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Diisobutylaluminum-promoted secondary rim selective de-*O*-methylation of permethylated cyclodextrins

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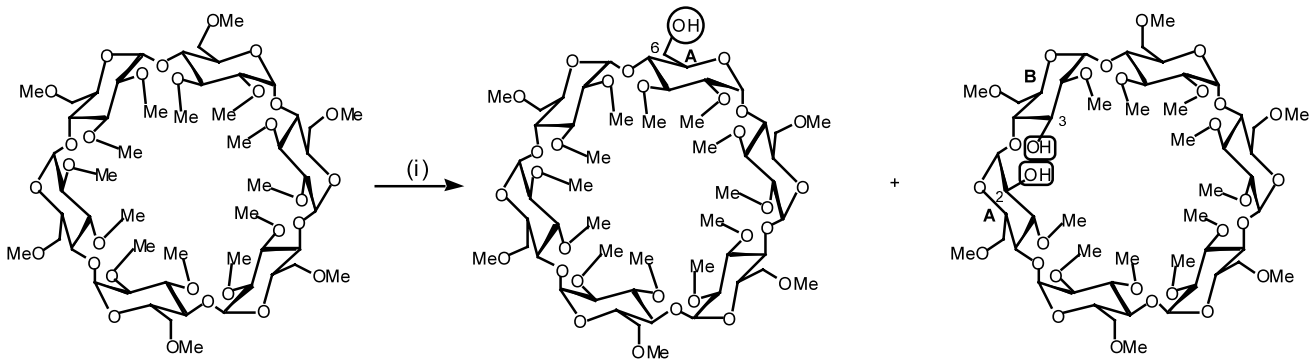
Abstract—Permethylated α- and β-cyclodextrins both undergo a remarkable regioselective DIBAL-promoted bis-*O*-demethylation on the secondary rim. This gave a one-step access to 2^A, 3^B diols, which were carefully characterised by NMR spectroscopy.

Natural cyclodextrins (CDs) have gained popularity among scientists due to their structural ability to form inclusion complexes in aqueous solution with appropriate hydrophobic guests.[1] The disadvantageous low water solubility of CDs and their complexes has been chemically by-passed by the employment of more soluble methylated derivatives. Moreover, inclusion complexes of methylated CDs are usually more stable than the corresponding complexes of unmodified CDs.[2] From this point on, the controlled chemical synthesis of methylated CDs having specifically located hydroxyl groups available for the construction of more elaborate molecular systems represents a relevant challenge.

Within the frame of a general program on the use of tri-(TRIBAL) or diisobutylaluminum (DIBAL) for the selective de-*O*-benzylation of perbenzylated carbohydrates,[3] we have recently discovered[4] that DIBAL is a reagent of choice for the achievement of a remarkable AD type regioselective bis de-*O*-benzylation on the primary upper rim of either α or β perbenzylated CDs. This exquisite selectivity is somewhat eroded in the case of the perbenzylated γ-CD. The resulting diols, directly obtained through such an unprecedented approach, are well suited for further transformations. In a recent extension[5] of this work, we found that Janus type fully alkylated α-CD carrying methyl groups on the primary rim and benzyl groups on the secondary one also undergoes regioselective AD type bis de-*O*-methylation, the benzyl ether protecting groups being untouched. The situation appeared less selective in the case of the corresponding mixed β-CD. We would like now to disclose the strikingly different behaviour of permethylated CDs.



Scheme 1. *Reagents and conditions*: (i) DIBAL (6 equiv.), toluene, 50°C, 3 h.

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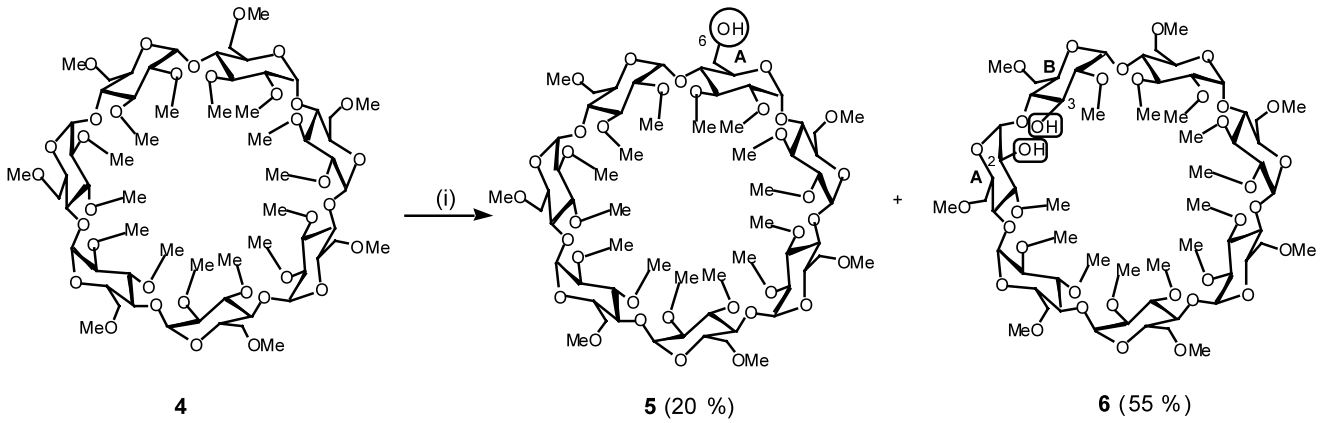
When commercially available α-CD(OMe)$_{18}$ **1** was treated with excess DIBAL in toluene at 50°C for 3 h, we observed the formation of two products **2** and **3** (Scheme 1), which have been separated by silica gel flash chromatography.† Some starting material **1** (20%) was also recovered. Compound **2** (20%) was identified as previously prepared[6,7] mono de-*O*-methylated α-CD on the primary rim. The major product of this reaction (55%) proved to be the 2^A, 3^B diol **3**,‡ resulting from an unprecedented direct selective bis de-*O*-methylation on



