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Synthesis of β-cyclodextrin derivatives functionalized with azobenzene

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ABSTRACT

Two approaches for the synthesis of β-cyclodextrin and bis(β-cyclodextrin) bearing azobenzene on the primary face are reported. First, the nucleophilic substitution of mono-6-tosyl-β-cyclodextrin by azobenzene anion derivatives was reinvestigated and found to produce mono-3,6-anhydro-β-cyclodextrin as a side product. A slight modification of the reported reaction conditions including the use of Cs_2CO_3 led to a substantial improvement of the yields. In addition, a convenient method based on the application of click chemistry led to 1,2,3-triazole-linked azobenzene–cyclodextrin derivatives in good yields.

1. Introduction

β-Cyclodextrin (β-CD) is a naturally occurring cyclic oligosaccharide comprising seven D-glucopyranose units linked by α-(1→4) bonds. Its relatively rigid thorus-shaped structure defines an inner hydrophobic cavity rimmed by two hydrophilic openings (Chart 1). As a consequence, β-CD is well-known to form inclusion complexes in aqueous solution with a large variety of organic molecules of hydrophobic nature and suitable size and geometry.[1] In addition to other applications, this feature has been explored for the design and construction of molecular machines in which the inclusion of the guest molecule can be controlled through external stimuli.[2] One of the strategies followed to reach this goal has been the conjugation of β-CD with a chemical group sensitive to pH variations,[3] metallic cations,[4] electrochemical signals[5] or irradiation with light.[6] Among the photosensitive groups, azobenzene has received much attention in recent years due to its easy and reversible cis–trans isomerization.[7] Azobenzene derivatives undergo trans to cis isomerization upon irradiation with UV light and isomerize back to trans with visible light exposure or simply in the dark. Such remarkable behaviour makes azobenzene a good building block for the preparation of photoswitchable molecular receptors by conjugation with molecules involved in molecular recognition processes.

As a part of a project that involved β-CD-based photoswitchable receptors, we turned our attention to the synthesis of azobenzene-containing β-CD derivatives.[8] Herein, we wish to report our studies for the synthesis of β-CD and bis(β-CD) bearing azobenzene on the primary face. We have reinvestigated the nucleophilic substitution of mono-6-tosyl-β-CD by azobenzene anion derivatives. As an alternative approach, we have applied click chemistry to access to the target compounds.

2. Results and discussion

In order to synthesize β-CD and bis(β-CD) bearing azobenzene on the primary face, we first investigated the O-alkylation of azobenzene derivatives **2** and **3** using mono-6-tosyl-β-CD **1** as electrophile (Scheme 1). This approach has been used before for the synthesis of β-CD derivatives **4**[8n] and **6**.[8o] However, while the monomacrocyclic derivative **4** was reported to have been obtained in 78% yield, azobenzene-linked face-to-face 6–6′ β-CD dimer **6** was prepared in 2.3% yield. Such poor yields achieved by the latter reaction attracted our attention and led us to investigate such synthetic approach in more detail. First, we carried out the reaction of **1**

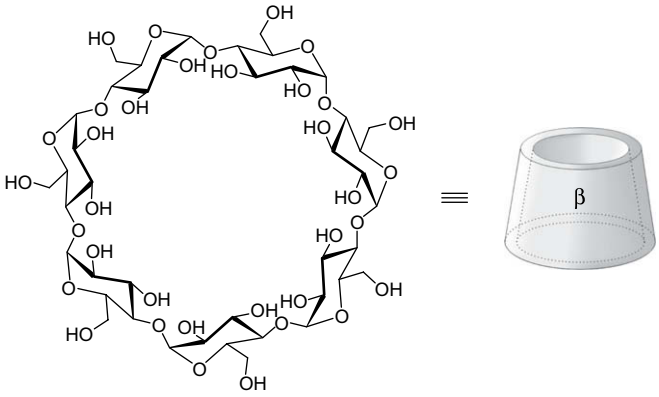

Chart 1. Schematic representation of β-CD.

