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New synthesis of heteroglycoclusters from *p*-*t*-butylcalix[4]arene tetraalkoxyheterohalides as key intermediates

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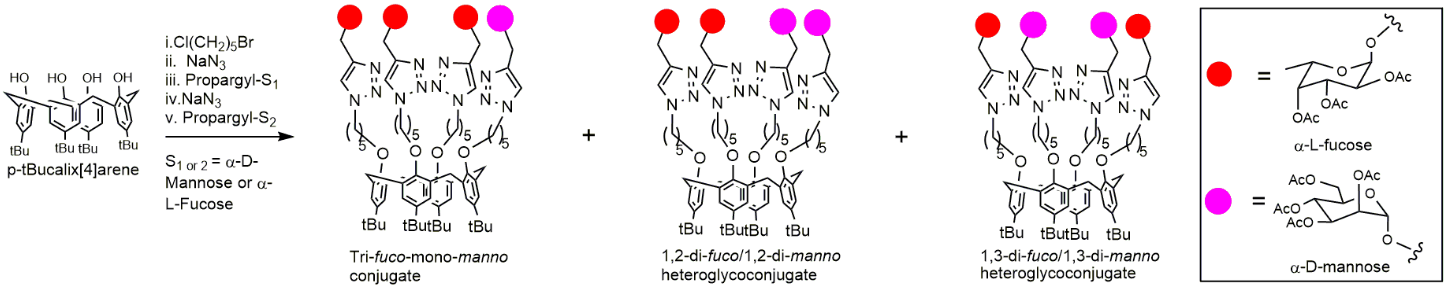
Abstract

A straightforward synthesis of heteroglycoclusters based *p*-*t*-butylcalix[4]arene has been achieved. The key step is the formation of hetero-halopentyloxy-*p*-*t*-butylcalix [4]arene mixture via haloalkylation with 1-bromo-5-chloropentane as asymmetric alkylating reagent. Subsequent selective exchange of bromide by azide under mild conditions provides selectively azido-chloro species suitable for click reaction with first propargylglycoside. The products here can then be subjected to further azidation to enable attachment of different glycosides via click chemistry reaction.

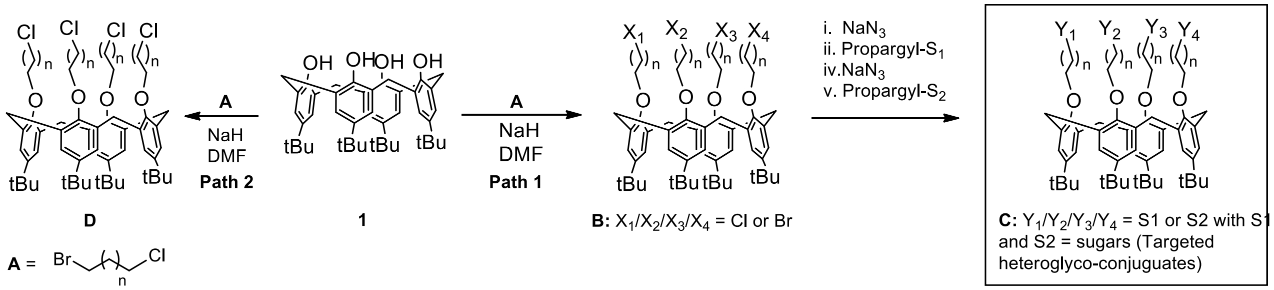


Keywords: Heteroglycoconjugate, Heterohalide, Calixarene, Halide exchange, Click chemistry

Introduction

Various pivotal biological events such cell-cell interactions, the immune response and cell signaling are based on carbohydrate-lectin recognition.[1-5] This is also the main microbial virulence factor involved in pathogen-host adhesion at the early stages of serious infections.[6] Inhibition of such processes by molecular mimics of the natural glycans, are therefore major therapeutic interest.[7,8] Synthetic multivalent homoglycoclusters formed by multiple copies of the same epitope have been widely investigated as lectins inhibitors over the past two decades.[9,10] Their design, however, is a simplification of the real biological state since natural glycans have heterooligosacharidic structures[11,12]referred to as the *sugar code*.[13] It is assumed now that a heterogeneous environment creates secondary interactions that increase the affinity of lectin recognition sites towards their epitopes.[14-17] Accordingly, various strategies allowing access to heteroglycoclusters have been developed.[18-21] Among these is the use of a multifunctional scaffold tailored for sequential grafting of various sugars.[22-24] Despite the promise of this concept, its exploitation is as yet limited and it remains a methodological challenge that warrants further development.

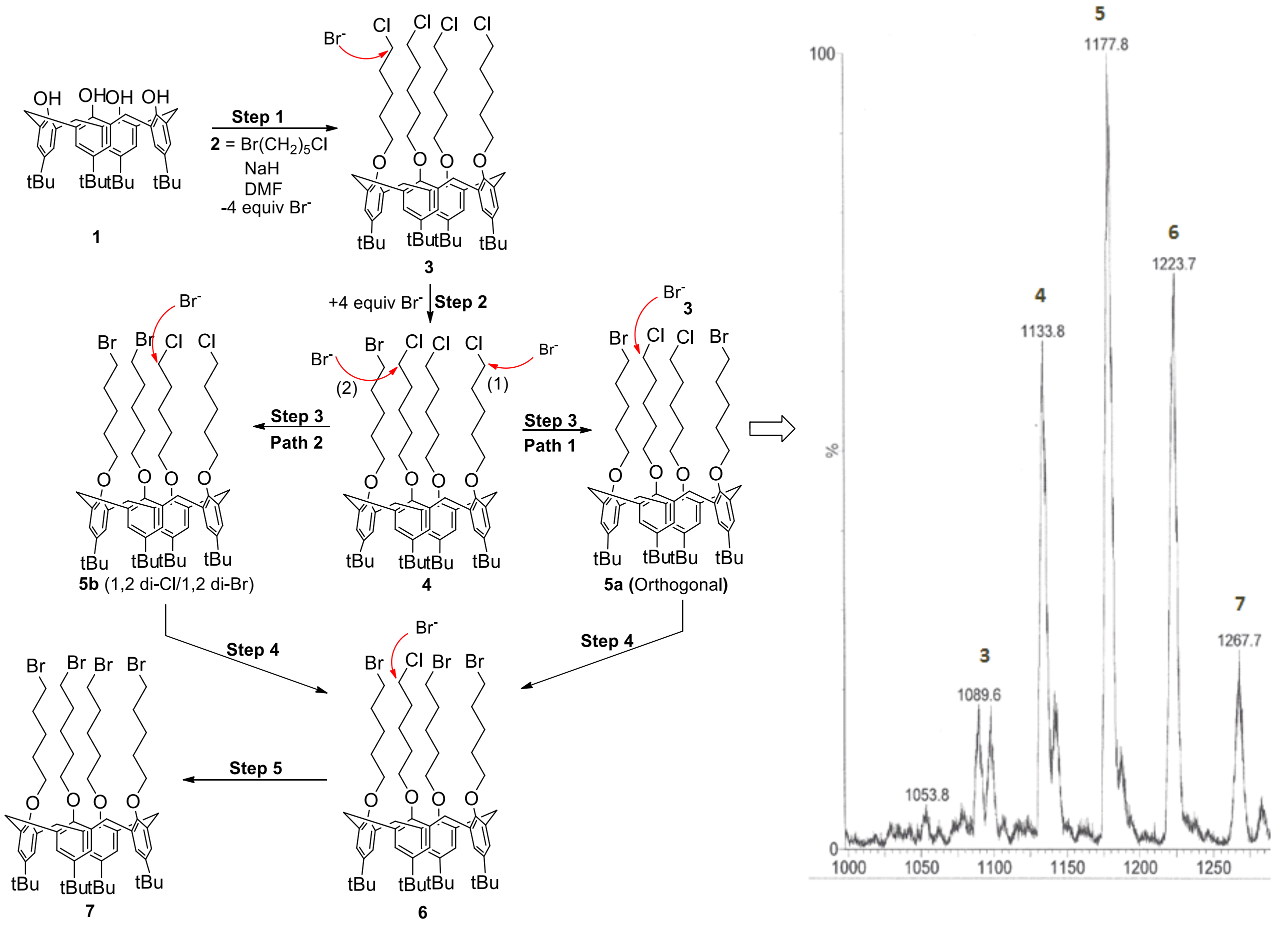
Calix[4]arene, with its preorganised shape has attracted much interest as a scaffold in several glycoconjugates customized, for instance, for bacterial lectins recognition and/or biofilm inhibition.[25-27] Although many exciting achievement have been witnessed in calixarene chemistry in the last few decades, there is still a need for a straightforward methodology enabling heterofunctionalisation in a rational manner. Recently we observed that the haloalkylation of *p*-*t*-butylcalix [4]arene **1** with α-chloro-ω-bromoalkane **A** instead of the most used homohalide counterpart in literature[28,29] (Scheme 1), led mainly to a mixture of heterohaloalkyloxy ethers **B** (Path 1) instead of the expected tetraalkoxy homohalide calixarene derivative **D** (Path 2). Then, here we decided to examine in-depth this one pot halide exchange reactions for subsequent synthesis of heteroglycoconjugate derivatives **C** via selective and iterative bromide/azide exchanges and subsequent azide-alkyne click chemistry reactions. The tetra-alkylation to the cone conformation of calixarene desired for the present work, occurs using suitable and well known conditions[30] involving NaH as the base and DMF as solvent.



