

DIBAL-H mediated triple and quadruple debenzylations of perbenzylated cyclodextrins†

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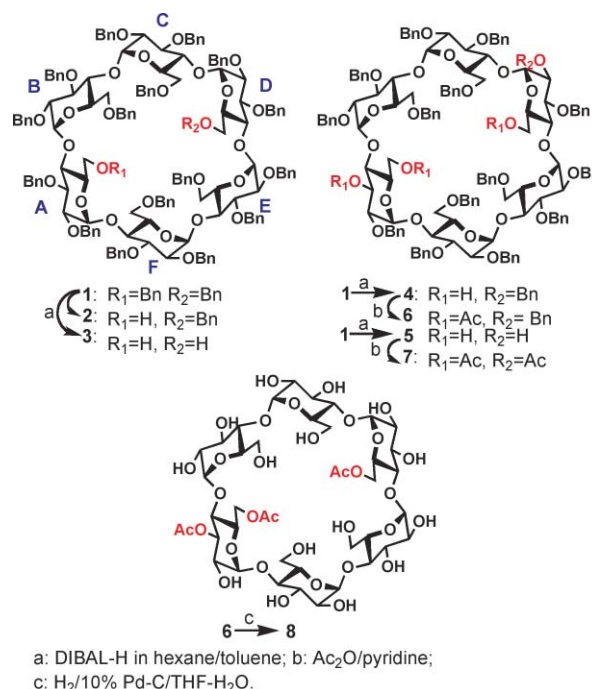
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Diisobutylaluminium hydride (DIBAL-H) mediated reductive removal of benzyl groups was investigated for perbenzylated α -, β - and γ -cyclodextrins using DIBAL-H in hexane as the reagent. It was found that under the new conditions, the debenzylation can be better controlled to provide sequentially tri- and tetra-debenzylated products in moderate yields and in a regioselective manner. In the case of α -cyclodextrin, the removal of the third and fourth benzyl groups took a different path involving the secondary rim, compared to β - and γ -cyclodextrins which both gave only 6-*O*-debenzylated products.

Introduction

Recently, there has been an increasing interest^{1–4} in developing methodologies for the regioselective substitution of cyclodextrins (CDs). These multi-functionalized CDs have great utility in many areas such as for use as novel host molecules to complex bioactive compounds with high affinities,⁵ as artificial enzymes⁶ and as gene delivery vehicles.⁷ Among all the hydroxyls present in a CD molecule, those attached to the C-6's of the glucopyranosyl units are sterically the most accessible and they are all located at the primary rim of the hydrophobic cavity; the remaining hydroxyl groups are all found at the secondary rim because they are attached to either C-2's or C-3's of the sugar units; they are sterically less accessible. It's relatively straightforward to persubstitute all hydroxyls or regioselectively differentiate one group of hydroxyls from the other.⁸ However, it is extremely challenging to regioselectively differentiate hydroxyls of the same group due to their identical chemical properties. There have been a few methods reported in literature involving the use of either bulky groups such as trityl⁹ and its variant¹⁰ or geometrically restricted capping reagents to react with close hydroxyl pairs at the primary rim.^{11–13} Several years ago, Sinaý's group introduced a distinct approach¹⁴ which involved the use of diisobutylaluminium hydride (DIBAL-H) in toluene as the reagent to remove 1–2 benzyl groups attached to *O*-6 positions of perbenzylated α -, β - and γ -CDs. The reaction conditions could be tuned to produce either mono- or didebenzylated CDs in moderate to excellent yields. The most prominent feature of the method was the high regioselectivity during the removal of the second benzyl group. For example, for α/β -CDs, the second debenzylation occurs exclusively at the *O*-6 of the D sugar unit of cyclic oligosaccharides to form 6^A,6^P-*O*-didebenzylated α/β -CD in high yields while in the case of perbenzylated γ -CD, a mixture of 6^A,6^D/6^A,6^E-*O*-didebenzylated products was formed in moderate yield. More recently, we reported our preliminary results¹⁵ on the one-pot triple

and quadruple debenzylations of perbenzylated α -CD by slightly modified conditions using DIBAL-H in hexane as reagent instead of the original DIBAL-H in toluene (Scheme 1). The simple switch of reagent resulted in much slower debenzylation thus allowing for a better monitoring and control of the progress of the reaction. In addition to the known mono- (**2**) and didebenzylated α -CD (**3**), we also observed the formation of two major debenzylated products, namely a triol (**4**, 32% yield) and a tetraol (**5**, 10% yield).



Scheme 1 Sequential debenzylations of perbenzylated α -CD.

As shown in the structures, both the third and fourth benzyl removals occurred at the secondary rim of the α -CD cavity and remarkably, the glucopyranosyl unit which had a prior *O*-6 debenzylation also preferred to have its *O*-3 benzyl removed. The structures of both **4** and **5** were determined *via* either a sequence of acetylation/hydrogenation to remove all the benzyl

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groups (4 → 6 → 8) or simply an acetylation (5 → 7). It is important to note that all acetylated products were stable after the removal of benzyl groups and no acetate migration was observed. For example, in compound 6, we observed that a glucopyranosyl unit had respectively an acetate at O-3 and O-6 positions by a combination of 1D/2D (GCOSY and GTOCSY) NMR experiments and these substitution patterns were further confirmed by a selective 1D TOSCY experiment (see supporting information†); the same acetate-substitution patterns were also observed in the fully debenzylated polyol 8 by NMR experiments. These results suggested that the catalytic hydrogenation step was carried out under extremely mild conditions therefore no acetate migration occurred. In this paper, we report further studies in applying our reported conditions to perbenzylated β- and γ-CDs. A rationale to explain the unusual debenzylation path is proposed.

Results and discussion

β-Cyclodextrin

The intriguing debenzylation path of 1 prompted us to investigate the debenzylation of perbenzylated β-CD (9). We treated compound 9 with DIBAL-H in hexane (40 equiv, 0.9 M) under similar heating conditions (50 °C). As shown in Table 1; it was confirmed

Table 1 DIBAL-H in hexane mediated stepwise debenzylation of 9

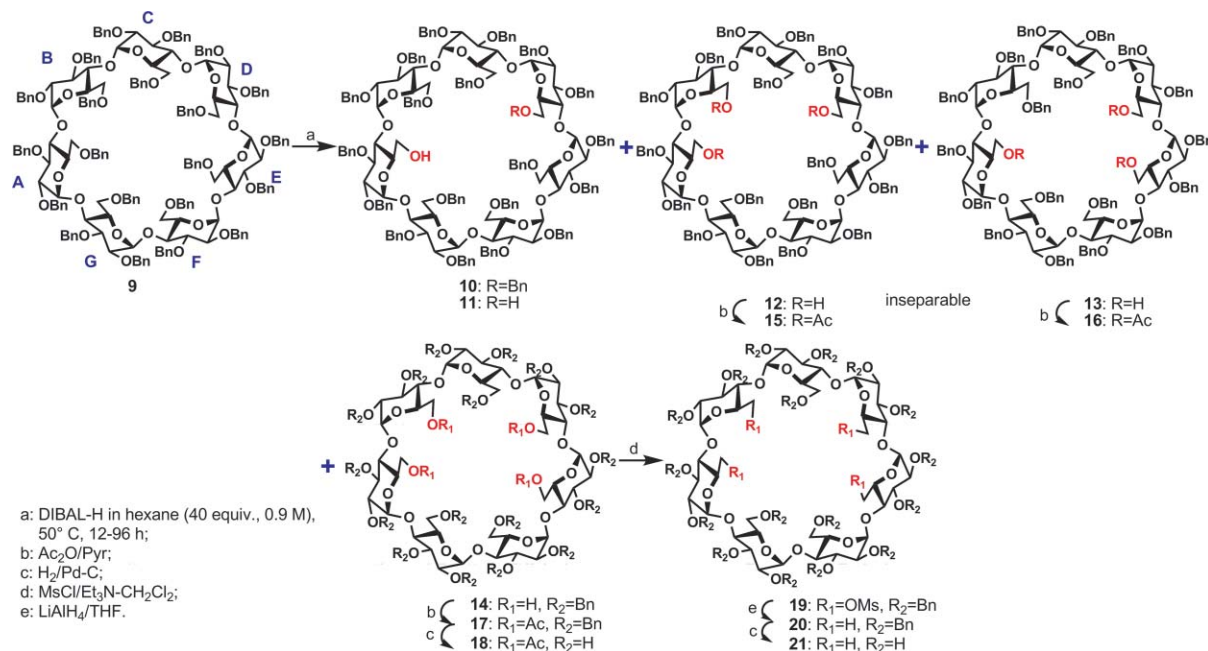
Conditions ^a	9	10	11	12 + 13	14
1 40 eq, 0.9 M, 50 °C, 12 h	15%	45%	25%		
2 40 eq, 0.9 M, 50 °C, 24 h		16%	52%	Trace	Trace
3 40 eq, 0.9 M, 50 °C, 48 h		5%	42%	16%	4%
4 40 eq, 0.9 M, 50 °C, 72 h			18%	30%	15%
5 40 eq, 0.9 M, 50 °C, 96 h			8%	25%	22%

^a In all conditions reported, DIBAL-H in hexane (1.4 M) was used.

again that the debenzylation process was sluggish. Even after 12 h, we still isolated 15% starting material, and the previously known 6-*O*-monodebenzylated β-CD (10) and its 6^A,6^D-*O*-didebenzylated analog (11) were isolated in only 45% and 25% yields respectively. However, in the literature, it was reported^{14a} that if DIBAL-H in toluene was used at 0.5 M concentration, compound 11 could be isolated in 87% yield after heating for just 2 h at 50 °C. After 24 h, the starting material was completely consumed and we started to observe the formation of some more polar compounds besides the monool 10 and diol 11 – both remained as the major components of the reaction mixture until 48 h (entries 2 and 3). The monool 10 finally disappeared after 3 days and the amounts of the two new spots gradually increased and eventually became the majority after 96 h. The less polar spot (R_f 0.5, 7 : 3 hexane : ethyl acetate) was isolated in 25% and the more polar spot (R_f 0.25, 1 : 1 ethyl acetate : hexane) in 22% yield (entries 4 and 5).