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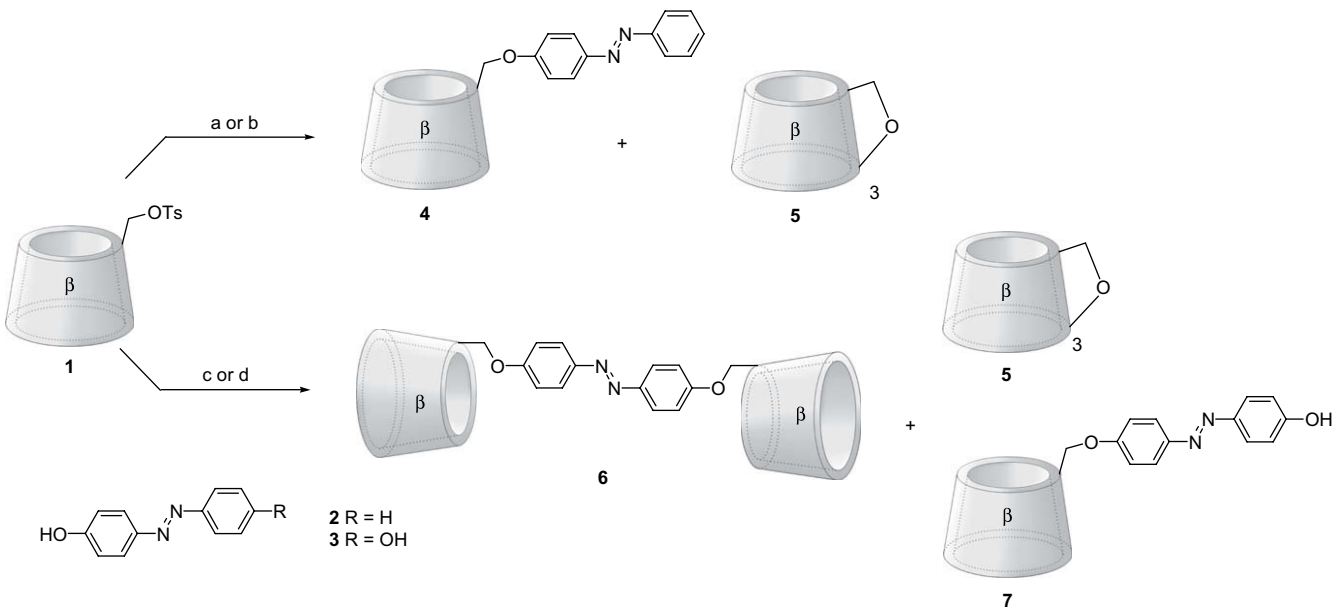


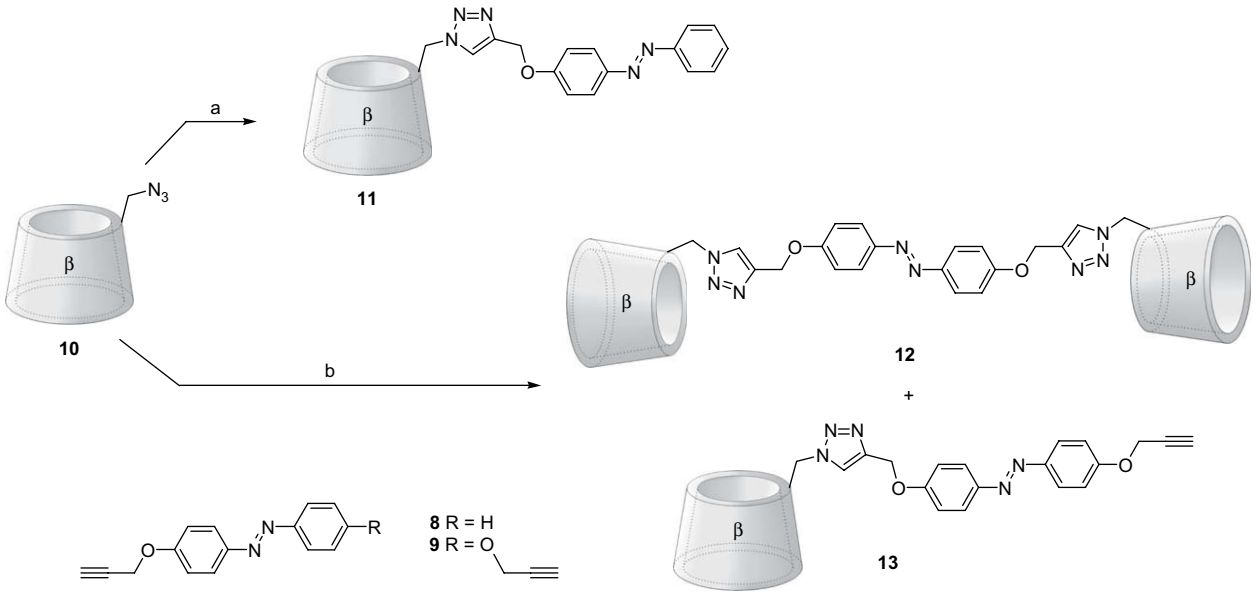
Scheme 1. Synthesis of β-CD derivatives **4** and **6**. Reagents and conditions: (a) **2** (1.3 equiv), K_2CO_3 (1 equiv), DMF, 90 °C, 24 h: **4** (39%), **5** (55%); (b) **2** (0.8 equiv), Cs_2CO_3 (0.8 equiv), DMF, 90 °C, 24 h: **4** (61%), **5** (38%); (c) **3** (0.45 equiv), Cs_2CO_3 (1.15 equiv), DMF, 90 °C, 24 h: **5** (33% referred to **1**), **6** (40%), **7** (53%); (d) **3** (0.37 equiv), Cs_2CO_3 (1.15 equiv), DMF, 90 °C, 24 h: **5** (49% referred to **1**), **6** (41%), **7** (56%).

