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Improved Synthesis of C2 and C6 Monoderivatives of α- and β-Cyclodextrin via the Click Chemistry Approach

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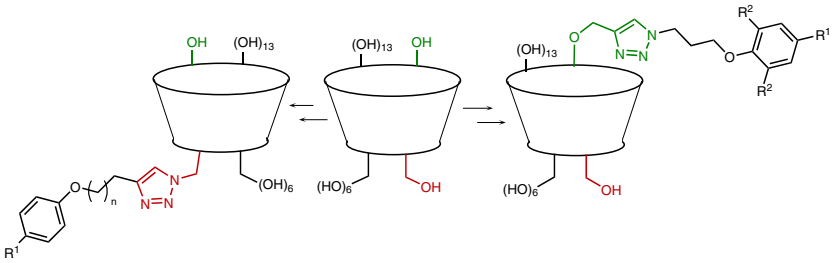

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Abstract An efficient multigram-scale azide-alkyne coupling of cyclodextrin derivatives mono-6-azido-6-deoxy-β-cyclodextrin, mono-2-*O*-propargyl-β-cyclodextrin, and mono-2-*O*-propargyl-α-cyclodextrin with terminal alkynyl aryl ethers or azides, mediated by copper(I) is reported. This process uses a stoichiometric ratio of substrates and 5 mol% of the copper catalyst to give the products with full conversion; thus, no chromatographic purification is necessary. The yields of both α- and β-cyclodextrin derivatives are in the range of 80 to 99%.

Key words cyclodextrins, azides, copper, cycloaddition, ligands

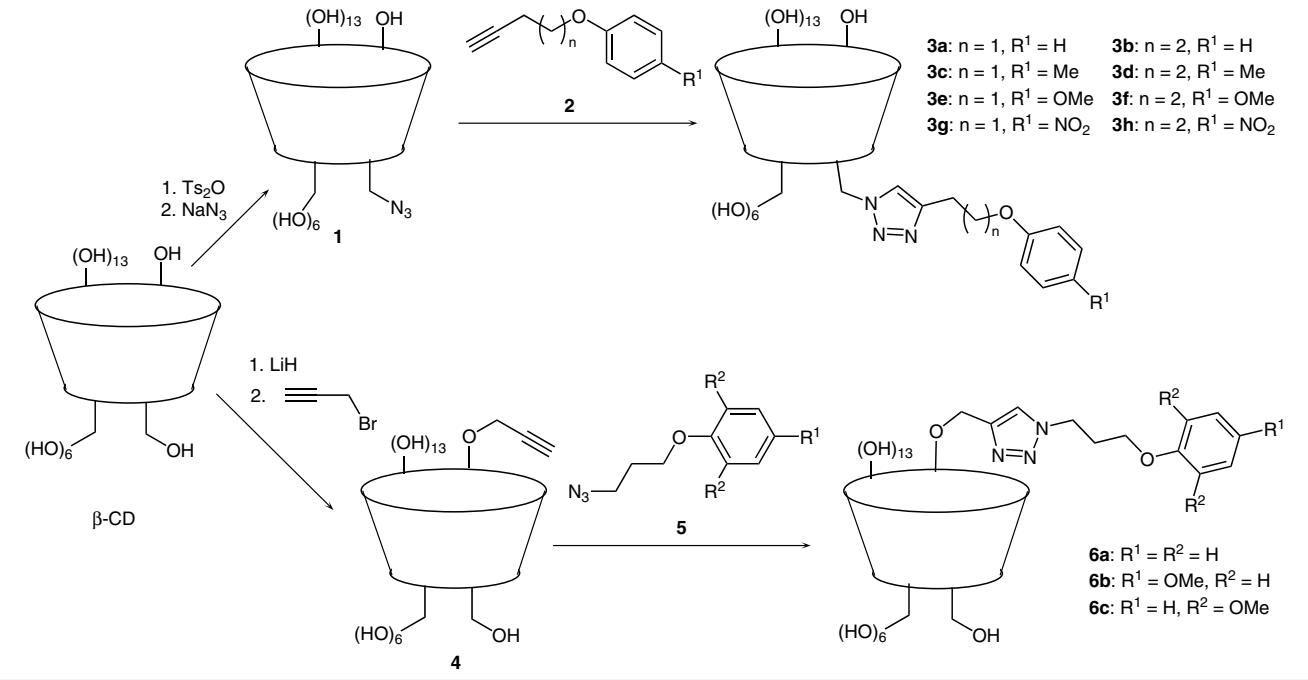
Cyclodextrins (CDs), readily accessible, nontoxic compounds, have excellent features for the formation of complexes with hydrophobic molecules. Therefore, they can be applied as hosts for active species (for which CD plays a protective role) or hydrophobic substances that are to be dissolved in water or/and other aqueous solvent systems.[1] Chemical modifications of CDs strongly affect their properties, such as solubility or catalytic and complexing abilities. Their derivatives bearing hydrophobic or hydrophilic substituents may form intramolecular complexes.[2] On the other hand, there are many examples of intermolecular complex formation; for example, Yamanoi et al.[3] described β-CD derivatives containing one or two arbutin moieties in the side chain. The affinity constants of complexes with doxorubicin were much higher than those measured for native β-CD (the $6^A,6^D$-disubstituted derivative showed K of 10^8 M^{-1} in comparison to 10^2 M^{-1} for β-CD). One of us (K.C.) has experience of similar work with target molecules of type **3**.[4]