Scheme 1. Possible synthesis of heteroglycoconjugates based calix[4]arene **C** from iterative strategy involving halide exchange, halide/azides exchanges and azido-alkyne click chemistry reactions.

Results and Discussion

It was anticipated that the base-catalysed reaction of *p*-*t*-butylcalix[4]arene **1** with 1-bromo-5-chloro-pentane **2** as the alkylating reagent would proceed by preferential displacement of bromide to give a chloropentyloxy ether **3** (Scheme 2, step 1). The native free bromide could then involve in the targeted one pot halide exchange reactions. The product mixture at any time should be determined by the relative rates of these reactions. The ESI-MS mass spectrum at early stages of reaction indicated little competition of halide exchange with the alkylation reaction. In fact, after 1 h at room temperature or 5 min at 90 °C the product appeared to be almost exclusively the tetrakis(chloropentylether) **3** (MNa^+ = 1089.6) (SI). The detection of traces of monobromo-trichloropentyloxycalixarene **4** (MNa^+ = 1133.7) coming from the first chloride/bromide exchange at room temperature supports the feasibility of the assumed halide exchange. At 50 °C, significant halide exchange have been detected after 24 h with mono-, di- and tri-bromo calixarene derivatives formation (**4**, **5** and **6** respectively). The most abundant being the dibromo derivative **5** (Step 3) (MNa^+ = 1179.5). Further exchange reaction converted **5** into the tribromo species **6** (MNa^+ = 1223.7) (Step 4) that disappeared rapidly in favor of the symmetrical perbromopentyloxy species **7** (MNa^+ = 1267.9) (Step 5). The kinetics of the reactions is complicated in part because the concentration of free bromide diminishes as the exchange proceeds. This fact has the advantage to enable the definition of the conditions where the mixed heterohalo-species **4**, **5** and **6** were the major products, with most of the initial product **3** being consumed and very little of **7** being produced, for example by limiting the reaction time to 16 h at 90 °C as shown in ESI-MS spectrum associated to scheme 2.



Scheme 2. Finkelstein halide exchange cascade from **3** to **7** triggered by free Br^-. MNa^+ (ESI-MS-spectrum) for reaction conditions: 16h reaction time at 90 °C.

The isolation as the individual pure halolakylated calixarene derivatives by chromatography was not unfortunately successful due to their very similar polarities on a stationary phase of silica-gel. Furthermore, the mixture nature is only revealed by MS-ESI and widely omitted by NMR-spectroscopy. In fact, despite some formal differences in symmetry between the five components, their mixture showed in ^{1}H-NMR spectrum (Figure 1) a single AB quartet (doublets at δ 3.17 and 4.40) for the diastereotopic protons of the calixarene methylene bridges, consistent with all having a *cone* conformation. In ^{13}C we observed a few distinguishing features, for example, in regard to the presence of CH_2OAr or CH_2Br groups after zone enlargement (Figures 2).

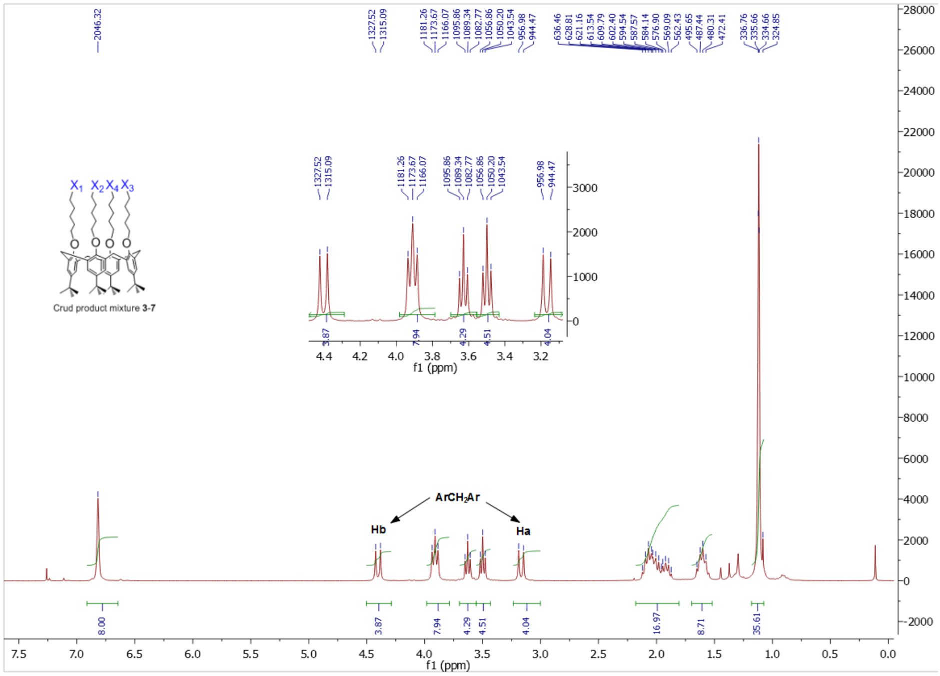


Figure 1. ^{1}H-NMR spectrum of **3-7** mixture.

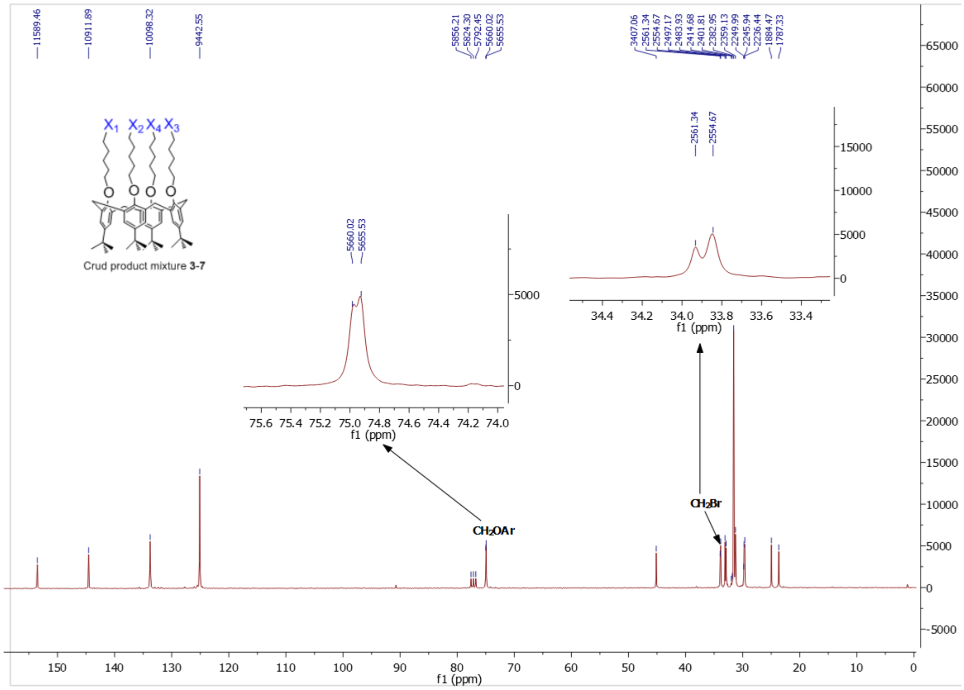
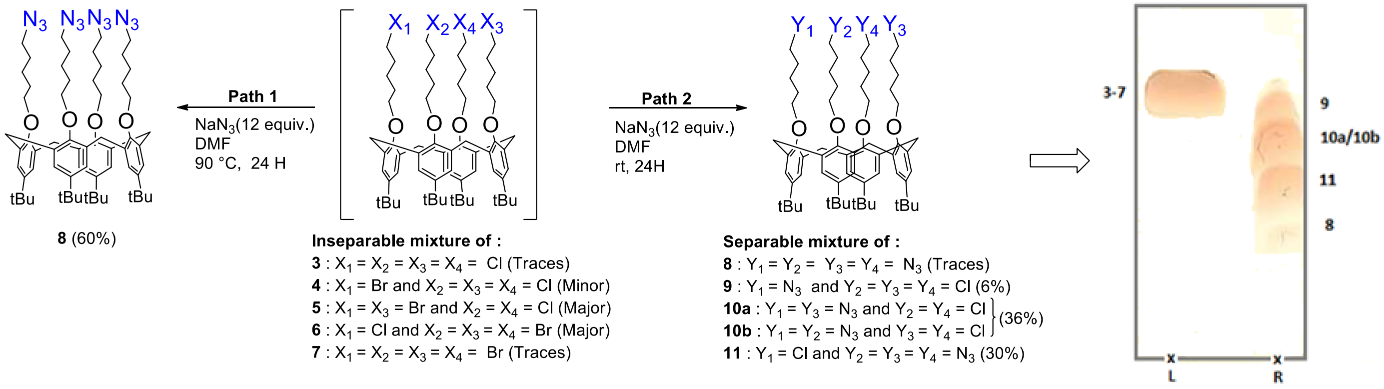


Figure 2. ^{13}C-NMR spectrum of **3-7** mixture.

