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Building Multivalent Iminosugar-Based Ligands on Calixarene Cores via Nitrone Cycloadditions

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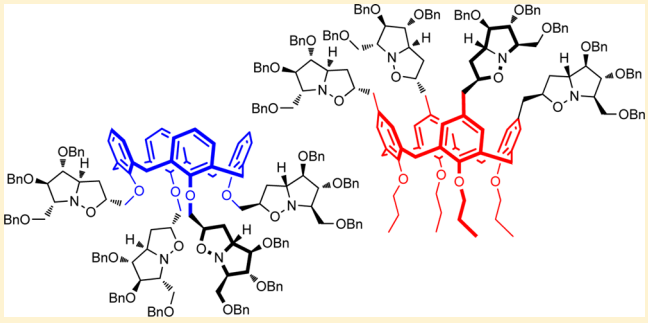
Supporting Information

ABSTRACT: A novel and challenging approach for the construction of multivalent iminosugar architectures directly on calixarene scaffolds is presented, which exploits multiple cycloaddition reactions of a carbohydrate-derived nitrone on diversely functionalized calix[4]arenes. Regardless of the 4-fold reiteration on a single calixarene, the reactions take place with high regio- and stereoselectivity, demonstrating this method as an appealing one for the synthesis of calixarene-based neoglycoconjugates.



INTRODUCTION

Carbohydrate−lectin interactions are intensively investigated as they play a pivotal role in a host of biological events. Monovalent carbohydrates typically bind to their lectin receptors with low affinity.[1] Nature has circumvented this tight binding limitation by exposing sugar residues in a multivalent fashion at the surface of cells. This multivalent or cluster glycoside effect is the affinity enhancement obtained with multivalent ligands compared to their monovalent counterparts, which is greater than predicted from the sum of every single saccharide-receptor recognition event.[2] On this basis, hundreds of multivalent glycomimetics have been synthesized for studying carbohydrate−lectin interactions.[3,4] Conversely, the concept of multivalency has remained essentially unexplored concerning specific glycosidase inhibition using iminosugars as glycomimetics. The different nature of the enzyme receptors involved, which usually have a single and deep active site and therefore do not appear prone to accept multivalent substrates, reasonably accounts for the paucity of studies on this subject. However, although a strong multivalent or cluster effect is generally associated with the interaction of receptors bearing multiple recognition sites with multivalent sugar ligands, significant affinity enhancements have also been observed for systems where the receptors possess a single binding site. In this case, an "intrinsic" multivalent effect associated with local concentration effects may be productive.[2c,5]

Early attempts to use multivalent iminosugar inhibitors were not encouraging,[6] apart from the results reported with a trivalent derivative of 1-deoxynojirimycin, which showed a 6-fold affinity enhancement toward jack bean-α-mannosidase.[7] Conversely, dramatic enhancement effects were reported more recently for a fullerene decorated with 12 iminosugar residues (up to 2150-fold)[8] and for a series of cyclodextrins conjugated with 7 and 14 iminosugars (up to 4 orders of magnitude).[9,10] These results demonstrated that the use of multivalent ligands can be applied, beyond carbohydrate−lectin recognition processes, to glycomimetic-enzyme inhibition for modulating the activity as well as the selectivity in the design of more potent glycosidase inhibitors from iminosugars, a class of compounds with several therapeutic applications.[11]

Following these findings, we wish to report here our results on the synthesis of novel enantiopure iminosugars linked to calix[4]arenes via highly selective 1,3-dipolar cycloaddition reactions of enantiopure cyclic nitrones to calix[4]arenes functionalized at the upper or the lower rim.

RESULTS AND DISCUSSION

Multiple glycosylations of calix[4]arene platforms to give glycoclusters have been extensively investigated in recent years.[12,13] Concerning the synthetic strategies adopted, they usually involve conjugation of a preformed sugar moiety to the calixarene scaffold through suitable linkers. In contrast, our approach to iminosugar decorated calixarenes is particularly innovative and challenging, regarding the direct construction of nascent iminosugars on the calixarene skeleton. Thus, an intriguing selectivity issue arises: several novel stereogenic centers are created in the same key step when the iminosugar moieties are generated on the calixarene. For the success of this strategy, availability of a highly selective reaction for formation of the iminosugars was essential in order to avoid complex

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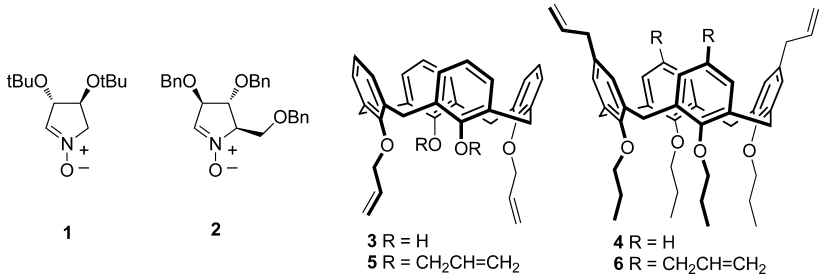
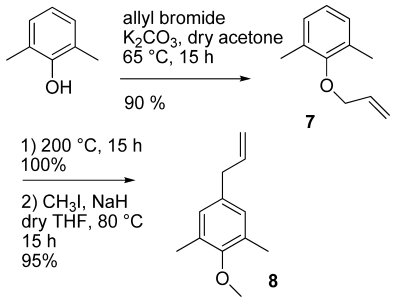
Scheme 1



mixtures of products. We demonstrate the feasibility of this approach through highly regio- and diasterostereoselective multiple cycloaddition reactions of nitrone **2** to calix[4]arenes **3**,**5** and **4**,**6** (Scheme 1) functionalized, respectively, at the lower and the upper rim with terminal double bonds.

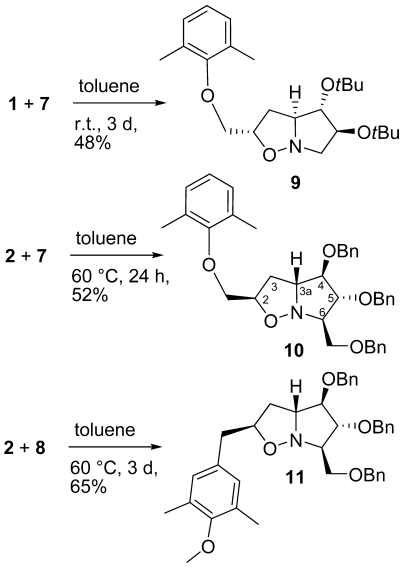
Dipolarophiles **7** and **8** were chosen as model substrates of calixarenes **3**,**5** and **4**,**6**, respectively, in order to investigate the optimal reaction conditions for the cycloaddition reaction. Compound **8** was synthesized from **7**, obtained in turn by allylation of xylenol, through a Claisen−Cope rearrangement followed by methylation of the phenolic hydroxy group with CH_3I in THF (Scheme 2).[14]

