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COMMUNICATION

Synthesis of functionalized copillar[4+1]arenes and rotaxane as heteromultivalent scaffolds

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In this study, novel copillar[4+1]arenes were used as central *hetero*multivalent scaffolds *via* orthogonal couplings with a series of biologically relevant molecules such as carbohydrates, α-amino acids, biotin and phenylboronic acid. Further modifications by introducing maleimides or cyclooctyne groups provided molecular probes adapted to copper-free click chemistry. An octa-azidated fluorescent rotaxane bearing two distinct ligands was also generated in a fully controlled manner.

Pillar[5]arenes were discovered in 2008 and quickly became a very important class of macrocyclic compounds.[1] Their unique topological architecture has been exploited in host-guest chemistry,[2] as sensors,[3] as light-harvesting systems,[4] as separation and storage crystals,[5] in drug delivery and biological chemistry.[6] For instance, our group demonstrated, for the first time, that glycosylated pillar[5]arenes could be exploited as competitors of the adhesion of uropathogenic bacteria to eukaryotic cells.[7] We then showed that glyco-pillar[5]arenes[8] as well as their rotaxanes[9] were potent ligands of bacterial lectins of *Pseudomonas aeruginosa*, a major human pathogen. However, to the best of our knowledge glyco-pillar[5]arenes[10] have never been reported as antibiofilm agent of this important human pathogen. In contrast, polycationic non-glycosylated pillararenes have shown very interesting antibiofilm properties, especially against Gram-positive pathogens.[11]
These studies also demonstrated that pillararenes are interesting scaffolds for the preparation of *hetero*multivalent structures, which can be exploited to probe complex biological phenomena. Heteromultivalency is met when at least two structurally distinct ligands are present on a central scaffold preferably in a topologically controlled manner.[12] Indeed, a non-regioselective functionalization yields mixtures of constitutional isomers that are difficult to characterize. One strategy to achieve regioselective bisfunctionalization of pillar[5]arenes is the differentiation of the two rims of these macromolecules (**A**, Figure 1),[13,12a, 14] Another way to display two distinct groups on a pillararene structure is to generate copillars (**B**, Figure 1). In copillars, at least one of the hydroquinone units bears different functional groups than the other ones.[15] Heteromultivalency can also be achieved by exploiting the pillar's cavity to generate rotaxanes **C** (Figure 1). Two major strategies have been developed for the preparation of copillar[5]arenes: the modification of pre-synthesized homopillar[5]arenes bearing identical units, and the co-oligomerization of different monomers.[1b, 16] The latter strategy usually requires less synthetic steps and milder reaction conditions, and provides better selectively. However, co-oligomerization techniques have also some drawbacks as they highly rely on the structural and electronic features of the monomers' substituents which can dramatically affect the yield.[17]

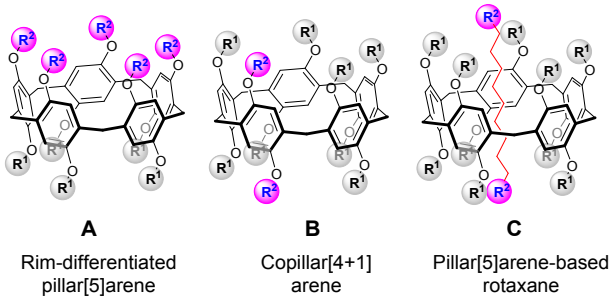
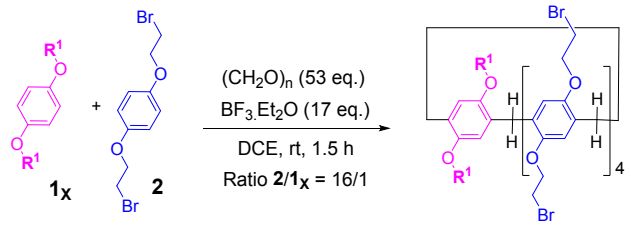


Figure 1. Generic structures of rim-differentiated pillar[5]arenes **A**, copillar[4+1]arenes **B** and pillar[5]arene-based rotaxane **C**.

