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SYNTHESIS, COMPLEXING PROPERTIES AND APPLICATIONS IN ASYMMETRIC SYNTHESIS OF BIS-LACTO-18-CROWN-6 COMPOUNDS

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Abstract – *The new chiral bis-lacto-18-crown-6 derivatives* **1** *and* **2** *have been synthesized in a straightforward and easy way from benzyl β-lactoside. The complexing properties of* **1**, **2**, *and the previously synthesized mono-lacto-crown-6 compounds* **3** - **6** *have been evaluated by different methods. Compounds* **1** *and* **2** *complexed to potassium tert-butoxide have been used as catalysts in the addition of phenylacetate to methyl acrylate to give the corresponding Michael adduct with reasonable enantiomeric excesses.*

Chiral derivatives of crown ethers could serve as models for the study of chiral recognition in enzymatic and other reactions. Cram first began using the binaphthyl units in the synthesis of optically active crown ethers.[1] Shortly thereafter Lehn, Stoddart and others reported their work on chiral crown synthesis using tartaric acid, monosaccharides, alditols and different chiral compounds.[2] The synthesis of chiral receptor molecules from natural and non natural products has been reviewed.[3,4]

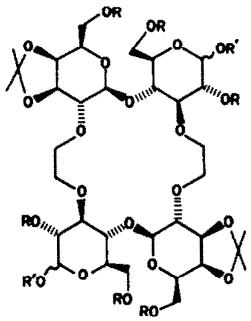
Carbohydrates and their derivatives are rich in substituted bis-methylenedioxy units, possess a high degree of chirality for incorporation into the 18-crown-6 structure and provide an uncountable potential to build a great variety of cavity shapes. Furthermore, carbohydrates may confer structural constraints upon macrocycles incorporating them since their conformational properties may strongly influence the geometry of the macrocyclic derivatives and hence their complexing properties.

We have previously reported the synthesis of new chiral macrocyclic ethers with different cavity shapes from disaccharides[5,6] and their application as catalysts in asymmetric Michael addition.[7] In these compounds polyethylene glycol linkages between different positions of each monosaccharide unit were introduced to obtain more rigid chiral crown ethers than those synthesized using monosaccharides and alditol derivatives. Chirality, rigidity and stereochemical factors can play a significant role in determining the stabilities of both organic and cationic complexes and seem to be necessary in order to achieve chiral recognition of guest molecules.[8]

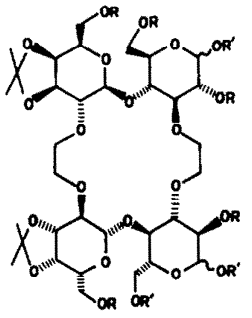
We now report on the synthesis of two bis-lacto-18-crown-6 **1** and **2** in a straightforward and simple way. These compounds present C_2 symmetry and more rigidity and chirality than the previously synthesized asymmetric chiral macrocyles mono-lacto derivatives **3** - **6**.[5,6] The complexing properties of **1** - **6** and the application of **1** and **2** in asymmetric synthesis are also described.

RESULTS AND DISCUSSION

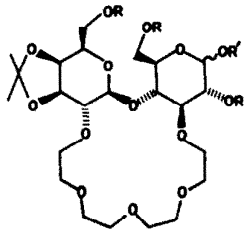
Synthesis. The methods available in the literature to obtain bis-chiral macrocycles[9-12] from non-symmetric carbohydrate residues have the disadvantage that in the final cyclization step, a mixture of two C_2 symmetric isomers are obtained. There is only one case, the synthesis of bis-manno- and bis-galacto-18-crown-6 in which only one isomer is obtained.[12] We have now synthesized the bis-lacto-18-crown-6 deriva-



1 R' = β-Bn, R = Bn
14 R' = α,β-Ac, R = Ac



2 R' = β-Bn; R = Bn
15 R' = α,β-Ac; R = Bn



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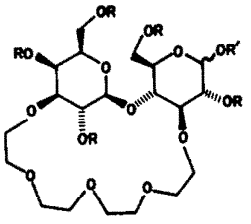
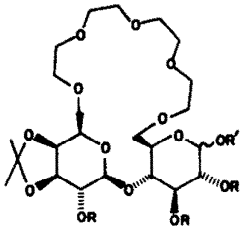
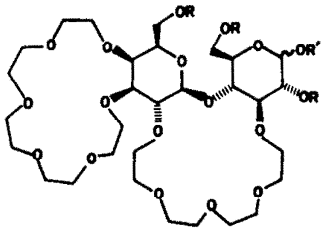


4 R' = β-Bn, R = Bn



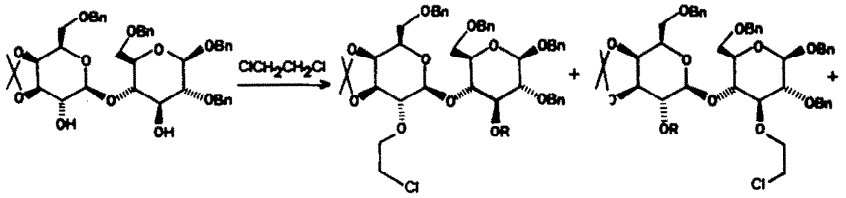
5 R' = β-Bn, R = Bn



6 R' = β-Bn, R = Bn

tives 1 and 2 in a direct, unequivocal and simple way (Scheme I).