Bearing 21 hydroxy groups, β-CD is certainly a compound that is difficult to modify in an accurate and selective manner. The similarity of the seven hydroxy groups in each 2-OH, 3-OH, and 6-OH subset has encouraged researchers to search for methods of simple derivatization for β-CD that would make one or two groups distinguishable from the others, and allow these groups to be used in further modifications. Of the derivatization methodologies available, copper(I)-mediated azide-alkyne coupling (CuAAC) is a useful method that could provide good yields and highly selective reactions.

There are two typical ways of achieving monosubstituted compounds: 1. monotosylation of the 6-OH position followed by substitution with sodium azide, and 2. propargylation of the 2-OH position (Scheme 1). Both give products that can be used as partners in CuAAC that have been investigated extensively, especially in the field of CD monoderivatives.[5]

Modifying the C6 position of β-CD with an alkyl moiety would be laborious due to the protection and deprotection procedures required for 2-OH and 3-OH, whereas the azide derivative is more readily available. Monomodifications at C6 proceed via the tosyl derivative that can be easily substituted with many nucleophiles; mono-6-azido-6-deoxy-β-CD **1** obtained in this manner is widely used in reactions with derivatives bearing terminal alkynes.

In our work we have obtained mono-6-*O*-tosyl-β-CD by treatment of native β-CD with *p*-toluenesulfonic anhydride (according to Bittman[6]). Next, we transformed the monotosylate into mono-6-azido-6-deoxy-β-CD **1** using sodium azide in *N*,*N*-dimethylformamide at 60 °C. As conjugation partners for this compound, alkyl aryl ethers of type **2**, bearing alkyl chains of various lengths with a terminal alkyne group were synthesized.[7] We then subjected compounds **1** and **2** to the CuAAC reaction. Several examples of typical conditions for this method are known, however, many papers report 'click chemistry' as laborious and complicated. To avoid these problems, an excess of one of substrates is often used, including stoichiometric amounts of Cu(I) catalyst.[8] This approach is especially inconvenient be-



Scheme 1 Monoderivatization of C6 (upper path) and C2 (lower path) positions of β-CD via CuAAC

cause of the difficult purification that results as it is necessary to remove unreacted hydrophobic substrate or Cu(I) and Cu(II) compounds that can remain complexed inside the CD cavity.[9] The use of dry, unstable copper catalysts [e.g., $Cu(MeCN)_4PF_6$, CuI–$P(OEt)_3$] typically provides reaction yields below 80%.[10] Ultrasonic or microwave irradiation rarely improves reaction yields, even when applied together.[11] Moreover, problems with the solubility of substrates are often identified. Therefore, to apply CuAAC for selective CD modification, we have to consider the solvent, temperature, substrate ratio, amount of catalyst.

Our first attempts of to react **1** with **2** via CuAAC methodology in *N*,*N*-dimethylformamide or dimethyl sulfoxide as solvent resulted with low conversion, due to copper(I) iodide disproportionation; replacing copper(I) iodide with copper(II) sulfate and ascorbic acid [Cu(I) ions were generated in situ] and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) provided higher, but not completely satisfactory yields (20–50%). The reaction can, however, be carried out almost quantitatively when the conditions are adjusted to fulfill three requirements: (a) a degassed mixture of dimethyl sulfoxide–water (4:1) is used; (b) the Cu(I) is generated in situ using sodium ascorbate; and (c) the reaction is performed under an inert atmosphere and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine is added as a stabilizing agent. These conditions appeared to be optimal for various alkyne partners used (Table 1). It is noteworthy that temperature used for this reaction (50 °C) was much lower than that reported by Ritter et al.[12]

Table 1 Results of the CuAAC Reaction of **1** with **2**

Product	R	n	Yield (%)
3a	H	1	90
3b	H	2	98
3c	Me	1	99
3d	Me	2	98
3e	OMe	1	94
3f	OMe	2	96
3g	NO_2	1	95
3h	NO_2	2	93

Monomodification of β-CD at the C2 position began by treating native β-CD with lithium hydride in dimethyl sulfoxide.[13] Initially generated C6 alkoxide rearranged into C2 alkoxide within 24 hours of stirring under inert atmosphere, and it was then transformed into intermediate **4** by alkylation with propargyl bromide, to give the product **4** in 38% yield after purification. Mono-2-*O*-propargyl-β-CD **4** was then subjected to CuAAC with reagent **5**[14] under the previously optimized conditions. Again the reactions proceeded with very good yields (Table 2), so there was no need for chromatography and the product was sufficiently pure after trituration with acetone.