Scheme 2



Cycloaddition of nitrone **1**[15] to lower rim model allyl ether **7** in toluene as solvent went to completion in 3 days at room temperature. Among various diastereoisomers visible in the crude mixture, one major adduct **9** was collected after flash column chromatography (FCC) in 48% yield (Scheme 3).[16] The structure of **9** was assigned as derived from an *exo*/*anti* approach of the dipole to the dipolarophile, on the basis of the analogy of its ^{1}H NMR spectrum to those of similar adducts from the same nitrone.[17] Cycloaddition of nitrone **2**[18] to the same model compound **7** required heating at 60 °C in toluene.[19] After 24 h, a single regio- and stereoisomer **10** was detected and isolated in 52% yield (Scheme 3), which was also assigned a structure deriving from an *exo*/*anti* approach on the basis of a correlation peak between H-2 and H-6 observed in the 1D NOESY spectrum (see Supporting Information, Figure S6). This stereochemical outcome was in agreement to those reported for other cycloaddition reactions of the same nitrone.[17c,20] Thus, nitrone **2** appeared to be, at least with model compound **7**, less reactive but more selective.[21] The upper rim calixarene model dipolarophile **8** was less reactive than **7**. Indeed, cycloaddition with nitrone **2** required 3 days at 60 °C for completion.[22] A single regio- and stereoisomeric adduct **11** was isolated in 65% yield (Scheme 3), again resulting from an *exo*/*anti* approach of the reacting partners. In both adducts **10** and **11**, a small vicinal coupling constant J = 4.0−4.6

Scheme 3



Hz was detected between protons H-3a and H-4, indicative of their *trans* relationship.[17a,b]

Calixarenes **3**−**6** were synthesized following literature procedures.[23] When performing the cycloaddition reaction on these multifuctionalized calixarenes, the stereoselectivity issue becomes crucial. Indeed, in the case of difunctionalized calixarenes **3** and **4**, formation of a diadduct will generate four novel stereocenters on the same molecule. Thus, assuming a complete regioselectivity and taking into account symmetry considerations, the reaction may afford up to 10 stereoisomers, besides the 4 possible monoadducts. The number of possible stereoisomers increases dramatically on going to the tetrafunctionalized calixarenes **5** and **6**. In this case, eight novel stereocenters are generated in a single synthetic step, in principle giving rise to 70 tetraadducts (strongly reduced from the theoretical 2^8 = 256 for symmetry reasons), besides the 64 possible trisubstituted adducts, 26 diadducts (16 vicinal + 10 distal) and 4 monoadducts, for a total of 164 possible products. In this quite complex scenario, it is essential that all the dipolarophiles react and the stereoselectivity of each cycloaddition reaction has to be virtually complete. This may happen if highly stereoselective reactions are chosen and the dipolarophilic moieties in the calixarene behave independently of each other; that is, each subsequent cycloaddition is not influenced by the already installed stereocenters in terms of stereoselectivity. On the basis of the results obtained with model compounds **7** and **8**, nitrone **2** appeared more suited than **1** for this study. Indeed, nitrone **1** reacted with calixarene **3**[23b] slightly faster than **2** but considerably less selectively. The

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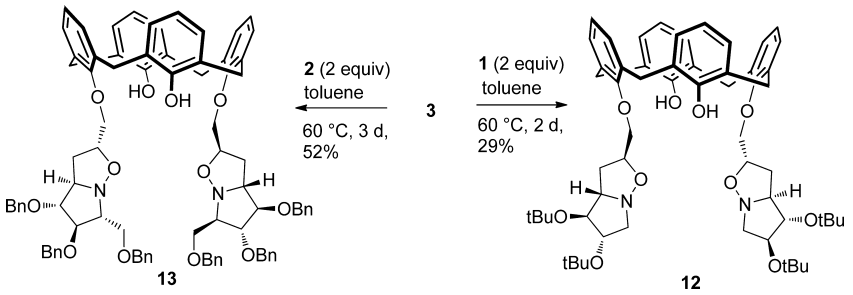
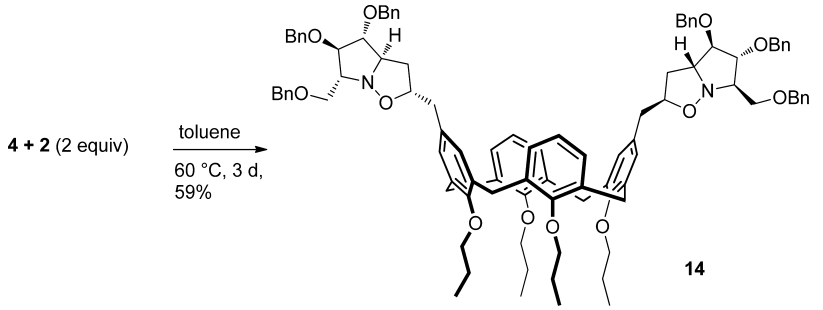
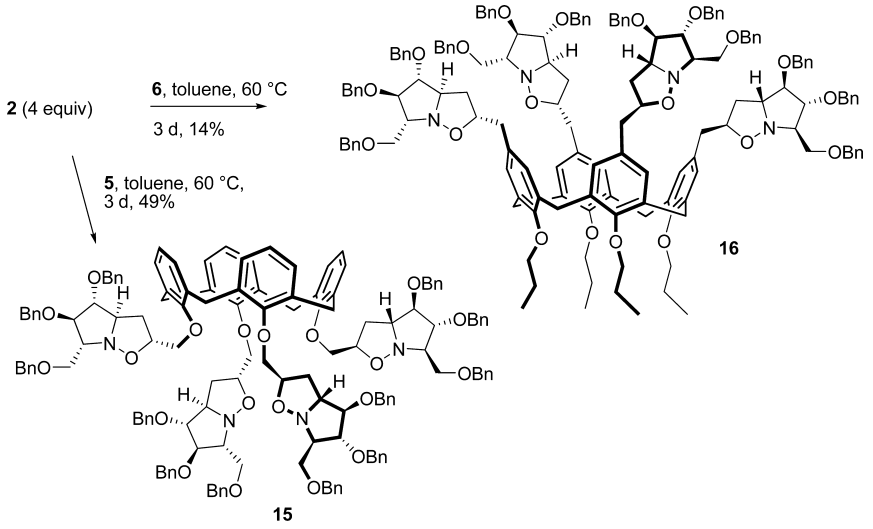
Scheme 4



Scheme 5



Scheme 6



reaction was complete after two days at 60 °C, but several TLC spots were detected on the crude; luckily, the major *exo/anti* diadduct **12** could be isolated by FCC, albeit with a moderate 29% yield (Scheme 4).[24]

Conversely, calixarene **3** reacted with 2 equiv of nitrone **2** in toluene at 60 °C to give, after 3 days,[25] the only detectable compound **13**, obtained in a satisfactory 52% yield after purification by FCC (Scheme 4). It is worth noting that the recovered yields of diadducts **12** and **13** are in line with those obtained with the model dipolarophiles, considering the different selectivities of nitrones **1** and **2**. These results confirmed that nitrone **1** is unsuitable for synthesizing multiple cycloadducts and justified continuing this study with the nitrone **2** exclusively. The structure of **13** was confirmed by 1D and 2D ^{1}H NMR experiments, and derived from an *exo/anti* approach of both allylic moieties of calixarene **3** to nitrone **2**, as demonstrated by the presence of NOESY correlation peaks between H-2 and H-6 of the pyrroloisoxazole nucleus (see Supporting Information, Figure S18), in analogy with the model system. As shown in the Supporting Information (Figure S14), the ^{1}H NMR spectrum of **13** showed a high symmetry, according to the anticipation that both cycloadditions proceeded with the same type of approach, thus providing a C_2 symmetric molecule. At least other two adducts were detected in the crude mixture by TLC, but they could be isolated only in traces, and they were not further characterized.

