Facile preparation of two tetrols from permethylated α-cyclodextrin and unambiguous NMR analysis

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An unprecedented straightforward approach wherein an excess of disobutylaluminum hydride is able to strip off in reasonable yield (45%) and in a regioselective manner four methyl groups from permethylated α-cyclodextrin, to provide a symmetric tetrol (2) in one chemical step from a commercially available material is described. An asymmetric tetrol (3) was also isolated from the reaction as a minor product (19%). Both compounds are unambiguously characterized by 1H NMR, 13C NMR, COSY, HSQC and HRMS.

Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of α(1→4) glucosyl residues. CDs are very popular building blocks for supermolecular structures and their derivatives are widely used in the fields of analytical chemistry and as enzyme mimics.1 CDs are known to function as host molecules making inclusion complexes with hydrophobic guest compounds in aqueous solution. Although native β-CD has a number of hydrophilic functional groups, such as primary and secondary hydroxyl groups, it has relatively low solubility in water which limits its application.2 Per-O-methylated CDs have attracted considerable attention due to their solubility in water as well as in organic solvents.3 In addition, inclusion complexes of methylated CDs are usually more stable than the corresponding complexes of unmodified CDs.3a Compared to those fully methylated CDs, partially methylated CDs with certain functional groups, such as permethylated CD–C60 conjugates,4 will be more useful for application. In the last few years, attempts have been made to the synthesis of methylated CD derivatives.5 The classical methods for selectively modified per-O-methylated CDs usually require many steps, including the temporary regioselective protection of peculiar hydroxyl groups of the native CD, followed by O-methylation and final removal of the protective groups to unmask the required functions.5a,b The purification processes are also very tedious because of the by products. The controlled chemical synthesis of modified methylated CDs having a few specifically located hydroxyl groups available for the further synthesis in facile method represents a true challenge for synthetic organic chemists. However, selective modifications of the CDs are difficult to control because of problems arising from steric and statistical factors imposed by the torus structure and the large number of hydroxyl groups.

We prepared 6*-monohydroxy per-O-methylated CDs and 2A,3B-dihydroxy per-O-methylated CDs from per-O-methylated CDs promoted by DIBAL-H in one step (Scheme 1).7 As an extension to this study, unprecedented regioselective tetra- or hexa-de-O-methylated β-CDs were discovered when a large excess of DIBAL-H was used as a chemical ‘scalpel’ (Scheme 2).8 As part of our ongoing program aiming at development of the functionalised CDs promoted by TRIBAL or DIBAL-H in a facile method,9 we would now like to report on the easy access of 2A,3B,2D,3E-tetrahydroxy-per-O-methylated α-cyclodextrin 2 and its isomer, 2A,3B,2C,3D-tetrahydroxy-per-O-methylated α-cyclodextrin 3, promoted by DIBAL-H from per-O-methylated α-CD 1.

The synthetic route is summarized in Scheme 3. When per-O-methylated α-CD 1 was treated with 40 equiv of DIBAL-H in toluene (1.0 M) at room temperature for 6 h, 2A,3B,2D,3E-tetrahydroxy-per-O-methylated α-cyclodextrin 2 and 2A,3B,2C,3D-tetrahydroxy-per-O-methylated α-cyclodextrin 3 were separated out by conventional silica gel column chromatography in 45% and 19% yield, respectively. Having a nice symmetry in the molecule, compound 2 shows only three sets of H1 signals appearing at 5.00, 5.04, and 5.10 ppm and three C1 signals appearing at 99.66, 99.71, and 102.49 ppm, respectively. For the same reason, the numbers of the other carbon signals are also appeared in half.
The structure of compound 2 was further confirmed by its acetylated derivative 4. The high-field signal at 2.16 ppm, referring to 12H, was assigned to four acetyl groups, and eight carbons appearing at 21.39, 21.63 and 169.76, 170.54 ppm could be assigned to four methyl and four carbonyl groups of the acetates, respectively. The low-field doublets of doublet at 4.71 ppm (four methyl and four carbonyl groups of the acetates, respectively). The high-field signal at 2.16 ppm, due to the acetylation of the four hydroxyls, was assigned to four acetyl groups, and eight carbons appearing at 72.18, 74.20 ppm, could be assigned to C_4^0, C_2^0 and C_5^0, C_5^0, respectively, due to the acetylation of the four hydroxyl groups.

As a minor product, compound 3 was isolated in 19% yield. The HRMS showed peaks at 1169.5443 [M+H^+]; or 1191.5292 [M+Na^+], indicating that it is also a tetrol. However its NMR spectra are much complicated than those of compound 2, suggesting an asymmetric molecule. In order to characterize this compound, the remaining hydroxyl groups of 3 were acetylated to afford 5. The HRMS spectrum of 5 showed four acetyl groups at δ 2.14, 2.15 ppm, while the 13C NMR spectrum displayed four methyl and carbonyl groups of the acetates at 21.33, 21.42, 21.59 and 169.87, 170.48, 170.58 ppm, respectively. Compared to 1H NMR of 4, 1H−1H COSY of 5 obviously exhibited four sets of down-field shift protons. The structure of compound 2 was further confirmed by its acetylated derivative 4. The high-field signal at 2.16 ppm, referring to 12H, was assigned to four acetyl groups, and eight carbons appearing at 21.39, 21.63 and 169.76, 170.54 ppm could be assigned to four methyl and four carbonyl groups of the acetates, respectively. The low-field doublets of doublet at 4.71 ppm (four methyl and four carbonyl groups of the acetates, respectively). The high-field signal at 2.16 ppm, due to the acetylation of the four hydroxyls, was assigned to four acetyl groups, and eight carbons appearing at 72.18, 74.20 ppm, could be assigned to C_4^0, C_2^0 and C_5^0, C_5^0, respectively, due to the acetylation of the four hydroxyl groups.

