Chiral crown ethers incorporating D-glucose

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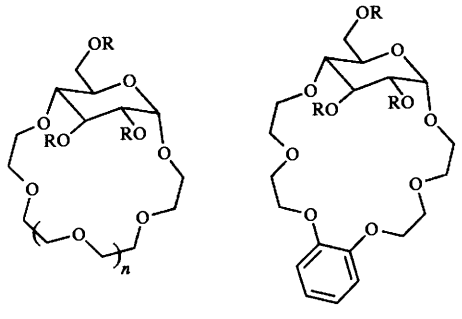
A novel class of crown ether derivatives incorporating D-glucose and poly(ethylene glycol) units has been synthesized from allyl α-D-glucopyranoside by a simple and efficient strategy. The complexing properties of these compounds with alkali metal cations and ammonium ion have been evaluated by Cram's picrate method. Catalytic activity of macrocycle **2** in asymmetric Michael addition reaction was also studied. The average cavity size of these macrocycles was determined by the application of the MMX programme.

Introduction

The concept of molecular recognition through non-bonded interaction between molecules is of vital significance in our understanding of various biological phenomena. Hence there has been enormous interest in the synthesis of such receptor molecules. Since the pioneering work of Pedersen, Cram and Lehn[1] different classes of receptors have been synthesized where the size, shape, flexibility and the arrangement of binding sites could be varied according to a rational plan.[2] The ability of chiral receptors[3] to serve as enzyme models along with their remarkable complexing properties lends great importance to the synthesis of such compounds.[4] Carbohydrates, being a versatile and inexpensive source of chirality, have received considerable attention in this context. Sugar units can provide structural constraints to the macrocycle and they are rich in substituted bismethylenedioxy units and functionalities which offer vast potential for building molecules with a variety of shapes and cavity sizes. Not surprisingly there has been some work on the synthesis of crown ether-type receptors from carbohydrates by Stoddart[5] and Penades.[6]

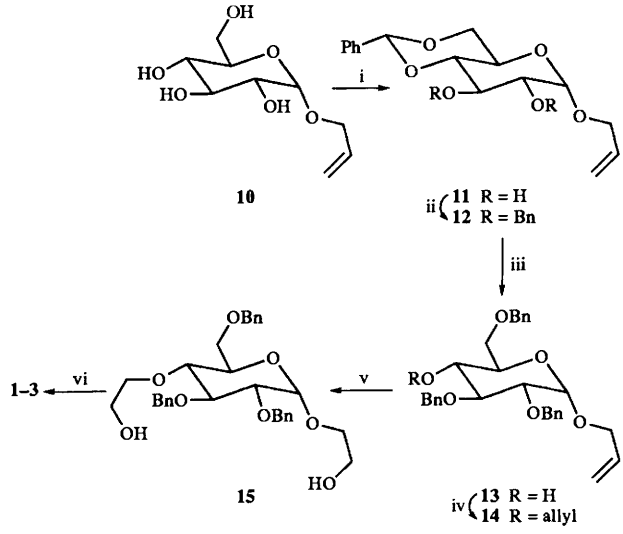
As part of our investigations in this area, we have synthesized[7] the novel class of D-glucose-based crown ether derivatives **1–9**. In these compounds the glucose unit is introduced into the crown ether periphery through the 1–4-hydroxy groups. In compounds **1–3**, the benzyl groups are placed closer to the cavity and thus offer a hydrophobic interior, whereas in compounds **4–6** the hydroxy groups at positions 2, 3 and 6 can act as additional binding and/or catalytic sites for molecular interactions.

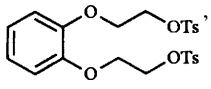


1 $n = 1$, R = Bn **2** $n = 2$, R = Bn **3** R = Bn
4 $n = 1$, R = H **5** $n = 2$, R = H **6** R = H
7 $n = 1$, R = Ac **8** $n = 2$, R = Ac **9** R = Ac

Results and discussion

Macrocycles **1–3** have been synthesized by condensation of 2-hydroxyethyl 2,3,6-tri-*O*-benzyl-4-O-(2-hydroxyethyl)-α-D-glucopyranoside **15** with the appropriate poly(ethylene glycol) units. The synthesis of this diol was achieved efficiently from allyl α-D-glucopyranoside as outlined in Scheme 1. The allyl



