**26,28-Dimethoxy-4,6,10,12,16,18,22,24-octamethylpentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,27-diol (6).** To a solution of 0.421 g (0.746 mmol) of **2** in 300 mL $CH_2Cl_2$ were added 10 mL of a solution of NaOH (10%), 1.8 mL of dimethyl sulfate, and 0.4 g (1.24 mmol) of tetrabutylammonium bromide. The mixture was refluxed overnight with stirring. The phases were separated, and to the organic phase was added a dilute solution of ammonium hydroxide. The phases were separated, and the organic phase was washed once with water and dried. Recrystallization of the residue from 1,2-dimethoxyethane afforded 0.165 g of **6** (37%): mp 330 °C dec; $^1$H NMR ($CDCl_3$, rt) $\delta$ 1.69 (s, $CH_3$, 12 H), 2.38 (s, $CH_3$, 12 H), 3.56 (d, $J$ = 15.2 Hz, $CH_2$, 4 H), 3.74 (s, $OCH_3$, 6 H), 4.15 (d, $J$ = 15.2 Hz, $CH_2$, 4 H), 5.25 (s, OH, 2 H), 6.31 (s, Ar-H, 2 H), 6.51 (s, Ar-H, 2 H); $^{13}$C NMR ($CDCl_3$, rt) $\delta$ 18.70, 20.10, 24.62, 62.36 (OMe), 122.85, 123.95, 128.88, 129.12, 134.17, 135.62, 154.19, 156.66; UV ($CHCl_3$) $\epsilon$ = 3148 ($\lambda_{max}$ = 280 nm); MS $m/z$ 564 (M, 15.8), 147 (B, 100), 91 (41); IR $\nu$ OH = 3540 cm$^{-1}$. Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.82; H, 7.85. Found: C, 80.66; H, 7.95.

**Acknowledgment.** We are indebted to Dr. Shmuel Cohen for the crystal structure determination. This work was supported by the Bat-Sheva de Rothschild Fund and the Israel-USA Binational Science Foundation.

**Registry No.** **2**, 123775-99-5; **2**·pyridine, 137172-87-3; **6**, 137122-95-3; 2,4-dimethyl-6-hydroxybenzyl alcohol, 67730-49-8; 2,6-dimethyl-4-hydroxylbenzyl alcohol, 28636-93-3.

**Supplementary Material Available:** Figures S1 and S2 (numbering scheme for **2**·pyridine and **6**), Table S1 (calculated and experimental parameters for the boat foam), and Tables S2-S7 (bond lengths and angles and positional parameters for **2**·pyridine and **6**) (10 pages). Ordering information is given on any current masthead page.

# Per-3,6-anhydro-$\alpha$-cyclodextrin and Per-3,6-anhydro-$\beta$-cyclodextrin[1]

Peter R. Ashton, Paul Ellwood, Ian Staton, and J. Fraser Stoddart*,†

*Department of Chemistry, The University, Sheffield S3 7HF, U.K.*

*Received March 28, 1991 (Revised Manuscript Received July 16, 1991)*

The synthesis of the per-3,6-anhydro derivatives of $\alpha$- and $\beta$-cyclodextrins (CDs) is described starting from the corresponding per-6-tosylates. These could only be obtained as pure compounds following repeated HPLC under reversed-phase conditions of the crude products isolated after tosylation of $\alpha$-CD and $\beta$-CD in pyridine with *p*-toluenesulfonyl chloride. Treatment of the per-6-*O*-tosyl-$\alpha$- and $\beta$-CDs with warm aqueous sodium hydroxide solutions (50-60 °C) afforded the per-3,6-anhydro-$\alpha$- and $\beta$-CDs in good yields. The development of an alternative and successful strategy for the synthesis of per-3,6-anhydro-$\alpha$-CD from the known per-2,3-di-*O*-benzoyl-6-*O*-tosyl-$\alpha$-CD relies upon the use of triethylamine as base in refluxing aqueous methanol. The per-3,6-anhydro-CDs have been fully characterized by FABMS and NMR spectroscopy. Their specific optical rotations, which are solvent dependent, confirm the chiral nature of these molecules. The anhydrides are soluble in such widely different solvents as dichloromethane and water. There is evidence from FABMS that per-3,6-anhydro-$\alpha$-CD forms a complex with the triethylammonium cation while per-3,6-anhydro-$\beta$-CD solubilizes nitrobenzene in deuterium oxide solutions.

## Introduction

In the 100 years since they were first isolated, but especially during the last 25 years, cyclodextrins have been the subject of much detailed investigation.[2] It is now well established[3] that these cyclic oligosaccharides, which are composed of $\alpha$(1-4) linked D-(+)-glucopyranose units, have the overall molecular shape of a truncated cone. The most characteristic aspect of their chemistry is their ability to form inclusion complexes with a wide variety of substrates. As a result, they have been investigated extensively as enzyme mimics,[4] as well as finding varied applications in chemical technology.[5]

Many research workers have sought to modify the binding properties and catalytic behavior of cyclodextrins through their chemical modification.[6] Unfortunately, because of problems associated with their chemoselective and regioselective functionalization and the subsequent purification of the derivatives, many reports have appeared that include highly exaggerated claims of selectivities operating in reactions and of the purities of the CD derivatives isolated. Although these problems were addressed a number of years ago in an excellent paper by Lehn,[7] the standards that were set by this research are still not being practiced universally.

The vast majority of the well-characterized derivatives that have been isolated have structures very similar to those of the parent compounds.[6] It has been our aim to synthesize CD derivatives whose gross structures differ significantly from those of the parent compounds. Such derivatizations of CDs would be expected to have a pro-

† Present address: School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

(1) The work described in this paper was presented in part at the Royal Society of Chemistry Carbohydrate Group Spring Meeting, Cardiff, UK, 25-28 Mar 1990, at the Fifth International Symposium on Cyclodextrins, Paris, France, 27-30 Mar 1990, and at the Smith Kline Beecham Pharmaceutical Research Symposium on "Chirality in Drug Design and Synthesis", Cambridge, UK, 27-28 Mar 1990. Subsequently, lecture reviews of the Symposia in Paris and Cambridge were published: see (a) Ellwood, P.; Stoddart, J. F. In *Minutes of the Fifth International Symposium on Cyclodextrins*; Duchêne, D., Ed.; Editions de Santé: Paris, 1990; pp 86-89. (b) Stoddart, J. F. In *Chirality in Drug Design and Synthesis*; Brown, C., Ed.; Academic Press: London, 1990; pp 5-22. A preliminary publication has also been published. See: Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 80-81.

(2) Stoddart, J. F. *Carbohyd. Res.* **1989**, *192*, xii-xv.

(3) Saenger, W. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984, Vol. 2, pp 231-259.

(4) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.