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To a solution of hexakis (2,3,6-tri-0-methyl)-<i>α</i>-cyclodextrin 1 (250 mg, 0.20 mmol) was added 8.2 mL (8.2 mmol, 40.0 equiv) of (1 M) was carefully added dropwise and the mixture was stirred for 1 h. After adding the solution, the mixture was stirred for an additional 3 h. The reaction mixture was stirred for 4 h. The mixture was filtered and the product was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine, dried over MgSO₄, and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (elucent: CH₂Cl₂/CH₃OH = 50:1–30:1) to give 108 mg of 2 (45%) and 44 mg of 3 (19%), both as white foams.

**Compound 2**

<math> R_f = 0.14 \text{(CH₂Cl₂/CH₃OH = 10:1); [a]_D +142 ^{(c = 1.0 \text{ in CHCl₃}); 1} H NMR (400 MHz, CDCl₃): } δ 3.17 (dd, 2H, J₂,₃ = 3.2 Hz, J₃,₄ = 9.0 Hz, H₃,₄), 3.20 (dd, 2H, J₂,₃ = 3.1 Hz, J₃,₄ = 9.7 Hz, H₃,₄), 3.41 (s, 6H, 2 * OCH₃ (C₆)), 3.42 (s, 12H, 4 * OCH₃ (C₆)), 3.47 (s, 6H, 2 * OCH₃ (C₆)), 3.51 (s, 6H, 2 * OCH₃ (C₆)), 3.59 (m, 2H, H₅,₆), 3.60 (s, 6H, 2 * OCH₃ (C₆)), 3.68 (m, 2H, H₅,₆), 3.71 (s, 6H, 2 * OCH₃ (C₆)), 3.71 (s, 6H, 2 * OCH₃ (C₆)) ; 1} H NMR (400 MHz, CDCl₃): } δ 3.17 (dd, 2H, J₂,₃ = 3.2 Hz, J₃,₄ = 9.0 Hz, H₃,₄), 3.20 (dd, 2H, J₂,₃ = 3.1 Hz, J₃,₄ = 9.7 Hz, H₃,₄), 3.41 (s, 6H, 2 * OCH₃ (C₆)), 3.42 (s, 12H, 4 * OCH₃ (C₆)), 3.47 (s, 6H, 2 * OCH₃ (C₆)), 3.51 (s, 6H, 2 * OCH₃ (C₆)), 3.59 (m, 2H, H₅,₆), 3.60 (s, 6H, 2 * OCH₃ (C₆)), 3.68 (m, 2H, H₅,₆), 3.71 (s, 6H, 2 * OCH₃ (C₆)), 3.71 (s, 6H, 2 * OCH₃ (C₆)).
2a,3b,2c,3c-tetra-O-acetyl per-O-methylated α-cyclodextrin (5)

By the procedure described above, compound 5 was obtained in 83% yield as a white foam. $R_f = 0.29$ (CH$_2$Cl$_2$/CH$_3$OH = 20:1); [α]$^D_{20} +139$ (c = 1.0 in CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.14 (br s, 6H, $2 \times$ CH$_2$), 2.15 (2 × s, 6H, $2 \times$ CH$_2$CO), 3.13–3.37 (m, 2H, H$_5$, H$_6$), 3.19 (dd, 1H, J$_{1,2}$ = 3.3 Hz, J$_{2,3}$ = 10.0 Hz, H$_3$), 3.22 (dd, 1H, J$_{1,2}$ = 3.1 Hz, J$_{2,3}$ = 9.9 Hz, H$_4$), 3.37 (s, 3H, OCH$_3$ (C$_6$)), 3.39 (br s, 18H, 5 × OCH$_3$ (C$_6$), OCH$_3$ (C$_2$)), 3.42 (s, 3H, OCH$_3$ (C$_2$)), 3.46 (s, 3H, OCH$_3$ (C$_2$)), 3.47 (s, 3H, OCH$_3$ (C$_2$)), 3.51 (s, 3H, OCH$_3$ (C$_1$)), 3.61 (s, 3H, OCH$_3$ (C$_3$)), 3.65 (m, 1H, H$_3$), 3.70 (m, 1H, H$_6a$), 3.72 (m, 1H, H$_6b$); $^{13}$C NMR (100 MHz, CDCl$_3$): 37.5 (m, 1H, H$_4$), 37.7 (m, 1H, H$_5$), 37.8 (m, 1H, H$_6$), 3.48–4.08 (m, 22H, 4 × CH$_3$); HRMS calculated for C$_{58}$H$_{96}$O$_{34}$Na$^+$: 1359.5673, found 1359.5698. Supplementary data (copies of $^1$H NMR, $^{13}$C NMR and HRMS spectra for compounds 2–5) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.137.

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Supplementary data

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References and notes


