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Easily Accessible Mono- and Polytopic β-Cyclodextrin Hosts by Click Chemistry

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A great variety of mono- and polytopic β-cyclodextrin hosts have been easily synthesized by using the Cu^{I}-catalyzed azide–alkyne cycloaddition reaction. Of particular interest for their multibinding properties, dimeric and trimeric CD compounds were obtained by "clicking" mono-6-azido-β-cyclodextrin derivatives with flexible or rigid dialkynyl spacers. The reaction is general, high-yielding for some of the synthesized molecules (>80 %) and proceeds under mild conditions. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

During the past 30 years cyclodextrins (CDs) have gained wide recognition for their ability to form inclusion complexes with organic, inorganic, organometallic or biological molecules.[1] However, the binding properties of native CDs are generally limited and more elaborated structures are often needed. Thus, modified CDs have been synthesized to efficiently accommodate structurally matched guests. The strength of the interaction between CD hosts and their guests can vary significantly depending on their structures. In particular, owing to multiple simultaneous interactions and collective binding properties, it has been shown that CD dimers and trimers are interesting polytopic supramolecular hosts with stronger binding ability than simple CD receptors.[2] In addition to the enhanced complexing power generated by the presence of two or three CDs around the guest, the linker that ties the CDs together may also contribute to an increased binding ability because it can provide an additional pseudo-cavity. This cooperative binding could have beneficial effects and has been turned to account in many fields, for example, in catalysis, templated synthesis, photochemistry, enzyme mimicking and molecular imprinting.[3] For this reason, numerous modified CDs have already been elaborated but the synthesis of many of them have proved to be fastidious, time-consuming and yields were often low especially for trimeric species due to steric hindrance.[4]

In recent years we have developed a synthesis of modified CDs and applied them to catalytic processes.[5] We are currently extending our approach to more complex but better performing systems. The need to easily access elaborated CDs prompted us to develop new synthetic pathways. In recent work we demonstrated that CD dimers are easily accessible by click chemistry starting from mono-6-azido-β-CD and *ortho*-, *meta*- or *para*-bis(prop-2-ynyloxy)benzenes as spacers.[6] Herein, we show that Cu^{I}-catalyzed azide–alkyne cycloaddition can be of general use in the synthesis of mono- and polytopic CD derivatives starting from a pool of easily accessible mono-azide CDs and alkynyl derivatives of different nature. The scope of the reaction was explored by using mono-, di- or trialkynyl linkers and hydroxylated or randomly methylated mono-6-azido-β-CDs. Randomly methylated mono- or polytopic β-CDs are particularly interesting species as it is well known that partially methylated CDs are much more water-soluble than hydroxylated ones.[7]

Results and Discussion

Synthesis of β-CD and Alkynyl Precursors

The hydroxylated mono-6-azido β-CD (**1**) was prepared by using a two-step approach with tosylation of the native β-CD followed by sodium azide substitution, as described previously.[8] The randomly methylated mono-6-azido-β-CD (**2**, Scheme 1) was synthesized by reaction of **1** in basic conditions with a dimethyl sulfate solution. After work-up, **2** was isolated as a pale yellowish-white powder in 85% yield. Compound **2** contained a mixture of partially methylated β-CDs with an average degree of substitution of 1.8 methyl groups per glucopyranose unit. The solubility of **2** in water is 30-fold that of **1** (500 vs. 17 $g\,L^{-1}$). Products synthesized from **2** are of particular interest in biphasic cataly-

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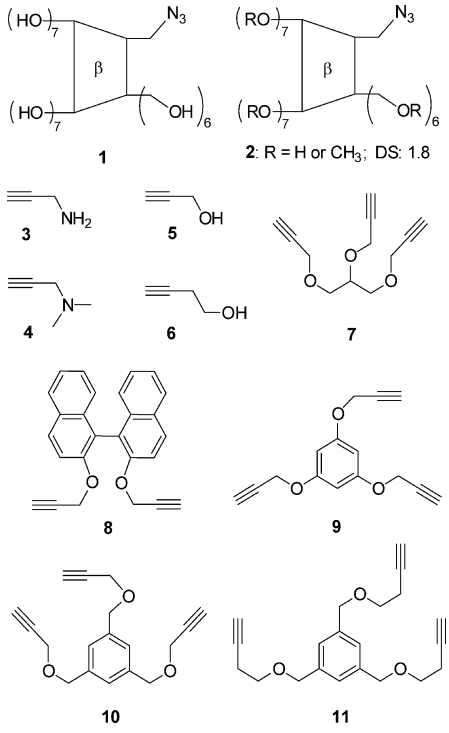
sis as we have demonstrated that partially methylated β-CDs efficiently adsorbed at the organic/aqueous interface promote mass-transfer.[9] Concerning alkynyl precursors, some of them were commercial and others were synthesized divergently starting with propargyl bromide and alcoholate derivatives or with propargyl alcohol and bromomethylbenzene derivatives, both in basic conditions (Scheme 1). For example, (±)-2,2′-dihydroxy-1,1′-binaphthalene or 1,3,5-trihydroxybenzene were propargylated by treatment with potassium carbonate and propargyl bromide to afford **8** and **9** in 98 and 61% yields, respectively. Conversely, **10** and **11** were successfully prepared in good yields (80 and 70%, respectively) from tris(1,3,5-bromomethyl)benzene and propargyl alcohol or butyn-1-ol, respectively.