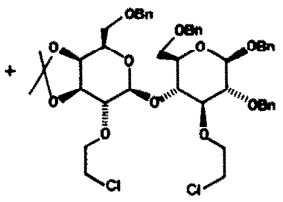
Scheme I



7

8 R = H
11 R = Ac

9 R = H
12 R = Ac



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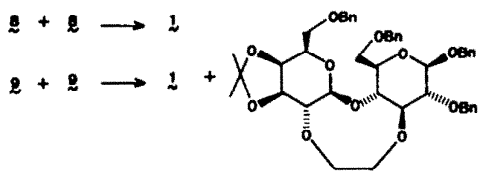


13

8 + 8 → 1

9 + 9 → 1 +

8 + 9 → 2 + 1 (traces)

The reaction of benzyl 2,6,6'-tri-O-benzyl-3',4'-O-isopropylidene-β-lactoside (**7**)[13] with 1,2-dichloroethane (used as solvent) under phase transfer conditions[14] yielded benzyl 2,6,6'-tri-O-benzyl-3',4'-O-isopropylidene-2'-O-(2-chloroethyl)- (**8**), -3-O-(2-chloroethyl)- (**9**) and 3,2'-di-O-(2-chloroethyl)-β-lactoside (**10**) in 32 %, 26 % and 11 % yield respectively. The position of the 2-chloroethyl substituent in each compound was determined by ^{1}H-NMR spectroscopy of the corresponding acetylated derivatives **11** and **12**. Self-condensation of either **8** or **9** in THF in the presence of NaH at 60°C in rigorously anhydrous conditions gave macrocycle **1** in 33 % yield from **8** and 18 % yield from **9**. The intramolecular cyclization compound **13** was also obtained from **9** in 6 % yield. Macrocycle **2**, the positional isomer of **1**, was obtained by cyclization of **8** with **9** under the same conditions in 35 % yield. Traces of isomer **1** were also detected. The structure of macrocycles **1** and **2** was confirmed by f.a.b.-mass spectrometry in thioglycerol matrix.[15] Peaks at 1554 $|M+NH_4^+|$ with intensities of 100 % for **1** and 40 % for **2** were present in the spectra. Hydrogenolysis of **1** and **2** and subsequent acetylation afforded **14** and **15** in 72 % and 70 % yield respectively. Compounds **14** and **15** were a mixture of non-separable α,β-anomers. The ^{1}H- and ^{13}C-NMR spectra of these compounds showed the signals corresponding to the three possible isomers (αα, ββ and αβ).

Complexing properties of the chiral macrocycles 1 - 6. The binding abilities of the new chiral bis-lacto-18-crown-6 **1** and **2** and the mono-lacto-crowns **3 - 6** were evaluated either by extraction of lithium, sodium, potassium, rubidium, cesium, methylammonium and (R,S)-α-phenylethylammonium picrates or by solid-liquid extraction with benzylammonium thiocyanate. Chiral recognition properties were also examined with (R,S)-α-phenylethylammonium hexafluorophosphate and the complex formation was followed by ^{1}H-NMR spectroscopy.

The association constants (K_a) and free energies of binding ($-\Delta G°$) of hosts **1 - 5** and of the acyclic model compound benzyl 2,3,6,2',6'-penta-O-benzyl-3',4'-O-isopropylidene-β-lactoside (**16**) in chloroform, free of ethanol, saturated with H_2O at 25°C were measured by the Cram's picrate method.[16] Solutions of the alkaline and ammonium picrates in H_2O were extracted with $CHCl_3$ in the absence and in the presence of host. The hosts were soluble only in the chloroform layer. The distribution constant (Kd) and the values of the extinction coefficient (ε) in acetonitrile at 380 nm determined by Cram and co-workers[16] were used in our experiments since the initial picrate concentration used in our experiments were identical to those used by the above authors. The values of ε and Kd for (R,S)-α-phenylethylammonium picrate were determined in the customary manner[16] (see Experimental Part). The position of the absorption maximum of the complexed picrate in chloroform gave the stoichiometry of the complex.[17] The K_a and $-\Delta G°$ values at 25°C in $CHCl_3$ saturated with H_2O were calculated from the results and are recorded in Table I. These values are approximately of the same order of magnitude as those reported in the literature for monosaccharide-derived crown ethers[3] and much lower than those for other crown ether derivatives. The results may be explained taking into account that compounds **1 - 3**, all of them showing an 18-crown-6 structure, cannot adopt the all-gauche conformation due to the configuration at C-3, C-4, C-1' and C-2' of the lactose moiety which also originates destabilizing interactions of methylene groups of the polyethylene glycol chain with the oxygen atoms at C-2 and C-3' of the lactose moiety.[18] The higher values for **4**, which does not have a 18-crown-6 structure, could be also explained by considering that no destabilizing interactions take place in the galactose moiety and that the oxygen atom at C-2' could also contribute to the complexation.