The less polar spot was subjected to an acetylation and from ¹H NMR, it was found to be a inseparable 1 : 1 mixture containing two triacetylated β-CD derivatives because 6 acetate peaks were observed (15 and 16); interestingly none of the acetyl groups were found to attach to a secondary hydroxyl group as after a debenzylation, we did not observe any proton resonating above 5.0 ppm (see supporting information†) which was the case for α-CD (compounds 5 and 7). This was further confirmed from the ¹H NMR spectra of the fully debenzylated products (not shown). The structures of the two triols were assigned to be 6^A,6^B,6^D-β-*O*-tridebenzylated β-CD 12 and 6^A,6^B,6^E-β-*O*-tridebenzylated 13 (Scheme 2) respectively, according to our proposed rationale (see later).

Similarly, the more polar spot was acetylated and fortunately, the ¹H and ¹³C NMR spectra revealed that it constitutes a single compound 17 with four acetates. Since we did not observe any ¹H NMR signals with chemical shifts greater than 5.0 ppm in the spectra of the fully debenzylated 18, we concluded that all the four



Scheme 2 Stepwise debenzylations of perbenzylated β-cyclodextrin.

Table 2 ^1H Chemical shifts of compound **21**

	H-1	H-2	H-3	H-4	H-5	H-6(a)	H-6b
I	5.74	4.17	4.82	4.36	4.56	4.50	4.42
II	5.60	4.14	4.69	3.59	4.45	1.58	
	5.59	4.14	4.69	3.59	4.45	1.58	
III	5.56	4.20	4.81	4.36 or 4.30	3.96	4.63–4.38	
	5.56	4.20	4.81	4.30 or 4.36	4.96	4.63–4.38	
IV	5.41	4.16	4.68	3.66	4.46	1.73	
	5.40	4.16	4.68	3.64	4.42	1.68	

debenzylations had taken place at the primary rim. In fact, in the ^1H spectra of the **14**, we also observed 4 sets of signals at 3.02, 2.79, 2.58, 2.48 ppm, each appeared as a doublet of doublets, they indeed corresponded to 4 sets of primary hydroxyl group signals. Thus the triple and quadruple debenzylations of perbenzylated β -CD took a different path than α -CD. The four debenzylation sites in tetraol **14** could not be unambiguously established even with the help of advanced 2D NMR experiments for both **17** and **18** due to significant overlaps in ^1H NMR spectra. Thus we performed a series of chemical derivatizations to assist the task. We decided to perform 6-deoxygenation to convert all the 6-*O*-debenzylated sites to 6-deoxygenated sites. This in principle should generate 4 sets of doublets (H-6s) which should appear at a distinct region (1.0–2.0 ppm), well separated from the rest of the sugar protons (3.2–5.5 ppm). Indeed, the tetraol **14** was smoothly converted to the tetramesylates (**19**, 84% yield) by treating **14** with methanesulfonyl chloride in anhydrous dichloromethane using triethylamine as a base. The activated sulfonyl ester was then reduced with excess lithium aluminium hydride (LAH) at room temperature (\rightarrow **20**); compound **20** was finally fully debenzylated under standard hydrogenation conditions to give the fully debenzylated **21**. In the ^1H NMR spectra of **21**, we observed four sets of doublets at the 1.50–1.80 ppm region (two of them overlapped), correlating to the H-6's of four 6-deoxygenated glucopyranosyl units, which reconfirm our earlier observation that the quadruple debenzylations had occurred only at the primary rim of β -CD.

In order to determine the exact sites of debenzylations, we performed a systematic NMR study of compound **21**, recorded in deuterated pyridine. As shown in Fig. 1, the ^1H - ^1H COSY and TOCSY spectra clearly showed 7 anomeric protons at 5.74, 5.60, 5.59, 5.56 ($\times 2$), 5.41, 5.40 ppm, which can be divided into four groups according to their chemical shift similarities (Table 2).

The group I consists of one sugar unit which has its anomeric proton resonating at 5.74 ppm; the other three groups consist of two sugar units each with their H-1's at 5.60/5.59 ppm for the group II, at 5.56/5.56 ppm for group III and at 5.41/5.40 ppm for group IV. The GTOCSY experiment revealed that the four sugar units of groups II and IV had 6-deoxygenations because the H-1 proton of each of them correlated with a CH_3 at the most upfield region. All 6-deoxygenated sugar units had a more upfield-shifted H-4; the H-4's of group II were observed slightly upfield than those of group IV. All the H-4's of group I and III were found to be more downfield at a very narrow 4.27–4.39 ppm region with the H-4 of group I resonating slightly upfield than H-4's of group III.

The 2D ^1H - ^1H ROESY experiment of compound **21** is shown in Fig. 2. By analyzing the across glycosidic ROE correlations

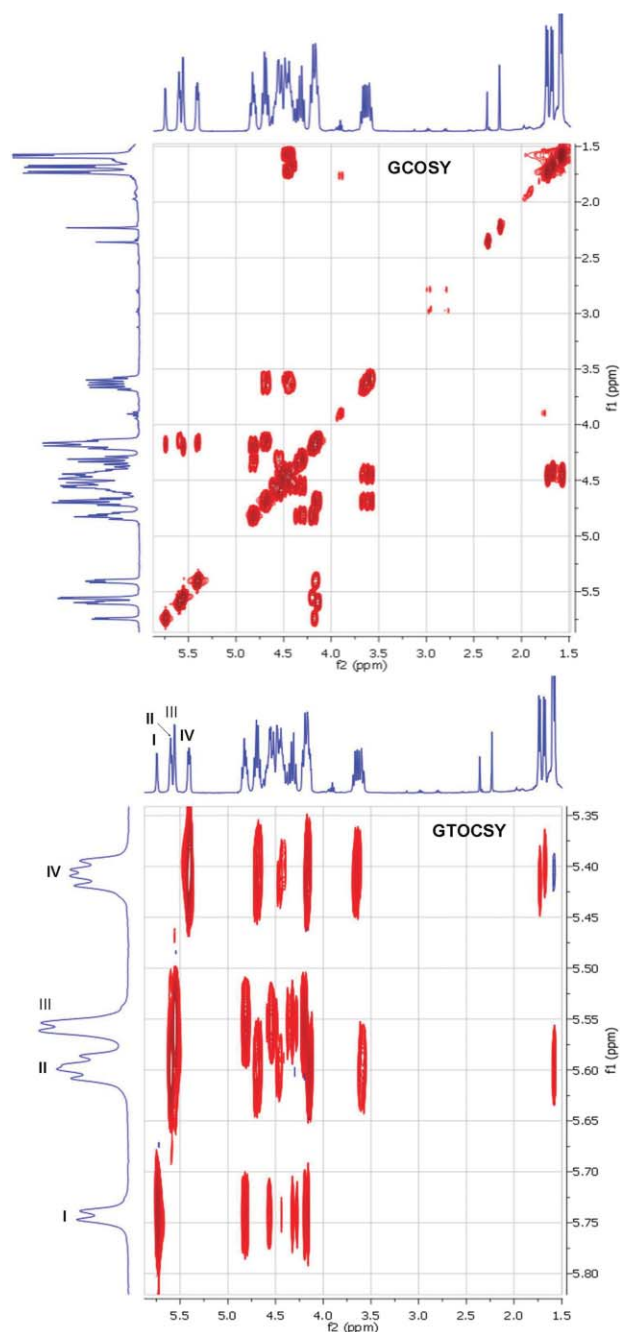


Fig. 1 ^1H - ^1H COSY and GTOCSY spectra of compound **21** in pyridine- d_5 recorded at 400 MHz.

between neighboring H-1 and H-4 pairs, we were able to unambiguously establish the connectivities of the cyclic oligosaccharide. For example, the H-1 of group I unit (non-deoxygenated) has a strong correlation with one of the H-4 of the sugar unit of group III (non-deoxygenated), while both H-1's of group III units correlate with H-4's of group IV (deoxygenated) units; and similarly, the H-1's of the group IV units correlate with the H-4's of group II units (deoxygenated). Additionally, when analyzing the anomeric H-1's of group II units, it was found that one of them correlates with H-4 of the group I monosaccharide, and another one correlates with the H-4 of one of the group III unit. These information suggested that the anomeric O-1 of monosaccharide of group I is connected

