Cyclodextrin Chemistry; Part I. Application of a Regioselective Acetolysis Method for Benzyl Ethers

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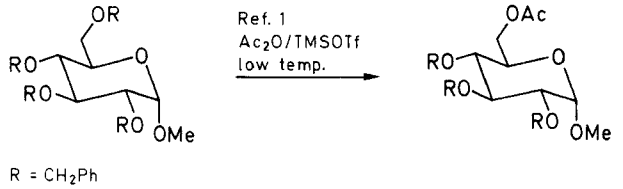
Regioselective acetolysis of cyclomaltohexaose perbenzyl ethers at C-6 with acetic anhydride in the presence of trimethylsilyl trifluoromethanesulfonate at low temperature constitutes an easy route to the C-6 acetylated intermediate **2**. Further transformation of **2** to intermediates **3** and **4** with protected primary or secondary hydroxy groups, respectively, are described.

We have recently observed that benzyl ethers of a series of methyl glycohexopyranosides undergo selective acetolysis of the protective group at C-6 by treatment with trimethylsilyl trifluoromethanesulfonate/acetic anhydride (TMSOTf/Ac_2O) at $-40\,^{\circ}C$. Furthermore, this reaction has been shown to be temperature dependent, and regiospecific discrimination between secondary benzyl groups between C-2 to C-4 also been observed as the temperature is raised.[1]

For example, treatment of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside with these reagents affords almost quantitatively the tri-*O*-benzylated derivative, methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (Scheme **1**).

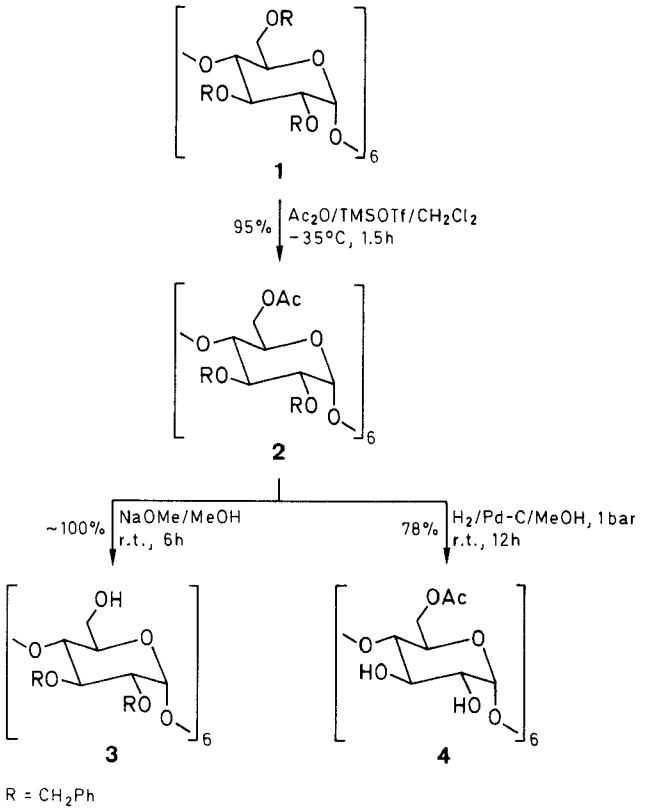


Scheme **1**

Thus, we were interested to investigate such a selectivity in another field, particularly in the domain of the cyclodextrin chemistry, where the search for selective reactions between primary and secondary hydroxy groups remains a crucial problem in spite of the interesting work of Lehn and collaborators[2] and other more recent results.[3-7]

For this purpose we started with the hexakis(2,3,6-tri-*O*-benzyl)cyclomaltohexaose (**1**) prepared, according to a recent method.[8] When **1** is submitted to the action of TMSOTf/Ac_2O at $-35\,^{\circ}C$ for 1.5 hour, a selective acetolysis of benzyl ether groups occurs at the C-6 positions giving compound **2** in excellent yield. ^{13}C-NMR spectrum of **2** shows the expected upfield shift for the C-6 signal from $\delta = 68.98$ to 63.67 and also the desired six fold symmetry. Treatment of **2** under the Zemplén conditions (sodium methoxide in methanol) leads in good yield to the expected product **3**; this compound was previously obtained by Takeo et al[3] by another route.

