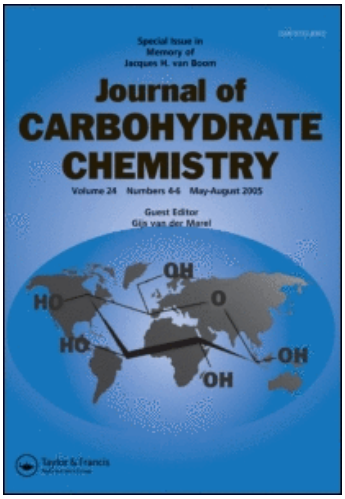

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DERIVATIVES OF α-CYCLODEXTRIN AND THE SYNTHESIS OF 6-O-α-D-GLUCOPYRANOSYL-α-CYCLODEXTRIN

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ABSTRACT

Regioselective silylation of α-cyclodextrin with tert-butyldimethylsilyl chloride in N,N-dimethylformamide in the presence of imidazole gave, in 75% yield, the hexakis(6-O-tert-butyldimethylsilyl) derivative 2, which was transformed into the hexakis(2,3-di-O-methyl, 6-O-methyl, 2,3-di-O-propyl, and 2,3-di-O-acetyl) derivatives. On methanesulfonylation and p-toluenesulfonylation, the hexakis(2,3-di-O-acetyl) derivative 16 afforded the hexakis(2,3-di-O-acetyl-6-O-methylsulfonyl 17 and 2,3-di-O-acetyl-6-O-p-tolylsulfonyl 18) derivatives, respectively. Nucleophilic displacement of 17 and 18 with iodide, bromide, chloride, and azide ions afforded the hexakis(6-deoxy-6-iodo 19, 6-bromo-6-deoxy, 6-chloro-6-deoxy, and 6-azido-6-deoxy) derivatives, respectively, of α-cyclodextrin dodeca-acetate. The hexakis(2,3-di-O-acetyl-6-deoxy) derivative was prepared from 19. Selective glucosylation of 16 with 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide under catalysis by halide ion, followed by removal of protecting groups, furnished 6-O-α-D-glucopyranosyl-α-cyclodextrin.

INTRODUCTION

The discrimination by selective reactions between the primary and secondary hydroxyl groups of cylcodextrins (cycloamyloses) is complicated by the statistical and steric problems imposed by the large number of hydroxyl groups and the torus structures.[1,2] Derivatives of α-cyclodextrin (1), in which all six primary hydroxyl groups have been selectively modified, include the hexakis(6-O-sulfonyl,[2-6] 6-azido-6-deoxy,[2,5] 6-amino-6-deoxy,[2,5] 6-acetamido-6-deoxy,[5] 6-O-methyl,[2] 6-bromo-6-deoxy,[7]

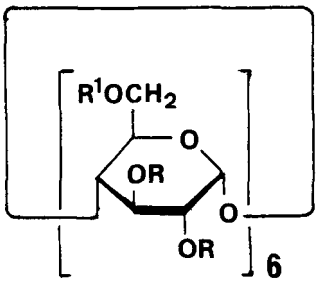
and 6-deoxy[6,7]) derivatives. However, the only synthesis reported of a derivative of 1, in which all twelve secondary hydroxyl groups have been selectively substituted, described the formation of the hexakis-(2,3-di-O-benzoyl) derivative[2] 14.

We now report the synthesis of several hexakis(6-substituted) and hexakis(2,3-di-substituted) derivatives of 1, using the hexakis-(6-O-tert-butyldimethylsilyl) derivative 2 as the key intermediate. Also reported is the first synthetic approach[8] to a branched cyclodextrin, 6-O-α-D-glucopyranosyl-α-cyclodextrin[9,10] (26).

RESULTS AND DISCUSSION

Treatment of dried[11] 1 with 6.6 mole equivalent of tert-butyl-dimethylsilyl chloride in N,N-dimethylformamide (DMF) in the presence of imidazole[12] for 1.5 h at room temperature gave, as the major product, 2 isolated crystalline in 75% yield after column chromatographic separation. The ^{13}C NMR spectrum of 2 showed the presence of only six skeleton carbon signals, indicating[2,13,14] a symmetrical pattern of substitution. Methylation of 2 with methyl iodide and sodium hydride in DMF[15] gave the crystalline hexakis(6-O-tert-butyldimethylsilyl-2,3-di-O-methyl) derivative 3 in 83% yield. O-Desilylation of 3 with tetrabutylammonium fluoride[12] in oxolane, followed by acetylation [to facilitate the isolation of the hexakis(2,3-di-O-methyl) derivative 5] afforded the crystalline hexakis-(6-O-acetyl-2,3-di-O-methyl) derivative 4, which was O-deacetylated to give the crystalline 5. Hydrolysis of 5, followed by reduction with sodium borohydride, and acetylation, produced 1,4,5,6-tetra-O-acetyl-2,3-di-O-methyl-D-glucitol as the sole product (GLC), confirming the structure of 2. Compound 5 was soluble both in water and common organic solvents. A similar reaction of 1 with 20 mole equivalent of the silylating reagent in DMF and pyridine for 20 h at 110 °C was reported to give hexakis(2,6-di-O-tert-butyldimethylsilyl)-α-cyclodextrin in 60% yield.[14]

