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Synthetic route for selective modification of the secondary hydroxyl face of cyclodextrins

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The synthesis and characterization of O2-pertosylated cyclodextrins and per-cyclo-α-1,4-manno-2,3-epoxides is described. ^{1}H and ^{13}C-NMR spectral analyses are given, showing the existence of strong hydrogen bonding between the tosyl S=O and the cyclodextrin C3–OH groups. Use of the ^{1}H-NMR coupling constants has allowed molecular modelling of cyclo-α-1,4-heptamannoepoxide, confirming a preference for the *gauche–trans* and *gauche–gauche* configurations at the primary hydroxy face. Fast atom bombardment mass spectral studies suggest a preferential interaction with K^+ rather than Na^+ ions.

INTRODUCTION

The cyclodextrins (CDs), cyclic oligomers of α-1,4-glucopyranose, are probably the most widely used molecular hosts in inclusion systems. They have been extensively used in the pharmaceutical, cosmetic, and food industries.[1] Their inherent chirality has also led to their widespread use in chiral separation techniques.[2] Considerable interest has developed in the chemical modification of these molecules in order to optimize their separation properties.[3] Routes used to change the basic chirality of the CDs have either involved total synthesis[4] or involved modification at one glucopyranose residue.[5–7] We have recently communicated the synthesis of per-O2-tosyl-β-CD[8] and a brief report concerning the cyclomannoepoxides.[9] In this paper, we present full details concerning the modification of α, β and γ-cyclodextrins at the secondary face. The molecular modelling of these compounds is discussed in terms of the results of ^{1}H-NMR studies.

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RESULTS AND DISCUSSION

Synthesis

The synthetic route employed involves the protection–deprotection strategy developed by Defaye[10] (per-halogenation), Fugedi[11] (per-silylation) and ourselves (per-silylation),[12] and is given in Figure 1.

The per-6-*O*-tert-butyldimethylsilyl cyclodextrins (**1a** = α, **1b** = β and **1c** = γ) are treated with *para*-toluenesulphonyl chloride in pyridine in the presence of 4-dimethylaminopyridine, as a catalyst, for 24 h at room temperature. Workup and chromatographic separation gives the per-O2-tosyl derivatives in good yield: **2a** = 55%, **2b** = 58%, **2c** = 60%.

During the course of the tosylation, under- and over-substituted derivatives are obtained and may be isolated. The yields are of the order of 5% or less, and the products show characteristically complex ^{1}H-NMR spectra.

Desilylation was achieved by treatment, at room temperature for 7 h, with boron trifluoride etherate in anhydrous chloroform. (Even though the $CHCl_3$ is distilled over $CaCl_2$ prior to use the solvent should be stabilized with amylene and *not* ethanol if high yields are to be obtained.) The unprotected tosylates **3a** (51%), **3b** (55%), and **3c** (60%) are purified by column chromatography.

The cyclomannoepoxides are then obtained via a base catalysed intramolecular substitution, using K_2CO_3 in methanol; yields of the desired products **4a**, **4b** and **4c** are ⩾90%.

In an alternative approac, the highly lipophilic epoxide **5b** was prepared from **2b** by treatment with sodium hydride in tetrahydrofuran. Purification via column chromatography gave the desired product in 75% yield.

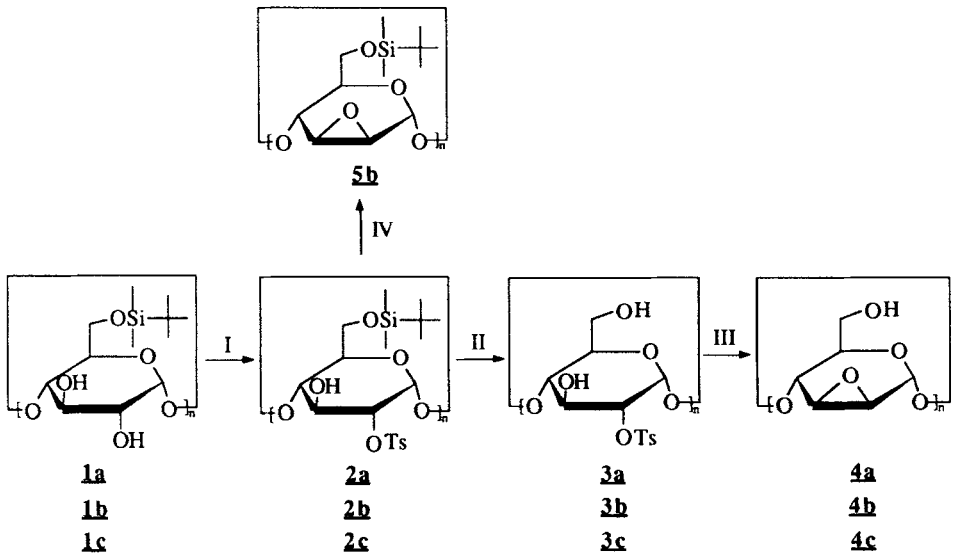

Figure 1 Synthetic route to secondary hydroxy substituted cyclodextrins. a, $n = 6$; b, $n = 7$; c, $n = 8$. I, *p*-toluenesulphonylchloride/dimethylamino/pyridine. II, $BF_3Et_2/CHCl_3$. III, K_2CO_3/MeOH. IV, NaH/THF.

