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Click chemistry as an efficient tool to access β-cyclodextrin dimers

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ABSTRACT

The Cu(I)-catalyzed azide–alkyne cycloaddition has enabled practical and efficient preparation of hydroxylated, permethylated and peracylated β-cyclodextrin dimers in good yields starting from mono-6-azido-β-cyclodextrin and *ortho*-, *meta*- or *para*-bis-(prop-2-ynyloxy)benzenes as spacers.

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1. Introduction

During the past 14 years, our intensive efforts to promote the use of native and modified α-, β- or γ-cyclodextrin (CD) in catalysis led us to understand the multifunctional properties of these glucopyranosic torus-like macro-rings.[1] We especially focused on their role as mass transfer promoter, substrate-discriminating tool, dispersing agent or nanoparticle stabilizers in water or unconventional media.[2] To carry our investigations a step further, the elaboration of more complex CD structures is now required. Among the possible CD-based derivatives, dimeric species were of particular interest because they could supramolecularly interact with several catalytic partners in a confined chemical environment and revealed enhanced molecular binding ability by multiple recognition. Thus, the closeness of these entities could have beneficial consequences on the catalytic system performances.

Since the first synthesis of a CD dimer by Breslow et al., researchers exercised creativity to prepare original dimeric CD-based structures.[3] Nevertheless, the synthesis of many dimers described in the literature was often fastidious and time-consuming. Consequently, we tried to develop new efficient synthetic pathways to access a library of bridged bis-(β-CD) hosts for supramolecular catalysis. For that purpose, we used one of the most reliable reactions in click chemistry, namely the copper-catalyzed azide–alkyne cycloaddition.[4] This reaction appeared to be a great alternative to the traditional thermal Huisgen 1,3-dipolar cycloaddition. Its development by Sharpless et al. a few years ago enabled the synthesis of numerous 1,2,3-triazole derivatives and constitutes one of the current main topic of interest in organic chemistry.[5] Although click chemistry has already been used in the synthesis of CD derivatives,[6] the preparation of CD dimers has never been described by this method. Herein, we report on the synthesis of bis-(β-CD) compounds by Cu(I)-mediated cycloaddition of mono-6-azido-β-CD derivatives with *ortho*-, *meta*- or *para*-diethynylbenzenes. In order to access dimers soluble in various solvents, the nature of the CD-substitutents has been varied. These new CDs were fully characterized by NMR, mass spectrometry (MALDI-TOF–TOF).

2. Results and discussion

In order to test the viability of our approach, we first set out to assess the ability of native β-CD to undergo 1,3-dipolar cycloaddition with alkynes. To this end, mono-6-azido-β-CD, prepared from native β-CD in two steps as previously described,[7] was treated with *ortho*-, *meta*- and *para*-bis-(prop-2-ynyloxy)benzenes in the presence of stoichiometric quantities of hydrated copper sulfate with regard to the alkyne function to effect cyclization (Scheme 1). The reaction was performed at room temperature overnight.

The obtained dimers were classically purified on silica gel with an acetonitrile/water gradient furnishing the desired 1,2,3-triazole rings in good yields (50–65%). As an example, the mass spectrum of **1a** is displayed on Figure 1.

Given that the *ortho* isomer is more sterically hindered than its *meta*- and *para*-derivatives, it was thought that this may have a detrimental effect on the double cycloaddition. In fact, despite the bulky environment of the *ortho* structure, no loss in yield was noted indicating that the cycloaddition can be efficiently realized whatever be the isomer. The use of stoichiometric amounts of

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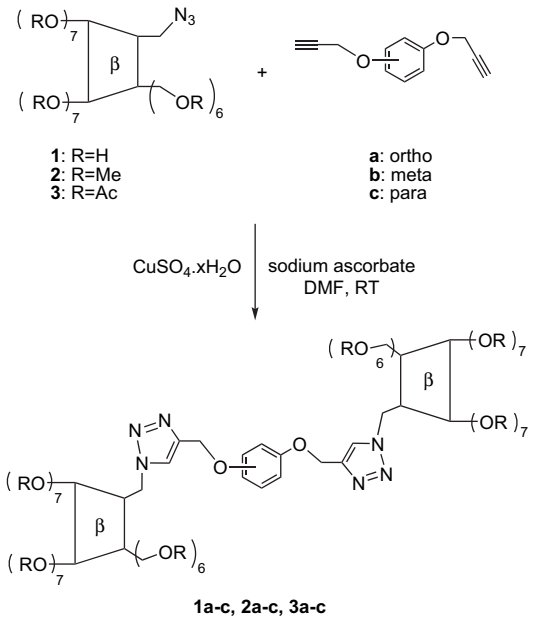

Scheme 1. Synthesis of hydroxylated, permethylated and peracylated β-CD dimers.

