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Complete Sets of Monosubstituted γ-Cyclodextrins as Precursors for Further Synthesis

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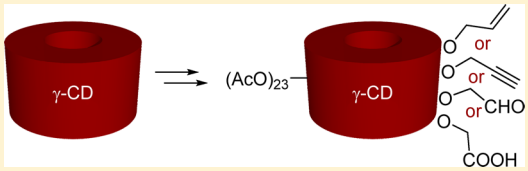
Supporting Information

ABSTRACT: Regioselective alkylation of γ-cyclodextrin with allyl or propargyl bromide, using optimized reaction conditions, followed by peracetylation of the remaining hydroxyl groups and separation of isomers resulted in the set of peracetylated 2^{I}-*O*-, 3^{I}-*O*- and 6^{I}-*O*-alkylated cyclodextrins in up to 19% yields. Ozonolysis or oxidative cleavage of peracetylated allyl derivatives resulted in a complete set of peracetylated 2^{I}-*O*-, 3^{I}-*O*-, and 6^{I}-*O*-formylmethyl or -carboxymethyl derivatives. All of these derivatives are useful precursors for further preparation of regioselectively monosubstituted derivatives of γ-cyclodextrin.



Cyclodextrins[1] (CDs) are macrocyclic compounds with cone-shaped cavity formed by α-1,4-linked D-glucopyranose units. The most widely used CDs are α-, β-, and γ-CD with 6, 7, or 8 glucose units respectively. CDs are very popular building blocks for supramolecular structures, and they are well-known to function as host molecules in aqueous solutions.[2] Chemically modified cyclodextrins allow numerous applications in separation methods,[3] as chemosensors,[4] as artificial enzymes,[5] and in the pharmaceutical industry.[6] CDs can be selectively modified by chemical derivatization. However, this selective modification remains a real challenge, originating from the statistic factors imposed by the large number of hydroxyl groups.[7] The precise structure is essential for the above-mentioned applications because properties of cyclodextrin derivatives highly depend on the position of substituents on the cyclodextrin skeleton.[8]

Preparation of monosubstituted cyclodextrin derivatives could be carried out in two steps: direct monosubstitution of cyclodextrin with a suitable functional group and subsequent transformation of this functional group already regioselectively attached to the cyclodextrin. The advantage of this approach is obvious: it is sufficient to examine reactivity of only a small number of alkylating agents for the preparation of a much larger number of derivatives. In this regard, ideal starting substrates should be selectively allylated, propargylated, formylmethylated, or carboxymethylated cyclodextrins in which the functional group could participate in further reactions, e.g., cross-metathesis,[9] copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[10] Wittig reaction,[11] amide formation,[12] etc. Formylmethyl or carboxymethyl derivatives can be prepared from allyl derivatives by oxidative cleavage.[13,14]

As to the currently widely used CuAAC, it should be mentioned that it is mostly carried out with the azide group attached to the CD skeleton and the alkyne group to the other reagent. This approach, however, does not allow easy substitutions in all positions on CD.

Although the majority of the complete sets of 2^{I}-*O*-, 3^{I}-*O*-, and 6^{I}-*O*-allyl, -propargyl, -formylmethyl, and -carboxymethyl-α-CD[9,10,14−16] or -β-CD[10,13,15,17−22] have already been prepared, γ-CD remains almost untouched. Only a few of the mentioned derivatives of γ-CD are known, and the description of their synthesis and properties is often incomplete.

Although Tarver et al. described[23] 2^{I}-*O*-allyl-γ-CD, it was only briefly mentioned, and no yield or characterizations were given. 2^{I}-*O*-Propargyl-6^{I-VIII}-octakis-*O*-(*tert*-butyldimethylsilyl)-γ-CD was described by Aime et al.[24] 6^{I}-*O*-Allyl-γ-CD and per-*O*-acetyl-6^{I}-*O*-allyl-γ-CD were recently fully characterized by our group.[9] 6^{I}-*O*-Carboxymethyl-γ-CD was only mentioned in claims of some patents,[25−27] but no synthetic procedures were given.

Herein, we report on the preparation of complete sets of peracetylated 2^{I}-*O*-, 3^{I}-*O*-, and 6^{I}-*O*-allyl, -propargyl, -formylmethyl, and -carboxymehyl derivatives of γ-CD.

At the outset, complete sets of acetylated 2^{I}-*O*-, 3^{I}-*O*-, and 6^{I}-*O*-allyl- and -propargyl-γ-cyclodextrins were prepared (Scheme 1). Our attempts to separate mixtures of 2^{I}-*O*- and 3^{I}-*O*- allyl or propargyl isomers (**1a**, **1b** or **2a**, **2b**) were unsuccessful. Column chromatography on silica gel (various ratios of propan-1-ol/water/aqueous ammonia or acetonitrile/water/aqueous ammonia) or on reversed silica gel phase (various ratios of methanol/water) did not lead to separation of single isomers; thus, peracetylation of a mixture of mono-*O*-allyl or propargyl derivatives was carried out. Peracetylated mono-*O*-alkyl derivatives were separated from each other by column chromatography. Peracetylation of remaining hydroxyl groups has another two advantages: (i) signals in NMR spectra are easier to assign and (ii) acetylated hydroxyl groups do not undergo side reactions during the oxidation of the double bond (in the case of allyl derivatives).