Table 1 ^{1}H chemical shift changes (ppm) of cyclodextrin derivatives

	H-1	*H-2*	*H-3*	*OH-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OH-6*	*CH_3-Si*	*CH_3-C*	*CH_3-tosyl*	*Tosyl A*	*Tosyl B*
2a[1]	5.15	4.30	N.A.	3.05	N.A.	3.56	N.A.	N.A.	–	0.00	0.86	2.45	7.79	7.33
2b[1]	5.20	4.27	N.A.	3.10	N.A.	3.48	N.A.	N.A.	–	0.00	0.86	2.45	7.80	7.33
2c[1]	5.39	4.32	3.90	3.07	N.A.	3.50	N.A.	N.A.	–	0.00	0.86	2.44	7.83	7.32
3a[2]	4.98	4.30	4.05	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–	–	2.57	7.98	7.57
3b[3]	5.02	3.95	3.80	4.86[3] 3.05[1]	N.A.	N.A.	N.A.	N.A.	4.45	–	–	2.40	7.81	7.41
3c[2]	5.42	4.32	4.15	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–	–	2.56	7.97	7.57
4a[2]	5.45	3.54	3.33	–	3.91	N.A.	N.A.	N.A.	4.78	–	–	–	–	
4b[2]	5.42	3.57	3.34	–	4.03	N.A.	N.A.	N.A.	4.71	–	–	–	–	
4c[2]	5.46	3.61	3.33	–	4.09	N.A.	N.A.	N.A.	4.66	–	–	–	–	
5b[2]	5.16	3.33	3.12	–	4.13	3.54	3.91	3.67	–	0.03	0.88	–	–	

[1] $CDCl_3$. [2] Acetone-d_6. [3] DMSO-d_6. N.A., not applicable.

Spectroscopic characterization

^{1}H and ^{13}C-NMR data for the compounds are presented in Tables 1 and 2, respectively. For compounds **2a**, **2b**, **2c**, the ^{1}H and COSY spectra obtained in $CDCl_3$ show considerable upfield displacement of the OH-3 resonance, displaced from 6.7 ppm to 3 ppm, as shown in Figures 2a and 2b.

In the ^{1}H-NMR spectrum of compound **3b** in $CDCl_3$, the OH-3 resonance is again observed at 3.05 ppm; however in dmso-d_6 a downfield shift to 4.86 ppm is observed. These effects may be ascribed to the formation of intramolecular OH...O=S-tosyl H-bonds in $CDCl_3$; in dmso-d_6 the solvent O=S– functionality is capable of acting as an H-bond acceptor, and partial disruption of the intramolecular H-bond network results in the shift to 4.86 ppm. For compound **3c** in acetone-d_6 the weaker H-bond accepter strength of acetone causes less disruption and the signal is now shifted to 4.28 ppm.

In the epoxides **4a**–**4c** and **5b** the H2 and H3 signals are observed as an AB pattern with $J^{2-3} = 3.5$ Hz and J^{1-2} and J^{3-4} effectively zero. This pattern is characteristic of the mannoepoxides in a half-chair conformation, and is in disaccord with an altro-conformation. The COSY 2D spectrum of **4b** in acetone-d_6 is given in Figure 3. The spectrum was obtained under normal COSY conditions at 200 MHz: interestingly, considerable additional correlation transfer occurs, in particularly for H1 where crosspeaks are observed with all the saccharide ring protons. In Table 3 are given the coupling constants for the H5, H6 and H6' protons of **4b** in pyridine-d_5 (25°C and

Table 2 ^{13}C chemical shift changes (ppm) of cyclodextrin derivatives

	C-1	*C-2*	*C-4*	*C-3*	*C-5*	*C-6*	*CH_3–Si*	*CH_3–C*	*CH_3–C*	*CH_3–tosyl*	*Tosyl*	
2a[1]	99.2	79.6	81.1	69.9	71.5	61.7	−5.3 −5.4	18.1	25.7	21.6	145.1 129.5	132.8 128.2
2b[1]	98.8	79.9	80.0	69.9	71.6	61.6	−3.2 −3.4	18.2	25.8	21.7	145.0 129.5	133.0 128.3
2c[1]	97.9	78.4	79.7	69.8	71.5	61.6	−5.2 −5.4	18.2	25.7	21.6	145.0 129.5	132.9 128.1
3a[2]	98.7	79.5	81.7	69.5	72.3	60.9	–	–	–	20.8	145.3 129.7	133.6 128.4
3b[3]	95.8	76.7	79.2	68.4	71.0	59.2	–	–	–	20.9	144.5 129.4	132.7 127.8
3c[2]	96.5	77.3	79.7	69.9	71.6	60.7	–	–	–	20.8	145.3 129.8	133.6 128.3
4a[2]	96.1	53.3	70.1	49.0	71.3	63.1	–	–	–	–	–	
4b[2]	95.2	53.7	68.8	49.4	70.5	62.5	–	–	–	–	–	
4c[2]	94.4	54.1	67.7	50.1	70.5	62.8	–	–	–	–	–	
5b[2]	96.9	53.7	68.7	49.4	69.8	62.8	−5.1 −5.3	18.4	25.9	–	–	

