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Macrocyclic receptors containing sucrose skeleton

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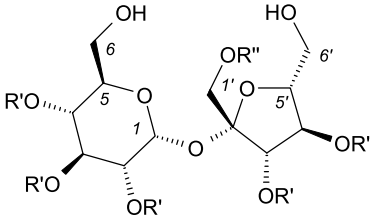
Abstract—Crown ether analogues with incorporated sucrose unit were prepared by reaction of 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose with polyethylene ditosylates in up to 52% yield. Stability constants of their complexes with Li^+, Na^+, K^+, NH_4^+ were determined by the NMR titration method. The macrocycles were also tested as catalysts in the enantioselective Michael reaction, but with little success (ee up to only 22%). The macrocycle containing nitrogen in the ring was also prepared in good yield. All prepared macrocycles were easily converted into the free sucrose crowns (H_2/Pd/C) without destroying the (very labile) glycosidic bond. The crystal structure of the selected receptor was determined.

1. Introduction

Sucrose (**1**) represents of a cheap raw material and is available in more than 100 million tons per year; most of it being consumed on the food market. This disaccharide is also a subject of interest for many laboratories, which apply it in chemical synthesis. For example, it maybe used for the preparation of bio-degradable polymers and surfactants,[1] or applied as a chiral matrix for the synthesis of complex natural products.[2,3] The very high purity of commercially available sucrose allows the use of this compound as a source of chirality for chemical synthesis without any additional purification.



1. R' = R" = H; **2.** R' = Bn, R" = H
3. R' = Bn, R" = BOM; **4.** R' = R" = Bn

As a part of an on-going program, we elaborated a convenient route to 2,3,3′,4,4′-penta-*O*-benzyl-sucrose[4] (**2**), a convenient starting material for the preparation of analogues modified at the terminal positions. The primary hydroxyl group in **2** can be differentiated, allowing the preparation of a number of sucrose derivatives, which—after removing the benzyl protecting groups—can be obtained in a free form.[3] Also, the diol **3** was prepared readily from **2**.[5] Recently, we prepared in high overall yield (48%) even more convenient dihydroxylated sucrose derivative: the hexa-*O*-benzylated diol **4**.[6]

2. Results and discussion

Easy access to the diol **4** opened the possibility for the preparation of the crown ether analogues with incorporated sucrose unit, in which the C-6 and C-6′ positions are connected via a heteroatomic bridge (Fig. 1).

Recently we synthesized several such derivatives (**5a–9a**)[6,7] albeit in moderate yields (ca. 12% for **5a** up to 31% for **9a**) by reaction of the diol **4** with the corresponding polyethylene ditosylates. By the improved procedure reported here, these yields are now improved up to 52%. The important feature of this methodology lies in the easy deprotection of the macrocycles without destroying the very labile glycosidic bond. Simple hydrogenolysis removes the benzyl protecting groups and allows to obtain the free compounds, further isolated as peracetates **5b–11b**.

The structure of one of these derivatives—**7b**—was assigned by X-ray analysis. The numbering scheme and overall conformation of **7b** is shown in Figure 2. The

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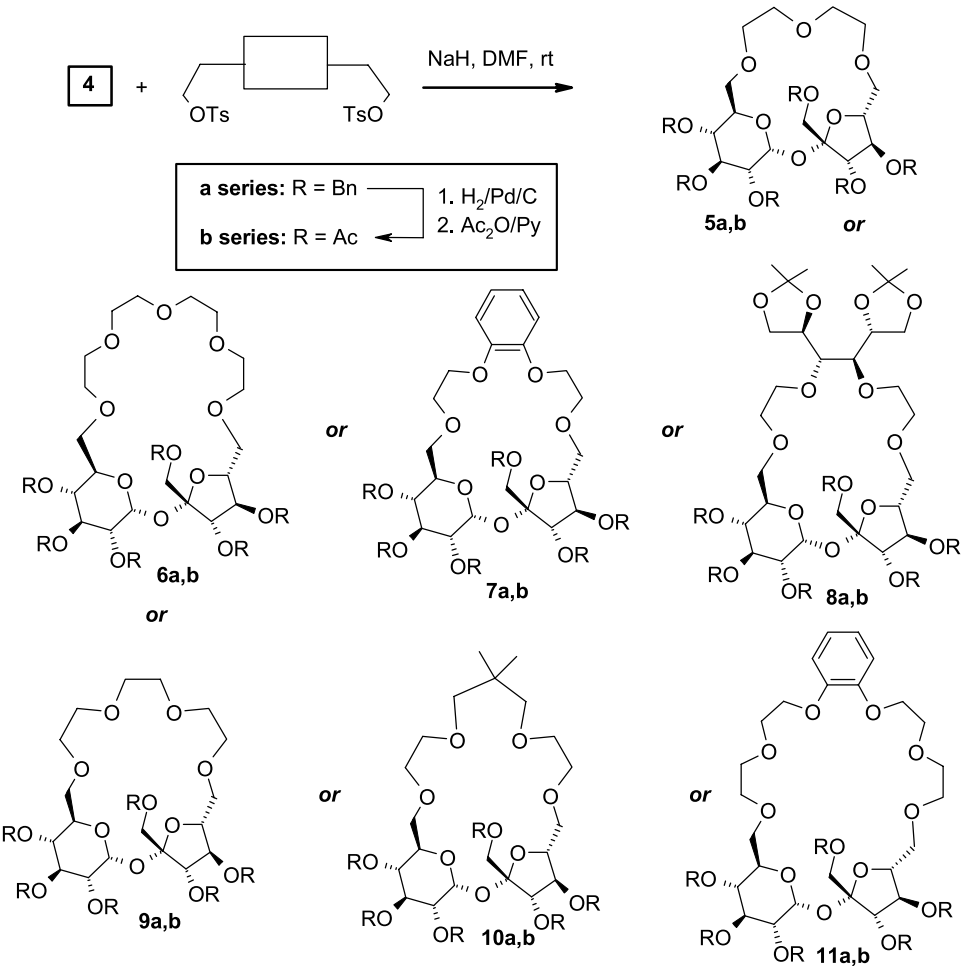


