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Diisobutylaluminium hydride (DIBAL-H) is promoting a selective clockwise debenzylation of perbenzylated $6^A,6^D$-dideoxy-α-cyclodextrin

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Abstract—A novel C_2 symmetric cyclodextrin (CD) was obtained possessing three pairs of functionalities on its primary rim. Its synthesis relies on a first generation diisobutylaluminium hydride (DIBAL-H) induced $6^A,6^D$-de-*O*-benzylation of a perbenzylated CD followed by a second generation $6^C,6^F$-de-*O*-benzylation on a resulting perbenzylated $6^A,6^D$-dideoxy-CD conceived to undergo a regioselective clockwise reaction.

Cyclodextrins (CDs) are cyclic oligosaccharides displaying a high level of symmetry-C_6 for the α-CD. As a result, the three groups of hydroxyls in positions 2, 3 and 6 of the pyranose rings can be distinguished through their different stereoelectronic properties (nucleophilicity and basicity); but inside each group, all hydroxyls 2, 3 or 6 are chemically equivalent, therefore the regioselective differentiation of two, three or more of them remains a difficult[1] but important[2] task. Among the three groups, selective functionalisation of the primary hydroxyls in position 6 has been the most extensively studied. It relies both on the higher availability of this position and on the cyclic rigid structure of CDs. The use of a controlled number of equivalents of bulky electrophilic reagents generates primary oligosubstituted CDs.[3] A clever[1] approach is using the geometry of rigid arenedisulfonyl chlorides to form regioselectively capped CDs.[4] None of these methods rely on the sugar structure itself, but only on the difference in reactivity between primary and secondary alcohols as well as on the cyclic-shape of CDs.

We have recently reported a conceptually different synthesis of diol **2**, based on the action of diisobutylaluminium hydride (DIBAL-H) on perbenzylated CD **1** (Scheme 1).[5,6] A challenging step forward is the duplication of this process. There are two distinct aspects in this quest: on the one hand, is there an –OR group compatible with a second generation A–D type deprotection and on the other hand, and more excitingly, is it possible to achieve it regioselectively, that is to say, as schematically alluded to in Scheme 2, in a clockwise or counterclockwise manner?[7]

We would like to describe how, based on the mechanism of the DIBAL-H induced deprotection,[6] we answered these intriguing questions, providing in an expeditious way an α-CD selectively derivatised on its primary rim with three pairs of functionalities.[8]

The first step of the proposed debenzylation mechanism[6] is the complexation of an aluminium atom with O-5 and O-6 of a given pyranosidic cycle B (Fig. 1). As a consequence and due to the particular cyclic and directional structure of CDs constituted of chiral sugar rings, we anticipated that such complexation is not only hampered by its substituent on position 6 (cycle B), but also by the one on position 6 of the neighbouring glucoside counterclockwise to it (view from the primary rim, cycle C), and not by the one clockwise (cycle A, Fig. 1). Therefore, by decreasing the steric hindrance of R_C on position 6 of the pyranosidic ring C, not only should we increase its own steric availability, but also that of

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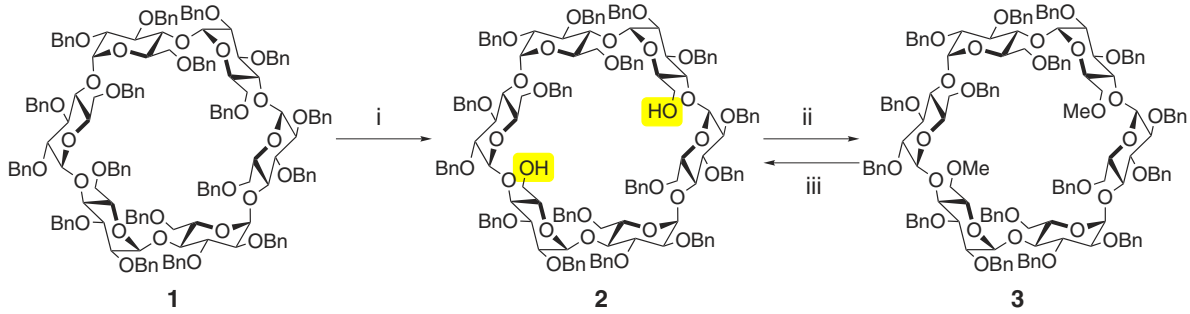
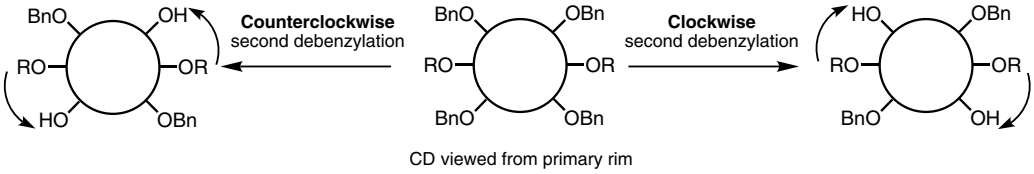


Scheme 1. Debenzylation of the perbenzylated CD **1** and functionalisation of the diol **2**. Reagents and conditions: (i) DIBAL-H, toluene, 50 °C, 2 h, 87%; (ii) MeI, NaH, DMF, rt, 2 h, 82%; (iii) DIBAL-H, toluene, 50 °C, 2 h, 83%.