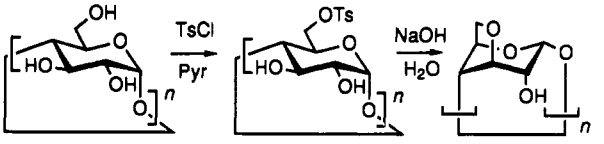
(5) (a) *Cyclodextrins and their Industrial Uses*; Duchêne, D., Ed.; Editions de Santé: Paris, 1987. (b) Szejtli, J. *Cyclodextrin Technology*; Kluwer: Dordrecht, 1988.

(6) Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417-1474.

(7) Boger, J.; Concoran, R. J.; Lehn, J.-M. *Helv. Chim. Acta* **1978**, *61*, 2190-2218.

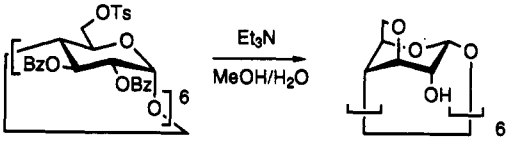
0022-3263/91/1956-7274$02.50/0 

**Scheme I. Synthesis of the Per-3,6-anhydro CDs 4 and 5 from the Corresponding Per-6-*O*-tosylates 2 and 3, Respectively**




α-CD (*n* = 6) **2** (*n* = 6) **4** (*n* = 6)
β-CD (*n* = 7) **3** (*n* = 7) **5** (*n* = 7)

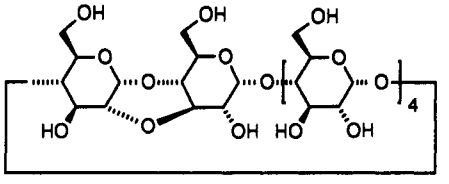
**Scheme II. Synthesis of Per-3,6-anhydro-α-CD (4) from Per-2,3-di-*O*-benzoyl-6-*O*-tosyl-α-CD (8)**




**8** **4**

found influence on their receptor properties.

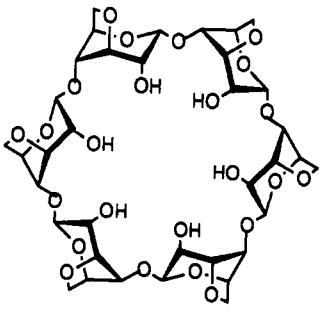
Recently, a number of chemical modifications have been carried out on CDs that have resulted in CD derivatives with novel structures. In particular, Fujita[8] has reported the synthesis of many interesting cyclodextrin derivatives, including $2^A,3^B$-anhydro-($2^A$R),($3^B$R)-α-CD (1). However,



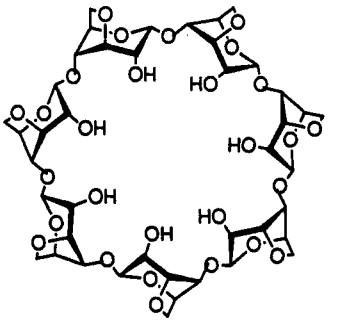
**1**

this research has involved the incomplete modification of the D-glucopyranose residues around the CD torus. In order to effect profound structural changes upon the gross structural features of CDs, then all the D-glucopyranose residues must be modified. In this regard, Ogawa[9] has been particularly successful and has achieved the syntheses of the manno isomers of α-, β- and γ-CD. The complexation properties of these wholly synthetic analogues should be intriguing.

As a consequence of an investigation[10] involving the conformational analysis of a number of chemically modified CDs, we were led to consider the possibility of inducing a change in the chair conformation of all the D-glucopyranose residues in the CD torus from the $^4C_1$ to the $^1C_4$ form. It is well established[11] that D-glucopyranose rings may be locked into the $^1C_4$ chair conformation by 3,6-anhydration. This reaction may be achieved within the CD constitutions by base treatment of a derivative in which each D-glucopyranose residue carries a good leaving group at C-6. Inspection of CPK space-filling molecular models indicates that the structures of the resulting per-3,6-anhydro derivatives in the α and β series (compounds **4** and **5**, respectively) are significantly different from those



**4**



**5**

displayed by the parent compounds. Thus, the cavities of these novel derivatives are dominated by the glucopyranosidic, the glucopyranose ring, and the free hydroxyl oxygen atoms, whereas the cavities of the parent molecules are significantly more hydrophobic by virtue of being lined with the H-3 and H-5 methine hydrogen atoms. All the methine hydrogens atoms in the per-3,6-anhydro derivatives are located on the periphery of the equally rigid cyclic oligosaccharides. In addition, the structures of the per-3,6-anhydro derivatives appear to be more strained, and—unlike the parent CD molecules—one cannot construct, from CPK space-filling molecular models, a symmetrical doughnut-shaped molecule. In both the α and β series, inspection of the models reveals that the molecules of the per-3,6-anhydro CDs are kinked.

Fujita[12] was the first to report the 3,6-anhydration of CD constitutions with the synthesis of mono-$3^A,6^A$-anhydro-β-CD from mono-6-*O*-tosyl-β-CD. Although further chemical modifications of CDs, which introduce more than one 3,6-anhydro ring, have been achieved by Fujita,[13] the functionalization of the complete CD torus in this manner had not been reported when our research in this area was begun. Our approach[14] to the synthesis of the per-3,6-anhydro CDs **4** and **5** involves the treatment of the per-6-*O*-tosyl derivatives **2** and **3**, respectively, in Scheme I with base. In this paper, we shall describe (1)

(8) (a) Fujita, K.; Egashira, Y.; Imoto, T.; Fujioka, T.; Mihashi, K.; Tahara, T.; Koga, T. *Chem. Lett.* **1989**, 429–432. (b) Fujita, K.; Tahara, T.; Sasaki, H.; Egashira, Y.; Shingu, T.; Imoto, T.; Koga, T. *Chem. Lett.* **1989**, 917–920.

(9) Mori, M.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1989**, *30*, 1273–1276. Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1989**, *192*, 131–146.

(10) Ellwood, P.; Spencer, N.; Spencer, C. M.; Stoddart, J. F.; Zarzycki, R. *J. Incl. Phenom. Mol. Recog. Chem.*, in press.

(11) Guthrie, R. D. In *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. 1A, pp 423–478.

(12) Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *Chem. Lett.* **1988**, 543–546.

(13) Fujita has achieved 3,6-anhydration at (i) one [(a) Fujita, K.; Matsunaga, A.; Yamamura, H.; Imoto, T. *Chem. Lett.* **1988**, 1947–1950. (b) Fujita, K.; Matsunaga, A.; Yamamura, H.; Imoto, T. *J. Org. Chem.* **1988**, *53*, 4520–4522] (ii) two [(a) Fujita, K.; Yamamura, H.; Imoto, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1988**, *53*, 1943–1947. (b) Fujita, K.; Egashira, Y.; Tahara, T.; Imoto, T.; Koga, T. *Tetrahedron Lett.* **1989**, *30*, 1285–1288] and (iii) three [(a) Fujita, K.; Ishizu, T.; Oshiro, K.; Obe, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2960–2962. (b) Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1990**, *55*, 877–880] D-glucopyranose residues of the parent CD molecules.

