Construction of a Fused Polycyclic Wall within the Cyclodextrin Belt To Ensure a Distorted Cavity: An Unusual *trans*-Diequatorial Ring-Opening Reaction of Cyclodextrin Epoxide Rings

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In the nucleophilic ring-opening reaction of 2^X,3^X-*manno*-epoxides, the incoming nucleophiles attack the 3^X-C position of the epoxide almost exclusively. However, a quite unusual but very interesting reversed regioselectivity is observed when intramolecular hydroxy groups act as nucleophiles, that is, only the attack by 3^{X-1}-OH at the 2^X-C position of the epoxide is observed. The reaction affords the apparent *trans*-diequatorial products and ensures an efficient construction of fused heterocycles within the cyclodextrin belt. In the case of 2^I,3^I:2^{II},3^{II}-di-*manno*-epoxy-β-cyclodextrin, a tandem-type reaction is initiated by the attack by the 3^{VII}-OH group at the 2^I-C position to generate a fused pentacycle.

Introduction

Cyclodextrins (CDs) are important materials in the construction of artificial enzymes and receptors since they provide hydrophobic cavities for molecular recognition and three types of hydroxy groups for functionalization.[1−3] However, their straitjacket structures may limit further investigation. In order to overcome this limitation, attempts have been made to transform the backbone of these macrocycles, for example, by chemical conversion of the glucose residue(s) to 3,6-anhydroglucose(s),[4−13] 2,3-anhydromannose(s),[14−23] 2,3-anhydroallose(s),[6,10,16,24] altrose(s),[25−36] or 3-deoxymannoses.[37−39] However, these transformations only occur within the monosaccharide residues, that is, the linkage between them remains unchanged. Examples of modifications to intersaccharide linkages in CDs are very scarce.[40,41] In this paper, we describe a methodology to construct an additional linkage between adjacent sugar subunits by transforming specific di- and trisaccharide residues into fused tri- or pentacyclic systems within CD backbones. The key step of the methodology involves a novel *trans*-diequatorial opening of the epoxide rings of several *manno*-epoxy-β-CDs by intramolecular nucleophilic attack by the CD−OH groups to generate an ether linkage between adjacent sugar residues (Scheme 1; the labeling, I, II, etc, of the sugar units changes after the reactions).[42]

Anhydro-CDs with the 3^{X-1}-C−O−2^X-C ether linkage seem to be very interesting in several respects. First, their formation is a regiospecific process which implies an unusual apparent *trans*-diequatorial opening of the epoxide rings instead of the usual *trans*-diaxial opening.[42,43] Secondly, the 3^{X-1}-C−O−2^X-C ether linkage causes significant contraction of the truncated cone structure of the CD along the aperture of the CD torus of the secondary hydroxy side.[44] Thirdly, a binding study has indicated that 3^I,2^{II}-anhydro-β-CD **2b** is the only candidate of various CDs with distorted cavities to exhibit a stronger affinity towards methyl orange than native β-CD,[45] even though some of them were able to mimic the induced-fit binding[31] of enzymes.[46]

Results and Discussion

2^I,3^I-*manno*-Epoxy-β-CD **1b**[18,19,29] and 2^I,3^I:2^M,3^M-di-*manno*-epoxy-β-CDs[19,29] **3a**−**3c** were treated with aqueous alkali to give **2b** (63%), **4a** (50%), **4b** (50%), and **4c** (63%), respectively.

The structure of **2b** was determined by analogy of its ^{1}H NMR spectrum (Figure 1) with that of the α-CD derivative **2a** whose structure had been previously established by ^{1}H and ^{13}C NMR of the acid-catalyzed hydrolysis product[42] and X-ray analysis.[44] The structures of **4a**−**4c** were determined as follows. The FAB mass spectra afforded the correct parent ions $[M + H]^+$ and pseudoparent ions. The ^{1}H and ^{13}C NMR spectra of **4a**−**4c** are shown in Figure 2 and