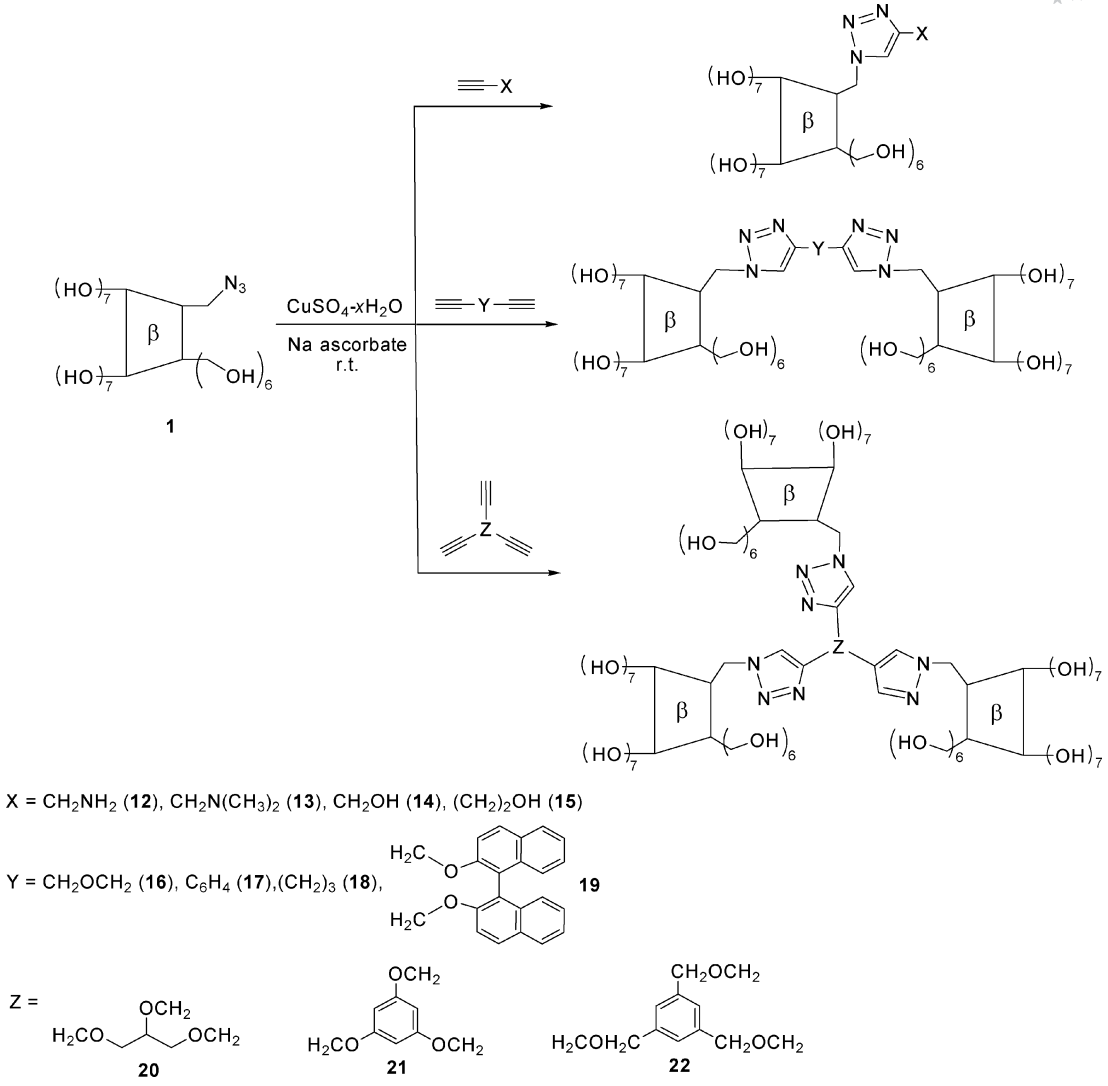


Scheme 1. β-CD and alkyne precursors. DS: degree of substitution.

Synthesis of Mono- and Polytopic Hydroxylated 1,2,3-Triazole-β-CD Derivatives

Once the reactants had been prepared, the Huisgen [2+3] cycloaddition reaction was applied to the synthesis of mono- and polytopic 1,2,3-triazole-β-CD derivatives. The procedure was slightly different depending on the CD substituents and the mono- or polytopic character. The Cu^{I}-catalyzed cycloaddition, which leads to hydroxylated monotopic compounds **12**–**15**, proceeded at room temperature in DMSO with 1.1 equiv. $CuSO_4{\cdot}xH_2O$ (with respect to the CD) required for completion in 18 h (Scheme 2). An excess of $CuSO_4{\cdot}xH_2O$ was also used to force the reaction to proceed quantitatively. DMSO was chosen as the solvent as it appeared to be far more efficient in terms of yields than DMF (solvent used in our previous study[6]). The more dissociating character of DMSO[10] certainly prevented Cu^{II} to associate with the CD secondary face[11] and thus improved their activity towards alkynyl derivatives. An excess alkynyl reactant (1.5 equiv.) with respect to the CD was also used to convert all the hydroxylated β-CD–N_3 and to avoid purification problems. After the addition of 3 equiv. sodium ascorbate the blue solution became orange-yellow. As the Cu^{I}-catalyzed triazole synthesis was somewhat sensitive to the steric environment of the azide,[12] a reaction time of 18 h was chosen to allow completion of the cycloaddition. Satisfyingly, after 18 h reaction time, the reaction was found to be clean as TLC analysis of the crude product only revealed three spots, two corresponding to the organic compounds (desired product and excess alkyne) and the third one to copper salts. The latter can be easily removed by addition of an ammoniac solution (8%) and subsequent chromatography on a silica gel column using water as eluent. The copper salts remained at the top of the column ($R_f = 0$), whereas the cycloaddition product easily migrated through the silica gel. Excess alkyne was also easily removed during the chromatographic purification. Depending on the nature of the alkyne, evaporation of water from the CD-containing fractions led to **12**–**15** in good yields (>61%). The compounds obtained were shown to be pure by MALDI-TOF/TOF mass spectrometry and ^1H and ^{13}C NMR spectroscopy. The four products were soluble in D_2O. Their ^1H NMR spectra revealed a characteristic peak at around 8 ppm, which was assigned to the triazole proton. On the other hand, as generally observed for substituted CDs, other signals were hardly exploitable due to overlapping and broadening. This suggests a modification of the conical β-CD structure leading to non-equivalent glucopyranose units. As a consequence, complete signal assignment was therefore difficult. By contrast, the ^{13}C NMR spectra were much more informative as distinct peaks could be detected. As an example, the carbon atoms adjacent to the triazole cycle were readily distinguished from the carbon atoms adjacent to the alkyne or azido groups. The purity of the compounds was fully established by mass spectra for which peaks were assigned with high confidence. Some of the mass spectra of the synthesized products are displayed in Figure 1.

A few modifications were required to access the hydroxylated dimeric derivatives **16**–**19** and hydroxylated trimeric species **20**–**22**. First, longer reaction times were required for trimers than for dimers (48 vs. 18 h) to achieve complete conversion of the di- or trialkyne linkers, probably because of the steric hindrance between the bulky CDs interfering with the formation of the terminal alkyne–Cu^{I} species.[13] Note that although trimers reacted over a longer period, yields could be high (87% for **20**), in contrast to those previously reported for hindered azides.[4] Secondly, to orient the reaction towards dimers or trimers, excess CD (1.33 equiv.) with respect to the alkynyl derivative was used. Consequently, at the end of the reaction, an additional purification step was necessary to remove excess mono-6-azido-β-CD. Addition of acetone to the reaction solution led to



Scheme 2. Synthesis of hydroxylated mono- and polytopic β-CD derivatives.

the precipitation of CDs. The solid was recrystallized in a water/acetone mixture and then purified as described above with an ammoniac solution. Compounds **16**–**22** were isolated as yellowish-white powders. Mass spectrometry confirmed the dimeric and trimeric nature of the products. NMR measurements also confirmed their polytopic character, in particular through a comparison of the integrations of CD protons with those of the spacers.

Synthesis of Mono- and Polytopic Randomly Methylated 1,2,3-Triazole-β-CD Derivatives

The reaction conditions were also optimised for randomly methylated CD precursors. In this case, the copper-catalyzed 1,3-dipolar cycloaddition proceeded at room temperature starting from an acetone solution containing stoichiometric amounts of alkynyl derivative, RAME-β-CD-N_3 and $CuSO_4{\cdot}xH_2O$. Addition of 2 equiv. sodium ascorbate led to a change of colour from blue to brown-red and finally to green-yellow at the end of the reaction (18 h reaction time). After evaporation of the solvent, the randomly methylated mono- or polytopic compounds were subjected to an ammoniac solution and purified by chromatography on a silica gel column. Evaporation of water gave **23**–**30** as yellowish-white powders in moderate-to-good yields (32–83%; Scheme 3).