Scheme 1 *Reagents and conditions*: i, C_6H_5CHO, DMF–Me_2SO_4, room temp., 18 h; ii, $C_6H_5CH_2Cl$, NaH, THF, 70 °C, 24 h; iii, $NaCNBH_3$–HCl(ether), THF, room temp., 10 min; iv, allyl bromide, NaH, THF, 70 °C, 5 h; v, O_3, MeOH, −78 °C, $NaBH_4$; vi, di(ethylene glycol) ditosylester/tri(ethylene glycol) ditosyl derivative  , NaH, THF, 70 °C, 24 h

glucoside **10** on treatment with benzaldehyde in the presence of $(CH_3)_2SO_4$–dimethylformamide (DMF) adduct as the catalyst[8] gave the 4,6-*O*-benzylidene derivative **11** in 69% yield. The ^1H NMR spectrum of compound **11** showed a singlet at δ 5.55 (C*H*Ph) and the anomeric proton appeared as a doublet at δ 4.95. Further, the two hydroxy groups present at positions 2 and 3 were protected by benzylation. The product **12** was obtained as a fine crystalline solid in 91% yield (mp 86–87 °C). In the next step, the benzylidene acetal was opened regioselectively using $NaCNBH_3$ and ethereal hydrogen chloride[9] at room temperature. Product **13** was isolated in 80% yield and its structure was established on the basis of IR, ^1H NMR and ^{13}C NMR spectral data. The IR spectrum showed a broad band at 3400 cm^{-1}. Both ^1H and ^{13}C NMR spectra were devoid of any resonance due to benzylidene proton (C*H*Ph); in the ^{13}C NMR spectrum, the primary hydroxy-bearing carbon (CH_2OH) was not visible around δ 62.0.

The hydroxy compound **13** was easily converted into the diallyl derivative **14** by using allyl bromide and NaH. Ozonolysis of diene **14** in methanol at −78 °C followed by a

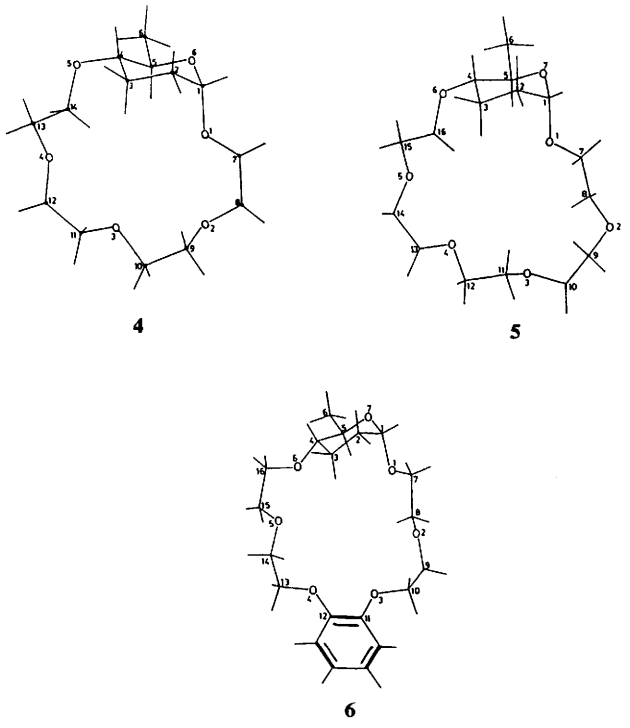


Fig. 1 MMX-calculated minimum-energy conformation of macrocycles **4–6** showing the numbering system

reductive work-up afforded the diol **15** in 79% yield. The ^{1}H NMR spectrum of diol **15** was devoid of any olefinic proton resonance and the ^{13}C NMR spectrum showed two new signals at δ 62.1 and 61.0 (CH_2OH). This diol was used for the subsequent cyclization reactions, which were carried out under rigorously anhydrous conditions to obtain macrocycles **1–3**.

Removal of the benzyl groups in compounds **1–3** was accomplished by catalytic hydrogenation over Pd/C under pressure (40 psi). The products **4–6** were obtained as glassy solids and these were acetylated to give the triacetyl derivatives **7–9**. The triacetate **7** was obtained as a syrup having $[\alpha]_D$ +87.9 (*c* 0.86, $CHCl_3$). Compound **8** was also obtained as a glassy solid, but crystallized as cubes (mp 134–135 °C) from a mixture of hexane and ethyl acetate (5:1) under refrigeration (30 days). Unlike the triacetates **7** and **8**, compound **9** readily crystallized from a mixture of hexane and ethyl acetate to afford cubic crystals (mp 147–148 °C). The IR spectra of the three compounds **7**, **8** and **9** indicated carbonyl absorptions at 1746, 1743 and 1747 cm^{-1}, respectively, and were free of absorption due to hydroxy groups. In the ^{1}H NMR spectra of the three compounds, the acetyl protons were observed at δ 2.10–1.98 and the relevant carbon signals were visible at δ 20.92–20.76 in the ^{13}C NMR spectra.

Application of the MMX programme provided the average cavity size of macrocycles **4–6**. Fig. 1 shows a view of the minimum-energy conformation of the macrocycles obtained by this programme. The distances among the oxygen atoms involved in the cavity of the different macrocycles are given in Table 1. In the values given, the minimum distance between vicinal oxygen atoms and the maximum distance between non-contiguous oxygen atoms correspond to the minimum and maximum diameter of the cavity.