Table 2 Results of the CuAAC Reaction of **4** with **5**

Product	R^1	R^2	Yield (%)
6a	H	H	87
6b	OMe	H	90
6c	H	OMe	93

Finally, we applied this methodology to the α-CD system to obtain compounds **7** (Figure 1) under similar reaction conditions; *tert*-butyl alcohol was added in order to eliminate inclusion complex formation between α-CD and the alkyl chains of **5**.

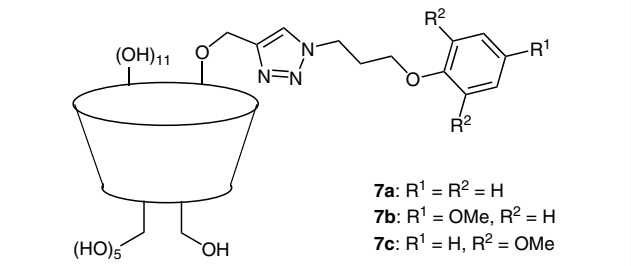


Figure 1 α-CD derivatives obtained via CuAAC reaction of mono-2-*O*-propargyl-α-CD with **5**

Although preparation of mono-2-*O*-propargyl-α-CD was less efficient, CuAAC proceeded with the high yields expected (Table 3).

Table 3 Results of the CuAAC Reaction of Mono-2-*O*-propargyl-α-CD with **5**

Product	R^1	R^2	Yield
7a	H	H	80
7b	OMe	H	89
7c	H	OMe	86

Summing up, the introduction of a highly specific CuAAC reaction provides an opportunity to combine these compounds with non-orthogonal functional groups. We have presented an example of using this method to create new functional hybrids that can potentially behave like drug-complexing agents. We have tuned the CuAAC reaction conditions to obtain products quantitatively, using a stable catalytic system and slightly elevated temperatures, without sophisticated equipment (e.g., microwaves or ultrasound) and chromatographic purification. Moreover, we have synthesized β-CD derivatives, containing electron-rich side chains at the primary as well as the secondary rim of the β-CD; this methodology also works efficiently for α-CD.

If not stated otherwise, all compounds are commercially available. Monoazide **1** and mono-2-*O*-propargyl-β-CD **4** were prepared in 60% and 40% yields, respectively, according to known procedures.[5,12] Mono-2-*O*-propargyl-α-CD was synthesized similarly to its β-analogue in 30% yield. Toluene was dried and distilled over Na. TLC was performed on silica gel plates (Merck Kieselgel 60 F_{254}) and spots were visualized with Mo-Ce spray. All NMR spectra were recorded on Bruker DRX 500 MHz and Varian VNMRS 500 MHz spectrometers in DMSO-d_6. Mass spectra were recorded using Shimadzu LCMS-IT-TOF spectrometer using ESI+.

Conjugation of Mono(6-azido-6-deoxy)-β-CD and Terminal Alkyne Containing Alkyl Aryl Ethers; General Procedure

A 3-necked flask was charged with mono-6-azido-6-deoxy-β-CD (1 mmol), alkyl aryl ether (1 equiv), and ascorbic acid [0.15 equiv, as a solution of acid (200 mg) in H_2O (10 mL)]. The contents of the flask were dissolved in DMSO–H_2O (4:1 mixture, 50 mL). A stream of argon was passed through the solution (in order to maintain O_2-free conditions). Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, 0.2 equiv) was added. A pressure-equalizing dropping funnel was charged with $CuSO_4$ [0.05 equiv as a solution in H_2O (10 mL)]. The solution was heated to 50 °C and the $CuSO_4$ solution was added to the vigorously stirred mixture (a transient brown coloration occurred). Stirring at 50 °C was continued overnight and the reaction was monitored by TLC. After 16 h the mono-azide spot disappeared and mixture was evaporated under reduced pressure. The solid residue was suspended in acetone (100 mL) and filtered on a sintered funnel. Next the residue was washed with acetone, CH_2Cl_2, and Et_2O (100 mL of each) and dried (P_2O_5).

Mono-6-[4-(2-phenoxyethyl)-1*H*-1,2,3-triazol-1-yl]-6-deoxy-β-CD (3a)

White powder after additional trituration with acetone; yield: 1175 mg (0.9 mmol, 90%).