Note that stoichiometric amounts of alkynes and CD were used because the randomly methylated products obtained and RAME-β-CD-N_3 were not easily separated by column chromatography. Complete conversion of RAME-β-CD-N_3 was therefore essential to avoid purification problems. The randomly methylated mono- and ditopic compounds could barely be characterized by their ^{1}H NMR spectra as the signals were even broader than those observed for hydroxylated β-CD derivatives because of the non-symmetric character of the partially methylated CDs. Conversely, the efficiency of the reaction was unambiguously proven by ^{13}C NMR and MALDI analysis, the latter

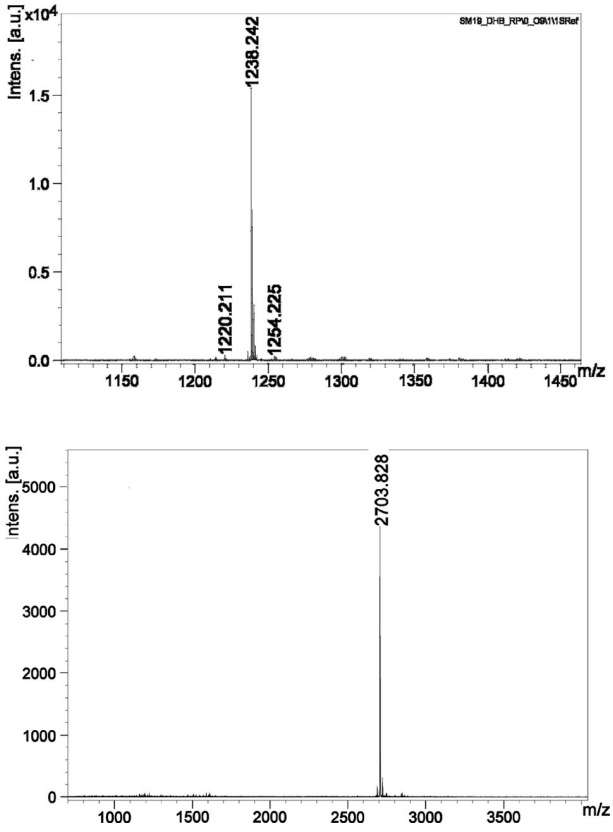


Figure 1. MALDI-TOF/TOF mass spectra of the hydroxylated 1,2,3-triazole β-CD derivatives **14** (top) and **19** (bottom).

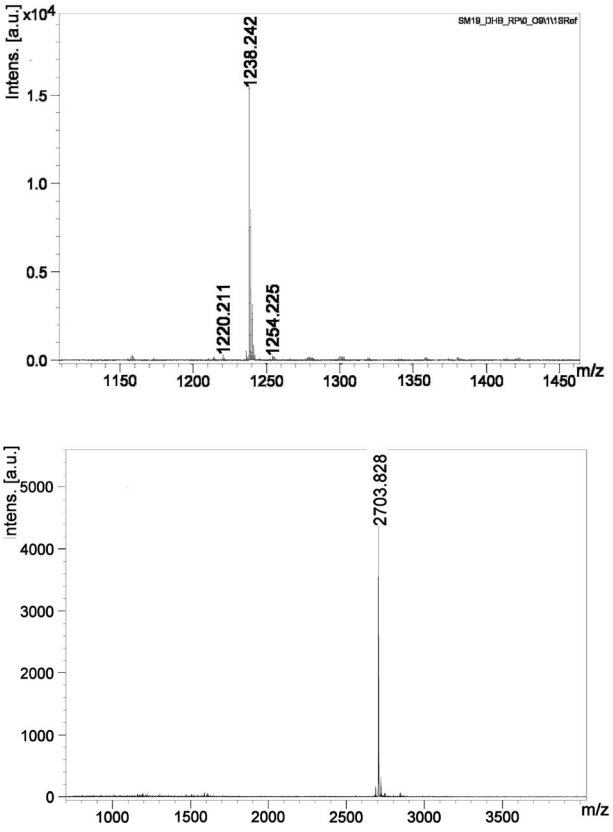
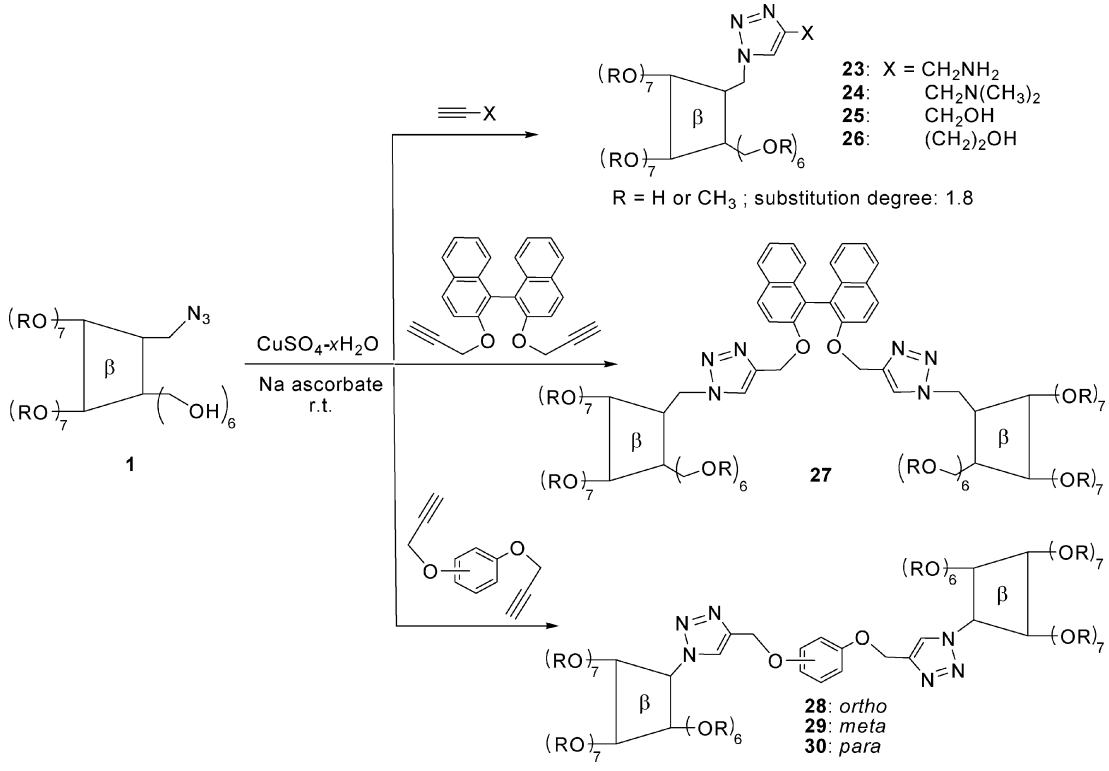


Figure 2. MALDI-TOF/TOF mass spectra of the randomly methylated 1,2,3-triazole-β-CD derivatives **25** (top) and **27** (bottom).



Scheme 3. Synthesis of randomly methylated mono- and polytopic β-CD derivatives.

showing a distribution of partially methylated β-CDs that was consistent with the assigned structures (Figure 2).