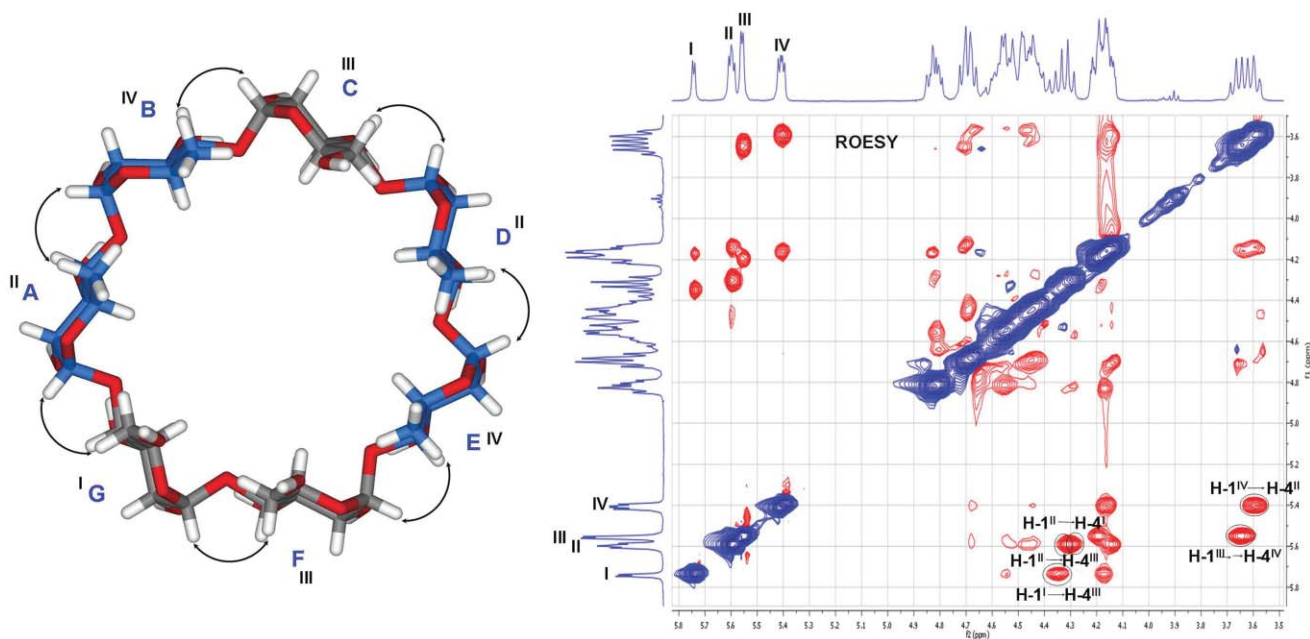


Fig. 2 Analysis of 2D ^1H - ^1H ROESY spectrum of compound **21** in pyridine- d_5 (Sugar units with carbons in blue have a 6-deoxy functionality).

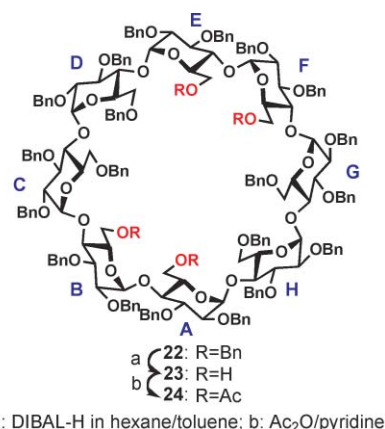
to the C-4 of one of the unit in group III; both anomeric O-1's of the group III are connected to C-4's of group IV and their anomeric O-1's are in turn connected to C-4's of group II; for the anomeric O-1's of group II, one of them is connected to C-4 of group I and another one is connected to C-4 of one of group III unit. The above information allowed us to conclude that the structure of compound **21** is the $6^A, 6^B, 6^D, 6^E$ -tetradeoxygenated β -CD, as shown in Fig. 2. Consequently, the original compound **14** had $6^A, 6^B, 6^D, 6^E$ -*O*-tetradebenzylations.

We noticed that a partially protected analog related to tetraol **14** was previously reported in the literature^{2b} which was synthesized in eight steps with an overall yield of $\sim 8\%$. The present method has clear advantage as it gives similarly tetrasubstituted β -CD in 22% yield in one step.

γ -Cyclodextrin

To further explore the potential of the current method, we attempted to study the one-pot triple and quadruple debenzylations of perbenzylated γ -CD (**22**). Due to the presence of an additional glucopyranosyl unit and three more benzyl groups than β -CD, it was expected that the removal of benzyl groups should be much more complex. Indeed, when we applied similar debenzylation conditions as before, we did not obtain encouraging results. After the treatment of **22** with DIBAL-H in hexane for one day as before, we observed two major spots – which were determined to be the known 6-*O*-mono and the inseparable $6^A, 6^D/6^A, 6^E$ -di-debenzylated γ -CDs. By prolonging the reaction time, we observed several more polar spots which were all found to contain a mixture of different triols from the acetylated products (not shown). The 1D ^1H and 2D GCOSY and GHSQC NMR spectra of all fully acetylated products revealed an absence of signals above 5.0 ppm (except benzyl protons), indicating that these mixtures were all 6-*O*-debenzylated.

The reaction mixture became even more complex when left reacting further (4 days); according to TLC, numerous small components with similar intensities were detected with no visually major spots produced. However, by following our previous knowledge about the polarity of the tetraols, we were able to isolate one product **23** (R_f 0.35, 9 : 1 dichloromethane : acetone) in 8% yield after repeated column chromatographies. Compound **23** was characterized as the $6^A, 6^B, 6^E, 6^F$ -*O*-tetradebenzylated γ -CD as both **23** and its subsequently acetylated form **24** had a C2 symmetry (Scheme 3). Clearly, the triple and quadruple debenzylation of perbenzylated γ -CD has little synthetic advantage due to the extreme low yields and difficulty to isolate products in pure form.



Scheme 3 DIBAL-H mediated quadruple debenzylation of perbenzylated γ -CD.

Rational for the observed regioselectivities

Our results were consistent with the literature reports^{14a} that the DIBAL-H mediated removal of first and second benzyls in all

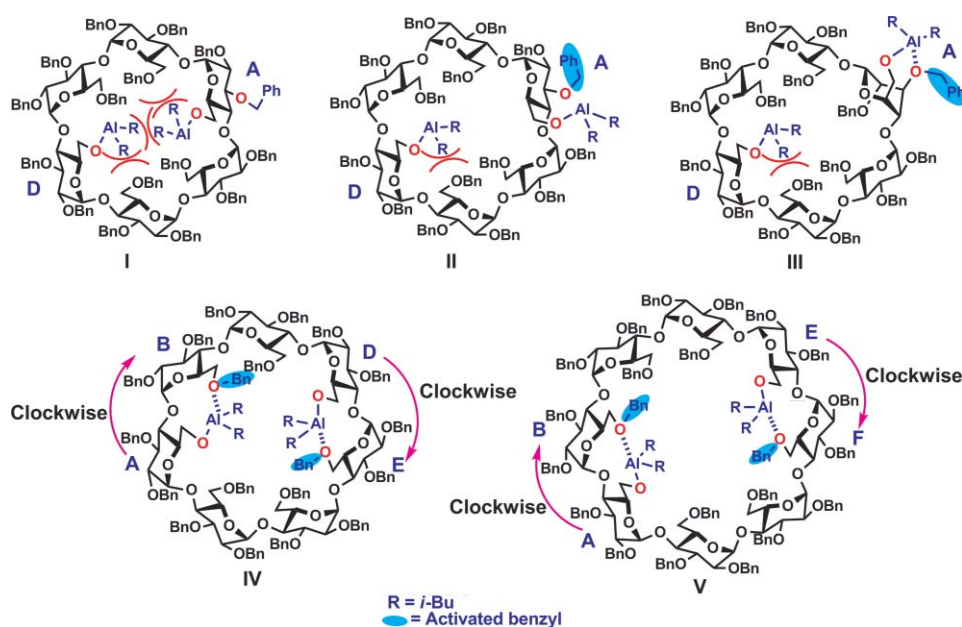


Fig. 3 Proposed rationale for the observed regioselectivities in triple and quadruple debenzylations of CDs.

perbenzylated CDs remained at the primary rim. However, our results also revealed that there are significant differences at the triple and quadruple debenzylation stages where in the case of perbenzylated α -CD (**1**), the DIBAL-H preferred attacking a benzyl group attached to a sterically more hindered secondary hydroxyl, specifically the one attached to the *O*-3 position(s) of the same glucopyranosyl unit which had a prior loss of *O*-6 benzyl; while in the case of perbenzylated β - (**9**) and γ -CDs (**22**), the reducing reagent kept attacking the more accessible benzyl groups at the primary rim. Considering that compound **1** has the smallest cavity size among the three substrates, we think that our results can be rationalized by the steric crowding existing at the primary rim.

As depicted in Fig. 3, in the case of perbenzylated α -CD, because of its smaller cavity and conical shape which bring the benzyl groups at the primary rim closer through space, after the second debenzylation (structure **I**), one of the $\text{OAl}(i\text{-Bu})_2$ groups was pushed out to avoid steric crowding and orients itself towards the outside of the cavity (structure **II**); consequently, the aluminium of the $\text{OAl}(i\text{-Bu})_2$ group becomes spaciouly close to the *O*-3 of the same sugar unit which could dynamically coordinate to the *O*-3 possibly after a ring flip which would bring *O*-3 and *O*-6 even closer (structure **III**). The coordination triggers the polarization of the corresponding benzylic C–O bond; a subsequent attack by hydride on the benzylic methylene carbon from another DIBAL-H molecule (present in excess) causes a regioselective removal of the benzyl at the *O*-3 position of the same unit to produce triol **4**. The other $\text{OAl}(i\text{-Bu})_2$ group can also bind to the *O*-3 of the same ring but to a lesser extent, because of the already decreased crowding, which results in the formation of tetraol **6** in lower yield.

Since the cavity sizes of CD derivatives **9** and **22** were larger, the steric crowding is much less prominent in these cases; thus after the second debenzylation, there was less steric crowding therefore no need for the $\text{OAl}(i\text{-Bu})_2$ to reorientate toward the outside of the

cavity because of the van der Waals attraction between isobutyl and benzyl groups. This is why we observed debenzylations only at the primary rim in both cases.