with **2** by treatment with K_2CO_3 in DMF at 90 °C, as described in the literature.[8n] Precipitation of crude product from acetone gave a yellowish orange solid in, apparently, 78% yield, as found by the authors. Despite that the recorded ^{1}H NMR spectrum of the solid was similar to that described, we observed that TLC (2:1 CH_3CN–H_2O) showed two spots (R_f=0 and 0.32), indicating the possible formation of at least two products. As is well-known, the treatment of 6-tosyl-β-CDs in basic conditions leads to 3,6-anhydro-β-CD derivatives.[9] As β-CD derivative **5** is soluble in water, we subjected the isolated solid to a Soxhlet extraction, first using acetone to remove the rest of **2** that did not react, followed by using water. The remaining orange residue showed on TLC only one spot (R_f=0 in 2:1 CH_3CN–H_2O), and both NMR and MALDI-TOF MS data were in agreement with the structure of **4**. Azobenzene-β-CD **4** was then isolated in 39% yield. Remarkably, the NMR spectrum of **4** looked very much like the one recorded before the workup. The water extract was lyophilized and the solid residue was purified by flash column chromatography to provide **5** as a white solid in 55% yield. Both the MALDI-TOF MS and the ^{1}H NMR spectra[9a,b] confirmed the structure of compound **5**, the former showing a single peak at *m*/*z* 1139.4 ($[M+Na]^+$). In an attempt to improve the reaction yield, we slightly modified the reaction conditions by using Cs_2CO_3 as a base, to introduce a softer cation, and a slight excess of 6-tosyl-β-CD **1** (1.2 equiv). Under the new conditions, azobenzene-β-CD **4** was isolated in 61% yield (51% yield if referred to **1**). Mono-3,6-anhydro-β-CD **5** was also isolated in 38% yield.

In light of these results, we then investigated the synthesis of azobenzene-bridge bis(β-CD) **6**. Thus, we performed the reaction of 2.2 equiv of monotosyl-β-CD **1** with 4,4′-dihydroxyazobenzene (**3**) in DMF at 90 °C, in the presence of Cs_2CO_3 (Scheme 1). The TLC (2:1 CH_3CN–H_2O) of the reaction mixture showed three spots at R_f=0.25, 0.32 and 0.49, later assigned to dimer **6**, mono-3,6-anhydro-β-CD **5**, and mono-hydroxyazobenzene-β-CD derivative **7**, respectively. The reaction mixture was separated by silica gel column chromatography allowing the isolation of compounds **6** and **7** in 40% and 53% yield, respectively, as well as mono-3,6-anhydro-β-CD **5**, as a result of a 33% conversion of starting compound **1.** Further attempts to improve the yields by changing the amounts of the starting material were unsuccessful. Both NMR and MALDI-TOF MS techniques were used for the characterization of the compounds.

In order to circumvent the problem of side products formation in the nucleophilic substitution reaction at C-6 of β-CD, we explored further approaches. In particular, we turned to the application of the Cu(I)-catalyzed azide-alkyne Huisgen [3+2] cycloaddition.[10] This so-called click chemistry reaction has shown to be highly efficient for coupling molecules, fully compatible with the presence of hydroxyl groups. Thus, first, azobenzene derivatives **2** and **3** were converted into the *O*-propargyl derivatives **8** and **9**. While the necessary counterpart azide function on the primary face of β-CD was provided by mono-6-azido-β-CD **10** (Scheme 2). The coupling reactions were performed in DMF at 100 °C with catalytic amounts of $(EtO)_3P{\cdot}CuI$ and generated the azobenzene-linked β-CD derivatives **11** and **12** in 74% and 72% yield, respectively. Nevertheless, the reaction of azido-β-CD **10** and azobenzene derivative **9** also gave the mono-coupled β-CD derivative **13** as a side product in 28% yield.

