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Synthesis of upper rim calix[4]arene divalent glycoclusters via amide bond conjugation

Uta Schädel, Francesco Sansone, Alessandro Casnati and Rocco Ungaro*

Dipartimento di Chimica Organica e Industriale, Università degli Studi, Parco Area delle Scienze 17/A, I-43100 Parma, Italy

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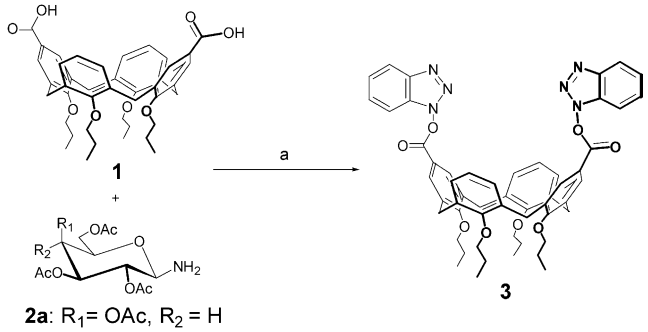
Abstract—Synthetic routes for linking two sugar units at the upper rim of cone calix[4]arenes, through the formation of amide bonds, have been explored. Steric effects prevent the coupling of calix[4]arene dicarboxylic acid with simple aminoglycosides, whereas the corresponding reaction with carbohydrates bearing a two or three carbon atoms spacer, terminating with a primary amino group, allows the synthesis of several difunctionalized calix[4]arene neoglycoconjugates, attractive in chemical glycobiology and supramolecular chemistry.

1. Introduction

Carbohydrate clusters are becoming interesting targets as model systems for studying protein–sugar[1] and sugar–sugar[2] interactions, which play a central role in glycobiology.[3] Neoglycoconjugates based on cyclodextrin and calixarene cores[4] have been used for this purpose and they are also attractive as potential molecular delivery systems.[5] For this purpose, the presence of binding groups in addition to the sugar units is useful in order to complex substrates to be delivered to a specific target. In the case of calix[4]arenes, the sugar moieties were almost exclusively attached at the lower or upper rim through the formation of ether bonds or carbon–carbon bonds[6] exploiting trimethylsilyl triflate[7a] and copper(II) triflate[7b] mediated glycosylation reactions on bis- and tetrahydroxymethylcalix[4]arenes, a Suzuki type reaction using calix[4]arene di- and monoboronic acid derivatives[7d] and Wittig reactions[7c,e] on formylated calix[4]arenes. Only a couple of examples of thiourea containing glycocalixarenes are known where the hydrogen bonding spacer is able to complex anionic species.[8] The dicarboxylic acid **1** is a well known cone calix[4]arene intermediate[9] and has been used for the synthesis of cleft-like[10] and macrobicyclic[11] N-linked peptidocalix[4]arenes and other molecular receptors.[12] We therefore explored the possibility of using compound **1** as a starting material for the synthesis of novel upper rim calix[4]arene glycoconjugates through amide bond formation, where the amide group could be exploited for the binding of acidic and/or basic substrates, and report in this paper the synthetic results obtained. An amide bond has been used to synthesize lower rim calix[4]arene–monosaccharide conjugates,[13] but to the best of our knowledge the synthesis of upper rim derivatives has never been reported.

2. Results and discussion

Reaction of the calix[4]arene diacid **1**[9] with 2,3,4,6-tetra-*O*-acetyl-β-D-galactosamine **2a**[14] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucosamine **2b**[14] in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and triethylamine (TEA) at rt (Scheme 1) did not give a glycosylated calixarene, but the benzotriazole ester **3**, which was isolated in yields higher than 70% and characterized since it is quite stable. Heating compound **3** with these monosaccharides overnight in presence of an excess of base in acetonitrile led to the complete



Scheme 1. (a) HBTU, TEA, CH_2Cl_2, rt, 5 h.

Keywords: Calix[4]arene; Neoglycoconjugates; Glycoside; Amide bond.
* Corresponding author. Tel.: +39 0521 905412; fax: +39 0521 905472; e-mail: rocco.ungaro@unipr.it

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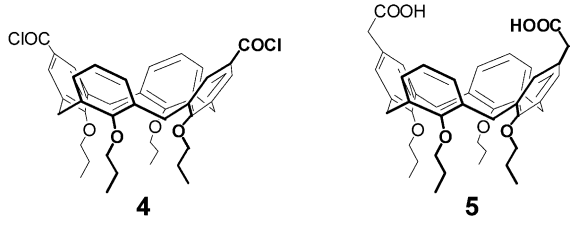
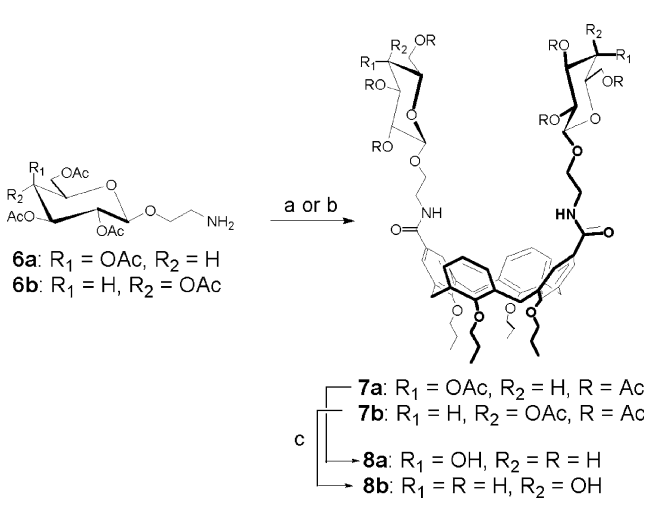
decomposition of **3** without forming any coupling product with glycosamines **2a**,**b**. Similarly, when the acid chloride **4**[11] was reacted with glycosylamines **2a**,**b** using TEA as base, the calix[4]arene acid **1** and the sugar were found after aqueous work-up and no coupling product could be detected.



