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Note

Acetolytic fission of a single glycosidic bond of fully benzoylated α-, β-, and γ-cyclodextrins. A novel approach to the preparation of maltooligosaccharide derivatives regioselectively modified at their nonreducing ends

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Recently, we found that careful acetolysis of fully acetylated cyclodextrins resulted in fission restricted to a single glycosidic bond [1], and that regioselectively functionalized cyclodextrin derivatives can be synthesized through interconversions between cyclic and acyclic structures [1,2]. Multistep modifications of the terminal glucose residues of maltooligosaccharides, usually involving *O*-benzylidenation of the nonreducing unit, are the crucial features of our procedure. Similar terminal modifications of aryl glycosides of maltooligosaccharide have been used to prepare substrates for measurements of α-amylase activity in human serum and urine samples [3].

In the process of the acetolytic cleavage of cyclodextrin derivatives two acetyl groups are newly introduced, one at the reducing and one at the nonreducing end of the maltooligosaccharides produced. This fact prompted us to examine the cleavage reaction employing different combinations of original acyl groups and acid anhydride, in the hope of obtaining versatile differentially substituted maltooligosaccharides. The present work describes a two-step procedure for the preparation of partially benzoylated maltooligosaccharide derivatives

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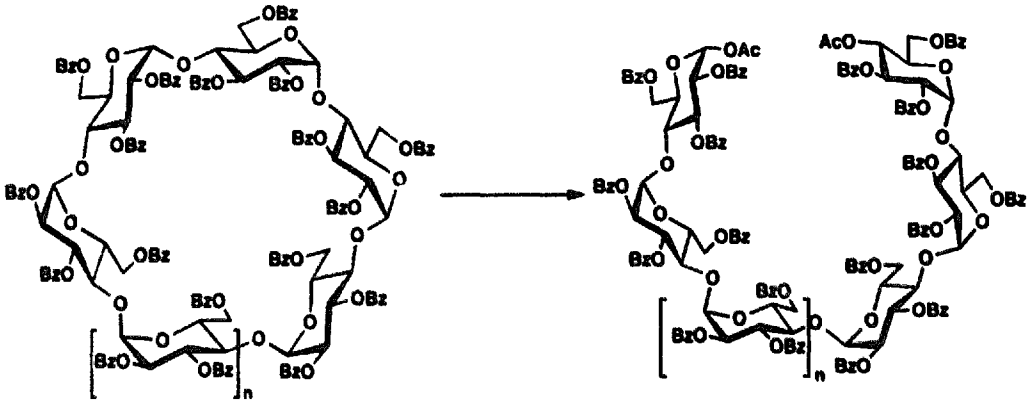
having acetyl groups at both ends, and the chemoselective modification of the acetylated functions.



1: n = 1

2: n = 2

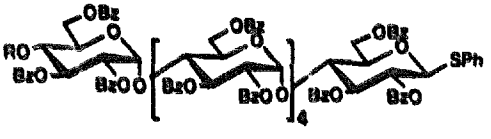
3: n = 3

4: n = 1

5: n = 2

6: n = 3

By a procedure similar to that for acetolysis [1], acetylated α-cyclodextrin was treated with chloroacetic anhydride or trifluoroacetic anhydride in the presence of a catalytic amount of sulfuric acid. These efforts, however, were unsuccessful because they gave complex mixtures of products, probably as a result of random cleavage of the glycosidic bonds and intra- or inter-molecular migration of the acetyl groups. After several attempts, we found that acetolysis of fully benzoylated α-cyclodextrin (**1**) proceeded selectively, affording a major product. Thus, **1** on treatment with 49:1 acetic anhydride–sulfuric acid at 50–60°C gave the $1^1,4^6$-di-*O*-acetyl derivative of octadeca-*O*-benzoyl-α-maltohexaose (**4**) in 51% yield, together with 39% of unchanged starting material. The ^{1}H NMR spectrum of **4** exhibited two three-proton singlets due to *O*-acetyl groups at δ 1.84 and 2.20, together with signals from the anomeric protons at δ 5.63 (*J* 3.66 Hz), 5.68 (*J* 3.66 Hz), 6.55 (*J* 3.66 Hz), and δ 5.59–5.61 as three one-proton doublets and a three-proton multiplet, respectively. Furthermore, the ^{13}C NMR spectrum of **4** showed six signals assignable to anomeric carbons, and no signals attributable to the β-acetate were observed. In a similar way, acetolysis of fully benzoylated β- and γ-cyclodextrins (**2** and **3**) gave the di-*O*-acetylated heneicosa-*O*-benzoyl-α-maltoheptaose and tetracosa-*O*-benzoyl-α-maltooctaose (**5** and **6**) in 37 and 48% yield, respectively. The yields of **4**, **5**, and **6** calculated from consumed starting materials were 75–80%.