Conclusions

Highly efficient Cu^{I}-catalyzed cycloaddition was achieved starting from easily accessible β-CD azides and alkyl- or arylalkynyl precursors. Thus, significant structural diversity of β-CD derivatives was obtained through the formation of a stable 1,2,3-triazole linkage. Of particular interest was the synthesis of randomly methylated mono- and polytopic β-CDs, which were very soluble in water. The methodology is general, high-yielding for some of the synthesized compounds, proceeds under mild conditions and affords building blocks useful for organic and supramolecular chemistry. The potential of the synthesized compounds as mono- and polytopic β-CD hosts is presently under progress and shall be reported in due course.

Experimental Section

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 F254). Compounds were identified by using UV fluorescence and/or staining with a solution of phosphomolybdic acid in aqueous sulfuric acid and ethanol. NMR spectra were recorded with a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and at 75 MHz for ^{13}C nuclei. $CDCl_3$ (99.50% isotopic purity), [D_6]DMSO (99.80% isotopic purity) and D_2O (99.92% isotopic purity) were purchased from Euriso-Top. Mass spectra were recorded with a MALDI-TOF/TOF Bruker Daltonics Ultraflex II spectrometer in positive reflectron mode with 2,5-DHB as the matrix.

Randomly Methylated Mono-6-azido-6^{A}-deoxy-β-D-cyclodextrin (2): A concd. NaOH solution was added dropwise to a suspension of mono-6-azido-6^{A}-deoxy-β-D-cyclodextrin (20 g, 17 mmol) in water (50 mL) at 0 °C over a period of 20 min. A solution of dimethyl sulfate (90 mL, 950 mmol) in THF (15 mL) at 0 °C was then added dropwise to the resulting clear solution. Ethanol (10 mL) was added to the solution which was brought to room temperature and stirred for 18 h. After addition of an ammoniac solution (20%, 10 mL), THF was evaporated and the product was extracted from the aqueous phase with chloroform (3 × 500 mL). The organic phase was dried with anhydrous $MgSO_4$. Chloroform was removed under reduced pressure to give the product as a white powder (19.33 g, 85%). ^{1}H NMR (300 MHz, D_2O): δ = 5.14 (br. s, 3.7 H), 4.93 (br. s, 3.3 H), 3.83–3.62 (m, 12.2 H), 3.59–3.47 (m, 32.6 H), 3.44 (br. s, 15.4 H), 3.29–3.22 (m, 22.1 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 101.8–101.6, 99.5–99.3, 82.9–81.6, 79.1–78.6, 73.6–70.0, 61.6, 60.2–58.7, 51.6, 32.0, 29.3, 28.6, 25.6 ppm. MS: *m/z* (%) = 1322.40 (2.1) (calcd. 1322.48 for [$C_{52}H_{89}N_3O_{34}$ + Na]$^+$), 1336.41 (14.8) (calcd. 1336.49 for [$C_{53}H_{91}N_3O_{34}$ + Na]$^+$), 1350.41 (10.6) (calcd. 1350.50 for [$C_{54}H_{93}N_3O_{34}$ + Na]$^+$), 1364.45 (53.4) (calcd. 1364.51 for [$C_{55}H_{95}N_3O_{34}$ + Na]$^+$), 1378.47 (13.6) (calcd. 1378.52 for [$C_{56}H_{97}N_3O_{34}$ + Na]$^+$), 1392.54 (5.5) (calcd. 1392.53 for [$C_{57}H_{99}N_3O_{34}$ + Na]$^+$). Average DS: 1.8.

1,2,3-Tris(prop-2-ynyloxy)propane (7): A 60% NaH (461 mg, 19.2 mmol) oil dispersion was added to a solution of glycerol (589 mg, 6.40 mmol) in THF (15 mL) at 0 °C. The solution was vigorously stirred for 10 min. Propargyl bromide (4.57 g, 38.4 mmol) in toluene was added at 0 °C and the solution was brought to room temperature. The mixture was stirred for 5 h. Excess NaH was then neutralized by the slow addition of ice–water. The solution was concentrated and the product extracted from the aqueous phase with CH_2Cl_2 (3 × 500 mL). Once dried on $MgSO_4$, the crude product was subjected to chromatography on a silica gel column with CH_2Cl_2/hexane (90:10) as eluent. After evaporation of the solvent, the expected product was isolated as an orange oil (830 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.34 (d, *J* = 2.1 Hz, 2 H), 4.19 (d, *J* = 2.1 Hz, 4 H), 3.92 (m, 1 H), 3.67 (m, 4 H), 2.43 (br. s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 80.31, 79.87, 76.58, 75.08, 74.84, 70.02, 59.02, 57.94 ppm.

(±)-2,2′-Bis(prop-2-ynyloxy)-1,1′-binaphthalene (8): Yield 925 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 9 Hz, 2 H), 7.92 (d, *J* = 8.1 Hz, 2 H), 7.62 (d, *J* = 9 Hz, 2 H), 7.38 (t, *J* = 6.7 Hz, 2 H), 7.26 (t, *J* = 6.7 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 4.64 (s, 4 H), 2.43 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.6, 134.4, 130.2, 129.8, 128.4, 126.9, 126.0, 124.5, 121.0, 116.4, 79.7, 75.7, 57.66 ppm.

1,3,5-Tris(prop-2-ynyloxy)benzene (9): The title compound was synthesized following a procedure described in the literature[13] (634 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.27 (s, 3 H), 4.65 (d, *J* = 2.2 Hz, 6 H), 3.53 (t, *J* = 2.2 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.5, 95.5, 78.4, 75.9, 56.1 ppm.

1,3,5-Tris(prop-2-ynyloxymethyl)benzene (10): A 60% NaH (0.18 g, 4.51 mmol) oil dispersion was added to a solution of propargyl alcohol (0.25 g, 4.51 mmol) in DMF (15 mL) at 0 °C under nitrogen. After stirring for 10 min, tris-1,3,5-bromomethylbenzene (0.5 g, 1.4 mmol) was added and the resulting solution was stirred for 5 h at room temperature. After addition of ice to the reaction solution to neutralize the excess NaH and subsequent addition of CH_2Cl_2, the organic phase was recovered. The aqueous phase was washed with CH_2Cl_2 (20 mL). After decantation and separation, the organic phases were gathered, dried with anhydrous $MgSO_4$, filtered and concentrated. Purification by chromatography on a silica gel column gave the product as a colourless oil (316 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 3 H), 4.61 (s, 6 H), 4.19 (d, *J* = 2.3 Hz, 6 H), 2.47 (t, *J* = 2.3 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.0, 127.2, 79.6, 74.9, 57.4 ppm.