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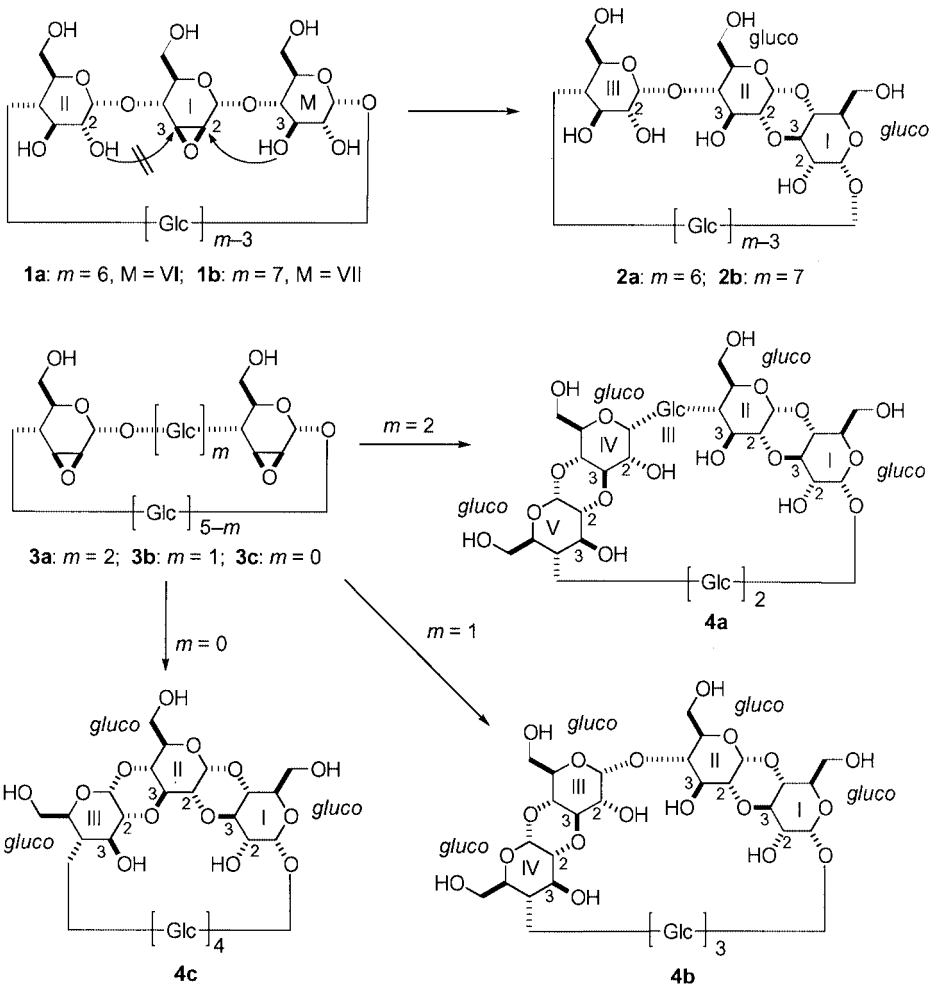


Scheme 1. Regioselective epoxide ring openings of mono- and di-*manno*-epoxy-β-CD systems (note: the labeling of the sugar units changes after the reactions)

3 and Figures 1S−3S (see Supporting Information, for Supporting Information see also the footnote on the first page of this article). In order to determine the stereo- and regiochemistry from the NMR spectra, it was necessary to assign the characteristic signals of 3^{I},2^{II}-anhydro-β-CD **2b** (Figure 1) whose structure has already been determined as mentioned above. In the ^{1}H,^{1}H-COSY NMR spectra ([D_6]DMSO as solvent), the 2-H at δ = 3.58 ppm is coupled with 3-H at δ = 4.15 ppm. The former does not correlate with any hydroxy proton, while the latter is coupled to a hydroxy proton with a characteristically small constant ($J \approx 2.5$ Hz), demonstrating that they are 2^{II}-H and 3^{II}-H, respectively. Moreover, the 3^{II}-C signal in [D_6]DMSO is broad and halved in height on 50% deuteration of the OH groups compared with the 3^{I}-C signal. Such differences are not observed in D_2O (Figure 1S in the Supporting Information), confirming the presence of OH on 3^{II}-C.[47−49] The notable downfield shift of 3^{II}-H may be caused by the ether linkage between 3^{I}-C and 2^{II}-C. This tendency will be seen again in the cases of **4a**−**c**.