7: R = Ac

8: R = H

9: R = Ms

With the key acyclic maltooligosaccharides in hand, chemoselective conversion of the acetyl groups was examined employing the hexaose derivative **4** as a model compound. Since thioglycosides are receiving considerable attention as enzyme inhibitors[4], enzyme substrates [5], and intermediates in the synthesis of various *O*-glycosides [6], the chemical modification of **4** was attempted by the preparation of the phenyl 1-thioglycoside (**7**). On treatment with phenylthiotrimethylsilane–zinc iodide the acetoxy group on the anomeric carbon of **4** underwent smooth displacement by a phenylthio group, giving **7** in almost quantitative yield. In contrast to this, attempts at removal of the second acetyl group, the first step in the modification of the nonreducing end, were at first accompanied by substantial losses of benzoyl groups. Thus, treatment of **7** with potassium *tert*-butoxide in oxolane or potassium carbonate in methanol at room temperature gave polar products, as detected by TLC. On the other hand, aminolysis of **7** with hydrazine hydrate or primary amines was slow, but the reaction proceeded at elevated temperature with high selectivity. The best result was obtained when **7** was treated with an excess of *n*-butylamine in oxolane at 60°C. Extractive workup, followed by chromatographic purification, gave the 4^6-unprotected derivative **8** in 34% yield, together with 52% of unchanged **7**. The structure of **8** was elucidated by comparison of its ^{1}H NMR spectrum with that of **7**. The signal due to H-4^6 of **8** was displaced to higher field, showing that the acetyl group was removed. Furthermore, the free hydroxyl group of **8** could be mesylated with mesyl chloride in pyridine–dichloromethane, to give the 4^6-sulfonate (**9**) in 68% yield.

Thus, acetolysis of fully benzoylated cyclodextrin proved to be useful for the preparation of partially benzoylated maltooligosaccharides having two acetyl groups, to which chemoselective modifications are applicable for the efficient synthesis of various derivatives differentially substituted at both terminal sugars.

1. Experimental

General methods.—Optical rotations were determined with a Jasco DIP-370 polarimeter, using a 10-cm micro cell. ^{1}H NMR spectra (400 or 500 MHz) were recorded at 20°C with Jeol JNM GX-500 or JNM α-400 spectrometers, for solutions in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra (50 MHz) were recorded at 20°C with a Jeol JNM α-400 spectrometer for solutions in $CDCl_3$. Chemical shifts (δ) are given in ppm relative to the signal for internal Me_4Si.

Reactions were monitored by TLC on precoated plates of Silica Gel 60 F_{254} (layer thickness 0.25 mm, E. Merck, Darmstadt, Germany). Products were isolated by column chromatography on Silica Gel 60 (70–230 mesh, E. Merck) or preparative TLC on a precoated plate of Silica Gel 60 F_{254} (layer thickness 2 mm, E. Merck). Evaporations were conducted in vacuo below 40°C. Analytical samples were dried over P_2O_5 at 70–80°C for 6–8 h under reduced pressure.

O-(4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-tetrakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-O-acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranose (**4**).—Hexakis(2,3,6-tri-*O*-benzoyl)cyclomaltohexaose [7] (**1**; 5.14 g, 1.81 mmol) was dried at 60°C for 2 h in vacuo and dissolved in 49:1 Ac_2O–concd H_2SO_4 (50 mL). The mixture was stirred at 50°C for 32 h, cooled, quenched by the addition of pyridine (5 mL),

