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Note

Facile preparation of phenyl 1-thioglycosides of partially methylated maltooligosaccharides by restricted thiolysis of fully methylated cyclodextrins

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Fully or partially methylated cyclomaltooligosaccharides (cyclodextrins, CDs) have been attracting significant attention because they have unique properties, such as enhanced ability to complex guest compounds and high solubility in both aqueous and organic solvents [1]. However, their lack of free hydroxyl groups has been a bar to the use of fully methylated CDs as starting materials for chemical modification. Recently, we found that careful acetolysis of fully acetylated and fully benzoylated cyclodextrins afforded the acyclic maltooligosaccharides resulting from the fission of only one glycosidic bond [2,3]. This efficient reaction led us to develop a novel procedure for the synthesis of a new type of CD analogs, "neocyclodextrins", through the coupling of the acyclic intermediates with a heterogeneous sugar unit and subsequent recyclization [2]. In order to apply the new methodology to fully methylated CDs, we undertook to examine the selective cleavage of one glycosidic bond in these substances. In this Note, we describe the thiolysis of fully methylated CDs to give key intermediates, the 1^1-thioglycosides of the corresponding maltooligosaccharides.

We first examined the thiolysis of octadeca-*O*-methylcyclomaltohexaose (**1**) under Hanessian conditions [4], because 1,6-anhydromaltose derivatives could be successfully converted into the corresponding thioglycosides without any effect on their internal glycosidic linkages [5]. Compound **1** was treated with phenylthiotrimethylsilane

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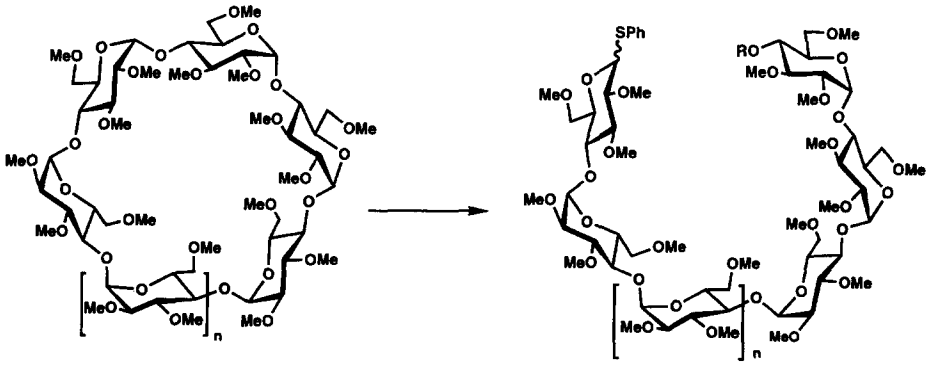
(PhSTMS) and zinc iodide in 1,2-dichloroethane at room temperature, whereupon a complex mixture was detected by TLC. Most of the spots moved more slowly than **1**, and showed no absorption of UV light. These results suggested that the methyl ether groups in **1** were more easily cleaved by the reagent system than the glycosidic bonds.



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

4: n = 1, R = H
5: n = 1, R = TMS
6: n = 1, R = Bz
7: n = 2, R = Bz
8: n = 3, R = Bz

The screening of Lewis acids other than zinc iodide was undertaken, and zinc bromide was found to be the best catalyst, among the reagents tested, for the selective fission of the glycosidic bonds. When the reaction was performed with PhSTMS (4 mol equiv) and zinc bromide (4 mol equiv) in 1,2-dichloroethane, two major products as well as the starting material were observed on TLC. On the basis of our previous experiments on the thiolysis of 1,6-anhydro sugars [5] we deduced that the slower-moving component, which showed almost the same chromatographic behavior as **1**, was the partially methylated phenyl 1^1-thiomaltohexaoside having an unprotected hydroxyl group (**4**), and that the faster-moving product was the corresponding *O*-trimethylsilyl (*O*-TMS) derivative **5**. However, purification of the products by column chromatography on silica gel was unsuccessful because of substantial loss of the *O*-TMS group. Consequently, the isolation and the characterization were performed after replacement of the *O*-TMS group by the *O*-benzoyl group. Replacement was accomplished by treatment of the mixture with triethylamine in methanol to remove *O*-TMS, then reaction with benzoyl chloride in pyridine. Flash column chromatography of the resulting mixture gave phenyl 4^6-*O*-benzoyloctadeca-*O*-methyl-1^1-thiomaltohexaoside (**6**) in 28% overall yield together with the starting material (68%). In the ^{1}H NMR spectrum of **6** in benzene-d_6 one triplet having J 9.7 Hz and attributable to H-4^6 was observed at low magnetic field (δ 5.67), showing that O-4^6 was benzoylated. Furthermore, a pair of doublets at δ 4.51 (J 9.8 Hz) and 5.49 (J 3.7 Hz) suggested that **6** was an anomeric mixture having an α/β ratio of 1:1.