As a consequence, copillar[5]arenes reported to date are still structurally limited to mostly alkyl and bromoalkyl substituents.[16b] Although rather simple copillar[5]arenes have been used to construct polymers,[18] fluorescent switches[19] and fluorescent sensors,[20] more advanced heteromutivalent scaffolds have never been applied in chemical biology. Here, we demonstrate that co-oligomerization is a versatile and selective technique to generate copillar[4+1]arenes bearing distinct biologically relevant ligands amenable to a broad range of applications in biological chemistry. We also describe the preparation of a clickable fluorescent heterovalent rotaxane.
First, we aimed at finding the optimal partners for the preparation copillar[4+1]arenes using the co-oligomerization protocols reported in the literature.[15, 19a] We selected bromide **2**[17b, 21] as a key building block to co-oligomerize with *p*- dialkoxy benzenes $\mathbf{1_A}$ -$\mathbf{1_F}$ using $BF_3.Et_2O$ as catalyst (Scheme 1).[17a, 17b] The results showed that the efficiency of the copillar[4+1]arene formation is extremely sensitive to the structures of the two *p*-alkoxybenzenes. The best building blocks for the co-oligomerization with **2** were $\mathbf{1_D}$ and $\mathbf{1_F}$ which

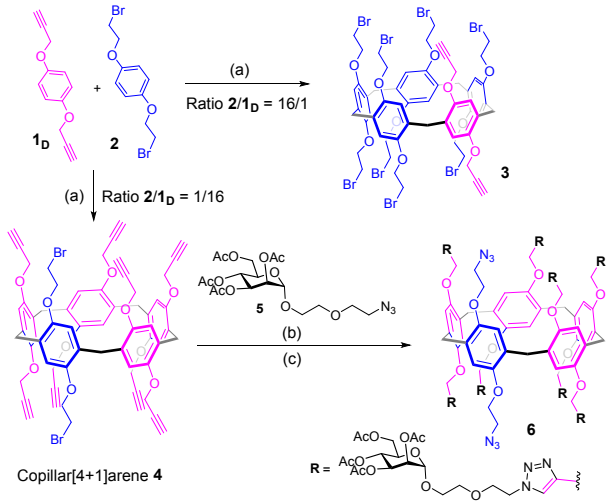
provided the corresponding copillar[4+1]arenes in 26% and 28% yields, respectively.



1A R^1= $CH_2CH_2N_3$ (yield<5%) **1D** R^1= ≡ (yield = 26%)
1B R^1= CH_2CH_2OH (yield<5%) **1E** R^1= $-CH_2(CH_2)_3CH=CH_2$ (yield<5%)
1C R^1= Bn (yield = 11%) **1F** R^1= $-CH_2(CH_2)_4CH_2Br$ (yield = 28%)

Scheme 1. Screening of the best building blocks **1X** for the co-oligomerization with **2**

Next, we optimized conditions to generate copillar[5]arene **3** using **1D** and **2** (Scheme 2 and Table S1). Among the catalysts usually used for pillar[5]arene syntheses ($FeCl_3$, methanesulfonic acid and $BF_3.Et_2O$), $BF_3.Et_2O$ gave the best yields. Interestingly, we found that the concentration **2** had a dramatic impact on the yield. This concentration effect may originate from the fact that the pillar[5]arene formation is a dynamic process[22] leading either to a cyclized oligomer of a defined size or to polymers.