Table 1 Distances between the oxygen atoms (Å) involved in the cavity of macrocycles **4–6** according to the MMX programme

Macrocycle		O(3)	O(4)	O(5)	O(6)
4	O(1)	4.13	5.20	4.58	
	O(2)	2.92	5.30	6.24	
	O(3)		3.01	4.99	
	O(4)	3.01		3.40	
	O(5)	4.99	3.40		
5	O(1)	4.34	4.87	5.19	4.38
	O(2)	3.33	5.75	7.51	7.50
	O(3)		2.91	5.35	6.71
	O(4)	2.91		2.82	5.03
	O(5)	5.35	2.82		3.49
	O(6)	6.71	5.03	3.49	
6	O(1)	4.73	5.50	5.13	4.01
	O(2)	3.02	4.93	5.98	5.76
	O(3)		2.65	4.85	5.78
	O(4)	2.66		2.93	4.77
	O(5)	4.90	2.93		2.80
	O(6)	5.99	4.77	2.80	

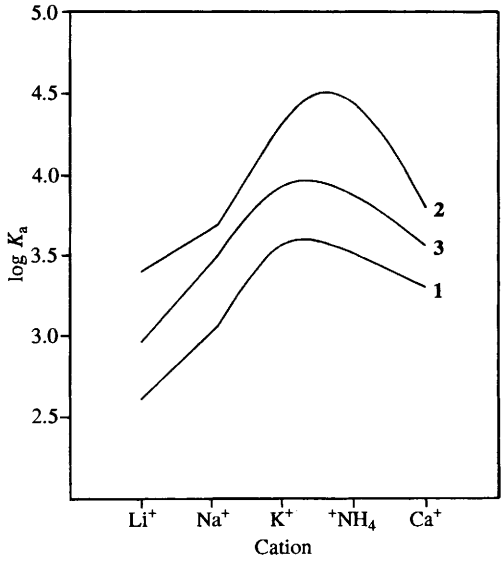


Fig. 2 Variation of log K_a with different cations for macrocycles **1–3**

Association constants

The binding abilities of the new macrocycles **1–3** were evaluated by Cram's picrate method.[10] This involves extraction of an aqueous solution of picrate salts[11] both in the presence and in the absence of host molecules.† Solutions of the macrocycles **1–3** in $CDCl_3$ (0.075 mol dm^{-3}) were used to extract aqueous solutions of lithium, sodium, potassium, caesium and ammonium picrates (0.015 mol dm^{-3}). The distribution constant and the extinction coefficient of the picrate salts were determined by a known procedure.[10]

The association constant values (K_a) were determined from the results obtained and Fig. 2 is a diagrammatic representation of the variation of log K_a with different cations.

From Fig. 2 it is evident that hosts **1** and **3** showed moderately good binding affinity for K^+, whereas host **2** showed a maximum affinity for both K^+ and NH_4^+. We assume that the incorporation of the sugar unit will introduce some sort of distortion to the crown ether portion, so that some of the oxygen atoms will be oriented towards the cavity and some away from the cavity. This was found to be the case from the computer-modelling studies of hosts **4–6** (Fig. 1) and we expect a similar situation with the macrocycles **1–3** also. One of

† The experiment was carried out precisely under the conditions described in ref. 10 using the same concentration and volume of picrate salts and hosts.

Table 2 Asymmetric Michael addition of methyl phenylacetate to methyl acrylate

Entry	Temp. (T/°C)	Substrate[a] proportions	Reaction period (t/h)	Yield[b] (%)	$[\alpha]_D^{EtOH}$	ee (%)[c,d]
1	−78	1:0:40:15	3	35		
2	−78	1:1:40:15	3	30	56.1	63(*S*)
3	−50	1:1:40:15	3	25	52.7	59(*S*)
4	30	1:1:40:15	3			
5	−78	5:1:20:15	4			
6	30	5:1:20:15	3	15	−41.6	47(*R*)

[a] Bu^{t}OK–host **2**–methyl phenylacetate–methyl acrylate. [b] Under two conditions (entries 4 and 5) the reaction did not proceed. The starting materials were recovered after the specified reaction period. [c] The % ee is based on a value of $[\alpha]_D$ +89° (c 5, EtOH) for the *S* isomer (ref. 12). [d] Absolute configurations are given in parentheses.

the reasons for the reasonably good selectivity of host **2** towards K^+ and NH_4^+ when compared with host **1** may be attributed to the larger size of the cavity. However, it is very clear from the figure that host **3**, having the same number of atoms on the crown ether periphery as that of host **2**, exhibited low binding affinity for K^+ and NH_4^+. From this observation it is conceivable that during complexation host **2** reorganizes itself in such a way that the oxygen atoms are in the right orientation to bind the spherically charged K^+ or the tetrahedral NH_4^+ more effectively. Such a reorganization is not easy for host **3**, since the aromatic ring offers more rigidity for the crown ether part.