The preferred formation of **14** and **23** could be explained by involving the respective clockwise coordination by the aluminium of the $\text{O6-Al}(i\text{-Bu})_2$ to the neighboring *O*6 (Fig. 3). In the case of β -CD, after the second removal of 6-*O*-benzyl at the **D**-unit, the aluminium attached at *O*-6's of **A** and **D** units coordinate to the *O*-6's of **B** and **E** units (Structure **IV**), resulting in the formation of $6^{\text{A}}, 6^{\text{B}}, 6^{\text{D}}, 6^{\text{E}}$ -*O*-tetradebenzylated β -CD **14**; at the stage of the third benzyl removal, a mixture of compounds: $6^{\text{A}}, 6^{\text{B}}, 6^{\text{D}}$ -*O*-tridebenzylated (**12**) and $6^{\text{A}}, 6^{\text{B}}, 6^{\text{E}}$ -*O*-tridebenzylated β -CD **13** was formed. In the case of γ -CD, the isolated product $6^{\text{A}}, 6^{\text{B}}, 6^{\text{E}}, 6^{\text{F}}$ -*O*-tetradebenzylated γ -CD **23** originated from one of the didebenzylated intermediates—the $6^{\text{A}}, 6^{\text{E}}$ -*O*-didebenzylated- γ -CD, after a clockwise activation of the neighboring 6-*O*-benzyl groups (Structure **V**). In the case of α -CD, because of its much reduced ring size at the primary face compared to β - and γ -CDs, if a clockwise coordination by the aluminium of the $\text{O6-Al}(i\text{-Bu})_2$ to the neighboring *O*6 occurred after the removal of second benzyl, the van der Waals repulsion between the benzyl groups and *i*-Bu groups might be too significant; therefore, debenzylation path *via* structure **V** became favored. Sollogoub *et al.* were the first to investigate the clockwise debenzylation mechanism^{2b,16} using some bridge-capped and 6-deoxygenated CD derivatives; however, their mechanism did not invoke the clockwise aluminium coordination to the neighboring *O*6, but using the diminished steric crowding argument. We think that in our cases, the clockwise aluminium coordination is more plausible which explains the observed regioselectivity. A molecular model is constructed (Fig. 4) to show the probable intermediate. It is noteworthy that previously, we also observed that in the ^1H NMR spectra of a $6^{\text{A}}, 6^{\text{B}}, 6^{\text{D}}, 6^{\text{E}}$ -tetra-tritylated α -CD compound, the trityl groups shield the anomeric region of the neighboring glucopyranosyl group in a clockwise fashion.^{9c}

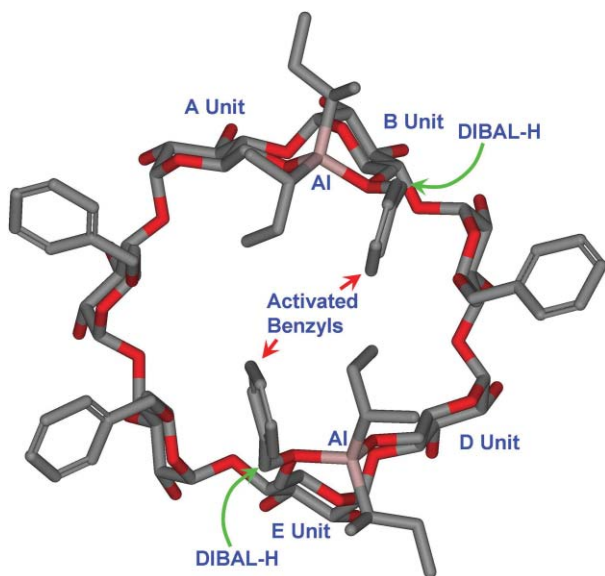


Fig. 4 The molecular model of a possible β -CD intermediate that shows the clockwise coordination by aluminium from the O_6 -Al(*i*-Bu)₂ group in unit A and B, to the neighboring benzylated O_6 (unit B and E). The coordination activates the related benzyl group, which facilitates the attack by another DIBAL-H from the exterior of the cavity. (For clarity, all H atoms and benzyl groups attached to the secondary face were removed.)

In conclusion, we have developed a one-pot synthesis of some multi-substituted CD derivatives, previously unable or difficult to obtain, using DIBAL-H mediated debenzilation. Although the yields for individual CD derivatives were low, the method allowed access to triply and quadruply functionalized α - and β -CD with ease; the short reaction sequence makes the syntheses of these novel CD derivatives feasible and we demonstrated that some compounds could be obtained in gram quantities. The unique topology of these CD derivatives should make them ideal candidates for use as scaffolds in the preparation of diverse supramolecular assemblies.

Experimental section

General methods

Optical rotations were determined in a 5 cm cell at 25 ± 2 °C. $[\alpha]_D$ values are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. Analytical TLC was performed on Silica Gel 60-F₂₅₄ (Merck, Darmstadt) with detection by quenching of fluorescence and/or by charring with 5% sulfuric acid in water or with a ceric ammonium molybdate dip. All commercial reagents were used as supplied unless otherwise stated. Column chromatography was performed on Silica Gel 60 (Silicycle, Ontario). Organic solutions from extractions were dried with anhydrous Na_2SO_4 prior to concentration under vacuum at < 40 °C (bath). ^1H NMR spectra were recorded at 300, and 400 MHz on Bruker spectrometers. The first order proton chemical shifts δ_{H} and δ_{C} are reported in δ (ppm) and referenced to either residual CHCl_3 (δ_{H} 7.24, δ_{C} 77.0, CDCl_3) or residual CD_2HOD (δ_{H} 3.30, δ_{C} 49.5, CD_3OD). ^1H and ^{13}C NMR spectra were assigned with the assistance of GCOSY, GHSQC. Matrix-assisted laser desorption/ionization and time-of-flight mass spectra (MALDI-TOF MS) were recorded on a Bruker Daltonics AUTOFLEX III

spectrometer using 2,5-dihydroxybenzoic acid (DHP) as matrix by the analytical services of the Department of Chemistry, University of Calgary.

2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^C,3^D,3^E,3^F,6^A,6^C,6^D,6^F-Hexadeca-O-benzyl- α -cyclodextrin (4) and 2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^C,3^D,3^F,6^A,6^C,6^D,6^F-hexadeca-O-benzyl- α -cyclodextrin (5)

To a solution of perbenzylated α -CD (**1**, 6.0 g, 2.32 mmol) in anhydrous toluene (36.6 mL), was added a solution of DIBAL-H in hexane (66 mL, 1.4 M solution, 92.4 mmol) with stirring under argon atmosphere at room temperature. The reaction mixture was heated to 50 °C for 4 days and then quenched by pouring the reaction mixture carefully into ice-cold water (40 mL) with vigorous stirring. The reaction mixture was subsequently diluted with more EtOAc (100 mL) and filtered off by passing through a thin bed of celite. This celite was then washed thoroughly with more hot EtOAc (3×30 mL). More H_2O (100 mL) was added to the filtrate and the organic layer was separated. After washing with brine (100 mL) and drying over anhydrous Na_2SO_4 , the organic phase was evaporated. The crude mixture was purified by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 15–40%) as the eluent to afford sequentially diol **3** (278 mg, 5% yield), triol **4** (1.72 g, 32% yield) and tetraol **5** (517 mg, 10% yield) as colorless solids.

Data for α -CD diol 3. R_f 0.50 (hexane:AcOEt 7:3); $[\alpha]_D^{25} +32.6^\circ$ (c 0.9, CHCl_3); ^1H and ^{13}C NMR data are identical to the literature.^{1b}

Data for α -CD triol 4. R_f 0.45 (hexane:AcOEt 6:4); $[\alpha]_D^{25} +42.2^\circ$ (c 0.9, CHCl_3); δ_{H} (400 MHz, CDCl_3) 7.46–7.07 (m, 75H, Aromatic), 5.62 (d, 1H, $J = 4.0$ Hz, H-1), 5.52 (d, 1H, $J = 11.0$ Hz, PhCH), 5.32 (d, 1H, $J = 10.6$ Hz, PhCH), 5.21 (d, 1H, $J = 10.8$ Hz, PhCH), 5.15 (d, 1H, $J = 11.2$ Hz, PhCH), 5.09 (d, 1H, $J = 3.8$ Hz, H-1), 5.01–4.67 (m, 13H, $4 \times$ H-1, $9 \times$ PhCH), 4.59–4.36 (m, 17H, $17 \times$ PhCH), 4.29–4.19 (m, 2H), 4.16–3.53 (m, 30H), 3.48–3.36 (m, 4H), 3.28 (dd, 1H, $J = 3.5, 9.9$ Hz, H-2), 3.10 (brs, 1H, OH), 2.76 (brs, 1H, OH); δ_{C} (100 MHz, CDCl_3) 139.66, 139.63, 139.27, 139.19, 139.16, 138.66, 138.41, 138.19, 138.09, 138.01, 137.93, 137.85, 137.56, 128.50, 128.46, 128.34, 128.30, 128.28, 128.21, 128.15, 128.10, 128.08, 128.06, 127.96, 127.93, 127.89, 127.82, 127.73, 127.68, 127.63, 127.61, 127.58, 127.50, 127.45, 127.33, 127.30, 127.25, 127.03, 126.90, 126.85, 126.54, 100.59, 100.33, 99.16, 98.43, 97.88, 97.80 ($6 \times$ C-1), 82.54, 82.17, 81.60, 81.52, 81.23, 81.14, 80.72, 80.68, 80.56, 79.81, 79.64, 78.67, 78.08, 77.65, 76.43, 76.34, 75.93, 75.81, 75.75, 74.38, 74.05, 73.38, 73.34, 73.34, 73.29, 72.80, 72.71, 72.46, 72.33 (C_{Bn}, C-2, C-3, C-4), 72.17, 72.12, 71.83, 71.61, 71.47, 71.29 ($6 \times$ C-5), 70.03, 69.92, 69.63, 69.33, 61.90, 61.85 ($6 \times$ C-6); m/z (MS MALDI-TOF) calcd for $[\text{C}_{141}\text{H}_{150}\text{O}_{30} + \text{Na}]^+$ 2346.0, found 2346.4.

