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Diisobutylaluminium Hydride (DIBAL-H) Promoted Secondary Rim Regioselective Demethylations of Permethylated β-Cyclodextrin: A Mechanistic Proposal

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Diisobutylaluminium hydride (DIBAL-H) promotes secondary rim regioselective bis-de-*O*-methylation at the 2^A- and 3^B-positions of permethylated β-cyclodextrin. This result contrasts with the selective bis-de-*O*-benzylation of perbenzylated cyclodextrins in which regioselective deprotection occurs at the primary rim. To gain an insight into the mechanism of this remarkable contrasting behavior, the two corresponding permethylated cyclodextrins with an alcohol function at either the 2- or 3-position were synthesized. The cyclodextrin with the alcohol at the 3-position reacts with DIBAL-H to afford the 2^A,3^B-diol whereas the cyclodextrin with the alcohol at the 2-position is unreactive. This observation allows us to propose a mechanism for the demethylation reaction that involves for each demethylation step two molecules of aluminium reagent, in accord with the previous hypothesis on the debenzylation reaction. The second demethylation step appears to be faster than the first, the coordination of aluminium now being an intramolecular process.

Introduction

Cyclodextrins (CDs) are involved in a wide spectrum of applications due to their ability to form water-soluble inclusion complexes with hydrophobic molecules.[1] Simple modifications of CDs, for example, by per-*O*-methylation, alter their chemophysical properties, including their solubility both in water and in organic solvents,[3] as well as the stability of their inclusion complexes. The efficient synthesis of methylated CDs bearing specifically located hydroxy groups is of considerable interest for their further modification and is a stimulating chemical challenge.[1,2] Up to now, selectively modified poly-*O*-methylated CDs have usually been synthesized[3] by temporary regioselective protection of specific hydroxy groups of the native CD followed by permethylation of the remaining hydroxy groups and final removal of the protecting groups to unmask the required hydroxy functions.

From the opposite point of view, we have developed over the years an approach that involves the deprotection of protected CDs. The methodology uses diisobutylaluminium hydride (DIBAL-H) as a dealkylating agent and has been successfully applied to benzylated sugars and CDs,[4,5] allowing access to polyhetero-functionalized CDs containing two, three or even four different functionalities[5–7] (Scheme 1). This approach allowed us to synthesize complex CD dimers used as supramolecular cross-linkers of biopolymers.[8] In all these syntheses, the last step is always the removal of the remaining benzyl groups. Use of permethylated CDs would suppress this step and, more interestingly, would allow modulation of the affinity and solubility of the CDs and thus avoid the drawbacks associated with the presence of free OH groups in applications such as catalysis. We report herein a full account of our work on the demethylation reaction of permethylated CDs.

Results and Discussion

We submitted per-*O*-methylated β-CD **4** to the action of DIBAL-H and observed demethylation reactions leading to a mixture of compounds. Careful optimization of the reaction conditions was necessary to drag the reaction towards a major product and we have been able to delineate three sets of conditions to access three different CDs, **5**, **6** and **7**, as major products. Note, CDs **5**, **6** and **7** are modified on the secondary rim in a regioselective manner, a rather difficult task to achieve.[9–11] The optimized results are summarized in Scheme 2 and Table 1.

When permethylated CD **4** was treated with 9 equiv. of a 0.2 M solution of DIBAL-H in toluene for 18 h at 0 °C, diol **5**[12,13] was obtained as the main compound in 56% yield, a result of double de-*O*-methylation on the secondary rim

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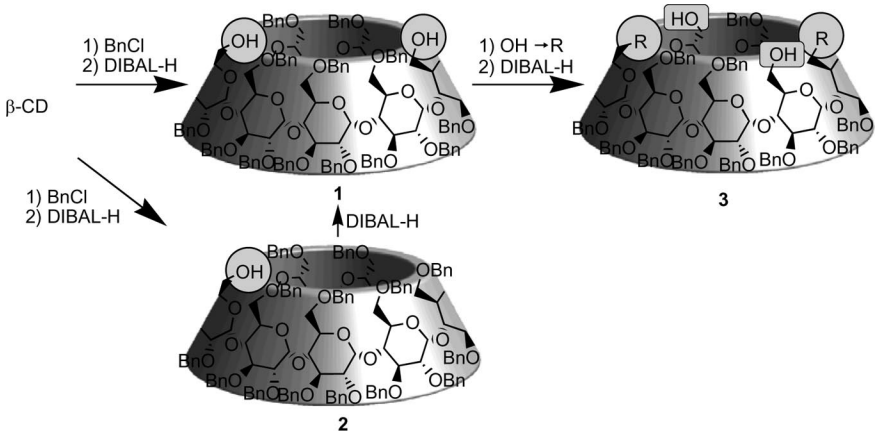
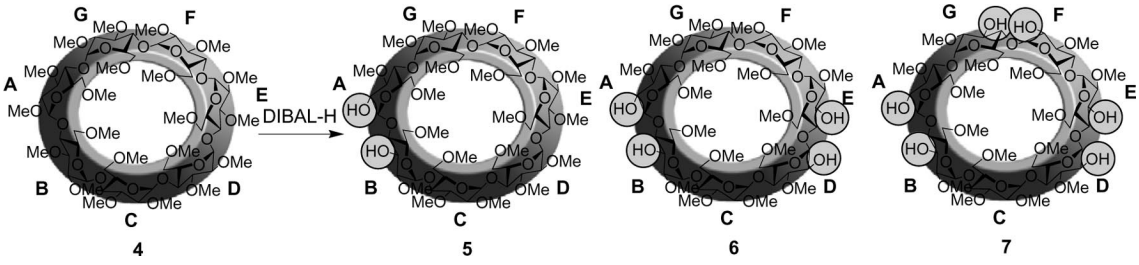


Scheme 1. The de-*O*-benzylation reactions of per-*O*-benzylated β-CD by DIBAL-H.



