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# Regioselective Mono-2-*C*-iodination of Fully Methylated Cyclodextrins through Interconversions between Cyclic and Acyclic Structures

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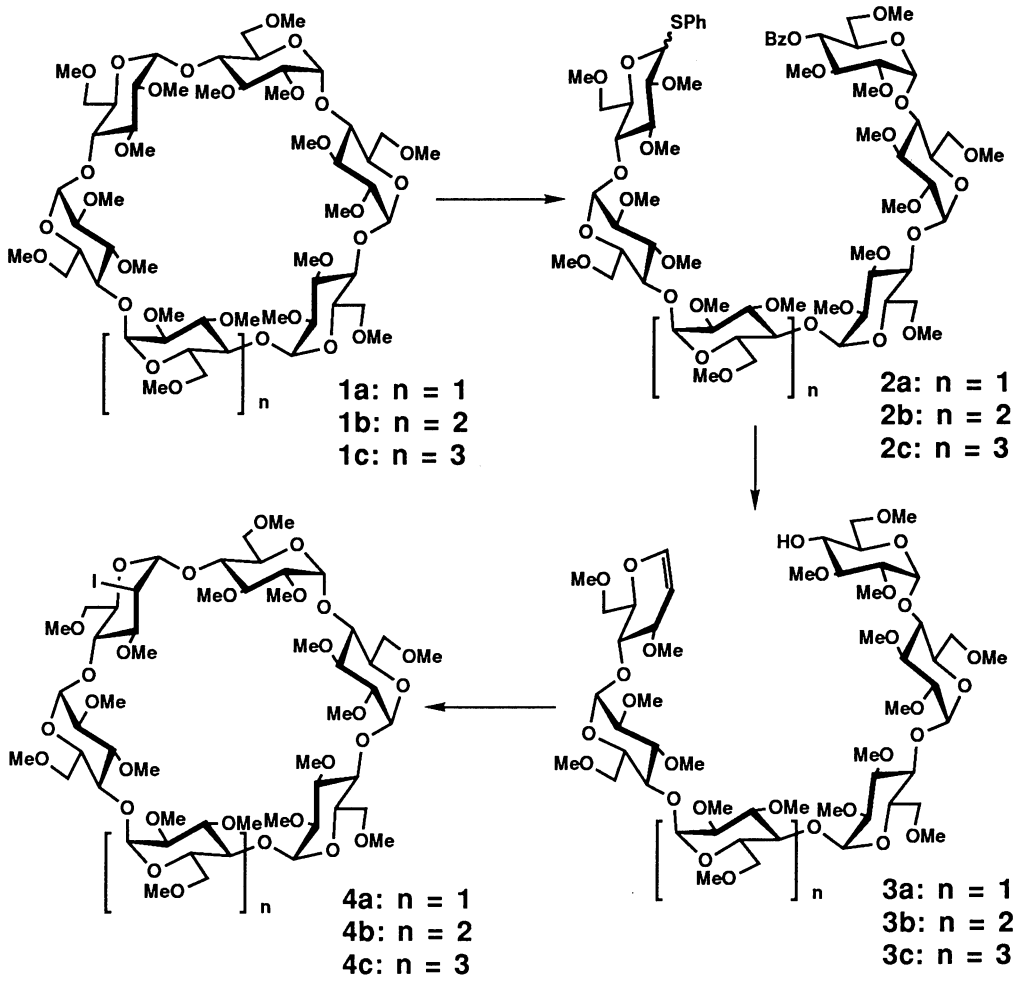
An efficient procedure for modification at C-2 position of fully methylated α-, β-, and γ-cyclodextrins was achieved by thiolytic fission of one of their glycosidic bonds, followed by conversion of the resulting 1-thioglycosides into glycals and addition of iodonium ion accompanied intramolecular glycosidation, giving novel methylated cyclooligosaccharides containing 2-deoxy-2-iodo-α-D-mannopyranosyl moiety as one of the constituents.