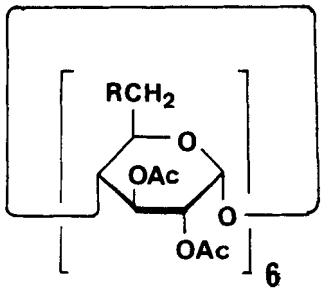
Benzylation of 2 with benzyl bromide and sodium hydride in DMF[15] gave in 79% yield after column chromatography, the crystalline hexakis(2,3-di-O-benzyl-6-O-tert-butyldimethylsilyl) derivative 6, which was O-desilylated, as above, to provide the hexakis(2,3-di-O-benzyl) derivative 7. Methylation[15] of 7 afforded the crystalline hexakis(2,3-di-O-benzyl-6-O-methyl) derivative 8, which was hydrogenolyzed catalytically in acetic acid in the presence of Pd/C, to furnish the known[2] 9. Acetylation of 9 gave the hexakis(2,3-di-O-acetyl-6-O-methyl) derivative 10. Similarly, alkylation of 2 with allyl bromide and sodium hydride in DMF gave the



	R	R^1		R	R^1
1	H	H	9	H	Me
2	H	t-$BuMe_2Si$	10	Ac	Me
3	Me	t-$BuMe_2Si$	11	All	t-$BuMe_2Si$
4	Me	Ac	12	All	H
5	Me	H	13	Pr	H
6	Bzl	t-$BuMe_2Si$	14	Bz	H
7	Bzl	H	15	Ac	t-$BuMe_2Si$
8	Bzl	Me	16	Ac	H

hexakis(2,3-di-O-allyl-6-O-tert-butyldimethylsilyl) derivative 11 in 84% yield after column chromatography. O-Desilylation of 11, as above, afforded the hexakis(2,3-di-O-allyl) derivative 12 which, on catalytic hydrogenation, gave the crystalline hexakis(6-O-propyl) derivative 13.

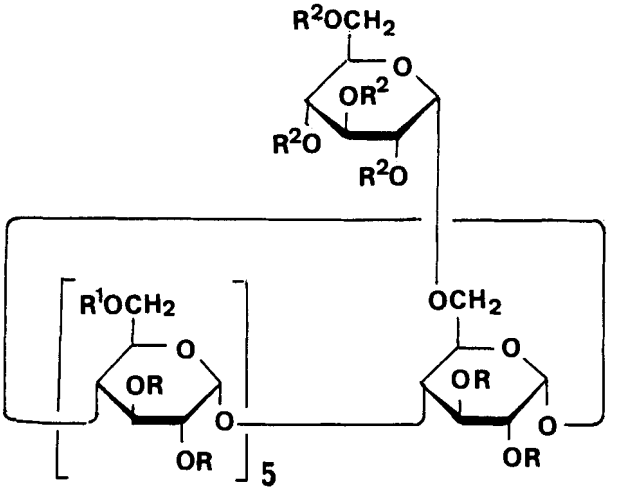
With a view to obtaining a precursor for 14, attempted benzoylation of 2 with excess of benzoyl chloride in pyridine gave a complex mixture that was difficult to separate by column chromatography. Acetylation of 2 with acetic anhydride-pyridine for 4 h at 100 °C gave the hexakis(2,3-di-O-acetyl-6-O-tert-butyldimethylsilyl) derivative 15 in 87% yield after column chromatography. When the acetylation was performed at room temperature, the reaction was sluggish and it required at least 5 days for completion. Attempts to O-desilylate 15 with tetrabutylammonium fluoride[12] in oxolane at room temperature resulted in the formation of a mixture of partially O-deacetylated products.[16] Attempted O-desilylation of 15 in acetic acid-oxolane-water[12] was also unsuccessful; most of 15 was recovered unchanged after 20 h at room temperature. In contrast, O-desilylation of 15 with boron trifluoride etherate[17] in dichloromethane proceeded smoothly, and the hexakis(2,3-di-O-acetyl) derivative 16 was isolated crystalline in 72% yield after column chromatography. Methylation of 16 with diazomethane-boron trifluoride etherate[18] produced 10, identical to the compound prepared earlier from 9, confirming the structure of 16.



	R		R
17	OMs	21	Br
18	OTs	22	Cl
19	I	23	N_3
20	H		

Methanesulfonylation of 16 gave the hexakis(2,3-di-O-acetyl-6-O-methylsulfonyl) derivative 17, isolated crystalline directly from the reaction mixture in 83% yield. p-Toluenesulfonylation of 16 afforded the crystalline hexakis(2,3-di-O-acetyl-6-O-p-tolylsulfonyl) derivative 18 in 77% yield after column chromatography. The physical constants (mp 138-141 °C, $[\alpha]_D$ +89.8°) of 18 were very different from those (mp 170-172 °C, $[\alpha]_D$ +67°) reported[4] for this compound. Compounds 17 (Ref. 3) and 18 (Ref. 4), prepared previously by selective sulfonylation of 1, followed by acetylation, may have been the mixtures not only having different degrees of substitution but also containing positional isomers,[2,19,20] as these compounds had not been purified by column chromatography.

Nucleophilic displacement of the sulfonates 17 and 18 with sodium iodide in DMF, followed by column chromatography, afforded the hexakis(2,3-di-O-acetyl-6-deoxy-6-iodo) derivative 19 as an amorphous solid, which was homogeneous by TLC analysis. Though the ^{13}C NMR spectrum of 19, prepared separately from 17 and 18, showed the six-fold symmetry expected for the structure of 19, the H-3 resonance in the ^{1}H NMR spectrum of 19 appeared as a broad signal and was not a doublet of doublets characteristic[7,21,22] of a symmetrical pattern of substitution, indicating that 19 obtained could not be freed from the traces of impurities by chromatographic fractionation. However, when 19 was subjected to reductive dehalogenation in methanol and 1,4-dioxane in the presence of Pd/C and triethylamine, the hexakis(6-deoxy) derivative[7] 20 was obtained crystalline in 80% yield after column chromatography. The structure of 20 was confirmed



