Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 6339–6345

# Addressing the scope of the azide–nitrile cycloaddition in glycoconjugate chemistry. The assembly of C-glycoclusters on a calix[4]arene scaffold through tetrazole spacers

Alessandro Dondoni* and Alberto Marra*

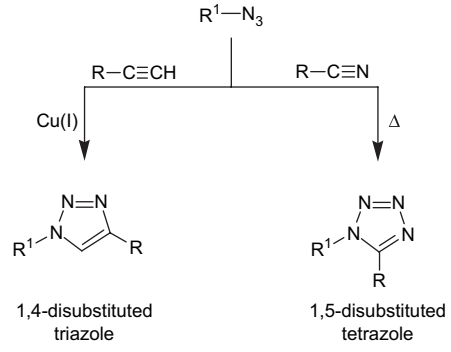
*Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy*

Received 21 January 2007; revised 2 March 2007; accepted 6 March 2007
Available online 12 March 2007

**Abstract**—New glycoclusters constituted of ribosylmethyl, galactosylmethyl, and glucosylmethyl fragments assembled on a calix[4]arene platform by means of propoxytetrazole spacers have been prepared by coupling the corresponding sugar azides with *p*-toluenesulfonyl cyanide, and then reacting 1-glycosylmethyl-5-sulfonyl-tetrazole derivatives thus formed with a calix[4]arene tetrol.


## 1. Introduction

While the azide–alkyne cycloaddition (Huisgen-type reaction),[1] catalyzed by Cu(I) salts[2] to give the1,4-disubstituted triazole system in high yield and selectivity, has reached in a few years the status of an extraordinary synthetic tool for covalently linking molecular entities in the most disparate fields,[3–6] the sister azide–nitrile coupling affording 1,5-disubstituted tetrazole[7] has not found so far a similar widespread application (Scheme 1). The tetrazole group may serve as a robust substrate for ligation because it is stable to both acids and bases, as well as to oxidizing and reducing conditions.[8] Unfortunately, the scope of the azide–nitrile cycloaddition is limited by its occurrence at a satisfactory extent only by the use of nitriles activated by strong electron-withdrawing groups.[9]




**Scheme 1**.

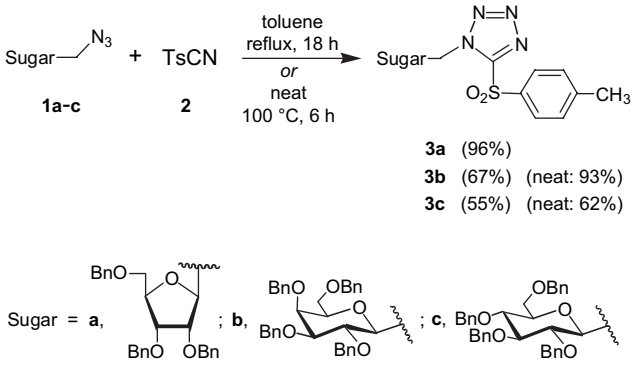
Hence in order to open a viable route to a wide variety of 1,5-disubstituted tetrazoles, Sharpless and Demko developed a simple and expedient two-step sequence. This involves the coupling of an organic azide with *p*-toluenesulfonyl cyanide **2** and then the displacement of the tosyl group in the 5-sulfonyl-tetrazole thus formed by a suitable nucleophile.[10] This chemistry enables the installation of two adjacent molecular fragments in the lipophilic tetrazole ring, i.e. to establish a connectivity pattern, which is analogous to that recently made accessible in triazoles via ruthenium-catalyzed azide–alkyne coupling.[11] Since the Sharpless approach as a ligation tool appears to have been so far applied to simple substrates,[10] we decided to investigate its potential in glycoconjugate chemistry and report here on the assembly of C-glycoclusters on a calix[4]arene platform through tetrazole spacers. This work follows our recent report on C-glycocluster synthesis via azide–alkyne ligation[12] and stems from our interest to provide access to multivalent and highly stable glycoconjugates, which may be used as probes in glycoside cluster effect studies and as potential leads for modulators of recognition processes responsible for various biological events.[13] To this aim C-glycoclusters, i.e. systems in which glycosyl fragments are linked to a suitable scaffold through an enzymatically and chemically resistant carbon–carbon bond, are considered more valuable tools than the easily degradable O- and N-linked derivatives.[12] Moreover, it has been pointed out[3b,d] that the presence of a heteroaromatic group next to the glycosidic bond may be beneficial as it enhances the interaction between the neoglycoconjugate and lectins by increasing the hydrophobicity.

*Keywords*: C-glycoside; Glycocluster; 1,3-Dipolar cycloaddition; Sugar azide; Tetrazole.
* Corresponding authors. Fax: +39 0532 455167; e-mail addresses: adn@unife.it; mra@unife.it

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.045

## 2. Results and discussion

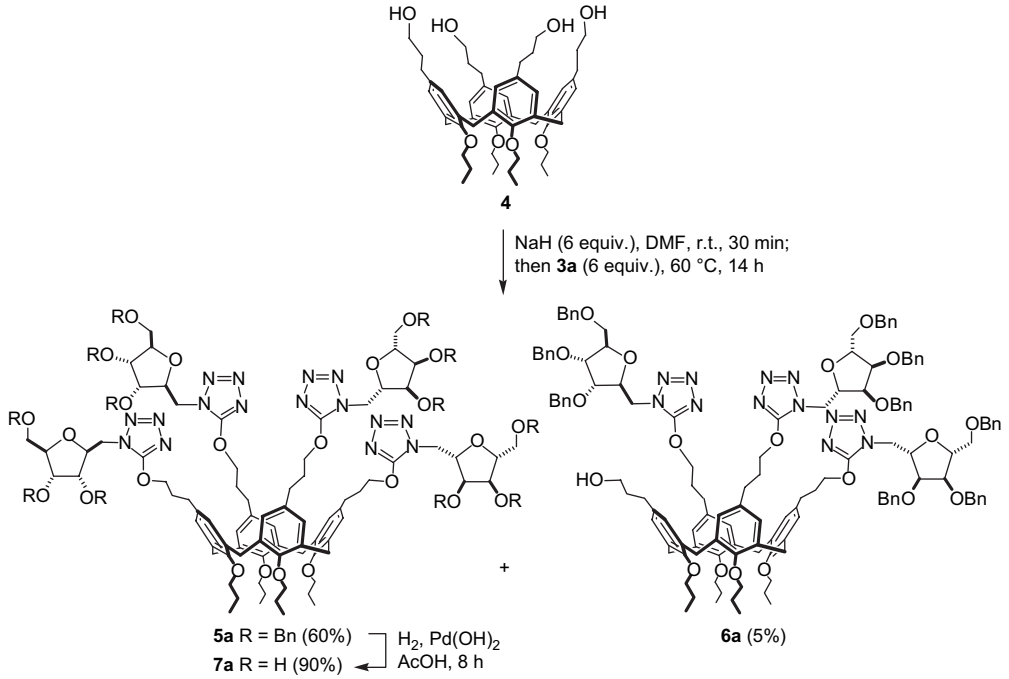
The unhindered β-linked sugar azide, azidomethyl tri-*O*-benzyl-*C*-ribofuranoside[14] **1a** was allowed to react with the nitrile **2** (1.5 equiv) in refluxing toluene (Scheme 2). The solvent was used to obtain a homogeneous mixture of the reactants and efficient stirring, as the sticky sugar **1a** made it unpractical to run the reaction neat. After 18 h a single product was isolated in excellent yield (96%), which was assigned the structure of 1-ribosylmethyl-5-tosyl tetrazole **3a**. In a similar way the sugar azides **1b** (azidomethyl *C*-galactopyranoside)[14] and **1c** (azidomethyl *C*-glucopyranoside)[12] treated with **2** afforded, although in lower yields, the corresponding 1-galactosylmethyl (**3b**, 67%) and 1-glucosylmethyl (**3c**, 55%) tetrazole derivatives. While microwave irradiation at 140 °C failed to improve the yields of these reactions, heating neat **1b** with **2** at 100 °C reduced the reaction time to 6 h and increased substantially the yield of **3b** to 93%. On the other hand coupling of **1c** with **2** under these solventless conditions afforded **3c** in the still moderate yield of 62%. Nevertheless it appears enough demonstrated that unhindered sugar azides of type **1** are able to engage the activated nitrile **2** in an efficient thermal coupling reaction to give 1-substituted-5-sulfonyl-tetrazoles **3**.