In order to obtain calixarenes functionalized at the upper rim, calixarene **4**[23a] was reacted with 2 equiv of nitrone **2** in toluene at 60 °C, affording a single adduct **14** isolated in 59% yield after FCC (Scheme 5). Again, the ^{1}H NMR spectrum was highly symmetric (see Supporting Information, Figure S19). The structure of **14** was confirmed to derive from an *exo/anti* approach of both 1,3-dipole molecules on the basis of 1D and 2D NMR spectra. In particular, the 2D NOESY spectrum

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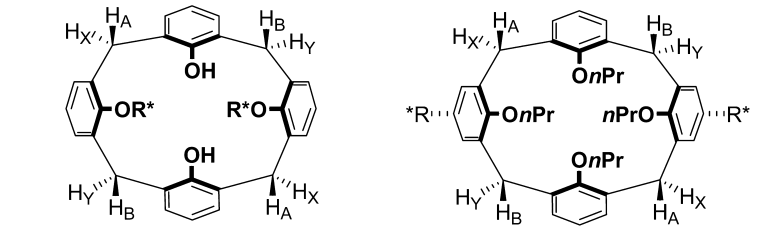

13 R* = isoxazolidine adduct **14** R* = isoxazolidine adduct

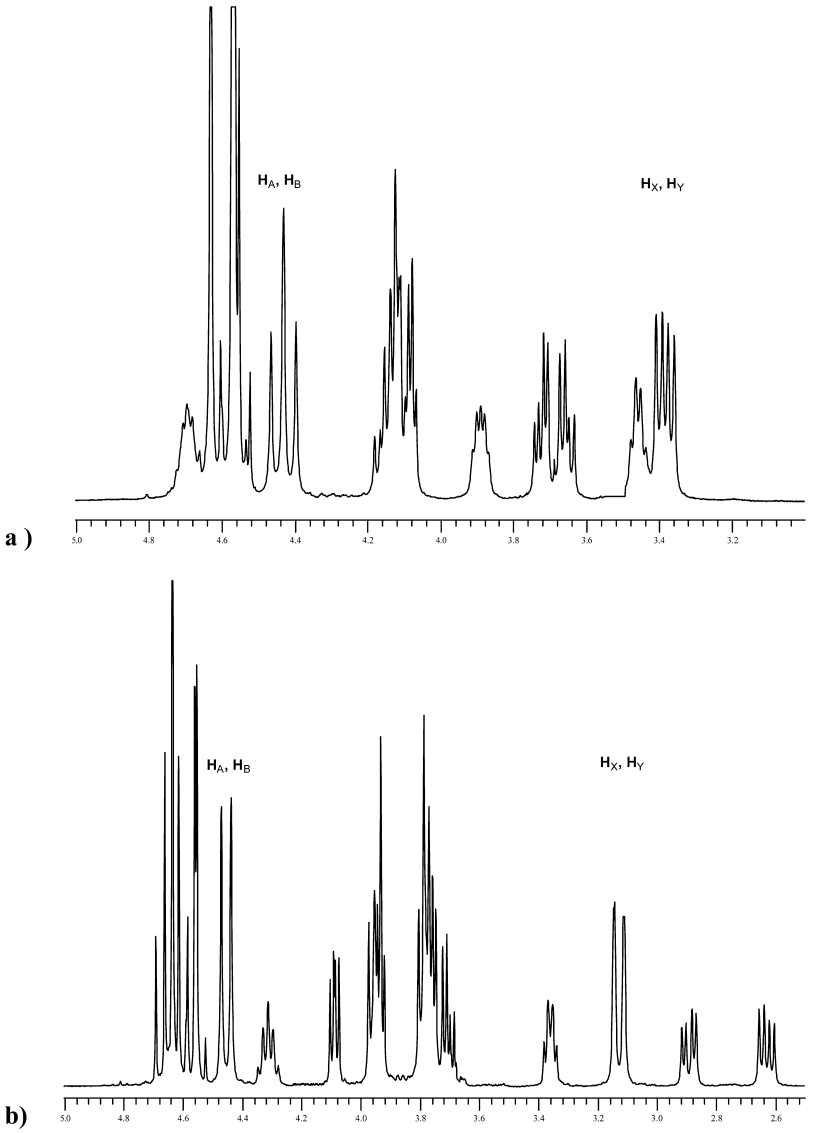

Figure 1. Spin systems for methylene protons in calixarenes **13** and **14** (relative positions within the couples A, B and X, Y have been indicated arbitrarily) and a section of ^{1}H NMR spectrum (400 MHz) of **13** (a) and **14** (b).

showed correlation peaks of H-2 with H-6 and H-4 and of H-3a with H-5 (see Supporting Information, Figure S21).

Tetrafunctionalization at lower and upper rim of calixarenes **5**[23c] and **6**,[23a] respectively, has been also achieved (Scheme 6). Four equivalents of nitrone **2** were reacted either with calixarene **5** or **6** in toluene at 60 °C, affording complete conversions after 3 days in both cases. However, isolation and purification of these tetrafunctionalized calixarenes was not a trivial task, mainly due to instability of the products on silica gel. Calixarene **15** was obtained in 49% yield after purification on alumina. Compound **15** showed a more complex ^{1}H NMR spectrum with some broadened signals (see Supporting Information, Figure S22), presumably as a consequence of higher energy barriers for the conformational mobility of the pyrroloisoxazole nuclei crowding at the lower rim of the macrocycle calixarene. However, the simplicity of NMR spectra with a limited number of signals show again that the newly formed stereocenters in each cycloaddition reaction did not influence the stereoselectivity of the subsequent cycloadditions, and each cycloaddition was established to proceed with an *exo/*

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anti approach, thus affording a C_4 symmetric compound. Purification of **16**, obtained by addition of **2** to the upper rim functionalized calixarene **6** was even more difficult, and the adduct **16** could be isolated in a poor 14% yield (Scheme 6) via FCC on silica, while purification on alumina did not give any improvement.

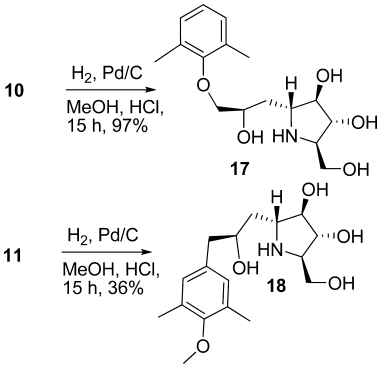
The ^{1}H NMR patterns originated by the protons of the methylene units connecting the aryl rings in the different calixarene adducts **13**, **14**, **15** and **16** deserve a further comment. In the starting calixarenes **3**−**6**, the presence of bulky groups (and hydrogen-bonding for compounds **3** and **4**) fixes the calixarene in the cone structure, inducing diastereotopicity in the four axial and four equatorial protons that give rise to an AX spin system.[26]

When a homochiral moiety is introduced in two distal positions in a calixarene, as it happens in adducts **13** and **14**, the symmetry planes are lost, and this generates two different spin systems AX and BY for the methylene bridge protons, as is apparent from the ^{1}H NMR spectrum of compound **13** (Figure 1a), which shows two couples of doublets at around 4.4 and 3.4 ppm. This effect is not observed for **14**, probably due to the larger distance of the homochiral moieties, which are placed in the upper rim, from the methylene protons, resulting in an accidental isochronism for their signals, with only two doublets, respectively at 4.42 and 3.12 ppm (Figure 1b).