Application of macrocycle 2 in asymmetric synthesis

Asymmetric C–C bond-forming reactions are of special interest in organic synthesis. Although many optically active crown ethers have been synthesized, only a few have been used as catalysts in asymmetric synthesis.[12–15] Some of these receptors complexed with potassium bases have been known to catalyse the addition of methyl phenylacetate to methyl acrylate.[6c,12,15,16] Since macrocycle **2** showed reasonably good selectivity for potassium ion, we examined the catalytic activity of this compound in the above reaction. The experiment was carried out in toluene using potassium *tert*-butoxide as the base as described in the Experimental section. The reactions were repeated under a variety of conditions. The asymmetric induction expressed in terms of enantiomeric excess (ee) was determined by measuring the optical rotations of the product ester. The experimental conditions and the results obtained are given in Table 2.

In two cases (entries 2 and 3) we obtained the product having '*S*' configuration and in one case (entry 6), the product obtained had '*R*' configuration. The reasons for this preference are not apparent.

Although the degree of chiral induction achieved in these experiments is modest it is comparable to the results reported by other workers who have employed crown ethers based on carbohydrates.[6c,15,16]

In summary, we have been able to synthesize a number of novel flexible crown ether derivatives with different cavity sizes. The synthetic strategy used for the preparation of hosts **1–3** will allow the synthesis of a variety of such compounds by a rational change in the sugar moiety.

Experimental

Mps were determined on a Buchi-530 melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter at ambient temperature (24–27 °C) and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer model 882 spectrophotometer. Proton and carbon NMR spectra were recorded on Varian Unity-400, Brucker AF-300 and JEOL GSX-270 NMR spectrometers. Mass spectra were obtained on a JEOL SX-102 or a Shimadzu QP-2000 spectrometer. Elemental analyses were performed on a Carlo Erba 1108 CHN analyser. Hydrogenations were carried out on a Parr hydrogenation apparatus. Light petroleum refers to the fraction with distillation range 60–80 °C. Silica gel (100–200 mesh) was used for column chromatography. NaH used was a 50–55% suspension in mineral oil. All solvent extracts were dried over anhydrous sodium sulfate.

Allyl 4,6-*O*-benzylidene-α-D-glucopyranoside 11

A solution of dimethyl sulfate (2.23 g, 17.67 mmol) in dry DMF (20 cm^3) was heated at 60 °C for 2 h under nitrogen. After cooling of this solution to room temperature, allyl glucoside[17] **10** (3.0 g, 13.62 mmol) was added. This was followed by the addition of freshly distilled benzaldehyde (1.88 g, 17.71 mmol). The reaction mixture was stirred at room temperature for 18 h and then was quenched by being stirred with Amberlite IR-45(OH$^-$). The resin was filtered off and the solvent was removed. The residue obtained was subjected to column chromatography on silica gel and eluted with 4% methanol in chloroform to obtain *title compound* **11** (2.9 g, 69%) as a solid. Crystallization from CCl_4 furnished needles, mp 118–119 °C (Found: C, 62.5; H, 6.3. $C_{16}H_{20}O_6$ requires C, 62.33; H, 6.54%); $[\alpha]_D$ +38.4 (*c* 0.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400, 2920, 2840 and 1600; δ_H(400 MHz; $CDCl_3$) 7.6–7.2 (5 H, m, ArH), 6.05–5.85 (1 H, m, CH), 5.55 (1 H, s, C*H*Ph), 5.4–5.2 (2 H, m, CH_2), 4.95 (1 H, d, *J* 3.9, 1-H), 4.5–3.4 (8 H, m) and 2.75 (2 H, br s, OH); δ_C(75.5 MHz; $CDCl_3$) 137.33, 133.60, 129.58, 128.66, 126.61, 118.65, 102.23, 98.19, 81.24, 73.14, 72.08, 70.97, 69.19 and 62.91.

Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 12

A solution of the partially protected sugar **11** (1.9 g, 6.16 mmol) in dry tetrahydrofuran (THF) (25 cm^3) was added dropwise to a suspension of NaH (1.33 g, ~28 mmol) in dry THF (25 cm^3). This was followed by the addition of benzyl chloride (2.73 g, 21.56 mmol) and the reaction mixture was heated under reflux for 24 h while being continuously stirred. After cooling of this mixture to room temperature, excess of NaH was destroyed by the dropwise addition of a methanol–water mixture. The resulting clear solution was partially concentrated and brine (30 cm^3) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 50 cm^3) and the combined organic extracts were dried. Removal of solvent followed by purification on silica gel column with 6% ethyl acetate in light petroleum as eluent afforded *title compound* **12** (2.75 g, 91%) as a solid. Crystallization from methanol gave fluffy needles, mp 86–87 °C (Found: C, 73.7; H, 6.6. $C_{30}H_{32}O_6$ requires C, 73.75; H, 6.60%); $[\alpha]_D$ +27.7 (*c* 0.8, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3040, 2920 and 1080; δ_H(300 MHz; $CDCl_3$) 7.55–7.17 (15 H, m, ArH), 6.05–5.80 (1 H, m, CH), 5.55 (1 H, s, C*H*Ph), 5.40–5.15 (2 H, m,