Suspecting that failure in the coupling reaction between **2a**,**b** and **3** or **4** could be mainly ascribed to repulsive steric interactions between the reacting partners, we decided to introduce a spacer either on the calixarene or on the sugar moiety. Nevertheless, the condensation reaction of calix[4]-arene–acetic acid derivative **5**[15] with galactosamine **2a** was unsuccessful in a variety of conditions. On the other hand, the reaction of the calix[4]arene dicarboxylic acid **1** with the galactosamine derivative **6a**,[16] having a two methylene unit spacer between the sugar moiety and the amine group, in the presence of HBTU and an excess of base (pH > 12) at 80 °C in acetonitrile, led to the synthesis of the coupling product **7a** (Scheme 2). Comparable results were obtained using glucosamine **6b** as glycosyl donor to obtain **7b**, and also reacting at rt the two glycosylamines **6a** and **6b** with the calixarene diacylchloride **4**. Deprotection of **7a**,**b** with triethylamine in aqueous methanol gave the amide-linked glycoconjugates **8a**,**b** in 30–33% overall yield. The ^{1}H NMR spectra of derivatives **7a**,**b** in $CDCl_3$ show sharp signals, which allow the exclusion of intermolecular aggregation phenomena. It is well known[17] that calix[4]arenes difunctionalized at the upper rim with hydrogen bonding donor and acceptor groups can experience intramolecular H-bonding in apolar solvents, which stabilize a closed flattened cone conformation (Fig. 1) with respect to the open flattened cone conformation, which is more stable in strong donor solvents. Usually, these conformational preferences can be recognized very clearly by inspecting the aromatic region of the ^{1}H NMR spectra of these compounds. In the case of glycocalixarenes **7a**,**b**, the aromatic protons of the unsubstituted aromatic rings resonate at $\delta \sim 6.30$ and those of the substituted ones at $\delta \sim 7.35$, thus confirming that these compounds exist mainly in the open flattened cone conformation, in $CDCl_3$.



Scheme 2. (a) **1**, HBTU, TEA, CH_3CN, 80 °C, 12 h, 35–37%; (b) **4**, TEA, CH_2Cl_2, rt; (c) TEA, MeOH, H_2O, rt, 16 h, 96–98%.

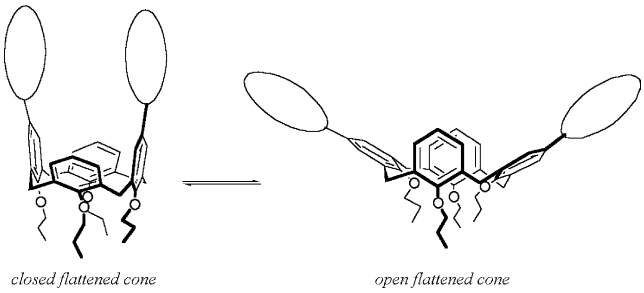
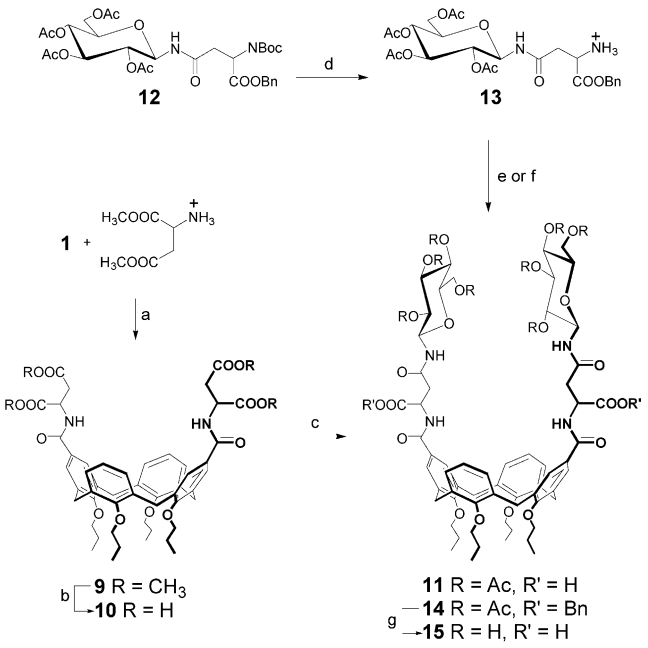


Figure 1. The two possible flattened cone conformers of a upper rim difunctionalised tetrapropoxycalix[4]arene.