1,3,5-Tris[(but-3-ynyl)oxymethyl]benzene (11): A 60% NaH (0.18 g, 4.51 mmol) oil dispersion was added to a solution of butyn-1-ol (0.31 g, 4.50 mmol) in DMF (15 mL) at 0 °C under nitrogen. After stirring for 10 min, 1,3,5-tris(bromomethyl)benzene (0.50 g, 1.4 mmol) was added and the resulting solution stirred at room temperature. After stirring for 5 h, ice and CH_2Cl_2 were added to the solution. After decantation and separation, the organic phase was recovered. The aqueous phase was washed with CH_2Cl_2 (20 mL). The organic phases were collected, dried with anhydrous $MgSO_4$, filtered and concentrated. Purification by chromatography on a silica gel column (CH_2Cl_2) gave the product as a colourless oil (317 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (s, 3 H), 4.55 (s, 6 H), 3.60 (t, *J* = 6.9 Hz, 6 H), 2.51 (td, J_1 = 6.9, J_2 = 2.2 Hz, 6 H), 1.99 (br. s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.2, 126.5, 82.8, 72.8, 72.4, 68.9 ppm.

General Procedure for the Synthesis of Hydroxylated Monotopic β-CD Derivatives: Mono-6-azido-β-CD (3.3 mmol) and hydrated copper sulfate (2.8 mmol) was added to a solution of the alkynyl derivative (2.8 mmol) in DMSO (25 mL). After subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (5.6 mmol) dissolved in water, the solution was stirred for 18 h at

room temperature. After evaporation of the solvents, the crude product was dissolved in an ammoniac solution (8%) and stirred overnight before being purified by column chromatography on silica gel with water as eluent.

1-(6^A-Deoxy-β-D-cyclodextrin)-4-(aminomethyl)-1,2,3-triazole (12): Yield 2.44 g, 61%. ^{1}H NMR (300 MHz, D_2O): δ = 8.06 (s, 1 H), 4.96–4.82 (m, 8 H), 4.08 (m, 2 H), 3.91–3.71 (m, 28 H), 3.60–3.34 (m, 11 H), 3.01 (m, 1 H), 2.68 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 156.0, 127.3, 101.9, 81.4, 73.4, 73.2, 72.7, 63.3, 60.6 ppm. MS: *m*/*z* = 1237.27 (calcd. 1237.42 for $[C_{45}H_{74}N_4O_{34} + Na]^+$).

1-(6^A-Deoxy-β-D-cyclodextrin)-4-[(dimethylamino)methyl]-1,2,3-triazole (13): Yield 2.91 g, 71%. ^{1}H NMR (300 MHz, D_2O): δ = 8.21 (s, 1 H), 5.08 (m, 1 H), 4.96 (m, 8 H), 4.14 (m, 2 H), 3.88–3.68 (m, 26 H), 3.58–3.35 (m, 12 H), 3.09 (d, *J* = 11.7 Hz, 1 H), 2.78 (d overlapped with s, 7 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 136.9, 129.6, 102.2, 83.3, 73.4, 72.7, 71.8, 60.8, 42.5, 30.6 ppm. MS: *m*/*z* = 1265.30 (calcd. 1265.41 for $[C_{47}H_{78}N_4O_{34} + Na]^+$).

1-(6^A-Deoxy-β-D-cyclodextrin)-4-(hydroxymethyl)-1,2,3-triazole (14): Yield 3.21 g, 80%. ^{1}H NMR (300 MHz, D_2O): δ = 7.99 (s, 1 H), 5.36 (s, 1 H), 5.03 (m, 8 H), 4.60 (m, 1 H), 4.16 (m, 1 H), 3.94–3.71 (m, 26 H), 3.68–3.48 (m, 12 H), 3.11 (d, *J* = 13.5 Hz, 1 H), 2.77 (d, *J* = 13.5 Hz, 1 H), 2.78 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 147.2, 125.8, 102.2, 81.6, 73.4, 72.4, 72.2, 60.7, 60.6, 59.5 ppm. MS: *m*/*z* = 1238.24 (calcd. 1238.39 for $[C_{45}H_{73}N_3O_{35} + Na]^+$).

1-(6^A-Deoxy-β-D-cyclodextrin)-4-(2-hydroxyethyl)-1,2,3-triazole (15): Yield 3.16 g, 78%. ^{1}H NMR (300 MHz, D_2O): δ = 7.87 (s, 1 H), 5.17 (s, 1 H), 4.98 (m, 8 H), 4.58 (m, 1 H), 4.19 (m, 1 H), 4.03–3.78 (m, 26 H), 3.76–3.48 (m, 12 H), 3.15 (d, *J* = 12.2 Hz, 1 H), 2.94 (s, 2 H), 2.78 (d, *J* = 12.2 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 163.5, 126.4, 102.4, 81.6, 73.4, 72.4, 71.2, 60.7, 35.2, 28.2 ppm. MS: *m*/*z* = 1252.42 (calcd. 1229.42 for $C_{46}H_{75}N_3O_{35}$ $[M]^+$).

General Procedure for the Synthesis of Hydroxylated Polytopic β-CD Derivatives: Mono-6-azido-β-CD (1.3 mmol) and hydrated copper sulfate (1.1 mmol) were added to a solution of the alkynyl derivative (0.5 mmol alkynyl function) in DMSO (25 mL). After the subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (2.2 mmol) dissolved in water, the solution was stirred for 18 h at room temperature. Addition of acetone (100 mL) induced the precipitation of a yellowish-white powder that was recrystallized from a water/acetone mixture. The solid was recovered, dissolved in an ammoniac solution (8%) and stirred overnight before being purified by column chromatography using silica gel with water as eluent.

Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethyl] Ether (16): Yield 759 mg, 63%. ^{1}H NMR (300 MHz, D_2O): δ = 7.96 (s, 2 H), 5.1–4.8 (m, 18 H), 4.02 (m, 2 H), 3.83–3.63 (m, 56 H), 3.55–3.42 (m, 22 H), 3.03 (m, 2 H), 2.81 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 144.0, 127.1, 102.2, 101.8, 83.4, 81.6, 73.4, 42.4, 71.8, 60.6, 51.6 ppm. MS: *m*/*z* = 2435.62 (calcd. 2435.79 for $[C_{90}H_{144}N_6O_{69} + Na]^+$).

1,4-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-yl]benzene (17): Yield 782 mg, 64%. ^{1}H NMR (300 MHz, D_2O): δ = 6.41 (s, 2 H), 7.93 (s, 4 H), 5.20–4.86 (m, 28 H), 4.01–3.36 (m, 66 H), 3.06 (d, *J* = 11.2 Hz, 2 H), 2.82 (d, *J* = 11.2 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 158.33, 147.31, 130.00, 126.61, 102.34, 83.56, 81.21, 73.61, 72.37, 71.34, 60.57 ppm. MS: *m*/*z* = 2467.71 (calcd. 2467.79 for $[C_{94}H_{144}N_6O_{68} + Na]^+$).

1,3-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-yl]propane (18): Yield 687 mg, 57%. ^{1}H NMR (300 MHz, D_2O): δ = 7.80 (s, 2 H), 5.15–4.95 (m, 28 H), 4.00–3.48 (m, 66 H), 3.13 (d, *J* = 12.3 Hz, 2 H), 2.78 (m, 6 H), 2.03 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 146.3, 123.3, 102.2, 81.6, 73.1, 72.4, 72.3, 72.1, 71.8, 71.6, 60.0, 30.7 ppm. MS: *m*/*z* = 2433.66 (calcd. 2433.80 for $[C_{91}H_{146}N_6O_{68} + Na]^+$).