Similar thiolysis reactions of fully methylated β-CD (**2**) and γ-CD (**3**) proceeded without any side reactions or excess cleavage of the glycosidic linkages. Treatment of **2** with PhSTMS (4 mol equiv) and zinc bromide (4 mol equiv) in 1,2-dichloroethane at room temperature for 4 days gave phenyl 4^7-*O*-benzoylhenicosa-*O*-methyl-1^1-thiomaltoheptaoside (**7**) in 40% overall yield. Although the low solubility of **3** in 1,2-dichloroethane precluded the use of this solvent, the reaction of **3** in dichloromethane afforded the 1^1-thiomaltooctaoside **8** in 41% yield.

Thus, the phenyl 1-thioglycosides of methylated maltooligosaccharides of dp 6–8 carrying a benzoyl group at their nonreducing ends became obtainable in two easy steps from the corresponding per-*O*-methylated CDs. The yields calculated from the starting material consumed were more than 80%. These maltooligosaccharides, able to function both as glycosyl donors and glycosyl acceptors, will serve as key intermediates for the synthesis of methylated neocyclodextrins [6].

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. ^{13}C NMR spectra (100 MHz) were recorded at 20°C with a JEOL JNM α-400 spectrometer. 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 flash column chromatography on Silica Gel 60 (70–230 mesh, E. Merck) or by 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.

Octakis(2,3,6-tri-O-methyl)cyclomaltooctaose (**3**).—Sodium hydride (60% dispersion in oil, 50 g, 1.25 mol) was washed with hexane several times under argon and dried under reduced pressure. To a solution of dried cyclomaltooctaose (γ-CD, 26 g, 20 mmol) in dimethyl sulfoxide (1 L) and 1,4-dioxane (300 mL) the sodium hydride was added in small portions, and the suspension was stirred at room temperature for 2 h. To the mixture vigorously stirred in an ice bath was added dropwise a solution of dimethyl sulfate (50 mL, 530 mmol) in 1,4-dioxane (100 mL), and stirring was continued at room temperature for 5 h. After cooling in an ice bath, methanol (100 mL) and concd aq ammonia (50 mL) were successively added dropwise, and the mixture was stirred at room temperature overnight. Most of the solvent was removed by evaporation, and the residue was partitioned between chloroform and water. The organic layer was successively washed with 3% HCl, saturated aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was subjected to column chromatography on silica gel employing 97:3 (v/v) chloroform–methanol to give **3** (28.1 g, 86%) as an amorphous powder; [α] +162° (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.19 (dd, 8 H, *J* 3.4, 9.6 Hz, H-2), 3.37 (s, 24 H, OMe), 3.50–3.60 (m, 40 H, OMe, H-5,6), 3.65 (s, 24 H, OMe), 3.65–3.77 (m, 16 H, H-3,4), 3.85 (dd, 8 H, *J* 2.9, 10.4 Hz, H-6), and 5.23 (d,

8 H, *J* 3.4 Hz, H-1). Anal. Calcd for $C_{72}H_{128}O_{40}$: C, 52.93; H, 7.90. Found: C, 52.60; H, 7.67.

Phenyl O-*(4-O-benzoyl-2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)-tetrakis[O-(2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)]-2,3,6-tri-O-methyl-1-thio-D-glucopyranoside* (**6**).—To a solution of hexakis(2,3,6-tri-*O*-methyl)cyclomaltohexaose [7] (**1**, 12.3 g, 10 mmol) in 1,2-dichloroethane (150 mL) were added PhSTMS (7.6 mL, 40 mmol) and anhydrous zinc bromide (9.0 g, 40 mmol), and the suspension was stirred at room temperature for 5 days. The precipitate was filtered through a Celite pad and washed with 1,2-dichloroethane (50 mL). To the combined filtrate and washings was then added 4:1 (v/v) methanol–triethylamine (100 mL). The mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. To a solution of the residual syrup in dry pyridine (20 mL) and chloroform (200 mL) benzoyl chloride (6 mL, 52 mmol) was added dropwise with stirring at 0°C. The solution was stirred at room temperature overnight, poured into ice–water, and extracted with chloroform. The extract was successively washed with 3% HCl, saturated aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was subjected to flash column chromatography on silica gel, employing toluene–acetone as the eluent, to give **6** (3.4 g, 28%), ^{1}H NMR (C_6D_6): δ 3.12–4.30 (m, OMe and ring protons), 4.51 (d, 0.5 H, *J* 9.8 Hz, H-1$^1\beta$), 5.49 (d, 0.5 H, *J* 3.7 Hz, H-1$^1\alpha$), 5.56 (t, 1 H, *J* 9.7 Hz, H-4^6), 5.67 (d, 0.5 H, *J* 3.3 Hz, H-1), 5.68 (d, 0.5 H, *J* 3.5 Hz, H-1), 5.72–5.74 (m, 4 H, H-1), 6.98–7.17, 7.51–7.62, and 8.13–8.15 (3 m, 10 H, 2 Ph); ^{13}C NMR ($CDCl_3$): δ 58.47, 58.79, 59.02, 59.77, 69.54, 70.47, 71.19, 71.33, 71.67, 73.68, 73.87, 74.00, 81.44, 82.29, 82.44, 86.30, 96.44, 96.67, 96.76, 125.26, 126.85, 128.02, 128.25, 128.58, 128.68, 130.12, 131.47, 132.83, and 165.10. Anal. Calcd for $C_{67}H_{106}O_{31}S$: C, 55.90; H, 7.42; S, 2.23. Found: C, 56.21; H, 7.51; S, 2.23.