Therefore, no intramolecular hydrogen bonding is taking place between the two amide groups in compounds **7a**,**b** which could be ascribed to the intrinsic weakness of the noncovalent interaction or to steric repulsion between the two protected sugar units. The ^{1}H NMR spectra of the deprotected glycocalixarenes **8a**,**b** in the same solvent give very broad signals, which tend to sharpen upon dilution, thus indicating extensive intermolecular aggregation due to the large number of free OH groups. In CD_3OD, the spectra show sharp signals instead. The relative position of the signals of the aromatic protons in this solvent indicates again a preference for the open flattened cone conformation also for compounds **8a**,**b**. Both for the protected and the deprotected compounds **7a**,**b** and **8a**,**b** no splitting could be observed for the signals of the *ortho* aromatic and of the axial and equatorial protons of the calixarene Ar–CH_2–Ar methylene bridge, which is indeed typical for other calix[4]arene derivatives bearing chiral units at the upper rim.[7b,10,11] Evidently, because of the spacer, the carbohydrate chiral units are too far away from the calixarene skeleton to influence its NMR signals.

The second approach we investigated was the formation of an amide bond with an amino acid spacer. This constitutes an attractive route to build up a novel type of hybrid sugar–peptidocalix[4]arene receptors to be used in the recognition of biologically relevant substrates. We focused our attention on aspartic acid as spacer, because of its wide use in natural and synthetic peptides for the linkage of sugar units, and on glucose as saccharide unit, because of its higher solubility in water in comparison with other neutral monosaccharides, which could lead to water soluble glycocalixarenes. L-Aspartic acid dimethyl ester hydrochloride was then reacted with the calix[4]arene diacid **1** giving **9** and, after hydrolysis, **10** in moderate overall yields. The reaction of compound **10** with glucosamine **2b** in the presence of HBTU (Scheme 3) gave a complex mixture of products in which the sugar–peptide conjugate **11** was detected by ESI-MS but could not be isolated. Significantly better results were obtained through the alternative synthetic route consisting in the condensation of the sugar–amino acid derivative **13** with calix[4]arene dicarboxylic acid **1** or diacylchloride **4** (Scheme 3). In these cases, the protected

sugar–peptidocalix[4]arene conjugate **14** was obtained in 68–72% yield and the full deprotection both from benzyl and acetyl groups with TEA in a 8/1 methanol/water mixture easily occurred, leading to the isolation of the glycopeptidocalix[4]arene **15** as bis triethylammonium salt.



Scheme 3. (a) HBTU, TEA, CH_2Cl_2, rt, 4 h, 64%; (b) LiOH, THF, H_2O, from 0 °C to rt, 6 h, 92%; (c) **2b**, HBTU, TEA, CH_2Cl_2, rt, 12 h; (d) CF_3COOH, CH_2Cl_2, from 0 °C to rt, 2 h, quantitative; (e) **1**, HBTU, TEA, CH_2Cl_2, rt, 4 h, 72%; (f) **4**, TEA, CH_2Cl_2, rt, 4 h, 68%; (g) TEA, MeOH, H_2O, rt, 16 h, Amberlite IR-120 resin, 95%.

The protected derivative **14** in $CDCl_3$ exists in the open flattened cone conformation and the corresponding deprotected glycocalix[4]arene **15** shows similar properties to those described above for compounds **8a**,**b** in $CDCl_3$ and CD_3OD. Titration of **15** with an aqueous solution of NaOH gave the corresponding sodium salt which shows good solubility in water up to 1.4×10^{-2} M. The ^{1}H NMR spectrum in D_2O of this compound is rather broad indicating extensive aggregation phenomena which are currently under investigation.

3. Conclusion

Several synthetic routes for linking two sugar units at the upper rim of cone calix[4]arenes, through the formation of amide bonds, have been investigated. Steric effects prevent the coupling of calix[4]arene dicarboxylic acid with simple aminoglycosides, whereas the corresponding reaction with carbohydrates bearing a two or three carbon atoms spacer terminating with a primary amino group was more successful. This strategy allowed the synthesis of several difunctionalized calix[4]arene neoglycoconjugates, attractive in chemical glycobiology and supramolecular chemistry. The conformational properties of the compounds synthesized have been established by ^{1}H NMR experiments in different solvents.

4. Experimental

All moisture sensitive reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points were determined on an Electrothermal apparatus with samples in tubes sealed under nitrogen atmosphere or on a Kofler apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers. Spectra are reported in ppm downfield from TMS as internal standard. Mass spectra by electrospray ionization (ESI) and chemical ionization (CI) methods were recorded on a Micromass ZMD and on a Finnigan Mat SSQ710 spectrometer, respectively. Elemental analyses were performed using a CHN 1106 Carlo Erba instrument and are reported as percentage. Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminum). Merck silica gel (40–63 μm) was used for flash-chromatography. *N*-Boc-L-Asp-OBn was purchased from Novabiochem. The calix[4]arene dicarboxylic acid **1**,[9] the corresponding diacyl chloride **4**,[11] the 2,3,4,6-tetra-*O*-acetyl-β-D-galacto- and β-D-glucosamine **2a**,**b**[14] and the 2,3,4,6-tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galacto- and β-D-glucoside **6a**,**b**[16] were synthesized according to literature procedures.

