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Per-6-bromo-per-2,3-dimethyl-ß-cyclodextrin

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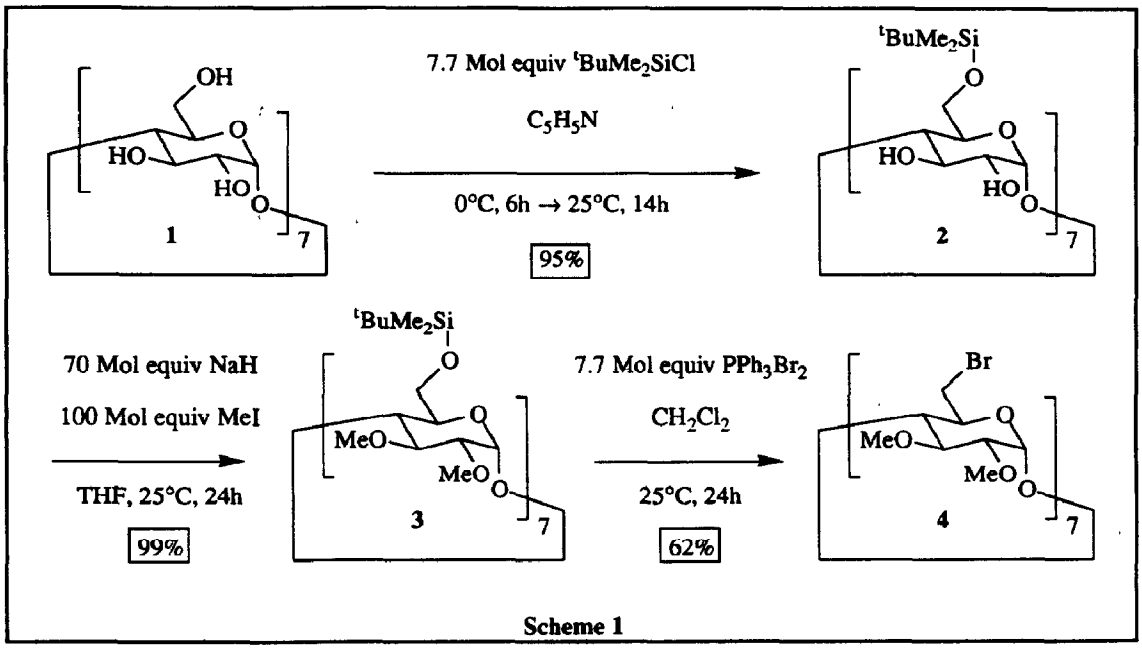
Abstract: An efficient synthesis of the title compound, per-6-bromo-per-2,3-dimethyl-ß-cyclodextrin, is described, giving access to a highly soluble cyclodextrin, which may be used for further chemical modification of ß-cyclodextrin. Crystals of the target compound were grown and the solid state structure was determined by X-ray crystallography, revealing a cyclodextrin derivative whose conformation deviates substantially from C_7 symmetry.

Cyclodextrins and their derivatives have been investigated[1] extensively as a consequence of their abilities to form inclusion complexes with a wide variety of substrates. The chemical modification[2,3] of cyclodextrins is of interest in order to change their solubilities as well as to alter their behaviour as host molecules. Unfortunately, the regioselective substitution of cyclodextrins often involves low yielding reactions and tedious separation procedures to obtain pure derivatives. Substitution of the primary hydroxyl groups in a cyclodextrin is a desirable chemical modification, as substitution at this position does not alter significantly the conformations of the D-glucopyranose residues or of the cyclodextrin torus. A very efficient and selective halogenation of the primary hydroxyl groups on cyclodextrins has been reported by Defaye and co-workers,[4,5] giving halogenated cyclodextrins as intermediates in the preparation of the per-3,6-anhydro cyclodextrins.[4,6,7] These halogenated cyclodextrins are also useful intermediates[8,9] for carrying out other synthetic modifications. However, a disadvantage of these halogenated derivatives[9] is that they can only be dissolved in high boiling point organic solvents. Furthermore, they are not amenable to conventional column chromatography on silica gel on account of their high polarities. For these reasons, an analogue of the halogenated derivatives was targeted in which all the secondary hydroxyl groups of the cyclodextrins are replaced by methoxyl groups, a modification which was expected to enhance their solubilities. The selectivity with which all the primary hydroxyl groups of a cyclodextrin can be converted into *tert*-butyldimethylsilyl ether groups[10,11] and the possibility of direct replacement[12] of these silyl ethers with bromine atoms, suggested to us an efficient route (**Scheme 1**) to the title compound **4**, starting from ß-cyclodextrin **1**. Here, we report the synthesis and the X-ray crystal structure of the per-6-bromo-per-2,3-dimethyl-ß-cyclodextrin **4**.