The ability of cyclodextrins (CDs) to bind hydrophobic molecules without formation of any covalent bonds has already led to numerous works in the field of enzyme mimetic chemistry.[1] A further development towards mimicking function of such enzymes as chymotrypsin, aldolase, and cytochrome P-450 has been attained by the use of partially methylated CDs[2] that have quite different properties from the parent CDs. In contrast to those partially methylated CDs, fully methylated CDs have been unable to undergo any chemical modifications because they are devoid of susceptible hydroxyl groups. This fact has definitively lowered the usefulness of the fully methylated CDs as the starting materials for construction of enzyme mimics.

Recently, we found that careful acetolysis of peracetylated CDs gave linear malto-oligosaccharides in good yields, as a result of the fission of only one glycosidic bond.[3] This efficient reaction led to the preparation of novel CD analogs through modification of the resulting acyclic oligosaccharides and subsequent recyclization.[3,4] Different from the acetylated CDs, acetolysis of fully methylated β-CD (**1b**) resulted in formation of a monosaccharide derivative as a main product. Now, we wish to describe how to restrain such over-fission of the fully methylated CDs and to use the resulting mostly methylated linear compounds.

After screening several combinations of acid catalysts and nucleophiles, we found that thiolysis with the reagent system of PhSTMS-$ZnI_2$ reported by Hanessian[5] was effective for the restricted cleavage of the glycosidic bonds of the permethylated CDs. Thus, **1b** was treated with PhSTMS (4 mol. equiv.) and $ZnI_2$ (4 mol. equiv.) in 1,2-dichloroethane at room temperature for 4 days, giving phenyl 1-thiomaltoheptaoside *O*-silylated at the $4^7$-position as a major product. For purification and characterization, the unstable *O*-TMS group was converted into the *O*-benzoyl group by successive treatments with methanolic sodium methoxide and benzoyl chloride-pyridine, giving an anomeric mixture (α/β = 1:1) of phenyl $4^7$-*O*-benzoyl-1-thiomaltoheptaoside (**2b**)[6] in 38% yield together with the starting material (56%). Application of this reaction to fully methylated α-CD (**1a**) and γ-CD (**1c**) required a few technical changes and the results are summarized in Table 1. The reaction of **1c** was performed in $CH_2Cl_2$ to improve the solubility of the starting material. Undesired removal of *O*-methyl groups observed in the thiolytic fission of **1a** became avoidable by use of $ZnBr_2$ as the catalyst instead of $ZnI_2$. In this way, phenyl 1-thioglycosides of




malto-oligosaccharides (D.P. = 6-8) carrying a benzoyl group at their non-reducing ends became obtainable in a short step from the corresponding permethylated CDs. The yields calculated from the starting material consumed were more than 80%.

Our previous success in iodonium ion promoted cycloglycosidation of benzylated glycal derivatives[4] prompted us to apply that procedure to the methylated intermediates (**2a, b, c**). The hydroxyglycals (**3a, b, c**)[6]

Table 1. Thiolysis of Fully Methylated Cyclodextrins[a]

| CDs | Solvent | Catalyst | Time | Product (Yield) | α/β | Recovery |
|---|---|---|---|---|---|---|
| **1a** (n = 1) | $(CH_2Cl)_2$ | $ZnBr_2$ | 5 d | **2a** (28%) | 0.67 | 68% |
| **1b** (n = 2) | $(CH_2Cl)_2$ | $ZnI_2$ | 4 d | **2b** (38%) | 1.0 | 56% |
| **1c** (n = 3) | $CH_2Cl_2$ | $ZnI_2$ | 4 d | **2c** (41%) | 0.25 | 50% |

a) All reactions were performed by the use of PhSTMS (4 equiv.) at room temperature.

