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Interglycosidic acetals. Part 3. [1] Synthesis and structure determination of cyclic monobenzylidene acetals of cyclodextrin derivatives bridging between two contiguous D-glucopyranosyl residues

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Abstract

Transacetalation of fully 6-*O*-pivaloylated α-, β-, and γ-cyclodextrins with benzaldehyde dimethylacetal in the presence of (+)-10-camphorsulfonic acid gave monobenzylidene acetals (**4**, **5**, **6**) in moderately good yields. Benzylation of the β-cyclodextrin derivative **5** followed by acid-catalyzed hydrolysis of the benzylidene group and acetylation afforded a di-*O*-acetyl-nonadeca-*O*-benzyl derivative **9**. NMR spectroscopic analysis of **9**, including two-dimensional HOHAHA and $^{1}H-^{13}C$ correlation experiments revealed that the benzylidene group bridged the O-2 and O-3 positions of contiguous D-glucopyranosyl residues. Reductive ring-opening of the benzylidene acetal with lithium aluminum hydride/aluminum chloride afforded predominantly a 2^{1}-*O*-unprotected derivative **10** in good yield. © 1996 Elsevier Science Ltd.

Keywords: Transacetalation; Cyclic benzylidene acetal; Cyclodextrin; Interglycosidic acetal; Selective protection

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[1] For parts 1 and 2, see refs. [1,2].

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1. Introduction

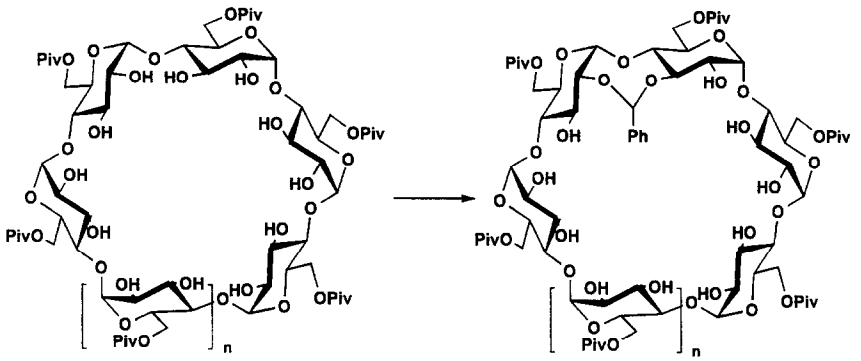
Cyclodextrins (CDs) are cyclic oligosaccharides composed of six or more α-(1 $\rightarrow$ 4) linked D-glucopyranosyl residues. Numerous investigations on chemical modification of CDs have been carried out in efforts to improve their substrate complexation properties and/or to attach novel reactive functional groups [3]. The available methods, however, have been limited by the rigid cyclic structures of CDs and the extreme congestion of hydroxyl groups. In particular, regioselective introduction of two functional groups into the CD skeleton have necessitated tedious separation procedures and/or peculiar reaction techniques, such as 'capping' [4].

Recently, we have found that acetal exchange reactions of phenyl α-maltoside and 1,6-anhydro-β-maltotriose under modified Evans conditions [5] provided interglycosidic benzylidene acetals having an eight-membered ring in good yield [1,6]. The usefulness of these interglycosidic acetals as synthetic intermediates was confirmed by their regioselective conversions into partially protected derivatives through reductive cleavage or acid hydrolysis [1]. Because CDs can be regarded as cyclic analogs of malto-oligosaccharides, we directed our attention to the applicability of acetalation to regioselective modification of CD derivatives. Following our preliminary report describing the preparation of the interglycosidic benzylidene derivative of β-CD [2], we describe here the procedure and the structural determination in detail as well as the results for other CD derivatives.