(14) After we had completed the research described in this paper, we learnt that Defaye had also recently synthesized the per-3,6-anhydro-CDs **4** and **5** in good yields from the corresponding per-6-deoxy-6-iodo-CD derivatives by dissolving them in DMSO and treating them with aqueous NaOH solutions at 60 °C. See: Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78–80.

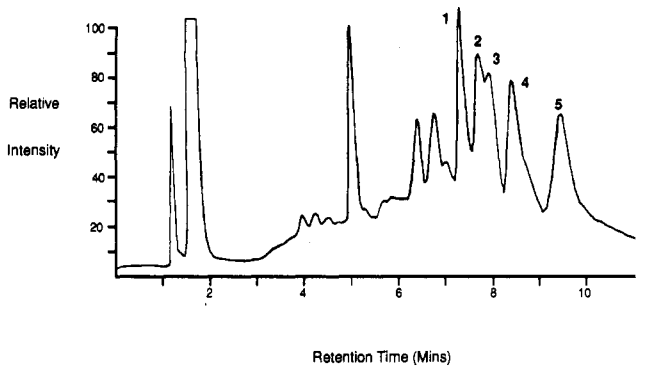



**Figure 1.** HPLC trace (relative intensity vs retention time) of the crude reaction product from the tosylation of α-CD. Fractions 1–5 were collected.

the preparation and purification of **2** and **3** and then (2) discuss how these per-6-*O*-tosyl CD derivatives may be converted into the per-3,6-anhydro-CDs **4** and **5**. Finally, we shall outline (Scheme II) a more efficient synthesis of the per-3,6-anhydro-α-CD **4** from per-2,3-di-*O*-benzoyl-6-*O*-tosyl-α-CD **8**—a known compound[7] that can be obtained easily and in pure form from α-CD.

## Results and Discussion

**1. Synthesis and Purification of the Per-6-*O*-tosylcyclodextrins.** The per-6-*O*-tosylcyclodextrins **2** and **3** were first synthesized in 1954 by Lehmann[15] using a procedure that involved adding *p*-toluenesulfonyl chloride to a pyridine solution of the appropriate cyclodextrin and allowing the reaction mixture to stand at room temperature for 24 h. Alterations to this procedure have since been made by Umezawa,[16] Cramer,[17] and Breslow[18] in the syntheses of derivatives that are amongst the most widely used in synthetic CD chemistry. Despite the large amount of research carried out on these compounds, analytical data on them are scarce. Generally, only $[\alpha]_D$ values, elemental analyses, and melting points have been reported, and furthermore, the actual numerical values of these data reported[15-18] by different authors are not in agreement. In only one instance has NMR spectroscopic data been reported,[19] and that was limited to a list of $^{13}C$ NMR chemical shifts. No $^1H$ NMR spectroscopic data have been reported. Furthermore, of all the practical procedures, only one[16] gives experimental details that involve the use of column chromatography as a means of purifying the derivatives. The remainder rely upon recrystallization. In our experience, chemically modified CDs can only be purified by chromatographic separation techniques. We therefore suspected that the crude products obtained by us using the established procedures were impure. All the pure products isolated after chromatography in the present investigation were scrutinized by NMR spectroscopy and FABMS as well as being subjected to detailed chromatographic analysis.

The procedure we used for the preparation of the tosylates was essentially the same as that described by Lehmann.[15] Thus, α-cyclodextrin was dissolved in pyridine, 6 molar equiv of *p*-toluenesulfonyl chloride were added, and the reaction mixture was stirred for 24 h under nitrogen. When the resulting solution was poured, with stirring, into water, a white precipitate was formed. After a short period of further stirring, this preciptate formed a gel, which could be crystallized from methanol to afford a white solid. FABMS of this product showed that it contained overtosylated and undertosylated derivatives as well as the desired per-6-*O*-tosyl-α-cyclodextrin **2** with $C_6$ symmetry. A detailed HPLC analysis of this crude mixture established the chromatographic conditions for the purification of per-6-*O*-tosyl-α-CD (**2**). The number of peaks in the chromatogram (Figure 1) bear testimony to the lack of selectivity associated with the reaction. Fractions 1–5 were collected, and the extent of tosylation was determined by FABMS in each case. Fraction 1 corresponded to an α-CD derivative containing five tosyl groups. Fractions 2–4 each corresponded to α-CD derivatives that contained six tosyl groups, while fraction 5 had seven tosyl groups associated with an α-CD derivative. Thus, the lack of selectivity is associated, not only with the extents of the tosylations, but also with the constitutional location of the tosyl groups. Unfortunately, the extremely poor solubility of the crude mixture in the eluants that had to be employed in the separation—as well as in all other common solvents—means that large quantities (>10 mg) of the desired hexatosylate **2** cannot be isolated routinely. An attempt to employ the chromatographic system recommended by Umezawa,[16] which involves using ordinary silica gel with benzene–ethanol (4:1 v/v) as the eluant, was unsuccessful.

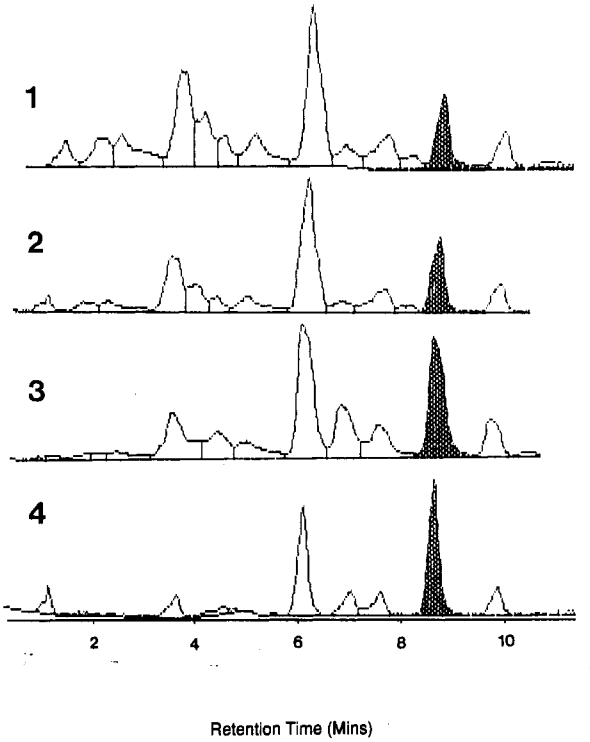



**Figure 2.** HPLC traces showing the effect of progressive recrystallization on the crude reaction product obtained from the tosylation of α-CD. The numbers to the left of the traces refer to the number of successive recrystallizations, the horizontal axis is the retention time in minutes, and the shaded peak in each chromatogram corresponds to per-6-*O*-tosyl-α-CD (**2**).

NMR spectroscopic analysis led to the identification of fraction 4 as the desired hexatosylate **2**. Interestingly, the elemental analysis obtained for the complex mixture was identical with that for the desired axially symmetrical pure per-6-*O*-tosyl-α-CD **2**. Contrary to the popularly held view in the field,[15-18] this observation demonstrates the un-

(15) Lautsch, Von W.; Wiechert, R.; Lehmann, H. *Koll. Zeit.* **1954**, *135*, 134–136.
(16) Umezawa, S.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 464–468.
(17) Cramer, F.; Mackensen, G.; Sensse, K. *Chem. Ber.* **1969**, *102*, 494–508.
(18) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762–770.
(19) Sangwan, N. K.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223–1227.