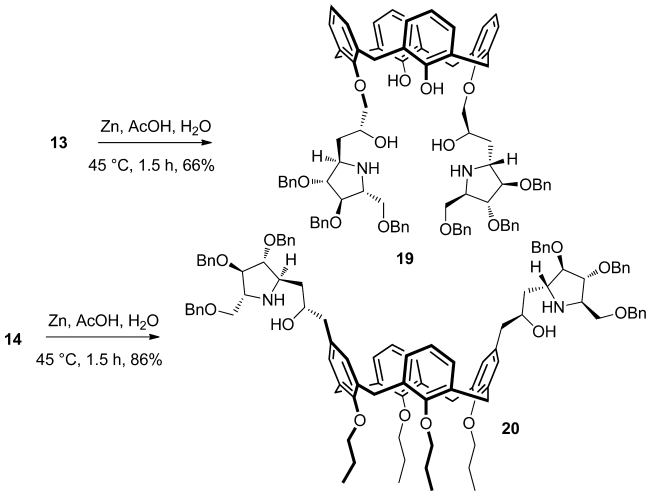
When the homochiral moiety is introduced in all of the arenes, as it happens for tetraadducts **15** and **16**, the methylene-bridge spin system does not change after the cycloaddition reaction with respect to the starting calixarenes **5** and **6**: two doublets are observed in the ^{1}H NMR spectrum, which reflect the AX spin system of the methylene protons. In conclusion, apart from accidental isochronisms, the observed spin systems are a proof of the symmetry of compounds **13**−**16**, thus confirming that each cycloaddition has occurred with the same stereoselective mode. With adducts in hand, we attempted at their further elaboration. Catalytic hydrogenation of model adducts **10** and **11** with Pd/C in MeOH as solvent and in presence of conc. HCl afforded the deprotected amino alcohols **17** and **18** after treatment with ion-exchange resin DOWEX 50WX8, by eluting with ammonia. However, while **17** was obtained pure and in high yield (97%) after the treatment with the resin, compound **18** required a further purification on silica gel in order to obtain an analytically pure sample in a moderate 36% yield (Scheme 7). Complete assignment of the relative configuration of compound **17** was possible on the basis of correlation peaks observed between H-3 and H-5, the protons at C_α and C_β of the side chain at C-2 and H-3 and H-5, and between H-2 and H-4 in its 2D NOESY spectrum (see Supporting Information, Figure S34) and furnished a confirmation of the previous structural assignment to the parent cycloadduct.

Unfortunately, catalytic hydrogenation of calixarene adducts **13** and **14** did not give any positive result. On reacting **13** with H_2 and Pd/C in the presence of conc. HCl in MeOH as solvent for 15 h, only decomposition products were obtained after treatment with ion-exchange resin. This may be ascribed to a sensitivity of the product to the acidic conditions, or to instability to the resin. Alternatively, catalytic hydrogenation performed without addition of HCl did not succeed in removing all the benzyl groups, even reacting for 4 days with 200% catalyst in weight, and thus confirming the difficulties observed, in some cases, in the debenzylation of calixarene derivatives.[27] We then turned to investigate the possibility to selectively cleave the N−O bond. A mixture of calixarene **13** and Zn in CH_3COOH/H_2O 9:1 was thus heated at 45 °C for 1.5 h as reported for similar cycloadducts to nitrone **2**,[18,20,28] affording amino alcohol **19** in 66% yield. Analogously, isoxazolidine ring cleavage of adduct **14** under the same conditions afforded compound **20** in 86% yield after purification on silica gel (Scheme 8). Unfortunately, when this reaction was performed on tetra-adduct **15** under the same conditions, no product was recovered, due to instability of the amino alcohol on silica gel.

Scheme 7



Scheme 8



In conclusion, in this work we showed that iminosugars can be introduced on calix[4]arenes by exploiting a challenging synthetic strategy that uses a highly regio- and stereoselective cycloaddition reaction of nitrone **2** to properly di- and tetra-allylated calixarenes **3**−**6**. Novel enantiopure calix iminosugars **13**−**16** were synthesized in good yields, and their further synthetic elaboration to give novel multivalent iminosugars was studied.

We therefore think that the nitrone cycloaddition to polyallylated scaffolds can be used to efficiently and selectively prepare a rich collection of polyvalent iminosugar ligands potentially useful in the inhibition of glycosidases.

EXPERIMENTAL SECTION

Commercial reagents were used as received. All reactions were magnetically stirred and monitored by TLC on 0.25 mm silica gel

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plates, and column chromatography was carried out on Silica Gel 60 (32−63 μm). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. All the peak assignments reported in ^{1}H NMR spectra were based on COSY, HMQC, and NOESY spectra.

Synthesis of 4-Allyl-2,6-dimethylphenyl Methyl Ether (8). Neat **7** (5 g) was heated at 200 °C for 15 h in a sand bath. TLC control showed complete conversion of the starting material. Then, a portion of the obtained red crude oil (512 mg, 3.14 mmol) was dissolved in dry THF (10 mL), and NaH (150 mg, 6.25 mmol) was added at 0 °C under nitrogen atmosphere. The mixture was left stirring at room temperature for 1 h, then CH_3I was added (2.2 mg, 15.8 mmol), and the mixture heated at 80 °C for 15 h. Water (20 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL). The organic phase was washed with H_2O (3 × 10 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded 520 mg (2.95 mmol, 95% yield over two steps) of pure **8** as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 6.86 (s, 2H; Ar−H), 5.97 (m, 1H; $ArCH_2CHCH_2$), 5.20−5.01 (m, 2H; $ArCH_2CHCH_2$), 3.72 (s, 3H; OCH_3), 3.31 (d, J = 6.6 Hz, 2H; $ArCH_2CHCH_2$), 2.29 (s, 6H; $ArCH_3$).

(2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-[2,6-dimethylphenoxy)methyl]hexahydropyrrolo[1,2-b]-isoxazole (10). A mixture of nitrone **2** (250 mg, 0.6 mmol) and **7** (194 mg, 1.2 mmol) in toluene (0.6 mL) was stirred at 60 °C for 24 h, and then a TLC control showed the disappearance of the starting material. Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography using an eluent with increasing polarity (petroleum ether/AcOEt 8:1 then 3:1) affording pure **10** (182 mg, 0.31 mmol, 52% yield) as a white solid (R_f = 0.6, petroleum ether/AcOEt 5:1): mp = 77−78 °C; $[\alpha]_D^{23}$ = −36.2 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41−7.28 (m, 15H; Ar−H), 7.02 (d, J = 7.2 Hz, 2H; Ar−H), 6.95 (m, 1H; Ar−H), 4.68−4.55 (m, 7H, 2-H; OCH_2Ar), 4.14 (dd, J = 5.6, 4.4 Hz, 1H; 5-H), 4.04 (t, J = 4.0 Hz, 1H; 4-H), 3.95 (dd, J = 10.4, 6.0 Hz, 1H; $ArOCH_2$); 3.87−3.82 (m, 2H; $ArOCH_2$, 3a-H), 3.80 (dd, J = 10.0, 4.4 Hz, 1H; CH_2OBn), 3.72 (dd, J = 9.6, 6.0 Hz, 1H; CH_2OBn), 3.45 (q, J = 5.4 Hz, 1H; 6-H), 2.38 (t, J = 6.8 Hz, 2H; 3-H), 2.31 (s, 6H; $ArCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.1 (s), 138.0 (s), 137.7 (s), 137.5 (s), 130.5 (s, 2C), 128.5−127.4 (d, 17C), 123.6 (d), 87.0 (d), 83.4 (d), 75.2 (d), 73.1 (t), 72.1 (t, 2C), 71.6 (t), 69.7 (t), 69.5 (d), 67.7 (d), 36.7 (t), 16.1 (q, 2C); MS (EI) m/z (%) = 579 (M^+, 0.2), 458 (6), 400 (7), 105 (14), 91 (100). Anal. Calcd for $C_{37}H_{41}NO_5$ (579.73): C, 76.66; H, 7.13; N, 2.42. Found C, 76.37; H, 7.15; N, 2.24.