Evidence for host: guest complex formation of **1 - 6** with benzylammonium thiocyanate was obtained by ^{1}H-NMR spectroscopy. Solutions of hosts **1-6** in $CDCl_3$ (0.01-0.02 M) were shaken with a large excess of the benzylammonium salt and its ^{1}H-NMR spectrum recorded. The chemical shifts of the signals in the spectra of **1**, **3 - 4**, **5** and **6** showed drastic changes (Table II). In the case of **1** and **5** homonuclear 2D-correlation (COSY) and partially relaxed ^{1}H-NMR[19] spectra were recorded. Integration of the signal for the benzylic protons of the guest molecules and the methylene and methine protons of the hosts indicated the formation of a 1:1 host:guest molar ratio complex for **1** and **5**, a 1:3 complex for **3**, and a 1:2 for **4** and **6**. The spectrum of **2** did not show any signal due to the ammonium salt. In the case of compounds **3**, **4** and **6** the benzylic protons appeared as a singlet about δ 4 ppm while in the case of **5** these protons were diasterotopic and appeared at δ 3.82 and 3.57 ppm with a J = 13.4 Hz. In the case of compound **1** this benzylic signal overlapped with those due to host molecule; addition of small amounts of CD_3OD to the $CDCl_3$ solution resulted in the appearance of this signal as a singlet at δ 3.90 ppm. The

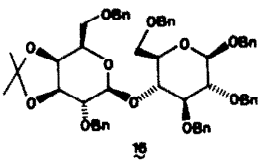
TABLE 1

Association constants (K_a) and binding free energies ($-\Delta G^o$) of hosts **1** - **5**, **16** for picrate salts in $CHCl_3$ saturated with H_2O at 25°C

Host	Guest	$K_a \times 10^{-3}$ [a] M^{-1}	$-\Delta G^o$ kcal/mol
1	Li^+	90.5	6.8
	K^+	26.0	6.0
	$PhCH(CH_3)NH_3^+$ [b]	0.5	3.7
2	Li^+	21.7	5.9
3	Li^+	63.1	6.5
	Na^+	36.9	6.2
	K^+	385.2	7.6
	Rb^+	99.6	6.8
	Cs^+	23.0	5.9
	$MeNH_3^+$	6.6	5.2
	$PhCH(CH_3)NH_3^+$ [b]	5.8	5.1
4	Li^+	69.0	6.6
	Na^+	23.6	6.0
	K^+	550.0	7.8
	Rb^+	268.4	7.4
	Cs^+	66.1	6.6
	$MeNH_3^+$	6.7	5.2
	$PhCH(CH_3)NH_3^+$ [b]	3.2	4.8
5	Li^+	63.8	6.5
	K^+	28.0	6.1
	Rb^+	9.7	5.4
	$MeNH_3^+$	3.9	4.9
	$PhCH(CH_3)NH_3^+$ [b]	2.0	4.5
16	Li^+	38.7	6.2

a) *The crown ether: cations complexes were 1 : 1 (see text).*
b) *Due to the high K_D, we have taken into account the concentration of free Pic^-X^+ in the chloroform phase.*

spectrum of the acyclic model compound **16** did not show any change under these conditions.



16

Chiral recognition experiments were carried out with (R,S)-α-phenylethylammonium hexafluorophosphate as guest following the procedure described by Cram and co-workers.[20] In the extraction experiments 0.25 mL of D_2O 1M in $LiPF_6$ and 1M in racemic α-phenylethylammonium bromide was shaken at room temperature with 0.8 mL of hosts **1**-**6** in $CDCl_3$ (0.015-0.03 M). The host-guest ratio, determined by ^1H-NMR was 1:0.85 for **1**, 1:1.4 for **3**, 1:1 for **4** and **5**, and 1:1.8 for **6**. The two diastereomeric CH_3 signal of the guest appeared as doublets, with integrated equally indicating that no chiral recognition took place, at δ 1.39, 1.54, 1.54, 1.58 and 1.57 (host-(S) diastereomer) and at δ 1.41, 1.56, 1.58, 1.62 and 1.59 (host-(R) diastereomer) for **1**, **3**, **4**, **5** and **6** respectively, each with a splitting of 7 Hz. The assignments were based on control experiments with the enantiomerically pure salts and the hosts. Host **3** appears to be the strongest binder. Neither macrocycle **2** nor the acyclic compound **16** extract any ammonium salt under the same conditions.

Application of macrocycles 1 and 2 in Asymmetric Synthesis. The use of chiral macrocycles as catalysts in asymmetric Michael addition has been previously investigated by Cram.[21] We have now used the new synthesized bis-lacto-18-crown-6 derivatives **1** and **2** complexed to potassium tertbutoxide in the addition of methyl phenylacetate to methyl acrylate. In the Table III the reaction conditions and yields of the addition are compared with the results previously reported[7] for **3**, **4** and **5**. Macrocycles **1** and **2** showed different behaviour as catalyst than **3**, **4** and **5**. The latter (entry 8, 9, 10) increased the rate of reaction compared to the reaction without catalyst (entry 1), giving reasonable enantiomeric excess (e.e.) and addition products of (S)-configuration. Compounds **1** and **2** inhibit the reaction under the same experimental conditions giving lower e.e. and products of (R)-configuration (entry 2, 3). When the amount of base was