**Table I. Effect of Recrystallizations on the Crude Reaction Product from the Tosylation of α-CD**

| sample | HPLC integration[a] | mp (°C) | $[\alpha]_D$[b] |
|---|---|---|---|
| crude | 7.5 | 173–174 | +70° |
| 1 ReX[c] | 8.7 | 175–176 | +78° |
| 2 ReX[c] | 12.4 | 177–178 | +98° |
| 3 ReX[c] | 21.0 | 178–179 | +88° |
| 4 ReX[c] | 31.3 | 179–180 | +92° |
| pure | | 181–182 | +83° |
| literature | | 184–188[d] | +101°[e] |
| | | 174[f,g] | +95°[h] |
| | | | +79°[i] |

[a] Area of peak corresponding to the desired product as a percentage of the total peak (using UV detection). [b] In acetone (c, 0.9–1.2). [c] ReX = recrystallization(s). [d] Reference 16. [e] In $CHCl_3$ (c, 0.72), ref 16. [f] Reference 15. [g] Reference 17. [h] 1% in $CHCl_3$, ref 15. [i] 0.1% in $CH_3OH$, ref 17.

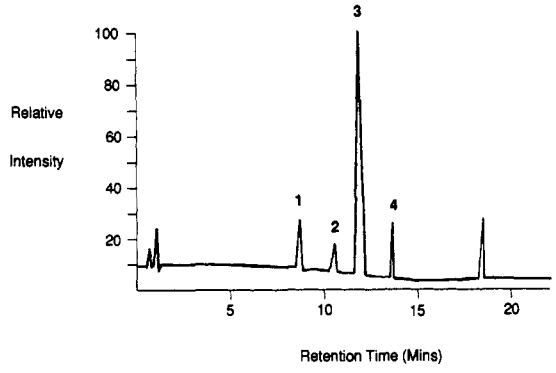



**Figure 3.** HPLC trace (intensity vs retention time) of the crude reaction product from the tosylation of β-CD. Fractions 1–4 were collected.

suitability of such analytical data as criteria for the purity of these tosylated CD derivatives.

Since recrystallization had previously been the method of choice to purify per-6-*O*-tosyl-α-CD **2**, the effects of successive recrystallizations were monitored by HPLC. While recrystallization leads to an enrichment of the crystalline material in **2** (see Table I and Figure 2), the product remains highly contaminated by other isomers and homologues.

The workup of the reaction involving tosylation of β-CD was similar to that described for α-CD except that, on pouring the crude reaction mixture into water, a white solid was obtained. It was filtered off and dried. FABMS of this product showed that it contained both overtosylated and undertosylated β-CD derivatives, as well as the desired per-6-*O*-tosyl-β-CD **3** with $C_7$ symmetry. Another chromatographic procedure, once again based on reversed-phase HPLC, was used to purify the heptatosylate **3**. As expected,[7] the chromatogram (Figure 3) was simpler than the one obtained after the tosylation of α-CD. Fractions 1–4 were collected separately. FABMS indicated that fractions 1 and 2 each corresponded to β-CD derivatives that contained six tosyl groups, fraction 3 to β-CD derivatives that had seven, and fraction 4 was an octatosylated β-CD. FABMS indicated that fraction 3 contained the desired per-6-*O*-tosyl-β-CD **3**, and NMR spectroscopy confirmed this conclusion. Although, once again, the poor solubility of the crude product prevented the isolation of large amounts of pure compound, the relative ease with which chromatography could be conducted meant that larger quantities (>100 mg) of per-6-*O*-tosyl-β-CD (**3**) could be isolated than of the corresponding α-CD derivative **2**.

The effect of successive recrystallizations on a crude sample of per-6-*O*-tosyl-β-CD (**3**) was monitored using analytical HPLC. The results are summarized in Table II. Integration of the HPLC trace suggests that repeated recrystallizations are quite ineffective at enriching the proportion of the heptatosylate **3** present in the mixture. Indeed, the main effect of the recrystallizations is to increase the relative proportions of the hexatosyl derivatives. The data presented in Table II show very convincingly that recrystallization alone is not successful in purifying the crude per-6-*O*-tosyl-β-CD **3**.

**Table II. Effect of Successive Recrystallizations on the Crude Reaction Product from the Tosylation of β-CD**

| sample | HPLC integration[a] | mp (°C) | $[\alpha]_D$[b] |
|---|---|---|---|
| crude | 55.8 | 179–180 | +86° |
| 1 ReX[c] | 57.0 | 174–175 | +84° |
| 2 ReX[c] | 56.0 | 176–177 | +84° |
| 3 ReX[c] | 56.0 | 177–178 | +83° |
| 4 ReX[c] | 51.7 | 177–178 | +83° |
| pure | | 181–182 | +84° |
| literature | | 170[d] | +105°[e] |
| | | 170–172[f] | +91°[g] |

[a] Area of peak corresponding to the desired material as a percentage of the total peak area (using UV detection). [b] In $CHCl_3$–$CH_3OH$ (c, 0.5–1.0). [c] ReX = recrystallization(s). [d] Reference 15. [e] c, 1% in $CHCl_3$, ref 15. [f] Reference 17. [g] 0.1% in $CH_3OH$, ref 16.