CH_2), 4.95–4.65 (5 H, m, OCH_2Ph and 1-H) and 4.30–3.50 (8 H, m); δ_C(75.5 MHz; $CDCl_3$) 139.12, 138.53, 137.74, 133.94, 129.22, 128.74, 128.62, 128.54, 128.38, 128.32, 128.18, 127.89, 126.34, 118.70, 101.55, 97.09, 82.53, 79.56, 78.96, 75.69, 73.93, 69.35, 68.82 and 62.87.

Allyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside 13

Powdered 3 Å molecular sieves (1 g) were suspended in dry THF (25 cm^3) containing the acetal **12** (1.75 g, 3.58 mmol). $NaCNBH_3$ (3.0 g, 47.73 mmol) was added to this solution. HCl in dry diethyl ether was then added dropwise at room temperature, until the evolution of gases ceased. After being stirred for another 10 min, the reaction mixture was diluted with water (10 cm^3), filtered, and extracted with CH_2Cl_2 (4 × 60 cm^3). The combined organic extracts were washed successively with saturated aq. $NaHCO_3$ and water, and dried. The residue obtained after removal of the solvent was purified by column chromatography on silica gel. Elution with 15% ethyl acetate in light petroleum furnished *title compound* **13** (1.4 g, 80%) as a syrup (Found: C, 73.25; H, 6.7. $C_{30}H_{34}O_6$ requires C, 73.45; H, 6.99%); $[\alpha]_D$ +24.8 (*c* 1.38, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400, 3040, 2900 and 1600; δ_H(400 MHz; $CDCl_3$) 7.65–7.15 (15 H, m, ArH), 6.05–5.85 (1 H, m, CH), 5.45–5.15 (2 H, m, CH_2), 5.10–4.40 (7 H, m, OCH_2Ph and 1-H), 4.18 (1 H, m), 4.02 (1 H, m), 3.90–3.40 (6 H, m) and 2.40 (1 H, br s, OH); δ_C(100.6 MHz; $CDCl_3$) 139.02, 138.21, 137.56, 133.50, 129.19, 128.62, 128.31, 128.26, 128.18, 128.09, 127.68, 118.31, 95.73, 81.80, 79.66, 75.48, 73.62, 73.02, 70.81, 70.16, 69.51 and 68.31.

Allyl 4-*O*-allyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside 14

Allyl bromide (0.40 g, 3.30 mmol) was added to a magnetically stirred solution of the glycoside **13** (1.30 g, 2.65 mmol) in dry THF (50 cm^3) containing NaH (0.25 g, 5 mmol). The reaction mixture was heated at 70 °C for 5 h and then was processed by the same procedure described in the synthesis of compound **12**. Evaporation of the solvent furnished a pale yellow residue, which was purified by column chromatography on silica gel (light petroleum–ethyl acetate, 9:1) to obtain compound **14** as a viscous liquid (Found: C, 74.5; H, 7.3. $C_{33}H_{38}O_6$ requires C, 74.69; H, 7.22%); $[\alpha]_D$ +49.0 (*c* 0.86, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3040, 2920, 2880 and 1500; δ_H(270 MHz; $CDCl_3$) 7.35–7.26 (15 H, m, ArH), 6.06–5.68 (2 H, m, CH), 5.40–5.02 (4 H, m, CH_2), 5.0–4.38 (7 H, m, OCH_2Ph and 1-H) and 4.36–3.20 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 139.1, 138.2, 136.5, 135.2, 134.1, 129.0–127.5, 118.1, 116.7, 96.1, 82.2, 80.1, 79.1, 77.9, 77.0, 76.0, 74.1, 73.9, 70.7 and 68.6.