As an alternative, separation of the products after azidation of the crude mixture **3**-**7** was examined. Under standard conditions using NaN_3 in DMF, reaction at 90 °C resulted in substitution of both chloro and bromo atoms leading to the tetra-azido derivative **8** that has been isolated by chromatography on silica gel in 60% yield (Scheme 3, path 1). At room temperature, however, the reaction could be conducted selectively, leading to substitution of the bromo atoms only (Path 2). ESI-MS monitoring showed the formation of monoazido-trichloro **9**, diazido-dichloro **10**, triazido-monochloro **11** and tetrazido **8** compounds (MNa^+ = 1094.7, 1101.7, 1108.7 and 1115.8 respectively) with significant greater ion-current intensities for **10** and **11** relative to those of **8** and **9** (SI). Fortunately, these derivatives proved to be separable by chromatography as shown by TLC associated to scheme 3. The subsequent flash chromatography on silica gel with a cyclohexane/DCM gradient eluant gave the three desired compounds **9**, **10** and **11** with traces of **8.** The monoazido-trichloro compound **9** was recovered as the least abundant (6% yield) and the diazido-dichloro **10a/b** and the triazido-monochloro **11** compounds were obtained in 36% and 30% yields respectively. The three calix scaffolds were characterised by NMR spectroscopy (SI). As noted for the mixture, the methylene-bridge protons appeared in the NMR spectra as a single AB quartet for each compound and this was taken to be indicative of a *cone* conformation although clearly the spectra did not reflect the true symmetry of the compounds in **10a/b**.

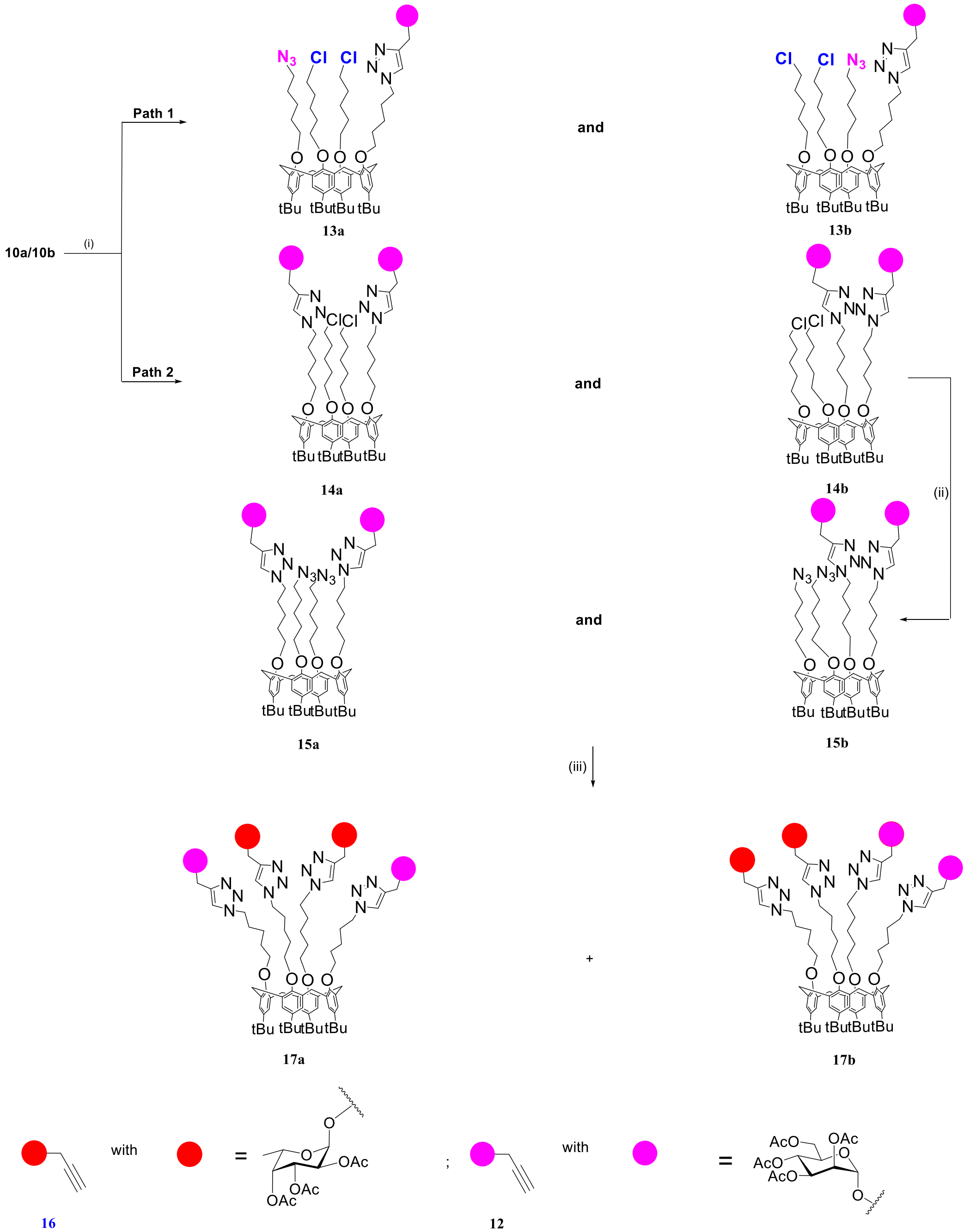


Inseparable mixture of :
3 : $X_1 = X_2 = X_3 = X_4$ = Cl (Traces)
4 : X_1 = Br and $X_2 = X_3 = X_4$ = Cl (Minor)
5 : $X_1 = X_3$ = Br and $X_2 = X_4$ = Cl (Major)
6 : X_1 = Cl and $X_2 = X_3 = X_4$ = Br (Major)
7 : $X_1 = X_2 = X_3 = X_4$ = Br (Traces)

Separable mixture of :
8 : $Y_1 = Y_2 = Y_3 = Y_4 = N_3$ (Traces)
9 : $Y_1 = N_3$ and $Y_2 = Y_3 = Y_4$ = Cl (6%)
10a : $Y_1 = Y_3 = N_3$ and $Y_2 = Y_4$ = Cl (36%)
10b : $Y_1 = Y_2 = N_3$ and $Y_3 = Y_4$ = Cl
11 : Y_1 = Cl and $Y_2 = Y_3 = Y_4 = N_3$ (30%)

Scheme 3. Overal yields from **1** after separation by chromatography of **8** (Path 1) and **9**, **10a/10b** and **11** (Path 2). TLC on silica gel using 5:3 cyclohexane-DCM as an eluent; L = Crude mixture of homo and heterohalide **3** to **7**; R = Crude mixture of tetraazido **8** and azido-chloro **9**, **10** and **11**.

This new heterohaloalkylating conditions of *p*-*t*-butylcalix[4]arene and subsequent selective azidation of crude product provide relevant azido-chloro species under mild conditions in relatively large quantities (e.g. from 3 g of starting material **1**, 1.19 g of **10** and 1 g of **11** were recovered) which could facilitate the synthesis of heteroglycocclusters as targeted in this work. These were indeed suitable materials for selective introduction of glycoside substituents through azide-alkyne click chemistry reactions. This Cu(I) catalyzed 1,3-dipolar cycloaddition has emerged as powerful tool that has allowed us[31] and many others[32,33] efficient access to complex glycoconjuguates. Starting firstly from **10a/b** plus 1-*O*-propargyl-α-D-mannose derivative **12**[34] in THF/tBuOH mixture as solvent and $CuSO_4.5H_2O$/sodium ascorbate in H_2O as catalyst (Scheme 4) we obtained the calixmonomannose derivatives **13a/b** as a by-product in 6 % total yield (Path 1) and mainly the di-*manno*conjuguates**14a/b** (Path 2) in 56 % total yield. Extending the application of these homoglycoconjugates to heteroglycoconjugates, the chlorinated *manno*calix derivatives **14a/b** were found to undergo an easy bis-azidation to give in good yield the diazido-dimannocalxarene derivatives **15a/b** as an acceptor of new propargylated sugars via a twofold click chemistry reaction. With 1-*O*-propargyl-α-L-fucose**16**[35] as the second sugar derivative, the first heteroglyco bis-*fuco*-bis-*manno* compounds **17a**/**b** were obtained in good total yield (87%) after chromatography on silica gel.

