Tetrahedron Vol. 45, No. 11, pp. 3605 to 3612, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

NEW SYNTHETIC STRATEGY TO HIGHLY SYMMETRIC CHIRAL MACROCYCLES FROM CARBOHYDRATE DERIVATIVES

Cristina Vicent, Manuel Martín-Lomas, and Soledad Penadés*

Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain.

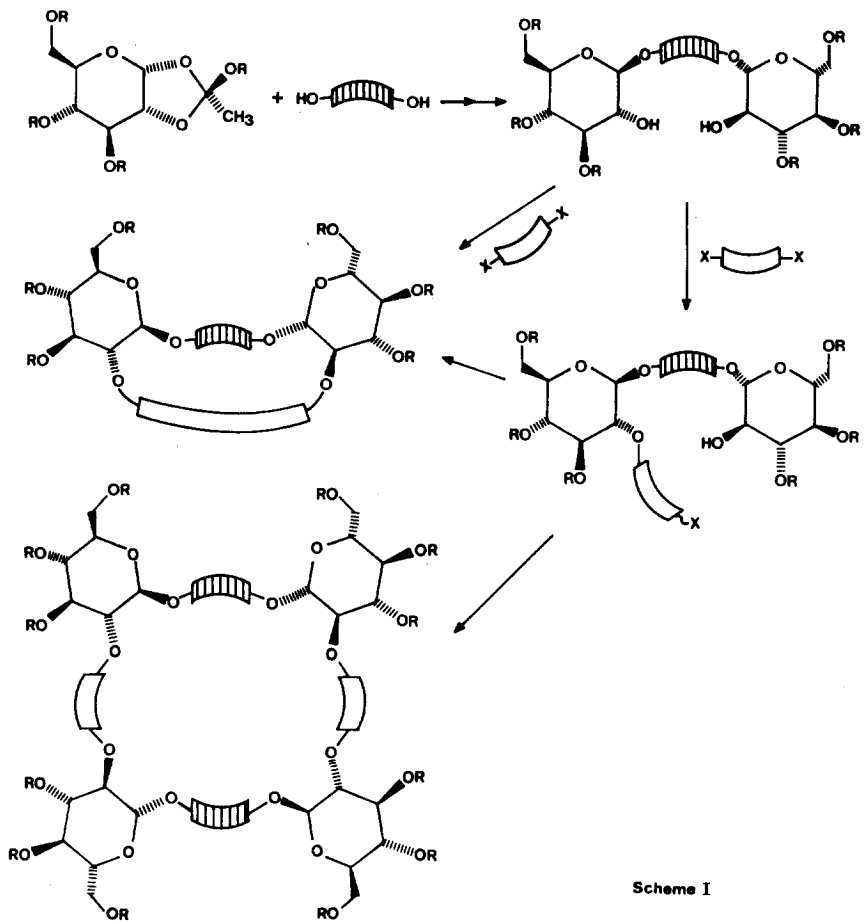
(*Received in UK* 8 *March* 1989)

Abstract - A simple strategy for the synthesis of highly symmetric macrocycles incorporating carbohydrates is presented. The application of this strategy to the synthesis of optically active tetra-*gluco*-24-crown-8 (**1**), bis-*gluco* -15-crown-5 (**3**), and bis-*gluco*-21-crown-8 (**5**) is described. Preliminary studies showed that macrocycles **1**, **3** and **5** complex ammonium salts. These macrocyclic compounds have been used as catalysts in the asymmetric Michael addition of methyl α-phenylacetate to methyl acrylate.

The synthesis of chiral receptor molecules provides models for a better understanding of the principles determining specific molecular interactions. An impressive variety of such molecules having remarkable binding characteristics have already been synthesized from natural and non natural products[1,2] and some of them have been used for the optical resolution of racemic cationic guests in organic solvents.[3] A few reports have appeared that describe the formation of diastereomeric complexes between fully synthetic optically active ligands and neutral guests in aqueous and organic solution.[4-6] The formation of diastereomeric complexes in solution is usually studied by NMR spectroscopy. Highly symmetric hosts with homotopic faces provide more simple spectra of the complexes and the conformational changes and interactions that take place under complexation can be better studied and understood using these receptors.