2-Hydroxyethyl 2,3,6-tri-*O*-benzyl-4-*O*-(2-hydroxyethyl)-α-D-glucopyranoside 15

A magnetically stirred solution of the diallyl derivative **14** (1.3 g, 2.45 mmol) in dry methanol (75 cm^3) was cooled to −78 °C. A slow stream of ozone was bubbled through the solution until a pale blue colour persisted. Excess of ozone was removed (by passing oxygen through) and $NaBH_4$ (0.31 g, 8.19 mmol) was added to the solution. The reaction mixture was stirred for 12 h (−78 °C ⟶ room temp.) before being diluted with water (10 cm^3) and partially concentrated to remove most of the methanol. Brine (25 cm^3) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 cm^3). The combined organic extracts were dried and concentrated. The crude product obtained was subjected to column chromatography on silica gel and elution with a mixture of light petroleum–ethyl acetate (1:1) afforded *compound* **15** (1.04 g, 79%) as a viscous liquid (Found: C, 69.3; H, 7.2. $C_{31}H_{38}O_8$ requires C, 69.13; H, 7.11%); $[\alpha]_D$ +45.9 (*c* 3.24, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3460, 3040 and 2930; δ_H(270 MHz; $CDCl_3$) 7.35–7.26 (15 H, m, ArH), 4.98 (1 H, d, *J* 4.1), 4.86–4.44 (6 H, m, OCH_2Ph), 4.0–3.40 (14 H, m) and 2.0 (2 H, br s); δ_C(22.4 MHz; $CDCl_3$) 138.8, 137.6, 128.8–127.5, 97.7, 81.9, 80.0, 78.1, 77.2, 75.4, 73.9, 73.5, 70.3, 68.6, 62.1 and 61.0.

Monogluco-17-crown-5 1

NaH (0.6 g, ~ 13 mmol) was suspended in dry THF (50 cm^3). A solution of the diol **15** (0.89 g, 1.65 mmol) in dry THF (50 cm^3) was added dropwise to this mixture and stirred at 70 °C for 30 min. A solution of di(ethylene glycol) ditosyl ester (0.83 g, 2.0 mmol) in dry THF (75 cm^3) was added dropwise to the reaction mixture over a period of 3 h. The stirring and heating of the mixture were continued for 24 h. After the mixture had cooled to room temperature, excess of NaH was destroyed by the dropwise addition of a methanol–water mixture. The reaction mixture was partially concentrated and brine (30 cm^3) was added to the residue. The mixture was extracted with CH_2Cl_2(3 × 25 cm^3). The combined organic extracts were dried and the solvent was evaporated off. The residue obtained was subjected to column chromatography on silica gel.

Careful elution with a mixture of light petroleum and ethyl acetate (2:3) furnished *compound* **1** (0.33 g, 33%) as a syrup (Found: C, 68.85; H, 7.1. $C_{35}H_{44}O_9$ requires C, 69.06; H, 7.29%); $[\alpha]_D$ +66.5 (*c* 0.68, $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 3040, 2876 and 1457; δ_H(300 MHz; $CDCl_3$) 7.4–7.1 (15 H, m, ArH), 4.95–4.40 (7 H, m, OCH_2Ph and 1-H) and 4.0–3.3 (22 H, m); δ_C(75.5 MHz; $CDCl_3$) 139.32, 138.74, 138.58, 128.65, 128.31, 128.13, 127.83, 97.57, 82.09, 80.17, 78.31, 75.90, 73.60, 71.12, 70.95 and 70.36.

Monogluco-20-crown-6 2

A solution of the diol **15** (0.68 g, 1.26 mmol) in dry THF (50 cm^3) was treated with NaH (0.50 g, ~ 10 mmol) in THF (50 cm^3) and then with a solution of tri(ethylene glycol) ditosyl ester (0.86 g, 1.88 mmol) as described above for the synthesis of **1**. The crude product obtained was purified by silica gel column chromatography. Careful elution with a mixture of light petroleum and ethyl acetate (2:3) furnished *title compound* **2** (0.28 g, 34%) as a syrup (Found: C, 68.5; H, 7.4. $C_{37}H_{48}O_{10}$ requires C, 68.08; H, 7.41%); $[\alpha]_D$ +12.0 (*c* 0.96, $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 3040, 2900 and 1460; δ_H(300 MHz; $CDCl_3$) 7.30–7.10 (15 H, m, ArH), 4.96–4.42 (6 H, m) and 4.25–3.22 (27 H, m); δ_C(75.5 MHz; $CDCl_3$) 139.13, 138.44, 129.90, 129.75, 129.64, 128.40, 128.0, 127.79, 127.61, 127.47, 127.40, 97.21, 82.0, 79.60, 77.80, 73.31, 71.63, 71.10, 69.83, 68.44 and 67.50; *m/z* 653 (MH^+, 100%).