2. Results and discussion

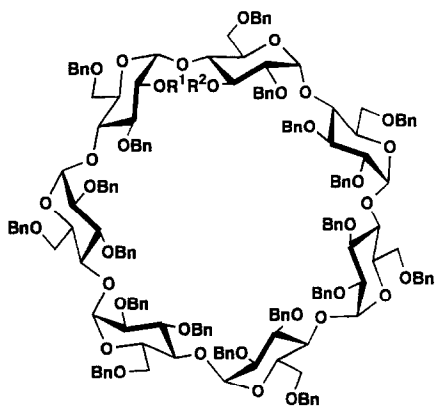
As in our previous experiments on di- and tri-saccharides [1], the direct benzylidenation of β-CD was first investigated under conditions reported by Evans [5]. No major product was obtained from the reaction mixture, however, probably due to the presence of reactive primary hydroxyl groups which can form unstable acyclic acetals bearing a methoxy group. To confine the reaction sites, we next used fully 6-*O*-protected β-CD derivatives, namely heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose [7] and heptakis(6-*O*-pivaloyl)cyclomaltoheptaose (**2**) [8], as substrates for the benzylidenation. The acetal-exchange reaction of the silylated β-CD was also unsatisfactory, giving a mixture of polar products because the *O*-silyl groups were substantially removed under the acidic conditions employed. On the other hand, the reaction of the pivaloyl derivative **2** proceeded smoothly, giving a single major product, unreacted **2**, and several less polar products. Based on this result, **2** was treated with 2 molar equivalents of benzaldehyde dimethylacetal in *N*,*N*-dimethylformamide (DMF) at 60 °C under reduced pressure ($\sim$ 2 kPa) in the presence of (+)-10-camphorsulfonic acid (CSA) as the catalyst. The major product **5** was isolated by column chromatography on Silica Gel in 46% yield. In the ^{1}H NMR spectrum of **5** at 500 MHz in Me_2SO-d_6–D_2O at 80 °C, a singlet assignable to the methine proton of the benzylidene acetal was observed, suggesting that **5** was a cyclic mono-benzylidene acetal. Unfortunately, NOESY experiments to elucidate regio- and stereochemistry of the *O*-benzylidene group were unsuccessful. Therefore, the position was determined after the conversion of **5** into the

diacetate **9**. Similar benzylidenations of hexakis(6-*O*-pivaloyl)cyclomaltohexaose **1** and octakis(6-*O*-pivaloyl)cyclomaltooctaose **3** proceeded smoothly, giving the corresponding mono-*O*-benzylidene derivatives of α- and γ-CD derivatives (**4** and **6**) in 37% and 54% yield, respectively. Noteworthy in these findings is that the yields of the interglycosidic benzylidene acetals were dependent on the ring sizes of the starting CDs.



1: n = 1
2: n = 2
3: n = 3

4: n = 1
5: n = 2
6: n = 3



	R^1	R^2
7	PhCH<	
8	H	H
9	Ac	Ac
10	H	Bn
11	Ac	Bn

To examine the usefulness of the benzylidene acetal, we effected the following chemical transformations using **5** as the model compound. Since the benzylidene acetal was stable under neutral or basic conditions, **5** was first treated with benzyl bromide/sodium hydride in DMF, and the reaction mixture was subsequently treated with aqueous ammonia to remove pivaloyl groups. After extractive workup with chloroform, a mixture of partially benzylated derivatives was subjected to the second benzylation under similar conditions to give the nonadeca-*O*-benzyl derivative **7** in 82% overall yield. The selective hydrolysis of the *O*-benzylidene group of **7** proceeded smoothly in aqueous methanol–oxolane employing CSA as the catalyst to give the diol **8** in 73% yield. Finally, the free hydroxyl groups were acetylated with acetic anhydride/pyridine to give the di-*O*-acetyl derivative **9** in 82% yield. Structure elucidation of **9** was performed mainly by 2D NMR spectroscopy.

The ^{1}H NMR spectrum of **9** in $CDCl_3$ at 40 °C revealed two 3-proton singlets for methyl groups of the two acetoxy groups at δ 1.89 and 1.90, and seven 1-proton doublets having small coupling constants (J 3.4–3.7 Hz) assignable to anomeric protons at δ 5.00–5.30. However, significant signal overlap in the ^{1}H NMR spectrum prevented identification of all proton resonances. The ^{13}C spectrum of **9**, which showed seven