$CuSO_4 \cdot xH_2O$ was justified by the complexing properties of the CD secondary hydroxyl face whose interaction with copper has been widely exploited in the synthesis of mono-tosylated β-CD.[8] An excess hydrated copper sulfate was therefore needed for the cycloaddition to take place on the CD primary face. Note that stoichiometric amounts of $CuSO_4 \cdot xH_2O$ were also required in click dendrimer synthesis because of Cu trapping in a nitrogen-based dendritic structure.[9]

Looking carefully at the ^{1}H NMR spectra, our attention was drawn by the presence of two distorted doublets at 6.86 and 6.77 ppm with a coupling constant of 7.45 Hz in the aromatic region of the **1c** *para*-isomer spectrum when a singlet was expected for a symmetric structure. This AB system was interpreted as two groups of magnetically nonequivalent phenyl protons. To get more information on this astonishing observation, 2D T-ROESY NMR experiments have been carried out and led to very interesting results (Fig. 2).

Indeed, cross-peaks were detected between the two H_A aromatic protons (6.86 ppm) and the H-5 (3.65 ppm) and H-6 (3.84 ppm) CD protons confirming the partial inclusion of the phenyl group in the CD cavities (Fig. 1). Cross-peaks between the two H_B aromatic protons (6.77 ppm) and protons in the environment of the triazole ring also confirmed the precise arrangement of

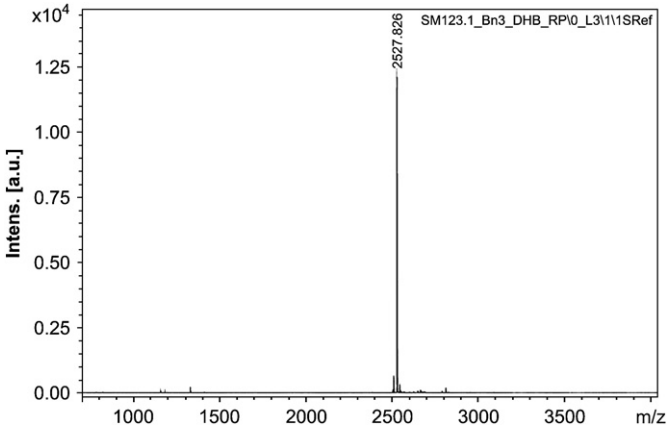

Figure 1. Mass spectrum of **1a**.

