4 bar of H_2 and then filtered through a plug of cotton and concentrated. The residue was eluted from a Sephadex LH-20 column (2 × 80 cm) with 5:1 CH_2Cl_2-MeOH to give **9** (26 mg, 48%) as an amorphous solid: $[\alpha]_D = +42.8$ (*c* 0.5, MeOH). ^{1}H NMR (CD_3OD): δ 6.90 and 6.82 (2 d, 4 H, $J = 2.0$ Hz, Ar), 6.52−6.40 (m, 6 H, Ar), 4.46 (d, 4 H, $J = 13.3$ Hz, 4 Hax of ArCH_2Ar), 4.46 and 4.32 (2 d, 4 H, $J = 11.0$ Hz, 2 ArCH_2O), 3.94−3.74 (m, 16 H, 2 H-5, 2 H-6, 4 H-7, 4 $CH_3CH_2CH_2O$), 3.91 (d, 2 H, $J_{3,4} = 9.8$ Hz, 2 H-3), 3.80 (s, 6 H, 2 $COCH_3$), 3.73 (dd, 2 H, $J_{4,5} = 3.5$ Hz, 2 H-4), 3.15 (d, 4 H, 4 Heq of ArCH_2Ar), 2.02−1.86 (m, 8 H, 4 $CH_3CH_2CH_2O$), 1.06 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$), 0.99 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$).

25,26,27,28-Tetrapropoxy-5,17-bis[[(α-D-*galacto*-heptulopyranosylonic acid)oxy]methyl]calix[4]arene (10). A solution of **9** (33 mg, 0.03 mmol) in 9:1 MeOH−H_2O (3 mL) was treated with freshly prepared 6 M NaOH (0.3 mL) for 3 h at rt and then applied to a short column (0.5 × 10 cm) of Amberlite IR 120 (16−45 mesh, H^+ form) and eluted with 9:1 MeOH−H_2O to give **10** (32 mg, 100%) as a solid: mp 118 °C dec; $[\alpha]_D = +40.4$ (*c* 0.5, MeOH). ^{1}H NMR (CD_3OD): δ 7.23 and 6.99 (2 d, 4 H, $J = 2.0$ Hz, Ar), 6.37−6.28 (m, 6 H, Ar), 4.55 and 4.45 (2 d, 4 H, $J = 10.7$ Hz, 2 ArCH_2O), 4.45 (d, 4 H, $J = 13.3$ Hz, 4 Hax of ArCH_2Ar), 3.99−3.71 (m, 16 H, 2 H-5, 2 H-6, 4 H-7, 4 $CH_3CH_2CH_2O$), 3.90 (d, 2 H, $J_{3,4} = 9.7$ Hz, 2 H-3), 3.78 (dd, 2 H, $J_{4,5} = 3.2$ Hz, 2 H-4), 3.15 (d, 4 H, 4 Heq of ArCH_2Ar), 2.04−1.86 (m, 8 H, 4 $CH_3CH_2CH_2O$), 1.09 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$), 0.96 (t, 6 H, $J = 7.5$ Hz, 2 $CH_3CH_2CH_2O$). FAB-MS for $C_{56}H_{72}O_{20}$: *m*/*z* 1088.2 ($M + Na^+$).

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Supporting Information Available: ^{1}H NMR spectra of compounds **4**, **5**, **7**, **8**, **9**, and **10** as evidence of the degree of purity (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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