4.1. General procedures for the coupling of amines with carboxylic calix[4]arene derivatives

(A) The amine and triethylamine (TEA) were added to a suspension in dry methylene chloride of the calix[4]arene dicarboxylic acid derivative. Then HBTU was added. The reaction was stirred for 4 h at rt unless otherwise specified. During the first 30 min, the pH-value was frequently checked and TEA was added if necessary to keep pH at ca. 8.5. The reaction was quenched with a 5% NH_4Cl water solution. The organic layer was separated, washed with 5% $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash-chromatography on silica gel.

(B) A solution of calixarene diacylchloride **4**, amine and TEA in dry methylene chloride was stirred at rt for 4 h, then the reaction was quenched by addition of a 5% NH_4Cl water solution. The organic layer was separated, washed with 5% $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash-chromatography on silica gel.

4.2. General procedure for the deprotection of the glycocalixarenes from the acetyl groups

(C) The protected glycocalixarene was treated with the mixture methanol/water/TEA 8/1/1 at rt overnight. The reaction was quenched by evaporation to dryness in vacuo, then the residue was dissolved in methanol and treated with Amberlite IR-120 resin until neutral pH. The resin was filtered off and the solution was evaporated to dryness in vacuo.

4.2.1. 5,17-Bis(benzotriazolyloxycarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (3). This compound was isolated as main product from the reaction of 5,17-

bis(hydroxycarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]-arene[9] (**1**) with 2,3,4,6-tetra-*O*-acetylgalactosamine[14] (**2a**) and with 2,3,4,6-tetra-*O*-acetylglucosamine[14] (**2b**) according to the reported general procedure A. White crystals; yield 75–78%; mp 237–238 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, J=8.0, 1.0 Hz, 2H, Ar), 7.89 (s, 4H, Ar), 7.39 (m_c, 6H, Ar), 6.52 (t, J=6.0 Hz, 2H, Ar), 6.44 (d, J=6.0 Hz, 4H, Ar), 4.55 (d, J=13.5 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.14 (t, J=7.7 Hz, 4H, $OCH_2CH_2CH_3$), 3.81 (t, J=7.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.34 (d, J=13.6 Hz, 4H, H_{eq} of $ArCH_2Ar$), 1.96 (m_c, 8H, $OCH_2CH_2CH_3$), 1.09 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 1.01 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7 (C=O, C_{ar}), 155.5, 143.4, 137.3, 132.9, 131.4, 128.4, 128.2, 124.6, 122.7, 120.1, 117.9, 108.4 (C_{ar}), 77.14, 77.09 ($OCH_2CH_2CH_3$), 30.9 ($ArCH_2Ar$), 23.3 ($OCH_2CH_2CH_3$), 10.5, 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{54}H_{54}N_6O_8$ (914.40): m/z 937.5 $[M^+ + Na]^+$. Anal. Calcd for $C_{54}H_{54}N_6O_8$: C, 70.88; H, 5.95; N, 9.18. Found C, 70.85; H, 5.96; N, 9.21.

4.2.2. 5,17-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (7a). 2,3,4,6-Tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galactoside (**6a**)[16] (0.61 g, 1.55 mmol) and compound **1** (0.26 g, 0.39 mmol) were reacted in presence of HBTU (0.43 g, 0.94 mmol) and TEA (1.00 mL, 7.64 mmol) following the general procedure A but using dry acetonitrile (20 mL) as solvent. In this case, the reaction was also heated to reflux overnight. Alternatively, 2,3,4,6-tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galactoside (**6a**)[16] (0.60 g, 1.53 mmol) and compound **4** (0.28 g, 0.39 mmol) were reacted in presence of TEA (0.2 mL, 1.53 mmol) following procedure B. The crude product was chromatographed with ethyl acetate. Light yellow oil; yield 0.19 g (37%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 4H, Ar), 6.51–6.39 (m, 4H, Ar, NH), 6.38–6.27 (m, 4H, Ar), 5.38 (d, J=3.4 Hz, 2H, H-4), 5.20 (dd, J=10.5, 7.9 Hz, 2H, H-2), 5.02 (dd, J=10.5, 3.4 Hz, 2H, H-3), 4.50 (d, J=7.8 Hz, 2H, H-1), 4.45 (d, J=13.4 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.15–4.04 (m, 4H, H-6,6′), 4.03–3.85 (m, 6H, H-5, $OCH_2CH_2CH_3$), 3.80–3.63 (m, 8H, $C(O)NHCH_2CH_2$, $OCH_2CH_2CH_3$), 3.63–3.45 (m, 4H, $C(O)NHCH_2CH_2$), 3.21 (d, J=13.4 Hz, 4H, H_{eq} of $ArCH_2Ar$), 2.13, 2.02, 1.97, 1.89 (4s, 6H each, $C(O)CH_3$), 2.01–1.82 (2m, 4H each, $OCH_2CH_2CH_3$), 1.04 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.92 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.3, 170.2, 170.1, 170.0, 169.6 ($C(O)NH$, $C(O)CH_3$), 160.5, 155.8, 135.9, 133.5, 128.1, 128.0, 127.7, 122.3 (C_{ar}), 101.4 (C-1), 76.8, 76.6 ($OCH_2CH_2CH_3$), 70.8, 70.7, 68.9, 68.0, 66.9, 61.2 (C-2, C-3, C-4, C-5, C-6, $NHCH_2CH_2O$), 39.5 ($NHCH_2CH_2O$), 30.9 ($ArCH_2Ar$), 23.3, 23.25, 23.20, 23.1 ($OCH_2CH_2CH_3$), 20.5, 20.4 ($C(O)CH_3$), 10.4, 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{74}H_{94}N_2O_{26}$ (1426.61): m/z 1449.6 $[M+Na]^+$. Anal. Calcd for $C_{74}H_{94}N_2O_{26}$: C, 62.26; H, 6.64; N, 1.96. Found C, 62.30; H, 6.63; N, 1.99.