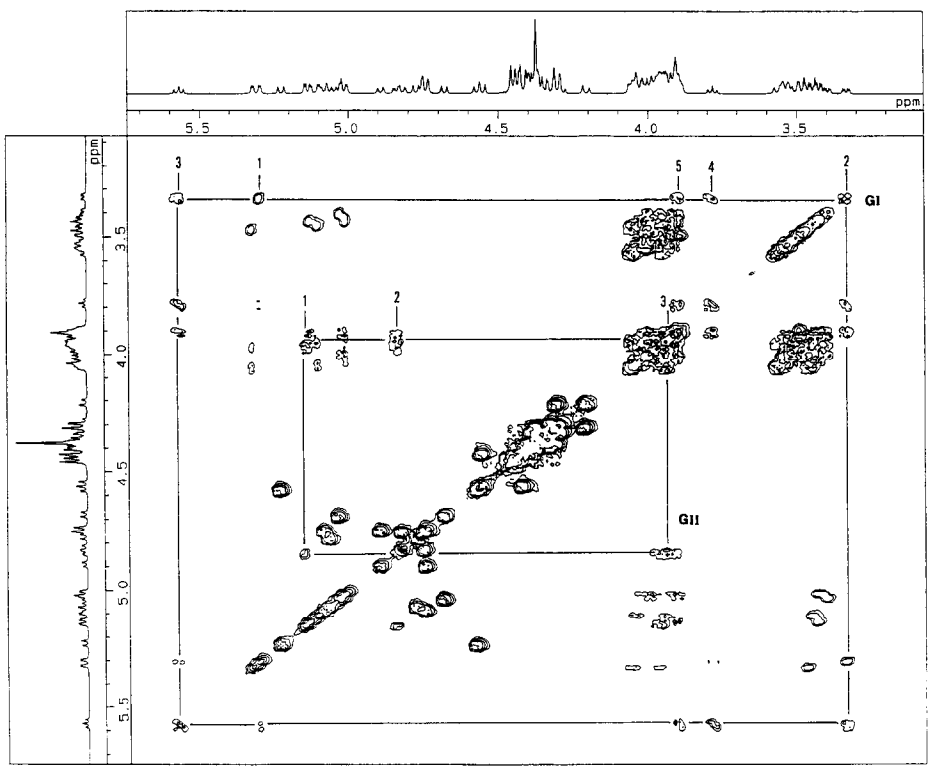


Fig. 1. 2D HOHAHA spectrum of **9** in $CDCl_3$ (600 MHz) showing the cross peak region of sugar proton resonances. GI and GII denote 3-*O*-acetyl-2,6-di-*O*-benzyl- and 2-*O*-acetyl-3,6-di-*O*-benzyl-α-D-glucopyranosyl residues, respectively.

carbon resonances due to the anomeric carbons at δ 97.0–99.3 as well as a pair of acetyl methyl carbons at δ 20.9 and 21.3, also suggested that **9** was a di-*O*-acetylated heptasaccharide. The structures of acetylated D-glucopyranose units were determined using 2D homonuclear Hartmann–Hahn (2D HOHAHA) spectroscopy (Fig. 1). The cross-peaks related to signals at δ 5.57 (H-3) were observed at δ 5.30 (H-1), 3.33 (H-2), 3.87 (H-4), and ~ 3.9 (H-5), suggesting that 3-*O*-acetyl-2,6-di-*O*-benzyl-α-glucopyranose (GI) was a component of the heptasaccharide. Similar observations were made for 2-*O*-acetyl-3,6-di-*O*-benzyl-α-D-glucopyranose unit (GII); the H-2 proton resonance δ 4.84) was connected to H-1 (δ 5.15) and H-3 (δ 3.90–3.95). Furthermore, the sequence of the monosaccharide residues of **9** was unequivocally established by 2D $^{13}C-^{13}C$ chemical-shift correlation experiments (Figs. 2 and 3) using inverse (^{1}H) detection and field gradients [9]. As shown in Fig. 2, it was possible to assign the signal due to C-1 (δ 97.8) and C-4 (δ 76.0) of GI and C-1 (δ 97.0) of GII using pulsed field gradient-heteronuclear multiple quantum coherence (PFG–HMQC) methods. Cross-peaks attributable to long-range coupling between C-1 in the GII unit and H-4 in the GI unit

