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CLEAVAGE OF THE ACETAL RINGS IN BIS(METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDO)-18-CROWN-6

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ABSTRACT

Treatment of bis(methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranosido [2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**1**) with aqueous acetic acid gave bis(methyl 2,3-dideoxy-α-D-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**2**). With $LiAlH_4$–$AlCl_3$, **1** gave a mixture of three *O*-benzyl derivatives in which bis(methyl 4-*O*-benzyl-2,3-dideoxy-α-D-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane preponderated. Methylation and butylation of **2** in a two-phase system gave the tetramethoxy and tetrabutoxy crowns. Bis(methyl 4-*O*-acetyl-2,3-dideoxy-6-*O*-trityl-α-D-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**5**) was obtained from **2** by tritylation and acetylation. Detritylation of **5** with acetic acid–hydrogen bromide gave bis(methyl 4-*O*-acetyl-2,3-dideoxy-α-D-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane. Treatment of **1** with *N*-bromosuccinimide gave the 4-benzoyl-6-bromo-6-deoxy compound which was suitable for making a new ring with a *trans*-annular connection. The complex stability constant of each new crown has been measured and evaluated.

INTRODUCTION

The preparation of chiral crowns and their use in the resolution of racemates, as catalysts in enantioface differentiating reactions, and as ligands in ion-selective electrodes have been described[1]. The sources of chirality for these crowns and cryptands, as well as for those we have synthesised[2–5], are monosaccharide derivatives, frequently 4,6-*O*-benzylidene-α-D-glucopyranose.

We now report on the removal of the benzylidene groups from bis(methyl 4,6-

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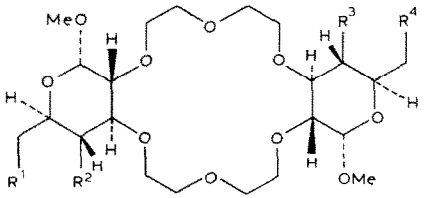
O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**1**).

The direction of opening of the 1,3-dioxane ring in simple *O*-benzylidene sugar derivatives is known[6,7], but there are no data for 4,6-*O*-benzylidene-D-glucose derivatives having large substituents, such as an 18-crown-6 moiety, at positions 2 and 3.

RESULTS AND DISCUSSION

In hydrochloric acid (molar ratio, 1:27; 100°, 4 h), both the benzylidene and methoxyl groups of the crown **1** were removed with the formation of a hexahydroxy crown derivative[4]. In boiling acetic acid (molar ratio, 1:524; 60 min), only the benzylidene groups of **1** were cleaved[2–4] to give the tetrahydroxy crown **2**.



	R^1	R^2	R^3	R^4
1[4]	*O*-benzylidene		*O*-benzylidene	
2[4]	OH	OH	OH	OH
3	OMe	OMe	OMe	OMe
4	OBu	OBu	OBu	OBu
5	OTr	OAc	OAc	OTr
6	OH	OAc	OAc	OH
7	Br	OBz	OBz	Br
8	H	OH	OH	H
9	Br	OH	OH	Br
10	OH	OBn	OBn	OH
11	OH	OBn	OH	OBn
12	OBn	OH	OH	OBn

Methylation and butylation of **2**, using a phase-transfer system involving aqueous 50% sodium hydroxide and tetrahydrofuran, occurred smoothly at room temperature to give excellent yields of the crystalline tetramethoxy (**3**) and tetrabutoxy (**4**) crowns. No catalyst was required in these alkylation reactions because this role was fulfilled by the crown compounds.

Treatment of **2** with trityl chloride in pyridine followed by acetylation in a one-pot reaction gave 78% of the ditrityl diacetate **5**. Treatment of **5** with acetic acid–hydrogen bromide afforded 43% of the 4,4′-diacetate **6**.