4.2.3. 5,17-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (7b). The compound was obtained following the general procedure B starting from calixarene **4**[11] (0.15 g, 0.21 mmol) and glucoside **6b**[16] (0.33 g, 0.84 mmol) in presence of TEA (0.12 mL, 0.84 mmol). The crude product was chromatographed using as eluent the mixture hexane/acetone from 1.5/1 to 1.2/1, v/v. Yield 0.10 g (35%); mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 4H, Ar), 6.48 (t, J=7.2 Hz, 2H, NH), 6.40–6.34 (m, 6H, Ar), 5.23 (t, J=9.6 Hz, 2H, H-3), 5.09 (t, J=9.9 Hz, 2H, H-4) 5.02 (dd, J=9.9, 8.4 Hz, 2H, H-2), 4.55 (d, J=8.4 Hz, 2H, H-1), 4.46 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.27 (dd, J=12.6, 5.1 Hz, H2, H-6), 4.14 (dd, J=12.6, 2.1 Hz, H2, H-6′), 4.02–3.95 (m, 6H, $OCHHCH_2$-NH and $OCH_2CH_2CH_3$), 3.80–3.67 (m, 10H, $OCHHCH_2$-NH, $OCH_2CH_2CH_3$, H-5 and OCH_2CHHNH), 3.62–3.50 (m, 2H, OCH_2CHHNH), 3.23 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 2.07 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.98–1.88 (m, 8H, $OCH_2CH_2CH_3$), 1.92 (s, 3H, CH_3CO), 1.06 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ =170.6, 170.1, 169.4 and 167.7 (C=O), 160.4, 155.6, 136.3, 133.3, 128.0, 127.8, 127.4 and 122.3 (C_{ar}), 100.9 (C-1), 77.0 and 76.6 ($OCH_2CH_2CH_3$), 72.6, 71.9, 71.3 and 68.3 (C-2, C-3, C-4, C-5), 69.1 (C-6), 61.8 ($NHCH_2CH_2O$), 39.5 ($NHCH_2CH_2O$), 30.9 ($ArCH_2Ar$), 23.3 and 23.1 ($OCH_2CH_2CH_3$), 20.7 and 20.6 (CH_3CO), 10.5 and 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{74}H_{94}N_2O_{26}$ (1426.61): m/z 1449.6 $[M+Na]^+$. Anal. Calcd for $C_{74}H_{94}N_2O_{26}$: C, 62.26; H, 6.64; N, 1.96. Found C, 62.30; H, 6.63; N, 1.99.

4.2.4. 5,17-Bis[(β-D-galactopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (8a). The compound was obtained following the general procedure C. Colorless crystals; yield 96%; mp 148–149 °C; ^{1}H NMR (300 MHz, CD_3OD): δ=7.57 (s, 4H, Ar), 6.30 (bs, 6H, Ar), 4.52 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.33 (d, J=7.4 Hz, 2H, H-1), 4.09 (t, J=7.2 Hz, 4H, $OCH_2CH_2CH_3$), 3.87 (d, J=2.4 Hz, 2H, H-4), 3.88–3.66 (m, 18H, H-2, H-3, H-5, H-6, $OCH_2CH_2CH_3$), 3.66–3.50 (m, 8H, $C(O)NHCH_2CH_2$), 3.27 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 1.97 (m_c, 8H, $OCH_2CH_2CH_3$), 1.14 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.97 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=170.8 (C=O), 162.3, 157.0, 138.2, 134.5, 129.5, 129.4, 129.2, 123.7 (C_{ar}), 105.5 (C-1), 78.4, 75.2, 72.9, 70.6, 70.0, 62.8 (C-2, C-3, C-4, C-5, C-6, $NHCH_2CH_2O$), 78.3, 77.0 ($OCH_2CH_2CH_3$), 41.5 ($C(O)NHCH_2CH_2$), 32.0 ($ArCH_2Ar$), 24.9, 24.7 ($OCH_2CH_2CH_3$), 11.6, 10.7 ($OCH_2CH_2CH_3$); ESI-MS for $C_{58}H_{78}N_2O_{18}$ (1090.52): m/z 1112.8 $[M+Na]^+$. Anal. Calcd for $C_{58}H_{78}N_2O_{18}$: C, 63.84; H, 7.20; N, 2.57. Found C, 63.88; H, 7.22; N, 2.54.