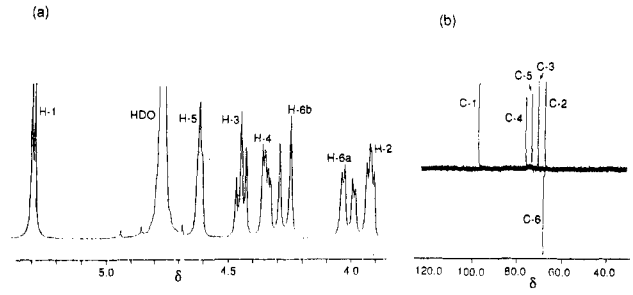



**Figure 4.** (a) $^1H$ NMR spectrum (250 MHz) and (b) $^{13}C$ NMR spectrum (63 MHz) of per-3,6-anhydro-β-CD (**5**).

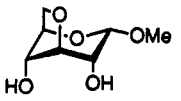
**2. Synthesis of Per-3,6-anhydrocyclodextrins.** Since sufficient quantities of pure per-6-*O*-tosyl-β-CD (**3**) could be isolated readily, the reaction shown in Scheme I was attempted on the β-CD derivative first of all. Suspending the pure heptatosylate **3** in 1 M aqueous sodium hydroxide solution and stirring the reaction mixture for 2 days at 60 °C gave, after reversed-phase chromatography, pure per-3,6-anhydro-β-CD (**5**) in 44% yield. FABMS of the pure compound showed peaks at 1031, 1053, and 1069 corresponding to[20] the pseudomolecular ions $[M + Na]^+$, $[M + 2Na - H]^+$, and $[M + Na + K - H]^+$, respectively. $^1H$ NMR spectra of the pure compound were obtained in $D_2O$ and $CD_2Cl_2$, and the resonances were assigned to the protons on the basis of homonuclear decoupling experiments. The $^1H$ NMR spectrum recorded in $D_2O$ is shown in Figure 4a. The rigidity and conformationally unsymmetrical nature of the macrocyclic ring indicated on inspecting CPK space-filling molecular models is clearly not apparent from these spectra, which reflect the averaged 7-fold symmetry of the derivative. When a $CD_2Cl_2$ solution of **5** was cooled down in an attempt to reduce the averaged 7-fold symmetry observed in the $^1H$ NMR spectrum, unfortunately the heptaanhydride **5** precipitated. The magnitudes of the coupling constants obtained in both solvents (see the Experimental Section) are consistent with the pyranose rings being locked into the $^1C_4$ chair conformation. Indeed, as shown in Table III, the chemical shifts and coupling constants observed for **5** in $D_2O$ are

(20) Usually, the FABMS of chemically modified CDs with *m*-nitrobenzyl alcohol as matrix reveals only one pseudomolecular ion, namely a sodium adduct. See, for example: Ashton, P. R.; Stoddart, J. F.; Zarzycki, R. *Tetrahedron Lett.* **1988**, *29*, 2103–2106.

Table III. Comparison of the Chemical Shifts ($\delta$) and Coupling Constants ($J$, Hz) for the Protons in Per-3,6-anhydro-$\beta$-CD (5) and Methyl 3,6-Anhydro-$\alpha$-D-glucopyranoside (6)

| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6a | H-6b |
|---|---|---|---|---|---|---|---|
| $\delta$ | 5.31 | 3.94 | 4.46 | 4.36 | 4.63 | 4.03 | 4.29 |
| 5 | ($J_{1,2}$ 3) | ($J_{2,3}$ 5) | ($J_{3,4}$ 5) | ($J_{4,5}$ 2) | m | ($J_{5,6a}$ 3) | ($J_{6a,6b}$ 11.5) |
| $\delta$ | 5.07 | 3.94 | 4.32 | 4.27 | 4.41 | 4.04 | 4.27 |
| 6 | ($J_{1,2}$ 2.6) | ($J_{2,3}$ 4.8) | ($J_{3,4}$ 4.8) | ($J_{4,5}$ 2.8) | m | ($J_{5,6a}$ 2.8) | ($J_{6a,6b}$ 10.8) |

very similar to those obtained for methyl 3,6-anhydro-$\alpha$-D-glucopyranoside (6), a suitable monosaccharide model compound. However, the chemical shifts, as well as the values of the specific optical rotations obtained for 5, show a small solvent dependence. This observation suggests[10] that an alteration in the gross conformation of the heptaanhydride 5 occurs with a change in solvent.

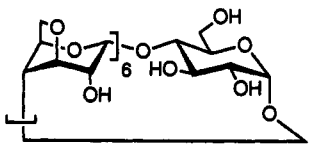



6

$^{13}C$ NMR spectra of per-3,6-anhydro-$\beta$-CD (5) were recorded in $D_2O$ and $CD_2Cl_2$. The peaks in the spectrum, obtained in $D_2O$, were assigned using C–H correlation spectroscopy. The $^1J_{CH}$ coupling constant associated with the anomeric centers was measured in a separate experiment. The value of 164 Hz, which was obtained, is consistent with the anomeric protons occupying an axial position on the D-glucopyranose rings.[21] This observation confirms the presence of 3,6-anhydro-D-glucopyranose units in their familiar $^1C_4$ chair conformation.

Single crystals suitable for X-ray crystallography were obtained by the vapor diffusion of methanol into an aqueous solution of 5. Although a full set of X-ray data have been collected,[22] a structural solution has not yet been achieved.

The relative simplicity of the crude product resulting from the tosylation of $\beta$-CD led us to investigate the possibility of using recrystallized, but impure, reaction product as the starting material for the per-3,6-anhydration. Thus, impure per-6-*O*-tosyl-$\beta$-CD (2) was treated with aqueous sodium hydroxide solution in the manner described previously. The FABMS spectrum of the white solid, which was obtained from this reaction, indicated the presence of the heptaanhydride 5, along with a compound we believe to be the hexa-3,6-anhydro-$\beta$-CD 7. The ease of the chromatographic purification of per-




7

3,6-anhydro-$\beta$-CD (5) means that larger quantities—in contrast with using the pure heptatosylate 3 as the starting material—of this compound can be obtained routinely using the above procedure. When a similar procedure was applied to the mixture of $\alpha$-CD tosylates, it was unsuccessful because of the large number of other CD derivatives

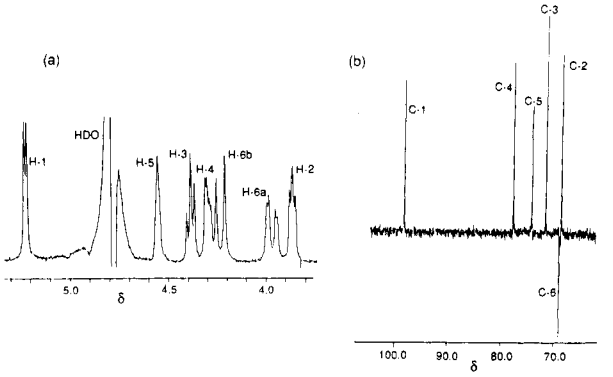



Figure 5. (a) $^1H$ NMR spectrum (250 MHz) and (b) $^{13}C$ NMR spectrum (63 MHz) of per-3,6-anhydro-$\alpha$-CD (4).

that were formed during the reaction.

On account of the difficulties encountered in obtaining large quantities of pure per-6-*O*-tosyl-$\alpha$-CD (2), an alternative synthetic strategy was sought in order to prepare the corresponding per-3,6-anhydro derivative 4. The synthetic protocol, which was eventually successful, employed per-2,3-di-*O*-benzoyl-6-*O*-tosyl-$\alpha$-CD (8) as the key intermediate. This compound can be obtained in bulk quantities employing a procedure described by Lehn.[7] It was anticipated (Scheme II) that treatment of this compound with an appropriate base would cause debenzoylation, followed by 3,6-anhydration, to give the desired product—namely, the hexaanhydride 4. A number of bases were experimented with, and the one that was finally successful in promoting reaction involved suspending 8 in $Et_3N$–MeOH–$H_2O$ (1:5:1 v/v)[23] and then refluxing the reaction mixture for 4 days. The resulting clear solution was neutralized with hydrochloric acid. Removal of the solvents under vacuum yielded a white solid. The $^1H$ NMR spectrum of this solid was recorded in $D_2O$. It revealed that the product was rich in triethylammonium chloride. However, the FABMS of the solid showed the presence of the per-3,6-anhydro-$\alpha$-CD 4 uncontaminated with any other CD derivative of a similar molecular mass. Interestingly, the pseudomolecular ion observed ($m/z$ = 966) corresponds to the triethylammonium adduct of 4. After extensive recycling of fractions, the hexaanhydride 4 was isolated in 22% yield, by employing reversed-phase chromatography. The $^1H$ and $^{13}C$ NMR spectra of the purified compound were recorded (Figure 5) in $D_2O$. The spectra are similar to those obtained for the $\beta$-CD derivative 5 and reflect the averaged 6-fold symmetry of the molecules. The magnitudes of the vicinal H–H coupling constants indicate that the 3,6-anhydro-D-glucose units adopt the expected $^1C_4$ chair conformation. FABMS of the pure compound showed peaks at 887, 903, and 909 corresponding to the pseudomolecular ions $[M + 2Na - H]^+$ and $[M + K]^+$, in addition to the expected $[M + Na]^+$.

