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Note

An efficient preparation of $6^{I,IV}$ dihydroxy permethylated β-cyclodextrin

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Abstract

We report on a straightforward synthesis of $2^{I-VII},3^{I-VII},6^{II,III,V-VII}$-nonadeca-*O*-methylcyclomaltoheptaose, a methylated β-cyclodextrin derivative bearing two $6^{I,IV}$ hydroxyl groups, from its easily available benzylated counterpart.

Keywords: β-Cyclodextrin; Methylation

1. Introduction

Due to their unique hollow truncated cone geometry, being well adapted to molecular recognition, easily available natural cyclodextrins (cyclomaltooligosaccharides, CDs) have attracted considerable attention. Important derivatives are methylated cyclomaltoheptaoses (methylated β-CDs) having a few specifically located hydroxyl groups. Firstly they are nicely soluble both in water[1] and in organic solvents,[2] two features of importance for their chemical manipulation and for the emergence of the expected properties in aqueous medium. Secondly, complexes of methylated β-CD are usually more stable[1] than the corresponding complexes of unmodified CDs. Lastly the availability of some hydroxyl groups allows the preparation of more elaborated molecular systems endowed with predictable properties. The currently available synthetic methods dealing with α[3–5] or β-CD[6,7] proceed through a temporary regioselective protection of particular hydroxyl groups of the native β-CD, followed by O-methylation and final removal of the protective groups to unmask the required hydroxyl function. A limitation of this approach, especially in the case of the larger β-CD, is the moderate regioselectivity of the initial protection, resulting in a low overall yield of the process.[8] As an example, the $6^{I,IV}$-dihydroxy permethylated β-cyclodextrin was obtained by Bradshaw and coworkers in 8.9% from β-cyclodextrin.[9] The authors nevertheless pointed out the superiority of their process compared to others to prepare and isolate dihydroxy permethylated β-cyclodextrin intermediates for bifunctionnal enzyme mimics. This is an illustration of the challenging aspect of this problem. We recently discovered that perbenzylated β-CD undergoes a very remarkable $6^{I,IV}$ high yielding bis(de-O-benzylation) upon reaction with a large excess of diisobutylaluminum hydride (DIBAL-H).[10] The behaviour of permethylated β-CD was strikingly different, giving selectively, but in more moderate yield (55%), the $2^{I},3^{II}$ diol.[11]

The aim of this work is to describe the transformation of the easily available $6^{I,IV}$ dihydroxy perbenzylated β-cyclodextrin into its permethylated counterpart.

2. Results and Discussion

The known diol **1**, which is prepared in 79% yield from β-CD, has directly been converted without any technical problem into the $6^{I,IV}$ dihydroxy permethylated β-CD **2** in about 70% yield (Scheme 1).

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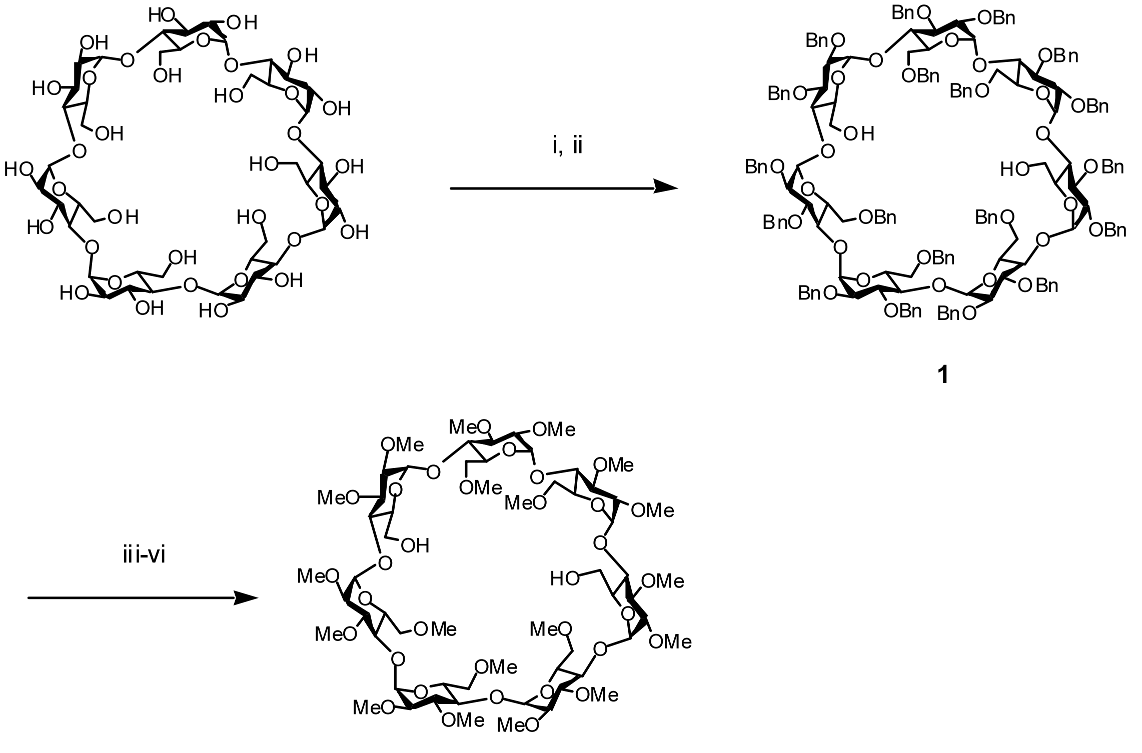