Scheme 2. *Reagents and conditions*: (i) DIBAL (7 equiv.), toluene, 50°C, 3 h.

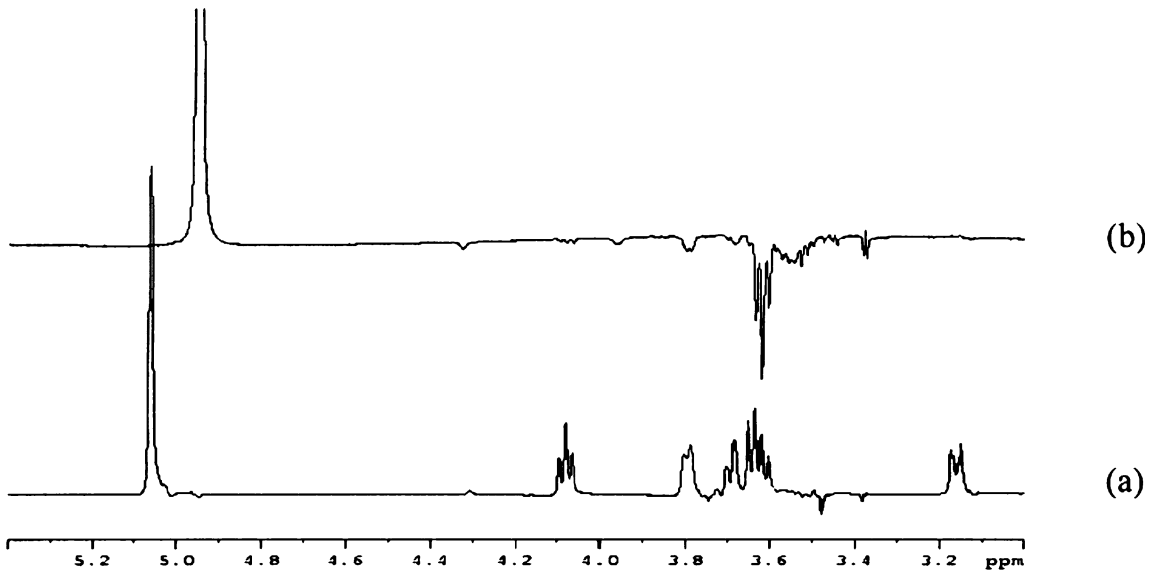


Figure 1. NMR selective ROESY 1D of compound **3** (600 MHz, $CDCl_3$, 25°C): (a) selective TOCSY of anomeric proton $H_1{}^B$; (b) selective ROESY of anomeric proton $H_1{}^A$.

† *Typical procedure*: DIBAL (9.8 mL, 14.7 mmol, 1.5 M in toluene, 6 equiv.) was added to a stirred solution of hexakis (trimethyl-2,-3,-6)-cyclomaltohexaose **1** (3.0 g, 2.45 mmol) in anhydrous toluene (150 mL) at room temperature under argon. The reaction mixture was heated at 50°C for 3 h under argon. The mixture was cooled to 0°C, aqueous HCl (1 M) was carefully added dropwise and the mixture was stirred vigorously at room temperature for 15 min. The mixture was filtered (Celite®) into a separating funnel and Celite was washed thoroughly with CH_2Cl_2 (300 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (eluent gradient 2–3% MeOH in CH_2Cl_2) to afford first **1** (recovered starting material, 600 mg, 20%), then **2** as a colourless foam (595 mg, 20%), and finally **3** as a colourless foam (1.61 g, 55%).