As a part of our programme on the synthesis, complexing properties and applications of new chiral macrocycles with different cavity shapes and flexibility from disaccharides[7-10] we are developing new synthetic approaches to highly symmetric neutral chiral macrocycles with good solubility properties both in water and organic solvents.

In this paper we report our synthetic strategy (Scheme I) for the preparation of chiral crown ethers based on the glycosylation of diols with carbohydrate orthoester derivatives. This strategy may allow to incorporate carbohydrate derivatives with different configuration (*manno-* , *galacto-*, etc) into a macrocycle to give receptors with different chiral barriers and different solubility properties depending on the nature of substituents of the hydroxyl groups. Our approach will also permit to vary widely the size and the properties of the cavities from crown ether type macrocycles to more lipophilic cavities depending on the starting diols (biphenyl, naphthyl derivatives, etc) giving water soluble chiral "glycophanes".[11]



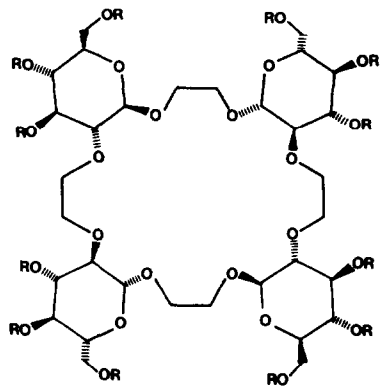
Scheme I

RESULTS AND DISCUSION

Macrocyles **1**, **3** and **5** have been synthesized using the strategy illustrated in Scheme I. Glycosylation of ethylene glycol with two molar equivalents of 3,4,6-tri-*O*-benzyl-1,2-*O*-(isopropoxyethylidene)-α-D-glucopyranoside (**7**) in the presence of 2,6-dimethylpyridinium perchlorate gave 1,2-di-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)ethylenediol (**8**) in 70% yield. Deacetylation of **8** afforded the 1,2-di-*O*-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)ethylenediol (**9**) in 95% yield.

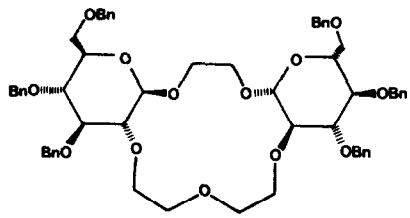
Alkylation of **9** with 1,2-dibromoethane at 50°C under phase transfer conditions, using the alkylating agent as solvent, afforded the monoalkyl derivative (**10**) in 40%. Compound **9** (50%) could be recovered from the reaction mixture and reused. The yield of compound **10** did not improve by increasing the reaction time and the temperature and, in all conditions studied, the reaction stopped at this stage and the formation of the expected dialkyl derivative was never observed.

The monoalkyl derivative **10** was then used as starting material for unequivocal syntheses of macrocycles incorporating two or four glucopyranosyl units. Intermolecular cyclization of **10** in THF



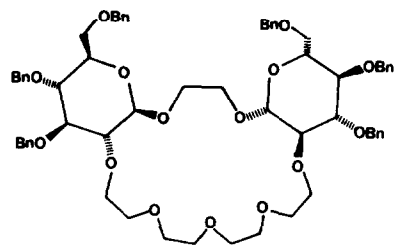
1 , R = Bn

2 , R = Ac



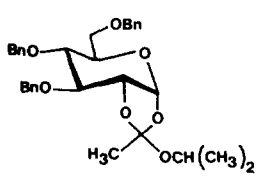
3 , R = Bn

4 , R = Ac



5 , R = Bn

6 , R = Ac



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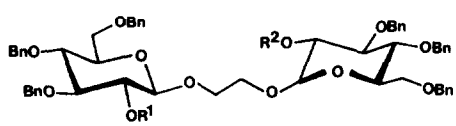