Further elution of the column with the same solvent gave unchanged **1** (8.54 g, 68%).

Phenyl O-*(4-O-benzoyl-2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)-pentakis[O-(2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)]-2,3,6-tri-O-methyl-1-thio-D-glucopyranoside* (**7**).—Heptakis(2,3,6-tri-*O*-methyl)cyclomaltoheptaose [8] (**2**, 14.29 g, 40 mmol) was treated with PhSTMS (7.6 mL, 40 mmol) and anhydrous zinc bromide (9.0 g, 40 mmol) in 1,2-dichloroethane (200 mL) for 4 days, and the mixture was worked up as described for the preparation of **6**. The benzoylated residue was subjected to column chromatography on silica gel with 3:1 (v/v) toluene–acetone to give the amorphous, powdery thioglycoside **7** (6.57 g, 40%), ^{1}H NMR (C_6D_6): δ 3.15–4.08 (m, OMe and ring protons), 4.50 (d, 0.5 H, *J* 9.8 Hz, H-1$^1\beta$), 5.46 (d, 0.5 H, *J* 4.2 Hz, H-1$^1\alpha$), 5.49 (t, 1 H, *J* 9.5 Hz, H-4^7), 5.62 (d, 0.5 H, *J* 3.7 Hz, H-1), 5.67–5.70 (m, 5.5 H, H-1), 6.96–7.15, 7.50–7.60, and 8.12–8.18 (3 m, 10 H, 2 Ph); ^{13}C NMR ($CDCl_3$): δ 58.79, 59.12, 59.99, 60.46, 70.15, 70.76, 71.06, 73.32, 77.22, 81.91, 82.77, 86.21, 96.31, 96.57, 126.70, 127.12, 128.18, 128.33, 128.67, 128.76, 129.46, 129.75, 131.42, 133.85, 131.25, and 165.05. Anal. Calcd for $C_{76}H_{122}O_{36}S$: C, 55.53; H, 7.48; S, 1.95. Found: C, 55.45; H, 7.56; S, 1.95.

Further elution of the column with 2:1 toluene–acetone gave **2** (7.7 g, 54%).

Phenyl O-*(4-O-benzoyl-2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)-hexakis[O-(2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)]-2,3,6-tri-O-methyl-1-thio-D-glucopyranoside* (**8**).—Compound **3** (1.63 g, 1 mmol) was treated with PhSTMS (0.8 mL, 4

mmol) and anhydrous zinc bromide (0.9 g, 4 mmol) in dichloromethane (20 mL) for 4 days, and the mixture was further processed as described for the preparation of **6**. The benzoylated residue was subjected to column chromatography on silica gel with 4:1 → 2:1 (v/v) toluene–acetone to give the amorphous, powdery thioglycoside **8** (0.76 g, 41%), ^{1}H NMR (C_6D_6): δ 3.12–4.09 (m, OMe and ring protons), 4.21–4.26 (m, 1 H), 4.36 (br d, 0.8 H, J 10 Hz, H-6), 4.50 (d, 0.8 H, J 9.8 Hz, H-1$^1\beta$), 5.49 (d, 0.2 H, J 4.0 Hz, H-1$^1\alpha$), 5.52 (t, 1 H, J 10.0 Hz, H-4^8), 5.65 (d, 0.2 H, J 3.7 Hz, H-1), 5.68–5.71 (m, 6.8 H, H-1), 6.99–7.15, 7.50–7.60, and 8.10–8.14 (3 m, 10 H, 2 Ph); ^{13}C NMR ($CDCl_3$): δ 59.09, 59.36, 60.20, 61.38, 70.47, 70.96, 71.27, 73.58, 77.90, 82.26, 82.53, 83.04, 87.49, 96.75, 96.78, 127.08, 127.31, 128.52, 128.95, 129.65, 129.95, 131.45, 131.62, 133.22, and 165.24. Anal. Calcd for $C_{85}H_{138}O_{41}S$: C, 55.24; H, 7.53; S, 1.74. Found: C, 55.34; H, 7.56; S, 1.79.

Further elution of the column with 2:1 toluene–acetone gave **3** (0.81 g, 50%).

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