Various conditions were used for the preparation of mono-*O*-allyl and propargyl derivatives (Table 1). These conditions were successfully used in our research group as the highest-

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Scheme 1. Preparation of Peracetylated 2^I-*O*-, 3^I-*O*-, and 6^I-*O*-Allyl- and -Propargyl-γ-cyclodextrins

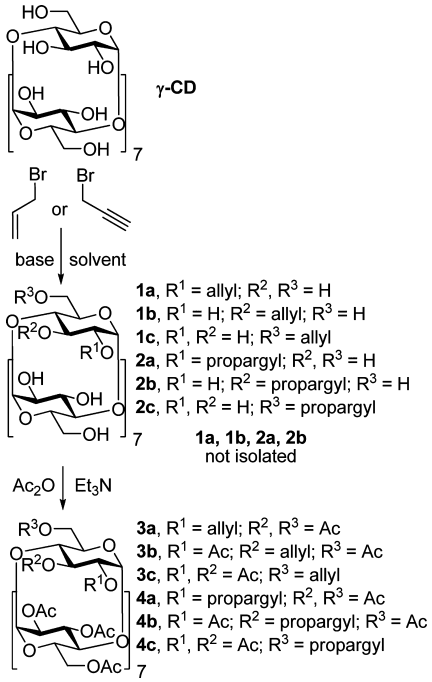


Table 1. Yields of Alkylation (after Acetylation)

			yields (%)		
entry	alk[a]	base, solvent	2^I-*O*-	3^I-*O*-	6^I-*O*-
1	all	LiH, LiI, DMSO	6	1	
2	pro	LiH, LiI, DMSO	4		
3	all	2 equiv of NaOH, H_2O/ACN	19	11	
4	pro	2 equiv of NaOH, H_2O/ACN	13	8	
5	all	30 equiv of NaOH, H_2O			18
6	pro	30 equiv of NaOH, H_2O			12

[a]Alkylation agent: allyl (all) or propargyl (pro) bromide.

yielding alkylation conditions for preparation of 2^I-*O*-, 3^I-*O*-, and 6^I-*O*-allyl or cinnamyl derivatives of α-CD.[14] Yields are stated after alkylation and acetylation so that 2^I-*O*-, 3^I-*O*-, and 6^I-*O*- (which were also isolated in nonacetylated form) derivatives could be compared.

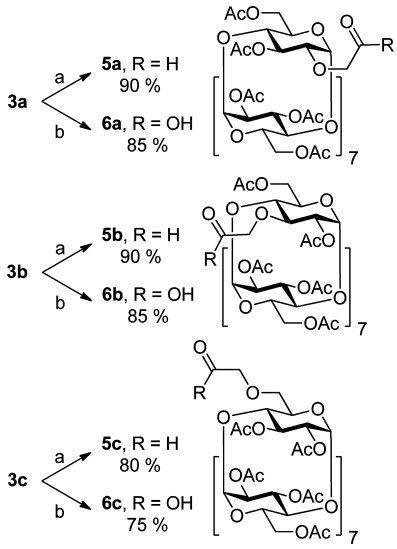
First, the procedure of Hanessian et al.[15] originally used for preparation 2^I-*O*-allyl-α-CD was tried out (entries 1 and 2, Table 1). Yields for this reaction on α- or β-CD usually vary from 24 to 29%.[14,15,28] Surprisingly, these reaction conditions did not lead, in the case of γ-CD, to the same yields. Only 6 and 4% yields were obtained.

Reaction conditions originally developed in our group for 3^I-*O*-cinnamylation of β-CD[13] and successfully applied in the synthesis 2^I-*O*- and 3^I-*O*-allyl derivatives of α-CD[14] were used herein for allylation and propargylation of γ-CD (entries 3 and 4, Table 1). Yields for allyl derivatives **3a** and **3b** (19 and 11%) were similar to those obtained for the corresponding derivatives of α-CD (17 and 10%).[14] In the case of propargyl derivatives **4a** and **4b**, the yields were slightly lower (13 and 8%). In light of these facts, it could be generalized that the reaction conditions consisting of 2 equiv of sodium hydroxide in a mixture of water and acetonitrile (ACN) are very good for preparation of otherwise hardly accessible 3^I-*O* derivatives of cyclodextrins and are the alternative choice when Hanessian's conditions for preparation of 2^I-*O* derivatives have failed.

Entry 5 of Table 1 shows, for comparison, the yield of 6^I-*O* derivative **3c** reported by our group.[9] The same conditions were used for the synthesis of propargyl derivative **4c**, which was obtained in 12% yield. The cooling of the reaction mixture used at the start of this reaction should prevent the eventual overheating and excessive hydrolysis of the alkylation reagent.

The 2^I-*O*-, 3^I-*O*- and 6^I-*O*-peracetylated allyl derivatives of γ-CD (**3a–c**) were used for the synthesis of sets of formylmethyl and carboxymethyl derivatives (Scheme 2). Aldehydes **5a–c**

Scheme 2. Preparation of Peracetylated 2^I-*O*-, 3^I-*O*-, and 6^I-*O*-Formylmethyl- and -Carboxymethyl-γ-cyclodextrins[a]



[a]Key: (a) (1) O_3, (2) Me_2S; (b) $NaIO_4$, $RuCl_3$.

were prepared by ozonolysis of **3a–c** followed by reduction with dimethyl sulfide in 80–90% yields. Carboxylic acids **6a–c** were prepared by oxidative cleavage of the same allyl derivatives by sodium periodate under catalysis of ruthenium(III) chloride in 75–85% yields.