8 , $R^1 = R^2 = Ac$

9 , $R^1 = R^2 = H$

10 , $R^1 = CH_2CH_2Br$, $R^2 = H$

11 , $R^1 = CH_2CH_2OCH_2CH_2Br$, $R^2 = H$

12 , $R^1 = R^2 = CH_2CH_2OCH_2CH_2Br$

in the presence of NaH yielded the chiral tetra-*gluco*-24-crown-8 (**1**) in 54% yield. Debenzylation and subsequent acetylation afforded **2** in 72% yield. Similarly alkylation of **9** with 1,5-dibromo-3-oxapentane at room temperature under phase transfer conditions gave the monoalkyl derivative **11** in 75% yield. In this case, the dialkyl derivative (**12**) was obtained in variable yields, depending on the reaction conditions, by increasing the reaction time or the temperature.

Intermolecular cyclization of **11** to the larger macrocycle 30-crown-10 failed, and the dehydrohalogenation product or the intracyclization product, 15-crown-5 (**3**), were obtained depending on the reaction conditions. Alternative routes to the chiral 30-crown-10 based on the intermolecular cyclization of the dialkyl derivative **12** and the diol **9** also failed and very complex

mixtures were obtained under different reaction conditions. The bis-*gluco*-15-crown-5 ether (**3**) was also obtained in 68 % yield by treatment of **9** in DMF with diethylene glycol ditosylate in the presence of NaH. The reaction was completed in 3 h at room temperature and no intermediate mono- or dialkylation products were detected. Debenzylation of **3** followed by conventional acetylation gave macrocycle **4** in 61 % yield. Similarly treatment of **9** with tetraethylene glycol ditosylate gave the bis-*gluco* -21-crown-7 compound (**5**) in 43 % yield. Debenzylation and acetylation of **5** afforded **6** in 73 % yield.

TABLE I

Asymmetric Michael addition of methyl phenylacetate to methylacrylate at -78° C

Host	Molar ratio[a]	t	Yield	e.e.[b]
-	20 : 1 : 0 : 15	2 h	30 %	-
1	36 : 9 : 1.5 : 27	35 min	81 %	40 % (S)
3	30 : 46 : 1.5 : 22	40 min	78 %	24 % (S)
5	41 : 20 : 2 : 31	15 min	72 %	12 % (R)

a) Methyl phenylacetate : KBu^tO : Host : methylacrylate
b) Based on data from the literature[16]

Preliminary studies have shown that macrocycles **1**, **3** and **5** complex ammonium salts at room or low temperature. We have also investigated these compounds as catalysts in the Michael addition of methyl α-phenylacetate to methyl acrylate. The corresponding adduct was obtained in 12-40 % enantiomeric excesses. Table I gives the reaction conditions and results for macrocycles **1**, **3** and **5**. In the case of **3** a large excess of base had to be added in order the reaction to proceed.

Attention will be next turned to the synthesis of water soluble neutral receptors with more hydrophobic cavities following this strategy to highly symmetric macrocycles, using different aromatic dihalides in conjuntion with other more rigid diols.

EXPERIMENTAL SECTION

General. Cyclization reactions were carried out under argon and in rigorously anhydrous conditions. Tlc was performed on aluminium sheets silica gel 60 F_{254} (Merck) with detection by charring with sulfuric acid. ^1H-(300 MHz) and ^{13}C-N.m.r. spectra (75 MHz) were recorded with a Varian XL-300 spectrometer in $CDCl_3$ unless otherwise specified. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. The f.a.b. mass spectra were obtained in a nitrobenzylalcohol matrix with a MS-50 Kratos instrument fitted with a 1.2 T. magnet using a f.a.b. 11 WF Ion Tech atom gun and with a ZAB instrument. 1,5-Dibromo-3-oxa-pentane was prepared as reported.[12] 3,4,6-Tri-*O*-benzyl-1,2,-*O*-(isopropoxyethylidene)-α-D-glucopyranose was prepared from its tri-acetyl derivative [13] following a method described in the literature[14] and used without further purification.