Scheme 2. Major product profile of the de-*O*-methylation reactions of per-*O*-methylated β-CD with DIBAL-H.

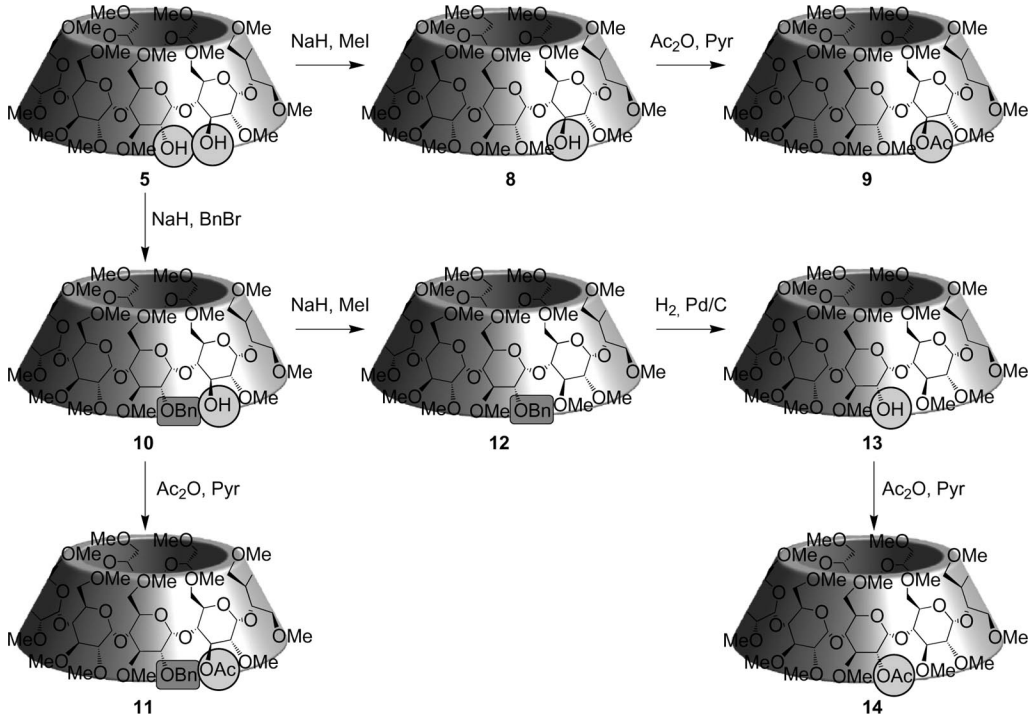
Table 1. Yields of the major products and reaction conditions of the de-*O*-methylation reactions of per-*O*-methylated β-CD with DIBAL-H.

Entry	Conc. of DIBAL-H [mol L^{-1}]	Equiv. of DIBAL-H	*T* [°C]	*t* [h]	Yield [%] **5**	**6**	**7**
1	0.2	9	0	18	56		
2	0.8	50	r.t.	3		51	
3	0.4	50	r.t.	28			45

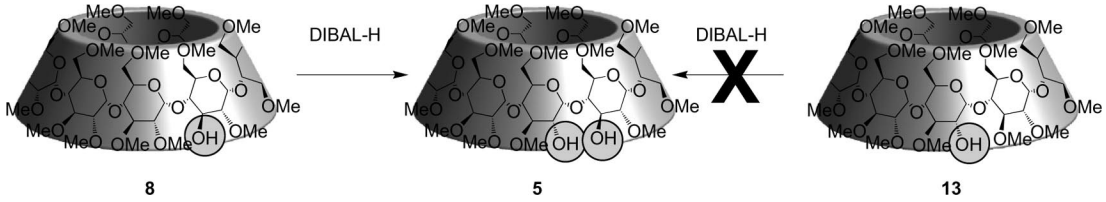
of two contiguous sugar units at the 2^{A}- and 3^{B}-positions. Treatment of **4** with 50 equiv. of DIBAL-H (0.8 M) for 3 h at room temperature gave tetrol **6**[14] as the major product in 51% yield. If left for a prolonged period of time but at a lower DIBAL-H concentration (0.4 M), the reaction led to hexol **7**[15] as the major compound (45% yield). These remarkable results appear to be in sharp contrast to the case of benzylated CDs in which debenzylation occurs on the primary rim of the CD and on two diametrically opposed sugar rings. Furthermore, we showed that such a bis-debenzylation reaction was a stepwise process because we could isolate alcohol **2** and resubmit it to the action of DIBAL-H to obtain diol **1**[5–7] (Scheme 1). In the case of permethylated CDs, and in spite of our efforts, we were unable to isolate a mono-alcohol on the secondary rim, which suggests a subtly different mechanism.