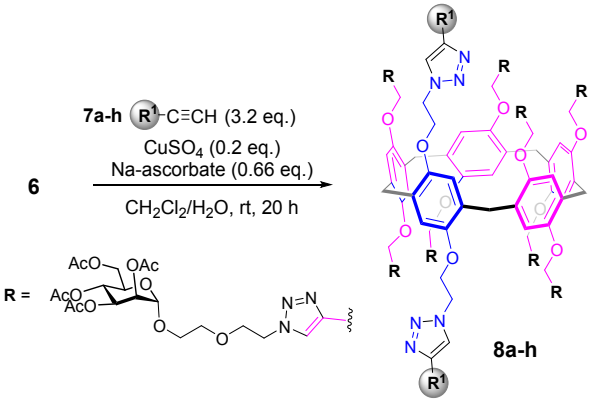


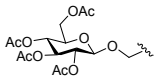
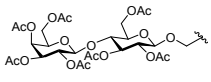
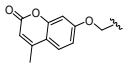
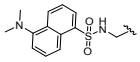
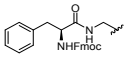
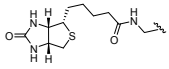
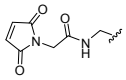
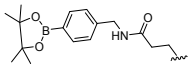
Reagents and conditions: (a) $BF_3.Et_2O$ (25.5 eq.), $(CH_2O)_n$ (53 eq.), DCE, rt, 1.5h, 40% yield for both reactions (b) **5** (10 eq.), Na-ascorbate (0.2 eq.), $CuSO_4$ (0.66 eq.), CH_2Cl_2/H_2O, rt, 20 h, 93%. (c) NaN_3 (6 eq.), DMF, rt, 20 h, 98%.

Scheme 2. Co-oligomerization of **1D** with **2** and synthesis of octa-mannosylated copillar[4+1]arene **6**

The optimal ratio between **1D** and **2** was then investigated (Table S1) and showed that 16 equivalents of **2** gave the best isolated yield. Finally, we increased the number of $BF_3.Et_2O$ equivalents to 25.5 eq. which reproducibly provided an optimized 40% yield, including at a larger scale (729 mg of **3**). Importantly, by just inverting the ratio between **1D** and **2**, we were able to obtain another clickable copillar[4+1]arene **4**, also in 40% yield, under the same reaction conditions (Scheme 2). With copillar[4+1]arene **4** in hand, we carried out the synthesis of the octa-mannosylated copillar[4+1]arene **6** (Scheme 2). Therefore, D-mannoside **5** (SI, S6) was clicked to copillar[4+1]arene **4** using standard CuAAC conditions to provide intermediate **6a** (93% yield) which was further azidated in DMF to afford the clickable octa-mannoside **6** in 98% yield (Scheme 1). D-mannose was selected because its multimers are competitors of the infection by major human pathogens such as HIV and Ebola viruses.[23]

Table 1. Scope of functionalization of **6** with **7a-7h**



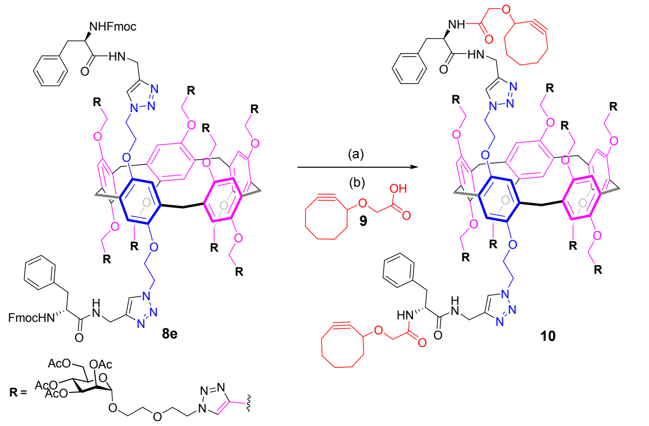
Entry	R^1CCH **7**	R^1	Product **8** (Yield in %)[a]
1	7a		**8a** (91)
2[b]	7b		**8b** (93)
3[b,c]	7c		**8c** (98)
4[b,c]	7d		**8d** (96)
5	7e		**8e** (90)
6[d]	7f		**8f** (52)
7[b,c,e]	7g		**8g** (53)
8[f]	7h		**8h** (86)

(a) Isolated yield. (b) $CuSO_4$ (0.4 eq.), Na-ascorbate (1.3 eq.). (c) **7c** (5 eq.). (d) **7d** (5 eq.), CuI (0.2 eq.), Et_3N (0.4 eq.), DMF. (e) **7g** (6 eq.). (f) CuI (0.2 eq.), TBTA (0.1 eq.), DMSO.