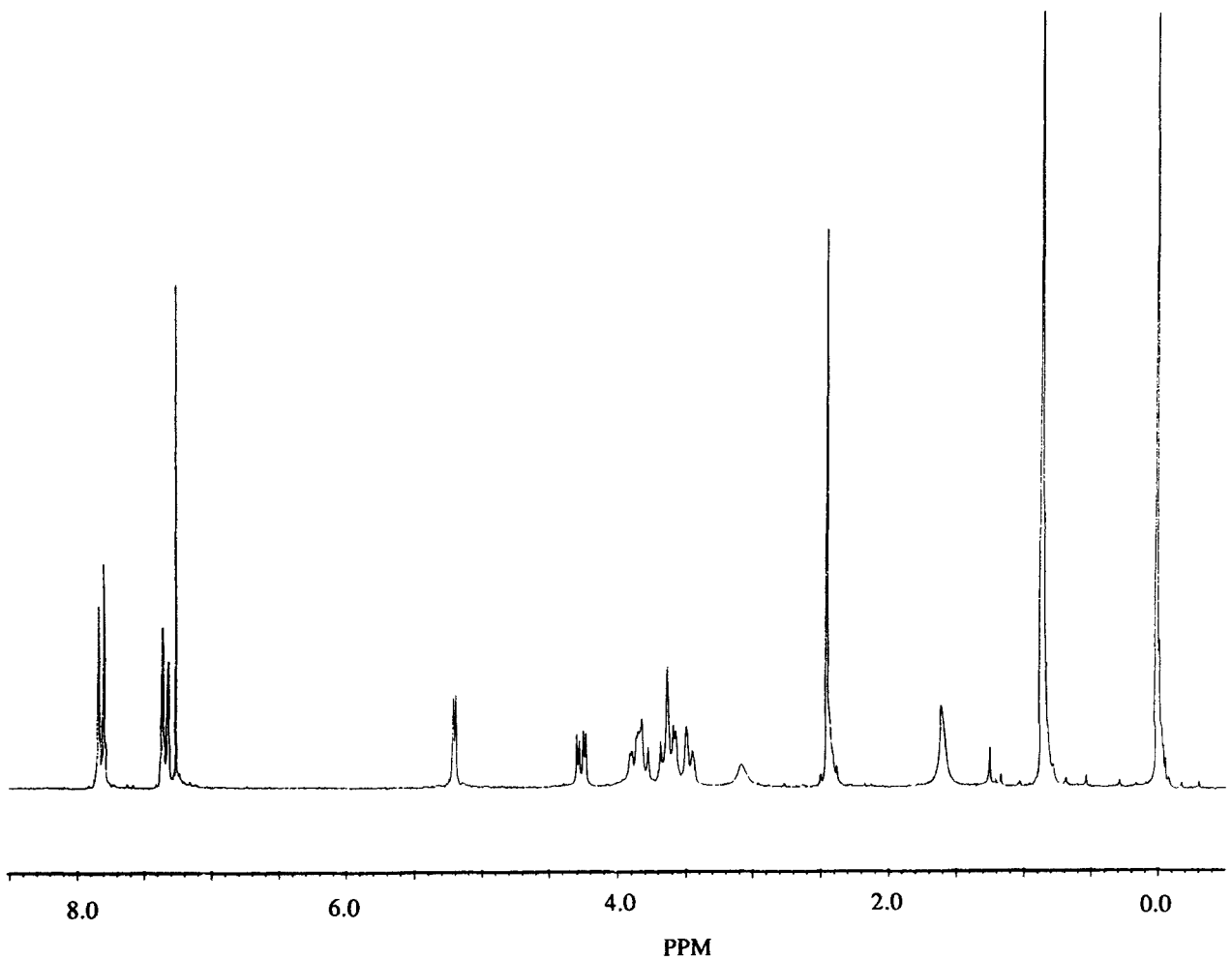

Figure 2a ^1H-NMR spectrum of **2b** in $CDCl_3$.

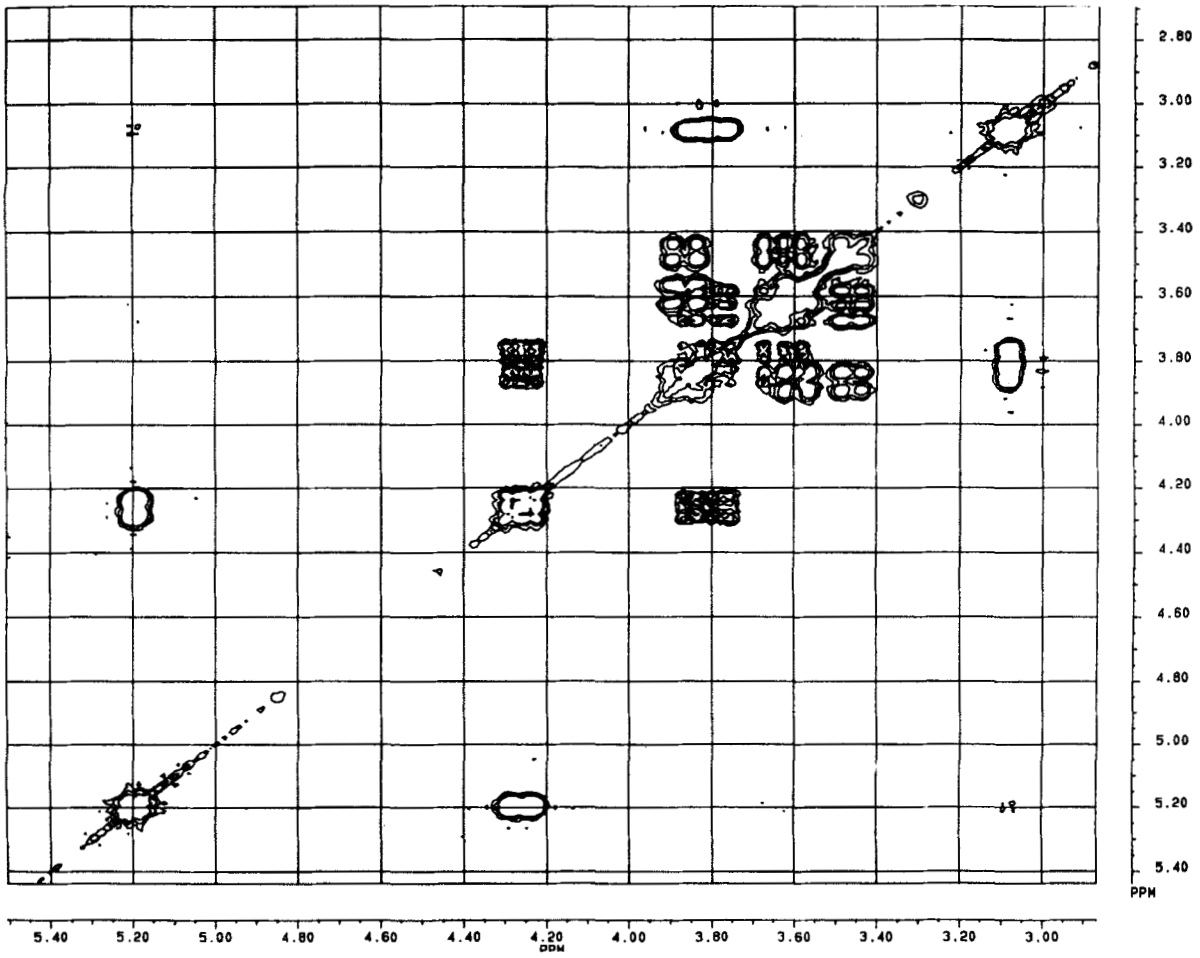

Figure 2b COSY spectrum of **2b** in $CDCl_3$.