MALDI-TOF MS spectra for β-CD derivatives **11**–**13** showed peaks at *m*/*z* 1418.5, 2632.9 and 1472.5, respectively, that correspond to ion $[M+Na]^+$. In addition, azobenzene β-CD derivatives **11** and **12** were characterized by NMR spectroscopic techniques with COSY, HMQC and HMBC experiments. Although ^{1}H NMR spectra revealed that the azobenzene had been successfully added to the macrocycle (downfield aromatic and triazole H-5 proton peaks appear, for example), the spectra were broadened and overlapped. The ^{13}C NMR signal for the anomeric carbons of the two β-CD derivatives **11** and **12** appeared at similar chemical shifts 102.2–101.2 ppm. The presence of the azobenzene group was revealed by the NMR carbon signals between 160 and 115 ppm. The resonances attributable to triazole ring C-4 and C-5 both show distinctive downfield shifts (142.1 and 125.6 ppm,



Scheme 2. Synthesis of β-CD derivatives **11** and **12**. Reagents and conditions: (a) **8**, $(EtO)_3P{\cdot}CuI$, DMF, 100 °C, 2 h, 74%; (b) **9**, $(EtO)_3P{\cdot}CuI$, DMF, 100 °C, 4 h: **12** (72%), **13** (28%).

respectively) upon conversion of the azide substituent to the triazole ring.

3. Conclusion

In conclusion, we have investigated two approaches for the synthesis of β-CD and bis(β-CD) bearing azobenzene on the primary face. In the first approach, the nucleophilic substitution of mono-6-tosyl-β-CD by azobenzene anion derivatives was reinvestigated and found to produce mono-3,6-anhydro-β-CD as a side product. A slight modification of the reaction conditions including the use of Cs_2CO_3 led to a substantial improvement of the yields. The second approach involved the application of click chemistry and resulted in a convenient way to access to 1,2,3-triazole-linked azobenzene–cyclodextrin compounds in good yields.

4. Experimental

4.1. General

TLC was performed on Merck silica gel 60 F_{254} aluminium sheets and developed by UV light and ethanolic sulfuric acid (5% v/v). Flash column chromatography was performed on Merck silica gel (230–400 mesh, ASTM). Melting points were measured on a Büchi B-450 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1030 polarimeter at room temperature. ^1H and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz Bruker Avance DPX spectrometers. Chemical shifts are given in parts per million and referenced to internal TMS (δ_H, δ_C 0.00). *J* values are given in hertz. DEPT135, COSY, HMQC and HMBC experiments were used for unequivocal assignment. MALDI-TOF mass spectra were recorded using α-cyano-4-hydroxycinnamic acid or 2,5-dihydroxybenzoic acid (DHB) as matrices. HRMS FAB mass spectra were recorded using 1-thioglycerol as matrix. β-CD was dried at 50 °C in vacuum in the presence of P_2O_5 until constant weight. Other reagents were used as purchased without further purification. 6^I-*O*-Tosylcyclomaltoheptaose (**1**),[11] 4,4′-dihydroxyazobenzene (**3**),[12] (6^I-azido-6^I-deoxy)cyclomaltoheptaose[13] (**10**) and $(EtO)_3P{\cdot}CuI$[14] were prepared as reported. Solvents were dried according to the literature procedures.[15]

4.2. Synthesis of β-CD derivatives 4 and 6

*4.2.1. Synthesis of {6^I-O-[4-(phenylazo)phenyl]} cyclomaltoheptaose (**4**)*

4.2.1.1. Procedure A. The reaction of **1** (300 mg, 0.233 mmol) with **2** (48 mg, 0.245 mmol) and K_2CO_3 (31 mg, 0.233 mmol) was performed as reported.[8n] The solid obtained after precipitation with acetone and filtration was then extracted (Soxhlet) with acetone (24 h) and water (24 h). Aqueous extract was cooled and the resulting precipitate was filtered off to give a solid that was joined to the main solid residue to yield **4** (120 mg, 39%) as an orange solid. Mp 304 °C dec; $[\alpha]_D$ +115 (*c* 0.25, DMSO); IR (KBr) 3377, 2923, 1636, 1500, 1252, 1155, 1078, 1054, 1028 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.86 (t, 4H, ^3J=8.7 Hz, H-$2'^{az}$,3^{az}), 7.60–7.52 (m, 3H, H-$3'^{az}$,$4'^{az}$), 7.15 (d, 2H, ^3J=8.8 Hz, H-2^{az}), 5.80–5.68 (m, 14H, OH), 4.91 (d, 1H, $^3J_{1,2}$=3.2 Hz, H-1^I), 4.86–4.83 (m, 6H, H-$1^{II–VII}$), 4.51–4.40 (m, 6H, OH), 4.32 (br s, 2H, H-6^I,$6'^I$), 4.03–4.00 (m, 1H, H-5^I), 3.74–3.55 (m, 29H), 3.48–3.32 (m, overlapped with HDO); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5 (C-1^{az}), 152.0 (C-$1'^{az}$), 146.1 (C-4^{az}), 130.8 (C-$4'^{az}$), 129.4 (C-$3'^{az}$), 124.5 (C-3^{az}), 122.2 (C-$2'^{az}$), 115.1 (C-2^{az}), 102.4–101.8 (C-$1^{I–VII}$), 82.2–81.6 (C-$4^{I–VII}$), 73.2–72.0 (C-$2^{I–VII}$,$3^{I–VII}$,$5^{II–VII}$), 69.5 (C-5^I), 67.4 (C-6^I), 59.9 (C-$6^{II–VII}$); MALDI-TOF-MS *m*/*z* calcd for $C_{54}H_{78}O_{35}N_2$ 1314.4, found 1225.5 $(M-C_6H_5N)^+$, 1315.5 $(M+H)^+$, 1337.5 $(M+Na)^+$. After filtration, the aqueous fraction was lyophilized and purified by column chromatography (CH_3CN–H_2O–NH_4OH 10:5:0.5) to yield **5** (143 mg, 55%) as a white solid. NMR data were in agreement with the literature;[9a,b] MALDI-TOF-MS *m*/*z* calcd for $C_{42}H_{68}O_{34}$ 1116.4, found 1139.4 $(M+Na)^+$.