Data for α -CD tetraol 5. R_f 0.25 (hexane:AcOEt 6:4); $[\alpha]_D^{25} +50.8^\circ$ (c 1.0, CHCl_3); δ_{H} (400 MHz, CDCl_3) 7.51–7.06 (m, 35H, aromatic), 5.44 (d, 1H, $J = 11.2$ Hz, PhCH), 5.24 (d, 1H, $J = 11.2$ Hz, PhCH), 4.94–4.84 (m, 3H, $2 \times$ PhCH + H-1), 4.83–4.70 (m, 4H, $2 \times$ PhCH, H-1), 4.61 (d, 1H, $J = 13.0$ Hz, PhCH), 4.53 (m, 2H, PhCH), 4.46–4.38 (m, 3H, PhCH), 4.35 (d, 1H, $J = 13.0$ Hz, PhCH), 4.29 (dd, 1H, $J = 9.33, 9.70$ Hz, H-3), 4.23 (d, 1H, $J = 13.0$ Hz, PhCH), 4.17 (dd, 1H, $J = 9.16, 8.56$ Hz, H-3), 4.04–3.94 (m, 2H, H-3, H-6), 3.90–3.72 (m, 6H, $3 \times$ H-5, $2 \times$ H-4,

1 × H-6), 3.71–3.56 (m, 5H, 4 × H-6, 1 × H-2), 3.45–3.35 (m, 2H, H-4, H-2), 3.29 (dd, 1H, $J = 3.4, 10.0$ Hz, H-2); δ_c (100 MHz, CDCl₃) 139.71, 139.46, 138.57, 138.46, 138.08, 138.06, 137.24, 128.78, 128.56, 128.33, 128.31, 128.22, 128.19, 128.14, 128.10, 127.93, 127.87, 127.82, 127.70, 127.61, 127.57, 127.46, 127.26, 127.15, 127.01, 126.83, 101.69 (C-1), 100.75 (C-1), 99.92 (C-1), 83.46 (C-4), 82.41 (C-4), 82.10 (C-4), 81.11 (C-3), 80.42 (C-3), 79.10 (C-2), 78.56 (C-2), 77.12 (C-2), 76.29 (PhCH), 75.73 (PhCH), 74.45 (PhCH), 73.44 (PhCH), 73.34 (PhCH), 72.92 (C-3), 72.45 (PhCH), 72.28 (PhCH), 72.13 (C-5), 71.93 (C-5), 71.04 (C-5), 69.73 (C-6), 69.25 (C-6), 61.78 (C-6); m/z (MS MALDI-TOF) calcd for [C₁₃₄H₁₄₅O₃₀ + H]⁺ 2234.0, found 2234.3.

3^A,6^A,6^P-Tri-*O*-acetyl-2^A,2^B,2^C,2^D,2^E,2^F,3^B,3^C,3^D,3^E,3^F,6^B,6^C,6^E,6^F-hexadeca-*O*-benzyl- α -cyclodextrin (6)

To the solution of triol **4** (232 mg, 0.1 mmol) in dry dichloromethane (2 mL) was added Ac₂O (0.5 mL), anhydrous pyridine (0.5 mL) and a catalytic amount of 4-*N,N*-dimethylaminopyridine, and the reaction mixture was stirred for 6 h at room temperature. The reaction was monitored by TLC, and when the reaction was complete, the mixture was concentrated under reduced pressure to afford syrup which was purified by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 10–25%) as eluent to give compound **6** (225 mg, 92% yield) as a white solid. R_f 0.65 (hexane:AcOEt 7:3); $[\alpha]_D^{25} +23.7^\circ$ (c 1.7, CHCl₃); δ_H (400 MHz, CDCl₃) 7.45–7.10 (m, 75H), 5.74 (dd, 1H, $J = 10.0, 9.6$ Hz, H-3), 5.35 (d, 1H, $J = 11.3$ Hz, PhCH), 5.32 (d, 1H, $J = 11.0$ Hz, PhCH), 5.26 (d, 1H, $J = 11.0$ Hz, PhCH), 5.22 (d, 1H, $J = 11.2$ Hz, PhCH), 5.11 (d, 1H, $J = 10.9$ Hz, PhCH), 5.10 (d, 1H, $J = 3.5$ Hz, H-1), 5.02–4.84 (m, 9H, 5 × PhCH, 4 × H-1), 4.73 (d, 1H, $J = 13.0$ Hz, PhCH), 4.63–4.55 (m, 2H, PhCH, H-1), 4.55–4.20 (m, 25H, 18 × PhCH, 4 × H-6, 3 × H-3), 4.18–3.95 (m, 8H, 4 × H-5, H-6, 3 × H-3), 3.87 (m, 7H, 2 × H-6, 2 × H-5, 3 × H-4), 3.78–3.63 (m, 4H, 3 × H-6, H-4), 3.62–3.53 (m, 3H, 2 × H-6, H-4), 3.49–3.36 (m, 6H, 6 × H-2), 1.97 (s, 3H, COCH₃), 1.92 (s, 3H, COCH₃), 1.92 (s, 3H, COCH₃); δ_c (100 MHz, CDCl₃) 170.72, 170.35, 170.16 (3 × C=O), 140.07, 140.04, 139.77, 139.61, 138.78, 138.69, 138.56, 138.51, 138.36, 138.31, 138.23, 138.22, 138.18, 138.13, 128.43, 128.33, 128.30, 128.29, 128.18, 128.13, 128.06, 128.05, 128.01, 127.96, 127.91, 127.82, 127.75, 127.72, 127.70, 127.65, 127.56, 127.53, 127.47, 127.43, 127.38, 127.18, 127.13, 127.07, 126.83, 126.78, 126.62, 126.53, 101.36, 101.08, 100.67, 100.24, 100.21, 99.89 (6 × C-1), 82.07, 81.94, 81.74, 81.62, 80.50, 80.37, 80.32, 80.13, 80.08, 79.36, 78.99, 78.81, 78.73, (5 × C-2, 5 × C-3, 6 × C-4), 76.41, 76.06, 75.96, 75.76, 75.02, 74.21, 73.34, 73.25, 72.95, 72.39, 72.22, 72.18, 72.14 (C_{Bn}), 1 × C-5, 1 × C-2), 71.78, 71.59, 71.53, 71.38, 69.96, 69.82 (5 × C-5, 1 × C-3), 69.16 (2 × C-6), 68.96 (C-6), 68.86 (C-6), 63.74 (C-6), 62.94 (C-6), 21.32, 20.94, 20.89 (3 × CH₃); m/z (MS MALDI-TOF) calcd for [C₁₄₇H₁₅₆O₃₃ + Na]⁺ 2472.0, found 2472.1.

3^A,3^D,6^A,6^P-Tetra-*O*-acetyl-2^A,2^B,2^C,2^D,2^E,2^F,3^B,3^C,3^D,3^E,3^F,6^B,6^C,6^E,6^F-hexadeca-*O*-benzyl- α -cyclodextrin (7)

To a solution of tetraol **5** (112 mg, 0.05 mmol) in dry dichloromethane (1.0 mL) was added Ac₂O (0.3 mL), anhydrous pyridine (0.3 mL) and a catalytic amount of 4-*N,N*-

dimethylaminopyridine, and the reaction mixture was stirred for 6 h at room temperature. The reaction was monitored and worked up as **6**. Compound **7** was obtained by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 10–25%) as eluent to give compound **7** as colorless solid (108 mg, yield 90%). R_f 0.65 (hexane:AcOEt 7:3); $[\alpha]_D^{25} +39.3^\circ$ (c 0.6, CHCl₃); δ_H (400 MHz, CDCl₃) 7.39–7.11 (m, 35H, aromatic), 5.80 (t, 1H, $J = 9.9$ Hz, H-3), 5.28 (d, 1H, $J = 11.9$ Hz, PhCH), 5.17 (d, 1H, $J = 11.5$ Hz, PhCH), 4.96 (d, 1H, $J = 3.1$ Hz, H-1), 4.94 (d, 1H, $J = 11.3$ Hz, PhCH), 4.90 (d, 1H, $J = 3.1$ Hz, H-1), 4.85 (d, 1H, $J = 11.7$ Hz, PhCH), 4.67 (d, 1H, $J = 13.0$ Hz, PhCH), 4.58 (d, 1H, $J = 13.2$ Hz, PhCH), 4.57 (d, 1H, $J = 3.1$ Hz, H-1), 4.55–4.46 (m, 2H, PhCH, H-6), 4.46–4.38 (m, 3H, 3 × PhCH), 4.34 (d, 1H, $J = 11.7$ Hz, PhCH), 4.30–4.18 (m, 3H, 2 × PhCH, H-6), 4.17–4.02 (m, 4H, 2 × H-3, H-5, PhCH), 3.98–3.74 (m, 6H, 2 × H-4, 2 × H-5, 2 × H-6), 3.66 (br d, 1H, $J = 9.7$ Hz, H-6), 3.60–3.51 (m, 2H, H-4, H-6), 3.39 (dd, 1H, $J = 3.1, 9.8$ Hz, H-2), 3.36 (dd, 1H, $J = 2.9, 10.2$ Hz, H-2), 3.32 (dd, 1H, $J = 3.1, 10.4$ Hz, H-2), 1.92 (s, 3H, COCH₃), 1.88 (s, 3H, COCH₃); δ_c (100 MHz, CDCl₃) 170.19, 169.97 (2 × C=O), 140.17, 140.12, 138.83, 138.57, 138.31, 138.29, 138.17, 128.38–126.47, 101.74 (C-1), 101.04 (C-1), 100.45 (C-1), 82.47 (C-4), 80.43 (C-4), 80.37 (C-2), 80.05 (C-3), 79.80 (C-3), 78.77 (C-2), 76.50 (C-2), 75.91 (PhCH), 75.49 (PhCH), 74.00 (PhCH), 73.29 (PhCH), 73.20 (PhCH), 72.19 (C-5), 72.16 (PhCH), 71.81 (PhCH), 71.44 (C-5), 71.26 (C-3), 69.94 (C-5), 69.17 (C-6), 68.71 (C-6), 63.11 (C-6), 21.16 (CH₃), 20.89 (CH₃); m/z (MS MALDI-TOF) calcd for [C₁₄₂H₁₅₂O₃₄ + Na]⁺ calcd 2424.0, found 2424.0.