and evaporated in vacuo. Toluene addition to the residual syrup and evaporation was carried out three times, and the residue was subjected to column chromatography on silica gel with 15:1 benzene–EtOAc as the eluant, giving unchanged **1** (1.84 g, 36%) and the diacetate **4** (2.68 g, 51%); $[\alpha]_D^{18}$ +76° (*c* 0.26, $CHCl_3$); ^{1}H NMR: δ 1.84 (s, 3 H, AcO), 2.20 (s, 3 H, AcO), 4.20–4.46 (m, 20 H), 4.84 (d, 1 H, *J* 11.0 Hz, H-6), 4.91 (d, 1 H, *J* 11.9 Hz, H-6), 4.98 (d, 1 H, *J* 11.0 Hz, H-6), 5.01–5.08 (m, 4 H, 4×H-2), 5.18 (dd, 1 H, *J* 4.0, 10.7 Hz, H-2), 5.20 (dd, 1 H, *J* 3.7, 10.4 Hz, H-2), 5.38 (t, 1 H, *J* 9.8 Hz, H-4^6), 5.59–5.61 (m, 3 H, 3×H-1), 5.63 (d, 1 H, *J* 3.7 Hz, H-1), 5.68 (d, 1 H, *J* 3.7 Hz, H-1), 5.86–6.01 (m, 6 H, 6×H-3), and 6.50 (d, 1 H, *J* 3.7 Hz, H-1^1); ^{13}C NMR: δ 20.43, 20.87, 62.08, 62.49, 62.57, 62.64, 62.70, 63.03, 68.49, 69.07, 69.99, 70.04, 70.17, 70.42, 70.58, 70.78, 70.88, 70.90, 71.06, 71.21, 71.77, 71.83, 72.01, 72.08, 72.26, 73.53, 73.61, 73.97, 77.21, 89.19, 96.58, 96.61, 96.71, 96.81, 96.93, 127.91–133.24, and 164.59–169.18. Anal. Calcd for $C_{166}H_{138}O_{51}$: C, 67.61; H, 4.72. Found: C, 67.35; H, 4.69.

O-(4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-pentakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-O-acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranose (**5**).—Heptakis(2,3,6-tri-*O*-benzoyl)cyclomaltoheptaose [8] (**2**; 9.96 g, 3.0 mmol) was treated with 49:1 Ac_2O–concd H_2SO_4 (35 mL) for 29 h. Workup as described for the preparation of **4** gave unchanged **3** (5.34 g, 54%) and the diacetate **5** (3.79 g, 37%) as an amorphous solid; $[\alpha]_D^{17}$ +67° (*c* 0.47, $CHCl_3$); ^{1}H NMR (50°C): δ 1.84 (s, 3 H, AcO), 2.15 (s, 3 H, AcO), 4.16–4.88 (m, 25 H), 5.01–5.10 (m, 5 H, 5×H-2), 5.19 (dd, 1 H, *J* 4.1, 9.7 Hz, H-2), 5.21 (dd, 1 H, *J* 3.7, 10.2 Hz, H-2^1), 5.36 (t, 1 H, *J* 4.1, 10.0 Hz, H-4), 5.56–5.06 (m, 4 H, 4×H-1), 5.61 (d, 1 H, *J* 3.7 Hz, H-1), 5.67 (d, 1 H, *J* 3.6 Hz, H-1), 5.82–5.91 (m, 5 H, 5×H-3), 5.95 (t, 1 H, *J* 8.6 Hz, H-3), 5.99 (t, 1 H, *J* 9.3 Hz, H-3), 6.49 (d, 1 H, *J* 3.6 Hz, H-1^1); ^{13}C NMR: δ 20.38, 20.83, 62.04, 62.41, 62.49, 62.60, 62.68, 62.95, 68.48, 69.04, 69.97, 70.07, 70.19, 70.40, 70.55, 70.75, 70.80, 70.86, 70.98, 71.19, 71.73, 72.01, 72.23, 73.53, 73.94, 77.20, 89.16, 96.47, 96.56, 96.61, 96.66, 96.78, 96.88, 127.63–133.26, and 164.34–169.14. Anal. Calcd for $C_{193}H_{160}O_{59}\cdot H_2O$: C, 67.36; H, 4.75. Found: C, 67.09; H, 4.71.

Octakis(2,3,6-tri-O-benzoyl)cyclomaltooctaose (tetracosa-O-benzoylcyclomaltooctaose) (**3**).—To a solution of dried cyclomaltooctaose (13.0 g, 10 mmol) and 4-dimethylaminopyridine (5.0 g) in pyridine (300 mL) was added dropwise benzoyl chloride (58 mL, 0.5 mol). The solution was stirred at 80–90°C for 48 h, poured into ice–water, and extracted with $CHCl_3$. The extract was successively washed with 3% HCl, aq satd $NaHCO_3$, and brine, dried over anhyd Na_2SO_4, and concentrated. The residue was chromatographed with 19:1 benzene–EtOAc, to give the perbenzoate **3** (32.1 g, 85%) as an amorphous powder; $[\alpha]_D^{17}$ +29° (*c* 0.87, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6, 100°C): δ 4.70 (br t, 8 H, *J* ~9.7 Hz, H-4), 4.88 (m, 8 H, H-5), 5.04 (dd, 8 H, *J* 3.3, 12.1 Hz, H-6), 5.19 (d, 8 H, *J* 11.9 Hz, H-6), 5.48 (dd, 8 H, *J* 4.0, 8.8 Hz, H-2), 5.89 (d, 8 H, *J* 4.2 Hz, H-1), and 6.07 (t, 8 H, *J* 8.9 Hz, H-3); ^{13}C NMR: δ 63.31, 70.40, 71.47, 71.83, 76.93, 97.29, 127.78–133.08, 164.62, 165.74, and 165.98. Anal. Calcd for $C_{216}H_{176}O_{64}$: C, 68.35; H, 4.67. Found: C, 68.47; H, 4.71.