The ^{1}H NMR spectra of both **4a** and **4b** show two triplets at δ ≈ 4.4 ppm (Figures 2S and 3S, see Supporting Information) whose chemical shifts and coupling constants are similar to those of 3^{II}-H of **2b**, indicating that the intramolecular interglucosidic reaction in the CD diepoxides is regioselective, just as it is in the case of the monoepoxide (Scheme 1). This is supported by the presence of two C signals at δ = 68.0 and 68.2 ppm for **4a** and δ = 67.7 and 68.3 ppm for **4b**, which compare well with the corresponding signal for 3^{II}-C of **2b** (Figures 2S and 3S in the Supporting Information). The H,H coupling constants $J_{1,2}$ (3.89, 4.12; 3.7, 3.7 Hz), $J_{2,3}$ (8.0, 9.4; 9.6, 9.6 Hz) and $J_{3,4}$ (8.0, 9.4; 9.6, 9.6 Hz for **4a** and **4b**, respectively) of the sugar residues with the characteristic 3-H protons imply an equatorial-axial relationship between 1-H and 2-H, and an axial-axial relationship between 2-H and 3-H, and also between 3-H and 4-H. From these data, **4a** and **4b** were assigned to 3^{I},2^{II}:3^{IV},2^{V}- and 3^{I},2^{II}:3^{III},2^{IV}-dianhydro-β-CDs, respectively.

Two triplet signals are also observed in the ^{1}H NMR spectrum of **4c** (in D_2O) at δ = 4.52 and 4.38 ppm (see b in Figure 2). Signals of all the protons except the methylenes were assigned on the basis of the DQFCOSY, HMQC, TOCSY, DDS, and ROEDS spectra (Table 1). Chemical

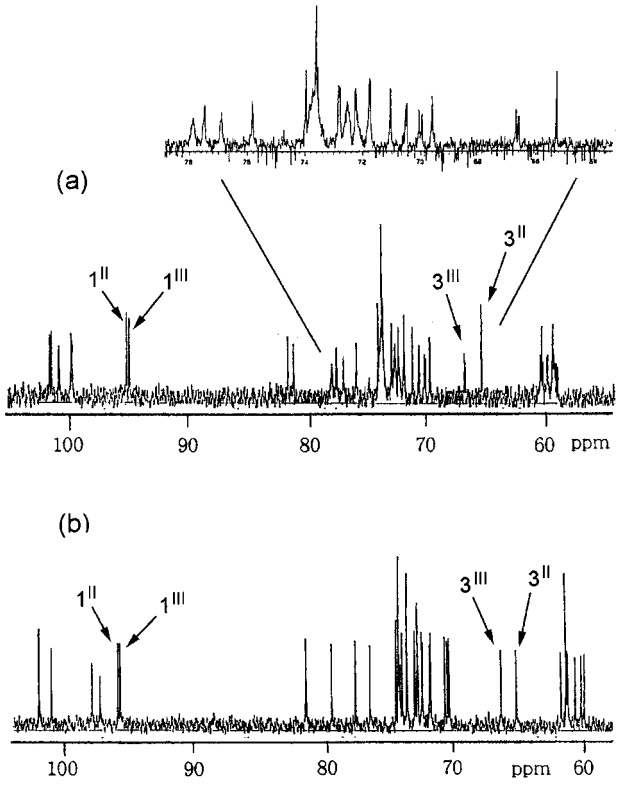


Figure 3. ^{13}C NMR spectra (125 MHz, 35 °C) of $3^{I},2^{II}$:$3^{II},2^{III}$-dianhydro-β-CD **4c** (a) in [D_6]DMSO (TMS int.) with the hydroxy groups of **4c** partially (ca. 50%) deuterated and (b) in D_2O (CH_3CN int.)