TABLE II

Changes in the chemical shifts ($\Delta\delta$) of selected protons of hosts upon complexation with benzylammonium salt in $CDCl_3$

Host	H-3	H-4	H-5	H-1'	H-2'	H-3'	H-4'	H-5'	CH_3 isoprop.
1	-	-	>0.17	0	0.06	0.32	0.19	>0.23	0.07/0.08
2	0.02	-0.01	0	0.01	-0.03	0.03	-0.01	-	0.01/-0.01
3	-	-	-	-0.01	>-0.21	0.34	0.10	-	-0.13/-0.11
4	-	-	-	0.07	-	-	-	-	
5	>0.10	-0.89	0	-0.05	-0.02	+0.18	+0.02	-	-0.05/-0.07
6	-	-	-	-	-	>0.15	-	-	

(-) *No determined.*

TABLE III

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

Entry	Host (conc. M)	Molar ratio [a]	t	Yield %	e.e. [b]
1	-	1 : 0 : 20 : 15	2 h	30	
2	1 (0.002)	1.5 : 1 : 20 : 14	7 h	8	22 (R)
3	2 (0.015)	1 : 1 : 20 : 14	6 h	17	7 (R)
4	1 (0.015)	5.5 : 1 : 20 : 15	8 min	86	45 (R)
5	2 (0.015)	5.5 : 1 : 20 : 15	8 min	60	24 (R)
6	1 (0.015)	5 : 1 : 20 : 15	7 h	77	41 (R)
7	1 (0.030)	5 : 2 : 20 : 16	25 min	75	44 (R)
8	3 (0.010)	1 : 1 : 33 : 23	1 h	67	26 (S)
9	4 (0.010)	1 : 1 : 40 : 19	1 h	73	70 (S)
10	5 (0.015)	1 : 1 : 42 : 24	1 h	98	36 (S)

a) $KBuO^t$: *host : methylphenylacetate : methylacrylate.*

b) *Based on data from ref. 21.*

increased the reaction was faster and the enantiomeric excess higher which may indicate a higher influence of this fact on the catalyzed than on the non-catalyzed reaction rate (entry 4, 5). No racemization was observed (entry 6). The increase of macrocycle concentration did not give better yields and e.e. (entry 7). The macrocycles were recovered after the reaction was completed and reused. Mukaiyama and co-workers have also observed a decrease of the yield in the Michael reaction of 1-nitrocyclohexene and a chiral oxazepine when the reaction was carried out in the presence of 24-crown-8.[22]

The synthesis of different cavities from several disaccharide derivatives following a similar methodology to that reported in this paper, is presently under way. The wealth of these compounds which can be obtained from readily available natural products makes this, in our opinion, a promising approach to the synthesis of chiral macrocycles with different interesting properties.

EXPERIMENTAL SECTION

General. Cyclization reactions were carried out under argon and in rigorously anhydrous conditions. NaH in oil (Fluka) was washed repeatedly with dried hexane under argon atmosphere, filtered and stored under argon before use. Tlc was performed on silica gel GF_{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. COSY experiment: the two dimensional map was composed of 1024-1024 data point spectra, each incremented by 0.4 ms. A delay of 5s. was allowed between each pulse sequence. The data were acquired with quadrature phase detection in both dimensions, and the final data symmetrised. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. U.V. were recorded with a Pye-Unicam SP-1700. Extraction experiments were carried out at constant speed using a Fisons Whirlimixer or a H. Mickle mixer. The f.a.b.-mass spectra were obtained in a thioglycerol matrix with a MS-50 Krator instrument fitted with a 1.2 T. magnet using a f.a.b. 11 WF Ion Tech atom gun and with a ZAB instrument.

Benzyl 2,6,6'-tri-O-benzyl-2'-O-(2-chloroethyl)-3',4'-O-isopropylidene β-lactoside (8), benzyl 2,6,6'-tri-O-benzyl-3-O-(2-chloroethyl)-3',4'-O-isopropylidene β-lactoside (9) and benzyl 2,6,6'-tri-O-benzyl-3,2'-di-O-(2-chloroethyl)-3',4'-O-isopropylidene β-lactoside (10).- A solution of **7**[13] (2.7 g, 3.64 mmol) and tetrabutylammonium hydrogen sulfate (1.23 g, 3.62 mmol) in 1,2-dichloroethane (26 mL) and 50 % aqueous sodium hydroxide solution (26 mL) were vigorously stirred at 50°C for 6 h. After cooling at room temperature dichloromethane-H_2O (20 mL/20 mL) was added to the mixture. The organic phase was decanted and the aqueous phase was washed with dichloromethane (3 × 100 mL). The combined organic phases were dried with Na_2SO_4 and concentrated under vacuum. The residue was treated once as indicated to complete the reaction. Crystallization from hot methanol afforded **8** |0.93 g, (32 %)| as needles; $|\alpha|_D^{25}$ -5.3°, (c = 0.6 $CHCl_3$), m.p. 158-159°C; ^1H-n.m.r. ($CDCl_3$) δ 7.35 (m, 20H, ArH), 4.50 (d, 1H, $J_{1,2}$ = 8 Hz, H-1), 4.36 (s, 1H, OH-3), 4.23 (d, 1H, $J_{1',2'}$ = 8 Hz, H-1'), 4.08 (dd, 1H, $J_{4',5'}$ = 2 Hz, $J_{3',4'}$ = 5.6 Hz, H-4'), 4.04 (t, 1H, $J_{2',3'}$ = 5.6 Hz, H-3'), 3.82 (m, 2H, H_{6a},H_{6b}), 3.50 (m, 1H, H-5), 3.43 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), 3.24 (dd, 1H, H-2'), 1.49 |s, 3H, $(CH_3)_2C$| and 1.31 |s, 3H, $(CH_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$), δ 128.4-127.3 (Ar), 110.2 |$(CH_3)_2C$|, 102.2, 102.1, (C-1, C-1'), 81.7, 81.3, 79.2, 75.4, 74.8, 74.2, 73.7 (double intensity), 73.6, 73.4, 72.3, 71.7, 71.1, 69.1, 68.7, 42.8 (H_2CCl), 27.3 and 26.2 |$(CH_3)_2C$|. (Found: C, 67.18; H, 6.35; Cl, 4.67. Calcd. for $C_{45}H_{53}O_{11}Cl$: C, 67.11; H, 6.63; Cl, 4.40 %).