IR (KBr): 3316, 2926, 2111, 2042, 1642, 1600, 1496, 1425, 1368, 1334, 1302, 1242, 1156, 1080, 1031, 945, 844, 757, 694, 580, 529 cm^{-1}.

^1H NMR: δ = 7.88 (s, 1 H), 7.28 (dd, *J* = 8.6, 7.4 Hz, 2 H), 7.01–6.85 (m, 3 H), 6.00–5.52 (m, 14 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.91–4.70 (m, 7 H), 4.64–4.35 (m, 6 H), 4.23 (t, *J* = 7.0 Hz, 2 H), 3.98 (t, *J* = 10.1 Hz, 1 H), 3.77–3.47 (m, 17 H), 3.47–3.19 (m, 21 H), 3.18–3.01 (m, 4 H).

^{13}C NMR: δ = 158.3, 155.6, 143.1, 129.5, 123.8, 120.6, 114.5, 102.2, 102.1, 102.0, 101.9, 101.3, 83.5, 81.9, 81.6, 81.5, 81.0, 77.6, 73.2, 73.1, 73.0, 72.9, 72.7, 72.4, 72.2, 72.1, 71.8, 70.1, 66.4, 60.1, 59.9, 59.0, 50.3, 28.2, 25.4, 22.5, 21.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{52}H_{80}N_3O_{35}$: 1306.4567; found: 1306.4599.

Mono-6-[4-(3-phenoxypropyl)-1*H*-1,2,3-triazol-1-yl]-6-deoxy-β-CD (3b)

White powder; yield: 1290 mg (0.98 mmol, 98%).

IR (KBr): 3268, 2927, 2109, 2043, 1642, 1601, 1496, 1415, 1369, 1335, 1302, 1245, 1157, 1080, 1037, 945, 845, 757, 693, 608, 581, 529 cm^{-1}.

^1H NMR: δ = 7.81 (s, 1 H), 7.38–7.21 (m, 3 H), 6.98–6.87 (m, 2 H), 5.73 (br s, 14 H), 5.03 (d, *J* = 3.6 Hz, 1 H), 4.91–4.69 (m, 7 H), 4.66–4.29 (m, 6 H), 4.08–3.92 (m, 3 H), 3.82–3.49 (m, 21 H), 3.49–3.14 (m, 17 H), 3.09 (d, *J* = 11.3 Hz, 1 H), 2.90 (d, *J* = 10.4 Hz, 1 H), 2.76 (d, *J* = 7.8 Hz, 2 H), 2.04 (tt, *J* = 10.8, 5.4 Hz, 2 H).

^{13}C NMR: δ = 172.4, 171.5, 158.6, 146.1, 129.5, 122.8, 120.4, 114.5, 102.2, 102.1, 101.2, 83.6, 82.1, 81.6, 81.4, 80.8, 73.1, 72.5, 72.4, 72.2, 72.1, 71.8, 70.0, 66.7, 59.9, 50.3, 40.4, 28.5, 22.5, 21.6, 21.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{53}H_{82}N_3O_{35}$: 1320.4723; found: 1320.4720.

Mono-6-[4-(2-(*p*-tolyloxy)ethyl]-1*H*-1,2,3-triazol-1-yl)-6-deoxy-β-CD (3c)

White powder; yield: 1305 mg (0.99 mmol, 99%).

IR (KBr): 3283, 2927, 2115, 2043, 1643, 1556, 1512, 1415, 1369, 1334, 1300, 1240, 1157, 1080, 1031, 945, 844, 818, 755, 706, 663, 607, 581, 531 cm^{-1}.

^{1}H NMR: δ = 7.87 (s, 1 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 5.91–5.55 (m, 14 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.93–4.72 (m, 7 H), 4.62–4.39 (m, 6 H), 4.30 (s, 1 H), 4.18 (t, *J* = 7.0 Hz, 2 H), 3.97 (t, *J* = 10.0 Hz, 1 H), 3.83–3.50 (m, 20 H), 3.50–3.18 (m, 20 H), 3.11 (d, *J* = 9.2 Hz, 1 H), 3.04 (t, *J* = 6.8 Hz, 2 H), 2.92 (br s, 1 H).

^{13}C NMR: δ = 171.5, 156.2, 143.2, 129.8, 129.2, 123.8, 114.4, 102.2, 102.1, 102.0, 101.9, 101.2, 83.5, 81.9, 81.6, 81.5, 81.0, 73.2, 73.1, 73.0, 73.0, 72.9, 72.7, 72.5, 72.4, 72.3, 72.1, 72.1, 71.8, 70.1, 66.5, 60.1, 59.9, 59.9, 59.0, 50.3, 40.4, 25.5, 22.5, 20.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{53}H_{82}N_3O_{35}$: 1320.4723; found: 1320.4747.