4.2.1.2. Procedure B. A solution of **1** (469 mg, 0.364 mmol), **2** (60 mg, 0.303 mmol) and Cs_2CO_3 (99 mg, 0.303 mmol) in anhydrous DMF (10 mL) was stirred at 90 °C for 48 h under nitrogen. The mixture was poured into acetone (100 mL) and the precipitate was filtered off. Purification was made as described in procedure A to give **4** (243 mg, 61%) and **5** (154 mg, 38%).

*4.2.2. Synthesis of 4,4′-bis(6^{I}-O-cyclomaltoheptaosyl) azobenzene (**6**)*

4.2.2.1. Procedure A. A solution of **1** (332 mg, 0.257 mmol), **3** (25 mg, 0.117 mmol) and Cs_2CO_3 (95 mg, 0.293 mmol) in anhydrous DMF (10 mL) was stirred at 90 °C for 28 h under nitrogen. The mixture was poured into acetone (100 mL) and the precipitate was filtered off. The crude product was purified by column chromatography (CH_3CN–H_2O–NH_4OH 10:5:0.5→7:7:0.5) to give **6** (114 mg, 40%) as an orange solid. Mp 242 °C dec; $[\alpha]_D$ +105 (*c* 0.25, H_2O); IR (KBr) 3416, 2927, 1649, 1599, 1238, 1154, 1078, 1028 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.82 (d, 4H, ^3J=9.0 Hz, H-2^{az}), 7.12 (d, 4H, ^3J=9.0 Hz, H-3^{az}), 5.89 (br s, 28H, OH), 4.90 (br s, 2H, H-1^{I}), 4.82 (br s, 12H, H-1$^{II–VII}$), 4.48 (br s, 12H, OH), 4.30 (br s, 4H, H-6^{I},6′^{I}), 4.02–3.99 (m, 2H, H-5^{I}), 3.75–3.51 (m, 58H), 3.48 (m, overlapped with HDO); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 160.7 (C-4^{az}), 146.2 (C-1^{az}), 124.0 (C-2^{az}), 115.0 (C-3^{az}), 102.4–101.9 (C-1$^{I–VII}$), 82.1–81.5 (C-4$^{I–VII}$), 73.0–71.8 (C-2$^{I–VII}$,3$^{I–VII}$,5$^{II–VII}$), 69.9 (C-5^{I}), 67.3 (C-6^{I}), 60.2–59.9 (C-6$^{II–VII}$); MALDI-TOF-MS *m*/*z* calcd for $C_{96}H_{146}O_{70}N_2$ 2446.8, found 1248.5 (M/2+Na)$^+$, 2470.9 (M+Na)$^+$. Column chromatography also gave **5** (95 mg, 33%) as a white solid and {6^{I}-*O*-[4-(4′-hydroxyphenylazo)phenyl]}cyclomaltoheptaose **7** (83 mg, 53%) as an orange-yellow solid. Mp 216 °C dec; $[\alpha]_D$ +67 (*c* 0.5, H_2O); IR (KBr) 3401, 2925, 1632, 1400, 1151, 1029 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.78 (d, 2H, ^3J=8.9 Hz, H-3^{az}), 7.75 (d, 2H, ^3J=8.7 Hz, H-2′^{az}), 7.10 (d, 2H, ^3J=8.9 Hz, H-2^{az}), 6.92 (d, 2H, ^3J=8.9 Hz, H-3′^{az}), 5.74–5.69 (m, 14H, OH), 4.91 (d, 1H, $^3J_{1,2}$=3.0 Hz, H-1^{I}), 4.83 (br s, 6H, H-1$^{II–VII}$), 4.45 (br s, 6H, OH), 4.29 (br s, 2H, H-6^{I},6′^{I}), 4.02–3.99 (m, 1H, H-5^{I}), 3.73–3.54 (m, 29H), 3.48–3.32 (m, overlapped with HDO); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 160.5 (C-4′^{az}), 160.3 (C-1^{az}), 146.2 (C-1′^{az}), 145.2 (C-4^{az}), 124.4 (C-2′^{az}), 123.9 (C-3^{az}), 115.8 (C-3′^{az}), 115.0 (C-2^{az}), 102.4–102.0 (C-1$^{I–VII}$), 82.1–81.6 (C-4$^{I–VII}$), 73.2–72.2 (C-2$^{I–VII}$,3$^{I–VII}$,5$^{II–VII}$), 69.7 (C-5^{I}), 67.3 (C-6^{I}), 59.9 (C-6$^{II–VII}$); MALDI-TOF-MS *m*/*z* calcd for $C_{54}H_{78}O_{36}N_2$ 1330.4, found 1248.6 (M−C_6H_5ON+Na)$^+$, 1353.6 (M+Na)$^+$.