The mother liquors were concentrated and the residue chromatographed on silica gel (hexane-AcOEt, 6.5 : 2) affording first **10** |0.35 g, (11 %)| as a syrup: $|\alpha|_D^{25}$ -6.3° (c = 0.6, $CHCl_3$); ^1H-n.m.r. ($CDCl_3$), δ 7.34 (m, 20H, ArH), 4.46 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 4.33 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 3.40 (m, 2H, H-2), 3.12 (dd, 1H, $J_{2',3'}$ = 6.7 Hz, H-2'), 1.49 |s, 3H, $(CH_3)_2C$| and 1.34 |s, 3H, $(CH_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$) δ 128.3-125.7 (Ar), 109.8 |$(CH_3)_2C$|; 102.4, 101.6 (C-1, C-1'); 83.8, 82.1, 81.3, 79.1, 76.9, 74.9 (double intensity); 73.7, 73.4, 73.2, 73.0, 72.1, 71.6, 70.9, 69.3, 68.2, 42.9 (CH_2-Cl, double intensity); 28.0 and 26.2 |$(CH_3)_2C$|. (Found: C, 64.75; H, 6.71; Cl, 8.12. Calcd. for $C_{47}H_{56}O_{11}Cl_2$: C, 65.04; H, 6.50; Cl, 8.17 %).

On elution with hexane-AcOEt, 6.5 : 4, a second product **9** was obtained (0.76, 26 %) as a syrup: $|\alpha|_D^{25}$ +6.7° (c = 0.3, $CHCl_3$); ^1H-n.m.r. ($CDCl_3$) δ 7.32 (m, 20H, ArH), 4.52 (d, 1H, J = 8.4 Hz, H1/1'), 4.44 (d, 1H, J = 7.4 Hz, H1/1'), 1.49 (s, 3H, |$(CH_3)_2C$| and 1.33 |s, 3H, $(CH_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$) δ 128.4-127.8 (Ar), 110.0 |$(CH_3)_2C$|, 102.9, 102.8, (C-1, C-1'), 84.1, 81.9, 79.1, 77.1, 74.9, 74.7, 74.3, 73.6 (triple intensity); 73.0, 72.7, 71.2, 69.7, 68.5, 43.5 (CH_2-Cl), 28.2 and 26.4 |$(CH_3)_2C$|. (Found: C, 66.81; H, 6.84; Cl, 4.17. Calcd. for $C_{45}H_{53}O_{11}Cl$: C, 67.11; H, 6.63; Cl, 4.40 %).

Benzyl 3-O-acetyl-2,6,6'-tri-O-benzyl-2'-O-(2-chloroethyl)-3',4'-O-isopropylidene-β-lactoside (11) and benzyl 2'-O-acetyl-2,6,6'-tri-O-benzyl-3-O-(2-chloroethyl)-3',4'-O-isopropylidene- β -lactoside (12). Conventional treatment of **8** (30 mg) and **9** (40 mg) with acetic anhydride (0.5 mL) in pyridine (1 mL) gave, after column chromatography ($CHCl_3$-AcOEt, 7 : 1) the monoacetate **11** (25 mg, 80 %) and **12** (25 mg, 60 %) respectively.

Compound **11** was a syrup: $|\alpha|_D^{25}$ +15° (c = 0.2, $CHCl_3$); ^1H-n.m.r. ($CDCl_3$) δ 7.33 (m, 20H, ArH), 5.10 (t, 1H, $J_{2,3} \simeq J_{3,4}$ = 9.5 Hz, H-3), 4.14 (d, 1H, $J_{1',2'}$ = 8 Hz, H-1'), 4.02 (d, 1H, $J_{3',4'}$ = 5.8 Hz,

H-4'), 3.95 (m, 1H, H-5'), 3.87 (m, 2H, H-4 and H-3'), 3.44 (t, 1H, H-2), 3.05 (t, 1H, H-2'), 1.92 (s, 3H, $C\underline{H}_3CO$), 1.46 |s, 3H, $(C\underline{H}_3)_2C$| and 1.31 |s, 3H, $(C\underline{H}_3)_2C$|. (Found: C, 66.30; H, 6.71; Cl, 3.94. Calcd. for $C_{47}H_{55}O_{12}Cl$: C, 66.62; H, 6.54; Cl, 4.18%).