(2*S*,3a*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(4-methoxy-3,5-dimethylbenzyl)-hexahydropyrrolo[1,2-b]-isoxazole (11). A mixture of nitrone **2** (250 mg, 0.6 mmol) and **8** (230 mg, 1.3 mmol) in toluene (0.6 mL) was stirred at 60 °C for 3 days, and then a TLC control (petroleum ether/AcOEt 1:4) showed the disappearance of the starting nitrone **2** (R_f = 0.5). Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography using an eluent with increasing polarity (petroleum ether/AcOEt 5:1 then 3:1) affording pure **11** (232 mg, 0.31 mmol, 65% yield) as a yellow oil (R_f = 0.33, petroleum ether/AcOEt 3:1): $[\alpha]_D^{23}$ = −29.8 (c = 0.5, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.25 (m, 15H; Ar−H), 6.86 (s, 2H; Ar−H), 4.67−4.54 (m, 6H; OCH_2Ar), 4.31 (quint, J = 6.6 Hz, 1H; 2-H), 4.07 (t, J = 5.8 Hz, 1H; 5-H), 3.91 (t, J = 4.6 Hz, 1H; 4-H), 3.78−3.66 (m, 3H; 3a-H, CH_2OBn), 3.73 (s, 3H; $ArOCH_3$), 3.36−3.34 (m, 1H; 6-H), 2.94 (dd, J = 14.0, 5.6 Hz, 1H; $ArCH_2$), 2.65 (dd, J = 14.0, 6.8 Hz, 1H; $ArCH_2$), 2.28 (s, 6H; $ArCH_3$), 2.10 (t, J = 6.8 Hz, 2H; 3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.6 (s), 138.4 (s), 138.1 (s), 137.9 (s), 133.3 (s) 130.6 (s, 2C), 129.5 (d, 2C), 128.4−127.5 (d, 15C, C−Ar), 87.6 (d,), 83.0 (d), 77.0 (d), 73.4 (t), 72.5 (t), 71.9 (t), 69.9 (t), 69.4 (d), 67.8 (d), 59.7 (q), 40.0 (t), 38.6 (t), 16.0 (q, 2C); MS (EI) m/z (%) = 593 (M^+, 1), 562 (1), 472 (3), 400 (5), 219 (8), 149 (18), 91 (100). Anal. Calcd for $C_{38}H_{43}NO_5$ (593.75): C, 76.87; H, 7.30; N, 2.36. Found C, 76.52; H, 7.47; N, 2.15.

26,28-Bis({(2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-hexahydropyrrolo[1,2-b]isoxazol-2-yl}-methoxy)-25,27-dihydroxy-calix[4]arene (13). A mixture of **3** (132 mg, 0.26 mmol) and nitrone **2** (217 mg, 0.52 mmol) in toluene (0.52 mL) was stirred at 60 °C for 3 days, and then a TLC control (petroleum ether/AcOEt 10:1) showed the disappearance of the starting calixarene (R_f = 0.5). Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography using an eluent with increasing polarity (petroleum ether/AcOEt 4:1 then 3:1) affording pure **13** (180 mg, 0.13 mmol, 52% yield) as a white solid (R_f = 0.4, petroleum ether/AcOEt 3:1): mp = 65−66 °C; $[\alpha]_D^{25}$ = −32.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (s, 2H; OH), 7.37−7.29 (m, 30H; Ar−H), 7.10 (d, J = 7.6 Hz, 4H; Ar−H), 6.88 (m, 4H; Ar−H), 6.74 (t, J = 7.6 Hz, 2H; Ar−H), 6.72 (t, J = 7.6 Hz, 2H; Ar−H), 4.72−4.66 (m, 2H; 2-H), 4.63−4.52 (m, 12H; OCH_2Ar), 4.46 (d, J = 13.2 Hz, 2H; $ArCH_2Ar$), 4.42 (d, J = 13.2 Hz, 2H; $ArCH_2Ar$), 4.18−4.06 (m, 8H; $ArOCH_2$, 4-H, 5-H), 3.89 (dt, J = 8.8, 4.8 Hz, 2H; 3a-H), 3.72 (dd, J = 9.8, 4.6 Hz, 2H, CH_2OBn), 3.65 (dd, J = 9.8, 5.8 Hz, 2H, CH_2OBn), 3.46 (q, J = 5.3 Hz, 2H; 6-H), 3.38 (d, J = 13.2 Hz, 2H; $ArCH_2Ar$), 3.36 (d, J = 13.2 Hz, 2H; $ArCH_2Ar$), 2.51−2.43 (m, 2H; 3-H), 2.37−2.31 (m, 2H; 3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 152.9 (s, 2C), 151.4 (s, 2C), 138.1 (s, 2C), 137.8 (s, 2C), 137.6 (s, 2C), 132.8 (s, 4C), 128.8 (d, 4C), 128.6 (d, 4C), 128.1−127.3 (d, 30C), 128.0 (s, 4C), 125.0 (d, 2C), 118.6 (d, 2C), 87.5 (d, 2C), 83.7 (d, 2C), 76.1 (t, 2C), 74.7 (d, 2C), 73.1 (t, 2C), 72.1 (t, 2C), 71.6 (t, 2C), 69.7 (t, 2C), 69.3 (d, 2C), 67.6 (d, 2C), 36.3 (t, 2C), 31.2 (t, 2C), 31.1 (t, 2C); IR ($CDCl_3$): 3369, 3028, 2918, 2863, 1465, 1452, 1089, 1026, 736, 697 cm^{-1}; ESI-MS calcd for $C_{86}H_{86}N_2NaO_{12}$ (M + Na^+) m/z 1361.6. Found m/z 1362.0. Anal. Calcd for $C_{86}H_{86}N_2O_{12}$ (1339.61): C, 77.11; H, 6.47; N, 2.09. Found C, 76.93; H, 6.48; N, 2.08.