	R	R^1	R^2
24	Ac	H	Bzl
25	Ac	H	H
26	H	H	H
27	Ac	Ac	Ac

by methanolysis and GLC examination of the trimethylsilyl derivatives of the methanolyzate. Compounds 17 and 18 underwent ready displacement with bromide, chloride, and azide ions in DMF to give the hexakis(2,3-di-O-acetyl-6-bromo-6-deoxy)[7] 21, hexakis(2,3-di-O-acetyl-6-chloro-6-deoxy) 22, and hexakis(2,3-di-O-acetyl-6-azido-6-deoxy)[2] 23 derivatives, respectively, in high yields; all the compounds being obtained in crystalline form. We have previously synthesized 20 and 21 by an alternative route, but these compounds had contained small amounts of D-glucose and unidentified side-products.[7]

Condensation of 16 with 2.9 mole equivalent of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide[23] in 1,2-dichloroethane and DMF in the presence of tetraethylammonium bromide[24] and molecular sieve for 20 h at room temperature gave [2,3-di-O-acetyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)]-pentakis(2,3-di-O-acetyl) derivative 24 in 39% yield after column chromatography. Catalytic hydrogenolysis of 24 (to give 25), and O-deacetylation of 25 furnished 26. The physical constants of 26 agreed with those given in the literature,[10] and the resonances observed in the ^{13}C NMR spectrum were consistent with those reported.[10] Acetylation of 26 gave the heneicosa-acetate 27. Interestingly, the ^{13}C NMR

spectra of 24 and 27 contained four and five signals, respectively for the anomeric carbon atoms.

Further synthesis of new derivatives of 1, starting from 2, as well as the application to β- and γ-cyclodextrins of a reaction sequence similar to those described here for 1 is now in progress.

EXPERIMENTAL

General Methods. Unless stated otherwise, these were the same as those described previously.[25] IR spectra were recorded with a Nicolet 5SXC FT-IR spectrometer in potassium bromide pellets. GLC analysis was performed under the same conditions as described previously.[26] The ^{1}H NMR spectrum of 19 and the ^{13}C NMR spectrum of 26 were recorded with a Jeol JNM-FX 200 spectrometer. The following solvent systems (v/v) were used for chromatography: (A) 50:10:1, (B) 40:10:1, and (C) 50:10:0.1 chloroform-methanol-water; (D) 8:1 chloroform-methanol; (E) 4:1, (F) 25:1, (G) 2:1, and (H) 20:1 hexane-ethyl acetate; (I) 95:5, (J) 97:3, and (K) 4:1 benzene-ethanol, and (L) 1:1 and (M) 2:1 benzene-ethyl acetate.

Hexakis(6-O-tert-butyldimethylsilyl)-α-cyclodextrin (2). A solution of tert-butyldimethylsilyl chloride (10.23 g, 67.9 mmol) in anhydrous DMF (50 mL) was added dropwise during 15 min at room temperature with exclusion of moisture to a stirred solution of dried[11] 1 (10.0 g, 10.3 mmol) and imidazole (9.24 g, 0.136 mol) in dry DMF (200 mL), and the mixture was stirred at room temperature. After ∿30 min, the mixture became cloudy and, after 1 h, TLC (solvent A) showed complete disappearance of 1 and the presence of a major component (R_F 0.41), together with some minor ones. The mixture was further stirred for 30 min and poured into ice-water (1.5 L). The precipitate formed was filtered off, washed with water, and dissolved in chloroform (500 mL). The solution was washed successively with cold 3% hydrochloric acid (50 mL), aqueous sodium hydrogencarbonate (50 mL), and water (100 mL), dried, and concentrated. The residue was triturated with hexane (50 mL), and the resulting white solid was filtered off, washed with hexane (10 mL), and dried, when TLC (solvent A) of the solid showed that most of the by-products moving faster than 1 had been removed. The solid was subjected to column chromatography. Elution with solvent D removed the remaining by-products. Subsequent elution with solvent A gave 2 (12.78 g, 75%), mp 323-326 °C (dec.) (from methanol-chloroform), $[\alpha]_D^{26}$ +102.3° (c 2.20, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 101.4 (C-1), 81.4 (C-4), 74.4, 73.0, and 72.2 (C-2, 3, 5), 61.9 (C-6), 26.0 [$(\underline{CH}_3)_3C$], 18.4 [$(CH_3)_3\underline{C}$], and -5.2 [$(CH_3)_3Si$].

Anal. Calcd for $(C_{12}H_{24}O_5Si)_6$: C, 52.15; H, 8.75. Found: C, 52.31; H, 8.84.

Hexakis(6-O-tert-butyldimethylsilyl-2,3-di-O-methyl)-α-cyclodextrin (3) Sodium hydride (3.24 g; 50% mineral oil) was added at 0 °C to a solution of 2 (3.11 g) in DMF (90 mL), and the mixture was stirred for 1 h at 0 °C. Methyl iodide (4.90 mL) was added dropwise, and the mixture was stirred for 1 h at 0 °C, allowed to attain room temperature, stirred for 2 h at room temperature, and then cooled to 0 °C. Methanol was added to decompose the excess of hydride, the mixture was concentrated, and the residue was partitioned between chloroform and water. The organic layer was separated, washed successively with water, aqueous sodium thiosulfate, and water, dried, and concentrated. Column chromatography (solvent E) of the residue gave 3 (2.85 g, 83%), mp 213-213.5 °C (from methanol), $[\alpha]_D^{26}$ +100.7° (c 1.14, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.04 (d, 6H, $J_{1,2}$ = 2.9 Hz, H-1), 3.62 and 3.46 (2s, each 18H, 12MeO), 0.88 [s, 54H, $6(CH_3)_3C$], and 0.04 [s, 36H, $6(CH_3)_2Si$]; ^{13}C NMR ($CDCl_3$): δ 99.4 (C-1), 82.4, 81.4, and 81.0 (C-2, 3, 4), 72.5 (C-5), 62.6 (C-6), 61.6 and 57.9 (MeO), 25.9 [$(CH_3)_3C$], 18.2 [$(CH_3)_3C$], and -4.9 and -5.1 [$(CH_3)_2Si$].