3^A,6^A,6^P-Tri-*O*-acetyl- α -cyclodextrin (8)

The perbenzylated derivative **6** (122 mg, 0.05 mmol) was dissolved in a mixture of THF–H₂O (3:1, 5 mL) and was stirred with 10% Pd–C (50 mg) under a hydrogen atmosphere overnight. The insoluble Pd–C was removed by filtration through celite and evaporation of the solvent under reduced pressure gave pure compound **8** (52 mg, quantitative yield). $[\alpha]_D^{25} +134.7^\circ$ (c 1.4, CH₃OH); δ_H (400 MHz, CD₃OD) 5.38 (dd, 1H, $J = 9.2, 9.7$ Hz, H-3), 5.01 (d, 1H, $J = 3.5$ Hz, H-1), 4.98–4.91 (m, 4H, 4 × H-1), 4.79 (d, 1H, $J = 3.3$ Hz, H-1), 4.66 (br d, 1H, $J = 10.8$ Hz, H-6), 4.58 (br d, 1H, $J = 10.8$ Hz, 1H, H-6), 4.36 (dd, 1H, $J = 6.0, 12.1$ Hz, H-6), 4.22 (dd, 1H, $J = 6.6, 11.9$ Hz, H-6), 4.16–4.09 (m, 1H, H-5), 4.09–4.02 (m, 1H, H-5), 4.02–3.78 (m, 17H), 3.67–3.38 (m, 12H), 2.11 (s, 3H, COCH₃), 2.10 (s, 3H, COCH₃), 2.09 (s, 3H, COCH₃); δ_c (100 MHz, CD₃OD) 172.36, 171.44, 171.42 (3 × CO), 102.49, 102.46, 102.43, 102.11, 102.02, 101.68 (6 × C-1), 82.45, 82.11, 82.08, 82.01, 81.28, 79.98 (6 × C-2), 73.90, 73.81, 73.77, 73.74, 72.62, 72.50, 72.44, 72.33, 72.25, 72.23, 72.14, 71.49, 70.97, 70.24, 69.67 (C-3's, C-4's, C-5's), 63.83 (C-6_OAc), 63.67 (C-6_OAc), 60.51, 60.46, 60.39, 60.17 (4 × C-6_OH), 20.40 (CH₃), 19.40 (2 × CH₃); m/z (MS MALDI-TOF) calcd for [C₄₂H₆₆O₃₃ + Na]⁺ 1121.3, found 1121.3; calcd for [C₄₂H₆₆O₃₃ + K]⁺ 1137.3, found 1137.2.

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^E-Hexadeca-*O*-benzyl- β -cyclodextrin (14)

To a solution of perbenzylated β -cyclodextrin **9** (5.0 g, 1.653 mmol) in anhydrous toluene (26.5 mL), was added a solution of

DIBAL-H in hexane (47 mL, 1.4 M solution, 66.1 mmol) with stirring under an atmosphere of argon at room temperature. The reaction mixture was heated to 50 °C for 4 days and then quenched by slowly pouring the reaction mixture into ice-cold water (35 mL) with vigorous stirring. The reaction mixture was diluted with EtOAc (80 mL) and filtered through celite. This celite was then washed thoroughly with hot EtOAc (3 × 25 mL). More water (100 mL) was added to the filtrate and the organic layer was separated and washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 10–50%) as eluent to afford sequentially the diol **11** (376 mg, 8% yield) and two major fractions. The less polar fraction (*R_f* 0.45, dichloromethane : acetone 85 : 15), possibly **12** and **13**, as confirmed from the acetylated products (see below) contained an inseparable mixture of two triols (1.138 g, 25% yield); the more polar fraction is the tetraol **14** (969 mg, 22% yield).

Data for β-CD diol 11. *R_f* 0.50 (hexane : AcOEt 7 : 3); $[\alpha]_D^{25} +34.8^\circ$ (*c* 1.2, CHCl₃); ¹H and ¹³C NMR data are identical to the literature.^{1b}

Data for β-CD tetraol 14. *R_f* 0.25 (ethyl acetate : hexane 1 : 1); *R_f* 0.30 (dichloromethane : acetone 85 : 15); $[\alpha]_D^{25} +25.4^\circ$ (*c* 0.3, CHCl₃); δ_H (400 MHz, CDCl₃) 7.37–7.01 (m, 85H, Ar-H), 5.42 (d, 1H, *J* = 3.7 Hz, H-1), 5.34 (d, 1H, *J* = 3.8 Hz, H-1), 5.17 (m, 4H, H-1, 3 × PhCH), 5.03 (d, 1H, *J* = 3.5 Hz, H-2), 4.98–4.87 (m, 3H, H-1, 2 × PhCH), 4.83–4.34 (m, 31H, PhCH), 4.08–3.59 (m, 35H, H-3, 7 × H-4, 7 × H-5, 7 × H-6, 7 × H-6'), 3.51 (m, 4H, 4 × H-2), 3.42 (dd, 1H, *J* = 9.7, 3.5 Hz, H-2), 3.39–3.32 (m, 2H, 2 × H-2), 3.03 (dd, 1H, *J* = 5.3, 5.3 Hz, OH-6), 2.79 (dd, 1H, *J* = 5.6, 5.6 Hz, OH-6), 2.68 (dd, 1H, *J* = 6.2, 6.2 Hz, OH-6), 2.48 (dd, 1H, *J* = 6.5, 6.5 Hz, OH-6); δ_C (100 MHz, CDCl₃) 139.39, 139.25, 139.20, 139.08, 138.93, 138.81, 138.58, 138.49, 138.36, 138.22, 138.17, 138.08, 138.03, 137.78, 128.37, 128.33, 128.31, 128.25, 128.22, 128.15, 128.11, 128.03, 127.98, 127.90, 127.82, 127.74, 127.69, 127.58, 127.53, 127.26, 127.21, 127.04, 127.00, 126.89, 98.71, 98.61, 98.24, 98.21, 97.98, 97.82, 97.68 (7 × C-1) 81.12, 80.85, 80.78, 80.69, 80.61, 80.47, 80.39, 80.23, 79.34, 79.26, 79.20, 78.78, 78.66, 78.19, 77.83, 76.65, 76.34, 76.21, 76.09, 75.63, 75.59, 75.40, 74.97, 74.78, 74.37, 73.46, 73.36, 73.07, 72.79, 72.75, 72.64, 72.61, 72.39, 72.00, 71.84, 71.77, 71.73 (PhCH, C-3's, C-4's, C-5's, C-6's), 69.41, 69.35, 69.29, 62.15, 62.10, 61.96, 61.82 (7 × C-2); *m/z* (MS MALDI-TOF) calcd for [C₁₆₁H₁₇₂O₃₅ + Na]⁺ 2688.2, found 2688.0.

Acetylation of the less polar fraction. The 1 : 1 mixture (200 mg) was acetylated for 6 h as **4** to afford an inseparable mixture (presumably **15** and **16**) by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 10–30%) (167 mg, yield 80%). *R_f* 0.45 (EtOAc : hexane 4 : 6); characteristic NMR data: δ_H (400 MHz, CDCl₃) 2.01 (s, 3H, COCH₃), 1.99 (s, 3H, COCH₃), 1.99 (s, 3H, COCH₃), 1.98 (s, 3H, COCH₃), 1.95 (s, 3H, COCH₃), 1.94 (s, 3H, COCH₃); δ_C (100 MHz, CDCl₃) 170.39, 170.37, 170.34, 170.31, 170.25 (2 × C) (CO), 20.95, 20.89, 20.86, 20.80; *m/z* (MS MALDI-TOF) calcd for [C₁₇₄H₁₈₄O₃₈ + Na]⁺ 2904.2, found 2903.8.