100°C), CD_3OD, acetone-d_6 and D_2O (80°C). It is clear that whilst the chemical shifts for these protons are highly solvent-dependent, the H5–H6′ coupling constants are effectively solvent-insensitive. The temperature dependence of the H5–H6 and H5–H6′ coupling constants in pyridine suggests that in this solvent, at lower temperatures, less mobility between the *gauche–gauche* and *gauche–trans* conformations exists.

In Figure 4 we show the $^1H-^{13}C$ correlation spectra of **4b**. The chemical shifts of C2 and C3 in all the epoxides are in the regions of 53–54 and 49–50 ppm, respectively, again in agreement with manno rather than altro stereochemistry.

Fast atom bombardment (FAB) mass spectra have been obtained for **4a**, **4b** and **4c**. Strong MH^+ peaks are observed at 865, 1009 and 1153 mass units, respectively, in agreement with the expected 144 mass difference of a mannoepoxide unit. In all three cases no significant ions are observed at the MH + 18 value which would correspond to an incomplete epoxidation.

For **4a** and **4c** there is a slight selectivity for Na^+ over K^+, with peak height ratios MNa^+:MK^+ of 78:72 and 72:54, respectively. However for **4b** the situation is reversed with an extremely high selectivity for K^+ (ratio 20:40). That this selectivity occurs for the β-CD derivative and not the α- and γ-CD derivatives may suggest a ring-size dependent complexation. However it is known that complexation of K^+ by β-CD itself occurs external to the ring[12] and it may be that geometry of **4b** is more favourable than that of **4a** and **4c** to $O-K^+$ interactions.

Molecular modelling

Molecular modelling was carried out on an Evans and Sutherland PS330-Microvax system using the SYBYL 5.10 package.[13] The geometry of the β-CD molecule was initially taken from the Cambridge Data Bank. The model was symmetrized by removal and reinstation of successive glucopyranose units. The cyclomannoepoxide was constructed under the Building sub-

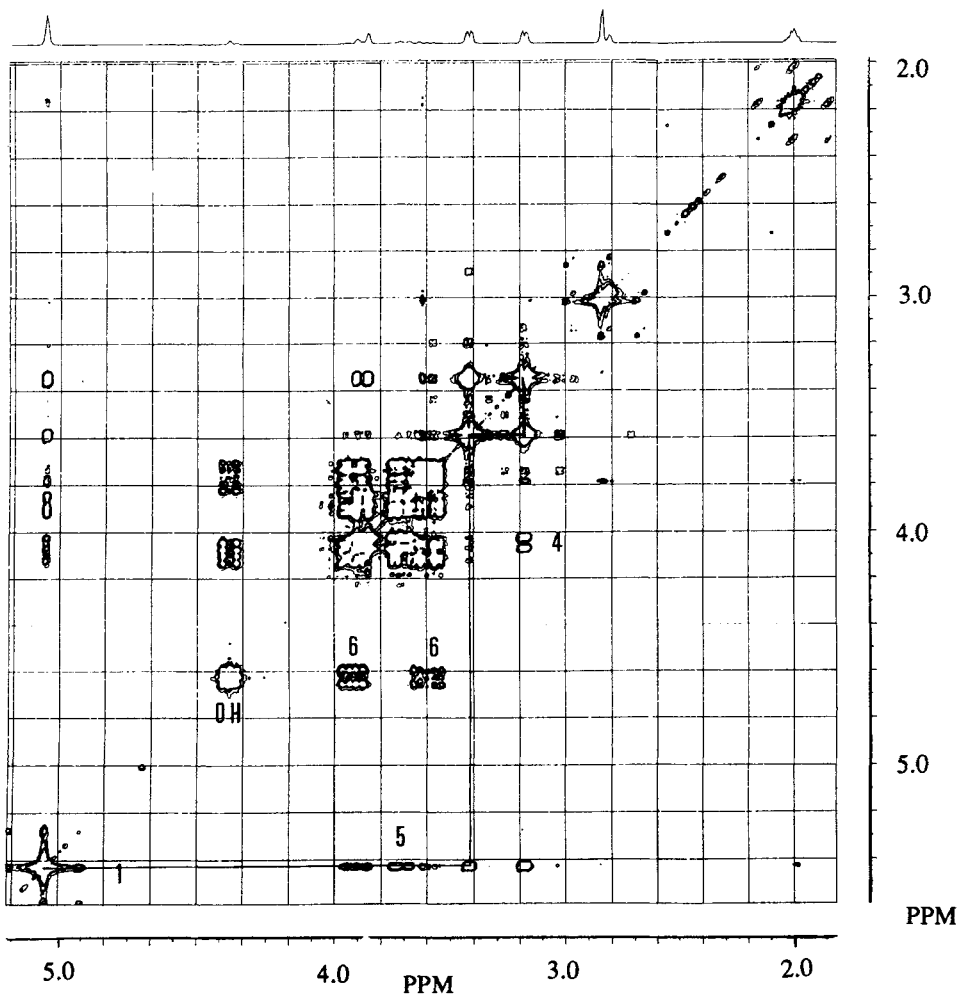

Figure 3 COSY spectrum of **4b** in acetone-d_6.

Table 3 Coupling constants (Hz) for protons H-5, H-6, H-6′ and OH-6 in different solvents

Solvent	J_{5-6}	$J_{5-6'}$	$J_{6-6'}$	J_{6-OH} / $J_{6'-OH}$
Pyridine-d_6 (25°C)	<2.0	3.0	10.0	5.5
Pyridine-d_6 (100°C)	2.9	5.1	11.6	
Acetone-d_6	2.0	5.7	12.0	5.1
CD_3OD	<2.0	4.5	14.4	
D_2O (80°C)	<2.0	5.1	14.4	

program and energy minimization carried out. The torsion angles obtained were compared with experimental values using the Karplus equation.[14] A conformational search about C5–C6 was carried out using 120° increments and the initial torsion angle about this bond was set to the *gauche–gauche* conformation.

In Figure 5 is shown the basic glucose pyranose ring in the calculated half-chair conformation. Figure 6 shows a ball and stick representation of the minimal energy conformation in which all seven rings are present in the *gauche–gauche* conformation.