The scope of functionalization of **6** with structurally diverse molecules was then explored. Compound **6** was clicked to a series of alkynes **7a-7h** (Table 1). The efficient grafting of a second mono- or di-saccharide yielded heterovalent structures **8a** and **8b** in 91% and 93% yields, respectively (Entries 1 and 2). The efficiency was also excellent with fluorescent probes **7c** and **7d** (98% and 96% yields, Entries 3-4). The coupling of ligand **7e** proved that peptides can be part of the repertoire of these novel glycosylated copillararenes (90% yield, Table 1, Entry 5). Biotin **7f** and maleimide **7g** which are extensively used in biochemistry, for instance to identify molecules in complex biological media, were also efficiently clicked to **6**

furnishing **8f** and **8g** in moderate yields (Entries 6-7). Moreover, boronates such as **7h**, commonly exploited for the design of biosensors were also successfully grafted to **6** (86% yield, Entry 8).[24] However, the cycloaddition of compound **7f** with **6** failed although the starting copillararene **6** was totally consumed. An alternative protocol employing CuI as a catalyst in dry DMF allowed us to isolate the desired product **8f** in a moderate 52% yield (Entry 6).

Moreover, we wished to demonstrate that copillararene **8e** bearing two Fmoc-protected amino acids and 8 peracetylated mannosides could be further functionalized by exploiting an orthogonal deprotection and peptide couplings (Scheme 3). Consequently, amine -**8e** was deprotected using DBU and cyclooctyne **9** was further coupled to the intermediate bisamine using EDCI to yield the copillarene **10** in 60% yield. Such a structure is interesting in chemical biology as many applications of cell engineering require copper free reactions.[25]

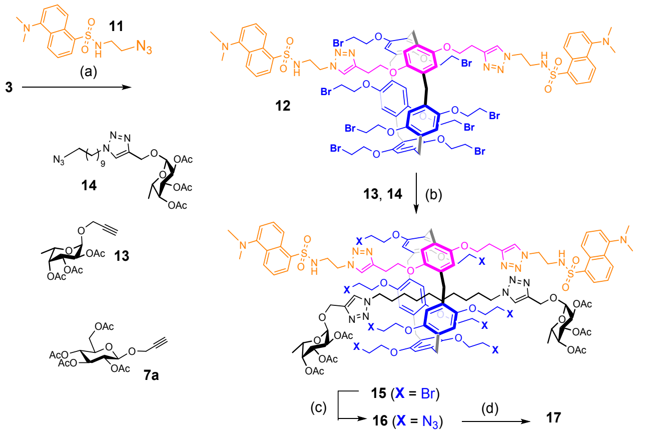


Reagent and conditions: (a) DBU (2.2 eq.), CH_2Cl_2, rt, 40 min. (b) EDCI (3 eq.), **9** (3 eq.), CH_2Cl_2, rt, overnight, 60% over two steps.