Mono-6-(4-[3-(*p*-tolyloxy)propyl]-1*H*-1,2,3-triazol-1-yl)-6-deoxy-β-CD (3d)

White powder; yield: 1310 mg (0.98 mmol, 98%).

IR (KBr): 3290, 2926, 2113, 2042, 1643, 1615, 1556, 1512, 1416, 1369, 1334, 1301, 1242, 1157, 1080, 1030, 946, 844, 817, 756, 706, 608, 580, 530 cm^{-1}.

^{1}H NMR: δ = 7.78 (s, 1 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 5.85 (d, *J* = 6.3 Hz, 1 H), 5.81–5.54 (m, 13 H), 5.03 (d, *J* = 3.1 Hz, 1 H), 4.92–4.68 (m, 7 H), 4.59–4.39 (m, 6 H), 4.28 (br s, 1 H), 3.97 (dd, *J* = 9.8, 6.3 Hz, 3 H), 3.79–3.48 (m, 20 H), 3.46–3.15 (m, 19 H), 3.10 (d, *J* = 8.1 Hz, 1 H), 2.91 (br s, 1 H), 2.75 (t, *J* = 7.5 Hz, 2 H), 2.07–1.93 (m, 2 H).

^{13}C NMR: δ = 156.5, 146.1, 129.8, 129.0, 122.8, 114.3, 102.2, 102.0, 101.9, 101.2, 83.5, 82.0, 81.6, 81.4, 80.8, 73.2, 73.1, 73.0, 72.9, 72.9, 72.6, 72.5, 72.4, 72.3, 72.1, 71.8, 70.1, 66.8, 59.9, 58.9, 50.3, 40.4, 29.6, 28.5, 25.5, 21.6, 20.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{54}H_{84}N_3O_{35}$: 1334.4880; found: 1334.4906.

Mono-6-{4-[2-(4-methoxyphenoxy)ethyl]-1*H*-1,2,3-triazol-1-yl]-6-deoxy-β-CD (3e)

White powder; yield: 1255 mg (0.94 mmol, 94%).

IR (KBr): 3322, 2926, 2129, 2042, 1743, 1643, 1510, 1415, 1369, 1334, 1302, 1231, 1156, 1080, 1030, 946, 830, 756, 707, 639, 607, 580, 529 cm^{-1}.

^{1}H NMR: δ = 7.87 (s, 1 H), 6.94–6.78 (m, 4 H), 5.74 (br s, 14 H), 5.03 (d, *J* = 3.3 Hz, 1 H), 4.92–4.72 (m, 7 H), 4.64–4.24 (m, 6 H), 4.16 (t, *J* = 6.9 Hz, 3 H), 3.98 (t, *J* = 9.9 Hz, 1 H), 3.82–3.50 (m, 20 H), 3.50–3.20 (m, 20 H), 3.12 (d, *J* = 11.7 Hz, 1 H), 3.03 (t, *J* = 6.8 Hz, 2 H), 2.92 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR: δ = 172.7, 171.5, 153.4, 152.3, 143.2, 129.8, 123.8, 115.5, 114.6, 114.4, 102.2, 102.1, 102.0, 101.9, 101.2, 83.5, 81.9, 81.5, 81.5, 81.0, 73.1, 73.0, 73.0, 72.9, 72.8, 72.7, 72.5, 72.4, 72.4, 72.2, 72.1, 72.0, 71.8, 70.0, 67.0, 60.0, 59.9, 59.0, 55.3, 54.9, 50.3, 40.4, 25.5, 22.5, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{53}H_{82}N_3O_{36}$: 1336.4673; found: 1336.4697.

Mono-6-{4-[3-(4-methoxyphenoxy)propyl]-1*H*-1,2,3-triazol-1-yl}-6-deoxy-β-CD (3f)

White polymorphic solid; yield: 1300 mg (0.96 mmol, 96%).

IR (KBr): 3303, 2927, 2119, 2043, 1644, 1509, 1442, 1416, 1369, 1334, 1300, 1231, 1156, 1080, 1030, 945, 829, 754, 706, 653, 608, 528 cm^{-1}.

^{1}H NMR: δ = 7.80 (s, 1 H), 6.97–6.74 (m, 4 H), 5.98–5.43 (m, 13 H), 5.03 (d, *J* = 3.6 Hz, 1 H), 4.95–4.68 (m, 7 H), 4.48 (br s, 6 H), 4.04–3.90 (m, 3 H), 3.79–3.49 (m, 21 H), 3.50–3.15 (m, 20 H), 3.10 (d, *J* = 11.5 Hz, 1 H), 2.91 (d, *J* = 10.4 Hz, 1 H), 2.74 (t, *J* = 7.7 Hz, 2 H), 2.06–1.94 (m, 2 H).