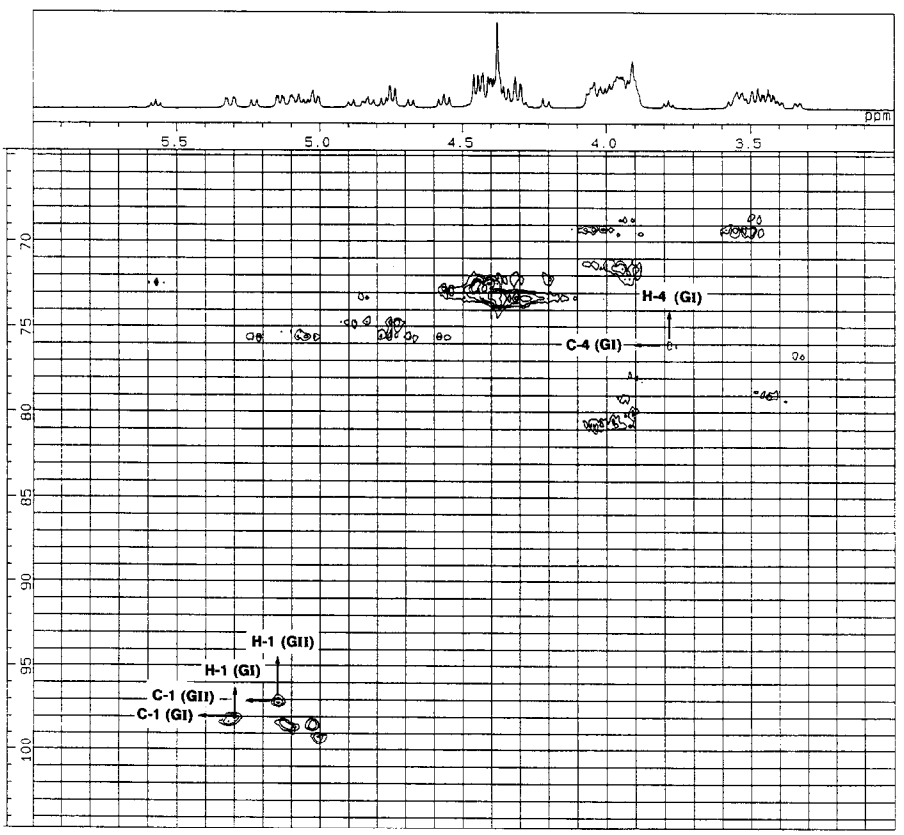


Fig. 2. 2D $^{1}H-^{13}C$ chemical shift correlation spectroscopy contour plot obtained for **9** in $CDCl_3$, using inverse (^{1}H) detection with field gradients (PFG–HMQC) at 600 MHz. Symbols as for Figs. 2 and 1.

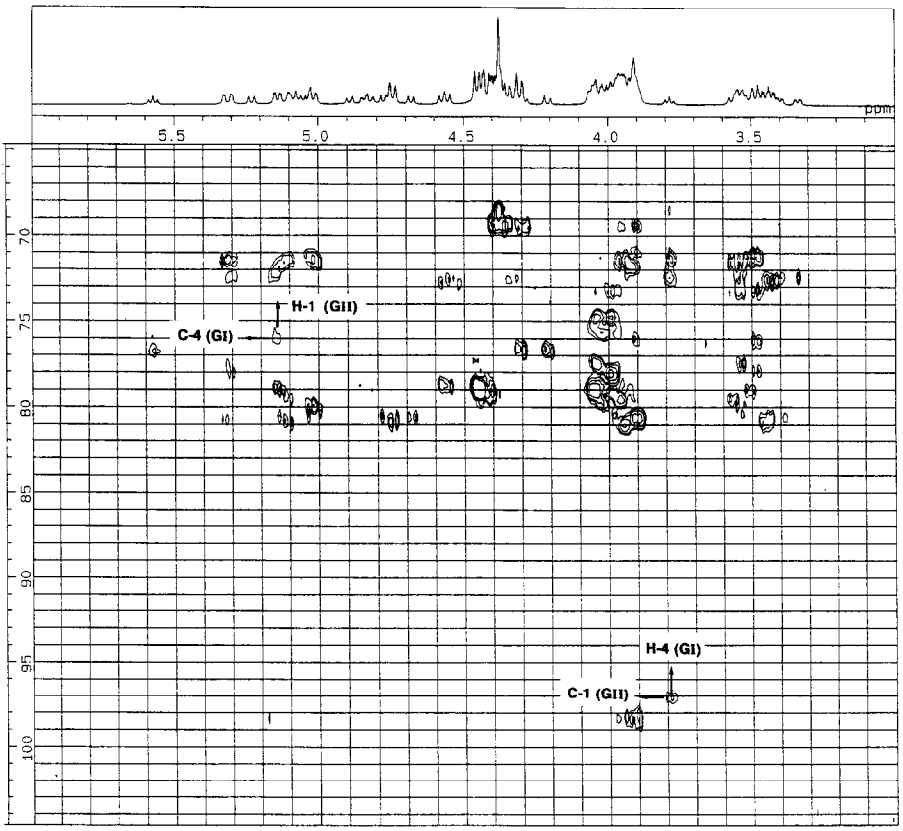


Fig. 3. PFG–HMBC spectrum of **9** in $CDCl_3$ under field gradient mode. Symbols as for Fig. 1.

and between C-4 in GI unit and H-1 in GII unit were observed in the pulsed field gradient-heteronuclear multiple bond correlation (PFG–HMBC) plot (Fig. 3). On the basis of these 2D NMR experiments, we concluded that the GII unit was connected to the 4-hydroxyl group of the GI unit through an α-glycosidic bond. Thus, the structure of **9** was determined to be $3^1,2^2$-di-*O*-acetyl-$2^1,6^1,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7$-nonadeca-*O*-benzylcyclomaltoheptaose. Therefore, the benzylidene group in **5** was demonstrated to bridge the O-2 and O-3 positions of two contiguous D-glucose constituents.

We next focused attention on the reductive cleavage of the interglycosidic benzylidene group. Compound **7** was treated with lithium aluminum hydride/aluminum chloride in dichloromethane–diethyl ether [10] at room temperature for 5 h. The cyclic benzylidene acetal in **7** underwent regioselective cleavage, giving the 2^1-unprotected derivative **10** in 70% yield. For structure elucidation, **10** was acetylated with acetic anhydride/pyridine to give the corresponding acetate **11** in 87% yield. In the ^{1}H NMR spectrum of **11**, a 1-proton doublet of doublets with coupling constants of 3.7 and 9.8 Hz assignable to H-2^1 was observed at low field (δ 5.13), suggesting that the acetyl group

is present at the O-2' position. Similar to our previous experiments with maltose and maltotriose derivatives [1], the regioselectivity observed in this case might be due to the electron-withdrawing effect of an anomeric center.