Compound **12** was a syrup: $|\alpha|_D^{25}$ -19° (c = 0.9, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$) δ 7.34 (m, 20H, ArH), 4.86 (1H, t, $J_{1',2'} \simeq J_{2',3'}$ = 7.8 Hz, H-2'), 4.43 (d, 1H, H-1'), 4.41 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.11 (m, 1H, H-4'), 3.92 (dd, 1H, $J_{3',4'}$ = 5.4 Hz, H-3'), 3.82 (t, 1H, $J_{3,4} \simeq J_{4,5}$ = 9 Hz, H-4), 3.71 (m, 2H, H-6a and H-6b), 3.52 (m, 1H, H-5'), 3.38 (m, 1H, H-2), 3.29 (m, 1H, H-5), 2.00 (s, 3H, $C\underline{H}_3CO$), 1.53 |s, 3H, $(C\underline{H}_3)_2C$| and 1.32 |s, 3H, $(C\underline{H}_3)_2C$|. (Found: C, 66.59; H, 6.50; Cl, 4.09. Calcd. for $C_{47}H_{55}O_{12}Cl$: C, 66.62; H, 6.54; Cl, 4.18%).

Preparation of bis-lacto-18-crown-6 (1). From **8**. Sodium hydride (150 mg, 6.25 mmol) in dry THF (16 mL), was heated at 60-70°C for 15 min. To the stirred mixture a solution of **8** (410 mg, 0.51 mmol) in dry THF (21 mL) was added dropwise and the stirring and heating continued for 21 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 (SO_4Na_2), concentrated and the residue was purified first on a column chromatography ($CHCl_3$: AcOEt, 5 : 1) and then on preparative TLC (hexane-acetone, 3 : 1) to afford **1** (130 mg, 33%): $|\alpha|_D^{25}$ -21.3° (c = 0.8, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$) δ 7.30 (m, 40H, ArH), 4.64 (d, 2H, $J_{1',2'}$ = 6.9 Hz, H-1'a, H-1'b), 4.34 (d, 2H, $J_{1,2}$ = 7.7 Hz, H-1a, H-1b), 3.90 (dd, 2H, $J_{4',5'}$ = 1.8 Hz, $J_{3',4'}$ = 6.0 Hz, H-4'a, H-4'b), 3.85 (t, 2H, $J_{2',3'}$ = 6.0 Hz, H-3'a, H-3'b); 3.81 (t, 2H, $J_{4,5} \simeq J_{3,4}$ = 9.3 Hz, H-4a, H-4b); 3.51 (m, 2H, H-5a, H-5b), 3.36 (dd, 2H, $J_{2,3}$ = 8.6 Hz, H-2a, H-2b), 3.24 (t, 2H, H-2'a, H-2'b), 1.42 |6H, s, $(C\underline{H}_3)_2C$| and 1.23 |6H, s, $(C\underline{H}_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$) δ 138.6, 138.5, 138.4, 137.5 (c-ipso), 129.2-126.8 (Ar), 105.6 |$(CH_3)_2\underline{C}$|; 102.6, 99.7 (anomers), 82.4, 81.1, 79.2, 77.8, 75.0, 74.4, 74.0, 73.3 (double intensity), 73.2, 71.7 (double intensity), 71.2 (double intensity), 69.6, 68.7, 27.8 and 25.8 |$(C\underline{H}_3)_2C$|. F.a.b.-MS, m/e 1554 ($M + NH_4^+$, 100), 1463 (20). (Found: C, 70.82; H, 7.03. Calcd. for $C_{90}H_{104}O_{22}$: C, 70.29; H, 6.82%).

From **9**. Compound **9** (0.78 g, 0.97 mmol) was treated as indicated for **8**. Column chromatography (hexane-AcOEt, 2 : 1) and then preparative TLC (hexane-acetone, 3 : 1) gave first **13** (43 mg, 6%) as a syrup; ^{1}H-n.m.r. ($CDCl_3$) δ 7.30 (m, 20H, ArH), 4.41 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1), 4.40 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 3.87 (m, 1H, H-2'), 3.35 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.0 Hz, H-3), 3.25 (dd, 1H, H-2), 1.48 |s, 3H, $(C\underline{H}_3)_2C$| and 1.27 |s, 3H, $(C\underline{H}_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$) δ 138.6 (double intensity), 137.9, 137.5 (C-ipso), 128.4-127.4 (Ph), 110.0 |$(CH_3)_2\underline{C}$|, 102.0, 99.3 (anomers), 86.7, 81.6, 80.3, 80.0, 77.6, 74.9, 74.7, 73.6, 73.5, 73.2, 72.5, 72.0, 71.5, 70.9, 70.6, 69.4, 28.3 and 26.5 |$(CH_3)_2C$|; MS, m/e 677 (1, M^+-$PhCH_2$), 660 (1), 569 (1) and finally **1** |136 mg (18%)| as a syrup.