Such a finding may be explained either by a concerted double demethylation or by a stepwise process in which the second dealkylation would be faster than the first. To this end, we synthesized both alcohols **8** and **13** to study their reactivity towards DIBAL-H. Diol **5** was selectively methylated at the 2-position in the presence of NaH and MeI to give CD **8** as the major product (70% yield).[16] The structure of CD **8** was confirmed by its acetylation to compound **9**, the NMR spectrum of which displays a deshielded triplet, clearly indicating the acetylation of 3-OH. The synthesis of alcohol **13** with a free OH at the 2-position required a roundabout approach due to the selectivity of the alkylation reaction in favor of the 2-position. Benzylation of CD **5**, as expected, afforded alcohol **10** as the major product (87%). In this case also, acetylation of the remaining OH to **11** confirmed it to be the correct regioisomer, as indicated by the appearance of a deshielded triplet in the NMR spectrum. Further methylation of alcohol **10** afforded CD **12** in 89% yield, which was debenzylated to give the desired CD **13** in 96% yield. Further acetylation of **13** induced the appearance of a deshielded double doublet in the NMR spectrum of **14**, which confirms the presence of a free 2-OH in CD **13** (Scheme 3).

Both 2-hydroxy-CD **13** and 3-hydroxy-CD **8** were then allowed to react with DIBAL-H. Although CD **8** afforded the 2^{A},3^{B}-dihydroxy-CD **5**, CD **13** did not react at all even



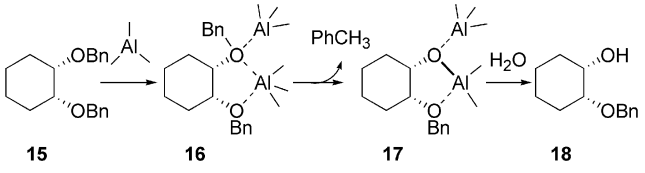
Scheme 3. Synthetic routes to the mono-functionalized methylated β-CDs **8** and **13**.[3,13]



Scheme 4. Only 3-hydroxy-CD **8** affords diol **5** upon action of DIBAL-H.

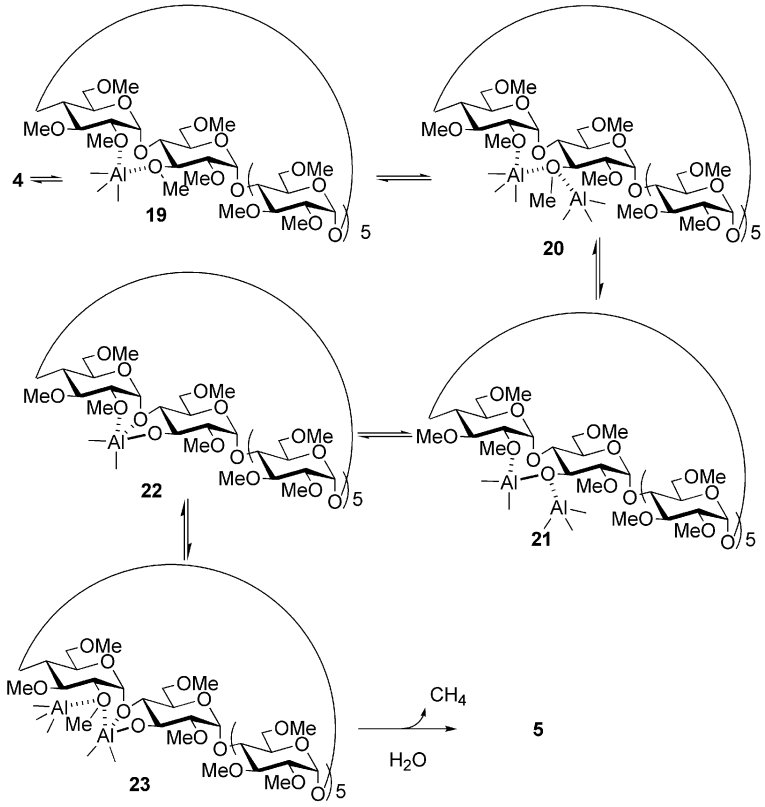
after prolonged reaction times. Remarkably, demethylation of CD **8** to diol **5** took place at a much faster rate than the double dealkylation of permethylated CD **4** to afford the same diol **5** (Scheme 4). This result indicates that the double 2^A,3^B-demethylation reaction is a stepwise mechanism, the first dealkylation occurring at the 3^B-position followed by a faster demethylation at the 2^A-position of the adjacent sugar.

We previously proposed a mechanism for the de-*O*-benzylation reaction involving two molecules of the aluminium reagent.[5] We also observed that two oxygen atoms were necessary for the reaction to occur. As illustrated in Scheme 5, with benzylated cyclohexanediol as a model, the first aluminium molecule is chelated by the two oxygen atoms and the second coordinates to the less hindered oxygen of the two to form **16**. In this situation, one aluminium plays the role of the Lewis acid and activates the C–O bond whereas the other is activated and can deliver its hydride leading to dealkylation to give **17**. It is the combination of the two that allows the dealkylation process. However, further debenzylation was never observed in such systems and alcohol **18** is inert to the action of DIBAL-H.