Figure 1. Preparation of sucrose-based crown ether analogues.

asymmetric part of the crystal consists of two symmetry independent molecules A and B. The sucrose units of both molecules are very similar. The Cremer and Pople ring-puckering parameters[8,9] Q, θ and ϕ (calculated using program PUCK2[10]) for glucopyranoid rings of molecules A and B [0.581(7) Å, 6.6(7)°, 309(6)° and 0.583(7) Å, 5.8(6)°, 312(6)°] indicate the typical $^4C_1$(D)-chair conformation and for the furanoid rings the q_2 and ϕ_2 parameters

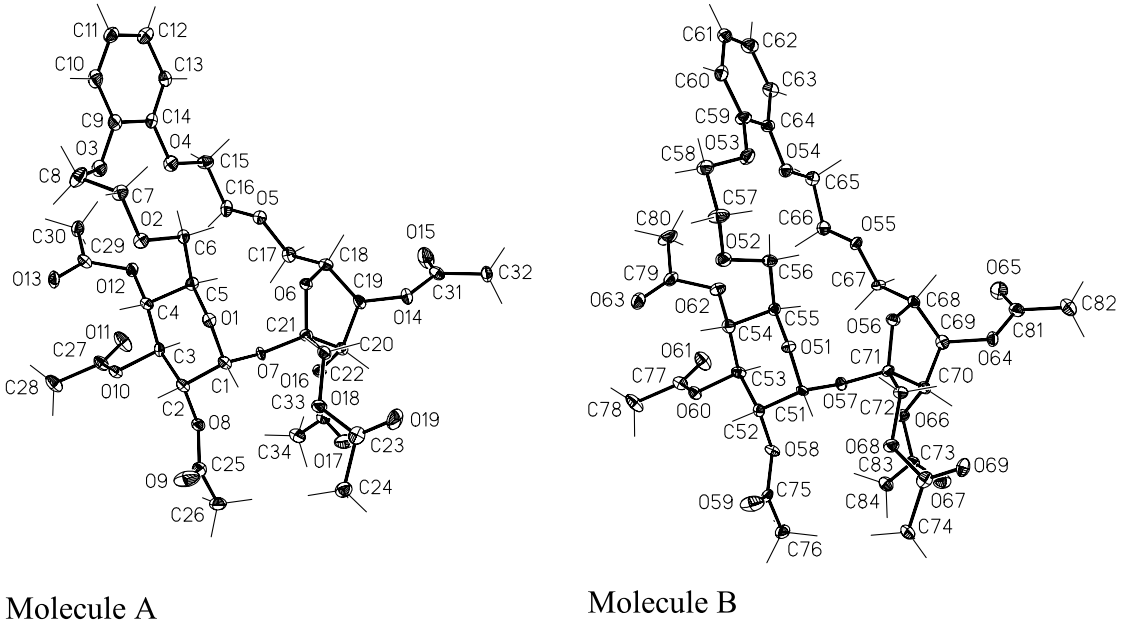


Figure 2. X-ray structure of compound **7b**.

Table 1. Selected torsion angles (°)

	Molecule A (i=0)	Molecule B (i=50)
C(5+i)–O(1+i)–C(1+i)–O(7+i)	56.4(7)	58.6(7)
C(1+i)–O(1+i)–C(5+i)–C(6+i)	−171.3(5)	−169.3(5)
O(1+i)–C(5+i)–C(6+i)–O(2+i)	−68.7(6)	−75.0(6)
C(7+i)–O(2+i)–C(6+i)–C(5+i)	−163.6(5)	169.1(6)
C(6+i)–O(2+i)–C(7+i)–C(8+i)	93.9(7)	77.4(8)
O(2+i)–C(7+i)–C(8+i)–O(3+i)	−66.7(8)	−67.0(9)
C(9+i)–O(3+i)–C(8+i)–C(7+i)	−89.6(8)	175.1(6)
C(8+i)–O(3+i)–C(9+i)–C(14+i)	151.1(6)	−146.1(7)
O(3+i)–C(9+i)–C(14+i)–O(4+i)	−7.2(9)	8.9(9)
C(15+i)–O(4+i)–C(14+i)–C(9+i)	178.5(6)	−175.5(6)
C(14+i)–O(4+i)–C(15+i)–C(16+i)	170.2(6)	−174.5(6)
O(4+i)–C(15+i)–C(16+i)–O(5+i)	−76.7(7)	−67.0(7)
C(17+i)–O(5+i)–C(16+i)–C(15+i)	−163.1(5)	−160.8(5)
C(16+i)–O(5+i)–C(17+i)–C(18+i)	179.7(5)	179.9(5)
O(5+i)–C(17+i)–C(18+i)–O(6+i)	67.3(7)	68.9(7)
C(21+i)–O(6+i)–C(18+i)–C(17+i)	93.6(6)	95.9(6)
C(18+i)–O(6+i)–C(21+i)–O(7+i)	−99.6(6)	−94.7(6)
C(1+i)–O(7+i)–C(21+i)–O(6+i)	−86.5(6)	−88.7(6)
C(21+i)–O(7+i)–C(1+i)–O(1+i)	63.2(7)	65.2(7)

[0.259(7), 142(2) and 0.218(6), 14(2)] indicate the ^{18}E-envelope [with the C(18) atom in the apex] and the $^{71}T_{70}$ twist conformations, respectively.