The conformational energy versus bond angle maps (Fig 7) show a clear preference for the *gauche–gauche* and gauche conformations for rotation about the glucopyranose ring. In Table 4 are given the torsion angles calculated from molecular graphics and the Karplus equation-derived torsion angles for the half-chair conformation. As can be seen, close agreement exists between theoretically calculated and experimentally derived values.

It is clear from the molecular modelling that the hydrophobic nature of the cavity is considerably increased with both H2 and H3 now being oriented towards the interior. This new structure reveals a system in which the hydrophilic–hydrophobic balance leads to an amphiphilic molecule which we have previously shown[9] to have surfactant properties.

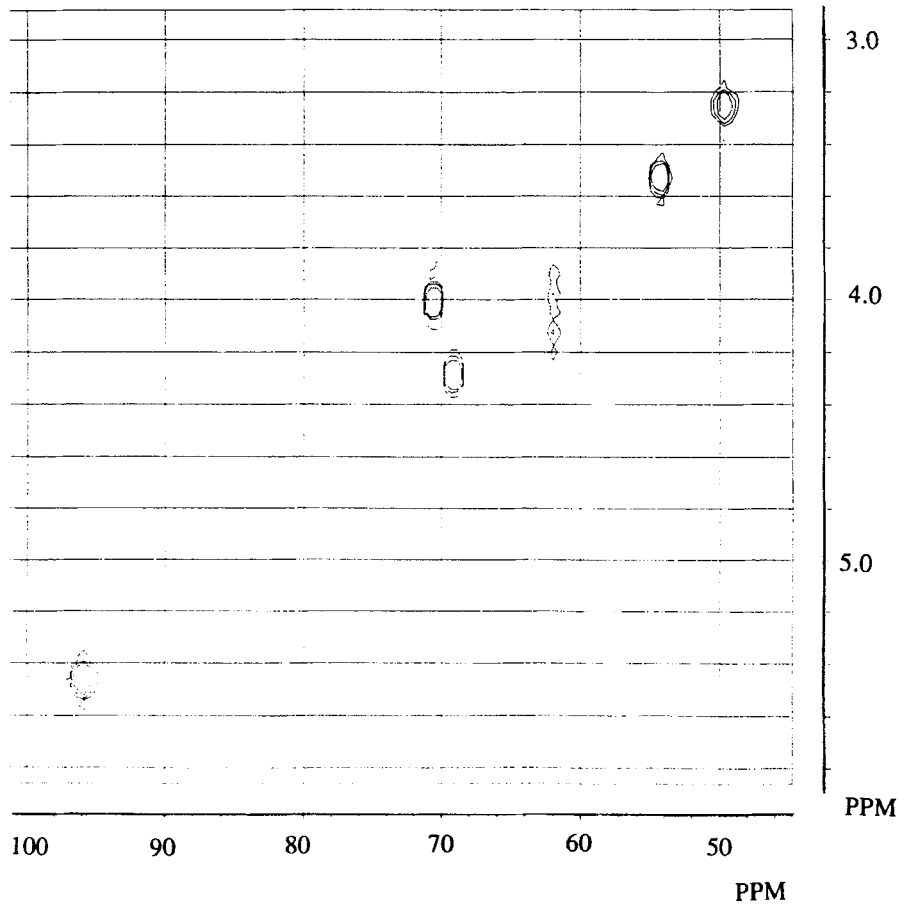

Figure 4 $^{1}H-^{13}C$ NMR correlation spectrum of **4b** in acetone-d_6.

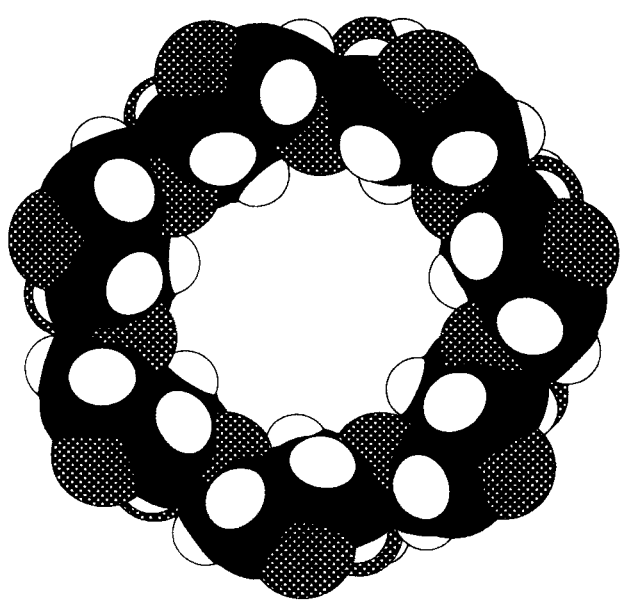

Figure 5 Molecular graphics-derived space filling model of the basic mannoepoxide ring in the calculated half-chair conformation.

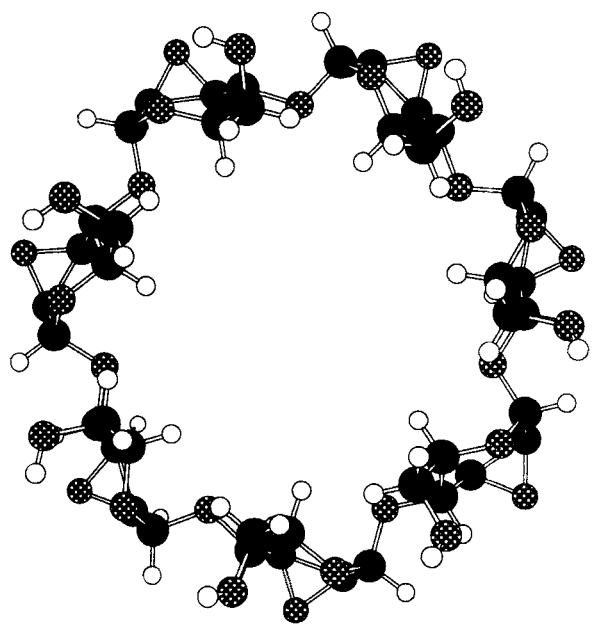

Figure 6 Molecular graphics-derived ball and stick representation of the minimal energy conformation of **4b**.