4.2.2.2. Procedure B. A solution of **1** (500 mg, 0.388 mmol), **3** (40 mg, 0.187 mmol) and Cs_2CO_3 (151 mg, 0.463 mmol) in anhydrous DMF (15 mL) was stirred at 90 °C for 72 h under nitrogen. Two portions of **1** (78 mg, 0.061 mmol) were added to the reaction mixture after 24 h and 48 h. The mixture was poured into acetone (100 mL) and the precipitate was filtered off. The crude product was purified by column chromatography (CH_3CN–H_2O–NH_4OH 10:5:0.5→7:7:0.5) to give **6** (188 mg, 41%) as an orange solid, **5** (281 mg, 49%) as a white solid and **7** (140 mg, 56%) as an orange-yellow solid.

4.3. Synthesis of propargyl derivatives 8 and 9

*4.3.1. Synthesis of 4-propargyloxyazobenzene (**8**)*

A solution of **2** (500 mg, 2.522 mmol) and K_2CO_3 (1.743 g, 12.610 mmol) in anhydrous acetone (30 mL) was stirred at rt for 30 min under nitrogen. Propargyl bromide (80% w/w in toluene, 1.5 g, 12.610 mmol) was added and the mixture was stirred at rt for 24 h. The solvent was removed by evaporation under vacuum and the crude product was purified by column chromatography (ether–hexane 1:1) to yield **8** (590 mg, 99%) as an orange solid. Mp 90 °C; IR (KBr) 3262, 3069, 2921, 2857, 1599, 1580, 1495, 1237, 1142 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.92 (d, 2H, $^3J_{2,3}$=8.8 Hz, H-2), 7.85 (d, 2H, $^3J_{2′,3′}$=7.0 Hz, H-2′), 7.61–7.50 (m, 2H, H-3′), 7.57 (d, 1H, $^3J_{3′,4′}$=8.0 Hz, H-4′), 7.19 (d, 2H, $^3J_{2,3}$=8.8 Hz, H-3), 4.94 (d, 2H, *J*=2.3 Hz, CH_2), 3.67 (t, 1H, *J*=2.2 Hz, ≡CH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.9 (C-4), 152.0 (C-1′), 146.5 (C-1), 131.0 (C-4′), 129.4 (C-3′), 124.4 (C-2), 122.3 (C-2′), 115.5 (C-3), 78.8, 78.7 (C≡C), 55.9 (CH_2); HRMS (FAB) *m*/*z* calcd for $C_{15}H_{12}ON_2$ 236.0945, found 237.1031 (M+H)$^+$.

*4.3.2. Synthesis of 4,4′-dipropargyloxyazobenzene (**9**)*

A solution of **3** (500 mg, 2.334 mmol) and K_2CO_3 (1.613 g, 11.670 mmol) in anhydrous acetone (30 mL) was stirred at rt for 30 min under nitrogen. Propargyl bromide (80% w/w in toluene, 1.666 g, 14.004 mmol) was added and the mixture was stirred at rt for 24 h. The solvent was removed by evaporation under vacuum and the crude product was purified by column chromatography (ether) to yield **9** (613 mg, 90%) as a yellow solid. Mp 193 °C; IR (KBr) 3273, 2918, 2856, 1592, 1496, 1245, 1144, 1015 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.86 (d, 4H, $^3J_{2,3}$=8.8 Hz, H-2), 7.17 (d, 4H, $^2J_{2,3}$=8.8 Hz, H-3), 4.92 (d, 4H, *J*=2.3 Hz, CH_2), 3.65 (t, 2H, *J*=2.3 Hz, ≡CH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.1 (C-4), 146.6 (C-1), 123.4 (C-2), 115.1 (C-3), 78.4, 77.5 (C≡C), 55.7 (CH_2); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{14}O_2N_2$ 290.1055, found 291.1133 (M+H)$^+$.