All prepared compounds were characterized by ^1H and ^{13}C NMR spectra, and the recognition between 2^I-*O*, 3^I-*O*, and 6^I-*O* isomers was done with the aid of 2D NMR techniques such as COSY, HSQC, and HMBC. An example of the assignment of the propargyl derivative **4a** is shown in Figure 1. COSY allows

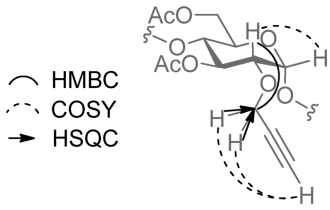


Figure 1. Example of the assignment of the propargyl derivative **4a**.

identification of hydrogen atoms of propargyl group. HMBC cross-peak of the methylene group of the propargyl group makes it possible to find hydrogen atom on cyclodextrin skeleton in the position where the propargyl group is attached. The position of this hydrogen can be deduced from COSY cross-peaks on the glucose unit.

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Moreover, our previously suggested method[14] for distinguishing single isomers from each other using only simple ^{1}H NMR spectrum was confirmed on all derivatives **3**–**6**. All peracetylated 2^I-*O* derivatives have one characteristic H-2 NMR signal (dd) shifted out of the usual region for acetylated CDs, 3^I-*O* derivatives have the integral of H-3 atoms reduced to 7, and 6^I-*O* derivatives have one C-6 methylene signal shifted downfiled in APT spectra.

All prepared acetylated cyclodextrins can be easily deprotected by Zemplene deacetylation (e.g., for applications in aqueous environments) as described previously.[8,9,13,14]

EXPERIMENTAL SECTION

I. General Information. Procedures with the highest yields for preparation of monosubstituted allyl and propargyl derivatives are described. All solvents were used as obtained unless otherwise noted. γ-Cyclodextrin was purchased from WAKO Chemicals (Germany) and was used as obtained unless otherwise noted. Other reagents were obtained from common commercial sources. Ozonolysis was performed in a Ozone Tech Systems (Sweden) ACT-3000 apparatus. ^{1}H NMR spectra were recorded at 600.17 MHz and ^{13}C NMR at 150.04 MHz as solutions in deuterated solvents and referenced to residual solvent peak. Chemical shifts are given on δ scale, and coupling constants *J* are given in Hz. Numbering of atoms for NMR spectra transcription was done analogous to Figure 2. The glucose unit

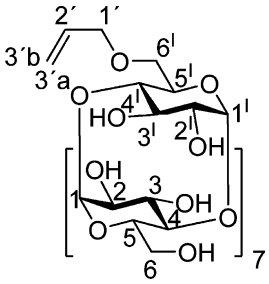

Figure 2. Numbering of atoms in cyclodextrin derivatives.

bearing an alkyl substituent is labeled with "I" where the assignment is unambiguous. All other glucose signals are numbered indiscriminately. The alkyl substituent is labeled with a prime. The assignment of the ^{1}H and ^{13}C signals was based on 2D NMR techniques (^{1}H–^{1}H COSY, HSQC, HMBC) and APT.

Infrared spectra were acquired in KBr by the DRIFT technique, and they are reported in wavenumbers (cm^{-1}). HRMS (MALDI-TOF) spectra were recorded with (*E*)-2-cyano-3-(4-hydroxyphenyl)acrylic acid as a matrix. Silica gel 60 (0.040–0.063 mm, Merck, Germany) was used for chromatography. TLC was performed on silica gel 60 F254-coated aluminum sheets (Merck, Germany). Spots were detected by spraying with 50% aqueous H_2SO_4 solution and carbonization with a heat-gun. All yields below 0.1 g were rounded down to the nearest multiple of 5%.

II. Synthesis of Cyclodextrin Derivatives. *6^I-O-Allyl-γ-cyclodextrin (1c).* Compound **1c** was prepared following a previously reported procedure.[9]

6^I-O-Propargyl-γ-cyclodextrin (2c). γ-Cyclodextrin (2 g, 1.54 mmol) was dissolved in solution of NaOH (3.2 g, 80 mmol) in water (10 mL). The solution was cooled to 0 °C, and propargyl bromide (0.245 mL, 80% solution in toluene, 2.32 mmol) was added dropwise with stirring. The mixture was then stirred for 2 days at room temperature. The reaction was monitored by TLC (propan-1-ol/water/ethyl acetate/aqueous ammonia, 6/3/1/1) and quenched with 50% H_2SO_4 to neutral pH. Products were precipitated with acetone (500 mL) and filtered off. 6^I-*O*-Propargyl-γ-cyclodextrin (**2c**) was separated by chromatography on a silica gel column (propan-1-ol/water/aqueous ammonia, 7/3/1). Na_2SO_4 (product of neutralization) was also removed in this step. Workup afforded 274 mg (13%) of the title compound as a white powder. Mp > 200 °C dec. $[\alpha]^{20}_D$ = +67 (*c* 1.0, H_2O). ^{1}H NMR (600 MHz, D_2O): δ = 5.17 (d, 1 H, H-1), 5.15–5.10 (m, 7 H, 7 × H-1), 4.31 (dd, *J* = 15.8, 1.9 Hz, 1 H, H-1′), 4.25 (dd, *J* = 15.8, 1.8 Hz, 1 H, H-1′), 4.04–3.56 (m, 48 H, 8 × H-2, 8 × H-3, 8 × H-4, 8 × H-5, 16 × H-6), 2.93 (s, 1 H, H-3′) ppm. ^{13}C NMR (150 MHz, D_2O): δ = 103.6–103.5 (6 × C-1), 103.3 (C-1), 103.0 (C-1), 82.4–71.7 (8 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 81.4 (C-2′), 78.1 (C-3′), 70.3 (C-6^I), 62.21–62.16 (7 × C-6), 60.2 (C-1′) ppm. IR (drift KBr): ν = 1108, 1078, 1027, 614 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{51}H_{82}O_{40}Na$ [M + Na]$^+$ 1357.4280, found 1357.4275.