Treatment[8] of **1** with boiling carbon tetrachloride containing *N*-bromo-

TABLE I

ASSOCIATION CONSTANTS (K_a, M^{-1}) OF CROWN COMPOUNDS IN CHLOROFORM AT 20°

Compound	$K_a \times 10^2$		*Compound*	$K_a \times 10^2$	
	K^+	NH_4^+		K^+	NH_4^+
1	1096	132	**8**	741	282
2	316	437	**9**	251	34
4	234	66	**10**	501	219
5	295	47	**11**	265	102
6	234	39	**12**	316	123
7	145	91			

succinimide, barium carbonate, and benzoyl peroxide for 3 h yielded 88% of the 4-benzoyl-6-bromo-6-deoxy derivative **7**. The structure of **7** was proved when treatment with lithium aluminium hydride in boiling tetrahydrofuran for 6 h gave 78% of the 6-deoxy derivative **8**, the ^{1}H-n.m.r. spectrum of which contained a doublet at δ 1.23 for CH_3CH. Zemplén debenzoylation of **7** gave 89% of the 6-bromo-6-deoxy derivative (**9**).

The crown **1** is soluble only in $CHCl_3$ and in CH_2Cl_2, but compounds **3–9** are also soluble in acetone and alcohol.

The reagent $LiAlH_4$–$AlCl_3$ has been used[6,7] for the reductive cleavage of the 1,3-dioxane ring in 4,6-*O*-benzylidene sugar derivatives in a study of the effect of the bulk of the substituent at position 3. When this reagent (1:1 ratio in boiling dichloromethane–ether) was applied to **1** for 3 h, a mixture of three products was formed from which the 4,4′-di-*O*-benzyl derivative **10** was isolated by crystallisation (34%) and column chromatography and t.l.c. (10%). This result accords with the finding of Lipták *et al.*[6,7] that, when a bulky substituent was present at position 3, the benzyl group of the main product was located at position 4.

The location of the benzyl group in **10** was established by ^{1}H-n.m.r. spectroscopy after the reaction of **10** with trichloroacetyl isocyanate[9]; a 4-proton AB-type signal appeared at δ 4.39 which was well separated from the signals of the other CH_2-O protons, indicating that HO-6 of **10** was unsubstituted.

The ^{1}H-n.m.r. spectra for **11** and **12** and the ^{13}C-n.m.r. spectra for **10–12** have been evaluated (see Experimental) using data for crowns[10] **1** and **2**, simple benzylidene sugar derivatives[11,12], and the products of acetal-cleavage[13] reactions.

Using Cram's method[14], the stability constants of the complexes of the new crowns with potassium and ammonium ions have been calculated and compared with those published[2,4] for **1** and **2** (Table I). Crown **1** has the highest value of K_a for K^+. Smaller values were obtained for the crowns **2, 6, 8, 9,** and **10**.

EXPERIMENTAL

General. — Melting points were obtained with a Büchi apparatus and are

uncorrected. The ^{1}H- and ^{13}C-n.m.r. spectra were recorded at ambient temperature for solutions in $CDCl_3$ in the pulsed F.t.-mode (16k data points for the f.i.d.) at 99.6 and 25.0 MHz, respectively, with internal deuterium lock, using a Jeol FX-100 spectrometer. Reactions were monitored, and the purity of products was assessed, by t.l.c. on Kieselgel $60F_{254}$ or Aluminiumoxid 150 F_{254} Type T (Merck), using toluene–methanol mixtures (10:1–10:5) and detection with Dragendorff's reagent[15]. Mass spectra were recorded with a Jeol JMS-OL SG-2 instrument and u.v. spectra with a Hitachi–Perkin–Elmer 124 spectrometer.