4.2.5. 5,17-Bis[(β-D-glucopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (8b). General procedure C. Yield 97%; mp 185–187 °C; ^{1}H NMR (300 MHz, CD_3OD): δ=7.52 (s, 4H, Ar), 6.32–6.26 (m, 6H, Ar), 4.49 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.34 (d, J=7.8 Hz, 2H, H-1), 4.08 (t, J=7.6 Hz, 4H, $OCH_2CH_2CH_3$), 4.09–4.00 (m, 2H, $NHCH_2CHHO$), 3.86 (d, J=10.8 Hz, 4H, H-6 and H-6′), 3.81–3.60 (m, 10H, $NHCH_2CHHO$, $OCH_2CH_2CH_3$, $NHCHHCH_2O$ and H-5), 3.59–3.49 (m, 2H, $NHCHHCH_2O$), 3.43–3.20 (m, 10H, H-3, H-4, H-2 and H_{eq} of $ArCH_2Ar$), 2.02–1.85 (m, 8H, $OCH_2CH_2CH_3$), 1.11 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, J=7.2 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=170.5 (C=O), 161.9, 156.7, 137.8, 134.3, 129.1 and 123.4 (C_{ar}), 104.6 (C-1), 78.1

($OCH_2CH_2CH_3$), 77.9, 75.1 and 71.6 (C-2, C-3, C-4, C-5), 69.6 (C-6), 62.7 ($NHCH_2CH_2O$), 41.1 ($NHCH_2CH_2O$), 31.9 ($ArCH_2Ar$), 24.6 and 24.4 ($OCH_2CH_2CH_3$), 11.2, 10.5 ($OCH_2CH_2CH_3$); ESI-MS for $C_{58}H_{78}N_2O_{18}$ (1090.52): *m/z* 1112.8 $[M+Na]^+$. Anal. Calcd for $C_{58}H_{78}N_2O_{18}$: C, 63.84; H, 7.20; N, 2.57. Found C, 63.88; H, 7.22; N, 2.54.

4.2.6. 5,17-Bis(*N*-L-aspartylcarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (10). The general coupling procedure A was used with aspartic acid dimethyl ester hydrochloride (0.31 g, 1.55 mmol) and dicarboxylic acid **1**[9] (0.26 g, 0.39 mmol) in presence of HBTU (0.43 g, 0.94 mmol) and TEA (0.44 mL, 3.12 mmol). The crude product was chromatographed using as eluent the mixture hexane/ethyl acetate 1/1 (v/v). Selected data for 5,17-bis(dimethoxy-L-aspartylcarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (**9**): colorless solid; yield 0.24 g (64%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, J=2.0 Hz, 2H, Ar), 7.46 (d, J=2.1 Hz, 2H, Ar), 7.20 (d, J=7.8 Hz, 2H, NH), 6.30–6.22 (m, 2H, Ar), 6.21–6.15 (m, 4H, Ar), 5.09–4.98 (m, 2H, $NHCHCH_2$), 4.42 (d, J=13.4 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.04 (t, J=7.9 Hz, 4H, $OCH_2CH_2CH_3$), 3.76 (s, 6H, OCH_3), 3.68 (s, 6H, OCH_3) 3.66 (t, J=8.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.5 Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.12 (dd, J=17.2, 4.4 Hz, 2H, $NHCHCH_2$), 2.99 (dd, J=17.2, 4.8 Hz, 2H, $NHCHCH_2$), 1.95–1.80 (m, 8H, $OCH_2CH_2CH_3$), 1.05 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.88 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ESI-MS for $C_{54}H_{66}N_2O_{14}$ (966.45): *m/z* 989.6 $[M+Na]^+$. A solution of compound **9** (0.088 g, 0.09 mmol) in THF (10 mL) was cooled to 0 °C. After addition of lithium hydroxide (0.008 g, 0.36 mmol) dissolved in water (3 mL), the mixture was stirred at rt for 6 h. The reaction was quenched by evaporation of the organic solvent and subsequent addition of 1 N HCl until acidic pH. Product **10** precipitated as white solid and was filtered and dried. Colorless solid; yield 0.075 g (92%); mp 142–143 °C; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ 1/10, v/v): δ=7.60 (bs, 4H, Ar), 6.28–6.12 (m, 6H, Ar), 4.97 (bs, 2H, $NHCHCH_2$), 4.47 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.10 (t, J=7.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.69 (t, J=6.7 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.00 (d, J=5.3 Hz, 4H, $NHCHCH_2$), 2.01–1.84 (m, 8H, $OCH_2CH_2CH_3$), 1.10 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.91 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=174.8, 162.7 (CO), 156.6, 138.5, 134.2, 129.7, 129.6, 129.3, 123.7 (C_{ar}), 78.5, 78.2 ($OCH_2CH_2CH_3$), 51.3 ($NHCHCH_2$), 37.4 ($NHCHCH_2$), 32.2 ($ArCH_2Ar$), 24.9, 24.7 ($OCH_2CH_2CH_3$), 11.6, 10.6 ($OCH_2CH_2CH_3$); ES-MS for $C_{50}H_{58}N_2O_{14}$ (910.39): *m/z* 967.9 $[M-H+Na+Cl]^-$. Anal. Calcd for $C_{50}H_{58}N_2O_{14}$: C, 65.92; H, 6.42; N, 3.07. Found C, 65.89; H, 6.46; N, 3.10.