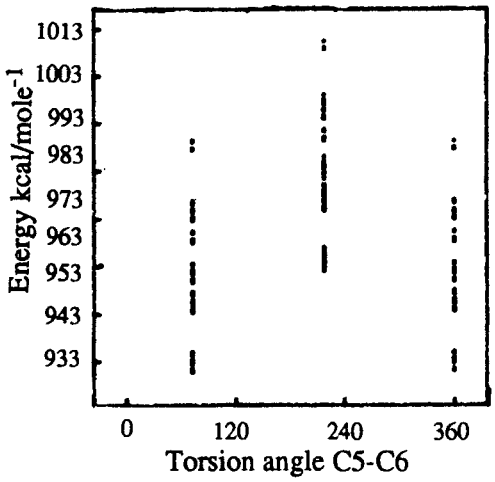

Figure 7 Energy versus bond angle map of **4b** about the C5–C6 torsion angle of one mannoepoxide fragment.

Table 4 Molecular graphics-calculated and Karplus equation-derived torsion angles for the mannoepoxide ring

	Angle (°)	
	Molecular graphics	*Karplus equation*
H1–C1–C2–H2	70.2	77.0
H3–C3–C4–H4	97.2	98.0
H4–C4–C5–H5	170.8	175.0

The relative ease of per-tosylation at the O2 hydroxy position contrasts strongly with the problems associated with the obtention of total tosylation at the O6 face.[15] The use of the tert-butyldimethylsilyl group to protect the O6 hydroxy groups leads to a more lipophilic molecule which has proved easier to separate. This protection allows use of the disparity in the reactivity between the O2 and O3 hydroxy groups, in contrast to attempts to tosylate at the O6, where clean, complete reaction is disfavoured by the only slight reactivity differences between O2 and O6.[15]

With regard to the epoxidation, formation of the ring at the secondary face yields an amphiphilic molecule, in which the glucopyranose ring is now present in a half-chair conformation. Formation of the 1,6-anhydro-cyclodextrins leads to conformational change with the glucopyranose now present in the $^1C_4$ conformation.[15] In 1,6-anhydro molecules the aqueous solubility is greatly increased, in contrast with our epoxides, where the solubility in water is further diminished.

The removal of both secondary hydroxy groups and the inversion at O2 increases the hydrophobic nature of the cavity which should lead to an increase in the compatibility between the cavity and hydrophobic guest molecules. Hence it might be expected that the inclusion capacities of these molecules would be greater than those of the parent cyclodextrins. However, the absence of the secondary hydroxy groups removes the possibility of formation of dimers: these dimers are essential for inclusion in the solid state for β-cyclodextrin. The effects of these two opposing characteristics on the stability of inclusion complexes are currently being studied.

CONCLUSION

We have demonstrated that clean, high yield tosylation at the O2 secondary hydroxyl function of cyclodextrins may be achieved. Such substitution depends on a protection–deprotection route at the primary hydroxy face. The use of combined molecular graphics and NMR techniques has allowed us to suggest a half-chair molecular conformation for the cyclomannoheptaepoxide structure. Routes to clean opening of the epoxide ring are currently being studied.

EXPERIMENTAL

α-CD, β-CD and γ-CD (Wacker) were recrystallized from water and dried at 0.1 mmHg and 120°C for 48 h. Pyridine and *N*,*N*-dimethylformamide (DMF) were dried over, and redistilled from, CaH_2, anhydrous alcohol-free chloroform was redistilled over $CaCl_2$ and methanol was dried over, and redistilled from, Mg. THF was dried over, and redistilled from sodium tert-butyldimethylsilyl chloride (Fluka). Boron trifluoride etherate (Fluka), *p*-toluenesulphonyl chloride (Fluka) and anhydrous potassium carbonate (OSI) were used without further purification. Aqueous-washed organic solutions were dried over anhydrous Na_2SO_4. TLC was performed on silica gel (F254, Merck) with detection by charring with H_2SO_4, and column chromatography was performed on a Silica Gel 60 (Merck, 9385). Optical rotations were determined on a Perkin–Elmer Model 241 MC polarimeter. Melting points were determined with a Kofler apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC200 spectrometer (200 MHz for ^1H- 50 MHz for ^{13}C) and chemical shifts (ppm) are relative to those of the deuterated solvents. FAB mass spectra were obtained on a Kratos MS-80 spectrometer using the Magic Bullets technique.

Hexakis(6-*O*-tert-butyldimethylsilyl-2-*O*-tosyl)cyclomaltohexaose (2a)

To a solution of anhydrous **1a** (1 g) in pyriding (50 ml) was added 4-dimethylaminopyridine (1.3 g) and *para*-toluenesulphonyl chloride (2.1 g), and the mixture was

stirred for 24 h at 50°C. Water (10 ml) was added, the mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (2 × 50 ml). The combined extracts were washed with 2N hydrochloric acid (2 × 25 ml), saturated aqueous sodium hydrogenocarbonate (25 ml) and water (2 × 25 ml), then dried and concentrated. Column chromatography (2-butanone/dichloromethane, 4:96) of the residue gave **2a** (1.4 g, 55%). R_f 0.14 ($CHCl_3$/2-butanone, 95:5), $[\alpha]_D^{20}$ + 78° (1.0, $CHCl_3$); ^{1}H-NMR: 5.10 (6H, d, H-1, J_{1-2} = 3.4 Hz), 4.25 (6H, dd, H-2, J_{1-2} = 3.4 Hz, J_{2-3} = 9.8 Hz), 3.05 (6H, brd, OH-3), 7.79 (12H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 7.33 (12H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 2.45 (18H, s, tosyl), 0.86 (54H, s, Me_3CMe_2Si—), 0.00 (36H, s, Me_3CMe_2Si—); ^{13}C-NMR ($CDCl_3$): 99.19 (C-1), 81.07, 79.55 (C-2, C-4), 71.52, 69.95 (C-3, C-5), 61.68 (C-6), 25.72, 18.14, −5.32, −5.40 ($Me_3CMe_AMe_BSi$—), 145.05, 132.82, 129.47, 128.19, 21.62 (tosyl).