1,2-Di-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)ethylenediol (8).- A solution of ethylenglycol (0.084 g, 1.36 mmol) in chlorobenzene (30 mL) under an argon atmosphere, was treated with orthoester **7** (1.5 g, 2.73 mmol) in chlorobenzene and lutidinium perchlorate as described by Kochetkov et al.[15] The reaction mixture was evaporated and the residue purified by column chromatography (hexane : ethyl acetate, 7 : 5) to give **8** as a syrup (0.963 g, 0.95 mmol, 70 %), $[\alpha]_D^{20} \simeq 0°$ (c 0.6, chloroform). ^{1}H-N.m.r. δ, 7.32 (m, 15H, aromatic), 4.81 (t, 1H, $J_{1,2}$ = 8.9 Hz, H-2), 4.81-4.47 (m, 6H, PhCH_2O), 4.49 (d, 1H, H-1), 3.9-3.6 (complex multiplet, 6H, H-3, H-4, H-6a,6b, CH_2-CH_2O), 1.95 (s, 3H, MeCO); ^{13}C-N.m.r. δ, 169.5 (CO), 138.3 (C-ipso), 138.1 (C-ipso), 128.4-127.8 (aromatic), 100.9 (C-1), 83.0, 78.6, 74.9, 73.5, 73.3, 68.8, 68.3 and 20.9 (MeCO). Anal. Calcd. for $C_{60}H_{66}O_{14}$: C, 71.25; H, 6.58. Found: C, 70.98; H, 6.66.

1,2-Di-*O*-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)ethylenediol (9).- To a solution of **8** (0.090 g, 0.09 mmol) in methanol (5 mL) sodium methoxide in methanol (1M, 10 mL) was added dropwise. After 1.5 h the solution was neutralized with Amberlite IR 120 (H^+ form). After evaporation compound **9** (0.079 g, 0.085 mmol) was obtained as a syrup in 95 % yield, $[\alpha]_D^{20}$ -3.0° (c 0.43, chloroform); ^{1}H-N.m.r. δ, 7.32 (m, 15H, aromatic), 4.95-4.44 (m, 6H, PhCH_2O), 4.37 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 4.05 (d, OCH_2CH_2O), 3.91 (d, OCH_2CH_2O), 3.70 (m, 2H, H-6a,6b), 3.57 (m, 3H, H-2, H-3, H-4), 3.55 (m, 1H, H-5); ^{13}C-N.m.r. δ, 138.7 (C-ipso), 138.2 (C-ipso), 128.3-127.6 (aromatic) 103.5 (C-1), 84.7, 77.5, 75.1 (double intensity), 74.9, 74.8, 73.5, 69.3 and 69.0. Anal. Calcd. for $C_{56}H_{62}O_{12}$: C, 72.54; H, 6.74. Found: C, 72.36; H, 6.96.

1-*O*-[2-*O*-(2-bromoethyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl]-2-*O*-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)ethylenediol (10).- A mixture of **9** (0.3 g, 0.323 mmol) in 1,2-dibromoethane (3 mL), tetrabutylammonium sulfate (0.110 g, 0.323 mmol) and a 50 % aqueous sodium hydroxide solution (3 mL) were stirred vigorously at 50°C for 6 h. After cooling at room temperature, dichloromethane : water (10 mL, 1 : 1) was added. The organic phase was decanted and the aqueous phase washed with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was treated once more as indicated above to complete the reaction. The residue was chromatographed (silica gel, hexane : ethyl acetate, 7 : 3) to give **10** (0.135 g, 0.130 mmol, 40 %) as a syrup, $[\alpha]_D^{20}$ -10.5° (c 0.48, chloroform); ^{1}H-N.m.r. δ, 7.30 (m, 30H, aromatic), 5.00-4.78 (m, 6H, PhCH_2O), 4.64-4.42 (m, 8H, PhCH_2O), H-1, H-1'), 4.30-3.87 (m), 3.70-3.40 (m), 3.28 (t, 1H, H-2); ^{13}C-N.m.r. δ, 138.2 (C-ipso), 128.3-127.6 (aromatic), 103.2 (double intensity, C-1, C-1'), 84.5 (double intensity), 82.9, 77.8, 77.4, 75.7, 75.2, 74.9, 73.5 (double intensity), 72.5, 69.2, 69.1, 68.8 (double intensity), 30.7 (CH_2Br). Anal. Calcd. for $C_{58}H_{65}O_{12}Br$: C, 67.35; H, 6.33; Br, 7.73. Found: C, 67.34; H, 6.81; Br, 7.28. Further elution gave starting material **9** (0.150 g, 0.16 mmol, 50 %).