2,2′-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]-(±)-1,1′-binaphthalene (19): Yield 1.17 g, 87%. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 8.04 (d, *J* = 9.1 Hz, 2 H), 7.92 (d, *J* = 7.8 Hz, 2 H), 7.77 (d, *J* = 9.1 Hz, 2 H), 7.62 (s, 1 H), 7.48 (s, 1 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 7.19 (t, *J* = 7.8 Hz, 2 H), 6.84 (t, *J* = 7.2 Hz, 2 H), 5.85–5.67 (m, 28 H), 5.18–5.11 (m, 4 H), 4.99 (br. s, 2 H), 4.83 (br. s, 10 H), 4.72 (br. s, 4 H), 4.49 (br. s, 12 H), 4.30 (br. s, 2 H), 3.65–3.59 (m, 40 H), 3.50–3.00 (m, overlapped with residual H_2O) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 154.0, 153.4, 144.0, 133.7, 130.3, 130.2, 129.9, 127.0, 125.5, 125.0, 124.6, 121.8, 118.7, 102.4, 83.6, 73.6, 72.7, 71.9, 60.5, 30.6 ppm. MS: *m*/*z* = 2703.83 (calcd. 2703.87 for $[C_{110}H_{156}N_6O_{70} + Na]^+$).

1,2,3-Tris[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]-propane (20): Yield 1.60 g, 87%. ^{1}H NMR (300 MHz, D_2O): δ = 8.05 (s, 3 H), 5.18–4.97 (m, 21 H), 4.64 (s, 6 H), 4.19 (m, 3 H), 3.98–3.83 (m, 24 H), 3.70–3.50 (m, 38 H), 3.13 (d, *J* = 10.8 Hz, 3 H), 2.81 (d, *J* = 10.8 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 144.2, 127.0, 101.9, 83.4, 81.6, 73.4, 72.3, 71.8, 70.8, 59.5, 51.5, 30.6 ppm. MS: *m*/*z* = 3707.30 (calcd. 3707.21 for $[C_{138}H_{221}N_9O_{105} + Na]^+$).

1,3,5-Tris[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (21): Yield 893 mg, 48%. ^{1}H NMR (300 MHz, D_2O): δ = 8.15 (br. s, 3 H), 6.42 (br. s, 3 H), 5.22–4.96 (m, 48 H), 4.19–3.22 (m, 99 H), 3.18 (d, *J* = 9.3 Hz, 3 H), 2.85 (d, *J* = 9.3 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 160.83, 143.08, 126.87, 103.03, 82.39, 73.85, 73.60, 73.19, 72.90, 72.57, 72.52, 61.26, 56.88 ppm. MS: *m*/*z* = 3740.66 (calcd. 3741.20 for $[C_{141}H_{219}N_9O_{105} + Na]^+$).

1,3,5-Tris[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxymethyl]benzene (22): Yield 771 mg, 41%. ^{1}H NMR (300 MHz, D_2O): δ = 8.04 (s, 3 H), 7.35 (s, 3 H), 5.14–4.95 (m, 42 H), 4.70 (s, 6 H), 4.66 (s, 6 H), 4.18–3.15 (m, 99 H), 3.14 (d, *J* = 11.0 Hz, 3 H), 2.81 (d, *J* = 11.0 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, [D_6] DMSO): δ = 160.83, 143.08, 126.87, 103.03, 82.39, 73.85, 73.60, 73.19, 72.90, 72.57, 72.52, 61.26, 56.88 ppm. MS: *m*/*z* = 3783.01 (calcd. 3783.24 for $[C_{144}H_{225}N_9O_{105} + Na]^+$).

General Procedure for the Synthesis of Randomly Methylated Mono- and Ditopic β-CD Derivatives: Randomly methylated mono-6-azido-6^A-deoxy-β-D-cyclodextrin (0.6 mmol) and hydrated copper sulfate (0.7 mmol) were added to a solution of the alkynyl precursor (0.7 mmol alkynyl function) in acetone (30 mL). After the subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (1.4 mmol) dissolved in water (3 mL) the solution was stirred for 18 h at room temperature. After evaporation of the solvent the crude product was dissolved in an ammoniac solution (8%) and stirred overnight before being purified by column chromatography on silica gel with water as eluent to give the product as a white powder.

Randomly Methylated 1-(6^A-Deoxy-β-D-cyclodextrin)-4-(aminomethyl)-1,2,3-triazole (23): Yield 300 mg, 36%. ^{1}H NMR (300 MHz, D_2O): δ = 8.10 (s, 1 H), 5.20–5.00 (m, 3.8 H), 5.00–4.80 (m, overlapped with D_2O), 4.32–4.18 (m, 8.2 H), 3.91–3.74 (m, 18.9 H), 3.58–3.27 (m, 34.2 H), 3.09 (br. s, 17.3 H), 3.00–2.88 (m, 12.2 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 146.2, 119.9, 118.4, 101.1–99.8, 83.0–81.6, 73.1–70.6, 86.4, 63.2, 59.2–58.5, 30.8 ppm. MS: *m*/*z* (%) = 1405.53 (7.0) (calcd. 1405.54 for $[C_{57}H_{98}N_4O_{34}$ +

Na]$^+$), 1419.54 (52.9) (calcd. 1419.55 for [$C_{58}H_{100}N_4O_{34}$ + Na]$^+$), 1433.55 (17.1) (calcd. 1433.56 for [$C_{59}H_{102}N_4O_{34}$ + Na]$^+$), 1447.55 (13.1) (calcd. 1447.57 for [$C_{60}H_{104}N_4O_{34}$ + Na]$^+$), 1461.56 (9.9) (calcd. 1461.58 for [$C_{61}H_{106}N_4O_{34}$ + Na]$^+$).

Randomly Methylated 1-(6^A-Deoxy-β-D-cyclodextrin)-4-[(dimethylamino)methyl]-1,2,3-triazole (24): Yield 707 mg, 83%. ^{1}H NMR (300 MHz, D_2O): δ = 8.27 (s, 1 H), 5.19 (m, 4.9 H), 4.98 (m, 50 H), 4.44 (m, 2.1 H), 4.13 (m, 3.1 H), 3.98–3.88 (m, 13.1 H), 3.68–3.53 (m, 43.9 H), 3.47–3.29 (m, 17.9 H), 2.82 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 137.4, 135.2, 112.8, 101.4–99.8, 99.0–97.4, 82.7–81.6, 78.5, 73.4, 73.3, 73.1, 72.6, 72.3, 72.2, 70.9, 70.3, 64.4–59.4, 42.4, 30.2, 20.2, 19.7 ppm. MS: *m*/*z* (%) = 1433.51 (11.6) (calcd. 1433.57 for [$C_{59}H_{102}N_4O_{34}$ + Na]$^+$), 1447.53 (69.9) (calcd. 1447.58 for [$C_{60}H_{104}N_4O_{34}$ + Na]$^+$), 1461.55 (16.1) (calcd. 1461.59 for [$C_{61}H_{106}N_4O_{34}$ + Na]$^+$), 1477.05 (2.3) (calcd. 1475.6 for [$C_{62}H_{108}N_4O_{34}$ + Na]$^+$).