‡ *Selected data for compound* ***3***: $[\alpha]_D^{23}=+159$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta=5.04$ (d, $^3J(1,2)=2.95$ Hz, 1H; $H_1{}^B$), 5.01 (d, $^3J(1,2)=3.42$ Hz, 1H; H_1), 4.99 (br d, $^3J(1,2)=3.45$ Hz, 2H; 2×H_1), 4.98 (d, $^3J(1,2)=3.76$ Hz, 1H; H_1), 4.92 (d, $^3J(1,2)=2.31$ Hz, 1H; $H_1{}^A$), 4.52 (br s, 1H; O*H*), 4.20 (br s, 1H; O*H*), 4.05 (t, $^3J(3,2)=^3J(3,4)=9.3$ Hz, 1H; $H_3{}^B$), 3.9–3.4 (m, 29H; 5×H_3, 6×H_4, 6×H_5, 12×H_6), 3.67 (s, 3H; Me(2)), 3.59 (s, 3H; Me(2)), 3.57 (s, 3H; Me(2)), 3.56 (s, 6H; 2×Me(2)), 3.52 (dd, $^3J(1,2)=2.34$ Hz, $^3J(2,3)=8.36$ Hz, 1H; $H_2{}^A$), 3.45, 3.44, 3.43, 3.42 (5×s, 15H; 5×Me(3)), 3.36 (s, 9H; 3×Me(6)), 3.35 (s, 9H; 3×Me(6)), 3.13 (m, 5H; 5×H_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): 102.21 (d, 1C; $C_1{}^A$), 100.11, 99.98, 99.80, 99.51, 99.40 (5×d, 5C; $C_1{}^{B-F}$), 82.72, 82.24, 82.19, 82.03, 81.93, 81.81, 81.78, 81.01, 80.91, 80.89, 80.83, 80.76 (15×d, 15C; 5C_2, 4×C_3, 6×C_4), 82.33 (br d, 2C; $C_3{}^A$+$C_4{}^B$), 73.04 (d, 1C; $C_2{}^A$), 71.4 (d, 1C; $C_3{}^B$), 71.33, 71.18, 71.15 (6×t; 6×C_6), 71.05, 70.99, 70.93, 70.86, 70.05 (6×d, 6C, 6C_5), 62.20, 61.60, 61.55, 61.51 (5×d, 5C; Me(2)), 58.90, 58.83, 58.80, 58.76, 58.74 (6×d, 6C; Me(6)), 57.63, 57.57, 57.46, 57.41, 57.39 (5×d, 5C; Me(3)); MS (FAB); *m*/*z* (%):1219.6 (100) [MNa^+]; anal. calcd for $C_{52}H_{92}O_{30}$: C, 52.17; H, 7.74. Found: C, 52.20; H, 7.84.

the secondary rim. Similarly, β-CD$(OMe)_{21}$ **4** was converted under the same conditions into a separable mixture of known[6,8–10] mono de-*O*-methylated β-CD **5** (20%) and 2^A, 3^B diol **6** (55%). Some starting material **4** (20%) was also recovered (Scheme 2). Diol **6** was found to be identical to a compound recently prepared through a four-step sequence.[11]

The structural assignment of secondary diols **3** and **6** was achieved through the careful combined analysis[12] of homonuclear (DQF-COSY, TOCSY, ROESY) and heteronuclear (HSQC) 2D NMR spectra.[§] The overlapping signals of the initial ^1H NMR spectra were first separated through TOCSY into sets of proton resonances belonging to the same glucopyranose unit. It was found that **3** and **6** were both carrying two hydroxyl groups on two different glucopyranose units (noted A and B, respectively, for C_2–OH and C_3–OH). The relative position of these two monodeprotected glucopyranose residues A and B has now to be determined. In this respect, it is important to note that some key signals such as the ones of $H_1{}^A$, $H_2{}^A$, $H_3{}^B$ and $H_4{}^B$ are unambiguously isolated. Compounds **3** and **6** both revealed NOE cross peak between $H_1{}^A$ and $H_4{}^B$. The ROESY spectrum for compound **3** is shown in Fig. 1. Compounds **3** and **6** were thus identified as 2^A, 3^B diols.

As already observed[4,5] in our previous studies, no simultaneous de-*O*-alkylation on both primary and secondary rims has been observed, at least after a short period of time. Once compounds **1** or **4** have been mono de-*O*-methylated on the primary rim, no bis de-*O*-methylation on the secondary rim takes place. The same holds for the alternate process. This may result from a conformational change upon initial de-*O*-alkylation on one rim (either primary or secondary), which turns off further de-*O*-alkylation on the other rim.

Together with previous work,[4] the one-step availability of diols **3** and **6** from commercially available permethylated α- and β-CDs highlights the remarkable behaviour of DIBAL, which acts as a regioselective chemical 'scalpel'.[13]

Acknowledgements

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[§] *NMR experimental procedure*: Selective 1D NMR experiments were carried out on a Brüker 600 MHz DRX spectrometer. The soft pulse is a Gaussian shape with 2% truncature and 80 ms of duration. Pulse sequence employed for TOCSY: 90°(ϕ1)-PFG-sel180°(ϕ2)-PFG-MLEV17-acqu(ϕ) with phase cycle: ϕ1 = x, −x; ϕ2 = x, x, y, y, −x, −x, −y, −y; ϕ = x, −x, −x, x; MLEV17 mixing time duration is 300 ms, PFG duration 1 ms. Pulse sequence employed for ROESY: 90°(ϕ1)-sel180°(ϕ2)-sel180°(ϕ3)-SL(ϕ4)-acqu(ϕ) with phase cycle: ϕ1 = x, −x; ϕ2 = x, x, y, y, −x, −x, −y, −y; ϕ3 = 8(x); ϕ4 = x; ϕ = x, −x, −x, x; ROESY Spin Lock (SL) has a 200 ms duration.