4.2.7. *N*-Boc-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester (12). Glucosamine **2b**[14] (1.5 g, 4.32 mmol) and *N*-Boc-L-Asp-OBn (1.16 g, 3.60 mmol) were reacted in presence of HBTU (3.0 g, 7.91 mmol) and TEA (1.10 mL, 7.91 mmol) in dry CH_2Cl_2 (30 mL) at rt for 1 h then the reaction was quenched by addition of a 5% $NaHCO_3$ aqueous solution (20 mL). The organic phase was separated, washed with water and evaporated to dryness in vacuo. The compound was obtained pure as colorless solid by flash-chromatography on silica gel (eluent: ethyl acetate/hexane 1/1, v/v). Yield 1.76 g (75%). The compound was identified by ^{1}H and ^{13}C NMR[18] and by ESI mass spectrometry: for $C_{30}H_{40}N_2O_{14}$ (652.68): *m/z* 675.2 $[M+Na]^+$, 1327.7 $[2M+Na]^+$.

4.2.8. 4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester·CF_3COOH (13). A solution of *N*-Boc-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester[18] (1.50 g, 2.24 mmol) in CH_2Cl_2 (25 mL) was cooled with ice-bath and TFA (2.5 mL) was added. The reaction proceeded without bath for 1 h, then was quenched by evaporation of the organic solvent and by removing the excess of TFA under high vacuum. The compound was then used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.15 (bs, 3H, NH_3^+) 7.53 (d, J=9.3 Hz, 1H, N*H*CO), 7.45–7.27 (m, 2H, Ar), 7.33 (t, J=7.5 Hz, 1H, Ar), 7.22 (d, J=7.5 Hz, 2H, Ar), 5.38 (t, J=9.3 Hz, 1H, H-3), 5.30–5.20 (m, 3H, CH_2Ph and H-1), 5.16 (t, J=9.3 Hz, 1H, H-4), 5.01 (t, J=9.3 Hz, 1H, H-2), 4.48 (bs, 1H, $CHCH_2$), 4.29 (dd, J=12.4, 4.3 Hz, 1H, H-6), 4.22 (dd, J=12.4, 6.4 Hz, 1H, H-6′), 3.85 (bd, 1H, H-5), 3.18 (bs, 2H, $CHCH_2$), 2.09, 2.08 and 1.99 (3s, 12H, $OCCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.3, 171.5, 171.0, 170.8, 170.5, 167.6 (CO), 160.3 (q, J=40 Hz, CF_3CO), 137.8, 129.1, 129.0, 128.7, 128.3, 128.2 (C_{ar}), 115.1 (q, J=285 Hz, CF_3CO), 78.0, 73.5, 70.5, 69.1, 68.3, 62.0 (C-1, C-2, C-3, C-4, C-5, C-6), 72.9 (OCH_2Ph), 50.2 ($CHCH_2$), 33.6 ($CHCH_2$), 20.3 and 19.9 (CH_3CO); ESI-MS for $C_{25}H_{32}N_2O_{12}$ (552.2): *m/z* 553.2 $[M+H]^+$, 575.2 $[M+Na]^+$, 1105.6 $[2M+H]^+$, 1127.5 $[2M+Na]^+$.

4.2.9. 5,17-Bis[(4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-1-benzyloxyaspartyl)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (14). The glycopeptidocalixarene **14** was obtained from **1** (0.1 g, 0.15 mmol) and **13** (0.4 g, 0.6 mmol) in presence of TEA (0.17 mL, 1.2 mmol) following the general procedure A (yield 0.19 g, 72%) or from **4** (0.11 g, 0.15 mmol) following the general procedure B (yield 0.18 g, 68%). Eluent for flash-chromatography: CH_2Cl_2/MeOH 30/1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.52 (d, J=1.8 Hz, 2H, *Ar*CO), 7.50 (d, J=1.8 Hz, 2H, *Ar*CO), 7.47 (d, J=7.2 Hz, 2H, ArCONH), 7.38–7.30 (m, 10H, Bn), 6.77 (d, J=9.3 Hz, 2H, N*H*COCH), 6.25–6.23 (m, 2H, Ar), 6.16–6.09 (m, 4H, Ar), 5.32 (t, J=9.3 Hz, 2H, H-3), 5.25–5.21 (m, 6H, H-1 and $PhCH_2$), 5.15–5.05 (m, 2H, NHC*H*CO), 5.08 (t, J=9.3 Hz, 2H, H-4), 4.96 (t, J=9.3 Hz, 2H, H-2), 4.43 (d, J=13.5 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.27 (dd, J=12.3, 4.2 Hz, 2H, H-6), 4.10–4.00 (m, 6H, H-6′ and $OCH_2CH_2CH_3$), 3.84–3.78 (m, 2H, H-5), 3.68 (t, J=6.9 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.5 Hz, 2H, H_{eq} of $ArCH_2Ar$), 3.20 (d, J=13.5 Hz, 2H, H_{eq} of $ArCH_2Ar$), 3.04 (dd, J=15.6, 3.9 Hz, 2H, $CHCHH$), 2.89 (dd, J=15.6, 4.2 Hz, 2H, $CHCHH$) 2.03–1.82 (m, 32H, CH_3CO and $OCH_2CH_2CH_3$), 1.10 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.90 (t, J=7.8 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=171.2, 171.1, 170.6, 169.9, 169.5 and 167.2 (C=O), 161.4, 155.2, 137.1, 137.1, 135.4, 132.6, 128.6, 128.4, 128.0, 127.9, 127.8, 126.9 and 122.3 (C_{ar}), 78.2 and 77.1 ($OCH_2CH_2CH_3$), 76.7, 73.7, 72.7, 70.5, 68.0 (C-1, C-2, C-3, C-4, C-5), 67.4 ($PhCH_2$), 61.6 (C-6), 49.2 ($CHCH_2$), 37.3 ($CHCH_2$), 30.9 ($ArCH_2Ar$), 23.5 and 23.1 ($OCH_2CH_2CH_3$), 20.7, 20.6 and 20.5 (CH_3CO), 10.8 and 9.9 ($OCH_2CH_2CH_3$); ESI-MS for $C_{92}H_{108}N_4O_{30}$ (1748.7): *m/z* 897.8 $[M+2Na]^{2+}$, 1771.9