In summary, we found that novel CD derivatives having a cyclic benzylidene group at the O-2 and O-3 positions of contiguous D-glucopyranosyl residues were readily synthesized using Evans acetal-exchange reaction. Applicability of the benzylidene acetals to selective hydrolysis and reductive ring-opening should make this reaction useful in protecting group strategies in cyclodextrin chemistry.

3. Experimental

General methods.—Optical rotations were determined with a JASCO DIP-30 polarimeter, using a 10 cm micro cell. ^{1}H NMR spectra were recorded at 400 MHz using a JEOL JNM-GX 400 spectrometer for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts (δ) are given in ppm relative to the signal for internal tetramethylsilane, and J values are given in Hz. ^{13}C NMR spectra were recorded at 67.8 MHz with a JEOL JNM-EX 270 spectrometer. Two-dimensional NMR spectra were recorded on a JEOL JNM α-600 spectrometer using standard JEOL software. Reactions were monitored by TLC on a pre-coated plate of Silica Gel 60 F_{254} (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). Column chromatography and flash chromatography were performed on Silica Gel 60 (70–230 mesh and 230–400 mesh, respectively; E. Merck). Analytical samples were dried at 60–70 °C for 5–7 h at ~ 100 Pa. DMF was first dried with P_2O_5 and subsequently with KOH, and distilled under reduced pressure.

General procedure for benzylidenation.—Per(6-*O*-pivaloyl)cyclomalto-oligosaccharides were dried over P_2O_5 at 80 °C under reduced pressure for 6–8 h and dissolved in DMF. To the solution was added benzaldehyde dimethylacetal, and the acidity was adjusted to pH 3 with wet pH paper by adding (+)-10-camphorsulfonic acid. The resulting solution was stirred at 60–70 °C for 4–7 h at 2 kPa, and the reaction was quenched by addition of $NaHCO_3$. The solution was concentrated under reduced pressure, and the remaining solvent was removed by azeotropic evaporation with xylene three times. The residual syrup was subjected to column chromatography on Silica Gel to give the monobenzylidene derivatives.

3^1,2^2-O-Benzylidene-6^1,6^2,6^3,6^4,6^5,6^6-hexa-O-pivaloyl-cyclomaltohexaose (**4**).—Hexakis(6-*O*-pivaloyl)cyclomaltohexaose **1** [8] (4.43 g, 3 mmol) was treated with benzaldehyde dimethylacetal (0.9 mL, 6 mmol) and CSA (0.8 g) in DMF (50 mL) for 5 h as described above. Purification by column chromatography with 19:1 → 9:1 v/v $CHCl_3$–MeOH gave a mixture of less polar products (2.52 g), **4** (1.76 g, 37%), and unreacted **1** (0.63 g, 14%). Compound **4**: $[\alpha]_D^{25}$ +88° (*c* 0.20, $CHCl_3$); selected ^{1}H NMR data (Me_2SO-d_6–D_2O, 70 °C): 4.78 (br s, 2 H, 2 × H-1), 4.81 (d, 1 H, J 3.2 Hz, H-1), 4.83 (d, 1 H, J 3.2 Hz, H-1), 4.87 (d, 1 H, J 3.2 Hz, H-1), 5.06 (d, 1 H, J 3.2 Hz, H-1), 6.08 (s, 1 H, C*H*Ph). Anal. Calcd for $C_{73}H_{112}O_{36} \cdot 2H_2O$: C, 54.74; H, 7.25. Found: C, 54.79; H, 7.08.

3^1,2^2-O-Benzylidene-6^1,6^2,6^3,6^4,6^5,6^6,6^7-hexa-O-pivaloyl-cyclomaltoheptaose (**5**).—Heptakis(6-*O*-pivaloyl)cyclomaltoheptaose **2** [8] (2.90 g, 1.68 mmol) was treated with

benzaldehyde dimethylacetal (0.5 mL, 3.3 mmol) and CSA (400 mg) in DMF (80 mL) for 7 h as described above. Purification by column chromatography with 19:1 → 9:1 v/v $CHCl_3$–MeOH gave a mixture of less polar products (1.60 g), **5** (1.35 g, 46%), and unreacted **2** (0.35 g, 12%). Compound **5**: $[\alpha]_D^{25}$ +93° (*c* 0.19, $CHCl_3$); selected ^1H NMR data: δ (500 MHz, Me_2SO-d_6–D_2O, 80 °C) 4.86 (d, 1 H, *J* 3.1 Hz, H-1), 4.89 (d, 1 H, *J* 3.3 Hz, H-1), 4.91 (d, 1 H, *J* 3.4 Hz, H-1), 4.93 (br s, 1 H, H-1), 4.94 (d, 1 H, *J* 3.7 Hz, H-1), 4.96 (d, 1 H, *J* 3.4 Hz, H-1), 5.29 (d, 1 H, *J* 3.3 Hz, H-1), 6.07 (s, 1 H, C*H*Ph). Anal. Calcd for $C_{84}H_{130}O_{42} \cdot 2H_2O$: C, 54.60; H, 7.31. Found: C, 54.50; H, 7.22.