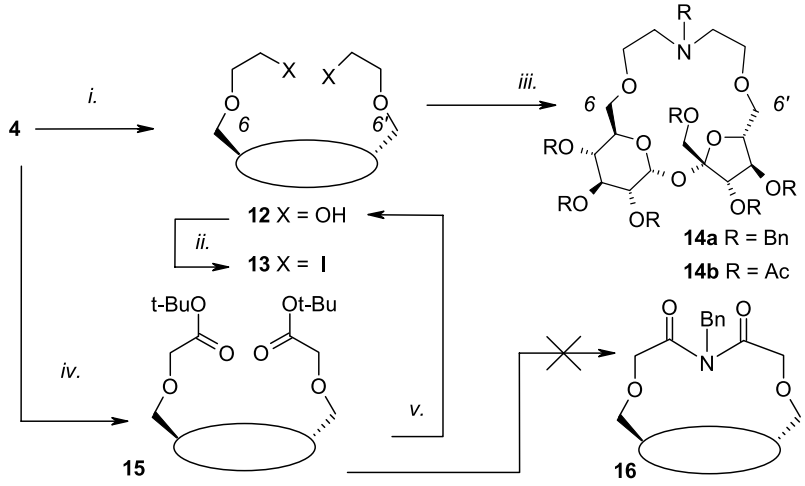
This difference has rather a minor influence on the crown ring conformation. The respective torsion angles listed in Table 1, which characterize this part of molecules have very similar values. On the other hand, the molecules A and B have different conformations near the aromatic ring. The C(9)–O(3)–C(8)–C(7) and C(59)–O(53)–C(58)–C(57) torsion angles are equal −89.6(8) and 175.1(6)°, and the C(8)–O(3)–C(9)–C(14) and C(58)–O(53)–C(59)–C(64) are equal 151.1(6) and −146.1(7)°, respectively.

The starting material for the preparation of the aza-analogue **14a**—the diol **12**—was synthesized by two different routes from **4** (Scheme 1). The first involved double allylation followed by cleavage of the double bonds with OsO_4/$NaIO_4$ and subsequent reduction. The second was based on the reaction of the diol **4** with *t*-butyl bromoacetate and reduction of the resulting diester **15** with $LiAlH_4$. The second method afforded diol **12** in higher yield (66 vs 49%). Surprisingly, reaction of diol **4** with methyl bromoacetate did not afford any diester. Compound **14a** was easily converted into the peracetylated analogue **14b** by simple hydrogenolysis followed by acetylation.

Reaction of **15** with benzylamine, which would provide the direct precursor of **14**-imide **16**—was unsuccessful. Also trans-esterification of **15** into dimethyl ester (which should react with benzylamine more readily than **15**) under various conditions failed.

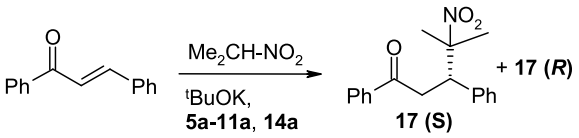
The 1,4-addition of nucleophiles to α,β-unsaturated ketones catalyzed by chiral crown ethers may provide the corresponding adducts in high optical purity. One such reaction is the addition of 2-nitropropane to chalcone leading to 1,4-adducts **17**. When such catalysts based on simple sugar were used, the optical purity of **17** amounted to 95%.[11] We tested our analogues in such a process, however, with no success. Optical purities of product **17** in the reaction catalyzed by sucrose crowns were very low and did not exceed 22% (see Table 2).

The stability constants of complexes formed can be easily determined by NMR titration;[12] the results obtained for



Scheme 1. (i) a. AllBr, NaH, DMF, 3 h, rt, 95%; b. OsO_4, $NaIO_4$, THF/H_2O (1:1) then $NaBH_4$, 52%; (ii) a. MsCl, Et_3N, DMAP, CH_2Cl_2, b. NaI, acetone, reflux, 6 h, 69%; (iii) $BnNH_2$, $NaCO_3$, CH_3CN, 50 h, reflux, 73%; (iv) $BrCH_2CO_2^tBu$, 50% NaOH, toluene, Bu_4NBr, 69%; (v) $LiAlH_4$, THF, 95%.

Table 2. Base-catalyzed 1,4-addition of 2-nitropropene to chalcone catalyzed by sucrose crowns



Catalyst	Chemical yield %	**17**% ee
5a	88	15 (***S***)
6a	88	22 (***S***)
7a	77	13 (***S***)
8a	56	9 (***R***)
9a	85	17 (***S***)
10a	9	16 (***S***)
14a	66	17 (***S***)

sucrose receptors are shown in Table 3. The stability constants are rather moderate; they depend on the cavity of the macrocycle, but do not depend on the counter ion as can be noticed for compound **7a** (entry 2; Table 3). The highest values were noted for complexes of **5a** with sodium and potassium and the aza-analogue **14a** for potassium cation.