$[M+Na]^+$. Anal. Calcd for $C_{92}H_{108}N_4O_{30}$: C, 63.15; H, 6.22; N, 3.20. Found C, 63.21; H, 6.15; N, 3.06.

4.2.10. 5,17-Bis[(4-(β-D-glucopyranosylamino)-1-aspartyl)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (15). Calixarene **14** was reacted following the general procedure C. In this case, the yellowish oil obtained was triturated with Et_2O to obtain a white solid corresponding to the bis triethylammonium salt of **15** [^{1}H NMR (300 MHz, MeOD) $\delta=7.70$ (s, 4H, Ar), 6.25–6.12 (bs, 6H, Ar), 5.00–4.85 (m, 4H, H-1 and C*H*CH_2), 4.53 (d, $J=13.5$ Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.16 (t, $J=8.1$ Hz, 4H, $OCH_2CH_2CH_3$), 3.87–3.60 (m, 10H, H-6,6′, H-5, $OCH_2CH_2CH_3$), 3.45–3.28 (m, 8H, H-4, H-2, H_{eq} of $ArCH_2Ar$), 3.15 (q, $J=7.5$ Hz, 12H, $HNCH_2CH_3$), 2.95–2.77 (m, 4H, $CHCH_2$), 2.08–1.88 (m, 8H, $OCH_2CH_2CH_3$),1.32 (t, $J=7.5$ Hz, 18H, $HNCH_2CH_3$), 1.17 (t, $J=8.1$ Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, $J=8.1$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, MeOD) $\delta=177.4$, 174.5 and 169.5 (C=O), 162.3, 156.5, 138.3, 133.9, 129.3, 129.0 and 123.4 (Ar), 81.3, 79.7, 78.9, 74.3, 71.6 (C-1, C-2, C-3, C-4, C-5), 78.2 and 77.9 ($OCH_2CH_2CH_3$), 62.9 (C-6), 53.5 ($CHCH_2$), 47.8 ($HNCH_2CH_3$), 40.5 ($CHCH_2$), 32.0 ($ArCH_2Ar$), 24.7 and 24.4 ($OCH_2CH_2CH_3$), 11.4 and 10.4 ($OCH_2CH_2CH_3$), 9.3 ($HNCH_2CH_3$)]. This was subsequently dissolved in methanol and treated with Amberlite IR-120 resin, to give the neutral product **15**. Yield 0.10 g (96%); mp 177 (dec.); ν_{max}/cm^{-1} (KBr) 1727, 1645 (CO); ^{1}H NMR (300 MHz, MeOD) $\delta=7.61$ (bs, 4H, Ar), 6.32–6.17 (m, 6H, Ar), 5.00–4.85 (m, 4H, C*H*CH_2 and H-1), 4.49 (d, $J=13.2$ Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.12 (t, $J=7.8$ Hz, 4H, $OCH_2CH_2CH_3$), 3.78 (d, $J=12.3$ Hz, 2H, H-6), 3.70 (t, $J=6.4$ Hz, 4H, $OCH_2CH_2CH_3$), 3.60 (dd, $J=12.3$, 4.8 Hz, 2H, H-6′), 3.42–3.23 (m, 8H, H-4, H-5, H-3 and H-2), 3.24 (d, $J=13.2$ Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.03–2.96 (m, 4H, $CHCH_2$), 2.05–1.85 (m, 8H, $OCH_2CH_2CH_3$), 1.13 (t, $J=7.2$ Hz, 6H, $OCH_2CH_2CH_3$), 0.93 ($J=7.5$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, MeOD) $\delta=173.7$, 173.4 and 170.0 (CO), 162.4, 156.6, 138.2, 134.0, 129.3, 129.1, 128.4 and 123.4 (C_{ar}), 81.1, 79.7, 79.0, 73.9, 71.4 and 62.7 (C-1, C-2, C-3, C-4, C-5, C-6), 78.2 and 78.0 ($OCH_2CH_2CH_3$), 51.1 ($CHCH_2$), 38.3 ($CHCH_2$) 31.9 ($ArCH_2Ar$), 24.5 and 24.4 ($OCH_2CH_2CH_3$), 11.3 and 10.4 ($OCH_2CH_2CH_3$); ESI-MS for $C_{62}H_{80}N_4O_{22}$ 1232.5): *m/z* 661.53 $[M-2H+4Na]^{2+}$, 1299.7 $[M-2H+3Na]^+$. Anal. Calcd for $C_{62}H_{80}N_4O_{22}$: C, 60.38; H, 6.54; N, 4.54. Found C, 60.23; H, 6.39; N, 4.50.

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