Randomly Methylated 1-(6^A-Deoxy-β-D-cyclodextrin)-4-(hydroxymethyl)-1,2,3-triazole (25): Yield 652 mg, 78%. ^{1}H NMR (300 MHz, D_2O): δ = 7.99 (s, 1 H), 5.19 (m, 4.7 H), 5.10 (m, 4.1 H), 4.67 (m, 2 H overlapped with H_2O), 4.32 (m, 2.1 H), 4.00–3.93 (m, 12.3 H), 3.92–3.47 (m, 32.4 H), 3.17 (br. s, 16 H), 3.20–3.09 (m, 14.6 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 138.6, 126.5, 121.2, 121.0, 101.2–99.7, 82.2–81.3, 73.5–70.9, 64.3, 63.5, 60.2–58.8, 54.9, 30.6 ppm. MS: *m*/*z* (%) = 1406.48 (14.4) (calcd. 1406.52 for [$C_{57}H_{97}N_3O_{35}$ + Na]$^+$), 1420.52 (59.7) (calcd. 1420.53 for [$C_{58}H_{99}N_3O_{35}$ + Na]$^+$), 1434.54 (24.7) (calcd. 1434.54 for [$C_{59}H_{101}N_3O_{35}$ + Na]$^+$), 1448.55 (1.2) (calcd. 1448.55 for [$C_{60}H_{103}N_3O_{35}$ + Na]$^+$).

Randomly Methylated 1-(6^A-Dexoy-β-D-cyclodextrin)-4-(2-hydroxyethyl)-1,2,3-triazole (26): Yield 600 mg, 71%. ^{1}H NMR (300 MHz, D_2O): δ = 7.81 (s, 1 H), 5.16–5.14 (m, 3.6 H), 5.04–4.92 (m, 4.3 H), 4.43 (m, 4.1 H), 4.09 (m, 4.5 H), 3.95–3.84 (m, 17.2 H), 3.78–3.59 (m, 32.6 H), 3.27 (m, 19.1 H), 3.20–3.12 (m, 8.5 H), 2.85 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 168.1, 166.6, 125.6, 125.4, 101.0, 99.3, 82.3–81.4, 80.8–73.2, 72.8–70.9, 64.4, 63.6, 63.2, 62.6, 60.9, 59.5, 58.8, 58.7, 58.6, 28.3 ppm. MS: *m*/*z* (%) = 1420.75 (15.4) (calcd. 1420.54 for [$C_{58}H_{99}N_3O_{35}$ + Na]$^+$), 1434.79 (55.2) (calcd. 1434.55 for [$C_{59}H_{101}N_3O_{35}$ + Na]$^+$), 1448.81 (23.3) (calcd. 1448.86 for [$C_{60}H_{103}N_3O_{35}$ + Na]$^+$), 1462.81 (6.2) (calcd. 1462.57 for [$C_{61}H_{105}N_3O_{35}$ + Na]$^+$).

Randomly Methylated (±)-2,2′-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]-1,1′-binaphthalene (27): Yield 1.02 g, 48%. ^{1}H NMR (300 MHz, D_2O): δ = 8.11 (m, 2 H), 8.09 (m, 2 H), 8.01–7.92 (m, 4 H), 7.43 (m, 2 H), 7.39–7.00 (m, 4 H), 5.18–4.92 (m, 24 H overlapped with H_2O), 4.32–4.13 (m, 10.2 H), 3.90–3.80 (m, 28 H), 3.71–3.52 (m, 70 H), 3.29–2.83 (m, 43 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 166.6–165.9, 142.3, 130.8, 128.4, 125.2, 101.4–99.8, 99.5–98.6, 81.6–80.9, 73.4–70.8, 64.4, 63.6, 63.2, 60.1–58.6, 30.8 ppm. MS: *m*/*z* (%) = 3054.22 (11.7) (calcd. 3031.13 for [$C_{135}H_{206}N_6O_{70}$ + Na]$^+$), 3068.26 (51.6) (calcd. 3045.14 for [$C_{136}H_{208}N_6O_{70}$ + Na]$^+$), 3082.27 (27.6) (calcd. 3059.15 for [$C_{137}H_{210}N_6O_{70}$ + Na]$^+$), 3096.28 (6.7) (calcd. 3073.16 for [$C_{138}H_{212}N_6O_{70}$ + Na]$^+$), 3110.21 (2.4) (calcd. 3087.17 for [$C_{139}H_{214}N_6O_{70}$ + Na]$^+$).

Randomly Methylated 1,2-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (28): Yield 740 mg, 37%. ^{1}H NMR (300 MHz, D_2O): δ = 7.81 (s, 2 H), 6.91 (m, 4 H), 5.23–4.93 (m, 16.3 H), 3.84–3.49 (m, 75.6 H), 3.39–3.04 (m, 80.8 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 159.8, 146.4, 146.0, 143.5, 102.1, 100.3, 81.6–80.8, 73.9, 73.2, 72.9, 61.8–59.3, 38.6 ppm. MS: *m*/*z* = 2877.89 (18.3) (calcd. 2878.07 for [$C_{121}H_{198}N_6O_{70}$ + Na]$^+$), 2891.63 (55.2) (calcd. 2892.08 for [$C_{122}H_{200}N_6O_{70}$ + Na]$^+$), 2906.01 (21.9) (calcd. 2906.09 for [$C_{123}H_{202}N_6O_{70}$ + Na]$^+$), 2919.93 (4.6) (calcd. 2920.10 for [$C_{124}H_{204}N_6O_{70}$ + Na]$^+$).

Randomly Methylated 1,3-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (29): Yield 640 mg, 32%. ^{1}H NMR (300 MHz, D_2O): δ = 7.78 (br. s, 2 H), 7.21 (m, 2 H), 6.64 (m, 2 H), 5.15–4.46 (m, 12.2 H), 4.10–4.08 (m, 5.9 H), 3.96–3.84 (m, 36.9 H), 3.68–3.44 (m, 74.8 H), 3.44–3.28 (m, 35.8 H), 2.88 (m, 14.8 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 160.1, 142.0–141.8, 122.1–121.9, 101.5–99.6, 81.7–80.9, 73.2–71.0, 70.9, 70.8, 70.6, 70.4, 64.4, 63.2, 63.3–58.5, 39.1 ppm. MS: *m*/*z* (%) = 2878.14 (13.0) (calcd. 2878.07 for [$C_{121}H_{198}N_6O_{70}$ + Na]$^+$), 2892.18 (52.8) (calcd. 2892.08 for [$C_{122}H_{200}N_6O_{70}$ + Na]$^+$), 2906.18 (27.1) (calcd. 2906.09 for [$C_{123}H_{202}N_6O_{70}$ + Na]$^+$), 2920.20 (4.9) (calcd. 2920.10 for [$C_{124}H_{204}N_6O_{70}$ + Na]$^+$), 2934.17 (2.1) (calcd. 2934.11 for [$C_{125}H_{206}N_6O_{70}$ + Na]$^+$).