Anal. Calcd for $(C_{14}H_{28}O_5Si)_6$: C, 55.23; H, 9.27. Found: C, 55.33, H, 9.39.

Hexakis(6-O-acetyl-2,3-di-O-methyl)-α-cyclodextrin (4). 1M Tetrabutylammonium fluoride in oxolane (7.5 mL) was added to a solution of 3 (2.02 g) in oxolane (20 mL), and the mixture was boiled for 3 h under reflux, and concentrated to dryness. A solution of the residue in 1:1 acetic anhydride-pyridine (20 mL) was stirred for 2 h at 100 °C, cooled, and concentrated. The residue was dissolved in chloroform, and the solution was washed successively with 1M hydrochloric acid, aqueous sodium hydrogencarbonate, and water. It was then dried and concentrated. Column chromatography (solvent I) of the residue afforded 4 (1.27 g, 82%), mp 249-252 °C (from ether-petroleum ether), $[\alpha]_D^{26}$ +154.1° (c 1.48, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.98 (d, 6H, $J_{1,2}$ = 3.1 Hz, H-1), 3.66 and 3.52 (2s, each 18H, 12MeO), and 2.08 (s, 18H, 6AcO); ^{13}C NMR ($CDCl_3$): δ 170.3 (C=O), 99.9 (C-1), 82.7, 82.0, and 81.3 (C-2, 3, 4), 69.9 (C-5), 63.5 (C-6), 61.7 and 58.2 (MeO), and 20.7 ($COCH_3$).

Anal. Calcd for $(C_{10}H_{16}O_6)_6$: C, 51.72; H, 6.94. Found: C, 51.84; H, 7.15.

Hexakis(2,3-di-O-methyl)-α-cyclodextrin (5). A solution of 4 (0.84 g) in methanol (20 mL) was treated with methanolic 1M sodium methoxide (1 mL) for 3 h at room temperature, neutralized with Amberlite IR-120

(H^+) resin, filtered, and concentrated. Crystallization of the residue from dichloromethane-hexane gave 5 (0.62 g, 90%), mp 215-218 °C after softening at 145-152 °C, $[\alpha]_D^{26}$ +170.0° (c 1.50, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.64 and 3.50 (2s, each 18H, 12MeO); ^{13}C NMR ($CDCl_3$): δ 99.0 (C-1), 81.9 (x 3) (C-2, 3, 4), 72.7 (C-5), 61.9 (C-6), and 61.5 and 58.0 (MeO).

Anal. Calcd for $(C_8H_{14}O_5)_6$: C, 50.52; H, 7.42. Found: C, 50.40; H, 7.34.

Successive hydrolysis of a portion of 5 with 2M trifluoroacetic acid for 18 h at 100 °C, reduction with sodium borohydride, acetylation, and GLC analysis of the resulting product gave a peak that had the retention time of the peracetate of 2,3-di-O-methyl-D-glucitol.

Hexakis(2,3-di-O-benzyl-6-O-tert-butyldimethylsilyl)-α-cyclodextrin (6). A solution of 2 (1.52 g) in DMF (45 mL) was treated with sodium hydride (1.58 g; 50% mineral oil), followed by benzyl bromide (3.75 mL), as described for the preparation of 3. The mixture obtained after decomposition of the excess of hydride with methanol was poured into ice-water, and the precipitate which separated was filtered off, washed with cold water, and dissolved in chloroform. The solution was washed with water, dried, and concentrated. Column chromatography (solvent F) of the product afforded 6 (1.98 g, 79%), mp 185-187 °C (from methanol), $[\alpha]_D^{26}$ +41.4° (c 1.52, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 139.3 and 138.1 (aromatic C-1), 98.0 (C-1), 81.0, 79.1, 78.0, 75.3, and 72.4 (x 2) (C-2, 3, 4, 5, $PhCH_2$), 62.4 (C-6), 26.0 [$(CH_3)_3C$], 18.3 [$(CH_3)_3C$], and -4.7 and -5.0 [$(CH_3)_2Si$].

Anal. Calcd for $(C_{26}H_{36}O_5Si)_6$: C, 68.39; H, 7.95. Found: C, 68.56; H, 8.13.

Hexakis(2,3-di-O-benzyl)-α-cyclodextrin (7). A solution of 6 (1.71 g) in oxolane (20 mL) was boiled for 4 h under reflux with 1M tetrabutylammonium fluoride in oxolane (5.0 mL), and then concentrated. A solution of the residue in chloroform was washed with water, dried, and concentrated. Column chromatography (solvent I) of the residue gave amorphous 7 (1.10 g, 86%), $[\alpha]_D^{26}$ +61.5° (c 1.42, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 139.1 and 138.1 (aromatic C-1), 97.9 (C-1), 80.8, 79.9, 79.6, 75.4, 73.1 (x 2) (C-2, 3, 4, 5, $PhCH_2$), and 62.2 (C-6).

Anal. Calcd for $(C_{20}H_{22}O_5)_6$: C, 70.16; H, 6.48. Found: C, 69.84; H, 6.72.