^{13}C NMR: δ = 153.3, 152.7, 146.1, 122.8, 115.4, 114.6, 102.2, 102.0, 101.9, 101.9, 101.2, 83.6, 82.1, 81.6, 81.5, 81.4, 80.8, 73.2, 73.1, 73.1, 73.0, 72.9, 72.9, 72.6, 72.5, 72.4, 72.3, 72.2, 72.1, 72.1, 71.9, 70.1, 67.3, 60.2, 59.9, 58.9, 55.4, 50.3, 40.4, 30.7, 29.6, 28.6, 22.5, 21.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{54}H_{84}N_3O_{36}$: 1350.4829; found: 1350.4796.

Mono-6-{4-[2-(4-nitrophenoxy)ethyl]-1*H*-1,2,3-triazol-1-yl}-6-deoxy-β-CD (3g)

White polymorphic solid; yield: 1280 mg (0.95 mmol, 95%).

IR (KBr): 3302, 2927, 2113, 2041, 1643, 1594, 1513, 1415, 1341, 1302, 1264, 1156, 1112, 1080, 1030, 848, 754, 706, 654, 608, 580, 530 cm^{-1}.

^{1}H NMR: δ = 8.19 (d, *J* = 9.3 Hz, 2 H), 7.90 (s, 1 H), 7.15 (d, *J* = 9.3 Hz, 2 H), 5.84 (d, *J* = 6.2 Hz, 1 H), 5.80–5.55 (m, 11 H), 5.00 (d, *J* = 3.4 Hz, 1 H), 4.90–4.71 (m, 6 H), 4.58–4.41 (m, 5 H), 4.41–4.34 (m, 2 H), 4.30 (br s, 1 H), 3.96 (t, *J* = 9.9 Hz, 1 H), 3.77–3.48 (m, 20 H), 3.44–3.19 (m, 18 H), 3.16–3.03 (m, 3 H), 2.88 (d, *J* = 10.4 Hz, 1 H).

^{13}C NMR: δ = 171.4, 163.7, 142.7, 140.9, 125.9, 123.9, 115.1, 109.6, 102.2, 102.1, 102.0, 101.9, 101.2, 83.5, 81.9, 81.6, 81.5, 81.4, 81.0, 73.2, 73.1, 73.0, 72.8, 72.7, 72.4, 72.4, 72.2, 72.1, 71.8, 70.1, 67.5, 60.1, 59.9, 59.0, 50.3, 40.4, 25.2, 22.5, 21.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{52}H_{79}N_4O_{37}$: 1351.4418; found: 1351.4419.

Mono-6-{4-[3-(4-nitrophenoxy)propyl]-1*H*-1,2,3-triazol-1-yl}-6-deoxy-β-CD (3h)

White polymorphic solid; yield: 1270 mg (0.93 mmol, 93%).

IR (KBr): 3314, 2927, 2111, 2041, 1650, 1607, 1593, 1513, 1415, 1340, 1301, 1264, 1156, 1111, 1080, 1030, 945, 848, 754, 706, 655, 608, 580, 530 cm^{-1}.

^{1}H NMR: δ = 8.21 (d, *J* = 9.3 Hz, 2 H), 7.84 (s, 1 H), 7.16 (d, *J* = 9.3 Hz, 2 H), 6.03–5.50 (m, 12 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.91–4.72 (m, 6 H), 4.63–4.39 (m, 5 H), 4.19 (t, *J* = 6.4 Hz, 2 H), 3.99 (t, *J* = 10.2 Hz, 1 H), 3.83–3.49 (m, 21 H), 3.48–3.19 (m, 19 H), 3.08 (d, *J* = 11.5 Hz, 1 H), 2.88 (d, *J* = 10.7 Hz, 1 H), 2.83–2.70 (m, 2 H), 2.10 (dt, *J* = 13.4, 6.5 Hz, 2 H).

^{13}C NMR: δ = 172.3, 171.5, 164.0, 145.9, 140.8, 125.9, 122.8, 115.1, 102.2, 102.1, 101.9, 101.8, 101.1, 83.6, 82.1, 81.6, 81.5, 81.4, 81.4, 80.7, 73.2, 73.1, 73.1, 73.0, 72.9, 72.6, 72.5, 72.4, 72.3, 72.2, 72.1, 72.0, 71.8, 70.1, 68.1, 60.2, 59.9, 58.8, 50.4, 40.4, 28.2, 22.5, 21.5, 21.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{53}H_{81}N_4O_{37}$: 1365.4574; found: 1365.4572.

Conjugation of Mono-2-*O*-propargyl-β-CD and Terminal Azide Containing Alkyl Aryl Ethers

Mono-2-*O*-propargyl-β-CD **4** and aryloxy-substituted alkyl azides reacted by the general procedure for mono(6-azido-6-deoxy)-β-CD.