Table 2. Intramolecular Glycosidation of Glycals by Iodonium Addition[a)]

| Glycal | Promoter | Solvent | Temp | Time | Yield |
|---|---|---|---|---|---|
| **3a** (n = 1) | A | $CH_2Cl_2$ | r.t. | 1 d | 13% |
| | B | $CH_2Cl_2$ | r.t. | 1 d | 39% |
| | C | $(CH_2Cl)_2$ | 80 °C | 2 d | 52% |
| **3b** (n = 2) | B | $CH_2Cl_2$ | r.t. | 2 d | 25% |
| | C | $(CH_2Cl)_2$ | 80 °C | 2 d | 28% |
| **3c** (n = 3) | B | $CH_2Cl_2$ | r.t. | 2 d | 11% |
| | C | $(CH_2Cl)_2$ | 80 °C | 5 d | 13% |

a) All reactions were performed in the presence of molecular sieves 4A under argon atmosphere using NIS (A; 4 equiv.), IDCP (B; 2.5 equiv.), or $BnMe_3NCl_2I$ (C; 5 equiv.).

desired for the cyclization were prepared in 80-90% yields by treatment of the thioglycosides (**2a, b, c**) with freshly prepared lithium naphthalenide (5-8 equiv.) at -80 °C.[7)] The next cycloglycosidation was examined using three iodonium reagents and the results are summarized in Table 2. Similarly to the benzylated derivative,[4)] **3a** was first treated with iodonium di(*sym*-collidine)perchlorate (IDCP)[8)] in $CH_2Cl_2$ to give a cyclic product (**4a**)[6)] in 39% yield. While treatment of **3a** with NIS at room temperature in $CH_2Cl_2$ gave **4a** in poor yield. The best result was obtained when **3a** was treated with benzyltrimethylammonium dichloroiodate ($BnMe_3NCl_2I$) at 80 °C in 1,2-dichloroethane, giving **4a** in 52% yield. In a similar way, treatments of **3b** and **3c** with the iodonium reagents afforded mono(2-deoxy-2-iodo) derivatives of permethylated β-CD (**4b**)[6)] and γ-CD (**4c**),[6)] respectively. The structure of **4a**, **4b**, and **4c** were determined to be 2-deoxy-2-iodo-α-D-mannopyranose containing oligosaccharides mainly on the basis of $^1H$ NMR spectroscopy that showed small coupling constants, $J_{1,2} < 1.5$ Hz and $J_{2,3} = 3$-4 Hz. The dissociation constants ($K_d$) of the inclusion complex of **4a** with *p*-nitrophenolate in phosphate buffer (*p*H 11.0) at 20 °C was $2.0 \times 10^{-4}$ mol/L.

In conclusion, thiolysis of the fully methylated CDs with PhSTMS-$ZnI_2$ (or $ZnBr_2$) resulted in restricted fission of only one glycosidic bond, giving the 1-thioglycosides of malto-oligosaccharides which are versatile intermediates to synthesize new type of methylated CD analogs. As an example, it was demonstrated that they were converted into permethylated mono(2-deoxy-2-iodo)CD derivatives in two steps.