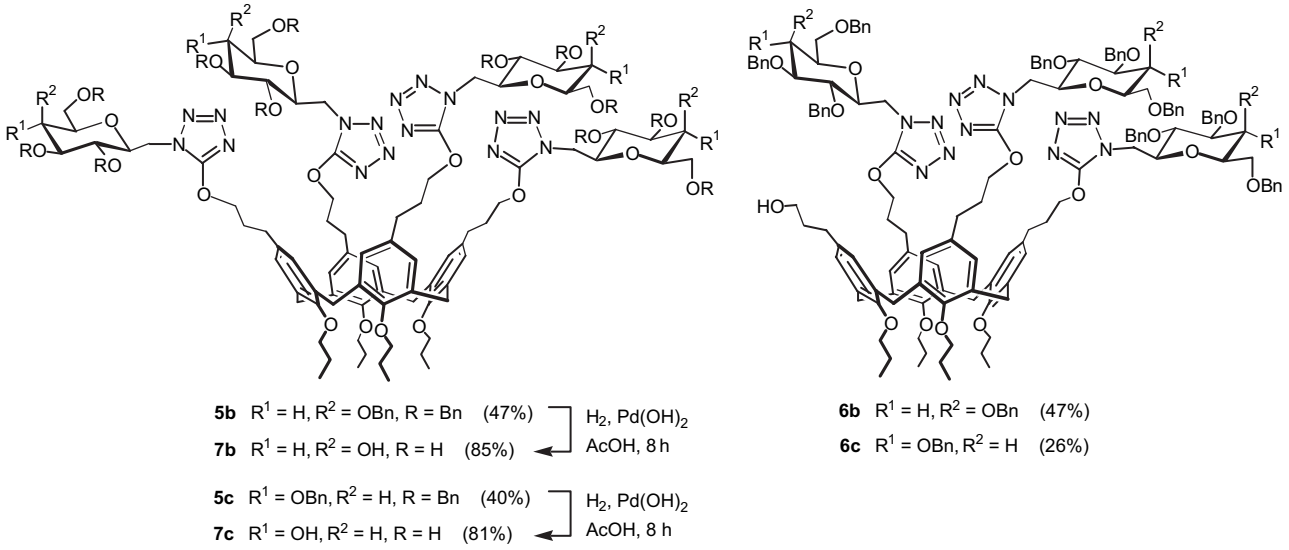

**Scheme 2**.

As platform of the target glycoclusters we selected the known calix[4]arene tetrol[15] **4**, which is well rigidified in the cone conformation owing to the presence of the four *O*-propyl groups at the lower rim. This structural feature of the scaffold should favor a spatial arrangement of the glycoclusters in which the four sugar fragments are in close proximity. The nucleophilic attack of the polydentate alcohol **4** on the 1-methylribosyl-5-sulfonyl-tetrazole **3a** was first carried out (Scheme 3). To this aim **4** was transformed into the corresponding tetraalkoxide upon treatment with excess NaH (6 equiv) in DMF at room temperature and this was allowed to react with **3a** (6 equiv) by heating at 60 °C for 14 h. Apparently under these conditions the nucleophilic attack of the alkoxide groups of **4** on four molecules of tetrazole **3a** proceeded at comparable rate thus giving rise to a multiple tetrazole-calix[4]arene ligation. In fact to our delight suitable workup and chromatography afforded the target tetravalent tetrazole C-glycocluster **5a** as the main product in respectable yield (60%) and only a small amount (5%) of the trivalent derivative **6a**.

In a similar way the calix[4]arene tetrol **4** was allowed to react in DMF at 60 °C with the 1-galactosylmethyl- and 1-glucosylmethyl-5-sulfonyl-tetrazoles **3b** and **3c** to give in both cases the tetravalent C-glycoclusters **5b** and **5c**, respectively, but in lower yields than **5a**. Substantial amounts of the trivalent derivatives **6b** and **6c** were also formed (Scheme 4). Higher temperature (80–120 °C) or longer reaction time (24 h) led to a lower tetra- to trivalent product ratio. Therefore, under the above mentioned conditions, the multiple nucleophilic substitution appeared to be highly dependent




**Scheme 3**.




**Scheme 4**.

on the steric hindrance of the monosaccharidic 5-tosyl-tetrazole substrate. The furanose **3a** gave better results than the pyranose derivatives **3b** and **3c**, the *galacto* **3b** being more reactive than the *gluco* isomer **3c**. Moreover, the conversion of isolated **6b** and **6c** into the corresponding tetravalent C-glycoclusters **5b** and **5c** by further treatment (DMF, 60 °C, 14 h) with NaH (1.5 equiv) and **3b** or **3c** (1.5 equiv), respectively, was also performed. However, the tetra-adducts **5b** and **5c** were isolated in only 25 and 20% yields, respectively, whereas unreacted **6b** (56%) and **6c** (67%) constituted the main products of the reaction mixtures.

Removing the *O*-benzyl protective groups of the sugar units was imperative for the use of the above glycoclusters in molecular recognition processes. This frequently carried out routinary operation in carbohydrate chemistry turned out to be quite difficult in triazole locked glycoclusters recently prepared in our laboratory.[12] The problem appeared to be associated to the presence of several triazole units. On the other hand, to our great delight O-debenzylation of the tetravalent glycoclusters **5a**–**5c** displaying tetrazole tethers was carried out quite efficiently by standard hydrogenolysis over palladium hydroxide as it afforded the corresponding free hydroxy products **7a**–**7c** in good yields (Schemes 3 and 4).

## 3. Conclusion

In conclusion we have reported the first synthesis of glycoclusters anchored on a rigid calix[4]arene scaffold and achieved via the Sharpless–Demko reaction sequence constituted of azide–nitrile 1,3-dipolar cycloaddition and nucleophilic substitution. Each sugar fragment is linked to the tetrazole heterocycle by a carbon–carbon bond and therefore the glycoclusters are expected to be quite resistant to chemical and enzymatic degradation. In addition to achieving the synthesis of the target glycoclusters, this work provides testimony for the first time that the Sharpless–Demko cycloaddition–substitution ligation sequence can be applied to complex molecular entities and gives confidence on its utility in synthetic methodology.