1-*O*-[2-*O*-(5-bromo-3-oxa-pentyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl]-2-*O*-(3,4,6-tri-*O*-benzyl glucopyranosyl)ethylenediol (11).- A mixture of **9** (0.540 g, 0.583 mmol) in 1,5-dibromo-3-oxa-pentane (1.5 mL), tetrabutylammonium sulfate (0.197 g, 0.583 mmol) and 50 % aqueous sodium hydroxide solution (1.5 mL) were stirred vigorously at room temperature for 1 h. The mixture was

extracted with dichloromethane. The organic phase was dried and concentrated and the residue was chromatographed (hexane : ethyl acetate, 7 : 3) to give **11** (0.471 g, 0.437 mmol, 75 %) as a syrup, $[\alpha]_D^{20}$ -13° (c 0.45, chloroform); ^{1}H-N.m.r. δ, 7.4 (aromatic), 5.0-4.4 (m, 12H, PhCH_2O), 4.43 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.28 (d, 1H, $J_{1',2'}$ = 7.1 Hz, H-1'), 4.20-4.0 (m, OCH_2CH_2O), 3.84-3.52 (m), 3.46 (m, 1H, H-5), 3.38 (t), 3.28 (t, 1H, H-2); ^{13}C-N.m.r. δ, 136.7 (C-ipso), 138.6 (C-ipso), 128.3-127.6 (aromatic), 103.5 (C-1), 103.2 (C-1'), 84.6, 84.4, 82.8, 77.5, 77.3, 75.5, 75.2, 74.9 (double intensity), 74.8, 74.6, 73.4 (double intensity), 73.4 (double intensity), 71.9, 71.1, 70.6, 69.1, 68.8, 68.7 (double intensity) and 29.9 (CH_2Br). Anal. Calcd. for $C_{60}H_{69}O_{13}Br$: C, 66.83; H, 6.45; Br, 7.42. Found: C, 66.97; H, 6.31; Br, 7.22.

Further elution gave 1,2-di-*O*-[2-*O*-(5-bromo-3-oxa-pentyl)-3,4,6-tri-β-benzyl-*O*-D-gluco-pyranosyl]-ethylenediol (**12**) in 20 % yield (143 mg, 0.116 mmol) as a syrup, $[\alpha]_D^{20}$ -14° (c 0.41, chloroform); ^{1}H-N.m.r. δ, 7.3 (aromatic), 5.0-4.3 (m, 12H, PhCH_2O), 4.36 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.1-3.3 (m); ^{13}C-N.m.r. δ, 138.7 (C-ipso), 138.0 (double intensity, C-ipso), 128.3-127.6 (aromatic), 103.5 (C-1), 84.4, 83.0, 77.5, 75.5, 74.9, 74.7, 73.4, 71.7, 70.9, 70.6, 68.8, 68.7, 30.2. Anal. Calcd. for $C_{64}H_{76}O_{14}Br_2$: C, 62.54; H, 6.23; Br, 13.00. Found: C, 62.30; H, 5.96; Br, 12.63.