Scheme 1. (i) BnCl (2 equiv/OH), NaH (2 equiv/OH), Me_2SO, rt, overnight, (95%); (ii) 0.5 M DIBAL-H (140 equiv), toluene, 50 °C, 2 h, (83%); (iii) DHP, CSA, CH_2Cl_2, rt, 2 h; (iv) H_2, (0.15 MPa) Pd/C 10%, THF–water (2.5:1), overnight; (v) MeI, NaH, DMF, 0 °C to rt, 8 h; (vi) 4:1 AcOH–water , 40 °C, 1.5 h (68% over four steps).

The tetrahydropyranyl protecting group was selected because such a group is both stable and non migrating during permethylation. The hydrogenolytic removal of the benzyl groups was found efficient when 2.5:1 THF–water (10 mg/mL) was employed as a solvent mixture. The final purification of **2** was very easily achieved through a regular silica gel column chromatography without any specific care. The diol **2** has physical properties in complete agreement with those previously reported by Bradshaw and co-workers.[9] Methylated β-cyclodextrin **2** has recently been used as starting material for the preparation of β-CD-encapsulated iron catalyst for the polymerisation of ethylene.[12]

In conclusion, $6^{I,IV}$-dihydroxy permethylated β-CD has now been prepared in about 50% yield from natural β-CD. The best yield so far reported[9] was about 9%.

3. Experimental

3.1. General methods

Optical rotations were measured at 20 ± 2 °C with a Perkin–Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained with a JMS-700 spectrometer. ^1H NMR spectra were recorded with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ at ambient temperature. ^{13}C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ adopting 77.00 ppm for the central line of $CDCl_3$. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, E. Merck).

3.2. 2^{I-VII},3^{I-VII},$6^{II,III,V-VII}$-nonadeca-*O*-methylcyclomaltoheptaose

Camphorsulfonic acid (2 mg, 8 μmol) and dihydropyran (94 μL, 1.05 mmol) were added to a solution of perbenzylated diol **1** (1 g, 351 μmol) in anhyd CH_2Cl_2 (5 mL), and stirred 2 h under argon. After addition of Et_3N (0.5 mL) and CH_2Cl_2 (50 mL), the mixture was washed with water (2 × 25 mL), dried over $MgSO_4$, and concentrated under diminished pressure. Pd/C 10% (1 g) was added to a solution of the residue in THF (75 mL) and water (30 mL), and stirred under H_2 atmosphere (1.5 bar) overnight. The reaction mixture was filtered through a Celite® pad, washed with 1:1 MeOH–water

(150 mL), concentrated, and dried over P_2O_5. Sodium hydride (60% w/w in oil, 800 mg, 20 mmol) and methyliodide (1 mL, 20 mmol) were carefully added to a solution of the crude product in DMF (40 mL), under argon at 0 °C. After 8 h stirring at room temperature (rt), the reaction mixture was quenched with water (100 mL), and extracted with Et_2O (4×125 mL). The combined organic layers were dried ($MgSO_4$), concentrated and co-evaporated with toluene (2×20 mL). The residue was stirred in 80% aq AcOH (25 mL) for 1.5 h, evaporated, and co-evaporated with toluene (2×20 mL). After silica gel chromatography (94:6 CH_2Cl_2–MeOH), permethylated diol **2** (334 mg, 68%) was obtained. Mp 97–99 °C, lit.[9] 96–98 °C; $[\alpha]_D^{20}$ +155 (*c* 1.0 $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ +153.7 (*c* 1.0 $CHCl_3$); MS (FAB, NBA) *m*/*z* (%) = 1423.7 (100) $[M+Na]^+$; ^1H NMR ($CDCl_3$): δ 5.30 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.27 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.15 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.10 (br d, 2 H, $J_{1,2}$ 3.0 Hz, H-1), 5.06 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.02 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.05–3.39 (m, 92 H), 3.27–3.20 (m, 7 H), 3.10–3.01 (2 × br s, 2 H, OH); ^{13}C NMR ($CDCl_3$): δ 99.26, 98.98, 98.94, 98.86 (4 × C-1), 98.82 (2 × C-1), 98.59 (C-1), 82.41, 82.32, 82.05, 82.0, 81.85 (5 × CH), 81.73 (2 × CH), 81.64 (3 × CH), 81.61, 81.47, 81.43, 81.38, 81.10, 81.0, 80.92, 80.83, 80.29, 78.04, 77.81 (11 × CH), 71.75 (2 × CH_2), 71.61 (2 × CH), 71.44 (CH_2), 71.42 (CH), 71.35 (2 × CH_2), 71.29 (CH), 71.23 (2 × CH_2), 71.19 (CH), 71.04 (2 × CH), 61.73 (3 × OMe), 61.53, 61.47 (2 × OMe), 60.92, 60.86, 59.32, 59.19, 59.10 (5 × OMe), 59.07 (2 × OMe), 59.03, 58.94 (2 × OMe), 58.52, 58.37, 58.25, 58.16, 58.01 (5 × OMe).

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