3^1,2^2-O-Benzylidene-6^1,6^2,6^3,6^4,6^5,6^6,6^7,6^8-octa-O-pivaloyl-cyclomaltooctaose (**6**). —Octakis(6-*O*-pivaloyl)cyclomaltooctaose **3** [8] (3.94 g, 2 mmol) was treated with benzaldehyde dimethylacetyl (0.6 mL, 4 mmol) and CSA (700 mg) in DMF (100 mL) for 5 h as described above. Purification by column chromatography with 19:1 → 5:1 v/v $CHCl_3$–MeOH gave a mixture of less polar products (1.14 g), **6** (2.24 g, 54%), and unreacted **3** (0.85 g, 22%). Compound **6**: $[\alpha]_D^{25}$ +83° (*c* 0.27, $CHCl_3$; selected ^1H NMR data: δ (500 MHz, Me_2SO-d_6–D_2O, 80 °C): 4.78 (d, 1 H, *J* 3.7 Hz, H-1), 4.80 (d, 1 H, *J* 3.4 Hz, H-1), 4.83 (d, 2 H, *J* 3.6 Hz, 2 × H-1), 4.80 (d, 1 H, *J* 3.4 Hz, H-1), 4.91 (d, 1 H, *J* 3.4 Hz, H-1), 4.93 (d, 1 H, *J* 3.4 Hz, H-1), 5.23 (d, 1 H, *J* 3.5 Hz, H-1), 5.92 (s, 1 H, C*H*Ph). Anal. Calcd for $C_{95}H_{148}O_{48} \cdot 3H_2O$: C, 54.02; H, 7.35. Found: C, 54.44; H, 7.05.

2^1,6^1,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7-Nonadeca-O-benzyl-3^1,2^2-O-benzylidenecyclomaltoheptaose (**7**).—Sodium hydride (60%; 200 mg) was washed with hexane several times, dried under argon in vacuo, and added to a stirred solution of **5** (50 mg, 29 μmol) in DMF (20 mL). The suspension was stirred and ultrasonicated at room temperature for 30 min, and then benzyl bromide (0.2 mL) was added to the mixture. The reaction mixture was stirred at room temperature for 5 h, quenched by successive addition of MeOH (1 mL) and concentrated aqueous ammonia (2 mL), stirred overnight, poured into ice–water, and extracted with chloroform. The extract was successively washed with ice-cold 1% hydrochloric acid, aqueous saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residual syrup was subjected to repeated benzylation in the same manner. Chromatographic purification of the product on a column of Silica Gel using 97:3 v/v benzene–EtOAc gave **7** (70 mg, 82%); $[\alpha]_D^{25}$ +36° (*c* 0.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): 4.55, 4.69, 4.71, 4.77, 4.79, 4.81, 4.84, 4.86, 4.98, 5.09, 5.10, 5.21, 5.27 (13 × d, 13 H, *J* 9.7–12.0 Hz, CH_2Ph), 4.87 (d, 1 H, *J* 3.7 Hz, H-1), 4.95 (d, 1 H, *J* 3.3 Hz, H-1), 5.00 (d, 1 H, *J* 3.3 Hz, H-1), 5.04 (d, 1 H, *J* 3.4 Hz, H-1), 5.19 (d, 1 H, *J* 3.1 Hz, H-1), 5.36 (d, 1 H, *J* 3.4 Hz, H-1), 5.38 (d, 1 H, *J* 3.9 Hz, H-1), 5.84 (s, 1 H, C*H*Ph). Anal. Calcd for $C_{182}H_{188}O_{35}$: C, 74.47; H, 6.43. Found: C, 74.29; H, 6.43.

2^1,6^1,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7-Nonadeca-O-benzyl-cyclomaltoheptaose (**8**).—To a stirred solution of **7** (200 mg, 68 μmol) in 10:20:1 v/v/v oxolane–MeOH–H_2O (6 mL) at 0 °C was added CSA (20 mg). The solution was stirred at room temperature for 1 day, quenched with $NaHCO_3$, and concentrated to dryness. The residue was diluted with dichloromethane, washed successively with aqueous saturated $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$, and concentrated. Chromatographic purification of the crude product on a column of Silica Gel with 19:1