The stability constants of complexes of sucrose receptors were low. First (most likely) reason results from a distorted crown structure of sucrose macrocycles described here. Second one is a consequence of a sugar unit being part of a macrocycle. It is reported, that the complexing abilities of monosaccharide based crown ethers strongly depend on the configuration of a sugar. For example, mannose derived receptor **18** forms strong complex with *t*butylammonium thiocyanate ($K_a = 39{,}000\ M^{-1}$), while analogous complex of macrocycle **19**—differing only in configuration at the C-3 atom of the sugar skeleton—is very weak ($K_a < 50\ M^{-1}$ see Fig. 3).[13]

3. Conclusion

The sucrose macrocycles—analogues of the crown ethers—are easily prepared from 'sucrose diol', which has the C6 and C6′ positions free and the other hydroxyl groups protected as benzyl ethers. These macrocyclic derivatives are easily converted into the free analogues by simple hydrogenation. The complexing properties of the 'crowns' studied are rather moderate. The highest stability constant with potassium ion was measured for compound **5a** and **14a** having a 16-membered ring.

Application of such sucrose-derived macrocycles as catalysts in enantioselective Michael reaction was not successful.

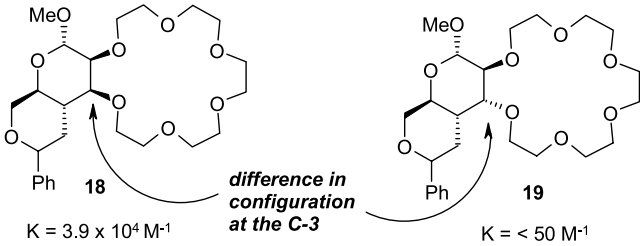


Figure 3. Complexes of sugar derived macrocycles with *t*-bytulammonium thiocyanate.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded with a Varian Mercury 400 BB (for **10b**), or a Bruker DRX 500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). NMR titration of macrocycles with thiocyanates (and KPF_6) was performed with a Varian Gemini 2000 BB spectrometer in acetone-d_6 according to a standard methodology.[12,14] Most of the proton resonances were assigned by the ^{1}H–^{1}H- and the carbon resonances in **5b** by the ^{1}H–^{13}C- correlations. Mass spectra (ESI) were recorded with PE SCIEX API 365, or Mariner PerSeptive Biosystems apparatus. Optical rotations were measured with a Digital Jasco polarimeter DIP-360 for solutions in chloroform ($c = 1$) at room temperature. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh). THF was distilled from potassium prior to use. For chromatography purposes a fraction of mineral oil with a boiling point in range 70–90 °C was used as mixture of hexanes. All solutions were dried over anhydrous sodium sulfate.

X-ray data of **7b** were collected at low temperature using an Oxford Cryosystem device on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The crystal was positioned at 65 mm from the CCD camera. 612 frames were measured at 0.75° intervals with a counting time of 20 s. Accurate cell parameters were determined and refined by least-squares fit of 3900 the strongest reflections. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Oxford Diffraction (Poland) Sp. z o.o. programs. The structure was solved by direct methods

Table 3. Stability constants of 1:1 complexes (calculated from the shift of the H-1 signal) of 'crown sucroses' with cations (compound **6a** formed complexes of different stoichiometry); measured in acetone-d_6

	Compound	LiSCN	NaSCN	KSCN	NH_4SCN
1.	**5a**	<5	250	258	17
2.	**7a**		31	57[a]	9
3.	**7b**		9	12	<5
4.	**8a**		19	18	
5.	**9a**	7	60	66	25
6.	**10a**		14	<5	
7.	**14a**	50		234	125

[a] $K = 63\ M^{-1}$ with KPF_6.

Table 4. Crystal data and structure refinement

Empirical formula	$C_{34}H_{44}O_{19}$
Formula weight	756.69
T/K	100(2)
λ/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	17.645(19)
b/Å	8.957(10)
c/Å	22.74(3)
β/°	92.370(10)
V/Å^3	3591(7)
Z	4
D_c/mg m^{-3}	1.400
μ/mm^{-1}	0.115
F(000)	1600
Crystal size/mm	0.25×0.17×0.10
θ range for data collection/°	3.34–28.54
Ranges of h,k,l	−23→22, −8→11, −30→29
Reflections collected	25,113
Independent reflections (R_{int})	11,423 (0.0816)
Data/parameters	11,423/968
GOF(F^2)	1.097
Final R_1/wR_2 indices ($I>2\sigma_I$)	0.0837/0.2093
Extinction coefficient	0.0123(15)
Largest diff. peak/hole (e Å^{-3})	0.330/−0.331

(program SHELXS97[15]) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL97[16] program. Non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps. During the refinement their parameters were fixed. Crystal data are given in Table 4, together with refinement details.

Crystallographic data for the structures reported in this paper (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 272641. Copies of this information may be obtained free of charge from the Director, CCDC, 12 UNION Road, Cambridge 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

4.2. Synthesis of the diol 4

This compound was prepared from 1′,2,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose according to Ref. 6 by substitution of both 6,6′chlorine atoms with acetates using 5 equiv of Bu_4NOAc (75% yield) followed by hydrolysis of acetates under Zemplen conditions.

We have found that Bu_4NOAc can be replaced with sodium acetate without significant decrease of the yield of 6,6′-diacetate, although the time of this substitution is much longer. Thus, to a solution of 1′,2,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose (400 mg) in DMF (100 mL) anhydrous sodium acetate (2 g) was added and the mixture was stirred at 100–110 °C for 20 days. After cooling it was poured into the water (150 mL) and the product was extracted with ether (3×100 mL) to afford diacetate **4-Ac** in (290 mg, 69%).