Per-O-acetyl-2^I-O-allyl-γ-cyclodextrin (3a). γ-Cyclodextrin (2 g, 1.54 mmol) was dissolved in a mixture of water (47 mL) and acetonitrile (16 mL). The mixture was cooled to 0 °C. Then solutions of allyl bromide (134 μL, 1.54 mmol) in acetonitrile (1 mL) and NaOH (124 mg, 3.08 mmol) in water (0.33 mL) were added. The mixture was stirred overnight at room temperature. The reaction was monitored by TLC (propan-1-ol/water/ethyl acetate/aqueous ammonia, 6/3/1/1). The reaction was quenched with 50% H_2SO_4 (to neutral pH). Products were precipitated with acetone (550 mL) and filtered off. Mono-*O*-allyl-γ-cyclodextrins were separated by chromatography on silica gel column (propan-1-ol/water/aqueous ammonia, 7/3/1). Na_2SO_4 (product of neutralization) was also removed in this step. The obtained mixture of mono-*O*-allyl-γ-cyclodextrins was then peracetylated. The suspension of mono-*O*-allyl-γ-cyclodextrins in acetic anhydride (4.5 mL) and triethylamine (4.5 mL) was stirred at 80 °C overnight. The reaction mixture was diluted with $CHCl_3$ and washed with 5% HCl, and the organic layer was evaporated in vacuo to give a brown residue that was purified by chromatography on silica gel ($CHCl_3$/MeOH, 70/1). Workup afforded as a main product 547 mg (19% overall yield) of the title compound as a white powder. Mp: 142–145 °C. $[\alpha]^{20}_D$ = +125 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.83 (ddt, *J* = 10.8, 5.7, 5.7 Hz, 1 H, H-2′), 5.39–5.16 (m, 10 H, 2 × H-3′, 8 × H-3), 5.15 (d, *J* = 3.8 Hz, 1 H, H-1), 5.13 (d, *J* = 3.3 Hz, 3 H, 3 × H-1), 5.11 (d, *J* = 3.9 Hz, 1 H, H-1), 5.09 (d, *J* = 3.7 Hz, 1 H, H-1), 5.08 (d, *J* = 3.6 Hz, 1 H, H-1), 4.87 (d, *J* = 3.0 Hz, 1 H, H-1^I), 4.80–4.69 (m, 7 H, 7 × H-2), 4.62–3.95 (m, 26 H, 2 × H-1′, 8 × H-5, 16 × H-6), 3.75–3.64 (m, 8 H, 8 × H-4), 3.28 (dd, *J* = 9.9, 3.1 Hz, 1 H, H-2^I), 2.16–1.99 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0–169.0 (23 × C═O), 134.4 (C-2′), 117.8 (C-3′), 98.4 (C-1^I), 96.6 (C-1), 96.52 (C-1), 96.45 (C-1), 96.3 (C-1), 96.22 (C-1), 96.16 (C-1), 96.1 (C-1), 78.3–69.1 (7 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 78.2 (C-2^I), 72.3 (C-1′), 62.9–62.4 (8 × C-6), 21.0–20.8 (23 × CH_3) ppm. IR (drift KBr): ν = 1757, 1368, 1236, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{97}H_{130}O_{63}Na$ [M + Na]$^+$ 2325.6866, found 2325.6861.

Per-O-acetyl-3^I-O-allyl-γ-cyclodextrin (3b). The procedure for preparation of compound **3a** also afforded as a product 319 mg (11% overall yield) of the title compound as a white powder. Mp: 145–148 °C. $[\alpha]^{20}_D$ = +135 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.91 (m, 1 H, H-2′), 5.49 (t, *J* = 9.4 Hz, 1 H, H-3), 5.38–5.23 (m, 7 H, H-3′, 6 × H-3), 5.15 (d, *J* = 3.9 Hz, 1 H, H-1), 5.13 (d, *J* = 3.7 Hz, 2 H, 2 × H-1), 5.13–5.07 (m, 5 H, H-3′, 4 × H-1), 5.05 (d, *J* = 3.6 Hz, 1 H, H-1), 4.75–4.62 (m, 8 H, 8 × H-2), 4.56–3.91 (m, 25 H, 2 × H-1′, 7 × H-5, 16 × H-6), 3.80 (d, *J* = 9.3 Hz, 1 H, H-5^I), 3.76–3.60 (m, 8 H, H-3^I, 7 × H-4), 3.53 (t, *J* = 9.2 Hz, 1 H, H-4^I), 2.12–1.99 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9–169.3 (23 × C═O), 135.5 (C-2′), 116.0 (C-3′), 97.4 (C-1), 96.6 (C-1), 96.5 (C-1), 96.4 (C-1), 96.3 (2 × C-1), 96.2 (C-1), 96.0 (C-1), 80.5 (C-4^I), 77.3 (C-3^I), 77.2–69.3 (8 × C-2, 7 × C-3, 7 × C-4, 7 × C-5), 74.9 (C-1′), 70.2 (C-5^I), 62.6–62.2 (8 × C-6), 21.0–20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1751, 1371, 1242, 1048 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{97}H_{130}O_{63}Na$ [M + Na]$^+$ 2325.6866, found 2325.6861.

