Chiral Crown Ethers Incorporating α,α-Trehalose. Unexpected Structure of a Trehalose-Containing 18-Crown-6

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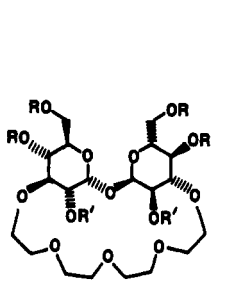
The reaction of 2,2'- (10), 3,2'- (11), and 3,3'-di-*O*-benzyl-4,6:4',6'-di-*O*-benzylidene-α,α-trehalose (12) with tetraethylene glycol ditosylate gave the corresponding chiral crowns mono-*trehalo*-3,3'- (1), bis-*trehalo*-3,3'- (3), mono-*trehalo*-2,3'- (5) and mono-*trehalo*-2,2'-tetraethylene glycol (7). The crystal structure of 1 was determined by X-ray analysis and the solution conformation of 1, 3, 5, and 7 by NMR spectroscopy and, in the case of 1, 3, and 7, molecular mechanics calculations. The geometry of the disaccharide moiety of 1, 3, and 5 was as expected according to the exo anomeric effect. However, an unexpected conformation around the glycosidic linkage was found for the 18-crown-6 mono-*trehalo*-2,2'-tetraethylene glycol (7). This conformation can be accounted for by semiempirical calculations of possible intermediate dianionic structures.

Besides chirality, the great structural variations and multiple interaction sites of carbohydrates make them very attractive molecules for the syntesis of chiral receptors. Chiral receptors with polar cavities (crown ether type) incorporating carbohydrates have been synthesized by Stoddart et al.,[1] but carbohydrates have also provided receptors with hydrophobic cavities, as is the case of the natural cyclodextrins[2] or the synthetic glycophanes of Wilcox.[3] We are involved in the synthesis of chiral receptors with different cavity shapes and flexibility from disaccharides. We have taken advantage of the conformational properties of the glycosidic bond to obtain more preorganized receptors than those synthesized using monosaccharides and alditols,[1] and we have prepared crown ether type cavities from lactose derivatives. These receptors have been used for enantiomeric differentiation and as catalysts in asymmetric Michael addition with interesting results.[4]

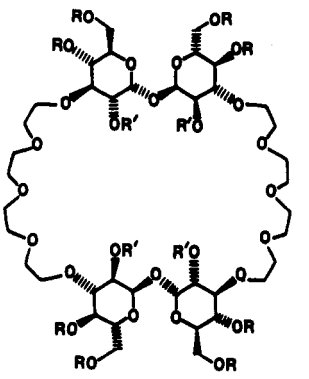
α,α-Trehalose is a disaccharide whose conformational features (C_2 symmetry and concave shape) are very appropriate for the preparation of highly symmetric chiral receptors. These receptors have been designed and synthesized by us by linking one hydroxyl group of each monosaccharide unit with a polyethylene glycol chain or an aromatic segment giving polar (crown ether type) or apolar (cyclophane type) cavities, respectively.[5] The crown ethers mono-*trehalo*-3,3'- (1), bis-*trehalo*-3,3'- (3), mono-*trehalo*-2,3'- (5), and mono-*trehalo*-2,2'-tetraethylene glycol (7), whose preparation is reported in this paper, are soluble in nonpolar organic solvents and will be used for the enantiomeric differentiation of ammonium salts and as catalysts in asymmetric synthesis. The water-soluble receptors 2, 4, 6, and 8 possess free hydroxyl groups as additional binding sites for the study of hydrogen bonding interactions. These interactions are one of the dominant forces in the molecular recognition of carbohydrates by carbohydrate-binding proteins.[6] Macrocycles 2, 4, 6, and 8 are being used as very simple models for the study of these interactions in water and polar organic solvents.[7]

During the synthesis of the crown ethers 1–8 by cyclization of the parent diols 10–12 with tetraethylene glycol ditosylate, we have observed an interesting conformational change in the disaccharide moiety depending on the position of the tetraethylene glycol linkage. While compounds 1–5 show the expected geometry around the glycosidic



1, R–R = PhCH, R' = Bn

2, R = R' = H



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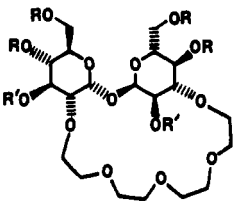
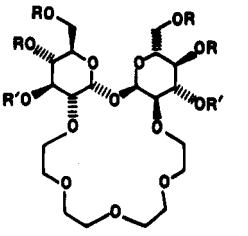


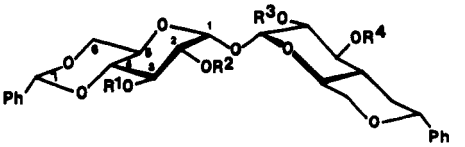
5, R–R = PhCH, R' = Bn

6, R = R' = H



7, R–R = PhCH, R' = Bn

8, R = R' = H



9, $R^1 = R^2 = R^3 = R^4 = H$

10, $R^1 = R^4 = H$, $R^2 = R^3 = Bn$

11, $R^2 = R^4 = H$, $R^1 = R^3 = Bn$

12, $R^1 = R^4 = Bn$, $R^2 = R^3 = H$

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Table I. ^{1}H NMR Chemical Shifts and Coupling Constants of the Diol Precursors 10–12 and Macrocycles 1, 3, 5, and 7