Bis(methyl 2,3-dideoxy-4,6-di-O-methyl-α-D-glucopyranosido[2,3-b][2′,3′-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**3**). — To a solution of **2** (1.0 g) in tetrahydrofuran (10 mL) was added aqueous 50% NaOH (1.5 mL). After stirring for 10 min, Me_2SO_4 (1 mL) was added slowly below 45°. Stirring was continued for 60 h at ambient temperature, and the mixture was then treated with aqueous 25% NH_4OH (1 mL) and poured into water (100 mL). The solution was extracted with dichloromethane (3 × 5 mL), and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated. Crystallisation of the residue from ether–light petroleum gave **3** (0.95 g, 85.2%), m.p. 125–127°, $[\alpha]_D^{20}$ +113° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 4.77 (d, 2 H, *J* 3.5 Hz, H-1,1′), 3.51 (s, 6 H, MeO-1,1′), 3.94–3.22 (m, 28 H), 3.37 (s, 12 H, MeO-4,4′, MeO-6,6′). Mass spectrum: *m/z* 584 (M^+).

Anal. Calc. for $C_{26}H_{48}O_{14}$: C, 53.42; H, 8.22. Found: C, 53.98; H, 8.31.

Bis(methyl 4,6-di-O-butyl-2,3-dideoxy-α-D-glucopyranosido[2,3-b][2′,3′-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**4**). — To a solution of **2** (1.0 g) in butyl bromide (45 mL) was added aqueous 50% NaOH (22.3 mL). The mixture was stirred for 80 h at 40° and then cooled, the aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined extracts were washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated. Treatment of the syrupy residue with water gave **4** (1.2 g, 84.5%), m.p. 88–90°, $[\alpha]_D^{22}$ +75° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 4.74 (d, 2 H, *J* 3.5 Hz, H-1,1′), 4.32–3.43 (m, 28 H), 3.32 (s, 6 H, 2 OMe), 1.89–1.11 (m, 24 H, butyl 12 CH_2), 0.89 (t, 12 H, butyl 4 CH_3). Mass spectrum: *m/z* 752 (M^+).

Anal. Calc. for $C_{38}H_{72}O_{14}$: C, 60.64; H, 9.57. Found: C, 60.19; H, 9.36.

Bis(methyl 4-O-acetyl-2,3-dideoxy-6-O-trityl-α-D-glucopyranosido[2,3-b][2′,3′-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**5**). — A mixture of **2** (3.0 g), trityl chloride (3.17 g), and dry pyridine (20 mL) was heated at 100° for 2 h and then cooled to room temperature. Acetic anhydride (3.2 mL) was added and, after storage for 18 h at room temperature, water was added to turbidity. The mixture was then poured into ice–water, and the precipitate was collected and recrystallised to give **5** (4.9 g, 79%), m.p. 225–230°, $[\alpha]_D^{22}$ +63.5° (*c* 1.4, chloroform). ^{1}H-N.m.r. data: δ 7.98 (m, 30 H, 6 Ph), 4.88 (d, *J* 3.0 Hz, 2 H, H-1,1′), 4.38–3.28 (m, 4 H), 3.48 (s, 6 H, MeO-1,1′), 3.11 (d, *J* 3.1 Hz, 4 H, 2 CH_2OTr), 1.66 (s, 6 H, 2 Ac).

Anal. Calc. for $C_{64}H_{72}O_{16}$: C, 70.03; H, 6.56. Found: C, 69.10; H, 6.78.

Bis(methyl 4-O-acetyl-2,3-dideoxy-α-D-glucopyranosido[2,3-b][2′,3′-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**6**). — To a stirred suspension of **5** (3.0 g) in acetic acid (20 mL) was added 33% HBr in acetic acid (1.5 mL). Stirring was

continued at 50° for 30 min, and the mixture was then filtered, poured into saturated aqueous $NaHCO_3$, and extracted with chloroform. The extract was washed with aqueous $NaHCO_3$ and water, dried, and concentrated. To a solution of the residue in methanol (20 mL) was added water (10 mL), and the mixture was kept at 5° for 24 h. The triphenylmethanol was removed, the filtrate was concentrated, and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated, and the residue was crystallised from ethanol–ether to give **6** (0.75 g, 43.3%), m.p. 116–118°, $[\alpha]_D^{22}$ +65° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 4.90 (d, 2 H, *J* 3 Hz, H-1,1′), 4.30–3.20 (m, 30 H), 3.48 (6 H, MeO-1,1′), 1.6 (s, 6 H, 2 Ac).