Preparation of bis-lacto-18-crown-6 (2). NaH (110 mg, 4.6 mmol) was suspended in dry THF (12 mL) and heated at 70°C for 15 min. A solution of **8** (150 mg, 0.19 mmol) and **9** (150 mg, 0.19 mmol) in dry THF (15 mL) was added dropwise to the stirred mixture for 3 h. The reaction was heated for 21 h, cooled and worked up as for **1**. The residue was eluted from a column ($CHCl_3$-AcOEt, 5 : 1) and then the impurities were removed by acetylation, acetic anhydride-pyridine, and preparative TLC (hexane-acetone, 3 : 1) to afford **2** |100 mg (35%)| as a syrup: $|\alpha|_D^{25}$ -14.0°, (c = 0.6, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$) δ 7.30 (m, 40H, aromatic), 4.37 (d, 2H, $J_{1',2'}$ = 7.7 Hz, H-1'a, H-1'b), 4.29 (d, 2H, $J_{1,2}$ = 7.7 Hz, H-1a, H-1b), 3.99 (dd, 2H, $J_{4',5'}$ = 1.6 Hz, $J_{3',4'}$ = 5.5 Hz, H-4'a, H-4'b), 3.84 (t, 2H, $J_{3,4} \simeq J_{4,5}$ = 9.3 Hz, H-4a, H-4b), 3.80 (t, 2H, $J_{2',3'}$ = 6 Hz, H-3'a, H-3'b), 3.59 (t, 2H, H-2'a, H-2'b), 3.44 (t, 2H, $J_{2,3}$ = 9.0 Hz, H-3a, H-3b), 3.40 (m, 2H, H-5a, H-5b), 3.28 (dd, 2H, H-2a, H-2b), 1.39 |s, 6H, $(C\underline{H}_3)_2C$| and 1.23 |s, 6H, $(C\underline{H}_3)_2C$|; ^{13}C-n.m.r. ($CDCl_3$) δ 138.9, 138.7, 138.4, 137.6 (c-ipso), 128.3-127.4 (Ph), 109.4 |$(CH_3)_2\underline{C}$|, 102.5, 100.6 (anomers), 83.2, 82.1, 79.1, 78.2, 74.9 (triple intensity), 74.0, 73.3 (double intensity), 72.5, 71.5, 70.9, 69.7, 69.5, 68.6, 28.3 and 26.0 |$(C\underline{H}_3)_2C$|. F.a.b.-MS, m/e 1554 ($M + MH_4^+$, 40), 1537 (13). (Found: C, 70.17; H, 6.95. Calcd. for $C_{90}H_{104}O_{22}$: C, 70.29; H, 6.82%).

Traces of **1** was also detected on TLC.

Preparation of bis-lacto-18-crown-6 (14). A solution of **1** (114 mg, 0.074 mmol) in ethanol-ethyl acetate (3 : 1, 10 mL) was hydrogenated over 10% Pd/C (70 mg) at room temperature for 7 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 (AcOEt : $CHCl_3$, 5 : 1.5), compound **14** (61.5 mg, 72%) as a syrup: $|\alpha|_D^{25}$ + 37.3°, c = 0.1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$) δ 6.18 (d, 1H, J = 3.7 Hz, H-1, α-OAc), 6.17 (d, 1H, J = 3.5 Hz, H-1, α-OAc), 5.51 (d, 1H, J = 8.1 Hz, H-1, β-OAc), 5.50 (d, 1H, J = 8.1 Hz, H-1, β-OAc), 5.00 (t, 1H, J = 8.5 Hz, H-2), 4.90 (d, 1H, J = 7.4 Hz, H-1'), 4.78 (d, 1H, J = 7.3 Hz, H-1'), 4.76 (d, 1H, J = 7.5 Hz, H-1'), 4.68 (d, 1H, J = 7.6 Hz, H-1'), 2.07-1.98 ($\underline{CH_3}CO$) and 1.47-1.26 $|(\underline{CH_3})_2C|$; ^{13}C-n.m.r. ($CDCl_3$) δ 171.1-169.3 ($CH_3\underline{C}O$), 110.9, 110.8, 110.7 |double intensity, $(CH_3)_2\underline{C}$-|, 100.0, 99.6, 99.0, 98.4 (C-1'), 92.3, 92.2 (C-1 from isomer ββ,βα) 89.8, 89.7 (C-1 from isomer αα,αβ), 63.8, 63.7, 63.3 (double intensity), 63.2 (double intensity), 62.9, 62.8 (C-6, C-6'), 28.2, 28.15, 28.10, 28.0, 26.4 (double intensity), 26.3, 26.2 $|(\underline{CH_3})_2C|$ and 21.1-21.0 ($\underline{CH_3}CO$); f.a.b.-MS, m/e 1170 ($M + NH_4^+$, 18), 1093 (20). (Found: C, 52.10; H, 6.50. Calcd. for $C_{50}H_{72}O_{30}$: C, 52.08; H, 6.29%).