Anal. calcd. for $C_{114}H_{180}O_{42}Si_6S_6$: C, 52.99; H, 7.02. Found: C, 52.79; H, 7.20.

Heptakis(6-*O*-tert-butyldimethylsilyl-2-*O*-tosyl)cyclomaltoheptaose (2b)

This compound is prepared via a procedure analogous to that of **2a**; yield 58%. R_f 0.25 ($CHCl_3$/2-butanone, 95:5); $[\alpha]_D^{20}$ + 57° (1.0, $CHCl_3$); ^{1}H-NMR: 5.19 (7H, d, H-1, J_{1-2} = 3.49 Hz), 4.26 (7H, dd, H-2, J_{1-2} = 3.5 Hz, J_{2-3} = 9.7 Hz), 3.08 (7H, d, OH-3, $J_{3\text{-OH}}$ = 3.2 Hz), 7.80 (14H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 7.33 (14H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 2.45 (21H, s, tosyl), 0.86 (63H, s, Me_3CMe_2Si—), 0.00 (42H, s, Me_3CMe_2Si—); ^{13}C-NMR ($CDCl_3$): 98.84 (C-1), 80.02, 79.85 (C-2, C-4), 72.62, 69.93 (C-3, C-5), 62.63 (C-6), 25.81, 18.23, −3.23, −3.41 ($Me_3CMe_AMe_BSi$—), 145.03, 133.00, 129.55, 128.25, 21.70 (tosyl).

Anal. calcd. for $C_{133}H_{210}O_{49}Si_7S_7$: C, 52.99; H, 7.02. Found: C, 52.87; H, 7.11.

Octakis(6-*O*-tert-butyldimethylsilyl-2-*O*-tosyl)cyclomaltooctaose (2c)

This compound is prepared via a procedure analogous to that of **2a**; yield 60%. R_f 0.31 ($CHCl_3$/2-butanone, 95:5), $[\alpha]_D^{20}$ + 75° (1.0, $CHCl_3$); ^{1}H-NMR: 5.34 (8H, d, H-1, J_{1-2} = 3.4 Hz), 4.28 (8H, dd, H-2, J_{1-2} = 3.4 Hz, J_{2-3} = 9.8 Hz), 2.78 (8H, brd, OH-3), 7.83 (16H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 7.32 (16H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 2.44 (24H, s, tosyl), 0.86 (72H, s, Me_3CMe_2Si—); ^{13}C-NMR ($CDCl_3$): 97.86 (C-1), 79.67, 78.45 (C-2, C-4), 71.52, 69.87 (C-3, C-5), 61.64 (C-6), 25.74, 18.19, −5.20, −5.43 ($Me_3CMe_AMe_BSi$—), 144.97, 132.93, 129.49, 128.12, 21.61 (tosyl).

Anal. calcd. for $C_{152}H_{240}O_{56}Si_8S_8$: C, 52.99; H, 7.02. Found: C, 52.78; H, 7.07.

Hexakis(2-*O*-tosyl)cyclomaltohexaose (3a)

A solution of **2a** (2 g) and boron trifluoride etherate (1.0 ml) in chloroform (50 ml) was stirred for 7 h at room temperature, then diluted with chloroform (25 ml), and poured into ice-water. The organic layer was separated and washed successively with water (40 ml), saturated aqueous sodium hydrogenocarbonate (40 ml) and water (40 ml), then dried and concentrated. Column chromatography (ethyl acetate/methanol, 80:20) of the residue gave **3a** (750 mg, 51%). R_f 0.20 (ethyl acetate/methanol, 80:20); $[\alpha]_D^{20}$ + 77° (1.0, $CHCl_3$); ^{1}H-NMR (CD_3COCD_3): 4.98 (6H, d, H-1, J_{1-2} = 3.3 Hz), 4.30 (6H, dd, H-2, J_{1-2} = 3.3 Hz, J_{2-3} = 9.9 Hz), 7.98 (12H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 7.57 (12H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 2.57 (18H, s, tosyl); ^{13}C-NMR (CD_3COCD_3): 98.75 (C-1), 81.66, 79.49 (C-4, C-2), 72.32, 69.55 (C-3, C-5), 60.94 (C-6), 145.27, 133.62, 129.73, 128.44, 20.79 (tosyl).

Anal. calcd. for $C_{78}H_{96}O_{42}S_6$: C, 49.36; H, 5.10. Found: C, 48.95; H, 5.28.

Heptakis(2-*O*-tosyl)cyclomaltoheptaose (3b)

This compound is prepared via a procedure analogous to that of **3a**; yield 55%. R_f 0.15 (ethyl acetate/methanol, 80:20); $[\alpha]_D^{20}$ + 70° (1.0, $CHCl_3$); ^{1}H-NMR (CD_3COCD_3): 5.13 (7H, d, H-1, J_{1-2} = 3.53 Hz), 4.36 (7H, dd, H-2, J_{1-2} = 3.31 Hz, J_{2-3} = 9.35 Hz), 7.97 (14H, d, tosyl, $J_{H_A-H_B}$ = 8.39 Hz), 7.57 (14H, d, tosyl, $J_{H_A-H_B}$ = 8.2 Hz), 2.57 (21H, s, tosyl); ^{13}C-NMR (DMSO-d_6): 95.76 (C-1), 79.19, 76.72 (C-4, C-2), 71.02, 68.37 (C-3, C-5), 59.15 (C-6), 144.46, 132.62, 129.36, 127.76, 20.85 (tosyl).

Anal. calcd. for $C_{91}H_{112}O_{49}S_7$: C, 49.36; H, 5.10. Found: C, 49.07; H, 5.40.