5,17-Bis({(2*S*,3a*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-hexahydropyrrolo[1,2-b]isoxazol-2-yl}-methyl)-25,26,27,28-tetrapropoxy-calix[4]arene (14). A mixture of **4** (106 mg, 0.16 mmol) and nitrone **2** (158 mg, 0.38 mmol) in toluene (0.38 mL) was stirred at 60 °C for 3 days, and then a TLC control (petroleum ether/AcOEt 10:1) showed the disappearance of the starting calixarene **4** (R_f = 0.8). Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography (petroleum ether/AcOEt 3:1) affording pure **14** (143 mg, 0.09 mmol, 59% yield) as a white solid (R_f = 0.3, petroleum ether/AcOEt 3:1): mp = 54−56 °C; $[\alpha]_D^{25}$ = −22.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40−7.28 (m, 30H; Ar−H), 6.75 (m, 4H; Ar−H), 6.43−6.35 (m, 6H; Ar−H), 4.70−4.54 (m, 12H, OCH_2Ar), 4.42 (d, J = 13.6 Hz, 4H; $ArCH_2Ar$), 4.34 (quint, J = 6.8 Hz, 2H; 2-H), 4.10 (dd, J = 6.2, 4.6 Hz, 2H; 5-H), 3.99−3.93 (m, 6H; 4-H, $ArOCH_2CH_2CH_3$), 3.82−3.69 (m, 10H; 3a-H, CH_2OBn, $ArOCH_2CH_2CH_3$), 3.37 (dt, J = 6.3, 5.5 Hz, 2H; 6-H), 3.12 (d, J = 13.6 Hz, 4H; $ArCH_2Ar$), 2.90 (dd, J = 14.0, 5.6 Hz, 2H; $ArCH_2$), 2.64 (dd, J = 14.0, 6.8 Hz, 2H; $ArCH_2$), 2.17−2.12 (m, 4H; 3-H), 2.04−1.90 (m, 8H; $ArOCH_2CH_2CH_3$), 1.11 (t, J = 7.6 Hz, 6H; $ArOCH_2CH_2CH_3$), 0.99 (t, J = 7.6 Hz, 6H; $ArOCH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.6 (s, 2C), 155.4 (s, 2C), 138.1 (s, 2C), 137.8 (s, 2C), 137.5 (s, 2C), 135.5 (s, 4C), 133.6 (s, 4C), 130.6 (s, 2C), 129.0 (d, 4C), 128.8 (d, 4C), 128.1−127.1 (d, 30C), 121.7 (d, 2C), 87.4 (d, 2C), 82.6 (d, 2C), 76.9, 76.5 (d, 2C and t, 4C), 73.1 (t, 2C), 72.2 (t, 2C), 71.5 (t, 2C), 69.6 (t, 2C), 68.9 (d, 2C), 67.4 (d, 2C), 39.7 (t, 2C), 38.5 (t, 2C), 30.7 (t, 4C), 23.1 (t, 2C), 22.8 (t, 2C), 10.4 (q, 2C), 9.8 (q, 2C); ESI-MS calcd for $C_{98}H_{110}N_2NaO_{12}$ (M + Na^+) m/z 1529.8. Found m/z 1530.5. Anal. Calcd for $C_{98}H_{110}N_2O_{12}$ (1507.93): C, 78.06; H, 7.35; N, 1.86. Found C, 77.96; H, 7.64; N, 1.68.

25,26,27,28-Tetrakis({(2*S*,3a*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydropyrrolo[1,2-b]isoxazol-2-yl}-methoxy)-calix[4]arene (15). A mixture of **5** (145 mg, 0.25 mmol) and nitrone **2** (460 mg, 1.1 mmol) in toluene (1.1 mL) was stirred at 60 °C for 3 days, and then a TLC control (petroleum ether/AcOEt 10:1) showed the disappearance of the starting calixarene **5** (R_f = 0.6). Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography on alumina (petroleum ether/AcOEt 5:1) affording pure **15** (277 mg, 0.12 mmol, 49% yield) as a white waxy solid (R_f = 0.4, petroleum ether/AcOEt

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3:1): $[\alpha]_D^{27} = -14.9$ (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30–7.23 (m, 60H; Ar–H), 6.67–6.44 (m, 12H; Ar–H), 4.59–4.42 (m, 32H; 2-H, OCH_2Ar, $ArCH_2Ar$), 4.15 (m, 4H; $ArOCH_2$), 4.06–4.03 (m, 8H; 5-H, $ArOCH_2$), 3.98 (m, 4H; 4-H), 3.73–3.71 (m, 8H; 3a-H, CH_2OBn), 3.63–3.59 (m, 4H; CH_2OBn), 3.35 (m, 4H; 6-H), 3.15 (d, J = 13.2, 4H; $ArCH_2Ar$), 2.26–2.24 (m, 4H; 3-H), 2.17–2.13 (m, 4H; 3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6 (s, 4C), 138.5 (s, 4C), 138.2 (s, 4C), 137.9 (s, 4C), 135.0 (s, 8C), 128.4–127.4 (d, 68C), 122.3 (d, 4C), 87.8 (d, 4C), 83.4 (d, 4C), 75.0, 74.8 (d, 4C and t, 4C), 73.3 (t, 4C), 72.2 (t, 4C), 71.7 (t, 4C), 69.9 (t, 4C), 69.1 (d, 4C), 67.5 (d, 4C), 37.5 (t, 4C), 31.3 (t, 4C); ESI-MS calcd for $C_{144}H_{148}N_4NaO_{20}$ ($M + Na^+$) m/z 2276.1. Found m/z 2276.1. Anal. Calcd for $C_{144}H_{148}N_4O_{20}$ (2254.73): C, 76.71; H, 6.62; N, 2.48. Found C, 76.42; H, 6.90; N, 2.56.

5,11,17,23-Tetrakis({(2*S*,3a*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-hexahydropyrrolo[1,2-b]isoxazol-2-yl}-methyl)-25,26,27,28-tetrapropoxy-calix[4]arene (16). A mixture of **6** (105 mg, 0.14 mmol) and nitrone **2** (257 mg, 0.62 mmol) in toluene (0.62 mL) was stirred at 60 °C for 3 days, and then a TLC control (petroleum ether/AcOEt 10:1) showed the disappearance of the starting calixarene **6** (R_f = 0.6). Evaporation of the solvent under reduced pressure afforded a crude, which was purified by flash column chromatography using an eluent with increasing polarity (petroleum ether/AcOEt 3:1 then 1:1) affording pure **16** (48 mg, 0.02 mmol, 14% yield) as a white solid (R_f = 0.3, petroleum ether/AcOEt 2:1): mp = 68–70 °C; $[\alpha]_D^{25} = -30.7$ (c = 0.41, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.26 (m, 60H; Ar–H), 6.44 (m, 8H; Ar–H), 4.66–4.50 (m, 24H; OCH_2Ar), 4.39 (d, J = 13.0, 4H; $ArCH_2Ar$), 4.17–4.14 (m, 4H; 2-H), 4.06–4.04 (m, 4H; 5-H), 3.89–3.83 (m, 12H, 4-H; $ArOCH_2CH_2CH_3$), 3.72–3.65 (m, 12H; 3a-H, CH_2OBn), 3.32 (m, 4H; 6-H), 3.06 (d, J = 13.0, 4H; $ArCH_2Ar$), 2.72–2.68 (m, 4H; $ArCH_2$), 2.46–2.41 (m, 4H; $ArCH_2$), 2.03–1.91 (m, 16H, 3-H; $ArOCH_2CH_2CH_3$), 1.04–1.00 (m, 12H; $ArOCH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.1 (s, 4C), 138.4 (s, 4C), 138.1 (s, 4C), 137.8 (s, 4C), 134.5 (s, 8C), 130.8 (s, 4C), 128.8 (d, 4C), 128.5 (d, 4C), 128.3–127.4 (d, 60C), 87.6 (d, 4C), 83.1 (d, 4C), 77.3 (d, 4C), 76.6 (t, 4C), 73.4 (t, 4C), 72.5 (t, 4C), 71.8 (t, 4C), 70.1 (t, 4C), 69.2 (d, 4C), 67.7 (d, 4C), 40.0 (t, 4C), 38.9 (t, 4C), 31.2 (t, 4C), 23.4 (t, 4C), 10.6 (q, 4C); ESI-MS calcd for $C_{156}H_{172}N_4NaO_{20}$ m/z 2444.3. Found m/z 2444.9. Anal. Calcd for $C_{156}H_{172}N_4O_{20}$ (2423.05): C, 77.33; H, 7.15; N, 2.31. Found C, 77.36; H, 7.25; N, 2.04.