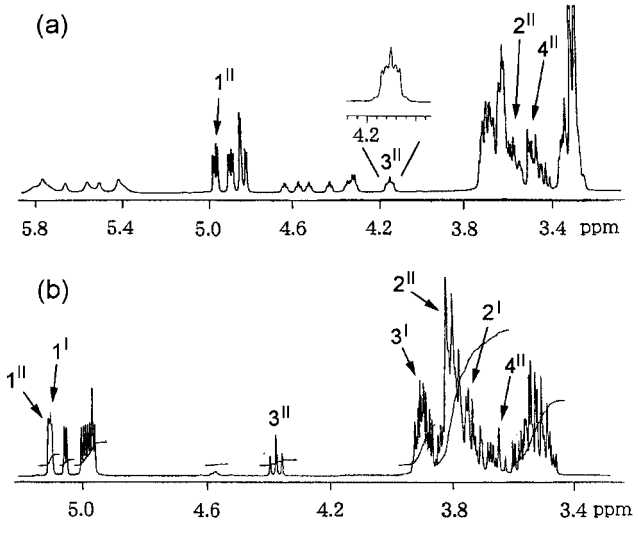


Figure 1. ^1H NMR spectra (500 MHz, 35 °C) of $3^{I},2^{II}$-anhydro-β-CD **2b** (a) in [D_6]DMSO (TMS int.) and (b) in D_2O (CH_3CN int.)

shifts in the same monosugar unit were collected from the TOCSY, DDS, and ROEDS spectra and the coupling constants were obtained from the ROEDS spectra and/or directly from the assigned ^1H NMR spectrum. The sequence of the monosugar units was determined from the ROEDS spectra between 4^{X-1}-H and 1^{X}-H. The coupling constants demonstrate that all the monosaccharide units are $^4C_1$ gluc-

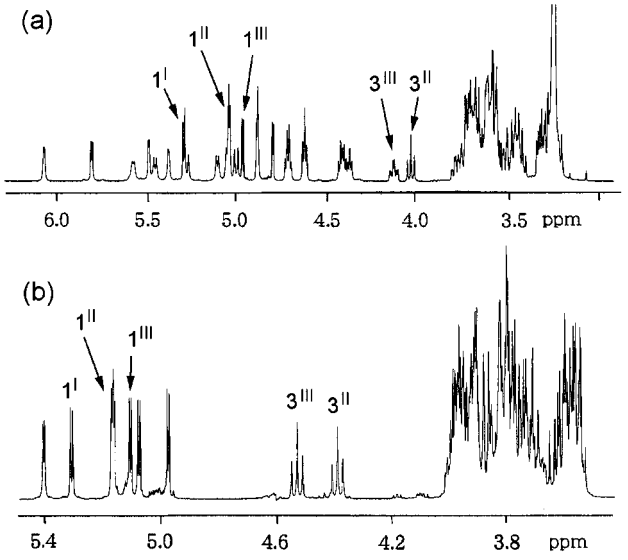


Figure 2. ^1H NMR spectra (500 MHz, 45 °C) of $3^{I},2^{II}$:$3^{II},2^{III}$-dianhydro-β-CD **4c** (a) in [D_6]DMSO (TMS int.) and (b) in D_2O (CH_3CN int.)

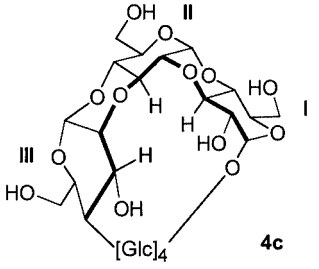
opyranosides, two of which had 3-H protons (3^{II}-H and 3^{III}-H) with very high chemical shifts (δ = 4.38 and 4.52 ppm, respectively) compared with the others (δ = 3.86−3.96 ppm). By changing the solvent from D_2O to [D_6]DMSO (see a in Figure 2), the triplet pattern of the 3^{III}-H signal changed to a doublet ($J_{H,HO}$ = 4.0 Hz) of triplet at δ = 4.13 while the triplet of 3^{II}-H at δ = 4.52 retained the original pattern at δ = 4.03, indicating that 3^{III}-C is linked to an OH group and 3^{II}-C is not linked to an OH, but to an OR group. Moreover, the 3^{III}-C signal at δ = 66.6 ppm in [D_6]DMSO (Figure 3, a) splits into a doublet with Δδ = 0.085 and halves in height upon 50% deuteration of the OH groups, confirming the presence of OH on 3^{III}-C and the absence of OH on the adjacent 2^{III}-C.[42,47−49] On the other hand, the 3^{II}-C signal at δ = 65.4 ppm neither splits nor decreases in height upon 50% deuteration. However, these two signals are almost the same height in D_2O (Figure 3, b). This observation indicates the presence of OR groups instead of OH groups on both 3^{II}-C and 2^{II}-C. Furthermore, the DQFCOSY spectrum of **4c** in [D_6]DMSO showed no coupling of 2^{III}-H with OH, indicating that 2^{III}-O forms an ether linkage.