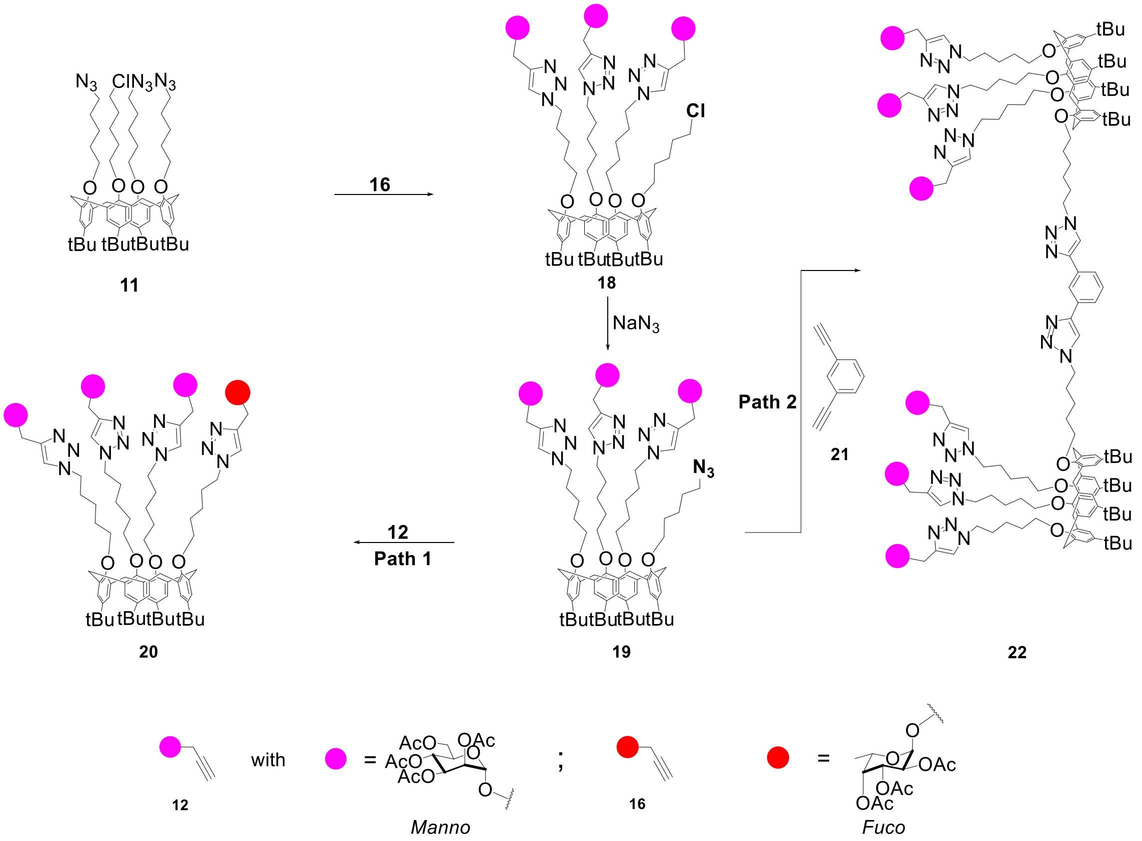


(i) **12** (2.4 eq), $CuSO_4.5H_2O$ (0.5 eq), Na-ascor (1eq); (ii) NaN_3 DMF 90 °C 16h; (iii) **16** (2.2 eq), $CuSO_4.5H_2O$ (0.5 eq), Na-ascor (1eq)

Scheme 4. Sequential synthesis of calixheteroclycoconjuguate **17** with mannose/fucose unites.

A second heteroglycocluster synthesis was carried out with the triazidomonochloro compound **11** as starting material. In contrast to **10** which is a mixture of inseparable regioisomers **10a** and **10b***,* **11** as heterofunctionalizedcalixarene is a single compound. A threefold Click reaction with the *fuco* derivative **16** gave the monochlorotrifucocalixarene **18** in 43% yield. The residual chloropentyl site is a key molecular feature enabling extension of the strategy towards a myriad of possibilities but especially in the present work to the synthesis of a second kind of heteroglycocluster. Indeed, the subsequent azidation to monoazidotri*fuco*calixarene **19** (66% yield) followed once again by a click reaction with the *manno* derivative **12** (Path 1), gave the heteroglycocluster **20** with three fucose and one mannose units in 44% yield. The ^{13}C-NMR spectrum shows two signals of the anomeric carbon atoms C-1$_{fuco}$ and C-1$_{manno}$ in a 3:1 ratio respectively at 96.9 and 95.7 ppm (Figure 38S). Both heteroglycoconjugates **17a/b** and **20** have preserved the cone conformation of their precursor, as indicated by the AB quartet for the bridge methylene protons (4.29/3.08 ppm with $J_{Ha\text{-}Hb}$ = 12.4 Hz and 4.31/3.11 ppm with $J_{Ha\text{-}Hb}$= 12.5 Hz respectively).

This new methodology is not only of unique utility for some calixheteroglycoconjugates synthesis but can also provide some valuable precursors of other scarce and sophisticated glycocalixarenes. An example is the synthesis of bis-calixareneglycodendrimer **22** endowed with dual tri*fuco*calixarene unites (Path 2). This was obtained from a Click reaction of the azidotri*fuco*calixarene **19** with the aryldiyne **21**.



Scheme 5. Synthesis of the heteroglycocluster **20** and the dendrimer fucocluster **22** from **11.**

Conclusions

The reactions described herein provide a new pathway to *p*-*t*-butylcalix[4]arene-based heteroglycoclusters using *p*-*t*-butylcalix[4]arene heterohaloalkyl ethers as starting materials. A key feature is the use of the long-known Finkelstein halide exchange reaction to sequentially modify the tetrakis(chloropentyloxy) derivative **3**. The source of the free halide used to induce the exchange is the initial reaction involving alkylation of *p*-*t*-butylcalix[4]arene by the unsymmetrical dihalide 1-bromo-5-chloropentane. This unprecedented regioselective transformation of **3** is arguably a real novelty and a significant contribution to the area of scaffold construction chemistry. Its present exploitation through subsequent azide substitution and Click chemistry has made possible the preparation of heteroglycoconjugates based calixarene containing the biologically ubiquitous sugars L-fucose and D-mannose. Of course the prospects for other kinds of grafting are numerous and will be developed in our ongoing program.

Experimental Section

General. Syntheses under microwave irradiation were performed under pressure with a single-mode apparatus (2450 MHz) using an external reaction temperature sensor. ^{1}H and ^{13}C NMR spectra were recorded on 300 and 600 WB spectrometers in appropriate deuterated solvents; chemical shifts are reported on the δ scale. All ^{13}C NMR signals were assigned through C–H correlated HSQC spectra. TLC was performed on Silica Gel 60 F254, 230 mesh (E. Merck) with cyclohexane-EtOAc or EtOAc-MeOH, and spots were detected by vanillin–H_2SO_4 reagent. Preparative column chromatography was performed using 230–400 mesh Merck silica gel (purchased from Sigma). Optical rotations were determined with a polarimeter having a 1 mL cell. Low resolution electrospray mass spectra (ESI-MS) in the positive or negative ion mode were obtained on a ZQ quadrupole instrument equipped with an electrospray (Z-spray) ion source. High resolution electrospray experiments (ESI-HRMS) were performed on a Q-TOF UltimaGlobal hybrid quadrupole time-of-flight instrument, equipped with an electro-spray (Z-spray) ion source**.** Infrared spectra recorded on an FTIR spectrometer.

Haloalkylation of *p*-*t*-butylcalix[4]arene: bromochloropentyloxy- *p*-*t*-butylcalix[4]arenes 3-7 synthesis. In a 250 mL round-bottomed, single-necked flask flushed with argon, 2 g (3.1 mmol) of *p*-*t*-butylcalix[4]arene (**1**) and 1.48 g (37 mmol) of NaH (60%) in DMF (50 mL) were reacted for 1h at rt under stirring. 1-Bromo-5-chloropentane (**2**) (11.43 g, 61.64 mmol) was then added and the mixture was heated at 90°C for 16 h. At the end of the reaction, MeOH (200 mL) was added and the solvent was concentrated in vacuum. The residue obtained was dissolved in 100 mL of dichloromethane and washed twice with 100 mL of HCl (1M), once with 100 mL of saturated $NaHCO_3$ and once with 100 mL of saturated NaCl. The organic layer was dried over $MgSO_4$ to give the **3**-**7** mixture (3.963 g).