Scheme 5. Proposed general mechanism for the debenzylation reaction.[5]

Based on these results, we would like to propose a plausible mechanism for the remarkable bis-demethylation of the secondary rim of permethylated β-CD. The first step must be the chelation of an aluminium species by two proximal and easily accessible oxygen atoms on the secondary rim. It has been shown that an acetal regioselectively forms between O-2^A and O-3^B on an unprotected secondary rim of a CD.[11] Hence, we propose that it is also O-2^A and O-3^B that preferentially chelate aluminium to form species **19**. Such chelation on the secondary rim is precluded with perbenzylated β-CD due to the steric congestion caused by the benzyl residues. The second aluminium reagent required for dealkylation would then select the less hindered O-3 oxygen



Scheme 6. Proposed mechanism for the formation of 2^A,3^B-diol **5** from per-*O*-methylated β-CD **4**.

of the chelate, which points away from the cavity of the CD, to form complex **20**. Dealkylation then occurs at the 3-position to give **21**. If this first transformation is indeed the rate-limiting step, the second dealkylation must be faster. This is the reason why we suppose that the aluminium atom already in place and coordinated to the O-2 to be dealkylated plays an essential role. Furthermore, the interglycosidic oxygen atom is perfectly situated to participate in a second coordination to yield the required chelate **22**; this reactive chelate is also formed by the reaction of DIBAL-H with alcohol **8**. This intramolecular coordination probably accounts for the increased rate of this step. Reduction then proceeds via complex **23** to afford diol **5** after hydrolysis (Scheme 6). Duplication and triplication of this mechanism, directed by the steric hindrance of the aluminium adducts, leads to the formation of tetrol **6** and hexol **7**, just as the conversion of alcohol **2** to diol **1** occurs by a duplication of the primary rim de-*O*-benzylation mechanism directed by the crowding induced by the aluminium species attached to the first debenzylation site.[5]

Conclusions

The action of DIBAL-H on permethylated CD **4** allows a one-step easy access to regioselectively modified di-, tetra- and hexa-functionalized CDs **5**, **6** and **7**, respectively, which are suitable for further transformations.[17] The striking reactivity difference between permethylated β-CD **4** and perbenzylated β-CD is certainly due to the ease of access to appropriate dioxygenated "tweezers", O-5^A/O-6^A in the case of hindered benzylated β-CD and O-2^A/O-3^B in the case of unhindered β-CD **4**. In the latter case, a third oxygen is situated in the vicinity and allows a second demethylation to rapidly occur after the first one, which is not possible in the case of the benzylation reaction.

Experimental Section

General: Optical rotations were measured at 20±2 °C with a digital polarimeter by using a 10 cm, 1 mL cell. High-resolution mass spectrometry (HRMS) was carried out with a spectrometer in the positive ESI mode. NMR spectra were recorded with a spectrometer at ambient temperature. ^{1}H NMR chemical shifts are referenced to residual protic solvent ($CDCl_3$; δH = 7.28 ppm). ^{13}C NMR chemical shifts are referenced to the solvent signal (δC = 77.00 ppm for the central line of $CDCl_3$). Assignments were aided by the COSY,J-mod technique and HMQC. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254 plates (layer thickness 0.2 mm) and detected by charring with a 10% solution of sulfuric acid in ethanol. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Solvents were freshly distilled from Na/benzophenone (THF, toluene), or P_2O_5 (CH_2Cl_2). Diisobutylaluminium was purchased from Aldrich as a 1.5 M solution in toluene.

2^A,3^B-Dihydroxy-per-*O*-methyl-β-cyclodextrin (5): A 1.5 M solution of DIBAL-H in toluene (2.52 mmol, 9 equiv., 1.7 mL) was added to a solution of heptakis-2,3,6-tri-*O*-methyl-β-cyclodextrin **4** (400 mg,

0.28 mmol) in anhydrous toluene (10.9 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 18 h under nitrogen. Aqueous HCl (1 M) was carefully added dropwise and the mixture was stirred vigorously at room temperature for 10 min. The toluene phase was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and the solvent removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH = 40:1–35:1) to give 220 mg (56%) of **5**. R_f = 0.2 (dichloromethane/methanol = 15:1). $[\alpha]_D$ = +154 (c = 1.0, $CHCl_3$). MS (FAB): m/z = 1423.7 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.14 (m, 6 H, 6 × 2-H), 3.35 [s, 12 H, 4 × OCH_3 (C-6)], 3.36 [s, 9 H, 3 × OCH_3 (C-6)], 3.45 [s, 9 H, 3 × OCH_3 (C-3)], 3.46 [s, 3 H, OCH_3 (C-3)], 3.47 [s, 6 H, 2 × OCH_3 (C-3)], 3.54 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.6 Hz, 1 H, 2^A-H), 3.57 [s, 3 H, OCH_3 (C-2)], 3.58 [s, 3 H, OCH_3 (C-2)], 3.59 [s, 3 H, OCH_3 (C-2)], 3.60 [s, 3 H, OCH_3 (C-2)], 3.61 [s, 3 H, OCH_3 (C-2)], 3.69 [s, 3 H, OCH_3 (C-2)], 3.40–3.90 (m, 34 H, 6 × 3-H, 7 × 4-H, 7 × 5-H, 14 × 6-H), 3.94 (t, $J_{2,3}$ = $J_{3,4}$ = 9.4 Hz, 1 H, 3^B-H), 4.07 (d, 1 H, OH), 4.37 (s, 1 H, OH), 4.95 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1^A-H), 5.05 (d, $J_{1,2}$ = 3.2 Hz, 2 H, 2 × 1-H), 5.07 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 5.09 (d, $J_{1,2}$ = 2.9 Hz, 2 H, 2 × 1-H), 5.10 (d, $J_{1,2}$ = 3.2 Hz, 1 H, 1^B-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.32, 58.34, 58.44, 58.50, 58.69, 58.92, 58.95, 58.98, 59.04 [13 C, 6 × OCH_3 (C-2), 7 × OCH_3 (C-6)], 61.30, 61.36, 61.38, 61.41, 61.55, 62.15 [6 C, 6 × OCH_3 (C-3)], 70.43, 70.83, 70.91, 70.99, 71.68 (7 × C-5), 71.22, 71.31, 71.37, 71.40, 71.54 (7 × C-6), 71.79 (C-3^B), 73.50 (C-2^A), 80.06, 80.39, 81.00, 81.03, 81.36, 81.43, 81.64, 81.67, 81.80, 81.93, 82.07, 82.26, 82.43, 82.97 (19 C, 6 × C-2, 6 × C-3, 7 × C-4), 98.72, 98.97, 98.99, 99.36, 99.48 (6 C, 6 × C-1), 102.03 (C-1^A) ppm. $C_{61}H_{108}O_{35}$ (1401.49): calcd. C 52.28, H 7.77; found C 52.09, H 7.81.