Octakis(2-*O*-tosyl)cyclomaltooctaose (3c)

This compound is prepared via a procedure analogous to that of **3a**; yield 60%. R_f 0.25 (ethyl acetate/methanol, 85:15); $[\alpha]_D^{20}$ + 88° (1.0, $CHCl_3$); ^{1}H-NMR (CD_3COCD_3): 5.42 (8H, d, H-1, J_{1-2} = 3.4 Hz), 4.32 (8H, dd, H-2, J_{1-2} = 3.4 Hz, J_{2-3} = 9.6 Hz), 7.97 (16H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 7.57 (16H, d, tosyl, $J_{H_A-H_B}$ = 8.3 Hz), 2.56 (24H, s, tosyl); ^{13}C-NMR (CD_3COCD_3): 96.49 (C-1), 79.72, 77.29 (C-4, C-2), 71.63, 69.87 (C-3, C-5), 60.71 (C-6), 145.28, 133.61, 129.84, 128.28, 20.82 (tosyl)

Anal. calcd. for $C_{104}H_{128}O_{56}S_8$: C, 49.36; H, 5.10. Found: C, 49.04; H, 5.29.

Cyclo-α-1,4-hexamanno-2,3-epoxide (4a)

To a solution of anhydrous **3a** (1 g) in methanol (20 ml) was added potassium carbonate (1.8 g). The mixture was stirred for 6 h at 60°C, then the mixture

was evaporated. Water (25 ml) was added, the pH was adjusted to 7, the precipitate was collected by filtration, and recrystallized from water to give **4a** (410 mg, 90%). M.p. 268–269.5°C (from MeOH). R_f 0.52 (2-butanone/1-butanol/H_2O, 9:1:1); $[\alpha]_D^{20}$ + 128° (1.0, DMF); ^{1}H-NMR (CD_3COCD_3): 5.39 (6H, s, H-1), 3.53 (6H, d, H-2, J_{2-3} = 3.5 Hz), 3.33 (6H, d, H-3, J_{2-3} = 3.5 Hz), 3.91 (6H, d, H-4, J_{4-5} = 8.7 Hz), 4.91 (6H, t, OH-6, $J_{6\text{-OH}}$ = 5.9 Hz); ^{13}C-NMR (CD_3COCD_3): 96.09 (C-1), 71.33 (C-5), 70.06 (C-4), 63.11 (C-6), 53.25 (C-2), 49.00 (C-3).

Anal. calcd. for $C_{36}H_{48}O_{24}$: C, 50.00; H, 5.59. Found: C, 49.71; H, 5.69.

Cyclo-α-1,4-heptamanno-2,3-epoxide (4b)

This compound is prepared via a procedure analogous to that of **4a**; yield 90%. M.p. 280–282°C (from MeOH). R_f 0.51 (2-butanone/1-butanol/H_2O, 9:1:1); ^{1}H-NMR (CD_3COCD_3): 5.42 (7H, s, H-1), 3.57 (7H, d, H-2, J_{2-3} = 3.5 Hz), 3.34 (7H, d, H-3, J_{2-3} = 3.5 Hz), 4.03 (7H, d, H-4, J_{4-5} = 9.2 Hz), 4.71 (7H, t, OH-6, $J_{6\text{-OH}}$ = 5.9 Hz); ^{13}C-NMR (CD_3COCD_3): 95.24 (C-1), 70.54 (C-5), 68.81 (C-4), 62.52 (C-6), 53.66 (C-2), 49.35 (C-3).

Anal. calcd. for $C_{42}H_{56}O_{28}$: C, 50.00; H, 5.59. Found: C, 49.82; H, 5.55.

Cyclo-α-1,4-octamanno-2,3-epoxide (4c)

This compound is prepared via a procedure analogous to that of **4a**; yield 93%. M.p. 290–291°C (from MeOH). R_f 0.53 (2-butanone/*n*-butanol/H_2O, 9:1:1); $[\alpha]_D^{20}$ 169° (1.0 DMF); ^{1}H-NMR (CD_3COCD_3): 5.46 (8H, s, H-1), 3.61 (8H, d, H-2, J_{2-3} = 3.6 Hz), 3.33 (8H, d, H-3, J_{2-3} = 3.6 Hz), 4.09 (8H, d, H-4, J_{4-5} = 9.2 Hz), 4.66 (8H, t, OH-6, $J_{6\text{-OH}}$ = 5.9 Hz); ^{13}C-NMR (CD_3COCD_3): 94.39 (C-1), 70.21 (C-5), 67.74 (C-4), 62.81 (C-6), 54.13 (C-2), 50.10 (C-3).

Anal. calcd. for $C_{48}H_{64}O_{32}$: C, 50.00; H, 5.59. Found: C, 49.65; H, 5.50.

Cyclo-α-1,4-hepta-6-*O*-tert-butyldimethylmanno-2,3-epoxide (5b)

To a solution of anhydrous **2b** (150 mg) in tetrahydrofuran (10 ml) was added NaH (30 mg, 60% in oil). The mixture was stirred for 3 h at 60°C and methanol (10 ml) was added. The pH was adjusted to 7, then the mixture was concentrated under reduced pressure, the residue was extracted with ethyl acetate (2 × 25 ml) and then dried and concentrated. Column chromatography (ethyl acetate/dichlormethane, 13:87) of the residue gave **5b** (70 mg, 75%). R_f 0.41 (dichloromethane/AcOEt, 83:17), $[\alpha]_D^{20}$ + 83° (1.0, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): 5.16 (7H, s, H-1), 4.13 (7H, d, H-4, J_{4-5} = 9.0 Hz), 3.91 (7H, dd, H-6, J_{5-6} = 3.0, $J_{6-6'}$ = 11.3), 3.67 (7H, d, H-6', $J_{6-6'}$ = 11.3 Hz), 3.54 (7H, m, H-5), 3.33 (7H, d, H-2, J_{2-3} = 3.5 Hz), 3.12 (7H, d, H-3, J_{2-3} = 3.5 Hz), 0.88 (63H, s, Me_3CMe_2Si—); ^{13}C-NMR data (CD_3COCD_3): 96.91 (C-1), 69.80 (C-5), 68.84 (C-4), 62.84 (C-6), 53.68 (C-2), 49.35 (C-3), 25.88, 25.56, 18.38, −5.10, −5.28 ($Me_3CMe_ACMe_BSi$—).

Anal. calcd. for $C_{84}H_{154}O_{28}Si_7$: C, 55.78; H, 8.58. Found: C, 55.69; H, 8.63.

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