Monoglucobenzo-20-crown-6 3

A solution of the diol **15** (0.53 g, 0.98 mmol) in dry THF (50 cm^3) was treated with NaH (0.36 g, ~ 7.0 mmol) in THF (50 cm^3) and then with a solution of 1,2-bis(toluene-*p*-sulfonyloxyethoxy)benzene[18] (0.75 g, 1.48 mmol) in THF as described for the synthesis of compound **1**. Removal of the solvent followed by purification on silica gel column with 35% ethyl acetate in light petroleum as the eluent afforded compound **3** (0.20 g, 29%) as a syrup; $[\alpha]_D$ +29.4 (*c* 1.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3040, 2900, 1600 and 1460; δ_H(300 MHz; $CDCl_3$) 7.50–6.75 (19 H, m, ArH), 5.0–4.5 (6 H, m), 4.34 (1 H, d, *J* 3.3, 1-H) and 4.25–3.45 (22 H, m); δ_C(75.5 MHz; $CDCl_3$) 145.69, 132.71, 130.97, 129.66, 128.76, 128.73, 128.58, 128.07, 127.85, 121.95, 121.60, 115.30, 112.50, 96.30, 80.12, 77.70, 75.81, 71.22, 70.60, 69.61, 69.0 and 68.73 (Found: M^+, 700.8200. $C_{41}H_{48}O_{10}$ requires M, 700.8202).

Hydrogenolysis: general procedure

The protected macrocycle (**1**, **2** or **3**, 0.30–0.45 mmol) was dissolved in a mixture of methanol and ethyl acetate (9:1). Nitrogen was bubbled through the solution for 10 min. 10% Pd/C (0.80 g) was added and the mixture was hydrogenated under pressure (40 psi), at room temperature, for 10–12 h. The

suspension was filtered over Celite, the residue was washed with methanol–ethyl acetate mixture and the filtrate was concentrated. The residue obtained was purified by column chromatography.

Monogluco-17-crown-5 4

A solution of the macrocycle **1** (0.20 g, 0.33 mmol) in methanol–ethyl acetate (30 cm^3) was hydrogenated for 12 h. The residue obtained was subjected to column chromatography on silica gel. Elution with a mixture of chloroform and methanol (3:1) afforded compound **4** (0.07 g, 63%) as a glassy solid; $[\alpha]_D$ +65.9 (*c* 0.8, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3450, 3020, 2990 and 1460; δ_H(270 MHz; D_2O) 4.91 (1 H, d, *J* 3.7, 1-H), 3.82 (1 H, m), 3.75 (19 H, m) and 3.34 (2 H, m); δ_C(67.8 MHz; D_2O) 98.5, 77.8, 72.5, 71.8, 70.0, 69.2, 67.7 and 60.2.

Monogluco-20-crown-6 5

A solution of the macrocycle **2** (0.28 g, 0.43 mmol) in the methanol-ethyl acetate mixture (40 cm^3) was hydrogenated for 8 h. Purification of the residue by column chromatography on silica gel (chloroform–methanol, 9:1) afforded compound **5** (0.15 g, 91%) as a glassy solid, $[\alpha]_D$ +74.7 (*c* 1.0, MeOH); ν_{max}(neat)/cm^{-1} 3400, 3020, 2985 and 1500; δ_H(400 MHz; $[^2H_4]$MeOH) 4.80 (1 H, d, *J* 3.9, 1-H), 4.04–3.54 (21 H, m), 3.43 (4 H, m) and 3.20 (1 H, t, *J* 8.0); δ_C(100.6 MHz; $[^2H_4]$MeOH) 100.28, 80.03, 75.12, 73.54, 72.61, 72.40, 72.02, 71.74, 71.69, 71.51, 71.40, 70.97, 68.75 and 62.38.

Monoglucobenzo-20-crown-6 6

A solution of the macrocycle **3** (0.25 g, 0.36 mmol) in the methanol–ethyl acetate mixture (30 cm^3) was hydrogenated for 10 h. The crude product obtained was purified by silica gel column chromatography. Elution with 5% methanol in chloroform afforded compound **6** (0.11 g, 72%) as a glassy solid, $[\alpha]_D$ +57.9 (*c* 0.7, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440, 3010, 2985 and 1510; δ_H(400 MHz; $CDCl_3$) 7.0–6.68 (4 H, m), 4.82 (1 H, d, *J* 3.8) and 4.26–3.18 (25 H, m); δ_C(100.6 MHz; $CDCl_3$) 148.87, 148.85, 121.85, 121.03, 115.10, 112.61, 98.79, 79.15, 74.22, 72.23, 71.11, 70.94, 70.82, 70.35, 70.18, 69.53, 69.06, 68.52, 67.56 and 62.20.

Acetylation: general procedure

Acetic anhydride (1.0–1.5 cm^3) was added dropwise to a solution of the deprotected macrocycle (**4**, **5** or **6**, 0.10–0.15 mmol) in pyridine (1.5–2.0 cm^3) kept at 0 °C. After being stirred for 5 h, the reaction mixture was quenched by being stirred with water (1.0 cm^3). The product was extracted with CH_2Cl_2 (3 × 20 cm^3) after dilution with more water (10 cm^3). The combined organic extracts were washed successively with ice-cold, 2 mol dm^{-3} HCl and water, and dried. The residue obtained after removal of the solvent was purified by column chromatography.