Anal. Calc. for $C_{26}H_{44}O_{16}$: C, 50.98; H, 7.18. Found: C, 50.12; H, 7.30.

*Bis(methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-α-*D*-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane* (**7**). — To a stirred suspension of **1** (2.8 g) in dry carbon tetrachloride boiling under reflux were added $BaCO_3$ (4.6 g), *N*-bromosuccinimide (1.7 g), and benzoyl peroxide (10 mg). After boiling for 3 h, the hot mixture was filtered, the precipitate was washed with carbon tetrachloride, and the combined filtrate and washings were washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. Crystallisation of the residue from ethanol gave **7** (3.0 g, 88.2%), m.p. 138–140°, $[\alpha]_D^{22}$ +45° (*c* 1.4, chloroform). ^{1}H-N.m.r. data: δ 7.7–7.2 (m, 10 H, 2 Ph), 5.0 (d, 2 H, *J* 2.4 Hz, H-1,1′), 4.90 (d, 4 H, 2 CH_2Br), 4.10–3.20 (m, 24 H), 3.40 (s, 6 H, MeO-1,1′).

Anal. Calc. for $C_{36}H_{46}Br_2O_{14}$: C, 50.2; H, 5.40; Br, 18.56. Found: C, 60.10; H, 5.35; Br, 18.45.

*Bis(methyl 2,3,6-trideoxy-α-*D*-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane* (**8**). — To a stirred suspension of $LiAlH_4$ (3.8 g) in tetrahydrofuran (40 mL) under N_2 was added dropwise a solution of **7** (2.1 g) in tetrahydrofuran (40 mL). The mixture was stirred for 6 h at room temperature, the excess of the reductant was then decomposed with ethyl acetate, and $Al(OH)_3$ was precipitated with water. The precipitate was removed, the filtrate was concentrated, and the residue was crystallised from ethanol–light petroleum to give **8** (1.0 g, 82.8%), m.p. 78–80°, $[\alpha]_D^{22}$ +79° (*c* 1.2, chloroform). ^{1}H-N.m.r. data: δ 4.66 (d, 2 H, *J* 3.0 Hz, H-1,1′), 3.90–2.90 (m, 26 H), 3.36 (s, 6 H, MeO-1,1′), 1.25 (d, 6 H, *J* 3.1 Hz, 2 CH_3).

Anal. Calc. for $C_{22}H_{40}O_{12}$: C, 53.22; H, 8.06. Found: C, 54.43; H, 8.18.

*Bis(methyl 6-bromo-2,3,6-trideoxy-α-*D*-glucopyranosido[2,3-*b*][2′,3′-*k*])-1,4,7,10,13,16-hexaoxacyclo-octadecane* (**9**). — To a solution of **7** (2.0 g) in dry methanol (150 mL) was added methanolic M sodium methoxide (1.5 mL). After storage for 1 day, the solution was neutralised with acetic acid and concentrated. A solution of the oily residue in chloroform was filtered and concentrated *in vacuo*, and the residue was crystallised from ethanol–light petroleum to give **9** (1.36 g, 89.5%), m.p. 148–150°, $[\alpha]_D^{22}$ +77° (*c* 1.2, chloroform). ^{1}H-N.m.r. data: δ 4.80 (d, 2 H, *J* 3.0 Hz, H-1,1′), 4.20 (d, 4 H, 2 CH_2Br), 4.0–3.10 (m, 26 H), 3.38 (s, 6 H, MeO-1,1′).

Anal. Calc. for $C_{22}H_{38}Br_2O_{12}$: C, 40.37; H, 5.81; Br, 24.26. Found: C, 40.41; H, 5.75; Br, 23.80.