Mono-2-*O*-{[1-(3-phenoxypropyl)-1*H*-1,2,3-triazol-4-yl]methyl}-β-CD (6a)

White powder; yield: 1170 mg (0.87 mmol, 87%).

IR (KBr): 3320, 2926, 2102, 1647, 1601, 1588, 1497, 1413, 1367, 1334, 1300, 1245, 1156, 1082, 1030, 946, 858, 757, 695, 609, 580, 529 cm^{-1}.

^1H NMR: δ = 8.15 (s, 1 H), 7.29 (t, *J* = 7.7 Hz, 2 H), 6.93 (dd, *J* = 7.5, 5.0 Hz, 3 H), 5.98–5.81 (m, 1 H), 5.79–5.54 (m, 8 H), 4.99–4.72 (m, 7 H), 4.63–4.27 (m, 8 H), 3.97 (t, *J* = 6.0 Hz, 2 H), 3.82 (t, *J* = 9.7 Hz, 1 H), 3.74–3.47 (m, 21 H), 3.47–3.20 (m, 23 H), 2.35–2.21 (m, 2 H).

^{13}C NMR: δ = 158.4, 129.5, 128.7, 128.0, 124.2, 120.7, 114.5, 102.0, 101.7, 100.2, 82.1, 81.6, 79.5, 73.2, 73.1, 73.0, 72.7, 72.4, 72.2, 72.1, 71.8, 71.7, 64.2, 59.9, 47.8, 46.6, 40.4, 29.6, 28.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{54}H_{84}N_3O_{36}$: 1350.4829; found: 1350.4797.

Mono-2-*O*-{[1-(3-(4-methoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl)-β-CD (6b)

White powder; yield: 1240 mg (0.90 mmol, 90%).

IR (KBr): 3302, 2926, 2060, 1649, 1510, 1414, 1368, 1334, 1299, 1232, 1157, 1082, 1030, 946, 830, 756, 706, 609, 579, 528 cm^{-1}.

^1H NMR: δ = 8.14 (s, 1 H), 6.93–6.77 (m, 4 H), 6.04–5.84 (m, 1 H), 5.84–5.55 (m, 8 H), 4.94–4.73 (m, 7 H), 4.61–4.31 (m, 8 H), 3.90 (t, *J* = 5.9 Hz, 2 H), 3.82 (t, *J* = 9.1 Hz, 1 H), 3.76–3.50 (m, 24 H), 3.48–3.24 (m, 22 H), 2.31–2.16 (m, 2 H).

^{13}C NMR: δ = 153.5, 152.4, 143.6, 124.2, 115.5, 114.7, 102.0, 100.2, 82.1, 81.6, 81.5, 81.4, 79.5, 73.2, 73.2, 73.1, 73.1, 73.0, 73.0, 72.7, 72.7, 72.5 (3 overlapping signals), 72.4, 72.1, 72.1, 72.1, 72.1, 71.8, 71.7, 64.9, 64.5, 60.0, 55.4, 46.6, 40.4, 29.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{55}H_{86}N_3O_{37}$: 1380.4935; found: 1380.4929.

Mono-2-*O*-({1-[3-(2,6-dimethoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl)-β-CD (6c)

White powder; yield: 1310 mg (0.93 mmol, 93%).

IR (KBr): 3333, 2930, 2139, 1649, 1600, 1480, 1368, 1299, 1257, 1157, 1110, 1081, 1029, 944, 856, 756, 705, 609, 579, 529 cm^{-1}.

^1H NMR: δ = 8.11 (s, 1 H), 7.00 (t, *J* = 8.3 Hz, 1 H), 6.67 (d, *J* = 8.3 Hz, 2 H), 6.03–5.85 (m, 2 H), 5.82–5.48 (m, 10 H), 4.98–4.73 (m, 7 H), 4.66–4.52 (m, 3 H), 4.52–4.32 (m, 7 H), 3.92–3.81 (m, 2 H), 3.77 (s, 6 H), 3.72–3.48 (m, 21 H), 3.47–3.22 (m, 21 H), 2.19–2.11 (m, 2 H).

^{13}C NMR: δ = 153.3, 143.6, 136.2, 124.2, 123.8, 105.5, 102.0, 81.6, 73.1, 72.4, 72.0, 69.1, 64.5, 59.9, 55.9, 46.7, 30.7, 30.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{56}H_{88}N_3O_{38}$: 1410.5040; found: 1410.5001.

Conjugation of Mono-2-*O*-propargyl-α-CD and Terminal Azide Containing Alkyl Aryl Ethers

Mono-2-*O*-propargyl-α-CD reacted with aryloxy-substituted alkyl azides by the general procedure for mono(6-azido-6-deoxy)-β-CD. *t*-BuOH (2 equiv) was added to the mixture before the addition of $CuSO_4$ and sodium ascorbate.