Full azidation of crude product 3-7 obtained from 1: Synthesis of tetraazidopentyloxy- *p*-*t*-butylcalix[4]arene 8. a 50 mL round-bottomed, single-necked flask, 0.972 g of **3-7** mixture and 0.710 g of NaN_3 in DMF (20 mL) were allowed to react for 24 h at 90 °C under stirring. After concentration, the crude product was dissolved in 60 mL of CH_2Cl_2 and washed twice with 60 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The compound **8** was separated as a solid by flash chromatography on silica gel and eluted under gradient elution using a mixture of Cyclohexane/CH_2Cl_2. Yield: 0.597 g (60%). R_f 0.5 (SiO_2, Cyclohexane/CH_2Cl_2:5/4). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ (ppm): 6.79(s, 8H, ArH), 4.37(d, 4H, ArCH_2Ar, *J* 12.5 Hz), 3.88(m, 8H, OCH_2), 3.34(t, 8H, CH_2N_3, *J* 6.8 Hz), 3.14 (d, 4H, ArCH_2Ar, *J* 12.5 Hz), 2.04 (m, 8H, CH_2), 1.71 (m, 8H, CH_2), 1.49 (m, 8H, CH_2), 1.09 (s, 36H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm): 153.5 (ArCOCH_2), 144.6 (ArC(C(CH_3)$_3$)), 133.9(ArCCH_2CAr), 124.9(CHAr), 74.9 (OCH_2), 51. 6(CH_2N_3), 33.9 (C(CH_3)$_3$), 31.5 (CH_3), 31.1 (ArCH_2Ar), 30.0 (CH_2),29.2 (CH_2), 23.5 (CH_2). HRMS (ESI-TOF) $[M+Na]^+$calcd for $C_{64}H_{92}N_{12}O_4Na$: 1115.7262, found: 1115.7272.

Selective azidation of crude product 3-7 obtained from 1: Synthesis of azidochloro-*p*-*t*-butylcalix[4]arenederivateives 9, 10 and 11. The **3-7** mixture (3.963 g) (obtained from haloalkylation of 2 g of calixarene **1** in 4.2.) was allowed to react with 2.898 g of NaN_3 in 80 mL of DMF at room temperature for 20 h. After concentration, the crude product was dissolved in 40 mL of EtOAc and washed twice with 60 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated. Separation by flash chromatography on silica gel under gradient elution with mixture of cyclohexane/CH_2Cl_2 gave the following products: **9** as a white solid, 0.186 g (6% yield), **10a** and/or **10b** as a white solid, 1.195 g (36% yield) and **11** as a white solid, 1.003 g (30% yield).

Monoazidotrichloro *p-t*-butylcalix[4]arene 9. R_f0.71 (SiO_2, Cyclohexane/CH_2Cl_2: 5/3); $[M+Na]^+$: *m/z* = 1096.7; *^{1}H*-NMR ($CDCl_3$, 300 MHz), δ(ppm): 6.80(s, 4H, ArH), 6.78(s, 4H, ArH), 4.37(d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 3.94-3.81 (m, 8H, CH_2O), 3.60 (t,6H, CH_2Cl, *J* 6.6 Hz), 3.34 (t, CH_2N_3, *J* 6.8 Hz), 3.14 (d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 2.13-1.96 (m, 8H, CH_2), 1.95-1.82 (m, 6H, CH_2CH_2Cl), 1.76-1.63 (m, 2H, $CH_2CH_2N_3$), 1.61-1.47 (m, 8H, CH_2), 1.10 (s, 18H, CH_3), 1.08 (s, 18H, CH_3); *^{13}C*-NMR ($CDCl_3$,75 MHz), δ(ppm): 153.5 ($ArCOCH_2$), 144.6 ($ArC(C(CH_3)_3)$), 133.8 ($ArCCH_2CAr$), 125.12 (CHAr), 75.01 (CH_2O), 51.6 (CH_2N_3), 45.1 (CH_2Cl), 33.9 ($C(CH_3)_3$), 32.9 (CH_2), 31.4 (CH_3), 31.2 ($ArCH_2Ar$), 29.7 (CH_2), 29.2 (CH_2), 23.6 (CH_2); HRMS (ESI-TOF): $[M+Na]^+$ calcd for $C_{64}H_{92}Cl_3N_3O_4Na$: 1094.6051, found 1094.6049

Di-azidodichloro-*p-t*-butylcalix[4]arenes 10a/10b. R_f 0.6 (SiO_2, Cyclohexane/CH_2Cl_2: 5/3); $[M+Na]^+$: *m/z* = 1101.7; *^{1}H*-NMR ($CDCl_3$, 300 MHz), δ (ppm): 6.79 (s, 8H, ArH), 4.37 (d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 3.88 (m, 8H, OCH_2), 3.60 (t, 4H, CH_2Cl, *J* 6.6 Hz),3.34 (t, 4H, CH_2N_3, *J* 6.8 Hz), 3.14 (d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 2.03 (m, 8H, CH_2), 1.89 (m, 4H, CH_2),1.71 (m, 4H, CH_2),1.52 (m, 8H, CH_2),1.09 (s, 36H, CH_3). *^{13}C*-NMR ($CDCl_3$, 75 MHz), δ (ppm): 153.5 ($ArCOCH_2$), 144.6 ($ArC(C(CH_3)_3)$), 133.8 ($ArCCH_2CAr$), 125.1 (CHAr), 74.9 (OCH_2), 51.6 (CH_2N_3), 45.1 (CH_2Cl), 33.9 ($C(CH_3)_3$), 32.9 (CH_2), 31.5 (CH_3), 31.2 ($ArCH_2Ar$), 30.0 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 23.6 (CH_2), 23.5 (CH_2). HRMS (ESI-TOF): $[M+Na]^+$calcd for $C_{64}H_{92}Cl_2N_6O_4Na$: 1101.6455, found 1101.6497

Tri-azidomonochloro-*p-t*-butylcalix[4]arene 11. R_f 0.47 (SiO_2, Cyclohexane/CH_2Cl_2: 5/3). ESI-MS: *m/z* = 1108.8 $[M+Na]^+$; *^{1}H*-NMR ($CDCl_3$, 300 MHz), δ (ppm): 6.8 (s, ArH, 4H), 6.7 (s, ArH, 4H), 4.3 (d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 3.9-3.8 (m, 8H, OCH_2), 3.6 (t, 2H, CH_2Cl, *J* 6.6 Hz),3.3 (t, 6H, CH_2N_3, *J* 6.8 Hz), 3.1 (d, 4H, $ArCH_2Ar$, *J* 12.4 Hz), 2.0 (m, 8H, CH_2), 1.9 (m, 2H, CH_2CH_2Cl),1.7 (m, 6H, $CH_2CH_2N_3$),1.5 (m, 8H, CH_2),1.1 (s, 18H, CH_3), 1.1 (s, 18H, CH_3). ^{13}C- NMR ($CDCl_3$, 75 MHz), δ (ppm): 153.5 ($ArCOCH_2$), 144.5 ($ArC(C(CH_3)_3)$), 133.7 ($ArCCH_2CAr$), 125.1 (CHAr), 74.9 (OCH_2), 51.6 (CH_2N_3), 45.1 (CH_2Cl), 33.9 ($C(CH_3)_3$), 32.9 (CH_2), 31.5 (CH_3), 31.2 ($ArCH_2Ar$), 30.0 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 23.6 (CH_2), 23.5 (CH_2); HRMS $[M+Na]^+$ calcd for $C_{64}H_{92}ClN_9O_4Na$: 1108.6859, found 1108.6863.

Synthesis of calixglycoconjuguates 13, 14, 15, 17, 18, 19, 20 and **22**

Synthesis of 14a/b from 10a/b. To a mixture of compound **10a/10b** 0.1 g (0.092 mmol) and 0.085 g (0.22 mmol) of propargyl mannose **12** in THF/*t*BuOH:2.5mL/3.75mL, was added a solution of 0.023g of $CuSO_4.5H_2O$ and 0.036g of sodium L-ascorbate in 3.75 mL of H_2O. Stirring was maintained for 3 h at 60°C. After concentration, the crude product was extracted with CH_2Cl_2/Saturated NaCl solution. The organic layer was concentrated and separated by chromatography on silica gel using 5/1/1:cyclohexane/EtOAc/acetone as eluant to give **13a**/**b** 0.008 g (6% yield) and 14**a**/**b** 0.097 g (56% yield).