Furthermore, hydrogenolysis of **2** using palladium on charcoal as catalyst gives the hexakis(6-*O*-acetyl)cyclomaltohexaose (**4**) having only C-2 and C-3 hydroxy groups deprotected. Compound **4** has also recently been prepared by us from the peracetylated cyclomaltohexaose by selective deprotection of the secondary acetyl groups[9] (Scheme **2**). Complete assignments for ^{1}H and ^{13}C signals have been made wherever possible by 2D NMR sequences.



Scheme **2**

NMR spectra were obtained at ambient temperature using Bruker AC 300 or AM 300 spectrometers. The measurements were carried out in $CDCl_3$. The proton assignments were determinated at 300 MHz by ^{1}H-^{1}H homonuclear shift correlated spectroscopy(COSY)[10,11] and ^{13}C signals were unambiguously attributed at 75 MHz by heteronuclear (^{1}H- ^{13}C COSY, XHCORR)[12] experiments. Mass spectra in the FAB (+) mode were recorded with a Nermag R 10.10C spectrometer or a ZAB-SEQ (V.G.) Manchester (for molecular weight > 2000).

Optical rotations were measured with a Perkin-Elmer 241 instrument. TMSOTf was purchased from Janssen Chemica and was used as a 50% solution in anhydrous CH_2Cl_2. Reactions were monitored by TLC on silica gel (precoated aluminium sheets, "Alufolia" 60 F_{254}, Merck) using appropriate hexane/EtOAc systems. Preparative flash column chromatography was performed on Silica Gel 60, 0.04-0.063 mm (Merck). Melting points were measured with a Leitz instrument and are uncorrected.

Hexakis(2,3,6-tri-O-benzyl)cyclomaltohexaose (**1**) was prepared according to a method described by T. Sato et al.[8] The best yields were obtained with rigorously dried DMSO.[13] The amorphous powder isolated after purification has correct elemental analyses; no definite melting point; $[\alpha]_D^{20} + 34^{\circ}$ (c = 2.3, $CHCl_3$).

MS [FAB (+)]: $m/z = 2592 + 23$ $(M + Na)^+$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.47$ (dd, 1 H, $J_{2,3} = 9.56$ Hz, H-2), 3.50 (dd, 1 H, H-6b), 3.92 (m, 1 H, $J_{4,5} = 9.15$ Hz, H-5), 4.03 (dd, 1 H, H-6a) ($J_{gem} = 11.03$ Hz), 4.05 (t, 1 H, $J_{4,5} = 8.35$ Hz, H-4), 4.15 (dd, 1 H, $J_{3,4} = 8.35$ Hz, H-3, 4.32, 4.42 (dd, 2 H, $J = 12.05$ Hz, CH_2Ph), 4.45, 4.51 (dd, 2 H, $J = 12.5$ Hz, CH_2Ph), 4.87, 5.19 (dd, 2 H, $J = 11.02$ Hz, CH_2Ph), 5.11 (d, 1 H, $J_{1,2} = 3.32$ Hz, H-1), 7.12–7.27 (m, 15 H_{arom}).

^{13}C-NMR ($CDCl_3$): $\delta = 68.98$ (C-6), 71.43 (C-5), 72.61, 73.25, 75.40 (CH_2Ph), 78.94 (C-2), 79.08 (C-4), 80.87 (C-3), 98.43 (C-1) 126.85–128.5 (C_{arom}), 138.16, 138.35, 139.31 (C-1_{arom}).

Hexakis(6-*O*-acetyl-2,3-di-*O*-benzyl)cyclomaltohexaose (2):
To a stirred solution of **1** (1 g, 0.4 mmol) in Ac_2O (15 mL) cooled to -35 °C is added dropwise a freshly prepared solution of TMSOTf in CH_2Cl_2 (50%, 1.06 mL, 2.4 mmol). After 1.5 h, the solution is poured into a cold mixture of aq $NaHCO_3$ solution (150 mL) and $CHCl_3$ (150 mL), and vigorously stirred for 0.5 h. The organic layer is separated, dried (Na_2SO_4), and the $CHCl_3$ is evaporated under reduced pressure. The residue is co-evaporated with toluene (2 × 50 mL) to remove acidic products. The crude product is purified by flash chromatography on silica gel using with hexane/EtOAc (3:1); yield: 0.84 g (95%); no sharp mp (~ 90 °C); amorphous powder; $[\alpha]_D^{20} + 30°$ ($c = 1$, $CHCl_3$).