Per-O-acetyl-6^I-O-allyl-γ-cyclodextrin (3c). Compound **3c** was prepared following a previously reported procedure.[9]

Per-O-acetyl-2^I-O-propargyl-γ-cyclodextrin (4a). γ-Cyclodextrin (1.15 g, 0.77 mmol) was dissolved in a mixture of water (24 mL) and acetonitrile (8 mL). The mixture was cooled to 0 °C. Then solutions of propargyl bromide (85 μL, 80% solution in toluene, 0.77 mmol) in acetonitrile (0.5 mL) and NaOH (56 mg, 1.4 mmol) in

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water (0.2 mL) were added. The mixture was stirred overnight at room temperature. The reaction was monitored by TLC (propan-1-ol/water/ethyl acetate/aqueous ammonia, 6/3/1/1). The reaction was quenched with 50% H_2SO_4 (to neutral pH). Products were precipitated with acetone (500 mL) and filtered off. Mono-*O*-propargyl-γ-cyclodextrins were separated by chromatography on silica gel column (propan-1-ol/water/aqueous ammonia, 7/3/1). Na_2SO_4 (product of neutralization) was also removed in this step. The obtained mixture of mono-*O*-propargyl-γ-cyclodextrins was then peracetylated. A suspension of mono-*O*-propargyl-γ-cyclodextrins in acetic anhydride (1.5 mL) and triethylamine (1.5 mL) was stirred at 80 °C overnight. The reaction mixture was diluted with $CHCl_3$ (100 mL) and washed with 5% HCl (2 × 100 mL), and the organic layer was evaporated in vacuo to give a brown residue that was purified by chromatography on silica gel ($CHCl_3$/MeOH, 100/1). Workup afforded as a main product 256 mg (13% overall yield) of the title compound as a white powder. Mp: 146−148 °C. $[\alpha]^{20}_D$ = +116 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.38−5.25 (m, 8 H, 8 × H-3), 5.15 (d, *J* = 3.8 Hz, 1 H, H-1), 5.13 (d, *J* = 3.5 Hz, 2 H, 2 × H-1), 5.12 (d, *J* = 2.5 Hz, 1 H, H-1), 5.11 (d, *J* = 3.8 Hz, 1 H, H-1), 5.09 (d, *J* = 3.8 Hz, 1 H, H-1), 5.08 (d, *J* = 3.7 Hz, 1 H, H-1), 4.99 (d, *J* = 3.4 Hz, 1 H, H-1^I), 4.76−4.68 (m, 7 H, 7 × H-2), 4.58−3.94 (m, 26 H, 2 × H-1′, 8 × H-5, 16 × H-6), 3.74−3.62 (m, 8 H, 8 × H-4), 3.48 (dd, *J* = 10.0, 3.4 Hz, 1 H, H-2^I), 2.44 (t, *J* = 2.3 Hz, 1 H, H-3′), 2.12−1.99 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9−169.0 (23 × C═O), 98.5 (C-1^I), 96.7 (C-1), 96.5 (C-1), 96.4 (C-1), 96.3 (C-1), 96.21 (C-1), 96.19 (C-1), 96.1 (C-1), 79.5 (C-2′), 78.4−69.1 (8 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 75.2 (C-3′), 62.8 (C-6), 62.62 (C-6), 62.61 (C-6), 62.5 (2 × C-6), 62.42 (C-6), 62.39 (C-6), 62.37 (C-6), 58.4 (C-1′), 21.0−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1748, 1368, 1239, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{97}H_{128}O_{63}Na$ [M + Na]$^+$ 2323.6710, found 2323.6704.

*Per-O-acetyl-3^I-O-propargyl-γ-cyclodextrin (**4b**).* The procedure for preparation of compound **4a** also afforded as a product 154 mg (8% overall yield) of the title compound as a white powder. Mp: 143−146 °C. $[\alpha]^{20}_D$ = +126 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.48 (t, *J* = 9.6 Hz, 1 H, H-3), 5.40−5.24 (m, 6 H, 6 × H-3), 5.16 (d, *J* = 3.5 Hz, 1 H, H-1), 5.16 (d, *J* = 3.9 Hz, 1 H, H-1), 5.15 (d, *J* = 4.1 Hz, 1 H, H-1), 5.12 (d, *J* = 3.6 Hz, 1 H, H-1), 5.10 (d, *J* = 3.6 Hz, 2 H, 2 × H-1), 5.09 (d, *J* = 3.5 Hz, 1 H, H-1), 5.05 (d, *J* = 3.5 Hz, 1 H, H-1), 4.76−4.61 (m, 8 H, 8 × H-2), 4.58−3.93 (m, 25 H, 2 × H-1′, 7 × H-5, 16 × H-6), 3.88 (t, *J* = 9.5 Hz, 1 H, H-3^I), 3.82−3.60 (m, 8 H, H-5^I, 7 × H-4), 3.52 (t, *J* = 9.3 Hz, 1 H, H-4^I), 2.63−2.60 (m, 1 H, H-3′), 2.17−2.00 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0−169.3 (23 × C═O), 97.64 (C-1), 96.61 (C-1), 96.4 (C-1), 96.3 (C-1, C-1^I), 96.2 (C-1), 96.10 (C-1), 96.08 (C-1), 80.7 (C-4^I), 80.3 (C-2′), 77.2−69.3 (7 × C-2, 7 × C-3, 7 × C-4, 7 × C-5), 76.9 (C-3^I), 75.1 (C-3′), 71.7 (C-2), 70.2 (C-5^I), 62.6 (C-6), 62.53 (C-6), 62.51 (C-6), 62.48 (C-6), 62.4 (C-6^I), 62.28 (C-6), 62.26 (C-6), 62.2 (C-6), 61.2 (C-1′), 21.2−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1751, 1368, 1242, 1045 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{97}H_{128}O_{63}Na$ [M + Na]$^+$ 2323.6710, found 2323.6704.