Monoazido-di-chloro-α-D-*manno*-*p-t*-butylcalix[4]arene 13a/**b.** R_f0.77 (SiO_2, Cyclohexane/EtOAc/acetone: 4/2/2).ESI-MS: *m/z* = 1490.2 $[M+Na]^+$; *^{1}H*-NMR($CDCl_3$, 400 MHz), δ (ppm): 7.59 (s, 1H, CHtriazole), 6.77 (m, 8H, CHAr), 5.35-5.23 (m, 3H, H-2man/H-4man/H-5man), 4.96 (d, 1H, H-1man, *J* =1.7 Hz), 4.86 (d, 1H, CH_2Oman, *J* 12.2 Hz), 4.67 (d, 2H, CH_2Oman, *J* 12.2 Hz), 4.44-4.31 (m, 7H, CH_2N/$ArCH_2Ar$/H-6'man), 4.17-4.06 (m, 2H, H-3man/H-6man), 3.87 (m, 8H, CH_2O), 3.59 (t, 2H, CH_2Cl, *J* 6.5 Hz), 3.32 (t, 2H, CH_2N_3, *J* 2.5Hz), 3.12 (2d, 4H, $ArCH_2Ar$, *J* 12.6 Hz), 2.14 (s,3H,CH_3), 2.12 (s,3H,CH_3), 2.04 (m, 11H, CH_2/CH_3), 1.98 (s, 3H, CH_3), 1.87 (m, 8H, CH_2), 1.07 (m, 44H, CH_2/CH_3);*^{13}C*-NMR ($CDCl_3$, 100 MHz), δ (ppm): 170.8 (C=O), 170.1 (C=O), 170.0 (C=O), 169.8 (C=O), 153.5 (ArCO), 144.6 ($ArC(C(CH_3)_3)$), 143.6 (Ctriazole), 133.8 ($ArCCH_2CAr$), 125.2 (CHAr), 122.8(CH triazole), 97.0 (C1), 74.9 (CH_2O), 69.6 (C2), 69.2 (C4), 68.8 (C3), 66.2 (C5), 62.5 (C6), 61.2 (CH_2Oman), 51.6 (CH_2N_3), 50.6 (CH_2N), 45.2 (CH_2Cl), 33.9 (($C(CH_3)_3$), 32.9 (CH_2), 31.5 (CH_3), 31.2 ($ArCH_2Ar$), 30.0 (CH_2), 29.9 (CH_2), 29.7 ($\underline{C}H_2$), 23.6 ($\underline{C}H_2$), 23.5 ($\underline{C}H_2$),23.4 ($\underline{C}H_2$), 21.0 ($\underline{C}H_3$), 20.9 ($\underline{C}H_3$), 20.8 ($\underline{C}H_3$). HRMS $[M+H]^+$calcd for $C_{81}H_{115}Cl_2N_6O_{14}$: 1465.7848, found: 1465.7839.

Di-chloro-di-α-D-*manno*-*p*-*t*-butylcalix[4]arene 14a/b. R_f0.32 (SiO_2, Cyclohexane/EtOAc/Acetone:4/2/2). ESI-MS: *m/z* = 1876.3 $[M+Na]^+$; ^{1}H-NMR ($CDCl_3$, 600 MHz), δ (ppm): 7.63 (s, 2H, $C\underline{H}$triazole), 6.73 (s, 8H, $C\underline{H}$Ar), 5.31-5.19 (m, 4H, $\underline{H}$-5/$\underline{H}$-4), 5.22 (s, 2H, $\underline{H}$-2), 4.94 (s, 2H, $\underline{H}$-1), 4.82 (d, 2H, $C\underline{H}_2$Oman, *J* 12.2 Hz), 4.64 (d, 2H, $C\underline{H}_2$Oman, *J* 12.2 Hz), 4.37 (m, 4H, $C\underline{H}_2N$), 4.29 (m, 6H, $ArC\underline{H}_2Ar$/H-6'), 4.07 (m, 4H, $\underline{H}$-3/$\underline{H}$-6), 3.83 (m, 8H, $C\underline{H}_2O$), 3.57 (m, 4h, $C\underline{H}_2Cl$), 3.09 (d, 2H, $ArC\underline{H}_2Ar$, *J* 12.2 Hz), 2.11 (s, 6H, $C\underline{H}_3$), 2.09 (s, 6H, $C\underline{H}_3$), 2.02 (m, 18H, $C\underline{H}_3/C\underline{H}_2$), 1.95 (s, 6H, $C\underline{H}_3$), 1.83 (m, 4H, $C\underline{H}_2$), 1.53 (m, 4H, $C\underline{H}_2$), 1.44 (m, 4H, $C\underline{H}_2$), 1.05 (s, 36H, $C\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.6 ($\underline{C}$=O), 170.0 ($\underline{C}$=O), 169.8 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 153.3 (Ar$\underline{C}$O), 144.5 ($Ar\underline{C}(C(CH_3)_3)$), 143.4 ($\underline{C}$triazole), 133.5 ($Ar\underline{C}CH_2\underline{C}Ar$), 124.9 (Ar$\underline{C}$H), 122.9 ($\underline{C}$H triazole), 96.8 ($\underline{C}$1), 74.7 ($\underline{C}H_2O$), 69.4 ($\underline{C}$2), 69.0 ($\underline{C}$4), 68.7 ($\underline{C}$3), 66.0 ($\underline{C}$5), 62.3 ($\underline{C}$6), 61.0 ($\underline{C}H_2$Oman), 50,4 ($\underline{C}H_2N$), 45.1 ($\underline{C}H_2Cl$), 33.8 (($\underline{C}(CH_3)_3$), 32.7 ($\underline{C}H_2$), 31.4 ($\underline{C}H_3$), 31.1 ($Ar\underline{C}H_2Ar$), 30.5 ($\underline{C}H_2$), 29.7 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 23.5 ($\underline{C}H_2$), 23.2 ($\underline{C}H_2$), 20.8 ($\underline{C}H_3$), 20.7 ($\underline{C}H_3$), 20.6 ($\underline{C}H_3$). HRMS (ESI-TOF): $[M+Na]^+$calcd for $C_{98}H_{136}Cl_2N_6O_{24}Na$: 1873.8881, found: 1873.8893.

Di-azido-di-α-D-*manno*-*p*-*t*-butylcalix[4]arene 15a/15b. Compounds **14a/14b** 0.084 g (0,0453mmol) were reacted with 0.017 g (0.271 mmol) of NaN_3 in 2 mL of DMF. After 24 h at 90 °C, the mixture was concentrated and extracted with 20 mL of CH_2Cl_2 and 20 mL NaCl saturated solution. The organic layer was dried over $MgSO_4$ and concentrated. After chromatography on silica gel with 4/1/1:Cyclohexane/Acetone/EtOAc as eluent, 0.054 g of **15a/15b** was obtained as a syrup (64% yield). R_f 0.23 (SiO_2, cyclohexane/Acetone/EtOAc:3/1/1). ESI-MS: *m/z* = 1888.9 $[M+Na]^+$. *^{1}H*-NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.63 (s, 2H, $C\underline{H}$triazole), 6.76 (s, 8H, $C\underline{H}$Ar), 5.32-5.18 (m, 6H, $\underline{H}$-2/H-4/$\underline{H}$-5), 4.95 (s, 2H, $\underline{H}$-1), 4.84 (d, 2H, $C\underline{H}_2$Oman, *J* 12.2 Hz), 4.65 (d, 2H, $C\underline{H}_2$Oman, *J* 12.2 Hz), 4.45-4.26 (m, 10H, $C\underline{H}_2N/ArC\underline{H}_2Ar$/$\underline{H}$-6'), 4.14-4.03 (m, 4H, $\underline{H}$-3/$\underline{H}$-6), 3.84 (m, 8H, $C\underline{H}_2O$), 3.31 (t, 4H, $C\underline{H}_2N_3$, *J* 6.7 Hz), 3.11 (d, 2H, $ArC\underline{H}_2Ar$, *J* 12.5 Hz), 2.13 (s, 6H, $C\underline{H}_3$), 2.10 (s, 6H, $C\underline{H}_3$), 2.02 (m, 14H, $C\underline{H}_2/C\underline{H}_3$), 1.96 (s, 6H, $C\underline{H}_3$), 1.66 (m, 4H, $C\underline{H}_2$), 1.46 (m,8H, $C\underline{H}_2$), 1.06 (s, 36H, $C\underline{H}_3$); *^{13}C*-NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.6 , 170.0, 169.8, 169.6 ($\underline{C}$=O), 153.2 (Ar$\underline{C}$O), 144.5 ($Ar\underline{C}(C(CH_3)_3)$), 143.4 (C triazole), 133.5 ($Ar\underline{C}CH_2\underline{C}Ar$), 125.0 (CHAr), 122.9 ($\underline{C}$H triazole), 96.9 ($\underline{C}$1), 74.7 ($\underline{C}H_2O$), 69.4 ($\underline{C}$2), 69.0 ($\underline{C}$4), 68.7 ($\underline{C}$3), 66.0 ($\underline{C}$5), 62.3 ($\underline{C}$6), 61.0 ($\underline{C}H_2$O-man), 51.4 ($\underline{C}H_2N_3$), 50.4 ($\underline{C}H_2N$), 33.8 (($\underline{C}(CH_3)_3$), 31.4 ($\underline{C}H_3$), 30.5 ($Ar\underline{C}H_2Ar$), 29.7 ($\underline{C}H_2$), 29.8 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 23.4 ($\underline{C}H_2$), 23.2 ($\underline{C}H_2$), 20.8 ($\underline{C}H_2$), 20.7 ($\underline{C}H_3$), 20.6 ($\underline{C}H_2$), 29.7 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 23.5 ($\underline{C}H_2$), 23.2 ($\underline{C}H_2$), 20.8 ($\underline{C}H_3$), 20.7 ($\underline{C}H_3$), 20.6 ($\underline{C}H_3$); HRMS (ESI-TOF): $[M+Na]^+$ calcd for $C_{98}H_{136}N_{12}O_{24}Na$: 1887.9688, found: 1887.9635.