6^A,6^B,6^D,6^E-Tetra-*O*-acetyl-2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^C,3^D,3^E,3^F,3^G-6^C,6^F,6^G-heptadeca-*O*-benzyl-β-cyclodextrin (**17**)

The pure β-CD tetraol **14** (200 mg, 0.075 mmol) was acetylated with Ac₂O (0.5 mL) in a mixture of anhydrous dichloromethane (2 mL) and anhydrous pyridine (0.5 mL) in the presence of a catalytic amount of 4-*N,N*-dimethylaminopyridine as before. The tetraacetate **17** (182 mg, yield 86%) was obtained as a white solid after column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 15–35%) as eluent. *R_f* 0.40 (EtOAc : hexane 4 : 6); $[\alpha]_D^{25} +20.4^\circ$ (*c* 0.4, CHCl₃); δ_H (400 MHz, CDCl₃) 7.36–7.01 (m, 85H, Ar-H), 5.37–5.23 (m, 4H, 2 × H-1, 2 × PhCH), 5.21 (d, 1H, *J* = 10.6 Hz, PhCH), 5.07 (d, 1H, *J* = 3.7 Hz, H-1), 5.05 (d, 1H, *J* = 3.5 Hz, H-1), 5.04–4.93 (m, 5H, 3 × H-1, 2 × PhCH), 4.84–4.73 (m, 9H, 9 × PhCH), 4.69–4.33 (m, 26H, 20 × PhCH, 6 × H-6), 4.31–4.25 (m, 2H, 2 × H-6), 4.23–3.97 (m, 17H, 3 × H-4, 3 × H-6, 4 × H-5, 7 × H-3), 3.92 (br d, 1H, *J* = 8.4 Hz, H-5), 3.88–3.68 (m, 6H, 4 × H-4, 2 × H-5), 3.66–3.58 (m, 3H, 3 × H-6), 3.57–3.45 (m, 5H, 5 × H-2), 3.45–3.39 (m, 2H, 2 × H-2), 2.01 (s, 3H, COCH₃), 1.99 (s, 3H, COCH₃), 1.99 (s, 3H, COCH₃), 1.94 (s, 3H, COCH₃); δ_C (100 MHz, CDCl₃) 170.39 (2 × CO), 170.37 (CO), 170.36 (CO), 139.43, 139.28, 139.26, 139.22, 139.17, 138.99, 138.95, 138.63, 138.55, 138.49, 138.34, 138.28, 138.26, 138.17, 138.12, 128.32, 128.28, 128.25, 128.22, 128.17, 128.16, 128.13, 128.11, 128.06, 128.02, 127.98, 127.94, 127.92, 127.87, 127.82, 127.79, 127.73, 127.64, 127.61, 127.51, 127.49, 127.42, 127.15, 127.09, 126.83, 99.19 (C-1), 98.93 (C-1), 98.81 (C-1), 98.63 (C-1), 98.37 (C-1), 98.30 (C-1), 98.23 (C-1), 80.95, 80.87, 80.58, 80.48, 79.80, 79.70, 79.22, 79.03, 78.60, 76.29 (PhCH), 76.16 (PhCH), 75.67 (PhCH), 74.90 (PhCH), 73.43 (PhCH), 73.36 (PhCH), 73.24 (PhCH), 73.20 (PhCH), 72.85 (PhCH), 72.82 (PhCH), 72.75 (PhCH), 72.43 (PhCH), 72.22 (PhCH), 71.79 (C-5), 71.72 (C-5), 71.57 (C-5), 69.83 (C-5), 69.59 (C-5), 69.48 (C-5), 69.32 (C-5), 68.84 (C-6), 68.75 (C-6), 68.58 (C-6), 63.68 (C-6_OAc), 63.59 (C-6_OAc), 63.48 (C-6_OAc), 63.42 (C-6_OAc), 20.91 (CH₃), 20.86 (CH₃), 20.83 (CH₃), 20.72 (CH₃); *m/z* (MS MALDI-TOF) calcd for [C₁₆₉H₁₈₀O₃₉ + Na]⁺ 2856.2, found 2856.0.

6^A,6^B,6^D,6^E-Tetra-*O*-acetyl-β-cyclodextrin (**18**)

Compound **18** was obtained in a similar fashion as **8** (yield: quantitative). δ_H (400 MHz, CD₃OD) 5.04–4.92 (m, 7H, 7 × H-1), 4.67–4.40 (m, 4H, 4 × H-6a_OAc), 4.30–4.08 (m, 4H, 4 × H-6b_OAc), 4.05–3.69 (m, 20H, 7 × H-5, 7 × H-3, 3 × H-6a_OH, 3 × H-6b), 3.63–3.37 (m, 14H, 7 × H-2, 7 × H-4), 2.10 (s, 6H, 2 × Ac), 2.07 (s, 6H, 2 × Ac); δ_C (100 MHz, CD₃OD) 171.45 (CO), 171.39 (CO), 171.29 (CO), 171.26 (CO), 103.01, 103.00, 102.72, 102.71, 102.40, 102.21, 102.04 (7 × C-1), 82.76, 82.73, 82.36, 82.35, 81.89, 81.27, 81.24, 73.46, 73.40, 73.38, 73.32, 73.26, 73.17, 72.89, 72.77, 72.63, 72.38, 72.29, 69.65, 69.60, 69.55, 63.53 (× 3, C-6_OAc), 63.44 (C-6_OAc), 60.45 (C-6_OH), 60.07 (C-6_OH), 59.95 (C-6_OH), 19.40 (× 2, Ac), 19.36 (× 2, Ac); *m/z* (MS MALDI-TOF) calcd for [C₅₀H₇₈O₃₉ + Na]⁺ 1325.4, found 1325.1.

6^A,6^B,6^D,6^E-Tetra-*O*-methanesulfonyl-2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^C,3^D,3^E,3^F,3^G,6^C,6^F,6^G-heptadeca-*O*-benzyl-β-cyclodextrin (**19**)

To the clear solution of tetraol **14** (156 mg, 0.0585 mmol) in anhydrous dichloromethane (4 mL) and triethylamine (0.0652 mL, 0.469 mmol, 8 eq), was added methanesulfonyl chloride (0.024 mL,

0.305 mmol, 5.2 eq) at 0 °C, and the reaction was continued at 15 °C for 4 h. The reaction was quenched with a few drops of cold water. More dichloromethane (20 mL) was added, and the organic solution was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 20–45%) as the eluent to afford pure tetramesylate **19** as a colorless solid (146 mg, yield 84%). *R_f* 0.30 (hexane : AcOEt 6 : 4); δ_H (400 MHz, CDCl₃) 7.37–6.92 (m, 85H, 17 × Ph), 5.45 (d, 1H, *J* = 3.8 Hz, H-1), 5.31 (d, 1H, *J* = 10.5 Hz, CHPh), 5.25 (d, 1H, *J* = 11.3 Hz, CHPh), 5.22 (d, 1H, *J* = 4.7 Hz, H-1), 5.20–5.16 (m, 2H, H-1, CHPh), 5.02 (d, 1H, *J* = 10.9 Hz, CHPh), 4.99 (d, 1H, *J* = 3.7 Hz, H-1), 4.98 (d, 1H, *J* = 3.6 Hz, H-1), 4.93 (d, 1H, *J* = 3.4 Hz, H-1), 4.91 (d, 1H, *J* = 3.4 Hz, H-1), 4.92–4.87 (m, 1H, CHPh), 4.81–4.27 (m, 29H, CHPh), 4.21–3.54 (m, 35H, 7 × H-3, 7 × H-4, 7 × H-5, 7 × H-6, 7 × H-6'), 3.52 (d, 1H, *J* = 3.7 Hz, H-2), 3.49 (dd, 1H, *J* = 5.5, 3.8 Hz, H-2), 3.47–3.44 (m, 2H, 2 × H-2), 3.44–3.41 (m, 1H, H-2), 3.38 (dd, 1H, *J* = 3.1, 2.5 Hz, H-2), 3.36 (dd, 1H, *J* = 3.2, 2.4 Hz, H-2), 2.93 (s, 3H, SO₂CH₃), 2.90 (s, 3H, SO₂CH₃), 2.87 (s, 6H, 2 × SO₂CH₃); δ_C (100 MHz, CDCl₃) 139.36, 139.20, 139.16, 139.15, 139.04, 138.81, 138.78, 138.59, 138.42, 138.38, 138.26, 138.23, 138.19, 138.01, 137.90, 137.77, 128.38, 128.35, 128.33, 128.24, 128.18, 128.15, 128.12, 128.05, 128.03, 127.98, 127.92, 127.86, 127.77, 127.73, 127.67, 127.58, 127.54, 127.48, 127.43, 127.33, 127.17, 127.16, 127.13, 127.09, 127.06, 126.94, 126.86, 126.66, 98.94, 98.84, 98.76, 98.60, 98.28, 98.21, 97.94 (7 × C-1), 80.91, 80.74, 80.67, 80.60, 80.47, 80.14, 79.74, 79.11, 78.97, 78.20, 77.88, 76.66, 76.33, 76.31, 76.08, 75.66, 75.30, 74.66, 73.48, 73.43, 73.36, 73.26, 72.89, 72.73, 72.43, 72.02, 71.76, 71.46, 69.59, 69.28, 69.16, 69.06, 68.98, 37.25, 37.13, 37.07, 37.03 (4 × SO₂CH₃); *m/z* (HRMS MALDI-TOF) calcd for [C₁₆₅H₁₈₀O₄₃S₄ + Na]⁺ 3000.06734, found 3000.06823.