The reaction illustrated in Scheme I was attempted with a small quantity (10 mg) of pure per-6-*O*-tosyl-$\alpha$-CD (2).

(21) Schwarz, J. A.; Perlin, A. S. *Can. J. Chem.* **1972**, *50*, 3667–3676. (b) Parfondry, A.; Cyr, N.; Perlin, A. S. *Carbohydr. Res.* **1977**, *59*, 299–309.

(22) Full three-dimensional diffraction data have been collected and the structural solution is being sought (Slawin, A. M. Z.; Williams, D. J. Unpublished results). Crystal data for 5: monoclinic, $a$ = 10.223 (3) Å, $b$ = 41.213 (12) Å, $c$ = 13.738 (4) Å, $\beta$ = 111.54 (2)°, $V$ = 5284 Å$^3$, space group $P2_1$, $Z$ = 4 (two crystallographically independent molecules).

(23) Tsuzi, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, *21*, 989–992. Ley, S. V.; Sternfield, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225–226.

The procedure was identical with that performed on the corresponding β-CD derivative **3**. It produced pure per-3,6-anhydro-α-CD (**4**) in 75% yield after reversed-phase chromatography. The spectroscopic and analytical data were the same as those obtained for the product synthesized by the de-*O*-benzoylation–3,6-anhydration route.

It is interesting to speculate on the mechanism of formation of these per-3,6-anhydro-CD derivatives. In particular, the possibility that a cooperative effect operates during the reaction is appealing. That is, does the formation of one 3,6-anhydro-D-glucose ring aid the formation, subsequently, of adjacent and/or nonadjacent residues around the macrocyclic ring? The evidence on which to base a discussion is currently only indirect and depends on the work of Fujita.[8,12,13]

On treating mono-6-*O*-tosyl-β-CD with aqueous barium hydroxide solution, Fujita[8] isolated mono-$3^A$,$6^A$-anhydro-β-CD in 88% yield, after chromatography. The main byproduct (8%) was β-CD itself. A similar preparation of mono-$3^A$,$6^A$-anhydro-α-CD proceeded in only 58% yield. In these reactions, 3,6-anhydration could be competing with the hydrolysis of the tosylate. If no cooperative effect is in operation, then one might expect the relative rates of 3,6-anhydration to hydrolysis to remain unchanged as the reaction proceeds to give the per-3,6-anhydro derivatives. On the basis of this argument, it can be predicted that the yield of the reaction affording per-3,6-anhydro-α-CD (**4**) should be $0.58^6 \times 100$ or 4%, while that affording per-3,6-anhydro-β-CD (**5**) should be $0.88^7 \times 100$ or 41%. If, however, a cooperative effect is operating, then 3,6-anhydration would become the increasingly favored process as the reaction proceeds, and the final yields obtained would be much higher than those predicted. In the reactions that involved the intermediacy of the per-6-*O*-tosyl derivatives, the yields of per-3,6-anhydro derivatives isolated were 75% and 44% for the α-CD and β-CD derivatives, respectively. These yields suggest that a significant cooperative effect is operating during the synthesis of per-3,6-anhydro-α-CD (**4**). However, the effect is less apparent in the case of the β-CD derivative **5**. This contrasting situation could be a direct consequence of the different diameters of the macrocycles in the α and β series. The distortion of adjacent D-glucopyranose residues, brought about by 3,6-anhydration, is expected to be greater in the smaller macrocyclic ring of an α-cyclodextrin derivative than in the relatively larger macrocyclic ring of a β-CD compound.

**3. Complex Formation: Some Preliminary Observations.** The complexation properties of these potentially novel hosts **4** and **5** have been investigated in a preliminary manner. Examination of CPK space-filling molecular models indicates that their cavities are dominated by oxygen atoms. It was therefore anticipated that the per-3,6-anhydro-CD derivatives might act as hosts for metal cations and/or ammonium ions. This prediction was borne out by the FABMS of these derivatives. In our experience with a wide variety of chemically-modified CDs, including alkylated and benzoylated derivatives, FABMS, using *m*-nitrobenzyl alcohol as the matrix, gives only one pseudomolecular ion—that of a sodium adduct. The presence of a number of pseudomolecular ions in the spectra suggests that there is a propensity for simple alkali-metal cations to bind to the cavities of **4** and **5**. Furthermore, the FABMS of the crude reaction product from the debenzoylation–3,6-anhydration of **8** revealed the presence of the triethylammonium cation adduct of **4**.

One of the most common methods for studying the complexing abilities of CDs is NMR spectroscopy. Since the cavities of α-CD and β-CD are lined by the H-3 and H-5 methine protons, the inclusion of guest molecules is generally reflected in substantial changes in the $^1$H NMR chemical shifts of these protons. Inspection of CPK space-filling molecular models indicates that all the protons in **4** and **5** are located on the exteriors of these molecules. It follows that the $^1$H NMR chemical shift changes induced on complexation would be small. Attempts have been made to form host–guest complexes in $CD_2Cl_2$ between per-3,6-anhydro-β-CD (**5**) and potential substrates such as CsI $[Co(NH_3)_6]3PF_6$, and $Me_4NI$. The lack of evidence from $^1$H NMR spectroscopy for complexation of any of these substrates by **5** was supported by their insolubilities in $CD_2Cl_2$ solutions. On the other hand, nitrobenzene is solubilized[24] in a $D_2O$ solution of **5**.

## Summary

The outcome of the research reported in this paper can be summarized as follows: (1) the per-3,6-anhydro-CDs **4** and **5** constitute potentially a new class of CD-derived molecular receptors; (2) the per-3,6-anhydro-α-CD **4** can be prepared by treating the per-2,3-di-*O*-benzoyl-6-*O*-tosyl-α-CD **8** in refluxing aqueous methanol with triethylamine; (3) both the per-3,6-anhydro-CDs **4** and **5** can be obtained from the corresponding per-6-*O*-tosyl-CDs **2** and **3** when they are reacted in warm aqueous sodium hydroxide solutions; and (4) repeated chromatography (HPLC) is necessary in order to obtain the per-6-*O*-tosyl-CDs **2** and **3** as pure compounds from the crude products resulting from tosylation of α-CD and β-CD in pyridine containing *p*-toluenesulfonyl chloride.