Scheme 3. Synthesis of **10** bearing cyclooctynes ready for copper-free click reactions-

We also proved that copillar[4+1]arene **3** can also be exploited to generate heteromultivalent scaffolds (see SI Scheme S11). The issue of the inherent planar chirality of pillararenes has been discussed in the literature[16b] and applies to the molecules generated in this study as carbohydrates are chiral ligands. Based on our own NMR study on mannosylated pillar[5]arenes[7] and the recent report of Sun et al.[26] who managed to isolate the two diasteroisomers of a decagalactosylated pillar[5]arenes and performed CD and NMR analyses, it can be concluded that carbohydrates grafted to pillar[5]arenes are bulky enough to prevent the oxygen-through-the-annulus-rotation racemization mechanisms, even at high temperature. Therefore, all the copillar[4+1]arenes and the rotaxanes described in the present study are diastereomeric mixtures. The complexity of the ^{1}H and ^{13}C-NMR of copillar[4+1]arenes also arises from the loss of the D_5 symmetry (as compared to Pillar[5]arenes). In addition, ^{1}H NMR spectra of molecule **8c** (See SI) were recorded at several temperatures and showed that lowering the temperature at -5°C resulted in the broadening of the signals whereas increasing the temperature to 55°C sharpened some of the signals. Noteworthy, all glycosylated pillar[5]arenes that have been designed to interact with lectins,[8-10, 27] enzymes,[28] bacteria,[7, 13] or cancer cells[29] have been assayed as diastereomeric inseparable mixtures. To date, there is a single report in the literature in which the two stereoisomers of a glycosylated pillar[5]arene could be separated and characterized.[26]

Finally, we wanted to determine whether those copillar[4+1]arenes still maintain the host-guest properties that would further expand their application scope. Therefore, we chose copillar[4+1]arene **3** to investigate the synthesis of a clickable fluorescent rotaxane **16**



Reagents and conditons: (a) **11** (2.4 eq.), $CuSO_4$ (0.2 eq.), Na-ascorbate (0.66 eq.), CH_2Cl_2/H_2O, rt, 12 h, 94% (b) **12** (4 eq.), **13** (1.2 eq.), **14** (1 eq.), $CuBr.SMe_2$ (2 eq.), $CHCl_3$, -20 °C-rt, 12 h, 48%. (c) NaN_3 (10 eq.), DMF, overnight, 97% (d) **7a** (10 eq.), $CuSO_4$ (0.2 eq.), Na-ascorbate (0.66 eq.), CH_2Cl_2/H_2O, rt, 20h, 79%.

Scheme 4. Synthesis of clickable fluorescent rotaxane **16** and octaglucosylated rotaxane **17**.

(Scheme 4). Copillar[4+1]arene **3** was first labeled with a fluorescent dansyl group **11** to yield **12** in 94% yield. Fucoside **13** was then clicked to the supramolecular assembly of decyl-bisazide **14** and copillararene **12** using $CuBr.SMe_2$ to yield intermediate rotaxane **15** in a satisfactory yield of 48%. To the best of our knowledge, rotaxanes constructed from a copillar[4+1]arene have been only reported twice in the literature for applications in fluoride sensing.[30] Rotaxane **16** was obtained by octa-azidation of **15** (Scheme 4). To demonstrate that rotaxane **16** can be further functionalized, we clicked it with an excess of **7a** to obtain a new rotaxane **17** bearing now 8 glucosides.

In conclusion, we have prepared two novel copillar[4+1]arenes **3** and **4** in 40% yield after screening a series of alkoxybenzenes and optimized a procedure of cocyclization. This study revealed that the concentration of the building blocks can strongly affect the cocyclization yield. The two copillar[4+1]arenes were shown to be versatile *hetero*multivalent platforms using CuAAC reaction sequences to introduce orthogonal functional groups selected for their applicability in chemical biology. Moreover, a fluorescent rotaxane was constructed from an easily accessible copillar[4+1]arene in a few steps, thus providing a tool that could be further functionalized. Work is in progress to evaluate such heterovalent copillar[4+1]arenes as lectin ligands with applications as antivirulence or antibiofilm agents or for multivalent enzyme inhibition.[28, 31] The fluorescent copillararenes and rotaxane developed in this study are ideally suited for cell-based assays and *in vivo* experiments, especially under copper-free conditions.

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Conflict of interest

The authors declare no competing financial interest.

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