Scheme 2. Clockwise or counterclockwise type of second bis-debenzylation.

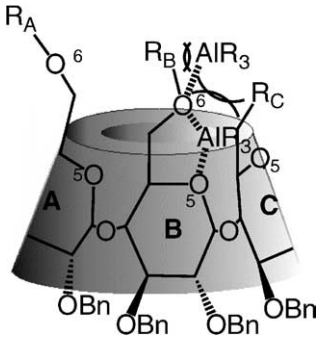


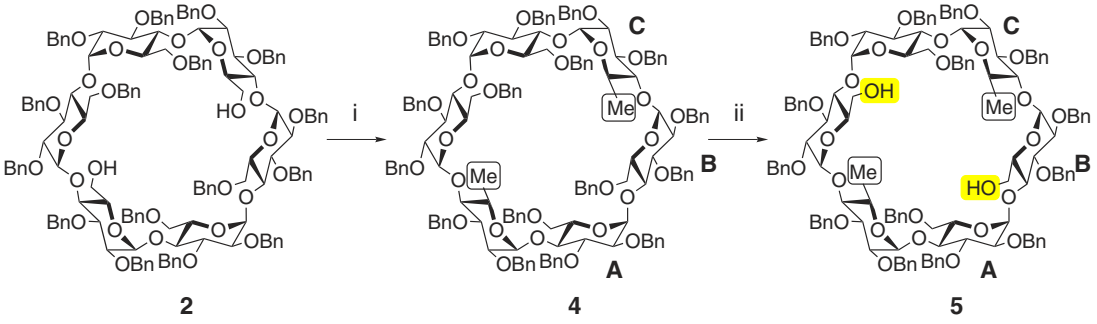
Figure 1. The approach of aluminium atoms on B is hampered by R_C on the counterclockwise sugar C (view from the primary rim) but not by R_A.

the clockwise one (B), hence their ability to be de-*O*-alkylated by DIBAL-H.

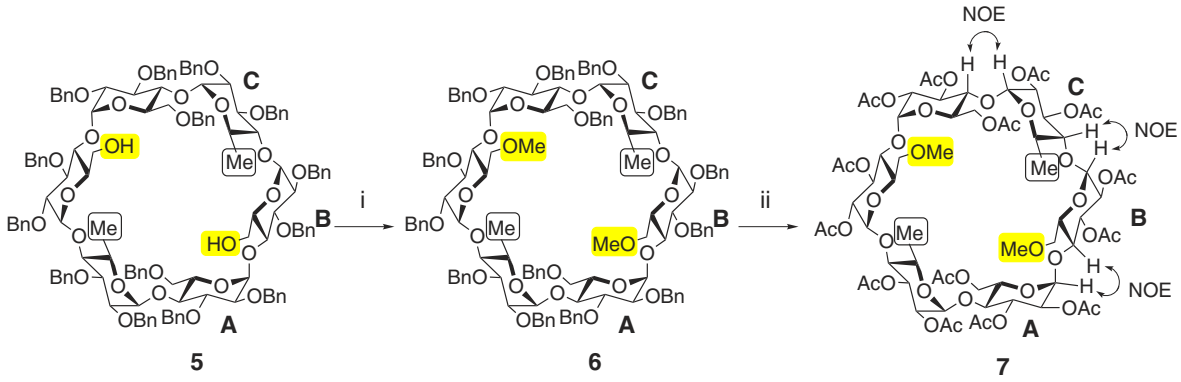
Therefore, by decreasing the size of an ether type protecting group on the primary position of ring C, we may predict a selective deprotection of this position or a preferential clockwise debenzylation of unit B. Indeed, upon reaction with DIBAL-H, dimethylated CD **3** exclusively delivered the starting diol **2**, a product of de-*O*-methylation (Scheme 1).

In order to fully materialise the concept of clockwise regioselectivity implicitly induced by our mechanism, and to prevent de-*O*-alkylation of the less hindered R group (see Scheme 2), we thus synthesised the di-deoxygenated CD **4** ($R_C = H$) through mesylation and subsequent reduction in 78% yield over two steps from diol **2**. Upon reaction with DIBAL-H, CD **4** gave the diol **5** in 75% yield, the expected product of a clockwise $6^C,6^F$-de-*O*-benzylation, hence validating our hypothesis (Scheme 3).