4.3. General procedure for the preparation of macrocycles 5a–11a

To a solution of **4** (0.66 g, 0.75 mmol) in dry DMF (25 mL), sodium hydride (50% suspension in mineral oil, 110 mg ca. 2.25 mmol) and a catalytic amount of imidazole (30 mg) were added under an argon atmosphere and the mixture was stirred for 20 min at room temperature. The corresponding ditosylate (0.98 mmol) in DMF (15 mL) was then added dropwise over 30 min, and stirring was continued for 12 h. The excess of hydride was then carefully decomposed with water and the products were extracted with ethyl acetate. The organic phase was washed with water, dried, concentrated and the products **5a–11a** were isolated by column chromatography (eluent: hexane–ethyl acetate).

This preparation essentially followed the procedure applied recently by us, except the solvent. When the reaction was performed in THF the yields of macrocycles were low.[6] However, changing the solvent to dry DMF increased the yields significantly.

- Compound **6a**, 35% (after column chromatography with hexane/ethyl acetate, 2:1 to 1:1). Previously reported yield: 12%.
- Compound **7a**, 48% (after column chromatography with hexane/ethyl acetate, 2:1, then HPLC with hexane/ethyl acetate, 5:2). Previously reported yield: 15%.
- Compound **9a**, 52% (after column chromatography with hexane/ethyl acetate, 3:2). Previously reported yield: 31%.

4.3.1. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-(5,5-dimethyl-3,7-dioxanonan-1,9-di-yl)-sucrose (10a). (Eluent: hexane/ethyl acetate, 4:1, then HPLC). Colorless oil, $[\alpha]_D$ +37.4. IR (film) ν 3031, 2868, 1454, 1092, 1028, 736, 698 cm^{-1}; ^{1}H NMR δ: 5.66 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 0.86, 0.83 (2× s, 2×3H, 2×CH_3). ^{13}C NMR δ: 138.9, 138.72, 138.67, 138.47, 138.40, 138.3 (6×C_q benzyl), 104.1 (C-2′), 89.4 (C-1), 83.4, 82.02, 81.99, 79.9, 79.7, 77.8 and 70.82 (C-2,3,3′,4,4′,5,5′), 76.6, 76.4, 75.4, 74.7, 73.3, 72.65, 72.57, 72.55, 71.7 (double intensity), 71.0, 70.78, 70.75, 70.73, 69.6 (C-1′,6,6′, 6×OCH_2Ph and 6×–OCH_2– from the macrocyclic ring) 36.1 (CMe_2), 22.3, 22.1 (2× CH_3). *m/z*: 1061 [M($C_{63}H_{74}O_{13}$)+Na^+]. Anal. Calcd for $C_{63}H_{74}O_{13}$: C, 72.81; H, 7.18. Found: C, 72.8; H, 7.2%.

4.3.2. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-(1,2-diphenoxy-3-oxapentylidene)-sucrose (11a). (Eluent: hexane/ethyl acetate, 1:1, then HPLC. Colorless oil, $[\alpha]_D$ +40.2. IR (film) ν 2918, 2869, 1498, 1454, 1257, 1127, 1091, 1028, 738, 698 cm^{-1}; ^{1}H NMR δ: 5.65 (d, $J_{1,2}$=3.6 Hz, 1H, H-1). ^{13}C NMR δ: 149.18, 149.13 (2×C from –C_6H_4–), 139.0, 138.7, 138.4, 138.34, 138.26, 138.0 (6×C_q benzyl), 121.6 (double intensity), 115.0, 114.7 (4×C from –C_6H_4–), 104.2 (C-2′), 89.4 (C-1), 83.4, 81.9, 81.8, 79.9, 79.5, 77.9 and 71.08 (C-2,3,3′,4,4′,5,5′), 75.4, 74.7, 73.3, 72.59, 72.58, 72.49, 71.8, 71.7, 71.1, 70.95, 70.92, 70.5, 69.84, 69.80, 69.7, 69.5, 69.4 (C-1′,6,6′, 6×OCH_2Ph and 8×–OCH_2– from macrocyclic ring). *m/z*: 1155 [M($C_{68}H_{76}O_{15}$)+Na^+]. Anal. Calcd for $C_{68}H_{76}O_{15}$: C, 72.07; H, 6.76. Found: C, 72.3; H, 6.6%.

4.4. General procedure for deprotection of macrocycles; synthesis of pearacetetas 5b–11b and 14b

To a solution of the appropriate perbenzylated derivative (0.4 mmol) in ethanol (7 mL), ethyl acetate (7 mL), and water (0.1 mL), 10% Pd/C (20 mg) was added, and the mixture was hydrogenolyzed for 24 h under standard conditions. Solvents were removed in vacuum, the residue was suspended in pyridine (5 mL), to which acetic anhydride (2 mL) and DMAP (ca. 30 mg) were added and the mixture was stirred at room temperature for 2 h. Products were isolated by column chromatography.