Di-α-L-*fuco*-di-α-D-*manno*-*p*-*t*-butylcalix[4]arene 17a/17b. The diazidocalixarene **15a/15b** (0.035g, 0.018 mmol) was reacted with 0.014 g (0.045 mmol) of 1-*O*-propargyl-▯-L-*f*ucose **16** in a THF/tBuOH:1mL/1.5mL mixture. The Click reaction was triggered by addition of 1.5 mL of a freshly prepared aqueous solution of $CuSO_4.5H_2O$ (0.004 g) and Na-L-ascorbic acid (0.007 g). The mixture was stirred for 3 h at 60 °C. After concentration, the crude product was extracted with CH_2Cl_2 and saturated aqueous NaCl. The organic layer was subsequently dried over $MgSO_4$, concentrated and purified by liquid chromatography on silica gel using cyclohexane/EtOAc/acetone 1.5/1/1 as eluent. Compound **17a/17b** was obtained as white solid in a total yield of 0.041 g (87 %). R_f0.37 (SiO_2, Cyclohexane/EtOAc/acetone:1/1/1). ESI-MS: *m/z* = 1284.1 $[M+2Na]^{2+}/2$; ^{1}H-NMR ($CDCl_3$, 600 MHz), δ (ppm): 7.72 (s, 2H, $C\underline{H}$triazole), 7.67 (s, 2H, $C\underline{H}$triazole), 6.74 (s, 8H, $C\underline{H}$Ar), 5.32 (dd, 2H, $\underline{H}$-3*F*uc, $J_{3,2}$ 10.9 Hz, $J_{3,4}$ 3.3 Hz), 5.31-5.27 (m, 4H, H-5man/$\underline{H}$-4man), 5.25 (d, 2H, $\underline{H}$-4Fuc, $J_{4,3}$ 3.3 Hz), 5.17 (d, 2H, $\underline{H}$-1Fuc, $J_{1,2}$ 3.6 Hz), 5.11 (dd, 2H, $\underline{H}$-2Fuc, $J_{2,1}$ 3.6 Hz, $J_{2,3}$ 10.9 Hz), 4.95 (s, 2H, $\underline{H}$-1man, $J_{1,2}$ 0 Hz), 4.81 (m, 4H, $C\underline{H}_2$Oman/$C\underline{H}_2$OFuc), 4.63 (m, 4H, $C\underline{H}_2$Oman/$C\underline{H}_2$OFuc), 4.39 (m, 8H, $C\underline{H}_2N$), 4.29 (m, 6H, $ArC\underline{H}_2Ar$/$\underline{H}$-6'man), 4.20 (m, 2H, $\underline{H}$-5Fuc), 4.14-4.04 (m, $\underline{H}$-6man-$\underline{H}$-3man), 3.82 (m, 8H, $C\underline{H}_2O$), 3.08 (d, 2H, $ArC\underline{H}_2Ar$, *J* 12.5 Hz), 2.14 (s, 6H, $C\underline{H}_3$), 2.12 (s, 6H, $C\underline{H}_3$), 2.09 (s, 6H, $C\underline{H}_3$), 2.07-2.0 (m, 24H, $C\underline{H}_3/C\underline{H}_2$), 1.99 (s, 6H, $C\underline{H}_3$), 1.95 (s, 6H, $C\underline{H}_3$), 1.94 (s, 6H, $C\underline{H}_3$), 1.43 (m,8H, $C\underline{H}_2$), 1.11 (d, 6H,$C\underline{H}_3$Fuc, *J* 6.5Hz), 1.05 (m, 36H, $C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm) : 170.7 (C=O), 170.6, 170.4, 170.1, 170.0, 169.7 (C=O), 153.3 (ArCO), 144.6 (ArC(C(CH$_3$)$_3$)), 143.9 (Ctriazole), 143.4 (Ctriazole), 133.7 (ArCCH$_2$CAr), 125.1 (CHAr), 123.3 (CH triazole), 123.0 (CH triazole), 96.9 (C1man), 95.7 (C1Fuc), 74.7 (CH$_2$O), 71.2 , 69.5 , 69.2 , 68.8, 68.0, 66.1, 64.8, 62.5 (C6man), 61.4 (CH$_2$O), 61.1 (CH$_2$O), 50.6 (CH$_2$N), 34.0 ((C(CH$_3$)$_3$), 31.5 (CH$_3$), 31.2 (ArCH$_2$Ar), 30.6 (CH$_2$), 29.8 (CH$_2$), 23.3 (CH$_2$), 20.9-20.5 (CH$_3$), 15.9 (CH$_3$Fuc). HRMS (ESI-TOF): [M+2Na]$^{2+}$/2 calcd for $C_{128}H_{176}N_{12}O_{40}Na_2$: 1283.5946, found: 1283.5883.

Mono-chloro-tri-*fuco*-*p*-*t*-butylcalix[4]arene 18. To a solution of compound **11** (0.157g, 0.144 mmol) and peracetylated 1-*O*-propargyl-⍰-L-*f*ucose **16** (0.170g, 0.519 mmol) in THF/tBuOH:3.5mL/4.75mL, a freshly prepared solution of CuSO$_4$.5H$_2$O (0.054g) and Na-L-ascorbic acid (0.086g) in 4.75 mL of H$_2$O was added. The solution was stirred for 3 h at 60 °C. The crude product obtained was then dissolved in 20 mL of CH$_2$Cl$_2$ and washed twice with brine. Liquid chromatography on silica gel using 4/1/1: cyclohexane/EtOAc/acetone as eluant gave 0.13 g (43% yield) of **18** as a white solid. R$_f$0.10 (SiO$_2$, Cyclohexane/EtOAc/Acetone:4/1/1). ESI-MS: *m/z* = 1058.6 [M+2Na]$^{2+}$/2. [α$_D$]^{20} = -91 (c, 0.115, CH$_2$Cl$_2$); ^{1}H-NMR (CDCl$_3$, 600 MHz) *δ* (ppm): 7.75 (2s, 8H, CHAr, 5.33 (dd, 3H, H-2, *J* 10.7, *J* 3.1 Hz), 5.27 (d, 3H, H-1, *J* 3.0 Hz), 5.17 (d, 3H, H-4, *J* 3.6 Hz), 5.11 (dd, 3H, H-3, *J* 10.7, *J* 3.5 Hz), 4.81(d, 3H, OCH$_2$triazole, *J* 11.4 Hz), 4.63 (d, 3H, OCH$_2$triazole, *J* 11.4 Hz), 4.36 –4.29 (m, 10H,CH$_2$N/ArCH$_2$Ar), 4.19 (m, 3H, H-5), 3.83 (m, 6H, CH$_2$OAr), 3.58 (m, 2H, CH$_2$Cl), 3.09 (d, 2H, ArCH$_2$Ar, *J* 12.4 Hz), 2.15 (s, 9H, CH$_3$), 2.01 (m, 21H, CH$_3$/CH$_2$), 1.93 (s, 9H, CH$_3$), 1.12 (d, 9H, H-6, *J* 6.1 Hz), 1.05 (2s, 36H, CH$_3$). *^{13}C*-NMR (CDCl$_3$, 75 MHz), δ (ppm): 170.6, 170.43, 170.0 (C=O), 153.57 (ArCO), 153.2 (ArCO), 144.6 (ArC(C(CH$_3$)$_3$)), 144.9 (ArC(C(CH$_3$)$_3$)), 133.87 (ArCCH$_2$CAr), 133.4 (ArCCH$_2$CAr), 125.1 (CHAr), 122.9 (ArCCH$_2$CAr), 95.7 (C-1), 74.7 (CH$_2$OAr), 71.2 (C-4), 68.12, 68.03 (C-2/C-3), 64.8 (C-5), 61.3 (OCH$_2$triazole), 50.5 (CH$_2$N), 45.3 (CH$_2$N), 33.8 ((C(CH$_3$)$_3$), 32.8 (CH$_2$), 31.5 (CH$_3$), 31.4 (CH$_3$), 31.2 (CH$_2$), 30.6 (CH$_2$), 29.8 (CH$_2$), 29.6 (CH$_2$), 27.0 (CH$_2$), 23.6 (CH$_2$), 23.3 (CH$_2$), 20.9 (CH$_2$), 20.7 (CH$_2$), 15.9 (C-6). HRMS (ESI-TOF): [M+2Na]$^{2+}$/2calcd for $C_{109}H_{152}ClN_9O_{28}Na_2$: 1058.0110, found: 1058.0081.