(2*R*,3*R*,4*R*,5*R*)-2-[(2*R*)-3-(2,6-Dimethylphenoxy)-2-hydroxypropyl]-5-(hydroxymethyl)pyrrolidine-3,4-diol (17). To a solution of compound **10** (180 mg, 0.31 mmol) in MeOH (25 mL), Pd/C (20 mg, 11% w) and 10 drops of concentrated HCl were added. The mixture was left under H_2 atmosphere at room temperature for 15 h, and then a TLC control showed disappearance of **10** (R_f = 0.5, petroleum ether/AcOEt 5:1). After filtration through Celite, the crude was passed through the ion-exchange resin DOWEX 50WX8, eluting with MeOH (15 mL), H_2O (10 mL) and a 10% aq solution of NH_3 (50 mL). Evaporation under reduced pressure afforded pure **17** (93 mg, 0.3 mmol, 97% yield) as a white solid: mp = 95–97 °C; $[\alpha]_D^{25}$ = +33.6 (c = 0.14, MeOH); ^1H NMR (400 MHz, D_2O) δ = 7.04 (d, J = 7.0 Hz, 2H; Ar–H), 6.95 (t, J = 7.2 Hz, 1H; Ar–H), 4.13 (ddt, J = 9.6, 6.8, 3.6 Hz, 1H; $CH_2CHOHCH_2$), 3.91 (t, J = 7.2 Hz, 1H, 4-H), 3.83 (t, J = 7.2 Hz, 1H, 3-H), 3.79–3.67 (m, 4H; CH_2–OH, $ArOCH_2$), 3.35 (td, J = 8.8, 4.4 Hz, 1H; 2-H), 3.27–3.22 (m, 1H; 5-H), 2.19 (s, 6H; $ArCH_3$), 1.97 (ddd, J = 14.8, 10.0, 4.8 Hz, 1H, $ArOCH_2CHOHCH_2$), 1.84 (ddd, J = 14.8, 8.0, 3.2 Hz, 1H, $ArOCH_2CHOHCH_2$); ^{13}C NMR (50 MHz, D_2O) δ = 153.5 (s), 130.4 (s, 2C), 128.0 (d, 2C), 124.0 (d), 78.8 (d), 75.2 (d), 74.9 (t), 66.3 (d), 60.9 (d), 59.2 (t), 56.1 (d), 33.9 (t), 14.4 (q, 2C); MS (EI) m/z = 311 (M^+, 2), 280 (60), 158 (28), 132 (100), 102 (31), 86 (84), 60 (10). Anal. Calcd for $C_{16}H_{25}NO_5$ (311.37): C, 61.72; H, 8.09; N, 4.50. Found C, 61.78; H, 7.86; N, 4.15.

(2*R*,3*R*,4*R*,5*R*)-2-[(2*S*)-2-Hydroxy-4-(4-methoxy-3,5-dimethylphenyl)butyl]5-(hydroxymethyl)pyrrolidine-3,4-diol (18). To a solution of compound **11** (220 mg, 0.37 mmol) in MeOH (30 mL), Pd/C (25 mg, 11% w) and 10 drops of concentrated HCl were added. The mixture was left under H_2 atmosphere at room temperature for 15 h, and then a TLC control showed disappearance of **11** (R_f = 0.5, petroleum ether/AcOEt 4:1). After filtration through Celite, the crude was passed through the ion-exchange resin DOWEX 50WX8, eluting with MeOH (15 mL), H_2O (10 mL) and a 10% aq solution of NH_3 (50 mL). Evaporation under reduced pressure afforded a product that was further purified by flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH (33%) 8:1.5:0.1) to obtain pure **18** (42 mg, 0.13 mmol, 36% yield) as a white solid: mp = 110–112 °C; $[\alpha]_D^{24} = +29.4$ (c = 0.58, MeOH); ^1H NMR (400 MHz, D_2O) δ = 6.83 (s, 2H; Ar–H), 3.86–3.85 (m, 1H; $CH_2CHOHCH_2$), 3.80 (t, J = 7.2 Hz, 1H, 4-H), 3.68–3.56 (m, 6H; 3-H, CH_2OH, $ArOCH_3$), 3.17–3.11 (m, 1H; 2-H), 3.07–3.03 (m, 1H, 5-H), 2.63–2.52 (m, 1H; $ArCH_2$), 2.14 (s, 6H; $ArCH_3$), 2.12 (m, 1H; $ArCH_2$), 1.73–1.66 (m, 2H; $ArCH_2CHOHCH_2$); ^{13}C NMR (50 MHz, D_2O) δ = 154.3 (s), 134.3 (s), 131.0 (s, 2C), 129.8 (d, 2C), 80.1 (d), 76.4 (d), 69.5 (d), 61.6 (d), 60.8 (t), 59.7 (q), 57.5 (d), 42.4 (t), 38.3 (t), 15.1 (q, 2C); MS (EI) m/z = 325 (M^+, 0.9), 276 (12), 176 (22), 149 (18), 132 (100), 86 (17), 60 (35). Anal. Calcd for $C_{17}H_{27}NO_5$ (325.40): C, 62.75; H, 8.36; N, 4.30. Found C, 62.85; H, 8.46; N, 4.15.

26,28-Bis({3-((2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2-benzyloxymethyl-pyrrolidin-5-)-(2*R*)-2-hydroxypropyl}-25,27-dihydroxycalix[4]arene (19). A mixture of **13** (100 mg, 0.075 mmol) and Zn dust (245 mg) in CH_3COOH/H_2O 9:1 (0.9 mL) was heated at 45 °C for 1.5 h, and then a TLC control (petroleum ether/AcOEt 1.5:1) showed the disappearance of the starting calixarene **13** (R_f = 0.4). After filtration through cotton, the solution was treated with a saturated Na_2CO_3 solution until basic pH was reached. The phase was extracted with AcOEt (3 × 25 mL), and the combined organic phases dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded a crude, which was purified through flash column chromatography (petroleum ether/AcOEt 1:1) to obtain pure **19** (67 mg, 0.05 mmol, 66% yield) as a white solid (R_f = 0.1): mp = 95–96 °C; $[\alpha]_D^{25} = -2.0$ (c = 1.22, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.67 (s, 2H; OH), 7.33–7.19 (m, 30H; Ar–H), 7.08–7.06 (m, 2H; Ar–H), 7.03–6.98 (m, 4H; Ar–H), 6.96–6.94 (m, 2H; Ar–H), 6.80 (t, J = 7.6 Hz, 2H; Ar–H), 6.65 (t, J = 7.6 Hz, 2H; Ar–H), 4.58–4.42 (m, 16H; OCH_2Ar, $CH_2CHOHCH_2$, $ArCH_2Ar$), 4.23 (d, J = 13.2 Hz, 2H; $ArCH_2Ar$), 4.13 (dd, J = 9.2, 2.8 Hz, 2H; $ArOCH_2$), 3.95 (t, J = 3.8 Hz, 2H; 4-H), 3.91–3.86 (m, 4H; 3-H, $ArOCH_2$), 3.68–3.58 (m, 2H; 2-H), 3.54–3.52 (m, 4H; CH_2OBn), 3.40–3.34 (m, 6H; 5-H, $ArCH_2Ar$), 2.10–2.00 (m, 2H; $ArOCH_2CHOHCH_2$), 1.92–1.85 (m, 2H; $ArOCH_2CHOHCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 152.2 (s, 2C), 150.8 (s, 2C), 138.2 (s, 6C), 134.0 (s, 4C), 133.5 (s, 4C), 129.4 (d, 2C), 128.7 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 128.2–127.5 (d, 30C), 125.9 (d, 2C), 119.8 (d, 2C), 89.2 (d, 2C), 86.1 (d, 2C), 80.7 (d 2C), 73.1 (t, 2C), 71.9 (t, 4C), 70.4 (t, 2C), 68.6 (t, 2C), 61.6 (d, 2C), 58.9 (d, 2C), 35.3 (t, 2C), 32.0 (t, 2C), 31.3 (t, 2C); ESI-MS calcd for $C_{86}H_{90}N_2NaO_{12}$ ($M + Na^+$) m/z 1365.6. Found m/z 1366.1. Anal. Calcd for $C_{86}H_{90}N_2O_{12}$ (1343.64): C, 76.87; H, 6.75; N, 2.08. Found C, 76.93; H, 7.18; N, 2.09.