Preparation of the tetra-*gluco*-24-crown-8 (1).- Sodium hydride (30 mg, 1.25 mmol) in dry THF (4 mL) was heated at 70°C for 15 min with stirring under an argon atmosphere. A solution of **10** (90 mg, 0.087 mmol) in dry THF (5 mL) was added dropwise during 3 h. The stirring and heating were continued for 24 h. After cooling, first MeOH and then H_2O were added until no hydrogen evolution was observed and the mixture was extracted twice with CH_2Cl_2. The organic phase was dried (Na_2SO_4), concentrated, and the residue purified by preparative TLC (hexane : acetone, 7 : 3) to afford **1** (45 mg, 54 %); $[\alpha]_D^{20}$ -11.0° (c 0.57, chloroform); ^{1}H-N.m.r. δ, 7.32 (m, 15H, ArH), 4.81-4.41 (m, 6H, PhCH_2O), 4.33 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.03 (d, 1H, OCH_2CH_2O), 3.83 (d, 2H, OCH_2CH_2O), 3.69 (d, 1H, OCH_2CH_2O), 3.64-3.56 (m, 2H, H-6, H-6'), 3.51-3.48 (m, 2H, H-3, H-4), 3.39-3.32 (m, 2H, H-5, H-2); ^{13}C-N.m.r. δ, 138.7 (C-ipso), 138.1 (C-ipso), 128.3-127.5 (Ar), 104.7 (C-1), 84.8 (C-4 or C-3), 83.1 (C-2), 77.9 (C-3 or C-4), 75.6 (PhCH_2), 75.1 (PhCH_2), 75.0 (C-5), 73.7 (PhCH_2), 71.5, 71.1 (OCH_2CH_2O), 69.2 (C-6). F.a.b.-MS, m/e 1904 $[M]^-$. Anal. Calcd. for $C_{116}H_{128}O_{24}$: C, 73.07; H, 6.77. Found: C,73.13; H, 6.99.

Preparation of tetra-*gluco* -24-crown-8 (2).- A solution of 1 (190 mg, 0.099 mmol) in ethanol : ethyl acetate (3 : 1, 10 mL) was hydrogenated under pressure (40 p.s.i) over 10 % Pd/C (70 mg) at room temperature for 4 h, filtered on Celite, and concentrated. Conventional treatment of the residue with acetic anhydride (0.5 mL) in pyridine (1 mL) gave, after column chromatography (hexane : acetone, 7 : 4), compound 2 (95 mg, 72 %) as a syrup, $[\alpha]_D^{20}$ +13° (c 0.2, chloroform); ^{1}H-N.m.r. δ, 5.05 (t, 1H, $J_{3,4} \simeq J_{2,3}$ = 9.5 Hz, H-3), 4.92 (t, 1H, $J_{3,4} \simeq J_{4,5}$ = 9.6 Hz, H-4), 4.47 (d, $J_{1,2}$ = 7.8 Hz, H-1), 4.21 (dd, 1H, $J_{6a,5}$ = 4.7 , $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.09-4.00 (m, 2H, H-6b, OCH_2CH_2O), 3.81 (d, 1H, AB system, OCH_2CH_2O), 3.72 (m, 2H, AB system, OCH_2CH_2O), 3.62-3.58 (m, 1H, H-5), 3.37 (dd, 1H, H-2), 2.0, 1.98 and 1.94 (s, each 3H, CH_3CO); ^{13}C- N.m.r. δ, 170.7, 170.2, 169.6 (CO), 103.9 (C-1), 79.9, 79.2, 76.6, 71.0, 68.2, 62.0, 20.8 and 20.7. Anal. Calcd. for $C_{56}H_{80}O_{36}$: C, 50.59; H, 6. 07. Found: C, 50.27; H, 6.41.