Hexakis(2,3-di-O-benzyl-6-O-methyl)-α-cyclodextrin (8). Compound 7 (0.84 g) was treated in DMF (10 mL) with sodium hydride (0.35 g; 50% mineral oil), followed by methyl iodide (0.9 mL), and the mixture was processed as described for the preparation of 3. Column chromatography

(solvent G) of the product afforded 8 (0.77 g, 89%), mp 132-134 °C (from methanol), $[\alpha]_D^{26}$ +19.1° (c 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.47 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), and 3.31 (s 18H, 6MeO); ^{13}C NMR ($CDCl_3$): δ 139.4 and 138.2 (aromatic C-1), 98.8 (C-1), 80.9, 79.45, 79.1, 75.3, 72.9, and 71.2 (C-2, 3, 4, 5, $PhCH_2$), 71.6 (C-6), and 58.9 (MeO).

Anal. Calcd for $(C_{21}H_{24}O_5)_6$: C, 70.77; H, 6.79. Found: C, 70.92; H, 6.68.

Hexakis(6-O-methyl)-α-cyclodextrin (9). A solution of 8 (0.55 g) in acetic acid (10 mL) was hydrogenated in the presence of 10% Pd/C (0.6 g) at atmospheric pressure for 2 days at room temperature. The catalyst was filtered off through a layer of Celite and washed with methanol. The combined filtrate and washings were concentrated, and the residue was crystallized from chloroform-hexane to give 9 (0.24 g, 89%), mp 261-266 °C (dec.), $[\alpha]_D^{26}$ +130.1° (c 1.12, DMSO); lit.[2] $[\alpha]_D^{22}$ + 133° (c 0.61, DMSO); ^{13}C NMR (DMSO): δ 101.7 (C-1), 82.2 (C-4), 73.1, 71.8, and 70.2 (C-2, 3, 5), 70.9 (C-6), and 57.9 (MeO).

Hexakis(2,3-di-O-acetyl-6-O-methyl)-α-cyclodextrin (10). A solution of 9 (0.13 g) in 1:1 acetic anhydride-pyridine (3 mL) was stirred for 2 h at 100 °C and then concentrated; the last traces of the solvents were removed by coevaporation of toluene. Column chromatography (solvent I) of the residue afforded amorphous 10 (0.17 g, 89%), $[\alpha]_D^{26}$ +110.3° (c 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.46 (dd, 6H, $J_{3,4}$ = 7.5 Hz, H-3), 5.10 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.80 (dd, 6H, $J_{2,3}$ = 7.5 Hz, H-2), 3.40 (s, 18H, 6MeO), and 2.06 (s, 36H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.5 and 169.2 (C=O), 96.4 (C-1), 76.0 (C-4), 71.6, 71.3, 70.9 (x 2) (C-2, 3, 5, 6), 59.1 (MeO), and 20.8 and 20.7 ($COCH_3$).

Anal. Calcd for $(C_{11}H_{16}O_7)_6$: C, 50.77; H, 6.20. Found: C, 50.93; H, 6.34.

Hexakis(2,3-di-O-allyl-6-O-tert-butyldimethylsilyl)-α-cyclodextrin (11). A solution of 2 (2.49 g) in DMF (75 mL) was treated with sodium hydride (2.59 g; 50% mineral oil), followed by allyl bromide (4.52 mL), as described for the preparation of 3. Column chromatography (solvent H) of the product gave 11 (2.70 g, 84%), mp 233-235 °C (from ethanol), $[\alpha]_D^{26}$ +88.1° (c 1.52, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 136.5, 135.5, 116.4, and 115.8 (CH_2=CH), 98.7 (C-1), 79.7, 79.5, 78.8, 74.6, 72.4, and 72.0 (C-2, 3, 4, 5, allyl OCH_2), 62.1 (C-6), 25.9 [$(CH_3)_3C$], 18.4 [$(CH_3)_3C$], and -4.8 and -5.1 [$(CH_3)_2Si$].

Anal. Calcd for $(C_{18}H_{32}O_5Si)_6$: C, 60.64; H, 9.05. Found: C, 60.47; H, 9.21.

Hexakis(2,3-di-O-allyl)-α-cyclodextrin (12). Treatment of 11 (2.37 g) in oxolane (30 mL) with 1M tetrabutylammonium fluoride in oxolane (8 mL), as described for the preparation of 7, followed by column chromatography (solvent L), afforded amorphous 12 (1.34 g, 83%), $[\alpha]_D^{26}$ +132.3° (c 1.35, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 136.1, 135.1, 116.5, and 115.6 (CH_2=CH), 98.2 (C-1), 80.0 (x 2), 79.1, 74.4, 73.0, 72.2 (C-2, 3, 4, 5, allyl OCH_2), and 62.1 (C-6).

Anal. Calcd for $(C_{12}H_{18}O_5)_6$: C, 59.49; H, 7.49. Found: C, 59.66; H, 7.64.

Hexakis(2,3-di-O-propyl)-α-cyclodextrin (13). A mixture of 12 (0.88 g) and 10% Pd/C (0.9 g) in methanol was shaken under hydrogen for 8 h at atmospheric pressure and room temperature, and processed as described for the preparation of 9. Column chromatography (solvent M) of the residue gave 13 (0.77 g, 87%), mp 237-239 °C (from ethanol), $[\alpha]_D^{26}$ +127.0° (c 1.44, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 97.6 (C-1), 80.6, 79.9, 79.1, 75.4, 73.2, and 72.9 (C-2, 3, 4, 5, propyl OCH_2), 62.2 (C-6), 23.5 (propyl CH_2), and 10.5 and 10.3 (propyl CH_3).

Anal. Calcd for $(C_{12}H_{22}O_5)_6$: C, 58.52; H, 9.00. Found: C, 58.61; H, 9.12.