## 4. Experimental

### 4.1. General

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Anhydrous solvents were dried over standard drying agents[16] and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 $F_{254}$ with detection by charring with sulfuric acid. Flash column chromatography[17] was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20±2 °C in the stated solvent; $[\alpha]_D$ values are given in deg mL $g^{-1}$ $dm^{-1}$. $^1H$ NMR (300 and 400 MHz) and $^{13}C$ NMR spectra (75 MHz) were recorded for $CDCl_3$ solutions at rt unless otherwise specified. In the $^1H$ NMR spectra reported below, the *n* and *m* values quoted in geminal or vicinal proton–proton coupling constants $J_{n,m}$ refer to the number of the corresponding sugar protons. MALDI-TOF mass spectra were acquired using 2,5-dihydroxy-benzoic acid as the matrix.

**4.1.1. 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-(5-*p*-toluenesulfonyl-1*H*-tetrazol-1-yl)-D-*allo*-hexitol (3a).** A solution of azide **1a** (138 mg, 0.30 mmol) and commercially available *p*-toluenesulfonyl cyanide **2** (82 mg, 0.45 mmol) in anhydrous toluene (1.5 mL) was stirred at 120 °C in a screw-capped vial for 18 h, then cooled to rt and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **3a** (184 mg, 96%) as a colorless syrup; $[\alpha]_D$ −40.6 (*c* 1.0, $CHCl_3$). $^1H$ NMR (400 MHz): $\delta$ 8.04–7.99 (m, 2H, Ar), 7.41–7.28 (m, 15H, Ar), 7.23–7.18 (m, 2H, Ar), 5.11 (dd, 1H, $J_{1a,2}$=4.8, $J_{1a,1b}$=14.0 Hz, H-1a), 4.84 (dd, 1H, $J_{1b,2}$=4.5 Hz, H-1b), 4.57 and 4.53 (2d, 2H, *J*=11.5 Hz, PhC$H_2$), 4.49 (ddd, 1H, $J_{2,3}$=7.8 Hz, H-2), 4.48 (s, 2H, PhC$H_2$), 4.37 and 4.16 (2d, 2H, *J*=12.3 Hz, PhC$H_2$), 4.14 (ddd, 1H, $J_{4,5}$=2.4, $J_{5,6a}$=3.3, $J_{5,6b}$=3.9 Hz, H-5), 3.89 (dd, 1H, $J_{3,4}$=5.2 Hz, H-3), 3.80 (dd, 1H, H-4), 3.15 (dd, 1H, $J_{6a,6b}$=10.5 Hz, H-6a), 3.11 (dd, 1H, H-6b), 2.46 (s, 3H, Me). $^{13}C$ NMR: $\delta$ 155.6 (C), 147.0 (C), 137.8 (C), 137.5 (C), 137.3 (C), 134.9 (C),

130.1–127.6 (CH), 82.5 (CH), 78.4 (CH), 77.8 (CH), 77.2 (CH), 73.1 ($CH_2$), 72.5 ($CH_2$), 71.7 ($CH_2$), 69.5 ($CH_2$), 50.2 ($CH_2$), 21.8 ($CH_3$). MALDI-TOF MS (640.76): 635.7 ($M^+-N_2$+Na), 663.6 ($M^+$+Na). Anal. Calcd for $C_{35}H_{36}N_4O_6S$: C, 65.61; H, 5.66; N, 8.74. Found: C, 65.90; H, 5.88; N, 8.98.

#### 4.1.2. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(5-*p*-toluenesulfonyl-1*H*-tetrazol-1-yl)-D-*glycero*-L-*manno*-heptitol (3b).

**4.1.2.1. Method A.** The azide **1b** (232 mg, 0.40 mmol) was treated with **2** (109 mg, 0.60 mmol) in anhydrous toluene (2 mL) as described for the preparation of **3a** to give, after column chromatography on silica gel (4:1 cyclohexane–AcOEt), **3b** (204 mg, 67%) as a colorless foam; $[\alpha]_D$ −50.0 (*c* 1.1, $CHCl_3$). $^1$H NMR (300 MHz): $\delta$ 7.97–7.92 (m, 2H, Ar), 7.43–7.20 (m, 22H, Ar), 5.10 and 4.81 (2d, 2H, $J$=11.5 Hz, PhC$H_2$), 5.05 (dd, 1H, $J_{1a,2}$=2.6, $J_{1a,1b}$=13.9 Hz, H-1a), 4.97 and 4.60 (2d, 2H, $J$=11.5 Hz, PhC$H_2$), 4.86 (dd, 1H, $J_{1b,2}$=8.0 Hz, H-1b), 4.80 and 4.70 (2d, 2H, $J$=11.5 Hz, PhC$H_2$), 4.34 and 4.29 (2d, 2H, $J$=12.5 Hz, PhC$H_2$), 4.02 (dd, 1H, $J_{4,5}$=2.6, $J_{5,6}$=0.5 Hz, H-5), 3.93 (dd, 1H, $J_{2,3}$=9.4, $J_{3,4}$=8.8 Hz, H-3), 3.85 (ddd, 1H, H-2), 3.69 (dd, 1H, H-4), 3.52–3.44 (m, 2H, H-6, H-7a), 3.33–3.26 (m, 1H, H-7b), 2.43 (s, 3H, Me). $^{13}$C NMR: $\delta$ 155.4 (C), 146.9 (C), 138.6 (C), 137.9 (C), 134.8 (C), 134.4 (C), 130.1–127.5 (CH), 84.4 (CH), 77.0 (CH), 76.6 (CH), 75.8 (CH), 75.1 ($CH_2$), 74.6 ($CH_2$), 73.4 (CH), 73.3 ($CH_2$), 72.0 ($CH_2$), 68.1 ($CH_2$), 50.6 ($CH_2$), 21.8 ($CH_3$). MALDI-TOF MS (760.92): 755.9 ($M^+-N_2$+Na), 784.3 ($M^+$+Na). Anal. Calcd for $C_{43}H_{44}N_4O_7S$: C, 67.88; H, 5.83; N, 7.36. Found: C, 68.15; H, 5.98; N, 7.50.

**4.1.2.2. Method B.** A mixture of azide **1b** (116 mg, 0.20 mmol) and *p*-toluenesulfonyl cyanide **2** (109 mg, 0.60 mmol) was stirred at 100 °C for 6 h in the absence of solvent under a nitrogen atmosphere, then cooled to rt. The crude mixture was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **3b** (141 mg, 93%) as a colorless foam.

#### 4.1.3. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(5-*p*-toluenesulfonyl-1*H*-tetrazol-1-yl)-D-*glycero*-D-*gulo*-heptitol (3c).