2^A,3^B,2^E,3^D-Tetrahydroxy-per-*O*-methyl-β-cyclodextrin (6):[14] DIBAL-H (35.1 mmol, 50 equiv., 1.5 M in toluene, 23.4 mL) was added to a stirred solution of permethylated CD **4** (1.0 g, 0.7 mmol) in anhydrous toluene (20 mL) at room temperature under argon. The reaction mixture was stirred at this temperature for 3 h. The solution was cooled to 0 °C, quenched with aqueous HCl (1 M) and the mixture was stirred vigorously at room temperature for 30 min. The toluene phase was collected and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and the solvent removed in vacuo. Purification of the crude product by silica gel chromatography, eluting with 96:4 dichloromethane/methanol, afforded 492 mg (51%) of **6** as a colourless foam. $[\alpha]_D$ = +152 (c = 1.3, $CHCl_3$) {ref.[14] $[\alpha]_D$ = +152 (c = 1.3, $CHCl_3$)}. MS (FAB): m/z = 1395.6 $[M + Na]^+$. MS (CI): m/z = 1390.7 $[M + NH_4]^+$. ^1H NMR (500 MHz, [D_6]DMSO): δ = 3.61, 3.64, 3.95 (7 H, 7 × 2-H), 3.85, 3.88, 3.90, 4.30, 4.31 (7 H, 7 × 3-H), 3.96, 3.97, 3.98, 4.01, 4.02 (7 H, 7 × 4-H), 4.27, 4.29, 4.32, 4.34, 4.35 (7 H, 7 × 5-H), 5.36, 5.37, 5.60, 5.61, 5.62 (7 H, 7 × 1-H), 6.23, 6.25, 6.47, 6.50 (4 H, 4 × OH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 74.61, 74.80, 74.82, 75.16, 75.22, 75.52, 75.55 (7 × C-5), 75.56, 75.58, 85.73, 85.79, 87.41, 87.54 (7 × C-3); 77.05, 77.24, 85.48, 85.79, 85.80 (7 × C-2), 84.11, 84.23, 84.30, 84.74, 84.86, 85.54, 85.56 (7 × C-4), 102.4, 102.5, 103.0, 105.6, 105.7 (7 × C-1) ppm. $C_{59}H_{104}O_{35}·2H_2O$ (1373.43): calcd. C 50.27, H 7.72; found C 50.28, H 7.77.

2^A,3^B,2^E,3^D,2^F,3^G-Hexahydroxy-per-*O*-methyl-β-cyclodextrin: (7):[15] DIBAL-H (7 mmol, 50 equiv., 1.5 M in toluene, 4.67 mL) was added to a solution of heptakis-2,3,6-tri-*O*-methyl-β-cyclodextrin (200 mg, 0.14 mmol) in anhydrous toluene (12 mL). The reaction mixture was stirred at room temperature for 28 h under argon. After quenching the reaction by adding an aqueous solution of HCl (1 M), the toluene phase was separated and the aqueous phase was concentrated to a quarter of the original volume. The residue was extracted with ethyl acetate (50 mL) and the combined organic phases wer washed with brine, dried with $MgSO_4$ and the solvents evaporated to dryness. The resultant solid was subjected to silica gel chromatography, eluting with CH_2Cl_2/MeOH (94:6, v/v), to give 85 mg (yield 45%) of **7**. R_f = 0.14 (CH_2Cl_2/MeOH, 91:9). $[\alpha]_D$ = +157 (c = 1.0, $CHCl_3$) {ref.[15] $[\alpha]_D$ = +156.7 (c = 1.0, $CHCl_3$)}. MS (FAB): m/z = 1367 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.12–3.93 (m, 97 H), 4.94–4.95, (m, 3 × 1-H), 5.03 (d, J = 3.3 Hz, 1-H), 5.06 (d, J = 3.4 Hz, 2 × 1-H), 5.09 (d, J = 3.4 Hz, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.94, 58.09, 58.18, 58.20, 58.75, 58.77, 58.79, 58.90, 60.95, 61.07, 61.64, 61.95 (15 × OCH_3), 70.21, 70.28, 71.20, 71.45, 71.51, 71.55, 71.60 (7 × C-5), 70.64, 70.93, 71.10, 71.20 (7 × C-6), 73.03, 73.19, 73.23, 81.09, 81.13, 81.20, 81.28, 81.40, 81.45, 81.56, 81.84, 82.05, 82.30, 82.74 (7 × C-2, 7 × C-3, 7 × C-4), 99.38, 99.61, 99.68, 99.73, 101.94, 102.12, 102.20 (7 × C-1) ppm. $C_{57}H_{100}O_{35}$ (1345.38)·$2H_2O$: calcd. C 49.56, H 7.59; found C 49.26, H 7.46.