4.4.1. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(3-oxapentan-1,5-diyl)-sucrose (5b). (Eluent: ethyl acetate). White, amorphous solid, $[\alpha]_D$ +26.8; ^{1}H NMR δ: 5.55 (dd, $J_{3',4'}=7.1$ Hz, $J_{4',5'}=7.1$ Hz, 1H, H-4′), 5.54 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.48 (d, 1H, H-3′), 5.43 (dd, $J_{3,4}=9.6$ Hz, $J_{2,3}=10.2$ Hz, 1H, H-3), 4.93 (dd, $J_{4,5}=10.3$ Hz, 1H, H-4), 4.92 (dd, 1H, H-2), 4.40–4.20 (m, 1H, H-5), 4.17–4.13 (m, 1H, H-5′), 4.09 (d, $J_{A,B}=11.7$ Hz, 1H, H-1′of AB) 4.04–4.01 (m, 2H, both H-6′), 4.00 (d, 1H, second H-1′ of AB), 3.73–3.52 (m, 10H, both H-6 and 4×CH_2O), 2.24, 2.125, 2.124, 2.11, 2.09, 2.02 (6×s, 6×3H, 6×$COCH_3$). ^{13}C NMR δ: 170.3, 170.2, 170.10, 170.06, 169.86, 169.82 (6×CO), 102.5 (C-2′), 89.5 (C-1), 79.8 (C-5′), 76.1 (C-4′), 76.0 (C-3′), 72.7 (C-6′), 72.5 (C-6), 70.44, 70.41, 70.25 (double intensity, 4×CH_2O), 70.22 (C-2), 69.8 (C-3), 69.7 (C-5), 69.5 (C-4), 63.8 (C-1′), 20.9, 20.7, 20.65, 20.64, 20.60, 20.56 (6×COCH_3). HRMS: 687.2132 [$C_{28}H_{40}O_{18}Na$ (M+Na^+) requires: 687.2107]. Anal. Calcd for $C_{28}H_{40}O_{18}$: C, 50.60; H, 6.07. Found: C, 50.8; H, 5.9%.

4.4.2. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(5,5-dimethyl-3,7-dioxanonan-1,9-diyl)-sucrose (10b). (Eluent: hexane/ethyl acetate, 1:1). Pale yellow oil, $[\alpha]_D$ +43.3. IR (film) ν 2955, 2872, 1750, 1370, 1224, 1097, 1038 cm^{-1}; ^{1}H NMR δ: 5.66 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.47–5.38 (m, 3H, H-3, H-3′, H-4′), 5.11 (dd, $J_{3,4}=9.8$ Hz, $J_{4,5}=9.8$ Hz, 1H, H-4), 4.88 (dd, $J_{2,3}=10.4$ Hz, 1H, H-2), 2.19, 2.10, 2.08, 2.06, 2.05, 2.01 (6×s, 6×3H, 6×$COCH_3$), 0.88, 0.86 (2×s, 2×3H, 2×CH_3). ^{13}C NMR δ: 170.22, 170.18, 170.02, 169.98, 169.93, 169.62 (6×CO), 103.3 (C-2′), 89.5 (C-1), 80.8, 75.7, 74.9, 70.3, 69.9, 69.5 and 69.1 (C-2,3,3′,4,4′,5,5′), 76.1, 75.9, 71.2 (double intensity), 71.0, 70.8, 70.6, 69.6, 63.1 (C-1′,6,6′ and 6×–OCH_2– from macrocyclic ring), 35.9 (*C*Me_2), 22.3, 22.2 (2×CH_3), 20.76, 20.72, 20.65, 20.61, 20.52 (double intensity, 6×COCH_3). HRMS: 773.2822 [$C_{33}H_{50}O_{19}Na$ (M+Na^+) requires: 773.2839]. Anal. Calcd for $C_{33}H_{50}O_{19}$: C, 52.80; H, 6.71. Found: C, 53.0; H, 6.5%.

4.4.3. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(1,2-diphenoxy-3-oxapentylidene)-sucrose (11b). (Eluent: hexane/ethyl acetate, 1:1). Colorless oil, $[\alpha]_D$ +46.6. IR (film) ν 2924, 2874, 1750, 1371, 1245, 1223, 1040 cm^{-1}; ^{1}H NMR δ: 6.92–6.86 (m, 4H, –C_6H_4–), 5.66 (d, $J_{1,2}=3.8$ Hz, 1H, H-1), 2.2, 2.09, 2.08, 2.05, 2.00, 1.99 (6×s, 6×3H, 6×$COCH_3$). ^{13}C NMR δ: 170.16, 170.15, 170.0 (double intensity), 169.9, 169.7 (6×CO), 149.1, 149.0, 121.5 (double intensity), 114.5, 114.4 (aromatic from macrocyclic ring), 103.6 (C-2′), 89.7 (C-1), 80.6, 75.9, 75.2, 70.4, 69.94, 69.7 and 69.1 (C-2,3,3′,4,4′,5,5′), 71.5, 71.4, 71.0, 70.9, 70.6, 69.86 (double intensity), 69.81, 69.3, 69.2, 63.1 (C-1′,6,6′ and 8×–OCH_2– from macrocyclic ring), 20.72, 20.67, 20.63 (double intensity), 20.57, 20.54 (6×COCH_3). HRMS: 867.2926 [$C_{38}H_{52}O_{21}Na$ (M+Na)$^+$ requires: 867.2893]. Anal. Calcd for $C_{38}H_{52}O_{21}$: C, 50.02; H, 6.20. Found: C, 49.8; H, 6.2%.