Preparation of bis-lacto-18-crown-6 (15). A solution of **2** (90 mg, 0.058 mmol) in EtOH-AcOEt (3 : 1, 5 mL) was hydrogenated over 10% Pd/C (50 mg) at room temperature for 6 h, filtered on celite, and concentrated *in vacuo*. Conventional treatment of the residue with acetic anhydride (0.5 mL) in pyridine (1 mL) gave, after column chromatography ($CHCl_3$-CH_3COCH_3, 5 : 1), compound **15** (46 mg, 70%) as a syrup: $|\alpha|_D^{25}$ - 41.8° (c = 0.4, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$) δ 6.15 (d, 1H, J = 2.9 Hz, H-1, α-OAc), 6.13 (d, 1H, J = 3.4 Hz, H-1, α-OAc), 5.48 (d, 1H, J = 8.3 Hz, H-1, β-OAc), 5.47 (d, 1H, J = 8.3 Hz, H-1, β-OAc), 5.00 (t, 1H, J = 8.9 Hz, H-2), 4.96 (t, 1H, J = 8.6 Hz, H-2), 4.77 (d, 1H, J = 7 Hz, H-1'), 4.68 (d, 1H, J = 7 Hz, H-1'), 3.46 (t, 1H, H-2'), 3.41 (t, 1H, H-2'), 3.36 (t, 1H, H-2'), 3.28 (t, 1H, H-2'), 2.08-2.00 ($\underline{CH_3}COO$) and 1.45-1.26 $|(\underline{CH_3})_2C|$; ^{13}C-n.m.r. ($CDCl_3$) δ 170.8-168.9 ($CH_3\underline{C}O$), 110.4, 110.3, 110.2, 110.1 $|(CH_3)_2\underline{C}|$, 100.8, 100.2, 98.8, 98.7 (C-1'), 91.9 (double intensity, C-1, from isomer ββ,βα), 89.4, 89.3 (C-1, from isomer αα,αβ), 63.6, 63.5, 63.4, 62.9, 62.8, 62.7, 62.3, 62.2 (C-6, C-6'), 27.8, 27.7, 27.6, 27.4, 26.0, 25.9, 25.8, 25.6, $|(\underline{CH_3})_2C|$ and 20.9-20.7 ($\underline{CH_3}COO$); f.a.b. MS, m/e, 1170 ($M + NH_4^+$, 100), 1093 (90). (Found: C, 51.95; H, 6.22. Calcd. for $C_{50}H_{72}O_{30}$: C, 52.08; H, 6.29%).

Asymmetric Michael Additions. In a typical experiment, methyl phenylacetate (1.49 mmol) in toluene (1 mL) was added dropwise to a suspension of powdered KBu^tO (0.39 mmol) in toluene (1 mL) under argon atmosphere at -78°C. A solution of **1** (0.073 mmol) in toluene (1.5 mL) was added after 15 min. and the mixture was stirred for a further 15 min. period. Methyl acrylate (1.14 mmol) in toluene (1 mL) was then added dropwise. After 8 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 (6 : 1 hexane-AcOEt) to give the adduct (231.8 mg, 86%): $|\alpha|_D^{20}$ - 40° (c = 2.4 EtOH). Compound **1** was recovered by elution with ethyl acetate and reutilized.

(R,S) α-Phenylethylammonium picrate. ε and Kd determinations. To a stirred solution of picric acid (17.5 mmol) in 95% ethanol (70 mL), (R,S) α-phenylethylamine (17.5 mmol) was added dropwise. The yellow solid, immediately formed, was filtered, recrystallized from 95% ethanol, and dried at 60°/10^{-3} torr. M.p. 193-195°C. (Found: C, 48.01; H, 4.10; N, 15.99. Calcd. for $C_{14}H_{14}N_4O_7$: C, 48.00; H, 4.03; N, 15.99%).

Extinction coefficient (ε) for this salt in CH_3CN at λ = 380 nm was determined in the concentration range of 10^{-6}-10^{-4}M of standard solutions prepared by serial dilutions of a 4.9 × 10^{-3}M solution directly prepared from the pure salt. The values obtained were fitted to a straight line by a linear regression method. The slope was 17,300 and the correlation coefficient was 0.9999. The distribution constant for this salt between H_2O-$CHCl_3$ was obtained in the customary manner[16], for a concentration in water of 3.59 × 10^{-3}M and had a value of 4.06 M^{-1}. The same concentration was used for the extraction experiments.

Solid-liquid extractions. Solutions of the hosts in $CDCl_3$ (0.01-0.02M) were mixed with $PhCH_2\overset{+}{N}H_3$ $SCN^{\ominus}$ (12 mg) for 1 min, filtered several times to ensure that no solid was present in the solution and the ^{1}H-n.m.r. spectra recorded.

Liquid-liquid extractions. Solutions (0.8 ml) of the hosts in $CDCl_3$ (0.015-0.030 M) were mixed with a D_2O solution (0.25 mL) of (R,S)- or (S)-, Ph-$CH(CH_3)$-$\overset{+}{N}H_3Br^{\ominus}$ (1M) and F_6PLi (1M) during 2 min. The phases were separated, and the chloroform solution was carefully removed with a syringe, dried, and the ^{1}H-n.m.r. spectra recorded.

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