O-(4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-hexakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-O-acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranose (**6**).—Octakis(2,3,6-tri-*O*-benzoyl)cyclomaltooctaose (**3**; 2.91 g, 0.77 mmol) was treated with 49:1 Ac_2O–concd H_2SO_4 (50 mL) for 27 h. Workup as described for the

preparation of **4** gave unchanged **3** (1.14 g, 39%) and the diacetate **6** (1.45 g, 48%) as an amorphous solid; $[\alpha]_D^{15}$ +72° (*c* 0.19, $CHCl_3$); ^1H NMR (50°C): δ 1.85 (s, 3 H, AcO), 2.16 (s, 3 H, AcO), 4.20–4.89 (m, 29 H), 5.02–5.07 (m, 6 H, 6×H-2), 5.20 (dd, 1 H, *J* 3.9, 10.2 Hz, H-2), 5.18 (dd, 1 H, *J* 3.9, 10.0 Hz, H-2^1), 5.38 (t, 1 H, *J* 9.8 Hz, H-4^8), 5.57–5.60 (m, 4 H, 5×H-1), 5.62 (d, 1 H, *J* 3.9 Hz, H-1), 5.68 (d, 1 H, *J* 4.2 Hz, H-1), 5.89–6.00 (m, 8 H, 8×H-3), 6.49 (d, 1 H, *J* 3.7 Hz, H-1^1); ^{13}C NMR: δ 20.41, 20.86, 62.6, 62.34, 62.41, 62.50, 62.64, 62.68, 62.96, 68.49, 69.05, 69.97, 70.07, 70.14, 70.22, 70.42, 70.57, 70.75, 70.85, 70.96, 70.99, 71.21, 71.73, 72.03, 72.24, 73.46, 73.54, 73.99, 77.20, 89.18, 96.48, 96.55, 96.58, 96.60, 96.66, 96.78, 96.88, 127.91–133.27, and 164.55–169.16. Anal. Calcd for $C_{220}H_{182}O_{67}$: C, 67.79; H, 4.71. Found: C, 67.85; H, 4.92.

Phenyl O-*(4-O-Acetyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-tetrakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside* (**7**).—To a solution of **4** (1.11 g, 0.38 mmol) in 1,2-dichloroethane (20 mL) was added zinc iodide (1.21 g, 3.78 mmol) and phenylthiotrimethylsilane (0.70 mL, 3.8 mmol). The suspension was stirred at room temperature for 17.5 h, filtered through a Celite pad, and washed with CH_2Cl_2. The combined filtrate and washings was successively washed with 3% HCl, satd aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Chromatographic purification on a silica-gel column with 19:1 benzene–EtOAC gave the amorphous, powdery thioglycoside (**7**; 1.11 g, 98%); $[\alpha]_D^{16}$ +65° (*c* 0.24, $CHCl_3$); ^1H NMR: δ 1.85 (s, 3 H, AcO), 4.07–4.71 (m, 21 H), 4.82 (d, 1 H, *J* 11.9 Hz, H-6), 4.88 (d, 1 H, *J* 10.7 Hz, H-6), 4.96 (d, 1 H, *J* 9.46 Hz, H-1^1), 5.00 (dd, 1 H, *J* 4.0, 9.8 Hz, H-2), 5.04–5.09 (m, 3 H, 3×H-2), 5.18 (t, 1 H, *J* 9.6 Hz, H-2^1), 5.39 (t, 1 H, *J* 9.8 Hz, H-4^6), 5.55 (d, 1 H, *J* 4.0 Hz, H-1), 5.60–5.81 (m, 3 H, 3×H-1), 5.68 (m, 2 H, H-1,3), 5.81 (m, 3 H, 3×H-3), and 5.95 (t, 1 H, *J* 9.5 Hz, H-3). Anal. Calcd for $C_{170}H_{140}O_{49}S$: C, 68.08; H, 4.71; S, 1.07. Found: C, 67.96; H, 4.72; S, 1.24.