Preparation of bis-*gluco*-15-crown-5 (3). a) **From 11.**- Sodium hydride (26 mg, 0.64 mmol) was suspended in dry THF (2 mL) and heated at 70°C for 15 min under an argon atmosphere. A solution of **11** (50 mg, 0.46 mmol) in dry THF was added dropwise to the stirred mixture for 3 h. The reaction was heated for 24 h, and worked up as for **1**. The residue was purified by preparative TLC (hexane : acetone, 7 : 2) to afford **3** (20 mg, 44 %) as a syrup, $[\alpha]_D^{20}$ -3° (c 0.36, chloroform); ^{1}H-N.m.r. δ, 7.2-7.1 (m, 15H, ArH), 4.83-4.43 (m, 6H, PHCH_2), 4.34 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.06 (m, 2H, OCH_2CH_2O), 3.72 (m, 1H, OCH_2CH_2O), 3.67-3.60 (m, H-6a, H-6b, OCH_2CH_2O), 3.57 (t, $J_{3,4} \simeq J_{3,2}$ = 8.6 Hz, H-3), 3.50 (t, 1H, H-4), 3.39-3.34 (m, 1H, H-5), 3.19 (t, 1H, H-2); ^{13}C-N.m.r. δ, 137.6 (C-ipso), 137.1 (C-ipso), 127.3-126.2 (Ar), 101.9 (C-1), 83.8, 82.5, 76.8, 74.6, 73.9, 72.5, 72.2, 69.5, 67.8. F.a.b.-MS, m/e 1019 $[M+Na]^+$. Anal. Calcd. for $C_{60}H_{68}O_{13}$: C, 72.26; H, 6.87. Found: C, 71.90; H, 7.10.

b) **From 9.**- A mixture of **9** (100 mg, 0.106 mmol) in dry DMF (1 mL) and NaH (15 mg, 0.639 mmol) was stirred until no hydrogen evolution was observed. To the stirred mixture diethylene glycol ditosylate (90 mg, 0.217 mmol) in DMF (0.5 mL) was added dropwise at room temperature and the stirring continued for 3 h. The mixture was filtered and the DMF evaporated. The residue was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), concentrated, and the residue purified by preparative TLC (hexane : acetone, 7 : 3) to afford **3** (72 mg, 68 %).

Preparation of bis-*gluco*-15-crown-5 (4).- A solution of **3** (80 mg, 0.080 mmol) in ethanol: ethylacetate (5 : 1, 30 mL) was hydrogenated under pressure (40 p.s.i.) over 10 % Pd/C (100 mg) for 24 h, filtered on Celite and concentrated. Acetylation of the residue with acetic anhydride (1 mL) in pyridine (2 mL) gave **4** as a syrup (32 mg, 61 %; $[\alpha]_D^{20}$ +8° (c 0.23, $CHCl_3$); ^{1}H-N.m.r. δ, 5.14 (t, 1H, $J_{3,4} \simeq J_{3,2}$ = 9.4 Hz, H-3), 4.98 (t, 1H, H-4), 4.49 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.28 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, $J_{6,5}$ = 4.8 Hz, H-6a), 4.06 (m, 3H), 3.66 (m, 5H), 3.40 (dd, 1H, H-2), 2.07, 2.03, 2.01 (s, each 3H, CH_3CO); ^{13}C-N.m.r. δ, 170.6, 169.7 (CO), 102.8 (C-1), 90.5, 74.3, 73.6, 71.6, 70.5, 68.8, 68.7, 62.0. Anal. Calcd. for $C_{30}H_{44}O_{19}$: C, 50.84; H, 6.25. Found: C, 50.52; H, 6.55.