v/v benzene–EtOAc gave **8** (142 mg, 73%); $[\alpha]_D^{25}$ +60° (c 0.26, $CHCl_3$); selected ^1H NMR data ($CDCl_3$): δ 3.22 (dd, 1 H, *J* 3.0 and 9.5 Hz, H-2), 3.32 (dd, 1 H, *J* 3.4 and 9.8 Hz, H-2), 4.63 (d, 1 H, *J* 12.6 Hz, CH_2Ph), 4.72 (d, 1 H, *J* 10.1 Hz, CH_2Ph), 4.78 (d, 1 H, *J* 9.8 Hz, CH_2Ph), 4.89 (d, 1 H, *J* 10.6 Hz, CH_2Ph), 4.91 (d, 1 H, *J* 11.0 Hz, CH_2Ph), 4.95 (d, 1 H, *J* 3.0 Hz, H-1), 5.04 (m, 2 H, H-1), 5.15 (d, 1 H, *J* 3.1 Hz, H-1), 5.17 (d, 1 H, *J* 3.4 Hz, H-1), 5.23 (d, 1 H, *J* 3.6 Hz, H-1), 5.27 (d, 1 H, *J* 11.8 Hz, CH_2Ph), 5.36 (d, 1 H, *J* 3.7 Hz, H-1). Anal. Calcd for $C_{175}H_{184}O_{35}$: C, 73.82; H, 6.51. Found: C, 73.47; H, 6.48.

$3^1,2^2$-Di-O-*acetyl-$2^1,6^1,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7$-nonadeca*-O-*benzylcyclomaltoheptaose* (**9**).—A solution of **8** (30 mg, 10.5 μmol) in pyridine (2 mL) and acetic anhydride (0.5 mL) was stirred at room temperature for 2 days, and then quenched with MeOH (2 mL). The mixture was concentrated and the remaining solvent was azeotropically evaporated with toluene. The residue was subjected to column chromatography on a column of Silica Gel with 97:3 v/v benzene–EtOAc as the eluant, giving **9** (25 mg, 82%); $[\alpha]_D^{25}$ +55° (*c* 0.22, $CHCl_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): 20.9 (Me), 21.3 (Me), 68.4 68.9, 69.1, 69,3, 70.9, 71.1, 71.3, 71.4, 72.0, 75.6, 76.0 (C-4^1), 78.3, 78.5, 78.6, 78.8, 78.9, 79.1, 79.3, 79.4, 79.8, 80.3, 80.5, 80.6, 80.7, 80.9, 97.0 (C-1^2), 97.8 (C-1^1), 98.1, 98.3, 98.4, 98.6, 99.3, 126.5–139.6, 169.7 (C=O), 170.5 (C=O); ^1H NMR (400 MHz, $CDCl_3$, 40 °C): 1.89 (s, 3 H, OAc), 1.90 (s, 3 H, OAc), 3.33 (dd, 1 H, *J* 3.7, 10.0 Hz, H-2^1), 3.39 (dd, 1 H, *J* 3.4, 11.0 Hz, H-2), 3.41–3.56 (m, 11 H, H-2,6a), 3.78 (t, 1 H, *J* 9.0 Hz, H-4^1), 3.85–4.06 (m, 27 H, H-3,4,5,6b), 4.18–4.55 (m, 27 H, CH_2Ph), 4.55 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.56 (d, 1 H, *J* 12.0 Hz, CH_2Ph), 4.68 (d, 1 H, *J* 11.0 Hz, CH_2Ph), 4.74 (d, 2 H, *J* 11.7 Hz, CH_2Ph), 4.76 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.82 (d, 1 H, *J* 10.3 Hz, CH_2Ph), 4.84 (dd, 1 H, *J* 3.4, 10.0 Hz, H-2^2), 4.89 (d, 1 H, *J* 11.2 Hz, CH_2Ph), 5.00 (d, 1 H, *J* 3.4 Hz, H-1), 5.02 (d, 1 H, *J* 3.6 Hz, H-1), 5.03 (d, 1 H, *J* 10.5 Hz, CH_2Ph), 5.06 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 5.08 (d, 1 H, *J* 10.7 Hz, CH_2Ph), 5.10 (d, 1 H, *J* 3.6 Hz, H-1), 5.13 (d, 1 H, *J* 3.7 Hz, H-1), 5.15 (d, 1 H, *J* 3.4 Hz, H-1^2), 5.23 (d, 1 H, *J* 10.4 Hz, CH_2Ph), 5.30 (d, 1 H, *J* 3.7 Hz, H-1^1), 5.32 (d, 1 H, *J* 3.6 Hz, H-1), 5.57 (t, 1 H, *J* 9.5 Hz, H-3^1). Anal. Calcd for $C_{179}H_{188}O_{37} \cdot 3H_2O$: C, 72.01; H, 6.55. Found: C, 71.87; H, 6.37.