Phenyl O-*(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-tetrakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside* (**8**).—A solution of **7** (206 mg, 68 mmol) and *n*-butylamine (510 mg, 7.0 mmol) in oxolane (5 mL) was stirred at 50°C for 6 h, cooled, and diluted with $CHCl_3$. The resulting solution was successively washed with 3% HCl, satd aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Preparative TLC of the residual syrup with 13:1 benzene–EtOAc gave unchanged **7** (70 mg, 34%) and the 4^6-unprotected derivative **8** (105 mg, 52%) as an amorphous solid; $[\alpha]_D^{16}$ +52° (*c* 0.28, $CHCl_3$); ^1H NMR: δ 3.44 (d, 1 H, *J* 5.5 Hz, OH), 3.92–4.67 (m, 21 H), 4.79 (d, 1 H, *J* 12.21 Hz, H-6), 4.86 (d, 1 H, *J* 13.1 Hz, H-6), 4.94 (d, 1 H, *J* 9.8 Hz, H-1^1), 4.99 (dd, 1 H, *J* 4.3, 10.4 Hz, H-2), 5.02–5.08 (m, 3 H, 3×H-2), 5.19 (t, 1 H, *J* 9.8 Hz, H-2^1), 5.21 (dd, 1 H, *J* 3.97, 10.7 Hz, H-2), 5.53 (d, 1 H, *J* 3.4 Hz, H-1), 5.57–5.60 (m, 4 H, 4×H-1), 5.66 (t, 1 H, *J* 9.2 Hz, H-3), 5.68 (t, 1 H, *J* 9.2 Hz, H-3), and 5.79 (m, 4 H, 4×H-3). Anal. Calcd for $C_{168}H_{138}O_{48}S$: C, 68.24; H, 4.70: S, 1.08. Found: C, 68.33; H, 4.75; S, 1.14.

Phenyl O-*(4-O-methylsulfonyl-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)-tetrakis[O-(2,3,6-tri-O-benzoyl-α-D-glucopyranosyl)-(1→4)]-2,3,6-tri-O-benzoyl-1-thio-β-D-glucopyranoside* (**9**).—To an ice-cold solution of **8** (20 mg, 6.8 mmol) in CH_2Cl_2 (4 mL) and pyridine (1 mL) was added methanesulfonyl chloride (0.10 mL, 1.3 mmol). The mixture was stirred at room temperature for 17 h, quenched with ice–water, and extracted with $CHCl_3$. The extract was successively washed with 3% HCl, aq satd $NaHCO_3$, and

brine, dried ($MgSO_4$), and concentrated. Preparative TLC of the residual syrup with 17:1 benzene–EtOAc gave the 4^6-mesylate (**9**; 14 mg, 68%); $[\alpha]_D^{16}$ +58° (*c* 0.20, $CHCl_3$); ^1H NMR: δ 2.75 (s, 3 H, MsO), 4.00–4.62 (m, 22 H), 4.47 (d, 1 H, *J* 11.9 Hz, H-6), 4.80 (d, 1 H, *J* 11.9 Hz, H-6), 4.87 (d, 1 H, *J* 9.8 Hz, H-1^1), 4.92 (dd, 1 H, *J* 3.7, 9.8 Hz, H-2), 4.96–5.02 (m, 3 H, 3×H-2), 5.08 (dd, 1 H, *J* 4.0, 10.2 Hz, H-2), 5.10 (t, 1 H, *J* 9.3 Hz, H-2^1), 5.46 (d, 1 H, *J* 4.0 Hz, H-2), 5.52–5.53 (m, 3 H, 3×H-1), 5.59 (d, 1 H, *J* 4.0 Hz, H-1), 5.61 (t, 1 H, *J* 9.6 Hz, H-3), 5.73 (t, 1 H, *J* 9.5 Hz, H-3), 5.80 (t, 1 H, *J* 9.3 Hz, H-3), 5.86 (t, 1 H, *J* 9.6 Hz, H-3), and 5.91 (t, 1 H, *J* 9.9 Hz, H-3). Anal. Calcd for $C_{169}H_{140}O_{50}S_2$: C, 66.88; H, 4.65; S, 2.11. Found: C, 66.66; H, 4.65; S, 2.04.

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