3^B-Hydroxy-per-*O*-methyl-β-cyclodextrin (8):[13] NaH (60%, 2.8 mg, 0.071 mmol, 1 equiv.) was added to a solution of **5** (100 mg, 0.071 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen. After stirring at 0 °C for 1 h, CH_3I (0.071 mmol, 1.0 equiv., 4.4 μL) was added. The reaction mixture was stirred at 0 °C for 6 h and then kept at room temperature for another 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtered and the solvent removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/EtOAc/CH_3OH = 2:8:0.6) to give 71 mg (70%) of **8** as a white foam. $[\alpha]_D$ = +136 (c = 1.0, $CHCl_3$) {ref.[13] $[\alpha]_D$ = +157 (c = 0.96, $CHCl_3$)}. The analytical data of **8** are in agreement with those reported previously.[13]

3^B-*O*-Acetyl-per-*O*-methyl-β-cyclodextrin (9):[13] DMAP (3.2 mg, 0.026 mmol, 1 equiv.) and Ac_2O (1 mL) were added to a solution of **8** (37 mg, 0.026 mmol) in dry pyridine (2 mL) at room temperature. The reaction mixture was stirred for 18 h under nitrogen. The solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: cyclohexane/acetone = 2:1) to give 36 mg (95%) of **9** as a white foam. R_f = 0.2 (cyclohexane/acetone = 3:2). $[\alpha]_D$ = +140 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3CO), 3.12 (dd, $J_{1,2}$ = 3.1, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 3.16–3.21 (m, 5 H, 5 × 2-H), 3.30 (dd, $J_{1,2}$ = 3.7, $J_{2,3}$ = 10.3 Hz, 1 H, 2^B-H), 3.39–3.42 [m, 21 H, 7 × OCH_3 (C-6)], 3.43 (m, 1 H, 3-H), 3.48, 3.49, 3.50, 3.51, 3.52, 3.53 [m, 21 H, 7 × OCH_3 (C-2)], 3.61, 3.63, 3.65, 3.66, 3.67, 3.68 [s, 18 H, 6 × OCH_3 (C-3)], 3.46–3.68 (m, 17 H, 5 × 3-H, 5 × 4-H, 7 × 6a-H), 3.75 (m, 1 H, 4^B-H), 3.71–3.96 (m, 13 H, 7 × 5-H, 6 × 6b-H), 4.05 (dd, $J_{5,6b}$ = 2.4, $J_{6a,6b}$ = 10.6 Hz, 1 H, 6b-H), 4.98 (d, $J_{1,2}$ = 3.0 Hz, 1 H, 1-H), 5.08 (d, $J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 5.12–5.14 (m, 4 H, 4 × 1-H), 5.30 (d, $J_{1,2}$ = 3.7 Hz, 1 H, 1^B-H), 5.41 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 9.0 Hz, 1 H, 3^B-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.32 (1 C, CH_3CO), 58.13, 58.22, 58.34, 58.52, 58.63, 58.86, 58.90, 58.94, 59.07, 59.26 [14 C, 7 × OCH_3 (C-2), 7 × OCH_3 (C-6)], 60.98, 61.45, 61.47, 61.62, 61.72, 61.79 [6 C, 6 × OCH_3 (C-3)], 70.45, 71.18, 71.38, 71.52, 71.89 (7 C, 7 × C-6), 70.50, 70.79, 70.87, 70.96, 71.23 (7 C, 7 × C-5), 71.32 (C-3^B), 78.66 (C-4^B), 79.21, 79.80, 80.48, 80.53, 80.56, 80.80, 81.16, 81.27, 81.52, 81.62, 81.68, 81.76, 81.94, 82.18, 82.24, 82.42, 82.55 (19 C, 7 × C-2, 6 × C-3, 6 × C-4), 98.63, 98.71, 98.90, 99.00, 99.29, 99.51, 99.61 (7 C, 7 × C-1), 170.45 (CH_3CO) ppm. HRMS: calcd. for $C_{64}H_{112}O_{36}$ $[M + Na]^+$ 1479.6831; found 1479.6826.