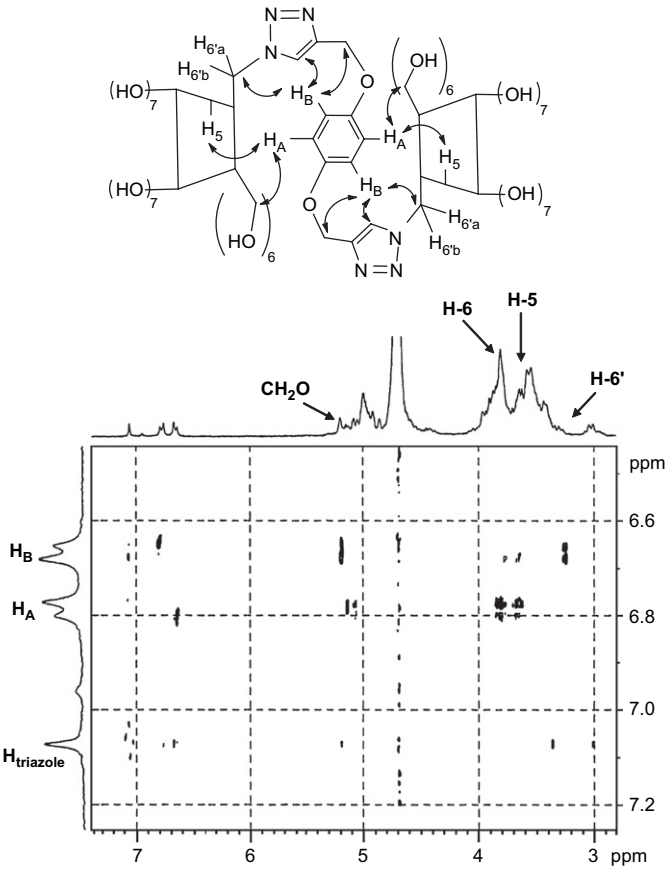

Figure 2. Partial 2D T-ROESY spectrum of **1c** at 25 °C in D_2O and deduced structure of **1c**.

the molecule in water. The situation was very different in DMSO-d_6 since a well-defined singlet integrating for 4H was obtained at 6.98 ppm indicating that the phenyl protons are magnetically equivalent. DMSO being a dissociating solvent, the structure of **1c** was deployed in those conditions. Note that T-ROESY spectra of **1a** and **1b** in D_2O did not reveale any contact between the phenyl and the CD protons. This observation suggested that the bent arrangement of the *ortho*- and *meta*-dialkynyl precursors **a** and **b** did not allow interaction between the phenyl group and the CD cavity. In that case, dimers with the phenyl group outside the CD cavity were obtained.

With the synthesis of the hydroxylated β-CD dimers in hand, attention next turned to the synthesis of permethylated β-CD dimers. Methylation of mono-tosylated β-CD with excess methyl iodide furnished the mono-tosylated permethylated β-CD that underwent a nucleophilic substitution with NaN_3. Subsequent Cu(I)-catalyzed cycloaddition in the presence of the diethynylbenzene isomers gave the permethylated β-CD dimers in very good yields (70–90%) after purification on silica gel with a dichloromethane–methanol mixture. Contrary to what was observed for **1c**, the aromatic protons of **2c** gave a singlet at 6.90 ppm integrating for 4H indicative of the absence of inclusion phenomenon. The steric hindrance generated by the methyls is probably the explanation of such behaviour. The presence of hydrophobic methyls also has influence on the solubility of the dimers since permethylated β-CD dimers were slightly soluble in water and very soluble in organic solvents. When compared to hydoxylated β-CD, the reaction time was shorter (15 min vs 18 h, respectively) and the yields higher. We suggested that both results were a consequence of the absence of interaction between the methylated CDs and the copper salt.

Finally, the study has been extended to peracylated β-CD. Acetylation of mono-6-azido-β-CD was carried out in an acetic anhydride–pyridine (1:2) mixture at 80 °C for 4 h giving the expected mono-azido-peracylated β-CD in quantitative yield. The Huisgen [2+3] cycloaddition was then performed in the same experimental conditions than those described above for hydroxylated β-CD and led, after purification on silica gel, to the peracetylated β-CD dimers in good yields (40–50%). The steric hindrance generated by the acyl groups might certainly explain the loss in reactivity since the accessibility to the azide function was strongly reduced. The peracylated dimers were not soluble in water but very soluble in organic solvents. Note that deacetylation of **3c** by a Zemplen reaction led to the hydroxylated dimer **1c** indicating that the whole dimeric structure was stable in basic conditions.

3. Conclusion

To sum up, we showed that click chemistry is a powerful tool to synthesize a library of dimeric β-CDs starting from mono-6-azido-β-CD and dialkynylbenzene derivatives. Further studies aimed at exploring and exploiting their complexing properties are currently in progress in our laboratory. Their catalytic behaviour is also under investigation in various solvents. Indeed, hydroxylated dimers are appropriate for aqueous catalysis when permethylated ones are of particular interest for catalysis in organic solvents. Peracylated dimers, for their part, are preferentially devoted to supercritical CO_2 catalysis.[10] Whatever the structure, their use should lead to enhanced complexing properties of substrates or phosphines. Surely, their field of application may be greatly broadened and an expanded appreciation of their potential in biology, for example, could also be envisaged.