**4.1.3.1. Method A.** The azide **1c** (174 mg, 0.30 mmol) was treated with **2** (82 mg, 0.45 mmol) in anhydrous toluene (2 mL) as described for the preparation of **3a** to give, after column chromatography on silica gel (5:1 cyclohexane–AcOEt), **3c** (125 mg, 55%) as a white solid (mp <40 °C), which could not be recrystallized; $[\alpha]_D$ −26.5 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz): $\delta$ 7.97–7.92 (m, 2H, Ar), 7.40–7.22 (m, 20H, Ar), 7.18–7.13 (m, 2H, Ar), 5.02 (dd, 1H, $J_{1a,2}$=3.2, $J_{1a,1b}$=14.1 Hz, H-1a), 5.01 and 4.79 (2d, 2H, $J$=11.5 Hz, PhC$H_2$), 4.97 and 4.91 (2d, 2H, $J$=11.3 Hz, PhC$H_2$), 4.79 and 4.60 (2d, 2H, $J$=10.9 Hz, PhC$H_2$), 4.74 (dd, 1H, $J_{1b,2}$=8.0 Hz, H-1b), 4.51 and 4.41 (2d, 2H, $J$=12.2 Hz, PhC$H_2$), 3.84 (ddd, 1H, $J_{2,3}$=9.6 Hz, H-2), 3.77 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.0 Hz, H-4), 3.67 (dd, 1H, $J_{5,6}$=9.7 Hz, H-5), 3.66 (dd, 1H, $J_{6,7a}$=3.8, $J_{7a,7b}$=11.2 Hz, H-7a), 3.60 (dd, 1H, $J_{6,7b}$=1.8 Hz, H-7b), 3.52 (dd, 1H, H-3), 3.35 (ddd, 1H, H-6), 2.44 (s, 3H, Me). $^{13}$C NMR: $\delta$ 155.5 (C), 147.1 (C), 138.2 (C), 137.9 (C), 137.6 (C), 134.8 (C), 130.2–127.4 (CH), 86.9 (CH), 79.3 (CH), 78.8 (CH), 78.0 (CH), 76.2 (CH), 75.6 ($CH_2$), 75.04 ($CH_2$), 74.96 ($CH_2$), 73.4 ($CH_2$), 68.5 ($CH_2$), 50.4 ($CH_2$), 21.9 ($CH_3$). MALDI-TOF MS (760.92): 761.8 ($M^+$+H), 783.8 ($M^+$+Na), 799.8 ($M^+$+K). Anal. Calcd for $C_{43}H_{44}N_4O_7S$: C, 67.88; H, 5.83; N, 7.36. Found: C, 68.10; H, 5.91; N, 7.60.

**4.1.3.2. Method B.** The azide **1c** (116 mg, 0.20 mmol) was treated with **2** (109 mg, 0.60 mmol) as described for the preparation of **3b** (Method B) to give, after column chromatography on silica gel (5:1 cyclohexane–AcOEt), **3c** (94 mg, 62%) as a white solid.

#### 4.1.4. 5,11,17,23-Tetrakis[1-(2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-*allo*-hexitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix[4]arene (5a).

To a stirred solution of calixarene tetrol **4** (25 mg, 0.03 mmol) in anhydrous DMF (1.5 mL) was added NaH (7 mg, 0.18 mmol, of a 60% dispersion in oil). The mixture was stirred at rt for 30 min and then diluted with a solution of sugar tetrazole **3a** (115 mg, 0.18 mmol) in anhydrous DMF (1 mL). The resulting yellow solution was stirred at 60 °C for 14 h, then diluted with saturated aqueous $NH_4Cl$ (10 mL) and extracted with AcOEt (2×50 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. The residue was eluted from a column of silica gel (from 2:1 to 1:1 cyclohexane–AcOEt) to give **5a** (50 mg, 60%) as a colorless syrup; $[\alpha]_D$ −22.2 (*c* 1.2, $CHCl_3$). $^1$H NMR (400 MHz): $\delta$ 7.33–7.23 (m, 52H, Ar), 7.21–7.18 (m, 8H, Ar), 6.39 (s, 8H, Ar calix.), 4.52 and 4.47 (2d, 8H, $J$=11.5 Hz, 4 PhC$H_2$), 4.47 (s, 8H, 4 PhC$H_2$), 4.41 and 4.32 (2d, 8H, $J$=11.9 Hz, 4 PhC$H_2$), 4.35 and 3.00 (2d, 8H, $J$=13.4 Hz, 4 ArC$H_2$Ar), 4.33 (t, 8H, $J$=7.0 Hz, 4 $ArCH_2CH_2CH_2$), 4.31 (ddd, 4H, $J_{1a,2}$=4.5, $J_{1b,2}$=5.0, $J_{2,3}$=7.0 Hz, 4 H-2), 4.22 (dd, 4H, $J_{1a,1b}$=14.0 Hz, 4 H-1a), 4.19 (dd, 4H, 4 H-1b), 4.15 (ddd, 4H, $J_{4,5}$=3.6, $J_{5,6a}$=$J_{5,6b}$=4.0 Hz, 4 H-5), 3.88 (dd, 4H, $J_{3,4}$=5.2 Hz, 4 H-3), 3.77 (t, 8H, $J$=7.0 Hz, 4 $CH_3CH_2CH_2O$), 3.75 (dd, 4H, 4 H-4), 3.25 (d, 8H, 8 H-6), 2.34 (t, 8H, $J$=7.2 Hz, 4 $ArCH_2CH_2CH_2$), 1.94–1.84 (m, 16H, 4 $ArCH_2CH_2CH_2$, 4 $CH_3CH_2CH_2O$), 0.95 (t, 12H, $J$=7.0 Hz, 4 $CH_3CH_2CH_2O$). $^{13}$C NMR: $\delta$ 161.7 (C), 154.9 (C), 137.8 (C), 137.6 (C), 137.5 (C), 134.7 (C), 133.5 (C), 128.4–127.6 (CH), 82.0 (CH), 78.6 (CH), 78.1 (CH), 77.0 (CH), 76.7 ($CH_2$), 73.3 ($CH_2$), 72.8 ($CH_2$), 72.5 ($CH_2$), 71.8 ($CH_2$), 70.0 ($CH_2$), 46.4 ($CH_2$), 31.0 ($CH_2$), 30.8 ($CH_2$), 30.4 ($CH_2$), 23.1 ($CH_2$), 10.2 ($CH_3$). MALDI-TOF MS (2763.31): 2787.0 ($M^+$+Na), 2802.6 ($M^+$+K). Anal. Calcd for $C_{164}H_{184}N_{16}O_{24}$: C, 71.28; H, 6.71; N, 8.11. Found: C, 71.50; H, 6.82; N, 8.30.

Eluted second was 5,11,17-tris[1-(2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-*allo*-hexitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-23-(3-hydroxypropyl)-25,26,27,28-tetrapropoxy-calix[4]arene (**6a**) (3.5 mg, 5%) as a colorless syrup; $[\alpha]_D$ −20.0 (*c* 0.9, $CHCl_3$). $^1$H NMR selected data (400 MHz): $\delta$ 7.35–7.24 (m, 39H, Ar), 7.23–7.18 (m, 6H, Ar), 6.54 and 6.52 (2d, 4H, $J$=2.1 Hz, Ar calix.), 6.29 (s, 2H, Ar calix.), 6.26 (s, 2H, Ar calix.), 3.83 (t, 4H, $J$=7.7 Hz, 2 $CH_3CH_2CH_2O$), 3.71 (t, 4H, $J$=7.5 Hz, 2 $CH_3CH_2CH_2O$), 3.45 (dt, 2H, $J$=5.5, 6.0 Hz, $ArCH_2CH_2CH_2$), 3.02 (d, 2H, $J$=13.3 Hz, 2 $H_{eq}$ of 2 ArC$H_2$Ar), 3.00 (d, 2H, $J$=13.3 Hz, 2 $H_{eq}$ of 2 ArC$H_2$Ar), 2.45 (t, 4H, $J$=7.5 Hz, 2 $ArCH_2CH_2CH_2$), 2.32 (t, 1H, $J$=5.5 Hz, OH), 2.27 (t,