The formation of anhydro bridges between 3^{I}-OH and 2^{II}-OH and between 3^{II}-OH and 2^{III}-OH in the reaction of **3c** is reasonably well supported by the data discussed above, except for the direct confirmation of the presence of OR instead of OH on 3^{I}-C in **4c**. However, the ROEDS spectrum shows 3^{II}-H to be in close proximity to 3^{I}-H as well as 3^{III}-H although such ROEs were not observed among the other glucoside units IV−VII. The anhydro bridge between 3^{I}-C and 2^{II}-C can bring about this unusual proximity (Scheme 2, one of the referees indicated that his model gave saccharide unit I as a half chair-to-boat conformation).

Table 1. Chemical shifts (δ) and coupling constants (Hz) of $3^{I},2^{II}$:$3^{II},2^{III}$-dianhydro-β-CD **4c** in D_2O[a]

	Chemical shifts [ppm] (coupling constants [Hz])[b]						
	Glucoside I	Glucoside II	Glucoside III	Glucoside IV	Glucoside V	Glucoside VI	Glucoside VII
1-H	5.32 d (4.5)	5.18 d (3.5)	5.12 d (3.5)	5.17 d (4.5)	5.42 d (4.5)	4.98 d (3.5)	5.08 d (4.0)
2-H	3.76 dd (4.5, 10.0)	3.94 dd (3.5, 10.0)	3.77 dd (3.5, 10.0)	3.56 dd (4.5, 10.0)	3.53 dd (4.5, 9.5)	3.53 dd (3.5, 10.0)	3.58 dd (4.0, 9.0)
3-H	3.86 t (10.0)	4.38 t (10.0)	4.52 t (10.0)	3.90 t (10.0)	3.95 t (9.5)	3.96 t (10.0)	3.86 t (9.0)
4-H	3.52 t (10.0)	3.57 t (10.0)	3.69 t (10.0)	3.62 t (10.0)	3.55t (9.5)	3.53 t (10.0)	3.56 t (9.0)
5-H	ca. 3.90	ca. 3.98	ca. 3.96	ca. 3.98	ca. 3.65	ca. 3.80	ca. 3.77

[a] At 35 °C, internal standard: CH_3CN. [b] d: doublet; dd: doublet of doublet; t: triplet.

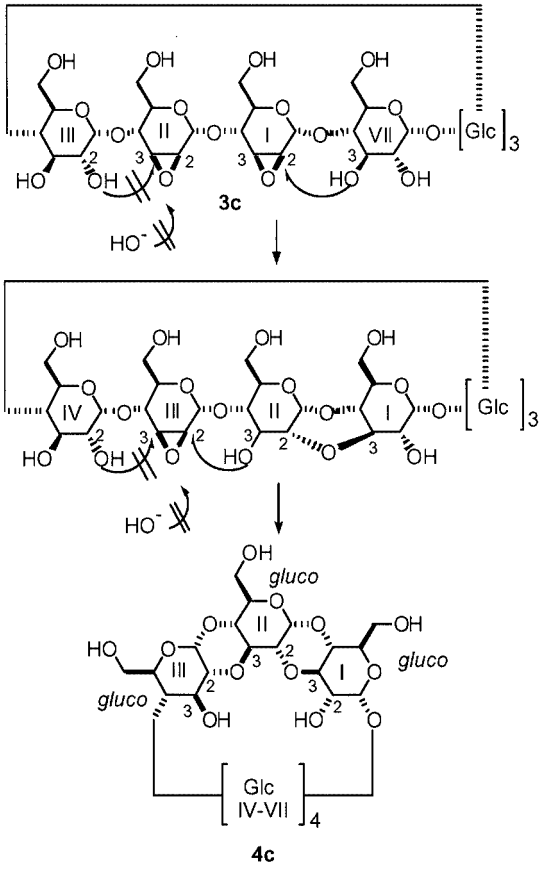


Scheme 2. Spatial proximity of 3^{II}-H to 3^{I}-H and 3^{III}-H in $3^{I},2^{II}$:$3^{II},2^{III}$-dianhydro-β-CD **4c**