*Per-O-acetyl-6^I-O-propargyl-γ-cyclodextrin (**4c**).* A suspension of propargyl derivative **2c** (274 mg, 0.21 mmol) in acetic anhydride (5 mL, 53 mmol) and triethylamine (5 mL, 36 mmol) was stirred at 80 °C overnight. The reaction mixture was diluted with $CHCl_3$ and washed with 5% HCl, and the organic layer was evaporated in vacuo to give a brown residue that was purified by chromatography on silica gel ($CHCl_3$/MeOH, 100/1). Workup afforded 448 mg (95%) of the title compound as a white powder. Mp: 147−149 °C. $[\alpha]^{20}_D$ = +135 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.38−5.27 (m, 8 H, 8 × H-3), 5.19 (d, *J* = 3.8 Hz, 1 H, H-1), 5.14 (d, *J* = 3.9 Hz, 1 H, H-1), 5.12 (d, *J* = 3.8 Hz, 1 H, H-1), 5.12 (d, *J* = 3.8 Hz, 1 H, H-1), 5.11 (d, *J* = 3.7 Hz, 2 H, 2 × H-1), 5.09 (d, *J* = 3.9 Hz, 1 H, H-1), 5.08 (d, *J* = 3.8 Hz, 1 H, H-1), 4.76−4.69 (m, 8 H, 8 × H-2), 4.59−3.63 (m, 32 H, 8 × H-4, 8 × H-5, 16 × H-6), 4.20 (dd, *J* = 15.9, 2.3 Hz, 1 H, H-1′), 4.16 (dd, *J* = 15.9, 2.3 Hz, 1 H, H-1′), 2.48 (t, *J* = 2.3 Hz, 1 H, H-3′), 2.13−2.01 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.7−169.3 (23 × C═O), 96.43 (C-1), 96.36 (C-1), 96.33 (C-1), 96.25 (C-1), 96.20 (2 × C-1), 96.18 (C-1), 96.16 (C-1), 79.0 (C-2′), 77.2−69.5 (8 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 75.4 (C-3′), 67.5 (C-6^I), 62.6 (2 × C-6), 62.53 (C-6), 62.51 (C-6), 62.43 (2 × C-6), 62.40 (C-6), 58.7 (C-1′), 20.8−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1748, 1371, 1239, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{97}H_{128}O_{63}Na$ [M + Na]$^+$ 2323.6710, found 2323.6704.

General Procedure for Ozonolysis of Peracetylated Mono-O-allyl γ-Cyclodextrins. Ozone was bubbled through a solution of peracetylated mono-*O*-allyl γ-cyclodextrin (100 mg, 43 μmol for **3a** and **3b**; 80 mg, 35 μmol for **3c**) in a mixture of MeOH (1 mL for **3a** and **3b**; 0.85 mL for **3c**) and $CHCl_3$ (1 mL for **3a** and **3b**; 0.85 mL for **3c**) at −78 °C for 10 min. The reaction was quenched by addition of dimethyl sulfide (0.5 mL for **3a** and **3b**; 0.4 mL for **3c**). The reaction mixture was evaporated after reaching laboratory temperature. Purification by chromatography on silica gel ($CHCl_3$/MeOH, 50/1) afforded the desired product.

*Per-O-acetyl-2^I-O-formylmethyl-γ-cyclodextrin (**5a**).* The reaction was run with compound **3a**. Workup afforded 92 mg (90%) of the title compound as a white powder. Mp: 143−146 °C. $[\alpha]^{20}_D$ = +119 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.37−5.27 (m, 8 H, 8 × H-3), 5.15 (d, *J* = 3.7 Hz, 1 H, H-1^I), 5.14 (d, *J* = 4.0 Hz, 1 H, H-1), 5.13 (d, *J* = 3.5 Hz, 2 H, 2 × H-1), 5.11−5.07 (m, 4 H, 4 × H-1), 4.76−4.68 (m, 7 H, 7 × H-2), 4.55−3.64 (m, 31 H, 7 × H-4, 8 × H-5, 16 × H-6), 4.21 (s, 2 H, 2 × H-1′), 3.62 (t, *J* = 9.5 Hz, 1 H, H-4^I), 3.30 (dd, *J* = 9.8, 3.2 Hz, 1 H, H-2^I), 2.13−1.93 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.8 (C-2′), 170.8−169.2 (23 × C═O), 98.2 (C-1), 96.6 (C-1), 96.4 (C-1), 96.32 (C-1), 96.26 (C-1), 96.21 (2 × C-1), 96.15 (C-1), 79.6 (C-2^I), 77.5−69.5 (7 × C-2, 7 × C-3, 8 × C-4, 8 × C-5), 76.6 (C-1′), 72.1 (C-3^I), 62.7−62.4 (8 × C-6), 21.0−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1748, 1371, 1239, 1039 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{64}Na$ [M + Na]$^+$ 2327.6659, found 2327.6654.