4.4. Synthesis of β-CD derivatives 11 and 12

*4.4.1. Synthesis of {6^{I}-deoxy-6^{I}-[4-(4-phenylazophenoxymethyl)-1H-1,2,3-triazol-1-yl]}cyclomaltoheptaose (**11**)*

To a solution of **10** (150 mg, 0.129 mmol) and **8** (37 mg, 0.155 mmol) in anhydrous DMF (7 mL) was added $(EtO)_3P{\cdot}CuI$ (9 mg, 0.030 mmol) and the reaction was stirred at 100 °C for 2 h under nitrogen. The solvent was removed by evaporation under vacuum and the crude was precipitated with acetone (100 mL) and filtered off. The solid was extracted (Soxhlet) with acetone (24 h), recrystallized in water, filtered off and washed with cold water, acetone and ether to yield **11** (133 mg, 74%) as a yellow solid. Mp 252 °C dec; $[\alpha]_D$ +90 (*c* 0.25, DMSO); IR (KBr) 3397, 2923, 1634, 1600, 1154, 1077, 1028 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.23 (s, 1H, H-5-C_2HN_3), 7.92 (d, 2H, $^3J_{2,3}$=8.7 Hz, H-3^{az}), 7.86 (d, 2H, $^3J_{2′,3′}$=7.0 Hz, H-2′^{az}), 7.61–7.52 (m, 3H, H-3′^{az},4′^{az}), 7.25 (d, 2H, $^3J_{2,3}$=8.8 Hz, H-2^{az}), 5.90 (d, 1H, *J*=6.3 Hz, OH), 5.79–5.65 (m, 13H, OH), 5.23 (br s, 2H, CH_2O), 5.06 (br s, 1H, H-1^{I}), 4.94 (d, 1H, ^2J=13.2 Hz, H-6^{I}), 4.84–4.79 (m, 6H, H-1$^{II–VII}$), 4.65–4.60 (m, 1H, H-6′^{I}), 4.53–4.48 (m, 5H, OH), 4.32 (t, 1H, *J*=5.4 Hz, OH), 4.01 (t, 1H, ^3J=9.2 Hz, H-5^{I}), 3.64–3.60 (m, 24H), 3.36 (br s, overlapped with HDO), 3.15–3.12 (m, 1H, H-6 of one of the II–VII units), 2.89 (t, 1H, *J*=8.5 Hz, H-6′ of one of the II–VII units); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 160.9 (C-1^{az}), 152.0 (C-1′^{az}), 146.3 (C-4^{az}), 142.1 (C-4-C_2HN_3), 130.9 (C-4′^{az}), 129.4 (C-3′^{az}), 125.6 (C-5-C_2HN_3), 124.6 (C-3^{az}), 122.3 (C-2′^{az}), 115.3 (C-2^{az}), 102.2–101.2 (C-1$^{I–VII}$), 83.5, 82.1–80.9 (C-4$^{I–VII}$), 73.2–71.8 (C-2$^{I–VII}$,3$^{I–VII}$,5$^{II–VII}$), 70.1 (C-5^{I}), 61.4 (CH_2O), 60.2–58.9 (C-6$^{II–VII}$), 50.5 (C-6^{I}); MALDI-TOF-MS *m*/*z* calcd for $C_{57}H_{81}O_{35}N_5$ 1395.5, found 1418.5 (M+Na)$^+$.

*4.4.2. Synthesis of 4,4′-bis{[1-(6^{I}-deoxycyclomaltoheptaosyl)-1H-1,2,3-triazol-4-yl]methyloxy}azobenzene (**12**)*

To a solution of **10** (400 mg, 0.345 mmol) and **9** (48 mg, 0.164 mmol) in anhydrous DMF (15 mL) was added $(EtO)_3P{\cdot}CuI$ (23 mg, 0.066 mmol) and the reaction was stirred at 100 °C for 4 h under nitrogen. The solvent was removed by evaporation under vacuum and the crude was precipitated with acetone (100 mL) and filtered off. The solid was extracted (Soxhlet) with acetone (2×24 h) and purified by column chromatography (CH_3CN–H_2O–NH_4OH 10:4:1→10:5:1→10:5:0.1) to yield **12** (309 mg, 72%) as a pale yellow solid. Mp 252 °C dec; $[\alpha]_D$ +108 (*c* 0.25, H_2O); IR (KBr) 3397, 2923, 1634, 1600, 1247, 1154, 1077, 1028 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.23 (s, 2H, H-5-C_2HN_3), 7.87 (d, 4H, $^3J_{2,3}$=9.0 Hz, H-2^{az}), 7.23 (d, 4H, $^3J_{2,3}$=9.0 Hz, H-3^{az}), 5.92 (d, 2H, *J*=4.5 Hz, OH), 5.80–5.66 (m, 26H, OH), 5.22 (d, 2H, ^2J=12.7 Hz, CHO), 5.20 (d, 2H, ^2J=12.7 Hz, CHO), 5.05 (d, 2H, ^3J=3.3 Hz, H-1^{I}), 4.94 (d, 2H, ^2J=12.7 Hz, H-6^{I}), 4.86–4.78 (m, 12H, H-1$^{II–VII}$), 4.61 (m, 2H, H-6′^{I}), 4.55–4.52 (m, 4H, OH), 4.50–4.45 (m, 6H, OH), 4.32 (t, 2H, *J*=5.8 Hz, OH), 4.03–3.99 (m, 2H, H-5^{I}), 3.74–3.56 (m, 50H), 3.39–3.30 (m, overlapped with HDO), 3.14–3.12 (m, 2H, H-6 of one of the II–VII units), 2.89 (t, 2H, *J*=8.2 Hz, H-6′ of one of the II–VII units); ^{13}C NMR