4.4.4. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-(3-azabenzyl-penta-1,5-di-yl)-sucrose (14b). (Eluent: hexane/ethyl acetate, 2:3–1:2). Yellowish oil, $[\alpha]_D$ +28.1. IR (film) ν 2929, 1748, 1643, 1370, 1224, 1046 cm^{-1}; ^{1}H NMR [Signals from two conformers in ratio 1.72 (a-major) to 1 (b-minor)] δ: 5.64 (d, $J_{1,2}=3.6$ Hz, 1H, H-1, b), 5.57 (d, $J_{1,2}=3.5$ Hz, 1H, H-1, a), 2.22 (a), 2.20 (b), 2.12 (a), 2.112 (b), 2.107 (a), 2.104 (a+b), 2.90 (a), 2.072 (b), 2.067 (a), 2.063 (b), 2.01 (b), 2.00 (a), 1.96 (b) (7×s, 6×3H, 6×$COCH_3$ from a and 7×s, 6×3H, 6×$COCH_3$ from b). ^{13}C NMR δ: 170.9 (a), 170.7 (b), 170.07 (b), 170.06 (a), 170.00 (b), 169.98 (a), 169.93 (a), 169.90 (double intensity, 2×a), 169.88 (double intensity, 2×b), 169.81 (b), 169.77 (b), 169.67 (a) (7×CO from a and 7×CO from b), 103.7 (C-2, a), 103.4 (C-2, b), 90.0 (C-1′, a), 89.6 (C-1, b), 81.0 (a), 80.0 (b), 76.4 (a), 76.3 (b), 76.0 (a), 75.1 (b), 70.4 (b), 70.28 (a), 70.1 (b), 69.7 (a), 69.57 (a), 69.4 (b), 69.3 (b), 69.2 (a) (C-2,3,3′,4,4′,5,5′ from a and C-2,3,3′,4,4′,5,5′ from b), 71.4 (a), 71.2 (a+b), 70.94 (a), 70.91 (b), 70.8 (b), 70.26 (b), 69.51 (a), 62.9 (a), (C-1′,6,6′ and 3× –OCH_2– from macrocyclic ring from a and 5× –CH_2– from b), 50.0 (NCH_2–, b), 49.4 (NCH_2–, a), 47.2 (NCH_2–, a), 46.5 (NCH_2–, b). HRMS: 728.2407 [$C_{30}H_{43}O_{18}NNa$ (M+Na)$^+$ requires: 728.2372]. Anal. Calcd for $C_{30}H_{43}O_{18}N$: C, 51.06; H, 6.17; N, 1.98. Found: C, 51.3; H, 6.1; N, 2.0%.

4.4.5. 6,6′-Bis-(*O*-2-hydroxyethyl)-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (12). *Method A*. 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (**4**) was converted into the diallyl ether as described previously[17] in 95% yield. Thus, obtained 6,6′-di-*O*-allyl-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (0.974 g, 1.0 mmol) was dissolved in THF (13 mL) and H_2O (13 mL), to which $NaIO_4$ (1.3 g, 6.0 mmol) was added followed by OsO_4 (70 μL of a ~2% solution in toluene). The resulting mixture was stirred at room temperature for 1.5 h and then partitioned between water (100 mL) and ether (80 mL). The organic phase was collected, dried, concentrated and the residue was dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The solution was cooled to −78 °C, $NaBH_4$ (0.6 g) was added in several portions, the mixture was stirred for 1 h at −78 °C, and 2 h at room temperature. Water (40 mL) was added and product was extracted with CH_2Cl_2 (50 mL). The organic layer was dried, concentrated, and the crude product was purified by column chromatography (hexane/ethyl acetate, 1:1–2:3) to afford the title compound **12** (0.508 g, 0.5 mmol, 52%; 49% overall from **4**) as a pale yellow oil, $[\alpha]_D$ +44.3. IR (film) ν 2916, 2866, 1454, 1086, 1072, 736, 697 cm^{-1}; ^{1}H NMR δ: 6.12 (d, $J_{1,2}=4.0$ Hz, 1H, H-1). ^{13}C NMR δ: 139.2, 138.8, 138.3, 138.2, 137.98, 137.95 (6×C_q benzyl), 103.8 (C-2′), 87.8 (C-1), 83.4, 82.0, 79.02, 78.95 (double intensity), 77.1 and 70.6 (C-2,3,3′,4,4′,5,5′), 75.2, 74.6, 73.4, 73.1, 73.0, 72.9 (double intensity), 72.3, 71.9 (C-1′,6,6′, 6×OCH_2Ph), 68.49, 68.47, 61.69, 61.66 (4×CH_2 from 2-hydroxyethyl). *m*/*z*: 993.5 [M($C_{58}H_{66}O_{13}$)+Na^+]. Anal: Calcd for

$C_{58}H_{66}O_{13}\times\frac{1}{2}H_2O$: C, 71.07; H, 6.89. Found: C, 71.0; H, 7.1%.

Method B. 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (0.15 g, 0.170 mmol) was dissolved in toluene (15 mL), to which a 50% aqueous solution of sodium hydroxide (15 mL) and tetrabutylammonium bromide (0.01 g, 0.03 mmol) were added. Then *tert*-butyl bromoacetate (0.15 mL) was added dropwise and the mixture was stirred vigorously at room temperature for 4 h. Water (30 mL) and toluene (15 mL) were added to the mixture, and the organic layer was separated, washed with water (10 mL) and brine (10 mL), dried and concentrated. Purification of the crude product by column chromatography (hexane/ethyl acetate, 7:1) afforded compound **15** as colorless oil (0.13 g, 0.117 mmol, 69%), $[\alpha]_D$ +30.7; ^{1}H NMR δ: 5.7 (d, $J_{1,2}$= 3.64 Hz, 1H, H-1), 1.50 (s, 9H, *tert*-butyl), 1.49 (s, 9H, *tert*-Bu). ^{13}C NMR (125 MHz) δ: 169.4, 169.2 (2×CO), 139.0, 138.8, 138.4, 138.3, 138.2, 138.0 (6×C_q benzyl), 104.6 (C-2′), 90.1 (C-1), 83.8, 82.4, 81.9, 79.7 (double intensity), 77.4, 70.6 (C-2,3,3′,4,4′,5,5′), 81.3, 81.2 (2×C, C_q *tert*-butyl) 75.4, 74.7, 73.4, 72.9, 72.7, 72.5, 72.3, 71.2 (6×O*C*H$_2$Ph, 2×*C*H$_2$COO), 28.1 (6×CH$_3$). *m/z*=1133.4 [M($C_{66}H_{78}O_{15}$)+Na$^+$]. Anal. Calcd for $C_{66}H_{78}O_{15}\times H_2O$: C, 70.21; H, 7.09. Found: C, 70.2; H, 7.1%.