*Per-O-acetyl-3^I-O-formylmethyl-γ-cyclodextrin (**5b**).* The reaction was run with compound **3b**. Workup afforded 90 mg (90%) of the title compound as a white powder. Mp: 145−148 °C. $[\alpha]^{20}_D$ = +131 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.68 (s, 1 H, H-2′), 5.48 (t, *J* = 9.6 Hz, 1 H, H-3), 5.39−5.26 (m, 6 H, 6 × H-3), 5.18 (d, *J* = 3.8 Hz, 1 H, H-1^I), 5.16 (d, *J* = 3.9 Hz, 1 H, H-1), 5.15 (d, *J* = 3.9 Hz, 1 H, H-1), 5.13 (d, *J* = 3.3 Hz, 1 H, H-1), 5.12 (d, *J* = 3.8 Hz, 1 H, H-1), 5.11 (d, *J* = 3.6 Hz, 1 H, H-1), 5.10 (d, *J* = 3.7 Hz, 1 H, H-1), 5.07 (d, *J* = 3.7 Hz, 1 H, H-1), 4.79 (d, *J* = 18.4 Hz, 1 H, H-1′), 4.75−4.62 (m, 8 H, 8 × H-2), 4.55−3.91 (m, 24 H, 8 × H-5, 16 × H-6), 4.33 (d, *J* = 18.4 Hz, 1 H, H-1′), 3.80−3.58 (m, 9 H, H-3^I, 8 × H-4), 2.13−1.98 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.3 (C-2′), 170.7−169.4 (23 × C═O), 97.5 (C-1), 96.7 (C-1), 96.5 (C-1), 96.28 (C-1), 96.25 (C-1), 96.2 (C-1), 96.1 (C-1), 95.9 (C-1), 80.3−69.3 (8 × C-2, 7 × C-3, 8 × C-4, 8 × C-5), 79.8 (C-1′), 79.2 (C-3^I), 62.5−62.2 (8 × C-6), 21.0−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1754, 1374, 1236, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{64}Na$ [M + Na]$^+$ 2327.6659, found 2327.6654.

*Per-O-acetyl-6^I-O-formylmethyl-γ-cyclodextrin (**5c**).* The reaction was run with compound **3c**. Workup afforded 67 mg (80%) of the title compound as a white powder. Mp: 144−147 °C. $[\alpha]^{20}_D$ = +121 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.38−5.28 (m, 8 H, 8 × H-3), 5.18 (d, *J* = 3.7 Hz, 1 H, H-1), 5.16 (d, *J* = 3.8 Hz, 2 H, 2 × H-1), 5.13−5.11 (m, 2 H, 2 × H-1), 5.11 (d, *J* = 3.9 Hz, 1 H, H-1), 5.10 (d, *J* = 3.9 Hz, 1 H, H-1), 5.09 (d, *J* = 3.8 Hz, 1 H, H-1), 4.75−4.68 (m, 8 H, 8 × H-2), 4.59−3.61 (m, 34 H, 2 × H-1′, 8 × H-4, 8 × H-5, 16 × H-6), 2.11−2.02 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.7 (C-2′), 170.7−169.3 (23 × C═O), 96.5 (2 × C-1), 96.4 (C-1), 96.34 (C-1), 96.32 (C-1), 96.23 (C-1), 96.20 (2 × C-1), 77.2−69.6 (8 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 77.1 (C-1′), 69.7 (C-6^I), 62.7−62.4 (7 × C-6), 20.8−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1748, 1371, 1236, 1045 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{64}Na$ [M + Na]$^+$ 2327.6659, found 2327.6654.

General Procedure for Oxidative Cleavage of Peracetylated Mono-O-allyl γ-Cyclodextrins. Peracetylated mono-*O*-allyl γ-cyclodextrin (100 mg, 43 μmol for **3a** and **3b**; 80 mg, 35 μmol for **3c**) was dissolved in a mixture of acetonitrile (0.9 mL for **3a** and **3b**; 0.7 mL for **3c**) and a saturated solution of sodium periodate (0.9 mL for **3a** and **3b**; 0.7 mL for **3c**). After addition of ruthenium(III) chloride (11 μL,

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5% solution in water, 3 μmol for **3a** and **3b**; 9 μL, 5% solution in water, 2 μmol for **3c**), the reaction mixture was stirred 1 h at room temperature. The reaction was monitored by TLC ($CHCl_3$/MeOH, 20/1). The reaction mixture was extracted with chloroform (5 mL) three times, and the collected organic layers were washed with $Na_2S_2O_5$ (5 mL, 2% solution in water) twice, dried with magnesium sulfate, and evaporated. Purification by chromatography on silica gel ($CHCl_3$/MeOH, gradient from 20/1 to 5/1) afforded the desired product.