## Experimental Section

**Instrumentation and General Procedures.** α-Cyclodextrin (α-CD) and β-cyclodextrin (β-CD) were obtained from the Aldrich Chemical Co. Prior to use, they were dried under high vacuum at 100 °C in the presence on $P_2O_5$. Pyridine (Pyr) was stirred over KOH pellets for 24 h and then distilled. *p*-Toluenesulfonyl chloride (TsCl) was recrystallized from light petroleum (bp 40–60 °C) immediately before use.

**$6^A$,$6^B$,$6^C$,$6^D$,$6^E$,$6^F$-Hexa-*O*-(*p*-toluenesulfonyl)-α-cyclodextrin (Per-6-*O*-tosyl-α-CD 2).** Dry α-CD (1 g, 1.03 mmol) was dissolved in pyridine (20 mL) under nitrogen, and *p*-toluenesulfonyl chloride (1.2 g, 6.4 mmol) was added. The reaction mixture was stirred for 24 h under nitrogen at room temperature. When the solution was poured with stirring into water, a copious amount of a white precipitate resulted. However, this precipitate soon formed a gel, rendering stirring impossible. The solid material was allowed to settle out and the mother liquor was decanted off. The residual gum was crystallized from methanol to give a white solid (1.8 g). HPLC, after injecting an acetone solution of the mixture onto an ODS column and using a gradient elution of water–methanol (4:1 v/v) linearly to water-methanol (1:1 v/v) over 1 min, and then, linearly to neat methanol over 20 min, showed the crude product to be extremely impure. Small amounts (ca. 10–20 mg) of the pure compound could be isolated by using a reversed-phase chromatography column and repeated runs (30–40). Fractions of the desired material were collected, and the solvents were removed under vacuum to give per-6-*O*-tosyl-α-CD (**2**): mp 181–182 °C; $[\alpha]_D$ +83° (*c* 0.95 in acetone); $^1$H NMR (250 MHz, $CD_3COCD_3$) δ 2.88 (s, 18 H, Me), 3.28 (br m, 6 H, H-2),

(24) This claim is supported by the following experimental observations. An excess of nitrobenzene was shaken with $D_2O$ and the two immiscible liquids were allowed to separate out. When an $^1$H NMR spectrum of the $D_2O$ layer was recorded, *only* a residual HOD peak was observed. However, when 2 mol equiv of nitrobenzene was added to a solution of 10 mg of the per-3,6-anhydro-β-CD (**5**) dissolved in 0.7 mL of $D_2O$, a clear solution was obtained. An $^1$H NMR spectrum of this solution revealed the presence of aromatic protons resonating with relative intensities 2:1:2 at δ 7.59 (t), 7.77 (t), 7.59 (t) for nitrobenzene in addition to the signals at higher field in the range δ 3.88–5.34 for per-3,6-anhydro-β-CD **5**.

3.38 (t, $J_{3,4} = J_{4,5} = 9$ Hz, 6 H, H-4), 3.80–3.90 (m, 12 H, H-3, H-5), 4.24 (m, $J_{5,6b} = 4$, $J_{6a,6b} = 11$ Hz, 6 H, H-6b), 4.37 (dd, $J_{5,6a} = 4$, $J_{6a,6b} = 11$ Hz, 6 H, H-6a), 4.61 (d, $J_{1,2} = 3.5$ Hz, 6 H, H-1), 5.07 (br s, OH), 5.67 (br s, OH), 7.41 (BB′ part of a AA′BB′ system, $J_{A,B} = J_{o,m} = 8.5$ Hz, 12 H, $C_m$-H), 7.78 (AA′ part of a AA′BB′ system, $J_{A,B} = J_{o,m} = 8.5$ Hz, 12 H, $C_o$-H); $^{13}C$ NMR ($CD_3COCD_3$, 63 MHz) $\delta$ 21.7 (Me), 69.7 (C-6), 71.1, 73.1, 74.1 (C-2,3,5), 82.4 (C-4), 103.0 (C-1), 128.8 (C-o), 130.9 (C-m), 134.3 (C-p), 145.9 (C-i); MS $m/z$ (positive-ion FABMS), 1919 for $[M + Na]^+$, calcd for $(C_{13}H_{16}O_7S)_6$ 1896. Anal. Calcd for $(C_{13}H_{16}O_7S)_6$: C, 49.4; H, 5.06; S, 10.1. Found C, 49.2; H, 4.98; S, 10.4.

**$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Hepta-*O*-(*p*-toluenesulfonyl)-$\beta$-cyclodextrin (Per-6-*O*-tosyl-$\beta$-CD 3).** Dried $\beta$-CD (1 g, 0.88 mmol) was added, with stirring, to distilled pyridine (20 mL). *p*-Toluenesulfonyl chloride (1.3 g, 6.8 mmol) was then added to the resulting solution. The reaction mixture was stirred at room temperature under nitrogen for 24 h. The solution was poured, with stirring, into water (500 mL), and the resulting white precipitate (1.7 g) was filtered off. HPLC, after injecting an acetonitrile–water (1:1 v/v) solution of the mixture onto a Technicol reversed-phase column with a gradient elution of acetonitrile–methanol (1:1 v/v) to acetonitrile linearly over 15 min, showed the crude product to be impure, even after many recrystallizations from acetonitrile–methanol (19:1 v/v). Small amounts of the pure material (ca. 100 mg) could be obtained using 30–40 repeated runs on a C-18 preparative column using the same eluant system as that described for the purification of **2**. The desired fractions were combined and the solvents were removed under vacuum to yield per-6-*O*-tosyl-$\beta$-CD (**3**): mp 181–182 °C; $[\alpha]_D$ +84° (*c*, 0.5 $CHCl_3$ – $CH_3OH$, 5:2 v/v); $^1H$ NMR (250 MHz, $CD_3SOCD_3$) $\delta$ 3.15 (m, 7 H, H-2), 3.22 (dd, $J_{3,4} = 9$, $J_{4,5} = 10$ Hz, 7 H, H-4), 3.30 (s, 21 H, Me), 3.51 (t, $J_{2,3} = J_{3,4} = 9$ Hz, 7 H, H-3), 3.68 (br d, $J_{4,5} = 10$ Hz, 7 H, H-5), 4.14 (m, $J_{5,6b} = 4$, $J_{6a,6b} = 11$ Hz, 7 H, H-6b), 4.26 (m, $J_{5,6a} = 1$, $J_{6a,6b} = 11$ Hz, 7 H, H-6a), 4.58 (d, $J_{1,2} = 3.5$ Hz, 7 H, H-1), 5.72 (d, $J_{3,OH} = 2$ Hz, 7 H, C(3)–OH), 5.81 (d, $J_{2,OH} = 7$ Hz, 7 H, C(2)–OH), 7.37 (BB′ part of a AA′BB′ system, $J_{A,B} = J_{o,m} = 8.5$ Hz, 14 H, $C_m$-H), 7.68 (AA′ part of AA′BB′ system, $J_{A,B} = J_{o,m} = 8.5$ Hz, 14 H, $C_o$-H); $^{13}C$ NMR (63 MHz, $CD_3SOCD_3$) $\delta$ 21.0 (Me) $\delta$ 68.6 (C-6), 69.2 (C-2), 71.6 (C-3), 72.2 (C-5), 81.0 (C-4), 101.7 (C-1), 127.4 ($C_m$), 129.8 ($C_o$), 132.6 (C-Me), 144.7 (C-$SO_2$); $^{13}C$ NMR (63 MHz, $CDCl_3/CD_3OD$ (5:2 v/v)) $\delta$ 20.0 (Me), 67.1 (C-6), 68.6 (C-2), 71.0 (C-3), 71.3 (C-5), 80.2 (C-4), 101.2 (C-1), 126.5 ($C_m$), 128.4 ($C_o$), 131.4 (C-Me), and (C-$SO_2$); MS $m/z$ (positive-ion FABMS), 2235 for $[M + Na]^+$, calcd for $(C_{13}H_{16}O_7S)_7$ 2212. Anal. Calcd for $(C_{13}H_{16}O_7S)_7$: C, 49.4; H, 5.1; S, 10.1. Found C, 48.9; H, 5.4; S, 10.0.