Compound **15** (0.126 g, 0.114 mmol) was dissolved in dry THF (45 mL), to which a suspension of $LiAlH_4$ (0.09 g, 2.368 mmol) in THF (15 mL) was added. The mixture was stirred at room temperature for 3 h and the excess of hydride was decomposed by careful addition of water. Then it was partitioned between water (75 mL) and diethyl ether (60 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2×60 mL). The extracts were combined, washed with water (30 mL), dried and the solvents were removed in vacuum to give product **14** (0.105 g, 0.108 mmol, 95%; 66% overall from **4**) identical in all respects with the material prepared in Method A.

4.4.6. 6,6′-Bis-(*O*-2-iodoethyl)-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (13). Compound **12** (0.300 g, 0.31 mmol) was dissolved in CH_2Cl_2 (25 mL) containing triethylamine (3 mL) and DMAP (ca. 7 mg) and cooled to 0 °C. Mesyl chloride (0.073 mL, 0.9 mmol) was added, the reaction mixture was stirred for 15 min at 0 °C, 1 h at room temperature, and then partitioned between water (70 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with water (50 mL), dried, concentrated, and the residue was dissolved in acetone (25 mL). Sodium iodide (1.3 g, 8.6 mmol) was added and the mixture was stirred under reflux for 6 h. Acetone was removed under reduced pressure, and the residue was partitioned between ethyl acetate (70 mL) and water (70 mL). The organic phase was washed with water (50 mL), dried, concentrated and the residue was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **13** (0.253 g, 0.21 mmol, 69%) as a brown oil, $[\alpha]_D$ +29.2. IR (film) ν 2921, 2867, 1454, 1090, 1074, 1027, 735, 697 cm^{-1}; ^{1}H NMR δ: 5.71 (d, $J_{1,2}$= 3.6 Hz, 1H, H-1). ^{13}C NMR δ: 138.8, 138.7, 138.3, 138.20, 138.17, 137.9 (6×C_q benzyl), 104.7 (C-2′), 90.2 (C-1), 83.9, 82.3, 81.9, 79.8, 79.6, 77.4 and 70.6 (C-2,3,3′,4,4′,5,5′), 75.5, 74.9, 73.4, 73.0, 72.47, 72.42, 72.2, 72.0, 71.8, 71.1, and 69.2, 2.78, 2.69 (C-1′,6,6′, 6×O*C*H$_2$Ph and 4× –CH$_2$). *m/z*: 1213.2 [M($C_{58}H_{64}O_{11}I_2$)+Na$^+$]. Anal. Calcd for $C_{58}H_{64}O_{11}I_2+2H_2O$: C, 56.78; H, 5.26. Found: C, 56.8; H, 5.5%.

4.4.7. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-(3-azabenzyl-penta-1,5-di-yl)-sucrose (14a). Compound **13** (0.48 g, 0.41 mmol) was dissolved in acetonitrile (25 mL), to which benzylamine (45 μL, 0.18 mmol) and Na_2CO_3 (0.15 g) were added. The reaction mixture was stirred under reflux for 50 h concentrated and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with water (30 mL), dried, and concentrated, and the product was isolated by column chromatography (hexane/ethyl acetate, 2:1–1:1) as a pale yellow oil (0.306 g, 0.29 mmol, 73%), $[\alpha]_D$ +28.7. IR (film) ν 2921, 2866, 1453, 1091, 1073, 1027, 734, 697 cm^{-1}; ^{1}H NMR δ: 5.44 (d, $J_{1,2}$=3.3 Hz, 1H, H-1). ^{13}C NMR δ: 139.5, 138.8, 138.7, 138.6, 138.3, 138.00, 137.98 (7×C from benzyl), 104.2 (C-2′), 90.1 (C-1), 84.9, 83.7, 81.6, 80.01, 71.98, 79.5, and 70.95 (C-2,3,3′,4,4′,5,5′), 75.4, 74.8, 73.4, 73.2, 72.7, 72.2 (double intensity), 71.7, 71.1, 70.7, 69.1, 60.4, 53.6, 53.2 (C-1′,6,6′, 7×O*C*H$_2$Ph and 4× –CH$_2$–). *m/z*: 1042.5 [M($C_{65}H_{71}O_{11}N$)+Na$^+$].

4.5. Reaction of chalcone with 2-nitropropane catalyzed by sucrose crown ether analogues[†]

Chalcone (200 mg, 0.96 mmol), 2-nitropropane (0.2 mL), and the appropriate crown analogue **5a**–**10a** and **14a** (0.067 mmol) were dissolved in dry toluene (5 mL). Potassium *tert*-butoxide (40 mg, 0.37 mmol) was added and the mixture was stirred at room temperature for 2 days. Then it was partitioned between water (25 mL) and ethyl acetate (25 mL), the organic phase was separated, washed with brine and water, dried and concentrated. The crude product **17** was isolated by column chromatography (hexane/ethyl acetate, 9:1). The optical purity of the adduct **17** was determined by comparison of the $[\alpha]_D$ value with the analogous data of the pure enantiomer.[18] The results are shown in Table 3.

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[†] The procedure essentially followed the method described in Ref. 18.

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