5,17-Bis({3-((2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2-benzyloxymethyl-pyrrolidin-5-)-(2*R*)-2-hydroxypropyl}-25,26,27,28-tetrapropoxy-calix[4]arene (20). A mixture of **14** (50 mg, 0.033 mmol) and Zn dust (108 mg) in CH_3COOH/H_2O 9:1 (0.4 mL) was heated at 45 °C for 2 h, and then a TLC control (petroleum ether/AcOEt 3:1) showed the disappearance of the starting calixarene **14** (R_f = 0.4). After filtration through cotton, the solution was treated with a saturated Na_2CO_3 solution until basic pH was reached. The phase was extracted with AcOEt (3 × 20 mL), and the combined organic phases dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded a crude, which was purified through flash column chromatography (CH_2Cl_2/MeOH/NEt_3 30:1:0.1) to obtain pure **20** (42 mg, 0.028 mmol, 86% yield) as a white waxy solid: $[\alpha]_D^{27} = +14.6$ (c = 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.28 (m, 30H; Ar–H), 6.69 (d, J = 6.4 Hz, 4H; Ar–H), 6.42 (m, 6H; Ar–H), 4.60–4.48 (m, 12H; OCH_2Ar), 4.45 (d, J = 13.6 Hz, 2H; $ArCH_2Ar$), 4.44 (d, J = 13.5 Hz, 2H; $ArCH_2Ar$), 4.00–3.95 (m, 4H; 4-H, $CH_2CHOHCH_2$), 3.90–3.85 (m, 6H; 3-H, $ArOCH_2CH_2CH_3$), 3.78 (t, J = 6.8 Hz, 4H; $ArOCH_2CH_2CH_3$), 3.60–3.56 (m, 6H; 2-H,

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CH_2OBn), 3.40 (q, J = 5.2 Hz, 2H, 5-H), 3.12 (d, J = 13.6 Hz, 2H; ArCH_2Ar), 3.10 (d, J = 13.6 Hz, 2H; ArCH_2Ar), 2.71 (dd, J = 13.4, 7.0 Hz, 2H; ArCH_2CHOH), 2.58 (dd, J = 13.4, 7.0 Hz, 2H; ArCH_2CHOH), 1.98−1.89 (m, 8H; ArOCH$_2$$CH_2CH_3$), 1.88−1.81 (m, 2H; ArCH$_2$CHOHCH_2), 1.63−1.56 (m, 2H; ArCH$_2$CHOHCH_2), 1.06 (t, J = 7.6 Hz, 6H; ArOCH$_2$CH$_2$CH_3), 0.93 (t, J = 7.6 Hz, 6H; ArOCH$_2$CH$_2$CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.7 (s, 2C), 155.6 (s, 2C), 138.0 (s, 2C), 137.9 (s, 4C), 135.6 (s, 4C), 134.1 (s, 4C), 131.6 (s, 2C), 129.2 (d, 4C), 128.3−127.6 (d, 34C), 122 (d, 2C), 88.6 (d, 2C), 85.5 (d, 2C), 76.8 (t, 2C), 76.5 (t, 2C), 73.2 (t, 2C), 72.1 (t, 2C), 71.9 (t, 2C), 71.3 (d, 2C), 69.4 (t, 2C), 61.2 (d, 2C), 59.2 (d, 2C), 43.3 (t, 2C), 36.7 (t, 2C), 31.1 (t, 4C), 23.5 (t, 2C), 23.3 (t, 2C), 10.8 (q, 2C), 10.3 (q, 2C); ESI-MS calcd for $C_{98}H_{114}N_2NaO_{12}$ (M + Na^+) m/z 1533.8. Found m/z 1534.6. Anal. Calcd for $C_{98}H_{114}N_2O_{12}$ (1511.96): C, 77.85; H, 7.60; N, 1.85. Found C, 77.73; H, 7.58; N, 2.11.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra of compounds **10**−**20**, ^{13}C NMR spectra of compounds **9**−**20**, COSY spectra of compounds **9**−**13** and **15**−**20**, HMQC spectra of compounds **11**, **13**, and **15**−**20**, 1D NOESY spectra of compounds **10** and **13**, and 2D NOESY spectra of compounds **14** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) Compound **12** was obtained >95% pure (from ^{1}H NMR) with traces of diastereoisomers and spectroscopically characterized: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (s, 2H), 7.09 (d, J = 7.6 Hz, 4H), 6.87−6.85 (m, 4H), 6.72 (t, J = 7.6 Hz, 2H), 6.69 (dd, J = 7.6, 7.2 Hz, 2H), 4.82 (m, 2H), 4.42 (d, J = 13.2 Hz, 2H), 4.40 (d, J = 13.2 Hz, 2H), 4.15−4.11 (m, 4H), 3.99 (dt, J = 6.8, 6.0 Hz, 2H), 3.88 (t, J = 5.2 Hz, 2H), 3.66 (m, 2H), 3.55 (dd, J = 10.4, 5.6 Hz, 2H), 3.40 (d, J = 13.6 Hz, 1H), 3.39 (d, J = 13.6 Hz, 1H), 2.96 (t, J = 9.2 Hz, 2H), 2.66−2.59 (m, 2H), 2.51−2.45 (m, 2H), 1.25 (s, 18H), 1.23 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 153.0 (s, 2C), 151.7 (s, 2C), 132.9 (s, 4C), 128.9 (d, 2C), 128.8 (d, 2C), 128.3 (d, 2C), 128.1 (s, 4C), 125.1 (d, 2C), 118.8 (d, 2C), 81.8 (d, 2C), 76.6 (t, 2C), 76.3 (d, 2C) 75.0 (d, 2C), 74.1 (s, 4C), 69.9 (d, 2C), 59.7 (t, 2C), 37.1 (t, 2C), 31.5 (t, 4C), 29.0 (q, 6C), 28.7 (q, 6C). Anal. Calcd for $C_{58}H_{78}N_2O_{10}$ (963.25): C, 72.32; H, 8.16; N, 2.91. Found C, 72.45; H, 8.27; N, 2.69.
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