Per-6-*tert*-butyldimethylsilyl-ß-cyclodextrin **2**[13] was prepared from **1** using literature procedures.[10,11] The per-2,3-dimethyl derivative **3** was accessible by exhaustive methylation of **2**, using iodomethane and oil-free sodium hydride in THF at room temperature. After 18 hours, the reaction was quenched with methanol, the solvents were removed under vacuum, and the residue was partitioned between dichloromethane and water.



Scheme 1

The organic layer was recovered, dried, and evaporated to dryness under reduced pressure to yield **3**.[14] Desilylation and simultaneous bromination were accomplished by adding **3** to a suspension of triphenylphosphine dibromide in dichloromethane.[15] As the reaction proceeded, the suspension slowly cleared. After 24 hours, the solution was washed with concentrated aqueous sodium hydrogen carbonate. The organic layer was separated and concentrated under reduced pressure to give a thick syrup, which yielded a white precipitate upon sonication in ethanol. This precipitate was filtered off, recrystallised from acetone, and characterised as the desired per-6-bromo-per-2,3-dimethyl-ß-cyclodextrin **4**.[16] The solubility of **4** in low

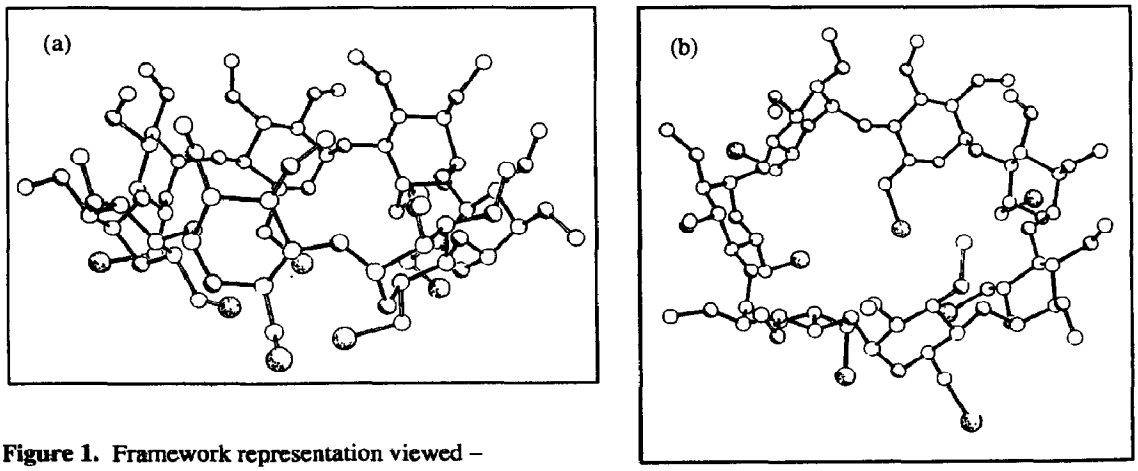


Figure 1. Framework representation viewed –

(a) from the side and (b) from above, *i.e.* the secondary face.

The large speckled spheres represent the bromine atoms.

boiling point organic solvents was noted to be much enhanced compared with that of the per-6-bromo-ß-cyclodextrin[4] and the possibility of using it as a starting material for further chemical modification of cyclodextrins is being investigated currently. Single crystals of the per-6-bromo-per-2,3-dimethyl-ß-cyclodextrin **4**, which proved to be of suitable quality for X-ray crystallographic analysis, were grown by slow evaporation of an acetone solution.

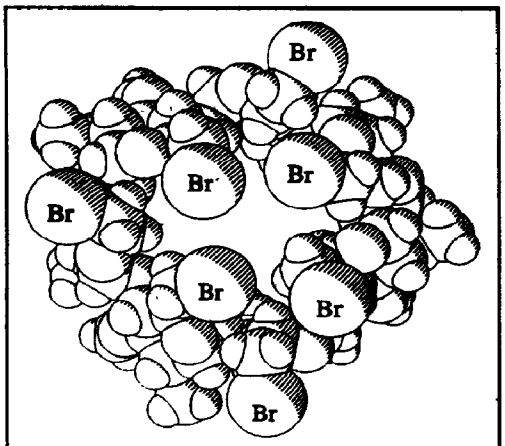


Figure 2. Space-filling representation of the solid state structure of **4** viewed from the primary face

The X-ray crystal structure[17] shows (**Figures 1** and **2**) that the conformation of the molecule departs significantly from C_7 symmetry. The α-1,4 linked D-glucopyranose rings adopt varying orientations with respect to each other, resulting in four of the bromomethyl groups being directed outwards and three inwards, partially blocking the free passage through the core of the molecule. The loss of symmetry within **4** is undoubtedly a consequence of the loss of the chain of circumferal intramolecular hydrogen bonds between the secondary hydroxyl groups of adjacent D-glucopyranose units in ß-cyclodextrin.[18]

The synthetic methodology, outlined in **Scheme 1**, has allowed us to prepare gram quantities of the perbromide **4** – a useful precursor for further chemical modifications of ß-cyclodextrin. Furthermore, the crystal structure of this highly functionalised ß-cyclodextrin shows significant differences in its solid state from the crystal structure which has been reported recently[19] for the analogue of **4** with hydroxyl instead of methoxyl groups.