2^A-*O*-Benzyl-3^B-hydroxy-per-*O*-methyl-β-cyclodextrin (10): NaH (60%, 2.8 mg, 0.071 mmol, 1.0 equiv.) was added to a solution of **5** (100 mg, 0.071 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen. After stirring the reaction mixture at 0 °C for 1 h, BnBr (0.071 mmol, 1.0 equiv., 8.6 μL) was added. The reaction mixture was stirred at 0 °C for 6 h and then kept at room temperature for 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtered and the solvent removed. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/EtOAc/CH_3OH = 2:8:0.4) to give 93 mg (87%) of **10** as a white foam. R_f = 0.3 (CH_2Cl_2/EtOAc/CH_3OH = 5:5:1). $[\alpha]_D$ = +132 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16–3.20 (m, 5 H, 5×2-H), 3.27 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.1 Hz, 1 H, 2^B-H), 3.33 [3 H, 1×OCH_3 (C-6)], 3.36 [3 H, 1×OCH_3 (C-6)], 3.39 [m, 17 H, 7×OCH_3 (C-6), 2^A-H], 3.46 (m, 1 H, 4^B-H), 3.50, 3.51, 3.56 [18 H, 6×OCH_3 (C-2)], 3.63, 3.65 [15 H, 5×OCH_3 (C-3)], 3.70 [3 H, 1×OCH_3 (C-3)], 3.47–3.70 (m, 19 H, 6×3-H, 6×4-H, 7×6a-H), 3.79–3.88 (m, 14 H, 7×5-H, 7×6b-H), 3.99 (t, $J_{2,3}$ = $J_{3,4}$ = 10.1 Hz, 1 H, 3^B-H), 4.62 (d, $J_{1,2}$ = 3.7 Hz, 1 H, 1^A-H), 4.72 (d, J_{gem} = 12.5 Hz, 1 H, PhCH_2), 4.89 (d, J_{gem} = 12.5 Hz, 1 H, PhCH_2), 5.05 (d, $J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 5.09–5.13 (m, 5 H, 4×1-H, 3^B-OH), 5.15 (d, $J_{1,2}$ = 3.5 Hz, 1 H, 1^B-H), 7.29–7.36 (m, 3 H, arom-H), 7.40–7.42 (m, 2 H, arom-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.40, 58.42, 58.44, 58.46, 58.52, 58.59, 58.80, 58.88, 58.90, 58.92 [13 C, 6×OCH_3 (C-2), 7×OCH_3 (C-6)], 61.34, 61.35, 61.41, 61.46, 61.56, 61.86 [6 C, 6×OCH_3 (C-3)], 70.01, 70.84, 70.91, 70.93, 70.97, 71.26 (7 C, 7×C-6), 70.81, 71.03, 71.31, 71.40 (7 C, 7×C-5), 71.70 (C-3^B), 73.87 (PhCH_2), 78.84 (C-2^A), 80.22, 80.10, 80.82, 81.20, 81.28, 81.40, 81.52, 81.65, 81.73, 82.00, 82.04, 82.07, 82.24, 82.34, 82.62, 83.21 (19 C, 6×C-2, 6×C-3, 7×C-4), 98.73, 98.87, 98.99, 99.38, 99.69, 99.81 (6 C, 6×C-1), 101.47 (C-1^A), 128.20, 128.48, 128.83, 137.12 (6 C, arom-C) ppm. HRMS: calcd. for $C_{68}H_{114}O_{35}$ [M + Na]$^+$ 1513.7038; found 1513.7033.

2^A-*O*-Benzyl-3^B-*O*-acetyl-per-*O*-methyl-β-cyclodextrin (11): DMAP (3.2 mg, 0.026 mmol, 1 equiv.) and Ac_2O (1 mL) were added to a solution of **10** (38 mg, 0.026 mmol) in dry pyridine (2 mL) at room temperature. The reaction mixture was stirred for 18 h under nitrogen. The solvent was removed in vacuo and the residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH = 40:1) to give 32 mg (80%) of **11** as a white foam. R_f = 0.3 (CH_2Cl_2/CH_3OH = 10:1). $[\alpha]_D$ = +136 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3 H, CH_3CO), 3.17–3.22 (m, 5 H, 5×2-H), 3.30 (dd, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 3.38 (dd, $J_{1,2}$ = 3.9, $J_{2,3}$ = 9.4 Hz, 1 H, 2^B-H), 3.35, 3.37, 3.40 [21 H, 7×OCH_3 (C-6)], 3.49, 3.50, 3.51, 3.52, 3.53 [18 H, 6×OCH_3 (C-2)], 3.62, 3.65, 3.67, 3.68 [18 H, 6×OCH_3 (C-3)], 3.47–3.72 (m, 19 H, 6×3-H, 6×4-H, 7×6a-H), 3.79 (m, 1 H, 4^B-H), 3.77–3.99 (m, 14 H, 7×5-H, 7×6b-H), 4.63 (d, J_{gem} = 12.3 Hz, 1 H, $PhCH_2$), 4.72 (d, $J_{1,2}$ = 3.3 Hz, 1 H, 1-H), 4.76 (d, J_{gem} = 12.3 Hz, 1 H, $PhCH_2$), 5.08–5.15 (m, 5 H, 5×1-H), 5.34 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1^B-H), 5.41 (pseudo-t, $J_{2,3}$ = $J_{3,4}$ = 9.4 Hz, 1 H, 3^B-H), 7.31–7.33 (m, 1 H, arom-H), 7.35–7.38 (m, 2 H, arom-H), 7.42–7.44 (m, 2 H, arom-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.17 (1 C, CH_3CO), 58.06, 58.28, 58.33, 58.50, 58.58, 58.62, 58.78, 58.89, 58.92, 58.95, 59.07, 59.38, 60.83 [13 C, 6×OCH_3 (C-2), 7×OCH_3 (C-6)], 61.41, 61.44, 61.46, 61.61, 61.77, 61.81 [6 C, 6×OCH_3 (C-3)], 70.27, 71.11, 71.27, 71.38, 71.41, 71.52, 71.98 (7 C, 7×C-6), 70.40, 70.78, 70.81, 70.93, 70.96, 71.15 (7 C, 7×C-5), 73.56 ($PhCH_2$), 78.17 (C-4^B), 78.74, 79.83, 80.31, 80.64, 80.67, 80.78, 81.23, 81.56, 81.64, 81.76, 81.82, 81.89, 82.06, 82.19, 82.24, 82.45 (20 C, 7×C-2, 7×C-3, 6×C-4), 98.71, 98.92, 98.96, 99.10, 99.41, 99.58, 99.74 (7 C, 7×C-1), 127.86, 128.28, 128.34 138.49 (6 C, arom-C), 170.63 (CH_3CO) ppm. HRMS: calcd. for $C_{70}H_{116}O_{36}$ [M + Na]$^+$ 1555.7144; found 1555.7139.