2H, $J$=7.5 Hz, ArC$H_2$CH$_2$CH$_2$), 2.23 (t, 2H, $J$=7.5 Hz, ArC$H_2$CH$_2$CH$_2$), 2.01–1.80 (m, 14H, 3 ArCH$_2$C$H_2$CH$_2$, 4 CH$_3$C$H_2$CH$_2$O), 1.57–1.50 (m, 2H, ArCH$_2$C$H_2$CH$_2$), 1.00 (t, 3H, $J$=7.4 Hz, C$H_3$CH$_2$CH$_2$O), 0.98 (t, 3H, $J$=7.4 Hz, C$H_3$CH$_2$CH$_2$O), 0.93 (t, 6H, $J$=7.5 Hz, 2 C$H_3$CH$_2$CH$_2$O). $^{13}$C NMR: $\delta$ 161.7 (C), 155.2 (C), 154.5 (C), 154.2 (C), 137.8 (C), 137.5 (C), 137.4 (C), 135.4 (C), 135.3 (C), 134.9 (C), 134.2 (C), 134.0 (C), 133.6 (C), 133.4 (C), 128.4–127.7 (CH), 82.0 (CH), 78.6 (CH), 78.1 (CH), 77.0 (CH), 76.6 (CH$_2$), 73.3 (CH$_2$), 73.1 (CH$_2$), 72.7 (CH$_2$), 72.5 (CH$_2$), 71.8 (CH$_2$), 70.0 (CH$_2$), 62.0 (CH$_2$), 46.5 (CH$_2$), 34.4 (CH$_2$), 31.3 (CH$_2$), 30.9 (CH$_2$), 30.8 (CH$_2$), 30.4 (CH$_2$), 29.7 (CH$_2$), 23.2 (CH$_2$), 23.1 (CH$_2$), 10.44 (CH$_3$), 10.39 (CH$_3$), 10.1 (CH$_3$). MALDI-TOF MS (2278.76): 2301.9 (M$^+$+Na). Anal. Calcd for $C_{136}H_{156}N_{12}O_{20}$: C, 71.68; H, 6.90; N, 7.38. Found: C, 71.82; H, 6.99; N, 7.48.

**4.1.5. 5,11,17,23-Tetrakis[1-(2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix-[4]arene (5b).** The calixarene tetrol **4** (25 mg, 0.03 mmol) was allowed to react with the sugar tetrazole **3b** (137 mg, 0.18 mmol) in anhydrous DMF as described for the preparation of **5a** to give, after column chromatography on silica gel (from 3:1 to 1:1 cyclohexane–AcOEt), first unreacted **3b** (31 mg, 23%).

Eluted second was **5b** (46 mg, 47%) as a colorless syrup; $[\alpha]_D$ −11.5 ($c$ 1.0, CHCl$_3$). $^1$H NMR (400 MHz): $\delta$ 7.35–7.22 (m, 72H, Ar), 7.20–7.17 (m, 8H, Ar), 6.39 (s, 8H, Ar calix.), 5.00 and 4.72 (2d, 8H, $J$=11.2 Hz, 4 PhC$H_2$), 4.87 and 4.55 (2d, 8H, $J$=11.6 Hz, 4 PhC$H_2$), 4.72 and 4.62 (2d, 8H, $J$=11.7 Hz, 4 PhC$H_2$), 4.34 and 3.00 (2d, 8H, $J$=13.2 Hz, 4 ArC$H_2$Ar), 4.33 and 4.27 (2d, 8H, $J$=11.5 Hz, 4 PhC$H_2$), 4.31 (t, 8H, $J$=7.0 Hz, 4 ArCH$_2$CH$_2$C$H_2$), 4.30 (dd, 4H, $J_{1a,2}$=2.6, $J_{1a,1b}$=14.3 Hz, 4 H-1a), 4.13 (dd, 4H, $J_{1b,2}$= 7.9 Hz, 4 H-1b), 3.96 (dd, 4H, $J_{4,5}$=2.8, $J_{5,6}$=0.5 Hz, 4 H-5), 3.80 (dd, 4H, $J_{2,3}$=$J_{3,4}$=9.3 Hz, 4 H-3), 3.75 (t, 8H, $J$=7.5 Hz, 4 CH$_3$CH$_2$C$H_2$O), 3.66 (ddd, 4H, 4 H-2), 3.61 (dd, 4H, 4 H-4), 3.50–3.45 (m, 8H, 4 H-6, 4 H-7a), 3.39 (dd, 4H, $J_{6,7b}$=9.1, $J_{7a,7b}$=12.6 Hz, 4 H-7b), 2.31 (t, 8H, $J$=7.2 Hz, 4 ArC$H_2$CH$_2$CH$_2$), 1.93–1.82 (m, 16H, 4 ArCH$_2$C$H_2$CH$_2$, 4 CH$_3$C$H_2$CH$_2$O), 0.93 (t, 12H, $J$=7.5 Hz, 4 C$H_3$CH$_2$CH$_2$O). $^{13}$C NMR: $\delta$ 161.7 (C), 154.9 (C), 138.6 (C), 138.1 (C), 138.0 (C), 137.8 (C), 134.7 (C), 133.6 (C), 128.5–127.5 (CH), 84.6 (CH), 76.9 (CH), 76.7 (CH$_2$), 75.7 (CH), 75.0 (CH$_2$), 74.5 (CH$_2$), 73.4 (CH$_2$), 73.3 (CH), 72.7 (CH$_2$), 72.0 (CH$_2$), 68.4 (CH$_2$), 46.6 (CH$_2$), 31.0 (CH$_2$), 30.8 (CH$_2$), 30.4 (CH$_2$), 23.1 (CH$_2$), 10.2 (CH$_3$). MALDI-TOF MS (3243.90): 3267.9 (M$^+$+H+Na), 3283.8 (M$^+$+H+K). Anal. Calcd for $C_{196}H_{216}N_{16}O_{28}$: C, 72.57; H, 6.71; N, 6.91. Found: C, 72.73; H, 6.88; N, 7.10.