Bis(methyl 4-O-benzyl-2,3-dideoxy-α-D-glucopyranosido[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**10**). — To a suspension of **1** (5.0 g) in ether (50 mL) and dichloromethane (150 mL) was added $LiAlH_4$ (2.2 g). The suspension was boiled and stirred, and a solution of $AlCl_3$ (7.5 g) in ether (65 mL) was added during 45 min. Boiling was continued for 3 h, the mixture was then cooled, the excess of reagent was decomposed with ethyl acetate (10 mL), and $Al(OH)_3$ was precipitated with water (10 mL). The precipitate was removed, the filtrate was concentrated, and the residue was crystallised from dry ethanol–ether to give **10** (1.7 g, 33.8%), m.p. 94–96°, $[\alpha]_D^{22}$ +94° (*c* 1.2, chloroform), R_F 0.42 (Al_2O_3; toluene–methanol, 10:2). N.m.r. data: ^1H, δ 7.30 (s, 10 H, 2 Ph), 4.82 (d, 2 H, H-1,1'), 4.70–4.10 (m, 6 H, 2 CH_2Ph and 2 OCH), 3.9–3.4 (m, 28 H), 3.37 (s, 6 H, MeO-1,1'); ^{13}C, δ 139.0, 128.4 (2 C), 127.8 (2 C), 96.4 (C-1), 82.0 (C-3), 80.6 (C-2), 77.5 (C-4), 72.2 (OCH_2-Ph), 71.4 (C-5), 70.3 (2 C), 74.1 (2 C), 69.8 (2 C), 69.5 (2 C, crown OCH_2), 61.7 (C-6), 55.0 (OMe).

Anal. Calc. for $C_{36}H_{52}O_{14}$: C, 61.02; H, 7.34. Found: C, 61.07; H, 7.54.

(Methyl 4-O-benzyl-2,3-dideoxy-α-D-glucopyranosido[2,3-b])-(methyl 6-O-benzyl-2,3-dideoxy-α-D-glucopyranosido[2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (**11**) *and bis(methyl 6-O-benzyl-2,3-dideoxy-α-D-glucopyranosido-[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane* (**12**). — The mother liquor from the crystallisation of **10** was concentrated. Elution of the residue (3.1 g) from a column of alumina (90 g, Brockmann II) with toluene–methanol (10:1) gave two fractions which were subjected to preparative t.l.c. (MN-Aluminiumoxid G, Macherey Nagel), yielding **10** (0.5 g, 9.9%), **11** (1.35 g, 26.8%), and **12** (0.3 g, 6.0%).

Compound **11** had m.p. 73–75°, $[\alpha]_D^{22}$ +79° (*c* 1.2, chloroform), R_F 0.51. N.m.r. data: ^1H, the same as for **10**, except δ 3.41 (s, 3 H, OMe), 3.37 (s, 3 H, OMe); ^{13}C, 138.7, 138.0, 128.4, 128.3, 127.9, 127.8, 127.5, 97.3 and 97.0 (C-1), 81.9 and 81.4 (C-3), 80.6 (C-2), 78.3, 77.1 (substituted C-4), 75.3, 74.9, 73.5, 72.3 (OCH_2Ph), 71.1 (C-5), 70.5 and 70.7 (C-4), 70.0 (C-6 *O*-benzyl), 69.5, 61.7 (C-6 OH), 55.0 (OMe).

Anal. Calc. for $C_{36}H_{52}O_{14}$: C, 61.02; H, 7.34. Found: C, 60.81; H, 7.28.

Compound **12** was a syrup, $[\alpha]_D^{22}$ +66° (*c* 1.2, chloroform), R_F 0.60. N.m.r. data: ^1H, the same as for **10**, except δ 3.41 (s, 6 H, 2 OMe); ^{13}C, δ 138.0, 127.7 (2 C), 127.9, 127.5 (2 C), 97.2 (C-1), 81.5 (C-3), 80.6 (C-2), 78.3, 75.8, 73.5, 72.7 (OCH_2Ph), 71.7 (C-5), 70.2 (C-4), 69.9 (C-6), 69.5, 55.1 (OMe).

Anal. Calc. for $C_{36}H_{52}O_{14}$: C, 61.02; H, 7.34. Found: C, 60.09; H, 7.63.

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