2^A-*O*-Benzyl-per-*O*-methyl-β-cyclodextrin (12):[3] NaH (60%, 2.8 mg, 0.071 mmol, 1 equiv.) was added to a solution of **10** (106 mg, 0.071 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen. After stirring at 0 °C for 1 h, CH_3I (0.071 mmol, 1.0 equiv., 4.4 μL) was added. The reaction mixture was stirred at 0 °C for 6 h and then kept at room temperature for another 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent was removed in vacuo. The residue was dissolved with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtered and the solvent removed in vacuo. The residue was subjected to flash chromatography (eluent: cyclohexane/acetone = 5:2) to give 95 mg (89%) of **12** as a white foam. $[\alpha]_D$ = +126 (c = 0.8, $CHCl_3$). Its NMR spectroscopic data are in agreement with those published earlier.[3]

2^A-Hydroxy-per-*O*-methyl-β-cyclodextrin (13):[3,13] Pd/C (10%, 135 mg, 0.13 mmol, 1.0 equiv.) was added to a solution of **12** (192.8 mg, 0.13 mmol) in methanol (10 mL). The suspension was purged three times with nitrogen and then subjected to a flow of hydrogen. The reaction mixture was stirred at room temperature for 16 h. The suspension was filtered through a pad of Celite, which was then washed with CH_3OH (3×4 mL). The combined filtrate was concentrated to dryness. The residue was subjected to flash chromatography (eluent: cyclohexane/acetone = 2:1) to give 174 mg (96%) of **13** as a white foam. R_f = 0.3 (cyclohexane/acetone = 1:1). $[\alpha]_D$ = +143 (c = 1.0, $CHCl_3$) {ref.[13] $[\alpha]_D$ = +160.6 (c = 1.57, $CHCl_3$)}. Its NMR spectroscopic data are in agreement with those reported previously.[13]

2^A-*O*-Acetyl-per-*O*-methyl-β-cyclodextrin (14):[13] DMAP (4.8 mg, 0.039 mmol, 1 equiv.) and Ac_2O (1.5 mL) were added to a solution of **13** (55 mg, 0.039 mmol) in dry pyridine (3 mL) at room temperature. The reaction mixture was stirred for 16 h under nitrogen. The solvent was removed in vacuo and the residue subjected to flash chromatography (eluent: cyclohexane/acetone = 2:1) to give 56 mg (99%) of **14** as a white foam. R_f = 0.25 (cyclohexane/acetone = 1:1). $[\alpha]_D$ = +164 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3CO), 3.14 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.18–3.21 (m, 5 H, 5×2-H), 3.37–3.39 [m, 21 H, 7×OCH_3 (C-6)], 3.50, 3.51, 3.52 [m, 18 H, 6×OCH_3 (C-2)], 3.61, 3.63, 3.64, 3.65, 3.66, [m, 21 H, 7×OCH_3 (C-3)], 3.47–3.70 (m, 20 H, 6×3-H, 7×4-H, 7×6a-H), 3.72 (m, 1 H, 3^A-H), 3.74–3.90 (m, 14 H, 7×5-H, 7×6b-H), 4.65 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.6 Hz, 1 H, 2^A-H), 5.11–5.17 (m, 6 H, 6×1-H), 5.18 (m, 1 H, 1^A-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.95 (CH_3CO), 58.31, 58.39, 58.48, 58.52, 58.71, 58.74, 58.90, 58.96 [13 C, 6×OCH_3 (C-2), 7×OCH_3 (C-6)], 61.13, 61.19, 61.25, 61.28, 61.42, 61.49, 61.52 [7 C, 7×OCH_3 (C-3)], 70.79, 70.85, 70.90, 71.00, 71.13 (7 C, 7×C-5), 71.26, 71.31, 71.41, 71.52, 71.55, 71.61 (7 C, 7×C-6), 74.09 (C-2^A), 79.90, 79.97, 80.02, 80.17, 80.20, 80.31, 80.37, 80.44, 81.43, 81.63, 81.72, 81.75, 81.79, 81.83, 81.94, 82.03, 82.18 (19 C, 6×C-2, 7×C-3, 7×C-4), 98.07 (C-1^A), 98.79, 98.87, 99.00, 99.10 (6 C, 6×C-1), 170.76 (CH_3CO) ppm. HRMS: calcd. for $C_{64}H_{112}O_{36}$ [M + Na]$^+$ 1479.6831; found 1479.6826.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **5**–**14**.

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