Hexakis(2,3-di-O-acetyl-6-O-tert-butyldimethylsilyl)-α-cyclodextrin (15). Acetylation of 2 (7.44 g) in 1:1 acetic anhydride-pyridine (150 mL) for 4 h at 100 °C, as described for the preparation of 10, followed by column chromatography (solvent I) of the product, gave amorphous 15 (8.43 g, 87%), $[\alpha]_D^{26}$ +88.3° (c 1.47, $CHCl_3$); ^1H NMR ($CDCl_3$):δ 5.55 (dd, 6H, $J_{3,4}$ = 7.8 Hz, H-3), 5.18 (d, 6H, $J_{1,2}$ = 3.3 Hz, H-1), 4.74 (dd, 6H, $J_{2,3}$ = 10.2 Hz, H-2), 2.07 and 2.05 (2s, each 18H, 12AcO), 0.90 [s, 54H, $6(CH_3)_3C$], and 0.06 [s, 36H, $6(CH_3)_2Si$]; ^{13}C NMR ($CDCl_3$): δ 170.5 and 169.2 (C=O), 96.4 (C-1), 75.0 (C-4), 72.1, 71.7, and 71.3 (C-2, 3, 5), 61.9 (C-6), 25.9 [$(\underline{CH_3})_3C$], 20.9 and 20.7 ($CO\underline{CH_3}$), 18.3 [$(CH_3)_3\underline{C}$], and -4.0 and -5.2 [$(CH_3)_2Si$].

Anal. Calcd for $(C_{16}H_{28}O_7Si)_6$: C, 53.31; H, 7.83. Found: C, 53.58; H, 8.04.

Hexakis(2,3-di-O-acetyl)-α-cyclodextrin (16). To a solution of 15 (5.21 g) in dichloromethane (60 mL) was added 47% boron trifluoride etherate in ether (5.2 mL). The mixture was stirred for 8 h at room temperature, diluted with dichloromethane (100mL), and poured into ice-water. The organic layer was separated, washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. The residue was chromatographed with solvent C to give 16 (2.56 g, 72%),

mp 188-192 °C (from ethanol), $[\alpha]_D^{26}$ +122.2° (c 1.45, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 170.4 and 169.1 (C=O), 96.0 (C-1), 72.3, 71.5, and 70.6 (C-2, 3, 5), 61.5 (C-6), and 20.7 and 20.6 ($\underline{C}OCH_3$).

Anal. Calcd for $(C_{10}H_{14}O_7)_6$: C, 48.78; H, 5.73. Found: C, 49.01; H, 5.61.

Diazomethane in dichloromethane was gradually added at -30 °C to a stirred solution of 16 (0.42 g) in dichloromethane (3 mL) containing a few drops of boron trifluoride etherate until a faint yellow color persisted and the mixture was kept for 1 h at room temperature. Polymethylene was filtered off, and the filtrate was washed successively with aqueous sodium hydrogencarbonate and water, dried, and concentrated. Column chromatography (solvent I) of the resulting syrup gave 10 (0.29 g, 66%), $[\alpha]_D^{26}$ +109.6° (c 1.1, $CHCl_3$); the ^1H and ^{13}C NMR spectra were identical with those of the compound prepared earlier from 9.

Hexakis(2,3-di-O-acetyl-6-O-methylsulfonyl)-α-cyclodextrin (17). A solution of 16 (2.96 g) in anhydrous pyridine (30 mL) was cooled to -10 °C, treated with methanesulfonyl chloride (2.83 mL), and kept overnight at 5 °C. The mixture was poured into ice-water and the precipitate formed was filtered off, washed with water, and dissolved in chloroform. The solution was washed with water, dried, and concentrated. The residue was crystallized from methanol-dichloromethane to afford 17 (3.24 g, 83%), mp 174-175 °C, $[\alpha]_D^{26}$ +93.2° (c 1.52, $CHCl_3$); lit.[3] mp 170 °C (dec.), $[\alpha]_D^{20}$ +106° (c 1, $CHCl_3$); IR: ν 1368 and 1177 cm^{-1} (sulfonate); ^1H NMR ($CDCl_3$): δ 5.49 (dd, 6H, $J_{3,4}$ = 8.4 Hz, H-3), 5.11 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.84 (dd, 6H, $J_{2,3}$ = 10 Hz, H-2), 3.91 (t, 6H, $J_{4,5}$ = 8.7 Hz, H-4), 3.12 (s, 18H, 6Ms), and 2.06 (s, 36H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.2 and 169.1 (C=O), 97.2 (C-1), 76.7 (C-4), 71.0, 70.4, and 69.7 (C-2, 3, 5), 68.7 (C-6), 37.4 (CH_3SO_2), and 20.8 and 20.7 ($CO\underline{C}H_3$).

Anal. Calcd for $(C_{11}H_{16}O_9S)_6$: C, 40.74; H, 4.97; S, 9.89. Found: C, 40.87; H, 5.12; S, 9.77.