4. Experimental

4.1. General

All chemicals were purchased from Acros and Aldrich Chemicals in their highest purity. All solvents were used as-supplied without further purification. Distilled water was used in all experiments. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-backed silica gel (Silica Gel F_{254}). Compounds were identified using UV fluorescence and/or staining with a solution of phosphomolybdic acid in aqueous sulfuric acid and ethanol. NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei. $CDCl_3$ (99.50% isotopic purity), DMSO-d_6 (99.80% isotopic purity) and D_2O (99.92% isotopic purity) were purchased from Euriso-Top. ^{1}H NMR data are reported as chemical shift, multiplicity (s, singlet; d, doublet; m, multiplet), relative integral, coupling constant (*J* in hertz). The 2D T-ROESY experiments were run using the software supplied by Bruker. T-ROESY experiments were preferred to classical ROESY experiments as this sequence provides reliable dipolar cross-peaks with a minimal contribution of scalar transfer. Mixing times for T-ROESY experiments were set at 300 ms. The data matrix for the T-ROESY was made of 512 free induction decays, 1 K points each, resulting from the co-addition of 32 scans. The real resolution was 1.5–6.0 Hz/point in F2 and F1 dimensions. They were transformed in the nonphase-sensitive mode after QSINE window processing. Mass spectra were recorded on a MALDI-TOF–TOF Bruker Daltonics Ultraflex II in positive reflectron mode with 2,5-DHB as matrix.

4.2. General procedure for the synthesis of the dialkynyl precursors

To a solution of hydroxyphenol in acetone (250 mL) was added propargyl bromide (2.3 equiv) and $CsCO_3$ (3 equiv). The solution was refluxed for 16 h. After evaporation of the solvent, the crude product was purified by column chromatography using silica gel and chloroform as eluant.

*4.2.1. 1,2-Bis(prop-2-ynyloxy)benzene (**a**)*

White powder. Yield 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (m, 2H), 6.98 (m, 2H), 4.76 (d, 4H, *J* 2.19 Hz, CH_2), 2.51 (t, 2H, *J* 2.19 Hz); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.6, 122.2, 115.1, 78.7, 73.9, 56.9. Anal. Calcd for $C_{12}H_{10}O_2$: C 77.40, H 5.41, O 17.18. Found: C 76.43, H 5.32, O 18.25.

*4.2.2. 1,3-Bis(prop-2-ynyloxy)benzene (**b**)*

White powder. Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 1H), 6.62 (m, 3H), 4.67 (d, 4H, *J* 2.19 Hz), 2.53 (t, 2H, *J* 2.19 Hz); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.9, 130.1, 108.0, 108.0, 78.6, 75.7, 56.0. Anal. Calcd for $C_{12}H_{10}O_2$: C 77.40, H 5.41, O 17.18. Found: C 76.36, H 5.61, O 18.03.

*4.2.3. 1,4-Bis(prop-2-ynyloxy)benzene (**c**)*

White powder. Yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 4H), 4.64 (d, 4H, *J* 2.19 Hz), 2.51 (t, 2H, *J* 2.19 Hz); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.5, 116.1, 78.9, 75.5, 56.6. Anal. Calcd for $C_{12}H_{10}O_2$: C 77.40, H 5.41, O 17.18. Found: C 76.45, H 5.55, O 18.00.

4.3. General procedure for the Huisgen [2+3] cycloadditions on mono-6-azido-β-CD

To a solution of dialkynyl derivative (67 mg, 0.36 mmol) in DMF (30 mL) was added mono-6-azido-β-CD (1 g, 0.87 mmol) and hydrated copper sulfate (180 mg, 0.36 mmol). After subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (288 mg, 1.44 mmol) dissolved in a water/DMF mixture (50/50), the solution was stirred for 18 h at room temperature. After evaporation of the solvent, the crude product was purified by column chromatography using silica gel with a CH_3CN–H_2O (7:3) mixture as eluant.