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6) All new compounds gave satisfactory data of elemental analyses. $[\alpha]_D^{19}$ Values in $CHCl_3$: **3a**; +168° (*c* 0.12); **3b**; +181° (*c* 0.23); **3c**; +199° (*c* 0.49); **4a**; +144° (*c* 0.14); **4b**; +127° (*c* 0.12); **4c**; +126° (*c* 0.22). $^1H$ NMR (500 MHz): **2a** ($CDCl_3$); δ=4.52 (0.6H, d, *J*=9.8 Hz, H-$1^1\beta$), 5.46 (1H, d, *J*=3.4 Hz, H-1), 5.58 (1H, t, *J*=9.6 Hz, H-$4^6$), 5.68 (0.4H, d, *J*=4.8 Hz, H-$1^1\alpha$), 5.72-5.80 (4H, m, H-1); **2b** ($CDCl_3$); δ=4.51 (0.5H, d, *J*=9.7 Hz, H-$1^1\beta$), 5.53 (1H, t, *J*=9.8 Hz, H-$4^7$), 5.66 (1H, d, *J*=3.7 Hz, H-1), 5.69 (0.5H, d, *J*=5.4 Hz, H-$1^1\alpha$), 5.72 (5H, m, H-1); **2c** ($CDCl_3$); δ=4.50 (0.8H, d, *J*=9.8 Hz, H-$1^1\beta$), 5.49 (1H, d, *J*=3.6 Hz, H-1), 5.52 (1H, d, *J*=9.7 Hz, H-$4^8$), 5.65-5.71 (6.2H, m, H-1); **3a** ($CD_3OD$); δ=3.10 (1H, dd, *J*=3.7, 9.9 Hz, H-2), 3.17 (1H, dd, *J*=3.6, 9.8 Hz, H-2), 3.19 (1H, dd, *J*=3.6, 10.2 Hz, H-2), 3.20 (1H, dd, *J*=3.7, 10.4 Hz, H-2), 3.22 (1H, dd, *J*=3.6, 9.8 Hz, H-2), 4.89 (1H, dd, *J*=6.1, 2.4 Hz, H-$2^1$), 5.51-5.53 (3H, m, H-1), 5.54 (1H, d, *J*=3.7 Hz, H-1), 5.56 (1H, d, *J*=3.6 Hz, H-1), 6.43 (1H, d, J=6.1 Hz, H-$1^1$); **3b** ($CD_3OD$); δ=3.11 (1H, dd, *J*=3.6, 9.8 Hz, H-2), 3.21 (1H, dd, *J*=3.6, 9.7 Hz, H-2), 4.90 (1H, dd, *J*=6.1, 2.4 Hz, H-$2^1$), 5.52-5.54 (5H, m, H-1), 5.57 (1H, d, *J*=3.6 Hz, H-1), 6.43 (1H, d, *J*=6.1 Hz, H-$1^1$); **3c** ($CD_3OD$); δ=3.07 (1H, dd, *J*=3.6, 9.8 Hz, H-2), 4.86 (1H, dd, *J*=6.1, 2.4 Hz, H-$2^1$), 5.48-5.52 (6H, m, H-1), 5.54 (1H, d, *J*=3.7 Hz, H-1), 6.41 (1H, d, *J*=6.1 Hz, H-$1^1$); **4a** ($C_6D_6$); δ=3.06 (1H, dd, *J*=3.0, 9.5 Hz, H-2), 4.16 (1H, dd, *J*=4.5, 10.6 Hz, H-6), 4.24 (1H, dd, *J*=3.4, 9.8 Hz, H-6), 4.72 (1H, dd, *J*=1.5, 4.3 Hz, H-$2^1$), 5.03 (1H, d, *J*=3.4 Hz, H-1), 5.09 (1H, d, *J*=3.3 Hz, H-1), 5.10 (1H, d, *J*=3.3 Hz, H-1), 5.11 (1H, d, *J*=3.6 Hz, H-1), 5.13 (1H, d, *J*=3.0 Hz, H-1), 5.42 (1H, br.s, H-$1^1$); **4b** ($C_6D_6$, at 40 °C); δ=4.84 (1H, m, H-$2^1$), 5.15 (1H, d, *J*=3.0 Hz, H-1), 5.20 (1H, d, *J*=3.4 Hz, H-1), 5.25 (1H, d, *J*=3.7 Hz, H-1), 5.26 (1H, d, *J*=3.9 Hz, H-1), 5.28 (1H, d, *J*=4.0 Hz, H-1), 5.30 (1H, d, *J*=3.3 Hz, H-1), 5.48 (1H, br.s, H-$1^1$); **4c** ($C_6D_6$); δ=4.92 (1H, s, H-$2^1$), 5.29 (1H, d, *J*=3.7 Hz, H-1), 5.34 (1H, d, *J*=3.4 Hz, H-1), 5.40 (1H, d, *J*=3.4 Hz, H-1), 5.43 (1H, d, *J*=3.7 Hz, H-1), 5.49 (1H, d, *J*=3.6 Hz, H-1), 5.52 (1H, d, *J*=3.5 Hz, H-1), 5.58 (1H, s, H-$1^1$), 5.60 (1H, d, *J*=3.7 Hz, H-1).

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