Mono-azido-tri-*fuco*-*t*Bucalix[4]arene 19. Mono-chloro-tri-*fuco* **18** (0.06 g, 0.028 mmol) was allowed to react with NaN$_3$ (0.0056 g, 0.086 m mol) in DMF (2 mL). The mixture was kept at 90°C for 24h. The crude product obtained after concentration was dissolved in 20 mL of CH$_2$Cl$_2$ and washed twice with (20 mL saturated solution of NaCl. After concentration of organic layer, liquid chromatography on silica gel using 4.5/1/1: cyclohexane/ EtOAc/acetone as eluant gave **19** (0.04 g, 66% Yield) as a colorless syrup. R$_f$ 0.10 (SiO$_2$, Cyclohexane/Acetone/EtOAc: 4.5/1/1). ESI-MS: *m/z* = 1062.2 [M+2Na]$^{2+}$/2. [α$_D$]^{20} = - 60 (c 0.11, CH$_2$Cl$_2$). ^{1}H-NMR (CDCl$_3$, 600 MHz) *δ(*ppm): 6.69 (2s, 8H, CHAr), 5.7 (m, 3H, H-4), 5.23-5.09 (m, 6H, H-2/H-3), 4.76 (m, 3H, OCH$_2$triazole), 4.58 (m, 3H, OCH$_2$triazole), 4.40-4.09 (m,13H, ArCH$_2$Ar/CH$_2$N/H-5), 3.83 (m, 8H, OCH$_2$Ar), 3.04 (d, 4H, ArCH$_2$Ar, *J* 11.0 Hz), 2.09 (s, 9H, CH$_3$), 1.93 (s, 34H, CH$_2$/ CH$_3$), 0.97 (m, 53H, CH$_3$, H-6, CH$_2$), 0.81 (m, 16H, CH$_2$). *^{13}C*-NMR (CDCl$_3$, 75 MHz), δ (ppm): 170.3 (C=O), 170.1,169.7 (C=O), 153.0 (ArCO), 144.3 (ArC(C(CH$_3$)$_3$)), 133.3 (ArCCH$_2$CAr), 124.7 (CHAr), 95.4 (C-1), 70.9 (C-4),70.2 (CH$_2$O), 69.9 (CH$_2$O), 67.8, 67.7 (C-2/C-3), 64,5 (C-5), 61.5, 61.1 (OCH$_2$triazole), 51.1, 50.4 (CH$_2$N), 33.5 ((C(CH$_3$)$_3$), 31.0 (CH$_3$), 30.4 (CH$_2$), 29.5 (CH$_2$), 23.0 (CH$_2$), 20.6 (CH$_3$), 20.4 (CH$_3$), 20.4 (CH$_3$), 15.6 (C-6).

Tri-α-L-*fuco*-*mono*-α-D-*manno*-*p*-*t*-butylcalix[4]arene 20. The mono-azido-tri-*fuco* **19** (0.1g, 0.048 mmol) was allowed to react with 0.026 g (0.067 mmol) of D-*manno*derivative **12** in THF/tBuOH:2.5mL/1.5mL. The Click reaction was triggred by addition 4 mL of a freshly prepared aqueous solution of CuSO$_4$.5H$_2$O (0.006 g, 0.024 mmol) and Na-L-ascorbic acid (0.010 g, 0.048 mmol) and stirred for 4 h at 65 °C. After concentration the crude product was extracted with CH$_2$Cl$_2$ and saturated aqueous NaCl. The organic layer was subsequently dried over MgSO$_4$, concentrated and purified by liquid chromatography on silica gel with cyclohexane/EtOAc/acetone: 4/2/2 as eluent. Compound **20** was obtained as a syrup, 0.052 g (44 %). R$_f$0.19 (SiO$_2$, Cyclohexane/EtOAc/acetone: 4/2/12). ESI-MS: *m/z* = 1255.2 [M+2Na]/2$^+$; *^{1}H*-NMR (CDCl$_3$, 400 MHz), δ (ppm):

7.71 (s, 1H, CHtriazole), 7.66 (s, 3H, CHtriazole), 6.76 (m, 8H, CHAr), 5.37-5.19 (m, 9H, H-3Fuc/H-4Fuc/H-5man/H-4man/H-2man), 5.17 (d, 3H, H-1Fuc, *J* 3.7 Hz), 5.10 (d, 3H, H-2Fuc, *J* 3.7 Hz, *J* 10.8 Hz), 4.94 (s, 2H, H-1man), 4.80 (m, 4H, CH_2OFuc/CH_2Oman), 4.63 (m, 4H, CH_2OFuc/CH_2Oman), 4.40(m, 8H, CH_2N), 4.28 (m, 5H, ArCH_2Ar/H'-6man), 4.19 (q, 3H, H-5Fuc, *J* 6.5 Hz), 4.11 (m, 2H, H-6man/H-3man), 3.82 (m, 8H, CH_2O), 3.08 (d, 4H, ArCH_2Ar, *J* 12.4 Hz), 2.14 (s, 9H, CH_3), 2.12 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.02-1.94 (m, 32H, CH_3/CH_2), 1.52-1.33 (m, 16H, CH_2), 1.08 (m, 49H, H-6Fuc/CH_3);*^{13}C*-NMR ($CDCl_3$, 100 MHz), δ (ppm): 170.7 (C=O), 170.6 (C=O), 170.4(C=O), 170.1 (C=O), 170.0 (C=O), 169.7 (C=O), 153.3 (ArCO), 144.6 (ArC($C(CH_3)_3$)), 143.9 (Ctriazole), 143.4 (Ctriazole), 133.7 (ArCCH_2CAr), 125.1 (CHAr), 123.4 (CH triazole), 123.1 (CH triazole), 96.9 (C1man), 96.7 (C1Fuc), 74.6 (CH_2O), 71.2 (C-Fuc), 69.5 (C-man), 69.2 (C-man), 68.7 (C-man), 68.1 (C-Fuc), 68.0 (C-Fuc), 66.1 (C-man), 64.8 (C-5 Fuc), 62.4 (CH_2O), 61.2 (C-6man), 61.0 (CH_2O), 50.5 (CH_2N), 33.9 (($C(CH_3)_3$), 31.5 (CH_3), 31.2 (ArCH_2Ar), 30.6 (CH_2), 29.8 (CH_2), 23.2 (CH2), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 15.9 (C-6Fuc). HRMS $[M+H]^+$for C126H175N12O38: calcd. 2464.2131, found 2464.2129.

Bis-[tri-α-L-*fuco*-*p*-*t*-butylcalix[4]arene] 22. The mono-azido-tri-*fuco* **19** (0.250 g, 0.12 mmol) was allowed to react with 1,3-diethynylbenzene (**20**) (0.0054g, 0.042 mmol) in a mixture of THF/tBuOH: 7mL/10.5mL. The Click reaction was triggered by addition of 10.5 mL of a freshly prepared aqueous solution of $CuSO_4.5H_2O$ (0.010 g, 0.042 mmol) and Na-L-ascorbic acid (0.017 g, 0.084 mmol) and the mixture was stirred for 3 h at 60 °C. After concentration, the crude product was extracted with CH_2Cl_2 and saturated aqueous NaCl. The organic layer was subsequently dried over $MgSO_4$, concentrated and purified by liquid chromatography on silica gel using cyclohexane/EtOAc/acetone : 2/1/1 as eluent. Compound **22** was obtained as white solid , 0.140 g (76%). R_f0.13 (SiO_2, Cyclohexane/EtOAc/Acetone: 2/1/1). $[\alpha_D]^{20}$ = -61 (c 0.16, CH_2Cl_2). *^{1}H*-NMR ($CDCl_3$, 600 MHz) *δ (*ppm): 7.50 (m, 8H, CHtriazole). 6.70 (2s, 8H, CHAr), 5.30 (m, 6H, H-Fuc), 5.20 (m, 6H, H-Fuc), 5.10 (m, 6H, H-Fuc), 4.79 (m, 6H, OCH_2triazole), 4.59 (m, 3H, OCH_2triazole), 4.4-4.1 (m, 26H, CH_2N/ArCH_2Ar, H-5), 3.80 (m, 16H, CH_2OAr), 3.10 (d, 8H, ArCH_2Ar, *J* 11.8 Hz), 2.23-1.9 (m, 86H, CH_3/CH_2) , 1.23-0.90 (m, 89H, CH_3/H-6). *^{13}C*-NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.6, 170.3, 170.0 (C=O), 153.2 (ArCO), 144.6 (ArC($C(CH_3)_3$)), 143.8 ($C_{triazole}$), 133.7 (ArCCH_2CAr), 131.1 (C_{Ph}), 129.6 (CH_{Ph}), 125.5 (CH_{Ph}), 125.0 (CHAr), 123.2 ($CH_{triazole}$), 95.7 (C-1), 74.7 (CH_2OAr), 71.1, 68.0, 64.7 (C-2, C-3, C-4, C-5), 61.3 (OCH_2triazole), 50.5 (CH_2N), 33.8 (($C(CH_3)_3$), 31.4 (CH_3), 31.3 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 23.2 (CH_2), 20.90 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 15.9 (C-6). HRMS $[M+3H]^{3+}$/3calcd for $C_{228}H_{310}N_{24}O_{56}H_3$: 1427.4095, found: 1427.4080.

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Supplementary Material

ES^+(ESI-MS) spectra and ^{1}H and ^{13}CNMR spectra for the **3**-**7** mixture and for compounds **8**, **9**, **10**, **11**, **13**, **14**, **15**, **17**, **18**, **19**, **20** and **22**. This supplementary data can be found in the online version.

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