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A solution of the deprotected macrocycle **4** (0.05 g, 0.15 mmol) in dry pyridine (1.96 g, 24.8 mmol) was treated with acetic anhydride (1.62 g, 12.3 mmol) as described in the general procedure. The residue obtained after work-up was charged on a silica gel column. Elution with chloroform–methanol (20:1) furnished *title compound* **7** (0.05 g, 73%) as a syrup (Found: C, 51.8; H, 7.0. $C_{20}H_{32}O_{12}$ requires C, 51.72; H, 6.94%); $[\alpha]_D$ +87.9 (*c* 0.86, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2930 and 1746; δ_H(400 MHz; $CDCl_3$) 5.50–5.38 (1 H, m), 4.92 (1 H, t, *J* 4.0), 4.82–4.68 (1 H, m), 4.48–4.19 (2 H, m), 4.10–3.36 (18 H, m) and 2.10–1.98 (9 H, m); δ_C(100 MHz; $CDCl_3$) 170.59, 170.42, 169.65, 95.87, 71.95, 71.23, 71.03, 70.76, 70.62, 70.59, 70.51, 70.48, 70.38, 70.32, 69.88, 68.09, 62.59, 20.92, 20.87 and 20.76; *m/z* 464 (M^+, 20%).

Monogluco-20-crown-6 8

A solution of the macrocycle **5** (0.045 g, 0.12 mmol) in dry pyridine (1.47 g, 12.6 mmol) was treated with acetic anhydride (1.08 g, 8.17 mmol) and the reaction mixture was worked up as described previously. Purification of the residue by column chromatography on silica gel with ethyl acetate as the eluent afforded *title compound* **8** (0.042 g, 70%) as a solid. Recrystallization from hexane–ethyl acetate afforded cubic crystals, mp 134–135 °C (Found: C, 51.75; H, 7.3. $C_{22}H_{36}O_{13}$ requires C, 51.96; H, 7.14%); $[\alpha]_D$ +90.1 (*c* 0.4, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2926 and 1743; δ_H(400 MHz; $CDCl_3$) 5.51 (1 H, t, *J* 12.5), 4.93 (1 H, d, *J* 4.6), 4.8 (1 H, m), 4.56 (1 H, m), 4.35 (2 H, m), 3.83–3.45 (21 H, m), 2.10 (3 H, s, OAc) and 2.05 (6 H, s, OAc); δ_C(100.6 MHz; $CDCl_3$) 170.54, 170.44, 169.63, 95.78, 72.12, 71.56, 71.46, 71.17, 71.08, 70.82, 70.78, 70.13, 67.86, 62.93, 20.96, 20.92 and 20.78; *m/z* 508 (M^+, 7%).

Monoglucobenzo-20-crown-6 9

A solution of the macrocycle **6** (0.05 g, 0.166 mmol) in dry pyridine (1.47 g, 12.6 mmol) was treated with acetic anhydride (1.08 g, 8.17 mmol) as described previously. The crude product obtained on purification by column chromatography on silica gel (light petroleum–ethyl acetate, 1:4) afforded *compound* **9** (0.045 g, 70%) as a solid. Recrystallization from a mixture of hexane and ethyl acetate gave needles, mp 147–148 °C (Found: C, 56.3; H, 6.5. $C_{26}H_{36}O_{13}$ requires C, 56.11; H, 6.52%); $[\alpha]_D$ +78.8 (*c* 0.6, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2935, 1747 and 1510; δ_H(400 MHz; $CDCl_3$) 6.85 (4 H, ArH), 5.53 (1 H, t, *J* 4.1), 4.78 (1 H, d, *J* 3.9), 4.58–3.46 (21 H, m), 2.05 (6 H, s, OAc) and 1.85 (3 H, s OAc); δ_C(100.6 MHz; $CDCl_3$) 170.52, 148.54, 121.97, 120.70, 115.95, 112.76, 95.93, 76.18, 71.42, 71.35, 70.53, 70.30, 70.02, 69.60, 69.48, 68.43, 67.67, 67.51, 62.81, 20.98 and 20.84.

Michael addition reactions

Methyl phenylacetate (4 mmol) in dry toluene (1.0 cm^3) was added to a suspension of potassium *tert*-butoxide (0.1 mmol) in toluene (1.0 cm^3) under argon and the mixture was stirred for 15 min. A solution of the host **2** (0.1 mmol) in toluene (1.5 cm^3) was then added and the mixture was stirred for another 15 min. A solution of methyl acrylate (1.5 mmol) in toluene (1.0 cm^3) was added and the mixture was stirred, then was poured into saturated aq. NH_4Cl (10 cm^3), extracted with toluene (3 × 20 cm^3), and the combined extracts were dried. The residue obtained after removal of the solvent was subjected to silica gel column chromatography and was eluted with 6% ethyl acetate to afford the adduct.

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