$(C_{22}H_{24}O_6)_6$	calc.	C 68.73	H 6.29
(2306.5)	found	68.47	6.50

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.08$ (s, 3 H, CH_3CO), 3.40 (dd, 1 H, $J_{2,3} = 9.78$ Hz, H-2), 3.63 (dd, 1 H, $J_{4,5} = 9.31$ Hz, H-4), 4.07 (m, 1 H, H-5), 4.09 (dd, 1 H, $J_{3,4} = 8.86$ Hz, H-3), 4.33 (2 H, H-6a, 6b), 4.35, 4.47 (dd, 2 H, $J = 12.52$ Hz, CH_2Ph), 4.8, 5.08 (dd, 2 H, $J = 12.52$ Hz, CH_2Ph), 4.85 (d, 1 H, $J_{1,2} = 3.27$ Hz, H-1), 7.12–7.27 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): $\delta = 20.94$ (CH_3CO), 63.67 (C-6), 69.45 (C-5) 72.96, 75.42 (CH_2Ph), 76.67 (C-4), 80.35 (C-3), 80.72 (C-2), 99.05 (C-1), 126.8-128.12 (C_{arom}) 138.21, 139.14 (C-1_{arom}), 170.50 (C=O).

MS [FAB(+)]: $m/z = 2304 + 23$ $(M + Na)^+$.

Hexakis(2,3-di-*O*-benzyl)cyclomaltohexaose (3):
A solution of **2** (0.45 g, 0.2 mmol) in 0.2 M methanolic MeONa/MeOH (20 mL) is magnetically stirred at r.t. for 6 h. After neutralization with a IRN 77 (H^+) resin, **3** is isolated as an amorphous powder; yield: 0.4 g (99%); $[\alpha]_D^{20} + 45°$ ($c = 1.9$, $CHCl_3$) (Lit.[3] $[\alpha]_D^{20} + 61.6°$).

MS [FAB(+)]: $m/z = 2052 + 23$ $(M + Na)^+$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.45$ (dd, 1 H, $J_{2,3} = 9.60$ Hz, H-2), 3.60 (dd, 1 H, $J_{4,5} = 9.01$ Hz, H-4), 3.87 (m, 1 H, H-5), 4.05 (dd, 1 H, $J_{3,4} = 8.20$ Hz, H 3), 4.07 (dd, 1 H, H-6a), 4.09 (dd, 1 H, H-6b), 4.41, 4.47 (dd, 2 H, $J = 12.20$ Hz, CH_2Ph), 4.79, 5.14 (dd, 2 H, $J = 11.00$ Hz, CH_2Ph), 4.99 (d, 1 H, $J_{1,2} = 3.52$ Hz, H-1), 7.11–7.26 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): $\delta = 62.26$ (C-6), 72.96 (C-5),[3] 72.88, 75.23 (CH_2Ph),[3] 79.00 (C-4), 80.80 (C-2), 97.95 (C-1), 126.9-128.3 (c_{arom}), 138.2, 139.13 (C-1_{arom}).

Hexakis(6-*O*-acetyl)cyclomaltohexaose (4):
A solution of **2** (0.45 g, 0.2 mmol) in anhydrous MeOH (30 mL) is magnetically stirred with 10% Pd-C (0.3 g) in an atmosphere of H_2 (1 bar) for 12 h. The catalyst is removed by filtration and washed several times with MeOH. Product **4** is crystallized from H_2O/MeOH (5:95); yield: 0.19 g (78%); mp > 270° (dec.); $[\alpha]_D^{20} + 59°$ ($c = 2.0$, pyridine).

$(C_8H_{12}O_6)_6$	calc.	C 47.06	H 5.92
(1225.1)	found	47.51	5.72

^{13}C-NMR (CD_3OD): $\delta = 21.44$ (CH_3CO), 64.84 (C-6), 71.04, 73.03, 74.70, 83.07 (C-5, C-4, C-3, C-2, no definite assignments), 103.02 (C-1), 174.56 (C=O) (Complete NMR data will be given elsewhere[9]).

MS [FAB(+)]: $m/z = 1224 + 23$ $(M + Na)^+$.

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In this paper the authors assign both the ^{13}C-NMR signals at $\delta = 72.96$ and 72.88 to CH_2Ph of benzyl groups. In fact, DEPT spectrum shows that the signals at $\delta = 72.96$ corresponds to C-5. Therefore signals at $\delta = 75.23$ and 72.88 are assigned to CH_2Ph.
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