The smaller values of $J_{3\text{-H},3\text{-OH}}$ (2−3 Hz) and the higher chemical shifts of 2-OH (δ = 5.77 ppm) and 3-OH (δ = 5.71 ppm) for β-CD than for α-methyl D-glucoside (4.76 Hz, δ = 4.72 and 4.76 ppm, respectively) provide evidence for interglucosyl hydrogen bonding between 3^{X-1}-OH and 2^{X}-O in β-CD in [D_6]DMSO.[50] Hence the chemical shifts of all the 2- and 3-OH protons (δ = 5.4−5.8 ppm) and all $J_{3\text{-H},3\text{-OH}}$ (2.5 Hz) in **2b** show that interglucosyl hydrogen bonds are maintained between 3^{X-1}-OH and 2^{X}-O after $3^{I},2^{II}$-anhydration in spite of some structural distortion of the macro-ring.

The structure of **4c** indicates that an effective and regioselective tandem reaction has occurred (Scheme 3). The initial attack is by 3^{VII}-OH on 2^{I}-C followed by the attack by the newly produced 3^{II}-OH on 2^{III}-C (*note: the labeling of the sugar units changes after the reactions*) to give the final product **4c** in a fairly high total yield (65.3%). Similar tandem reactions have been reported to give cyclic ethers from rather simple epoxide systems[51−56] and cases involving the hydroxide anion as the catalyst in aqueous solution are rare.[55,56] The present transformation from **3c** into **4c** represents a unique case in that a rather complex sugar diepoxide is used as the starting material.

The diaxial ring-opening rule is a general one for epoxides that also operates in the attack by external nucleophiles at the 3-C position in CD mono- (**1a**,**b**) and poly-*manno*-epoxides, including **3a**−**3c**,[15,25,27−33,36,37−39,57] as well as 4,6-di-*O*-protected methyl 2,3-epoxymannoside, which has no neighboring sugar unit.[58] However, in the reactions of **1a**, **1b** and **3a**−**3c**, the intramolecular attack at 2^{X}-C by



Scheme 3. Regioselective tandem epoxide ring openings of $2^{I},3^{I}$:$2^{II},3^{II}$-di-*manno*-epoxy-β-CD **3c** (note: the labeling of the sugar units changes after the reactions)

3^{X-1}-OH occurred exclusively. Thus, the attack at 2-C seems to be abnormal but is common in *intramolecular* cases.

Molecular dynamics simulations of $2^{I},3^{I}$-*manno*-epoxy-α-CD **1a** in water revealed a shorter distance between 3^{VI}-O and 2^{I}-C (3.59 Å) and a longer one between 2^{II}-O and 3^{I}-C (3.93 Å) compared with the rather equal and uniform 2^{X}-C···3^{X-1}-O and 3^{X}-C···2^{X+1}-O distances between the unmodified glucose units (3.62 Å).[44] The spatial situation should be similar in β-analogue **1b**: the epoxy carbon 2^{I}-C

is protected by 3^{VII}-OH from external nucleophile attack. Since 3^{VII}-OH and 2^{II}-OH, in contrast to those in β-CD, do not possess hydrogen bonding partners on the adjacent sugar unit I, their pK_as must be higher than those of the secondary OH groups of CDs. Under reaction conditions that are insufficiently basic to deprotonate 3^{VII}-OH and 2^{II}-OH, both the protection of 2^{I}-C by 3^{VII}-OH and the *trans*-diaxial ring-opening rule favor external nucleophilic attack on 3^{I}-C.[59−61] Only at high pH, could the 3^{VII}-OH deprotonate and become active enough to attack 2^{I}-C with the advantage of a shorter C···O distance than that of deprotonated 2^{II}-OH. This reaction implies that intramolecular attack at the 2^{I}-C position of the epoxide by the deprotonated 3^{VII}-OH predominates, and even the external hydroxide anion (OH^-) in high concentration cannot compete with it. This reaction represents a very good case of a reaction pathway that is strictly controlled by the proximity of the reaction site and nucleophiles.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM-A500 or VARIAN UNITY plus 500 NMR spectrometer by setting the frequency at 500 MHz for ^{1}H spectra and at 125 MHz for ^{13}C spectra. FAB mass spectra were recorded with a JEOL JMS-DX303, optical rotation was measured with a JASCO DIP-370 digital polarimeter, and melting points were measured with a Yanaco MP-micro melting point apparatus. TLC was run on precoated silica gel plates (Art. No. 5554). Spot detection was carried out by staining with 0.1% 1,3-dihydroxynaphthalene in EtOH/H_2O/H_2SO_4 (200:157:43, v/v).