$2^1,6^1,2^2,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7$-Icosa-O-*benzylcyclomaltoheptaose* (**10**).—To a stirred ice-cold solution of **7** (150 mg, 51 μmol) and lithium aluminum hydride (30 mg, 0.8 mmol) in diethyl ether (5 mL) was added dropwise a solution of aluminum chloride (100 mg, 0.75 mmol). The mixture was stirred at room temperature for 5 h, and the reaction was quenched by successive addition of EtOAc (1 mL) and MeOH (1 mL). The mixture was partitioned between aqueous saturated potassium sodium tartrate and diethyl ether. The separated organic layer was washed with aqueous saturated potassium sodium tartrate, dried with anhydrous sodium sulfate, and evaporated. Chromatographic purification on Silica Gel with 19:1 v/v benzene–EtOAc gave **10** (105 mg, 70%); $[\alpha]_D^{25}$ +53° (*c* 0.27, $CHCl_3$); selected ^1H NMR data ($CDCl_3$ at 40 °C): δ 4.70 (d, 1 H, *J* 11.3 Hz, CH_2Ph), 4.75 (d, 1 H, *J* 11.5 Hz, CH_2Ph), 4.78 (d, 1 H, *J* 10.0 Hz, CH_2Ph), 4.81 (d, 1 H, *J* 10.3 Hz, CH_2Ph), 4.89 (d, 1 H, *J* 11.3 Hz, CH_2Ph), 4.91 (d, 1 H, *J* 10.0 Hz, CH_2Ph), 4.93 (d, 1 H, *J* 11.0 Hz, CH_2Ph), 4.99 (d, 1 H, *J* 3.5 Hz, H-1), 5.06 (d, 1 H, *J* 11.4 Hz, CH_2Ph), 5.08 (d, 1

H, *J* 11.5 Hz, CH_2Ph), 5.10 (br s, 1 H, H-1), 5.14 (d, 1 H, *J* 3.4 Hz, H-1), 5.18 (d, 1 H, *J* 3.9 Hz, H-1), 5.20 (d, 1 H, *J* 3.9 Hz, H-1), 5.26 (d, 1 H, *J* 3.9 Hz, H-1), 5.27 (d, 1 H, *J* 3.7 Hz, H-1). Anal. Calcd for $C_{182}H_{190}O_{35}$: C, 74.42; H, 6.52. Found: C, 74.52; H, 6.60.

2^1-O-Acetyl-3^1,6^1,2^2,3^2,6^2,2^3,3^3,6^3,2^4,3^4,6^4,2^5,3^5,6^5,2^6,3^6,6^6,2^7,3^7,6^7-icosa-O-*benzylcyclomaltoheptaose* (**11**).—A solution of **10** (25 mg, 8.5 μmol) in pyridine (5 mL) and acetic anhydride (2 mL) was stirred at 60 °C for 8 h, and the reaction was quenched with MeOH (1 mL). Solvent was removed by evaporation, and the residue was chromatographed on Silica Gel with 97:3 v/v benzene–EtOAc to give **11** (22 mg, 87%); $[\alpha]_D^{25}$ +50° (c 0.23, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): 1.95 (s, 3 H, OAc), 3.41 (dd, 1 H, *J* 3.7, 9.8 Hz, H-2), 3.45–3.52 (m, 5 H, H-2), 3.99 (t, 1 H, *J* 9.2 Hz, H-3), 3.78–3.81, 4.08–4.30, 4.33–4.55 (m, H-3,4,5,6 and CH_2Ph), 4.71 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.85 (d, 1 H, *J* 11.0 Hz, CH_2Ph), 4.89 (d, 1 H, *J* 11.6 Hz, CH_2Ph), 4.94 (d, 1 H, *J* 12.8 Hz, CH_2Ph), 4.95 (d, 1 H, *J* 11.5 Hz, CH_2Ph), 5.05 (d, 1 H, *J* 11.0 Hz, CH_2Ph), 5.12 (dd, 1 H, *J* 3.7, 9.8 Hz, H-2^1), 5.16 (d, 1 H, *J* 11.3 Hz, CH_2Ph), 5.21 (d, 1 H, *J* 10.7 Hz, CH_2Ph), 5.25 (d, 1 H, *J* 11.9 Hz, CH_2Ph), 5.27 (d, 1 H, *J* 11.9 Hz, CH_2PH), 5.13 (dd, 1 H, *J* 3.7, 9.8 Hz, H-2^1), 5.34 (d, 1 H, *J* 3.3 Hz, H-1), 5.37 (d, 1 H, *J* 3.6 Hz, H-1), 5.39 (d, 1 H, *J* 3.4 Hz, H-1), 5.40–5.43 (m, 3 H, H-1), 5.65 (d, 1 H, *J* 3.6 Hz, H-1^1). Anal. Calcd for $C_{184}H_{192}O_{36} \cdot 3H_2O$: C, 72.85; H, 6.58. Found: C, 72.89; H, 6.37.

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