Preparation of bis-*gluco*-21-crown-7 (5).- A mixture of **9** (200 mg, 0.213 mmol) in DMF (4 mL) and NaH (9.2 mg, 0.424 mmol) was stirred at room temperature until no hydrogen evolution was observed. To the stirred mixture tetraethylene glycol ditosylate (106.8 mg, 0.213 mmol) in DMF (2 mL) was added dropwise and the stirring continued for 4 h. The mixture was worked up as for **3** (method **b**). The residue gave, after column chromatography (hexane : ethyl acetate, 7 : 5), **5** (100 mg, 43 %), $[\alpha]_D^{20}$ -3° (c 0.24, $CHCl_3$); ^{1}H-N.m.r. δ, 7.40-7.12 (ArH), 4.90 (d, 1H, PhCH_2O), 4.77 (2H), 4.61-4.48 (m, 3H, PhCH_2O), 4.38 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.08 (m, 2H, OCH_2CH_2O), 3.78 (m, 2H, OCH_2CH_2O), 3.68 (m, 2H, H-6a, H-6b), 3.62 (m, 6H, OCH_2CH_2O), 3.55 (m, 2H, H-3, H-4), 3.41 (m, 1H, H-5), 3.27 (t, 1H, $J_{2,3}$ = 8.5 Hz, H-2); ^{13}C-N.m.r. δ, 136.6 (C-ipso), 137.1 (C-ipso), 126.9-126.5 (Ar), 102.6 (C-1), 83.5 (C-3), 81.9 (C-2), 76.6 (C-4), 74.5, 73.9, 73.6 (C-5), 72.4, 71.0, 70.0, 69.6, 69.1, 67.8. F.a.b.-MS, m/e 1108 $[M-H+Na]^+$. Anal. Calcd. for $C_{64}H_{76}O_{15}$: C, 70.83; H, 7.06. Found: C, 70.64; H, 7.14.

Preparation of bis-*gluco*-21-crown-7 (6).- A solution of **5** (80 mg, 0.074 mmol) in ethanol :

ethyl acetate (5:1, 20 mL) was treated as for **4**. Compound **6** (43 mg, 73%) was obtained after column chromatography (hexane:acetone, 7:6), $[\alpha]_D^{20}$ +10° (c 0.38, chloroform); ^{1}H-N.m.r. δ, 5.11 (t, 1H, $J_{4,5} \simeq J_{4,3}$ = 9.3 Hz, H-4), 4.99 (t, 1H, $J_{2,3}$ = 8.7 Hz, H-3), 4.47 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.8 (m, 2H, H6a, H6b), 4.06-3.9 (m, 4H), 3.7-3.5 (m, 7H), 3.34 (t, 1H, H-2), 2.08, 2.05, 2.02 (s, each 3H, CH_3CO); ^{13}C-N.m.r. δ, 170.6, 170.1, 169.6 (CO), 106.7 (C-1), 79.6, 77.7, 72.0, 71.5, 70.9, 70.2, 69.1, 68.4, 61.9 and 20.7. Anal. Calcd. for $C_{34}H_{52}O_{21}$: C, 51.25; H, 6.57. Found: C, 50.96; H, 6.77.

Asymmetric Michael Additions.- In a typical experiment, methyl phenylacetate (0.73 mmol) in toluene (1 mL) was added dropwise to a suspension of powdered KBu^{t}O (0.18 mmol) in toluene (0.5 mL) under argon atmosphere at -78°C. A solution of macrocycle (0.036 mmol) in toluene was added after 15 min and the mixture was stirred for a further 15 min period. Methyl acrylate (0.55 mmol) in toluene (0.5 mL) was then added dropwise. After 35 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (15 mL) and extracted with toluene. The extract was dried (Na_2SO_4), evaporated, and chromatographed on a column of silica gel (hexane:ethyl acetate, 6:1) to give the adduct (60 mg, 81%), $[\alpha]_D^{20}$ +36° (c 1.5, ethanol). Macrocycle **1** was recovered by elution with ethyl acetate and reutilized.

ACKNOWLEDGMENTS. We thank Dr. C. Bosso (Centre de Recherches sur les Macromolécules Végétales) and Mr. P. R. Ashton (Department of Chemistry, University of Sheffield) for the fab-ms spectra. Mr. G. Corrales for the excellent technical assistance, the CAICYT and CSIC for financial support and the Comunidad de Madrid for a fellowship (C. V.).

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