$3^{I},2^{II}$:$3^{M},2^{N}$-Dianhydro-β-CDs (4a−c) ([M,N]: [IV,V], [III,IV], and [II,III]): A solution of $2^{I},3^{I}$:$2^{IV},3^{IV}$-di-*manno*-epoxy-β-CD **3a**[19,29] (380 mg, 0.35 mmol) in 0.25 M NaOH (40 mL) was stirred for 3 d at 80 °C, neutralized with 1 M HCl, and filtered. The filtrate was subjected to column chromatography on a Merck Lobar Rp 18 C-type column with a gradient elution from 20% (500 mL) to 50% aqueous MeOH (500 mL) to give **4a** (189 mg, 50%). Similarly, $2^{I},3^{I}$:$2^{III},3^{III}$- or $2^{I},3^{I}$:$2^{II},3^{II}$-di-*manno*-epoxy-β-CD[19,29] (**3b**, 118 mg, 0.11 mmol or **3c**, 377 mg, 0.34 mmol, respectively) afforded **4b** (59 mg, 50%) or **4c** (235 mg, 63%).

$3^{I},2^{II}$:$3^{IV},2^{V}$-Dianhydro-β-CD (4a): FAB mass: *m*/*z* = 1099 [M + H]$^+$, 1121 [M + Na]$^+$; m.p. 210 °C (dec.). $[\alpha]_D^{13}$ = 108.3 (*c* = 0.4, H_2O). ^{1}H NMR (D_2O, 500 MHz, CH_3CN int.): δ = 3.48−3.97 (m, 40 H), 4.40 (t, *J* = 9.4 Hz, 1 H), 4.42 (t, *J* = 9.4 Hz, 1 H), 4.98 (d, *J* = 3.7 Hz, 1 H), 4.99 (d, *J* = 3.4 Hz, 1 H), 5.02 (d, *J* = 3.4 Hz, 1 H), 5.03 (d, *J* = 3.0 Hz, 1 H), 5.07 (d, *J* = 3.7 Hz, 1 H), 5.11 (d, *J* = 4.1 Hz, 1 H), 5.12 (d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 125 MHz, CH_3CN int.): δ = 60.4, 60.5, 60.6, 60.8, 61.1, 61.3, 68.0, 68.2, 69.7, 70.1, 70.8, 71.0, 71.2, 72.6, 72.8, 72.9, 73.2, 73.4, 73.5, 73.6, 74.0, 74.0, 74.1, 74.1, 74.4, 75.8, 76.2, 80.1, 81.7, 81.7, 82.1, 82.6, 95.1, 95.1, 101.9, 102.6, 102.9, 102.9, 103.2 ppm. R_f = 0.33 (*n*PrOH/EtOAc/H_2O, 7:7:2 v/v/v, five times development).