Hexakis(2,3-di-O-acetyl-6-O-p-tolylsulfonyl)-α-cyclodextrin (18). To a stirred solution of 16 (2.05 g) in pyridine (20 mL), maintained at -10 °C, was added portionwise p-toluenesulfonyl chloride (4.76 g) during 20 min. The mixture was further stirred for 1 h at -10 °C, allowed to warm to room temperature, and then stirred overnight at room temperature. The solution was processed as described for the preparation of 17, and the residue was chromatographed with solvent J to give 18 (2.56 g, 77%), mp 138-141 °C (from methanol), $[\alpha]_D^{26}$ +89.8° (c 1.43, $CHCl_3$); lit.[4] mp 170-172 °C, $[\alpha]_D^{24}$ +67° (c 0.1, MeOH); IR: ν 1368 and 1178 cm^{-1} (sulfonate);

^{1}H NMR ($CDCl_3$): δ 7.78 and 7.34 (each d, 24H, J = 8.4 Hz, aromatic hydrogens), 5.35 (dd, 6H, $J_{3,4}$ = 8.4 Hz, H-3), 4.71 (d, 6H, $J_{1,2}$ = 3.3 Hz, H-1), 4.51 (dd, 6H, $J_{2,3}$ = 10.3 Hz, H-2), 3.73 (t, 6H, $J_{4,5}$ = 8.8 Hz, H-4), 2.45 (s, 18H, 6 aryl CH_3), and 2.01 and 2.00 (2s, each 18H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.0 and 169.2 (C=O), 145.2, 132.6, 129.9, and 127.9 (aromatic C), 96.4 (C-1), 75.6 (C-4), 70.6, 70.2, and 69.7 (C-2, 3, 5), 68.7 (C-6), 21.7 (aromatic CH_3), and 20.7 ($CO\underline{C}H_3$).

Anal. Calcd for $(C_{17}H_{20}O_9S)_6$: C, 51.00; H, 5.03; S, 8.01. Found: C, 51.17; H, 4.94; S, 7.87.

Hexakis(2,3-di-O-acetyl-6-deoxy-6-iodo)-α-cyclodextrin (19). A solution of 17 (0.51 g) in DMF (10 mL) containing sodium iodide (0.9 g) was stirred for 3 h at 100 °C. The mixture was concentrated, and the residue was partitioned between chloroform and water. The organic layer was separated, washed with water, dried, and concentrated. Column chromatography (solvent J) of the product gave 19 as a powder (0.45 g, 80%). On precipitation from a boiling solution of ethanol, 19 was obtained as an amorphous solid, mp 168-173 °C, $[\alpha]_D^{26}$ +87.4° (c 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.17 (d, 6H, $J_{1,2}$ = 3.4 Hz, H-1), 4.82 (dd, 6H, $J_{2,3}$ = 10.4 Hz, H-2), and 2.07 and 2.05 (2s, each 18H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.2 and 169.0 (C=O), 96.5 (C-1), 80.8 (C-4), 70.5 (x 2) and 70.0 (C-2, 3, 5), 20.7 ($CO\underline{C}H_3$), and 8.5 (C-6). A satisfactory elemental analysis was not obtained for this compound.

Similar treatment of 18 (0.41 g), as just described, gave 19 (0.28 g, 78%), $[\alpha]_D^{26}$ +86.9° (c 0.58, $CHCl_3$); the ^{1}H and ^{13}C NMR spectra were identical with those of the compound prepared from 17.

Hexakis(2,3-di-O-acetyl-6-deoxy)-α-cyclodextrin (20). A solution of 19 (0.47 g) in methanol (5 mL) and 1,4-dioxane (10 mL) containing triethylamine (0.3 mL) was hydrogenated in the presence of 10% Pd/C (0.5 g) at atmospheric pressure overnight at room temperature. The mixture was processed as described for the preparation of 9, and the resulting syrup was dissolved in chloroform. The solution was washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. The residue was chromatographed with solvent J to give 20 (0.24 g, 80%), mp 165-168 °C, $[\alpha]_D^{26}$ +111.3° (c 1.24, $CHCl_3$); lit.[7] mp 160-163 °C $[\alpha]_D^{25}$ +89° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.43 (dd, 6H, $J_{3,4}$ =8.6 Hz, H-3), 5.00 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.80 (dd, 6H, $J_{2,3}$ = 10.0 Hz, H-2), 3.46 (t, 6H, $J_{4,5}$ = 8.6 Hz, H-4), 2.04 (s, 36H, 12AcO), and 1.39 (d, 18H, $J_{5,6}$ = 5.9 Hz, $6CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.6 and 169.0 (C=O), 96.3 (C-1), 82.6 (C-4), 71.7 and 71.1 (C-2, 3), 67.1 (C-5), 20.8 and 20.7 ($CO\underline{C}H_3$), and 18.2 (CH_3).

Anal. Calcd for $(C_{10}H_{14}O_6)_6$: C, 52.17; H, 6.13. Found: C, 52.26; H, 6.20.

Methanolysis of a portion of 20 with 1% methanolic hydrogen chloride, and GLC of the resulting methyl glycosides as the per(trimethylsilyl)-ethers gave peaks corresponding to methyl 6-deoxy-α,β-D-glucopyranosides. No other peaks were detected.

Hexakis(2,3-di-O-acetyl-6-bromo-6-deoxy)-α-cyclodextrin (21). A solution of 17 (0.48 g) in DMF (10 mL) was stirred with sodium bromide (0.5 g) for 4 h at 100 °C. The mixture was processed as described for the preparation of 19, and the residue was chromatographed with solvent J to give 21 (0.38 g, 83%), mp 171-174 °C (from methanol), $[\alpha]_D^{26}$ +90.0° (c 1.46, $CHCl_3$); lit.[7] mp 179-181 °C, $[\alpha]_D^{25}$ +89° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.52 (dd, 6H, $J_{3,4}$ = 8.1 Hz, H-3), 5.19 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.81 (dd, 6H, $J_{2,3}$ = 10.1 Hz, H-2), and 2.07 and 2.06 (2s, each 18H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.2 and 169.1 (C=O), 96.4 (C-1), 78.5 (C-4), 70.6 (x 2) and 70.4 (C-2, 3, 5), 33.6 (C-6), and 20.7 and 20.6 ($CO\underline{C}H_3$).

Anal. Calcd for $(C_{10}H_{13}O_6Br)_6$: C, 38.86; H, 4.24. Found: C, 38.66; H, 4.37.