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13. Spectroscopic data for **2**: δ_H (300 MHz, $CDCl_3$) = 0.03 (21H, s, SiMe), 0.04 (21H, s, SiMe), 0.86 (63H, s, CMe_3), 3.55 (7H, t, J = 9.5 Hz, H-4), 3.59 (7H, bs, H-5), 3.65 (7H, dd, J = 3, 9.5 Hz, H-2), 3.70 (7H, bd, J = 11 Hz, H-6), 3.89 (7H, dd, J = 2, 11 Hz, H-6), 4.03 (7H, t, J = 9.5 Hz, H-3), 4.88 (7H, d, J = 3 Hz, H-1), 5.26 (7H, s, HO-2), 6.72 (7H, s, HO-3); δ_C (75 MHz, $CDCl_3$) = -5.2 (SiMe), -5.1 (SiMe), 18.3 (CMe_3), 25.9 (CMe_3), 61.7 (C-6), 72.6, 73.4, 73.6 (C-2, C-3, and C-5), 81.8 (C-4), 102.0 (C-1).

14. Spectroscopic data for **3**: δ_H (300 MHz, $CDCl_3$) = 0.02 (21H, s, SiMe), 0.03 (21H, s; SiMe), 0.86 (63H, s, CMe_3), 3.04 (7H, dd, J = 3.5, 10 Hz, H-2), 3.47-3.75 (28H, m, H-3, H-4, H-5, H-6), 3.49 (21H, s, OMe), 3.64 (21H, s, OMe), 4.10 (7H, dd, J = 2, 12 Hz, H-6), 5.18 (7H, d, J = 3.5 Hz, H-1); δ_C (75 MHz, $CDCl_3$) = -5.2 (SiMe), -4.8 (SiMe), 18.3 (CMe_3), 25.9 (CMe_3), 58.6 and 61.5 (OMe-2 and OMe-3), 62.3 (C-6), 72.2, (C-5), 78.7, 82.0, 82.2 (C-2, C-3, and C-4), 98.1 (C-1); *m/z* (FABMS) = 2153 for $[M+Na]^+$ Calc. for $C_{98}H_{196}O_{35}Si_7$: M = 2130.

15. Triphenylphosphine dibromide was prepared *in situ* by careful addition of bromine to a triphenylphosphine solution in dichloromethane maintained on an ice bath. Upon warming the reaction mixture up to room temperature, a white suspension was formed.

16. Spectroscopic and analytical data for **4**: δ_H (300 MHz, $CDCl_3$) = 3.22 (7H, dd, J = 3.5, 9.5 Hz, H-2), 3.47-3.65 (14H, m, H-3, H-4), 3.53 (21H, s, OMe), 3.65 (21H, s, OMe), 3.76-3.95 (21H, m, H-5, H-6, H-6), 5.24 (7H, d, J = 3.5 Hz, H-1); δ_C (75 MHz, $CDCl_3$) = 34.3 (C-6), 58.9 and 61.5 (OMe-2 and OMe-3), 70.8 (C-5), 81.5, 81.6, 81.9 (C-2, C-3, and C-4), 98.3 (C-1); *m/z* (FABMS) = 1794 for $[M+Na]^+$ Calc. for $C_{56}H_{91}Br_7O_{28}$: M = 1771; for an analytical sample the compound was subjected to column chromatography on silica gel: 5% MeOH in CH_2Cl_2. Found: C, 37.9; H, 5.50%. Calc. for $C_{56}H_{91}Br_7O_{28}$: C, 38.0; H, 5.18%.

17. Crystal data for **4**: $C_{56}H_{91}O_{28}Br_7.Me_2CO$, M = 1829.7, orthorhombic, a = 18.910(8), b = 21.516(9), c = 23.042(7) Å, V = 9406 Å^3, space group $P22_12_1$, ρ = 1.29 g cm^{-3}, μ(Cu-K_α) = 41 cm^{-1}, 7854 independent measured reflections ($2\theta \leq 122°$) of which 3607 were considered to be observed [$|F_o| > 4\sigma(|F_o|)$]. Data were measured on a Siemens P4/PC with graphite monochromated Cu-K_α radiation using ω scans. The data were corrected for absorption: maximum and minimum transmission factors of 0.745 and 0.165. The structure was solved by direct methods and found to contain two partial weight solvent (Me_2CO) molecules and to have partial disorder (*ca.* 7%) of the orientations of two of the bromomethyl groups. The structure was refined by full matrix least squares to R = 0.094, R_w = 0.086. Computations were carried out using the SHELXTL program system (Silicon Graphics Indigo Version). Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ (UK) on quoting the full journal citation.

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