*4.3.1. Bis-1,2-[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**1a**)*

White powder. Yield 53%. ^{1}H NMR (300 MHz, D_2O) δ 7.82 (s, 2H), 7.31 (m, 2H), 6.90 (m, 2H), 5.30–5.20 (m, 32H), 4.09–3.42 (m, 70H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 159.7, 158.3, 146.4, 143.9, 102.3, 91.0, 81.4, 73.9, 73.5, 72.6, 59.3, 51.6; MS calcd for $C_{96}H_{148}N_6O_{70}Na$ 2527.82, found 2527.83. Anal. Calcd for $C_{96}H_{148}N_6O_{70}\cdot 58H_2O\cdot 3CH_3CN$: C 33.34, H 7.49, N 3.43, O 55.74. Found: C 34.22, H 6.27, N 3.55, O 56.96.

*4.3.2. Bis-1,3-[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**1b**)*

White powder. Yield 65%. ^{1}H NMR (300 MHz, D_2O) δ 7.99 (s, 2H), 7.71 (s, 1H), 7.05 (m, 3H), 5.41–5.21 (m, 32H), 4.21–3.21 (m, 70H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 149.1, 147.8, 143.8, 126.2, 123.3, 101.9, 88.3, 85.1, 73.9, 72.9, 72.3, 59.6, 51.5; MS calcd for $C_{96}H_{148}N_6O_{70}Na$ 2527.82, found 2528.10. Anal. Calcd for $C_{96}H_{148}N_6O_{70}\cdot 53H_2O$: C 33.32, H 7.40, N 2.43, O 56.86. Found: C 32.49, H 6.08, N 2.63, O 58.80.

*4.3.3. Bis-1,4-[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**1c**)*

White powder. Yield 64%. ^{1}H NMR (300 MHz, D_2O) δ 7.62 (br s, 2H), 6.86 (d, 2H, *J* 7.45 Hz), 6.77 (d, 2H, *J* 7.45 Hz), 5.34–5.26 (m, 32H), 4.21–2.99 (m, 70H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 2H), 6.98 (s, 4H), 5.88–5.66 (m, 28H), 5.03 (s, 4H), 4.78 (m, 14H), 4.48 (m, 14H), 4.31 (m, 2H), 3.99 (m, 2H), 3.65–3.47 (m, 26H), 3.40–3.28 (m, overlapped with residual H_2O in DMSO-d_6); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 154.6, 150.7, 121.4, 115.4, 102.2, 83.3, 81.7,

74.1, 73.5, 72.7, 60.6, 51.5; MS calcd for $C_{96}H_{148}N_6O_{70}Na$ 2527.82, found 2528.10. Anal. Calcd for $C_{96}H_{148}N_6O_{70}\cdot 48H_2O\cdot 3CH_3CN$: C 35.06, H 7.30, N 3.61, O 54.03. Found: C 36.57, H 6.59, N 3.39, O 55.45.

4.4. General procedure for the Huisgen [2+3] cycloadditions on mono-6-azido-permethylated β-CD

To a solution of dialkynyl derivative (12 mg, 0.065 mmol) in DMF (30 mL) was added mono-azido permethylated β-CD (244 mg, 0.156 mmol) and hydrated copper sulfate (32 mg, 0.30 mmol). After subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (51 mg, 0.259 mmol) dissolved in a water/DMF mixture (50/50), the solution was stirred for 15 min at room temperature. After evaporation of the solvent, the crude product was purified by column chromatography using silica gel with a CH_2Cl_2–CH_3OH (9:1) mixture as eluant.

*4.4.1. Bis-1,2-[1-(6^A-deoxy-permethylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**2a**)*

White powder. Yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 2H), 6.95 (m, 2H), 6.82 (m, 2H), 5.17 (br s, 4H), 5.05 (br s, 28H), 4.02–3.21 (m, 190H), 3.20–2.86 (m, 14H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.2, 143.4, 130.9, 125.5, 121.9, 98.8, 81.9, 77.6, 71.2, 70.9, 70.7, 61.3, 58.9, 29.6; MS calcd for $C_{136}H_{228}N_6O_{70}Na$ 3088.44, found 3088.83.

*4.4.2. Bis-1,3-[1-(6^A-deoxy-permethylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**2b**)*

White powder. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.10 (s, 1H), 6.51 (m, 2H), 6.41 (m, 1H), 5.05 (br s, 18H), 3.88–3.72 (m, 28H), 3.71–3.22 (m, 162H), 3.20–2.96 (m, 14H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.4, 143.2, 130.0, 125.0, 107.2, 101.8, 99.1, 81.9, 81.8, 71.1, 70.8, 70.7, 61.4, 59.0, 29.6; MS calcd for $C_{136}H_{228}N_6O_{70}Na$ 3088.44, found 3088.83.