Compound 21 (0.24 g, 83%) was also obtained from 18 (0.38 g).

Hexakis(2,3-di-O-acetyl-6-chloro-6-deoxy)-α-cyclodextrin (22). Compound 17 (0.42 g) was stirred in DMF (10 mL) with lithium chloride (0.7 g) for 5 h at 100 °C. Processing of the mixture, as described for the preparation of 19, followed by column chromatography (solvent J) of the product, afforded 22 (0.29 g, 85%), mp 257-258 °C (from methanol), $[\alpha]_D^{26}$ +103.3° (c 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.50 (dd, 6H, $J_{3,4}$ = 8.0 Hz, H-3), 5.16 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.83 (dd, 6H, $J_{2,3}$ = 10.0 Hz, H-2), and 2.07 and 2.06 (2s, each 18H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.2 and 169.1 (C=O), 96.5 (C-1), 77.3 (C-4), 71.1, 70.8, and 70.3 (C-2, 3, 5), 44.7 (C-6), and 20.8 and 20.7 ($CO\underline{C}H_3$).

Anal. Calcd for $(C_{10}H_{13}O_6Cl)_6$: C, 45.38; H, 4.95. Found: C, 45.72; H, 5.12.

Compound 22 (0.18 g, 82%) was also obtainable from 18 (0.35 g).

Hexakis(2,3-di-O-acetyl-6-azido-6-deoxy)-α-cyclodextrin (23). Treatment of 17 (0.51 g) in DMF (10 mL) with sodium azide (0.6 g) for 4 h at 100 °C, as described for the preparation of 19, followed by column chromatography (solvent J) of the product, gave 23 (0.36 g, 84%), mp 127-130 °C (from ethanol-acetone), $[\alpha]_D^{26}$ +131.7° (c 1.43, $CHCl_3$); lit.[2] $[\alpha]_D^{22}$ +133° (c 1.1, $CHCl_3$); IR: ν 2108 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): δ 5.45 (dd, 6H, $J_{3,4}$ = 8.1 Hz, H-3), 5.06 (d, 6H, $J_{1,2}$ = 3.5 Hz, H-1), 4.82 (dd, 6H,

$J_{2,3}$ = 10.0 Hz, H-2), and 2.06 and 2.05 (2s, each 18H, 12AcO); ^{13}C NMR ($CDCl_3$): δ 170.2 and 169.1 (C=O), 98.7 (C-1), 77.4 (C-4), 71.1, 70.9, and 70.4 (C-2, 3, 5), 51.8 (C-6), and 20.8 and 20.7 ($COCH_3$).

Compound 23 (0.20 g, 83%) was also prepared from 18 (0.36 g).

[2,3-di-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)]-pentakis(2,3-di-O-acetyl)-α-cyclodextrin (24). A solution of 16 (2.01 g, 1.4 mmol) in dry 1,2-dichloroethane (25 mL) and DMF (8.5 mL) was stirred for 2 h at room temperature in the presence of tetraethylammonium bromide (0.95 g, 4.5 mmol) and molecular sieve 4A (7 g). A solution of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide [freshly prepared[23] from the 1-(p-nitrobenzoate)[27] (2.82 g, 4.1 mmol)] in 1,2-dichloroethane (10 mL) was added, and the mixture was stirred for 20 h at room temperature. TLC (solvent K) showed the presence of 24 (R_F 0.55), together with minor faster-moving by-products and the traces of unchanged 16. The solids were removed by filtration and washed with chloroform. The combined filtrate and washings were washed successively with water, aqueous sodium hydrogencarbonate, water, dried, and concentrated. The residue was subjected to column chromatography, eluting first with solvent I and then with solvent K, to give amorphous 24 (1.06 g, 39%), $[\alpha]_D^{26}$ +122.9° (c 1.44, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 97.1, 96.5, 96.3, and 96.0 (x 2) (anomeric carbons).

Anal. Calcd for $C_{94}H_{118}O_{47}$: C, 56.45; H, 5.95. Found: C, 56.63; H, 6.16.

6-O-α-D-Glucopyranosyl-α-cyclodextrin (26). A solution of 24 (0.75 g) in acetic acid (15 mL) was hydrogenated in the presence of 10% Pd/C (0.6 g) overnight at atmospheric pressure and room temperature. The mixture was processed as described for the preparation of 9, and purification of the product by column chromatography (solvent A) gave (2,3-di-O-acetyl-6-O-α-D-glucopyranosyl)-pentakis(2,3-di-O-acetyl)-α-cyclodextrin (25) as an amorphous powder (0.52 g, 84%), $[\alpha]_D^{26}$ +117.3° (c 1.48, $CHCl_3$). O-Deacetylation of 25 (0.37 g), as described for 4, afforded 26 (0.22 g, 85%), mp 285-295 °C (dec.), $[\alpha]_D^{26}$ +151.3° (c 1.17, H_2O); lit.[10] mp >280 °C (dec.), $[\alpha]_D^{22}$ +151.1° (H_2O); the ^{13}C NMR spectrum was consistent with that reported.[10]

6-O-α-D-Glucopyranosyl-α-cyclodextrin heneicosa-acetate (27). Acetylation of 26 (75 mg) in 1:1 acetic anhydride-pyridine (2 mL) for 6 h at 100 °C, as described for 9, followed by column chromatography (solvent I) of the product, gave amorphous 27 (121 mg, 91%), $[\alpha]_D^{26}$ +112.5° (c 1.50, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 96.9, 96.7, 96.5, 96.3, and 96.1 (anomeric carbons).

Anal. Calcd for $C_{84}H_{112}O_{36}$: C, 50.00; H, 5.60. Found: C, 50.24; H, 5.72.

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