$3^{I},2^{II}$:$3^{III},2^{IV}$-Dianhydro-β-CD (4b): FAB mass: *m*/*z* = 1099 [M + H]$^+$, 1121 [M + Na]$^+$; m.p. 210 °C (dec.). $[\alpha]_D^{13}$ = 108.7 (*c* = 0.4, H_2O). ^{1}H NMR (D_2O, 500 MHz, CH_3CN int.): δ = 3.47−3.95 (m, 40 H), 4.40 (t, *J* = 9.6 Hz, 1 H), 4.40 (t, *J* = 9.5 Hz, 1 H), 5.01 (d, *J* = 3.4 Hz, 1 H), 5.06 (d, *J* = 3.4 Hz, 1 H), 5.08 (d, *J* = 4.1 Hz, 1 H), 5.11 (d, *J* = 3.7 Hz, 2 H), 5.14 (d, *J* = 3.2 Hz, 1 H), 5.18 (d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 125 MHz, CH_3CN int.): δ = 60.3, 60.5, 61.0, 61.2, 61.4, 61.5, 67.7, 68.3, 69.8, 70.5, 70.6, 71.0, 71.2, 72.2, 72.6, 72.9, 73.0, 73.5, 73.7, 73.8, 74.0, 74.0, 74.2, 74.5, 76.0, 76.7, 77.6, 81.2, 82.0, 82.6, 95.3, 95.4, 99.2, 100.2, 102.3, 102.5, 103.6 ppm. R_f = 0.33 (*n*PrOH/EtOAc/H_2O, 7:7:2 v/v/v, five times development).

$3^{I},2^{II}$:$3^{II},2^{III}$-Dianhydro-β-CD (4c): FAB mass: *m*/*z* = 1099 [M + H]$^+$, 1121 [M + Na]$^+$, 1137 [M + K]$^+$; m.p. 200 °C (dec.). $[\alpha]_D^{13}$ = 118.5 (*c* = 0.4, H_2O). ^{1}H NMR (D_2O, 500 MHz, CH_3CN int.): δ = 3.47−3.96 (m, 40 H), 4.35 (t, *J* = 9.6 Hz, 1 H), 4.49 (t, *J* = 9.7 Hz, 1 H), 4.96 (d, *J* = 3.2 Hz, 1 H), 5.06 (d, *J* = 3.7 Hz, 1 H), 5.10 (d, *J* = 3.4 Hz, 1 H), 5.14 (d, *J* = 3.9 Hz, 1 H), 5.15 (d, *J* = 3.4 Hz, 1 H), 5.30 (d, *J* = 4.6 Hz, 1 H), 5.38 (d, *J* = 3.0 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 60.0, 60.3, 60.77, 61.3, 61.5, 61.9, 65.4, 66.6, 70.5, 70.6, 70.8, 71.9, 72.0, 72.5, 72.6, 72.8, 72.9, 73.1, 73.1, 73.7, 74.1, 74.2, 74.3, 74.4, 74.5, 76.6, 77.8, 79.6, 81.6, 81.6, 95.8, 96.0, 97.4, 98.0, 101.1, 102.0, 102.1 ppm. R_f = 0.28 (*n*PrOH/EtOAc/H_2O, 7:7:2 v/v/v, five times development).

$3^{I},2^{II}$-Anhydro-β-CD (2b): This compound was prepared from **1b**[18,19,29] in 63.4% yield by a method similar to that reported for α-CD.[42] M.p. 225 °C (dec.). $[\alpha]_D^{23}$ = 159.9 (*c* = 0.55, H_2O). ^{1}H NMR (D_2O, 500 MHz, CH_3CN int.): δ = 3.46−3.94 (m, 41 H), 4.38 (t, *J* = 9.6 Hz, 1 H), 4.97 (d, *J* = 3.9 Hz, 1 H), 4.98 (d, *J* = 3.9 Hz, 1 H), 4.99 (d, *J* = 3.7 Hz, 1 H), 5.01 (d, *J* = 3.7 Hz, 1 H), 5.06 (d, *J* = 3.9 Hz, 1 H), 5.11 (d, *J* = 3.9 Hz, 1 H), 5.11 (d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 59.0, 59.3, 59.6, 59.8, 59. 9, 60.0, 60.0, 66.6, 68.6, 69.4, 69.7, 70.9, 71.1, 71.1, 71.4, 71.4, 71.5, 71.7, 71.8, 71.9, 72.2, 72.3, 72.4, 72.7, 72.8, 72.8, 72.9, 72.9, 74.9, 78.8, 78.9, 79.8, 80.4, 80.7, 80.9, 93.8, 100.2, 100.6, 100.7, 101.1, 101.2, 101.8 ppm.

Supporting Information (Figures 1S−3S**)** for this article is available on the WWW (see footnote on first page of this article).

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