Randomly Methylated 1,4-Bis[1-(6^A-deoxy-β-D-cyclodextrin)-1,2,3-triazol-4-ylmethoxy]benzene (30): Yield 761 mg, 38%. ^{1}H NMR (300 MHz, D_2O): δ = 7.81 (s, 2 H), 7.00–6.80 (m, 4 H), 5.21–5.04 (m, 10.9 H), 5.00–7.89 (m, overlapped with H_2O), 4.44–4.36 (m, 9.4 H), 4.25–4.14 (m, 9.3 H), 3.75–3.40 (m, 110.8 H), 3.28–3.25 (m, 24.1 H), 2.88 (m, 11.6 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 156.2, 155.3, 122.2–121.8, 118.3, 82.0–81.4, 73.3–71.0, 70.9–70.7, 70.4, 64.8, 64.2, 63.4–59.1, 40.2 ppm. MS: *m*/*z* (%) = 2849.71 (0.9) (calcd. 2850.05 for [$C_{119}H_{194}N_6O_{70}$ + Na]$^+$), 2863.73 (5.3) (calcd. 2864.06 for [$C_{120}H_{196}N_6O_{70}$ + Na]$^+$), 2877.75 (22.9) (calcd. 2878.07 for [$C_{121}H_{198}N_6O_{70}$ + Na]$^+$), 2892.17 (45.9) (calcd. 2892.08 for [$C_{122}H_{200}N_6O_{70}$ + Na]$^+$), 2905.78 (19.9) (calcd. 2906.09 for [$C_{123}H_{202}N_6O_{70}$ + Na]$^+$), 2919.79 (4.0) (calcd. 2920.10 for [$C_{124}H_{204}N_6O_{70}$ + Na]$^+$), 2931.72 (1.1) (calcd. 2934.11 for [$C_{125}H_{206}N_6O_{70}$ + Na]$^+$).

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[1] a) M. Komiyama, E. Monflier in *Cyclodextrins and Their Complexes: Chemistry, Analytical Methods, Applications* (Ed.: H. Dodziuk), Wiley-VCH, Weinheim, **2006**, pp. 93–105; b) F. Hapiot, S. Tilloy, E. Monflier, *Chem. Rev.* **2006**, *106*, 767–781.

[2] See, for example: a) R. Breslow, N. Greenspoon, T. Guo, R. Zarzycki, *J. Am. Chem. Soc.* **1989**, *111*, 8296–8297; b) R. Breslow, S. Halfon, B. Zhang, *Tetrahedron* **1995**, *51*, 377–388; c) F. Sallas, J. Kovacs, I. Pinter, L. Jicsinszky, A. Marsura, *Tetrahedron Lett.* **1996**, *37*, 4011–4014; d) Y. Okabe, H. Yamamura, K. Obe, K. Ohta, M. Kawai, K. Fujita, *J. Chem. Soc., Chem. Commun.* **1995**, *111*, 581–582; e) R. Deschenaux, T. Ruch, P.-F. Deschenaux, A. Juris, R. Ziessel, *Helv. Chim. Acta* **1995**, *78*, 619–628; f) M.-M. Luo, R.-G. Xie, D.-Q. Yuan, W. Lu, P.-F. Xia, H.-M. Zhao, *Chin. J. Chem.* **1999**, *17*, 384–385; g) D. K. Leung, J. H. Atkins, R. Breslow, *Tetrahedron Lett.* **2001**, *42*, 6255–6258; h) S. Menuel, J.-P. Joly, B. Courcot, J. Elysée, N.-E. Ghermani, A. Marsura, *Tetrahedron* **2007**, *63*, 1706–1714; i) D. T. Pham, P. Clements, C. J. Easton, J. Papageorgiou, B. L. Maya, S. F. Lincoln, *New J. Chem.* **2008**, *32*, 712–718.

[3] L. Liu, Y. Chen, *Acc. Chem. Res.* **2006**, *39*, 681–691.

[4] M. Luo, W. Chen, D. Yuan, R. Xie, *Synth. Commun.* **1998**, *28*, 3845–3848.

[5] See, for example: a) H. Bricout, L. Caron, E. Monflier, *Catal. Today* **2001**, *66*, 355–361; b) J. Cabou, H. Bricout, F. Hapiot,

E. Monflier, *Catal. Commun.* **2004**, *5*, 265–270; c) C. Torque, H. Bricout, F. Hapiot, E. Monflier, *Tetrahedron* **2004**, *60*, 6487–6493; d) L. Leclercq, F. Hapiot, S. Tilloy, K. Ramkisoensing, J. N. H. Reek, P. W. N. M. van Leeuwen, E. Monflier, *Organometallics* **2005**, *24*, 2070–2075; e) C. Torque, B. Sueur, J. Cabou, H. Bricout, F. Hapiot, E. Monflier, *Tetrahedron* **2005**, *61*, 4811–4817; f) A. Nowicki, Y. Zhang, B. Léger, J. P. Rolland, H. Bricout, E. Monflier, A. Roucoux, *Chem. Commun.* **2006**, 296–298; g) A. Cassez, A. Ponchel, F. Hapiot, E. Monflier, *Org. Lett.* **2006**, *8*, 4823–4826; h) D. Kirschner, T. Green, F. Hapiot, S. Tilloy, L. Leclercq, H. Bricout, E. Monflier, *Adv. Synth. Catal.* **2006**, *348*, 379–386; i) M. Ferreira, H. Bricout, A. Sayede, A. Ponchel, S. Fourmentin, S. Tilloy, E. Monflier, *Adv. Synth. Catal.* **2008**, *350*, 609–618.

[6] M. Mourer, F. Hapiot, E. Monflier, S. Menuel, *Tetrahedron* **2008**, *64*, 7159–7163; for other examples of cyclodextrins modified by click chemistry, see: a) O. David, S. Maisonneuve, J. Xie, *Tetrahedron Lett.* **2007**, *48*, 6527–6530; b) Y. Liu, C.-F. Ke, H.-Y. Zhang, J. Cui, F. Ding, *J. Am. Chem. Soc.* **2008**, *130*, 600–605; c) S. Amajjahe, S. Choi, M. Munteanu, H. Ritter, *Angew. Chem. Int. Ed.* **2008**, *47*, 3435–3437; d) R. Hoogenboom, B. C. Moore, U. S. Schubert, *Chem. Commun.* **2006**, 4010–4012; e) Y. Liu, Z.-X. Yang, Y. Chen, *J. Org. Chem.* **2008**, *73*, 5298–5304.

[7] F. Hapiot, L. Leclercq, N. Azaroual, S. Fourmentin, S. Tilloy, E. Monflier, *Curr. Org. Synth.* **2008**, *5*, 162–172.

[8] L. D. Melton, K. N. Slessor, *Carbohyd. Res.* **1971**, *18*, 29–37.

[9] L. Leclercq, H. Bricout, S. Tilloy, E. Monflier, *J. Colloid Interface Sci.* **2007**, *307*, 481–487.

[10] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**, p.140.

[11] J. Defaye, S. Crouzy, N. Evrard, H. Law, *PCT Int. Appl.*, WO 9961483, CAN 132:24077 **1999**.

[12] A. K. Feldman, B. Colasson, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 13444–13445.

[13] D. K. Leung, J. H. Atkins, R. Breslow, *Tetrahedron Lett.* **2001**, *42*, 6255–6258.

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