*4.4.3. Bis-1,4-[1-(6^A-deoxy-permethylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**2c**)*

White powder. Yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 2H), 6.90 (s, 4H), 5.12 (br s, 18H), 3.92–3.68 (m, 28H), 3.65–3.21 (m, 162H), 3.20–3.18 (m, 14H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 152.9, 143.6, 125.1, 116.2, 93.9, 77.6, 76.7, 71.3, 71.0, 69.8, 61.4, 59.2, 29.7; MS calcd for $C_{136}H_{228}N_6O_{70}Na$ 3088.44, found 3088.79.

4.5. General procedure for the Huisgen [2+3] cycloadditions on mono-6-azido-peracylated β-CD

To a solution of dialkynyl derivative (47 mg, 0.25 mmol) in DMF (30 mL) was added mono-azido peracylated β-CD (1.1 g, 0.55 mmol) and hydrated copper sulfate (125 mg, 0.50 mmol). After subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (200 mg, 1 mmol) dissolved in a water/DMF mixture (50/50), the solution was stirred for 18 h at room temperature. After evaporation of the solvent, the crude product was purified by column chromatography using silica gel with a CH_2Cl_2–CH_3OH (96:4) mixture as eluant.

*4.5.1. Bis-1,2-[1-(6^A-deoxy-peracylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**3a**)*

White powder. Yield 48%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.02 (m, 2H), 6.89 (m, 2H), 5.63–5.10 (m, 32H), 5.06–4.95 (m, 14H), 4.86–4.74 (m, 14H), 4.64–4.10 (m, 28H), 3.78–3.42 (m, 14H), 2.07 (m, 120H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.0, 169.8, 148.7, 144.3, 131.3, 126.5, 116.2, 97.3, 77.0, 71.7, 70.5, 70.0, 63.9, 63.0, 21.2; MS calcd for $C_{176}H_{228}N_6O_{110}Na$ 4208.24, found 4207.94.

*4.5.2. Bis-1,3-[1-(6^A-deoxy-permethylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**3b**)*

White powder. Yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (br s, 2H), 7.20 (m, 1H), 6.65 (m, 2H), 6.58 (m, 1H), 5.32–5.06 (m, 32H), 4.85–4.62 (m, 14H), 4.58–4.49 (m, 14H), 4.35–4.01 (m, 28H), 3.75–3.64 (m, 14H), 2.08 (m, 120H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.9, 169.6, 162.7, 159.6, 143.8, 131.1, 128.9, 107.6, 96.8, 71.4, 69.8, 69.7, 69.3, 63.6, 62.75, 20.9; MS calcd for $C_{176}H_{228}N_6O_{110}Na$ 4208.24, found 4209.19.

*4.5.3. Bis-1,4-[1-(6^A-deoxy-permethylated-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (**3c**)*

White powder. Yield 36%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 2H), 6.95 (s, 4H), 5.37–5.06 (m, 32H), 4.84–4.60 (m, 14H), 4.58–4.16 (m, 42H), 3.75–3.58 (m, 14H), 2.11 (m, 120H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.9, 169.6, 162.7, 159.6, 143.8, 131.1, 128.9, 107.6, 96.8, 71.4, 69.8, 69.7, 69.3, 63.6, 62.75, 20.9; MS calcd for $C_{176}H_{228}N_6O_{110}Na$ 4208.24, found 4208.54.

4.6. Synthesis of 1c by deacetylation of 3c (Zemplen reaction)

To a solution of **3c** (12 mg, 0.006 mmol) in methanol (20 mL) was slowly added MeONa (13 mg, 0.24 mmol). After 20 min stirring at room temperature, the solution was neutralized with Amberlyst 15 resin. The suspension was filtered and the filtrate evaporated. The resulting product was purified by column chromatography using silica gel with a CH_3CN–H_2O (7:3) mixture as eluant to give **1c**. Yield: 98%.

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