In order to determine the structure of CD **5** by NMR spectroscopy, we have to remove the benzyl groups, which greatly complicate the spectrum. The diol **5** was thus dimethylated under standard conditions in 83% yield, the resulting CD **6** was then debenzylated and the resulting polyol was peracetylated to deliver CD **7** (85% over two steps), which was carefully analysed by



Scheme 3. Dehydroxylation and regioselective clockwise de-*O*-benzylation. Reagents and conditions: (i) (a) MsCl, Et_3N, DCM, 0 °C → rt, 1 h; (b) $LiAlH_4$, THF, rt, 2 h, 78% over two steps; (ii) DIBAL-H, toluene, 50 °C, 1 h, 75%.



Scheme 4. Synthesis of CD **7** and its structural analysis by NMR. Reagents and conditions: (i) MeI, NaH, DMF, rt, 1 h 30 min, 83%; (ii) (a) H_2, Pd/C, THF/H_2O, rt, 12 h; (b) Ac_2O, Pyr., DMAP, rt, 24 h, 85% over two steps.

NMR spectroscopy. The molecule being C_2 symmetric, we only analyse the rings A–C (Scheme 4). The A,D-pair of peracetylated sugars was easily characterised by the observed deshielding of the H-6 signals (around 4.4 ppm), due to the acetylation of the primary position. The two dehydroxylated units C,F differ from the others by the presence of a shielded doublet ($J = 6.1$ Hz) at 1.41 ppm corresponding to the methyl at C-6. The third set of signals corresponds to the *O*-methylated pair B,E (H-6a and H-6b around 3.6 and 3.9, respectively). All signals of each pyranoside ring were attributed by COSY[9] and, finally, the order of the connections between the units was determined by NOE experiment thanks to cross peaks between H-1 and H-4 of two successive units (Scheme 4).[10]

The understanding of the reaction mechanism allowed us to conceive a CD **4** that undergoes a regioselective clockwise second generation de-*O*-benzylation providing a novel C_2 symmetric CD **5** possessing three pairs of functionalities on its primary rim. This result also irrigates our proposed de-*O*-benzylation mechanism involving two aluminium atoms and highly dependent on steric hindrance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.09.046.

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9. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (d, $^3J = 6.1$ Hz, 3H, CH_3–6^C), 2.04–2.10 (m, 21H, $7 \times CH_3C{=}O$), 3.43 (s, 3H, OCH_3), 3.47 (t, $^3J_{4,3} = {}^3J_{4,5} = 8.7$ Hz, 1H, H-4^C), 3.62 (br d, $^2J = 10.6$ Hz, 1H, H-6^B), 3.87 (t, $^3J_{4,3} = {}^3J_{4,5} = 9$ Hz, 1H, H-4^A), 3.95–4.05 (m, 3H, H-4^B, H-5^C, H-$6'^B$), 4.10 (br d, $^3J_{5,4} = 9.0$ Hz, 1H, H-5^B), 4.15 (br d, $^3J_{5,4} = 9.2$ Hz, 1H, H-5^A), 4.30–4.42 (m, 2H, 25H-6^A), 4.81 (dd, $^3J_{2,1} = 3.6$ Hz, $^3J_{2,3} = 10.1$ Hz, 1H, H-2^C), 4.83 (dd, $^3J_{2,1} = 3.3$ Hz, $^3J_{2,3} = 10.1$ Hz, 1H, H-2^A), 4.85 (dd,

$^{3}J_{2,1} = 3.4$ Hz, $^{3}J_{2,3} = 10.2$ Hz, 1H, H-2^{B}), 5.05 (d, $^{3}J_{1,2} = 3.4$ Hz, 1H, H-1^{A}), 5.08 (d, $^{3}J_{1,2} = 3.3$ Hz, 1H, H-1^{C}), 5.10 (d, $^{3}J_{1,2} = 3.3$ Hz, 1H, H-1^{B}), 5.47 (dd, $^{3}J_{3,2} = {}^{3}J_{5,4} = 8.5$ Hz, 1H, H-3^{A}), 5.52 (dd, $^{3}J_{3,2} = {}^{3}J_{5,4} = 9.0$ Hz, 1H, H-3^{C}), 5.53 (dd, $^{3}J_{2,3} = {}^{3}J_{5,4} = 9.0$ Hz, 1H, H-3^{B}). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.5$ (CH_3), 20.9–20.7 ($7\times C H_3C{=}O$), 59.25 (OCH_3), 63.25 (C-6^{A}), 67.5 (C-4^{B}), 68.9 (C-5^{A}), 70.8 (C-6^{B}), 70.4–71.3 (C-2^{A}, C-5^{B}, C-3^{C}, C-2^{B}, C-2^{C}, C-3^{B}), 71.5 (C-5^{C}), 72.2 (C-3^{A}), 75.9 (C-4^{A}), 76.8 (C-4^{B}), 83.1 (C-4^{C}), 96.3 (C-1^{C}), 96.6 (C-1^{A}), 96.7 (C-1^{B}), 169.15, 169.2, 169.3, 170.45, 170.5, 170.55, 170.9 ($7\times CH_3 C{=}O$).

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