Mono-2-*O*-{[1-(3-phenoxypropyl)-1*H*-1,2,3-triazol-4-yl]methyl}-α-CD (7a)

White powder; yield: 950 mg (0.80 mmol, 80%).

IR (KBr): 3316, 2928, 2149, 1649, 1601, 1497, 1456, 1407, 1363, 1333, 1296, 1243, 1154, 1080, 1036, 949, 846, 757, 696, 608, 574, 532 cm^{-1}.

^1H NMR: δ = 8.14 (s, 1 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 6.93 (dd, *J* = 7.8, 4.0 Hz, 3 H), 5.72 (d, *J* = 6.4 Hz, 1 H), 5.65–5.39 (m, 7 H), 4.92–4.71 (m, 6 H), 4.60–4.42 (m, 6 H), 4.35–4.27 (m, 1 H), 3.96 (t, *J* = 5.6 Hz, 2 H), 3.85–3.71 (m, 4 H), 3.71–3.49 (m, 14 H), 3.49–3.19 (m, 18 H), 2.35–2.21 (m, 2 H).

^{13}C NMR: δ = 158.4, 143.9, 129.6, 128.8, 128.1, 127.8, 124.2, 120.7, 114.5, 102.1, 102.0, 101.9, 100.1, 82.7, 82.3, 82.1, 82.1, 79.3, 73.3, 73.2, 72.7, 72.1, 71.9, 71.8, 64.3, 64.2, 60.0, 46.6, 40.4, 30.8, 29.6, 15.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{48}H_{74}N_3O_{31}$: 1188.4301; found: 1188.4317.

Mono-2-*O*-({1-[3-(4-methoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl)-α-CD (7b)

White powder; yield: 1080 mg (0.89 mmol, 89%).

IR (KBr): 3357, 2928, 2055, 1647, 1509, 1462, 1407, 1363, 1333, 1295, 1231, 1154, 1080, 1032, 949, 831, 750, 705, 608, 574, 526 cm^{-1}.

^1H NMR: δ = 8.12 (s, 1 H), 6.92–6.76 (m, 4 H), 5.81–5.33 (m, 8 H), 4.91–4.66 (m, 6 H), 4.58–4.41 (m, 6 H), 4.29 (s, 1 H), 3.95 (s, 1 H), 3.93–3.84 (m, 2 H), 3.84–3.71 (m, 4 H), 3.71–3.49 (m, 16 H), 3.48–3.34 (m, 18 H), 3.28 (dd, *J* = 8.7, 6.2 Hz, 4 H), 2.29–2.19 (m, 2 H).

^{13}C NMR: δ = 153.5, 152.4, 128.8, 128.3, 128.0, 124.3, 115.5, 114.6, 102.1, 102.0, 101.9, 100.1, 82.7, 82.3, 82.1, 79.3, 73.3, 72.7, 72.1, 71.9, 71.8, 64.8, 64.3, 60.0, 55.3, 46.5, 40.4, 29.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{49}H_{76}N_3O_{32}$: 1218.4406; found: 1218.4380.

Mono-2-*O*-({1-[3-(2,6-dimethoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl)-α-CD (7c)

White powder; yield: 1070 mg (0.86 mmol, 86%).

IR (KBr): 3333, 2930, 2844, 2095, 1651, 1509, 1480, 1463, 1409, 1364, 1334, 1297, 1257, 1155, 1111, 1080, 1032, 949, 845, 751, 705, 608, 573, 529 cm^{-1}.

^1H NMR: δ = 8.11 (s, 1 H), 7.00 (t, *J* = 8.4 Hz, 1 H), 6.67 (dd, *J* = 8.4, 2.4 Hz, 2 H), 5.71 (d, *J* = 6.6 Hz, 1 H), 5.65–5.37 (m, 7 H), 4.91–4.73 (m, 6 H), 4.59 (t, *J* = 7.1 Hz, 2 H), 4.54–4.42 (m, 5 H), 4.33 (s, 1 H), 4.04–3.94 (m, 1 H), 3.87 (t, *J* = 5.9 Hz, 2 H), 3.84–3.71 (m, 9 H), 3.72–3.49 (m, 14 H), 3.47–3.18 (m, 17 H), 2.14 (dd, *J* = 13.3, 6.3 Hz, 2 H).

^{13}C NMR: δ = 153.3, 143.7, 136.2, 128.8, 128.1, 127.8, 124.2, 123.9, 105.5, 102.1, 102.0, 101.9, 100.0, 82.7, 82.3, 82.1, 79.3, 73.2, 73.2, 72.7, 72.1, 71.9, 71.7, 69.1, 64.3, 60.0, 55.9, 46.7, 40.4, 30.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{50}H_{78}N_3O_{33}$: 1248.4512; found: 1248.4487.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380701.

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