6^A,6^B,6^D,6^E-Tetradecyloxy-2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^C,3^D,3^E,3^F,3^G,6^C,6^F,6^G-heptadeca-*O*-benzyl-β-cyclodextrin (20)

To the clear solution of the tetramesylate **19** (140 mg, 0.0486 mmol) in anhydrous tetrahydrofuran (4 mL), was added lithium aluminium hydride (14.8 mg, 0.389 mmol, 8 eq), and the reaction was continued at room temperature for 15 h. The excess amount of hydride was destroyed by AcOEt (0.5 mL) and the mixture was evaporated to dryness, and the residue was re-dissolved in dichloromethane (15 mL) and the solution was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na₂SO₄ and evaporated. The crude material was purified by column chromatography on silica gel using a mixture of AcOEt in hexane (gradient 10–20%) as the eluent to afford pure tetradecyloxy **20** (98.5 mg, yield 78%). *R_f* 0.4 (hexane : AcOEt 7 : 3); δ_H (400 MHz, CDCl₃) 7.23–7.03 (m, 85H, 17 × Ph), 5.27–5.22 (m, 2H, CHPh), 5.21 (d, 1H, *J* = 3.7 Hz, H-1), 5.18 (d, 1H, *J* = 3.8 Hz, H-1), 5.13 (d, 1H, *J* = 10.9 Hz, CHPh), 5.08 (d, 1H, *J* = 11.1 Hz, CHPh), 5.04 (d, 2H, *J* = 3.7 Hz, 2 × H-1), 4.99 (d, 1H, *J* = 3.5 Hz, H-1), 4.94–4.88 (m, 3H, H-1, 2 × CHPh), 4.85 (d, 1H, *J* = 3.4 Hz, H-1), 4.83–4.36 (m, 28H, CHPh), 4.16–3.59 (m, 27H, 7 × H-3, 7 × H-4, 7 × H-5, 3 × H-6, 3 × H-6'), 3.56–2.72 (m, 7H, 7 × H-2), 1.33 (d, 1H, *J* = 6.2 Hz, CH₃), 1.28 (d, 1H, *J* = 5.8 Hz, CH₃), 1.27 (d, 1H, *J* = 6.0 Hz, CH₃), 1.25 (d, 1H, *J* = 6.4 Hz, CH₃); *m/z* (HRMS MALDI-TOF) calcd for [C₁₆₁H₁₇₂O₃₁ + Na]⁺ 2624.1780, found 2624.1775.

6^A,6^B,6^D,6^F-Tetradecyloxy-β-cyclodextrin (21)

Compound **20** (90 mg, 0.0346 mmol) in a mixture of tetrahydrofuran–H₂O (3 : 1, 4 mL), was hydrogenated in the presence of 10% Pd–C (35 mg) as **8** to give pure compound **21** (34 mg, quantitative yield). [α]_D²⁵ +85.3° (*c* 0.2, CH₃OH); δ_H (400 MHz, pyridine-*d*₅) 5.74 (d, 1H, *J* = 3.5 Hz, H-1), 5.60 (d, 1H, *J* = 3.5 Hz, H-1), 5.58 (d, 1H, *J* = 3.6 Hz, H-1), 5.55 (d, 2H, *J* = 3.1 Hz, 2 × H-1), 5.41 (d, 1H, *J* = 3.8 Hz, H-1), 5.40 (d, 1H, *J* = 3.7 Hz, H-1), 4.86–4.78 (m, 3H, 3 × H-3), 4.73–4.65 (m, 4H, 4 × H-3), 4.62–4.39 (m, 13H, 7 × H-5, 3 × H-6, 3 × H-6'), 4.35 (dd, 1H, *J* = 9.2 Hz, H-4), 4.31 (dd, 2H, *J* = 9.3 Hz, 2 × H-4), 4.23–4.12 (m, 7H, 7 × H-2), 3.66 (dd, 1H, *J* = 8.6 Hz, H-4), 3.64 (dd, *J* = 8.6 Hz, 1H, H-4), 3.60 (overlap two dd, *J* = 9.0 Hz, 2H, 2 × H-4), 1.73 (d, 3H, *J* = 6.2 Hz, -CH₃), 1.68 (d, 3H, *J* = 6.2 Hz, -CH₃), 1.58 (d (two overlapping), 6H, *J* = 6.2 Hz, 2 × -CH₃); δ_C (100 MHz, pyridine-*d*₅) 104.62, 104.60, 104.31, 104.28, 104.01, 103.91, (7 × C-1), 90.25, 90.22, 90.13, 90.05 (4 × C-4), 83.67, 83.52, 83.38 (3 × C-4), 75.12, 75.07, 74.81, 74.79, 74.76, 74.69 (7 × C-2, 7 × C-3), 74.43, 74.40, 74.34 (3 × C-5), 68.58, 68.46, 68.39, 68.36 (4 × C-5), 62.02, 61.92, 61.83 (3 × C-6), 18.72, 18.62, 18.59 (4 × CH₃); *m/z* (MS MALDI-TOF) calcd for [C₄₂H₇₀O₃₁ + Na]⁺ 1093.4, found 1093.0.

2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^B,3^C,3^D,3^E,3^F,3^G,3^H,6^A,6^B,6^E,6^F-Eicosa-*O*-benzyl-γ-cyclodextrin (23)

To a solution of perbenzylated γ-cyclodextrin **22** (3.0 g, 0.868 mmol) in anhydrous toluene (13.5 mL) was added a solution of DIBAL-H (25 mL, 1.4 M solution in hexane, 34.7 mmol) with stirring under argon atmosphere, and the mixture was heated to 50 °C for 4 days and then quenched by pouring the reaction mixture into ice-cold water (40 mL). The spot with an *R_f* 0.35 (dichloromethane : acetone, 9 : 1) was isolated by repeated column chromatographies on silica gel using a mixture of AcOEt in hexane (gradient 15–50%), and then repurification using a mixture of dichloromethane : acetone 9 : 1 as eluent to afford **23** (215 mg, 8% yield). *R_f* 0.35 (dichloromethane : acetone 9 : 1); [α]_D²⁵ +40.0° (*c* 0.4, CHCl₃); δ_H (400 MHz, CDCl₃) 7.38–7.07 (m, 50H, Ar-H), 5.36 (d, 1H, *J* = 3.5, H-1), 5.25–5.20 (m, 2H, H-1, PhCH), 5.12–5.03 (m, 1H, PhCH), 4.91 (d, 1H, *J* = 3.5, H-1), 4.87 (d, 1H, *J* = 3.5, H-1), 4.84–4.37 (m, 23H), 4.09–3.61 (m, 26H), 3.58–3.51 (m, 2H), 3.49 (dd, 1H, *J* = 9.1, 3.5, H-2), 3.36 (dd, 1H, *J* = 9.6, 3.4, H-2), 3.26 (s, 1H, OH), 2.59 (s, 1H, OH); δ_C (100 MHz, CDCl₃) 139.53, 139.14, 138.70, 138.63, 138.34, 138.20, 138.14, 137.90, 128.43, 128.38, 128.32, 128.29, 128.27, 128.22, 128.15, 128.12, 128.09, 128.00, 127.87, 127.79, 127.74, 127.69, 127.63, 127.55, 127.43, 127.18, 127.02, 126.85, 98.44, 98.26, 97.93, 97.53 (C-1), 81.19, 80.87, 80.35, 80.24, 79.53, 78.95, 78.10, 76.15, 76.01, 75.93, 75.27, 74.78, 74.12, 73.46, 73.35, 73.30, 72.85, 72.78, 72.62, 72.45, 72.14, 71.69, 71.35, 68.92, 68.82, 62.07, 61.64 (C-6); *m/z* (MS MALDI-TOF) calcd for [C₁₈₈H₂₀₀O₄₀ + Na]⁺ 3120.3, found 3120.0.

6^A,6^B,6^E,6^F-Tetra-*O*-acetyl-2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^C,3^D,3^E,3^F,3^G,3^H,6^C,6^D,6^G,6^H-eicosa-*O*-benzyl-γ-cyclodextrin (24)

The tetraol **23** (155 mg, 0.05 mmol) was acetylated in a similar fashion as before to afford the desired tetraacetate **24** after column chromatography on silica gel using a mixture of

AcOEt–hexane (gradient 10–20%) as eluent (140 mg, 86% yield). R_f 0.40 (EtOAc:hexane 4:6); $[\alpha]_D^{25} +26.6^\circ$ (c 0.2, CHCl_3); δ_H (400 MHz, CDCl_3) 7.44–7.02 (m, 50H, Ar-H), 5.46 (d, 1H, $J = 10.6$, PhCH), 5.37 (d, 1H, $J = 10.6$, PhCH), 5.24 (d, 1H, $J = 3.7$, H-1), 5.11 (d, 1H, $J = 3.5$, H-1), 5.08 (d, 1H, $J = 3.1$, H-1), 5.04 (d, 1H, $J = 3.5$, H-1), 4.97 (2 × d, 2H, $J = 11.0$, PhCH), 4.90–4.77 (m, 4H, PhCH), 4.61–4.41 (m, 12H), 4.31–3.91 (m, 14H), 3.85–3.71 (m, 3H), 3.69–3.57 (m, 3H), 3.53–3.42 (m, 4H, 4 × H-2), 1.94 (s, 3H, Ac), 1.92 (s, 3H, Ac); δ_C (100 MHz, CDCl_3) 170.27, 170.25 (CO), 139.58, 139.52, 139.16, 138.92, 138.65, 138.36, 138.33, 138.22, 138.07, 128.33, 128.29, 128.24, 128.14, 128.09, 127.96, 127.95, 127.81, 127.73, 127.61, 127.58, 127.50, 127.47, 127.10, 126.95, 99.23, 98.35, 98.25, 98.16 (C-1), 81.07, 80.99, 80.95, 80.80, 80.66, 80.57, 79.37, 79.04, 78.95, 78.20, 76.47, 76.37, 75.28, 74.98, 73.58, 73.31, 73.17, 72.74, 72.40, 71.77, 71.58, 69.44, 69.24, 68.86, 68.79, 63.35, 20.89 (Ac), 20.78 (Ac); m/z (HRMS MALDI-TOF) calcd for $[\text{C}_{196}\text{H}_{208}\text{O}_{44} + \text{Na}]^+$ 3288.39363, found 3288.39382.

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