(75 MHz, DMSO-d_6) δ 160.4 (C-4^{az}), 146.3 (C-1^{az}), 142.1 (C-4-C_2HN_3), 125.6 (C-5-C_2HN_3), 124.2 (C-2^{az}), 115.2 (C-3^{az}), 102.2–101.2 (C-1$^{I–VII}$), 83.5–80.9 (C-4$^{I–VII}$), 73.0–71.8 (C-2$^{I–VII}$,3$^{I–VII}$,5$^{II–VII}$), 70.0 (C-5^{I}), 61.4 (CH_2O), 59.8–58.8 (C-6$^{II–VII}$), 50.3 (C-6^{I}); MALDI-TOF-MS m/z calcd for $C_{102}H_{152}O_{70}N_8$ 2608.9, found 2632.9 $(M+Na)^+$. Column chromatography also gave {6^{I}-deoxy-6^{I}-{4-[4-(4′-propargyloxiphenylazo)phenoxymethyl]-1*H*-1,2,3-triazol-1-yl}}cyclomaltoheptaose **13** (67 mg, 28%) as a pale yellow solid. Mp 221 °C dec; $[\alpha]_D$ +60 (c 0.25, H_2O); IR (KBr) 3393, 3273, 2923, 1632, 1400, 1108, 1030 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (s, 1H, H-5-C_2HN_3), 7.86 (d, 4H, J=8.9 Hz, H-2′^{az},3^{az}), 7.23 (d, 2H, ^3J=8.9 Hz, H-2^{az}), 7.17 (d, 2H, ^3J=9.1 Hz, H-3′^{az}), 5.90–5.73 (m, 14H, OH), 5.21 (br s, 2H, CH_2O), 5.05 (d, 1H, $^3J_{1,2}$=3.2 Hz, H-1^{I}), 4.93–4.88 (m, 1H, H-6^{I}), 4.92 (d, 2H, ^3J=2.2 Hz, $CH_2C{\equiv}$), 4.83–4.77 (m, 6H, H-1$^{II–VII}$), 4.64–4.58 (m, 1H, H-6′^{I}), 4.54–4.48 (m, 5H, OH), 4.33 (br s, 1H, OH), 4.01 (t, 1H, ^3J=8.8 Hz, H-5^{I}), 3.73–3.56 (m, 25H), 3.34 (br s, overlapped with HDO), 3.15–3.11 (m, 1H, H-6 of one of the II–VII units), 2.90–2.87 (m, 1H, H-6′ of one of the II–VII units); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4 (C-1^{az}), 159.3 (C-4′^{az}), 146.6, 146.3 (C-1′^{az},4^{az}), 142.1 (C-4-C_2HN_3), 125.6 (C-5-C_2HN_3), 124.2, 124.0 (C-2′^{az},3^{az}), 115.4 (C-3′^{az}), 115.2 (C-2^{az}), 102.2–101.2 (C-1$^{I–VII}$), 83.5, 81.6–80.7 (C-4$^{I–VII}$), 78.9, 78.7 (C≡C), 73.1–72.1 (C-2$^{I–VII}$,3$^{I–VII}$,5$^{II–VII}$), 70.0 (C-5^{I}), 61.3 (CH_2O), 60.2–59.8 (C-6$^{II–VII}$), 55.8 ($CH_2C{\equiv}$), 50.4 (C-6^{I}); MALDI-TOF-MS m/z calcd for $C_{60}H_{83}O_{36}N_5$ 1449.5, found 1329.5 $(M-C_9H_7ON+Na)^+$, 1472.5 $(M+Na)^+$.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for compounds **4**, **6**–**9** and **11**–**13**) associated to this article can be found, in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.098.

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