*Per-O-acetyl-2^I-O-carboxymethyl-γ-cyclodextrin (**6a**).* The reaction was run with the compound **3a**. Workup afforded 87 mg (85%) of the title compound as a white powder: mp 143−146 °C. $[\alpha]^{20}_D$ +118 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.37−5.28 (m, 8 H, 8 × H-3), 5.14−5.08 (m, 8 H, 8 × H-1), 4.74−4.68 (m, 7 H, 7 × H-2), 4.52−3.77 (m, 24 H, 8 × H-5, 16 × H-6), 4.17 (s, 2 H, 2 × H-1′), 3.72−3.64 (m, 7 H, 7 × H-4), 3.62 (t, *J* = 8.9 Hz, 1 H, H-4^I), 3.43 (dd, *J* = 9.3, 3.2 Hz, 1 H, H-2^I), 2.13−1.96 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4 (C-2′), 170.8−169.4 (23 × C═O), 98.1 (C-1), 96.6 (C-1), 96.34 (C-1), 96.30 (C-1), 96.23 (C-1), 96.15 (3 × C-1), 79.0 (C-2^I), 77.2−69.6 (7 × C-2, 7 × C-3, 8 × C-4, 8 × C-5), 71.9 (C-3^I), 68.1 (C-1′), 62.7−62.4 (8 × C-6), 21.0−20.3 (23 × CH_3) ppm. IR (drift KBr): ν = 1751, 1368, 1242, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{65}Na$ [M + Na]$^+$ 2343.6608, found 2343.6603.

*Per-O-acetyl-3^I-O-carboxymethyl-γ-cyclodextrin (**6b**).* The reaction was run with the compound **3b**. Workup afforded 87 mg (85%) of the title compound as a white powder. Mp: 142−145 °C. $[\alpha]^{20}_D$ = +128 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.51 (t, *J* = 9.5 Hz, 1 H, H-3), 5.39−5.26 (m, 6 H, 6 × H-3), 5.20 (d, *J* = 3.8 Hz, 1 H, H-1^I), 5.16 (d, *J* = 3.9 Hz, 1 H, H-1), 5.15 (d, *J* = 4.4 Hz, 1 H, H-1), 5.14 (d, *J* = 4.0 Hz, 1 H, H-1), 5.12 (d, *J* = 4.1 Hz, 1 H, H-1), 5.10 (d, *J* = 4.0 Hz, 1 H, H-1), 5.10 (d, *J* = 3.6 Hz, 1 H, H-1), 5.08 (d, *J* = 3.6 Hz, 1 H, H-1), 4.75−4.62 (m, 9 H, H-1′, 8 × H-2), 4.57−3.62 (m, 33 H, H-1′, H-3^I, 7 × H-4, 8 × H-5, 16 × H-6), 3.60 (t, *J* = 9.4 Hz, 1 H, H-4^I), 2.16−1.99 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0−169.4 (C-2′, 23 × C═O), 97.2 (C-1), 96.5 (C-1), 96.4 (C-1), 96.2 (3 × C-1), 96.0 (C-1), 95.9 (C-1), 80.0 (C-4^I), 78.8 (C-3^I), 77.2−69.2 (8 × C-2, 7 × C-3, 7 × C-4, 8 × C-5), 70.9 (C-1′), 62.5−62.2 (8 × C-6), 21.0−20.6 (23 × CH_3) ppm. IR (drift KBr): ν = 1754, 1368, 1245, 1048 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{65}Na$ [M + Na]$^+$ 2343.6608, found 2343.6603.

*Per-O-acetyl-6^I-O-carboxymethyl-γ-cyclodextrin (**6c**).* The reaction was run with compound **3c**. Workup afforded 64 mg (75%) of the title compound as a white powder. Mp: 140−143 °C. $[\alpha]^{20}_D$ = +125 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.42−5.26 (m, 8 H, 8 × H-3), 5.25 (d, *J* = 3.9 Hz, 1 H, H-1), 5.17 (d, *J* = 3.9 Hz, 1 H, H-1), 5.14 (d, *J* = 3.9 Hz, 1 H, H-1), 5.12 (d, *J* = 3.7 Hz, 1 H, H-1), 5.09 (d, *J* = 4.4 Hz, 1 H, H-1), 5.08 (d, *J* = 4.4 Hz, 1 H, H-1), 5.07 (d, *J* = 4.1 Hz, 1 H, H-1), 5.06 (d, *J* = 3.7 Hz, 1 H, H-1), 4.76−4.64 (m, 10 H, 8 × H-2, 2 × H-6), 4.55−3.60 (m, 32 H, 2 × H-1′, 8 × H-4, 8 × H-5, 14 × H-6), 2.14−1.97 (m, 69 H, 23 × CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.5 (C-2′), 171.0−169.3 (23 × C═O), 96.5 (C-1), 96.4−96.3 (5 × C-1), 96.2 (C-1), 95.6 (C-1), 77.2−69.4 (8 × C-2, 8 × C-3, 8 × C-4, 8 × C-5), 70.1 (C-6^I), 68.8 (C-1′), 62.7 (2 × C-6), 62.64 (C-6), 62.58 (C-6), 62.5 (C-6), 62.3 (2 × C-6), 20.9−20.7 (23 × CH_3) ppm. IR (drift KBr): ν = 1751, 1368, 1236, 1042 cm^{-1}. HRMS (MALDI): *m*/*z* calcd for $C_{96}H_{128}O_{65}Na$ [M + Na]$^+$ 2343.6608, found 2343.6603.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra (including 2D NMR spectra) of all cyclodextrin derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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