Eluted third was 5,11,17-tris[1-(2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-23-(3-hydroxypropyl)-25,26,27,28-tetrapropoxy-calix[4]arene (**6b**) (37 mg, 47%) as a colorless syrup; $[\alpha]_D$ −10.0 ($c$ 1.2, CHCl$_3$). $^1$H NMR selected data (300 MHz): $\delta$ 7.40–7.20 (m, 60H, Ar), 6.62–6.58 (m, 4H, Ar calix.), 6.30 (s, 2H, Ar calix.), 6.28 (s, 2H, Ar calix.), 5.05 (d, 2H, $J$=11.2 Hz, 2H of 2 PhC$H_2$), 5.04 (d, 1H, $J$=11.0 Hz, 1H of PhC$H_2$), 4.92 (d, 2H, $J$=11.7 Hz, 2H of 2 PhC$H_2$), 4.91 (d, 1H, $J$=12.0 Hz, 1H of PhC$H_2$), 4.77 and 4.67 (2d, 4H, $J$=11.5 Hz, 2 PhC$H_2$), 4.01 (dd, 2H, $J_{4,5}$=2.8, $J_{5,6}$=0.5 Hz, 2 H-5), 4.00 (dd, 1H, $J_{4,5}$=2.8, $J_{5,6}$=0.5 Hz, H-5), 3.05 (d, 2H, $J$=13.0 Hz, 2 H$_{eq}$ of 2 ArC$H_2$Ar), 3.04 (d, 2H, $J$=13.0 Hz, 2 H$_{eq}$ of 2 ArC$H_2$Ar), 2.49 (t, 4H, $J$=7.3 Hz, 2 ArC$H_2$CH$_2$CH$_2$), 2.27 (t, 2H, $J$=7.3 Hz, ArC$H_2$CH$_2$CH$_2$), 2.22 (t, 2H, $J$=7.3 Hz, ArC$H_2$CH$_2$CH$_2$), 1.03 (t, 3H, $J$=7.5 Hz, C$H_3$CH$_2$CH$_2$O), 1.01 (t, 3H, $J$=7.5 Hz, C$H_3$CH$_2$CH$_2$O), 0.94 (t, 6H, $J$=7.5 Hz, 2 C$H_3$CH$_2$CH$_2$O). $^{13}$C NMR: $\delta$ 161.7 (C), 155.3 (C), 154.4 (C), 154.1 (C), 138.6 (C), 138.1 (C), 137.9 (C), 137.7 (C), 135.5 (C), 135.4 (C), 135.0 (C), 134.0 (C), 133.8 (C), 133.7 (C), 133.5 (C), 128.4–127.5 (CH), 84.6 (CH), 76.9 (CH), 76.6 (CH$_2$), 75.7 (CH), 75.1 (CH$_2$), 74.5 (CH$_2$), 73.4 (CH$_2$), 73.3 (CH), 73.0 (CH$_2$), 72.6 (CH$_2$), 72.1 (CH$_2$), 68.4 (CH$_2$), 61.9 (CH$_2$), 46.6 (CH$_2$), 34.3 (CH$_2$), 31.3 (CH$_2$), 30.9 (CH$_2$), 30.8 (CH$_2$), 30.4 (CH$_2$), 30.3 (CH$_2$), 29.7 (CH$_2$), 23.3 (CH$_2$), 23.2 (CH$_2$), 23.0 (CH$_2$), 10.5 (CH$_3$), 10.4 (CH$_3$), 10.1 (CH$_3$). MALDI-TOF MS (2639.27): 2662.8 (M$^+$+Na), 2677.5 (M$^+$+K). Anal. Calcd for $C_{160}H_{180}N_{12}O_{23}$: C, 72.81; H, 6.87; N, 6.37. Found: C, 73.02; H, 7.02; N, 6.50.

**4.1.6. 5,11,17,23-Tetrakis[1-(2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-D-*gulo*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix[4]-arene (5c).** The calixarene tetrol **4** (25 mg, 0.03 mmol) was allowed to react with the sugar tetrazole **3c** (137 mg, 0.18 mmol) in anhydrous DMF as described for the preparation of **5a** to give, after column chromatography on silica gel (2.5:1 cyclohexane–AcOEt), first unreacted **3c** (8 mg, 6%).

Eluted second was **5c** (39 mg, 40%) as a colorless syrup; $[\alpha]_D$ −12.0 ($c$ 1.1, CHCl$_3$). $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 7.36–7.02 (m, 80H, Ar), 6.69 (s, 8H, Ar calix.), 4.92 and 4.72 (2d, 8H, $J$=11.5 Hz, 4 PhC$H_2$), 4.84 and 4.76 (2d, 8H, $J$=11.5 Hz, 4 PhC$H_2$), 4.76 and 4.55 (2d, 8H, $J$=11.2 Hz, 4 PhC$H_2$), 4.56 and 3.20 (2d, 8H, $J$=13.0 Hz, 4 ArC$H_2$Ar), 4.49 (t, 8H, $J$=6.6 Hz, 4 ArCH$_2$CH$_2$C$H_2$), 4.43 and 4.32 (2d, 8H, $J$=12.0 Hz, 4 PhC$H_2$), 4.19 (dd, 4H, $J_{1a,2}$=3.0, $J_{1a,1b}$=14.4 Hz, 4 H-1a), 4.06 (dd, 4H, $J_{1b,2}$=6.6 Hz, 4 H-1b), 3.85 (t, 8H, $J$=7.5 Hz, 4 CH$_3$CH$_2$C$H_2$O), 3.65–3.50 (m, 20H), 3.40–3.34 (m, 4H), 3.22–3.17 (m, 4H), 2.49 (t, 8H, $J$=7.2 Hz, 4 ArC$H_2$CH$_2$CH$_2$), 2.02 (tt, 8H, 4 ArCH$_2$C$H_2$CH$_2$), 1.92 (tq, 8H, $J$=7.4, 7.5 Hz, 4 CH$_3$C$H_2$-CH$_2$O), 0.91 (t, 12H, $J$=7.4 Hz, 4 C$H_3$CH$_2$CH$_2$O). $^{13}$C NMR: $\delta$ 161.8 (C), 155.0 (C), 138.3 (C), 138.0 (C), 137.9 (C), 134.7 (C), 133.5 (C), 128.5–127.6 (CH), 87.0 (CH), 79.1 (CH), 78.6 (CH$_2$), 78.0 (CH), 76.7 (CH$_2$), 76.3 (CH), 75.5 (CH$_2$), 75.0 (CH$_2$), 74.9 (CH$_2$), 73.4 (CH$_2$), 72.8 (CH$_2$), 68.6 (CH$_2$), 46.0 (CH$_2$), 31.0 (CH$_2$), 30.8 (CH$_2$), 30.5 (CH$_2$), 23.1 (CH$_2$), 10.3 (CH$_3$). MALDI-TOF MS (3243.90): 3268.2 (M$^+$+H+Na), 3283.4 (M$^+$+K). Anal. Calcd for $C_{196}H_{216}N_{16}O_{28}$: C, 72.57; H, 6.71; N, 6.91. Found: C, 72.85; H, 6.96; N, 7.08.

Eluted third was 5,11,17-tris[1-(2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-D-*gulo*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-23-(3-hydroxypropyl)-25,26,27,28-tetrapropoxy-calix[4]arene (**6c**) (20 mg, 26%) as a colorless syrup; $[\alpha]_D$ −10.7 ($c$ 0.7, CHCl$_3$). $^1$H NMR selected data (400 MHz): $\delta$ 7.34–7.22 (m, 54H, Ar), 7.14–7.10 (m, 6H, Ar), 6.55–6.51 (m, 4H, Ar calix.), 6.28–6.25 (m, 2H, Ar calix.), 6.24 (s, 2H, Ar calix.), 4.93 and 4.88 (2d, 4H,