**$3^A,6^A$-$3^B,6^B$-$3^C,6^C$-$3^D,6^D$-$3^E,6^E$-$3^F,6^F$-$3^G,6^G$-Heptaanhydro-$\beta$-cyclodextrin (Per-3,6-anhydro-$\beta$-CD 5).** Per-6-*O*-tosyl-$\beta$-CD (20 mg, $9 \times 10^{-6}$ mol) was suspended in aqueous sodium hydroxide (2 mL of a 1 M solution), and the reaction mixture was stirred at 50 °C for 2 days. The clear solution was neutralized with hydrochloric acid (0.1 M), and the water was removed under vacuum to leave a white residue. The desired compound was isolated using reversed-phase HPLC. Thus, injecting a water–methanol (3:2 v/v) solution of the white residue onto a reversed-phase column and eluting with the same mixed solvent achieved a good separation of per-3,6-anhydro-$\beta$-CD (**5**, 4 mg, 44%): mp 226–227 °C; $[\alpha]_D$ −33° (*c*, 0.4 in $CH_2Cl_2$), $[\alpha]_D$ 0° (*c*, 0.6 in $H_2O$); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ 3.94 (dd, $J_{1,2} = 3.5$, $J_{2,3} = 5$ Hz, 7 H, H-2), 4.03 (dd, $J_{5,6b} = 3$, $J_{6a,6b} = 11.5$ Hz, 7 H, H-6b), 4.29 (d, $J_{6a,6b} = 11.5$ Hz, 7 H, H-6a), 4.36 (dd, $J_{3,4} = 5$, $J_{4,5} = 2$ Hz, 7 H, H-4), 4.46 (t, $J_{2,3} = J_{3,4} = 5$ Hz, 7 H, H-3), 4.63 (m, 7 H, H-5), 5.31 (d, $J_{1,2} = 3$ Hz, 7 H, H-1); $^{13}C$ NMR (63 MHz, $D_2O$) $\delta$ 68.0 (C-2), 68.6 (C-6), 71.0 (C-3), 73.8 (C-5), 76.5 (C-4), 97.5 (C-1); MS $m/z$ (positive-ion FABMS), 1031 for $[M + Na]^+$, 1053 for $[M + 2Na - H]^+$, 1069 for $[M + Na + K - H]^+$, calcd for $(C_6H_8O_4)_7$ 1008. Anal. Calcd for $(C_6H_8O_4)_7$: C, 50.0; H, 5.55. Found: C, 48.7; H, 5.76.

**$3^A,6^A$-$3^B,6^B$-$3^C,6^C$-$3^D,6^D$-$3^E,6^E$-$3^F,6^F$-Hexaanhydro-$\alpha$-cyclodextrin (Per-3,6-anhydro-$\alpha$-CD, 4). A.** Per-6-*O*-tosyl-2,3-*O*-benzoyl-$\alpha$-CD (**8**) (50 mg, 0.016 mmol) was suspended in triethylamine–methanol–water (1:5:1) (7 mL), and the suspension was heated under reflux for 4 days. The resulting solution was cooled and neutralized with hydrochloric acid (ca. 0.1 M), and then the solvents were removed under vacuum to give a white residue. HPLC, using a reversed-phase column and methanol–water (1:4 v/v) as eluant provided, after extensive recycling of fractions, a pure sample of per-3,6-anhydro-$\alpha$-CD (**4**, 3 mg, 22%): mp 236–237 °C; $[\alpha]_D$ 10° (*c*, 0.25 in $H_2O$); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ 3.87 (dd, $J_{1,2} = 4$, $J_{2,3} = 5$ Hz, 6 H, H-2), 3.98 (dd, $J_{5,6b} = 3$, $J_{6a,6b} = 11.5$ Hz, 6 H, H-6b), 4.24 (d, $J_{6a,6b} = 11.5$ Hz, 6 H, H-6a), 4.31 (dd, $J_{3,4} = 5.5$, $J_{4,5} = 2$ Hz, 6 H, H-4), 4.39 (t, $J_{2,3} = J_{3,4} = 5$ Hz, 6 H, H-3), 4.56 (m, 6 H, H-5), 5.24 (d, $J_{1,2} = 3$ Hz, 6 H, H-1); $^{13}C$ NMR (63 MHz, $D_2O$) $\delta$ 68.4 (C-2), 68.8 (C-6), 71.3 (C-3), 74.0 (C-5), 77.5 (C-4), 98.0 (C-1); MS $m/z$ 887 for $[M + Na]^+$, 904 for $[M + K]^+$, 909 for $[M + 2Na - H]^+$, calcd for $(C_6H_8O_4)_6$ 864. Anal. Calcd for $(C_6H_8O_4)_6$: C, 50.0; H, 5.55. Found: C, 47.7; H, 5.29.

**B.** Per-6-*O*-tosyl-$\alpha$-CD (10 mg, $5.3 \times 10^{-6}$ mol) was suspended in aqueous sodium hydroxide solution (4 mL, 1 M), and the reaction mixture was heated for 48 h at 60 °C. The resulting solution was neutralized with hydrochloric acid (ca. 1 M), and the water was removed under vacuum. HPLC, using a reversed-phase column and methanol–water (1:4 v/v) as eluant, led to the isolation of per-3,6-anhydro-$\alpha$-CD (**4**, 3.4 mg, 75%). The analytical and spectroscopic data were identical with those reported under heading A.

**Acknowledgment.** We are grateful to the Science and Engineering Research Council and the Johnson Matthey Technology Centre in the United Kingdom for financial support.

**Registry No.** 1, 10016-20-3; 3, 23734-54-5; 2, 21884-25-3; 4, 131105-39-0; 5, 131105-40-3; 6, 13407-60-8; 7, 7585-39-9; 8, 68715-48-0.