$J$=11.3 Hz, 2 PhC$H_2$), 4.92 and 4.87 (2d, 2H, $J$=11.2 Hz, PhC$H_2$), 4.76 and 4.53 (2d, 4H, $J$=10.8 Hz, 2 PhC$H_2$), 4.75 and 4.51 (2d, 2H, $J$=10.8 Hz, PhC$H_2$), 4.28 (dd, 1H, $J_{1a,2}$=2.9, $J_{1a,1b}$=14.3 Hz, H-1a), 4.19 (dd, 1H, $J_{1b,2}$=5.0, $J_{1a,1b}$=14.5 Hz, H-1b), 4.17 (dd, 1H, $J_{1b,2}$=5.0, $J_{1a,1b}$= 14.5 Hz, H-1b), 4.13 (dd, 1H, $J_{1b,2}$=6.7, $J_{1a,1b}$=14.3 Hz, H-1b), 3.82 (t, 4H, $J$=7.8 Hz, 2 $CH_3CH_2CH_2O$), 3.01 (d, 1H, $J$=13.2 Hz, $H_{eq}$ of ArC$H_2$Ar), 3.00 (d, 1H, $J$= 13.2 Hz, $H_{eq}$ of ArC$H_2$Ar), 2.98 (d, 2H, $J$=13.2 Hz, 2 $H_{eq}$ of 2 ArC$H_2$Ar), 2.45 (t, 4H, $J$=7.0 Hz, 2 ArC$H_2$$CH_2CH_2$), 2.31–2.28 (m, 1H, OH), 2.25 (t, 2H, $J$=7.6 Hz, ArC$H_2$$CH_2CH_2$), 2.21 (t, 2H, $J$=7.6 Hz, ArC$H_2$$CH_2CH_2$), 1.00 (t, 3H, $J$=7.5 Hz, C$H_3$$CH_2CH_2O$), 0.98 (t, 3H, $J$=7.5 Hz, C$H_3$$CH_2CH_2O$), 0.92 (t, 6H, $J$=7.5 Hz, 2 C$H_3$$CH_2CH_2O$). $^{13}$C NMR: $\delta$ 161.8 (C), 155.3 (C), 154.5 (C), 154.2 (C), 138.3 (C), 137.9 (C), 137.8 (C), 135.5 (C), 135.4 (C), 134.9 (C), 134.1 (C), 133.9 (C), 133.6 (C), 133.4 (C), 128.5–127.6 (CH), 87.0 (CH), 79.0 (CH), 78.6 (CH), 78.0 (CH), 76.6 ($CH_2$), 76.4 (CH), 75.5 ($CH_2$), 75.0 ($CH_2$), 74.9 ($CH_2$), 73.4 ($CH_2$), 73.1 ($CH_2$), 72.7 ($CH_2$), 68.6 ($CH_2$), 61.8 ($CH_2$), 46.1 ($CH_2$), 34.2 ($CH_2$), 31.3 ($CH_2$), 30.8 ($CH_2$), 30.4 ($CH_2$), 26.9 ($CH_2$), 23.2 ($CH_2$), 23.0 ($CH_2$), 10.5 ($CH_3$), 10.1 ($CH_3$). MALDI-TOF MS (2639.27): 2662.6 ($M^+$+Na), 2678.4 ($M^+$+K). Anal. Calcd for $C_{160}H_{180}N_{12}O_{23}$: C, 72.81; H, 6.87; N, 6.37. Found: C, 72.98; H, 6.96; N, 6.53.

**4.1.7. 5,11,17,23-Tetrakis[1-(2,5-anhydro-1-deoxy-D-*allo*-hexitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix[4]arene (7a).** A vigorously stirred mixture of **5a** (33 mg, 0.012 mmol), 20% palladium hydroxide on carbon (35 mg), and AcOH (2 mL) was degassed under vacuum and saturated with hydrogen (by an $H_2$-filled balloon) 10 times. The suspension was stirred at rt for 8 h under a slightly positive pressure of hydrogen (balloon) and then concentrated. A suspension of the residue in $CH_3OH$ was filtered through a plug of cotton and concentrated. The crude product was eluted from a C18 silica gel cartridge (1.5×2 cm, d×h) with $CH_3OH$ to give **7a** (18 mg, 90%) as a colorless syrup; $[\alpha]_D$ −16.4 (*c* 0.7, $CH_3OH$). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 6.51 (s, 8H, Ar calix.), 4.40 and 3.07 (2d, 8H, $J$=13.1 Hz, 4 ArC$H_2$Ar), 4.37 (t, 8H, $J$=6.5 Hz, 4 ArC$H_2$$CH_2$C$H_2$), 4.37 (dd, 4H, $J_{1a,2}$=4.7, $J_{1a,1b}$=14.5 Hz, 4 H-1a), 4.32 (dd, 4H, $J_{1b,2}$=6.5 Hz, 4 H-1b), 4.13 (ddd, 4H, $J_{2,3}$=6.1 Hz, 4 H-2), 3.96 (dd, 4H, $J_{3,4}$=5.5 Hz, 4 H-3), 3.92 (dd, 4H, $J_{4,5}$= 3.9 Hz, 4 H-4), 3.85 (ddd, 4H, $J_{5,6a}$=3.8, $J_{5,6b}$=4.5 Hz, 4 H-5), 3.82 (t, 8H, $J$=7.5 Hz, 4 $CH_3CH_2CH_2O$), 3.53 (dd, 4H, $J_{6a,6b}$=11.8 Hz, 4 H-6a), 3.48 (dd, 4H, 4 H-6b), 2.44 (t, 8H, $J$=7.3 Hz, 4 ArC$H_2$$CH_2CH_2$), 2.00–1.90 (m, 16H, 4 ArC$H_2$C$H_2$$CH_2$, 4 $CH_3$C$H_2$$CH_2O$), 1.01 (t, 12H, $J$=7.4 Hz, 4 C$H_3$$CH_2CH_2O$). $^{13}$C NMR ($CD_3OD$): $\delta$ 163.0 (C), 156.1 (C), 136.1 (C), 135.2 (C), 129.3 (CH), 86.6 (CH), 81.2 (CH), 78.0 ($CH_2$), 74.2 (CH), 74.1 ($CH_2$), 72.8 (CH), 63.3 ($CH_2$), 48.8 ($CH_2$), 31.9 ($CH_2$), 31.7 ($CH_2$), 24.4 ($CH_2$), 10.9 ($CH_3$). MALDI-TOF MS (1681.84): 1704.7 ($M^+$+Na). Anal. Calcd for $C_{80}H_{112}N_{16}O_{24}$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.20; H, 6.89; N, 13.41.

**4.1.8. 5,11,17,23-Tetrakis[1-(2,6-anhydro-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix[4]arene (7b).** The glycocluster **5b** (32 mg, 0.01 mmol) was debenzylated as described for the preparation of **7a** to give, after a similar purification, **7b** (15 mg, 85%) as a colorless syrup; $[\alpha]_D$ +0.8 (*c* 0.3, $CH_3OH$). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 6.52 (s, 8H, Ar calix.), 4.54 (dd, 4H, $J_{1a,2}$=2.3, $J_{1a,1b}$=14.5 Hz, 4 H-1a), 4.40 and 3.07 (2d, 8H, $J$=13.0 Hz, 4 ArC$H_2$Ar), 4.37 (t, 8H, $J$=7.5 Hz, 4 ArC$H_2$$CH_2$C$H_2$), 4.30 (dd, 4H, $J_{1b,2}$=7.8 Hz, 4 H-1b), 3.88 (dd, 4H, $J_{4,5}$=3.0, $J_{5,6}$=0.5 Hz, 4 H-5), 3.82 (t, 8H, $J$=7.4 Hz, 4 $CH_3CH_2CH_2O$), 3.64 (dd, 4H, $J_{6,7a}$=6.0, $J_{7a,7b}$=11.0 Hz, 4 H-7a), 3.62–3.54 (m, 12H, 4 H-2, 4 H-3, 4 H-7b), 3.48 (dd, 4H, $J_{3,4}$=8.6 Hz, 4 H-4), 3.42 (ddd, 4H, $J_{6,7b}$=5.8 Hz, 4 H-6), 2.43 (t, 8H, $J$=7.2 Hz, 4 ArC$H_2$$CH_2CH_2$), 2.00–1.88 (m, 16H, 4 ArC$H_2$C$H_2$$CH_2$, 4 $CH_3$C$H_2$$CH_2O$), 1.01 (t, 12H, $J$=7.5 Hz, 4 C$H_3$$CH_2CH_2O$). $^{13}$C NMR ($CD_3OD$): $\delta$ 163.1 (C), 156.1 (C), 136.1 (C), 135.3 (C), 129.3 (CH), 80.1 (CH), 79.1 (CH), 78.0 ($CH_2$), 76.2 (CH), 74.0 ($CH_2$), 70.5 (CH), 62.3 ($CH_2$), 48.4 ($CH_2$), 32.0 ($CH_2$), 31.6 ($CH_2$), 24.4 ($CH_2$), 10.8 ($CH_3$). MALDI-TOF MS (1801.94): 1825.6 ($M^+$+Na), 1841.6 ($M^+$+K). Anal. Calcd for $C_{84}H_{120}N_{16}O_{28}$: C, 55.99; H, 6.71; N, 12.44. Found: C, 56.27; H, 6.82; N, 12.58.

**4.1.9. 5,11,17,23-Tetrakis[1-(2,6-anhydro-1-deoxy-D-*glycero*-D-*gulo*-heptitol-1-yl)-1*H*-tetrazol-5-yloxypropyl]-25,26,27,28-tetrapropoxy-calix[4]arene (7c).** The glycocluster **5c** (32 mg, 0.01 mmol) was debenzylated as described for the preparation of **7a** to give, after a similar purification, **7c** (14.5 mg, 81%) as a colorless syrup; $[\alpha]_D$ −4.9 (*c* 0.5, $CH_3OH$). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 6.50 (s, 8H, Ar calix.), 4.55 (dd, 4H, $J_{1a,2}$=2.8, $J_{1a,1b}$=14.8 Hz, 4 H-1a), 4.40 and 3.06 (2d, 8H, $J$=13.2 Hz, 4 ArC$H_2$Ar), 4.37 (t, 8H, $J$=7.2 Hz, 4 ArC$H_2$$CH_2$C$H_2$), 4.30 (dd, 4H, $J_{1b,2}$= 8.0 Hz, 4 H-1b), 3.82 (t, 8H, $J$=7.4 Hz, 4 $CH_3CH_2CH_2O$), 3.73 (dd, 4H, $J_{6,7a}$=2.3, $J_{7a,7b}$=12.0 Hz, 4 H-7a), 3.65 (ddd, 4H, $J_{2,3}$=9.5 Hz, 4 H-2), 3.60 (dd, 4H, $J_{6,7b}$=5.3 Hz, 4 H-7b), 3.38 (dd, 4H, $J_{3,4}$=$J_{4,5}$=8.7 Hz, 4 H-4), 3.29 (dd, 4H, $J_{5,6}$=9.5 Hz, 4 H-5), 3.22 (dd, 4H, 4 H-3), 3.18 (ddd, 4H, 4 H-6), 2.43 (t, 8H, $J$=7.2 Hz, 4 ArC$H_2$$CH_2CH_2$), 1.99–1.90 (m, 16H, 4 ArC$H_2$C$H_2$$CH_2$, 4 $CH_3$C$H_2$$CH_2O$), 1.01 (t, 12H, $J$=7.5 Hz, 4 C$H_3$$CH_2CH_2O$). $^{13}$C NMR ($CD_3OD$): $\delta$ 163.1 (C), 156.1 (C), 136.1 (C), 135.2 (C), 129.3 (CH), 81.6 (CH), 79.6 (CH), 78.4 (CH), 78.0 ($CH_2$), 74.1 ($CH_2$), 73.2 (CH), 71.4 (CH), 62.7 ($CH_2$), 48.3 ($CH_2$), 32.0 ($CH_2$), 31.6 ($CH_2$), 24.4 ($CH_2$), 10.8 ($CH_3$). MALDI-TOF MS (1801.94): 1825.7 ($M^+$+Na), 1840.7 ($M^+$+K). Anal. Calcd for $C_{84}H_{120}N_{16}O_{28}$: C, 55.99; H, 6.71; N, 12.44. Found: C, 56.11; H, 6.92; N, 12.62.

## References and notes


1. (a) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494–2507; (b) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; pp 1–176.
2. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
3. Bioconjugate chemistry: (a) Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147–1149; (b) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoyo-Gonzales, F. *Org. Lett.* **2003**, *5*, 1951–1954; (c) van Maarseveen, J. H.; Back, J. W. *Angew. Chem., Int. Ed.* **2003**,

*42*, 5926–5928; (d) Zhu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1081–1085; (e) Dondoni, A.; Giovannini, P. P. *Org. Lett.* **2004**, *6*, 2929–2932; (f) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123–3126; (g) Dorner, S.; Westermann, B. *Chem. Commun.* **2005**, 2852–2854; (h) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215–2220; (i) Weller, R. L.; Rajski, S. R. *Org. Lett.* **2005**, *7*, 2141–2144; (j) Jang, H.; Fafarman, A.; Holub, J. M.; Kirshenbaum, K. *Org. Lett.* **2005**, *7*, 1951–1954; (k) Wong, C.-H. *J. Org. Chem.* **2005**, *70*, 4219–4225; (l) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *Org. Lett.* **2005**, *7*, 4479–4482; (m) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331–2336; (n) Cheshev, P.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2006**, *4*, 3225–3227.

4. Drug discovery: (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128–1137; (b) Cavalli, S.; Tipton, A. R.; Overhand, M.; Kros, A. *Chem. Commun.* **2006**, 3193–3195.
5. Resin and dendrimer synthesis: (a) Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753–1755; (b) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928–3932.
6. Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 5292–5296.
7. Butler, R. N. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, 1966; Vol. 4.
8. Benson, F. R. *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley & Sons: New York, NY, 1966; Vol. 4.
9. (a) Carpenter, W. R. *J. Org. Chem.* **1962**, *27*, 2085–2088; (b) Quast, H.; Bieber, L. *Tetrahedron Lett.* **1976**, *18*, 1485–1486.
10. Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110–2113.
11. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.
12. Dondoni, A.; Marra, A. *J. Org. Chem.* **2006**, *71*, 7546–7557.
13. (a) Lee, Y. C.; Lee, R. T.; Rice, K.; Ichikawa, Y.; Wong, T.-C. *Pure Appl. Chem.* **1991**, *63*, 499–506; (b) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–326; (c) Sigal, G. B.; Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 3789–3800; (d) Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555–578.
14. Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979–6994.
15. Dondoni, A.; Kleban, M.; Hu, X.; Marra, A.; Banks, H. D. *J. Org. Chem.* **2002**, *67*, 4722–4733.
16. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Amsterdam, 2003.
17. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.