	10	1	3	11		5		12	7
H1	5.11	5.11	5.06	5.18	5.20	5.10	5.19	5.20	6.05
$J_{1,2}$		3.6				3.6	3.6		3.7
H2	3.47	3.49	3.50	3.56	3.77	3.48	3.48	3.80	3.38
$J_{2,3}$		9.3				9.4			9.2
H3	4.17	4.40	3.96		3.95	4.57	3.58–3.66	3.91	3.88
$J_{3,4}$		9.6				9.5			9.3
H4	3.42	3.47	3.51	3.51		4.29	4.14–4.24	3.68	3.59
H5	4.13	4.23	4.20					4.13	4.20
$J_{5,6}$		4.9							4.9
$H6_{eq}$	4.05	4.12	4.10					4.29	4.28
$J_{6eq,6ax}$		−10.1							−9.9
$H6_{ax}$	3.59	3.64	3.58					3.73	3.74
PhC*H*	5.42	5.50	5.48	5.52	5.51	5.53	5.53	5.58	5.57
PhCH_2	4.70/4.70	4.86/4.72	4.84/4.70	4.99/4.73	4.77/4.76	4.78/4.69	4.91/4.90	5.03/4.77	4.90/4.83
Etg		4.05–3.99	3.90–3.96			4.16–3.88			4.11
Etg		3.64–3.54	ca. 3.45			3.36–3.76			3.60
Etg		3.30–3.50							3.48

linkage according to the exo anomeric effect[8] and similar to that of trehalose and the parent diols, the tetraethylene glycol chain of 7 and 8 seems to force the conformation of the disaccharide moiety to give an unexpected structure on the basis of NMR data. We now report on the synthesis and the structural study of receptors 1–8.

Results and Discussion

Receptors 1, 3, 5, and 7 have been synthesized by condensation of tetraethylene glycol ditosylate with the corresponding diol precursors (10–12)[9] previously obtained by regioselective dibutyltin-mediated alkylation of 4,6:4,6′-di-*O*-benzylidene-α,α-trehalose (9). Condensation of 2,2′-di-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (10) with 1.5 mol equiv of tetraethylene glycol ditosylate in dry refluxing THF using potassium hydroxide as base yielded the mono-*trehalo*-3,3′-tetraethylene glycol (1) in 15% yield and the bis-*trehalo*-3,3′-tetraethylene glycol (3) in 10% yield. The ^{1}H NMR spectra of 1 and 3 in $CDCl_3$ showed a doublet at δ 5.11 and 5.06, respectively (Table I), assigned to the anomeric protons. When CsOH or LiOH were used as base, the yield of either 1 or 3 was not improved. Condensation of 2,3′-di-*O*-benzyl-4,5:4′,6′-di-*O*-benzylidene-α,α-trehalose (11) with tetraethylene glycol ditosylate under similar conditions gave the disymmetric receptor mono-*trehalo*-2,3′-tetraethylene glycol (5) in 43% yield. No other cyclization product was detected. The ^{1}H NMR spectrum of 5 showed two doublets at δ 5.19 and 5.10 assigned to H1 and H1′. Receptor mono-*trehalo*-2,2′-tetraethylene glycol (7) was obtained in good yield (70%) as the only cyclization product by condensation of the diol 3,3′-di-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (12) with tetraethylene glycol ditosylate (1.5 equiv) in the conditions described for 1, 3, and 5. The ^{1}H NMR spectrum of 7 in $CDCl_3$ showed an unexpected chemical shift (δ 6.05) of the doublet assigned to the anomeric protons. All four macrocycles have been characterized by their NMR and FAB-MS spectra. The positional isomers 1, 5, and 7 gave a peak at m/z 879 corresponding to $(M + Na)^+$.

Table II. Chemical Shift Values (δ) of the Anomeric Protons and Anomeric Carbons of Macrocycles (1, 5, 7, 8) and Their Precursors (10–12) in $CDCl_3$

macrocycles	H1	C1	precursors	H1	C1
1	5.11	94.2	10	5.11	94.5
5	5.10/5.19	92.4	11	5.18/5.20	95.4/93.9
7	6.05	100.5	12	5.20	95.2
8	5.82[a]	100.2[a]	α,α-trehalose	5.18[a]	94.8[a,c]
	5.78[b]			4.87[b]	

[a] D_2O as solvent. [b] CD_3SOCD_3 as solvent. [c] Reference 21.

Table III. NOE Values and Calculated (MM2) Distances (Å) between H1 and H5′ of Macrocycles (1, 5, 7) and Their Precursors (10 and 12)

	NOE (%)		distance (Å)	
macrocycles	H5′	H2	NOE[a]	MM2
1	2.8	10	2.4	3.0[b]
5	3/5	10/9	2.4/2.8	2.6/2.7
7	<2	9	>3	2.2–2.5
10	7	14	2.5	
12	4	11	2.6	

[a] Calculated from NOE values after reference 22. [b] In crystal, 2.8 Å.

Table IV. Relevant Torsion Angles for 1 Determined by X-ray and Calculated (MM2) for 1 and 5 and the Two Isomers 7A and 7B

	X-ray (deviation)	MM2			
angles	1	1	5	7A	7B
O5–C1–O1–C1′ (Φ)	76.3 (6)	74	60	53	123
O5′–C1′–O1–C1′ (Φ′)	70.7 (6)	72	58	53	89
O1–C1–C2–O2	62.3 (6)	59	53	44	57
O2–C2–C3–O3	62.6 (6)	66	70		
O3–C8–C9–O9	74.6 (7)	87	79		
O2–C8–C9–O9			60	64	−59
O9–C10–C11–O11	78.6 (8)	69	63	−49	66
O11–C12–C13–O13	−86.3 (9)	−83	−81	64	67
O13–C14–C15–O3′	71.3 (7)	53	60		
O13–C14–C15–O2′				−65	−55
O3′–C3′–C2′–O2′	63.4 (6)	65			
O2′–C2′–C1′–O1	60.3 (6)	59	56	49	59

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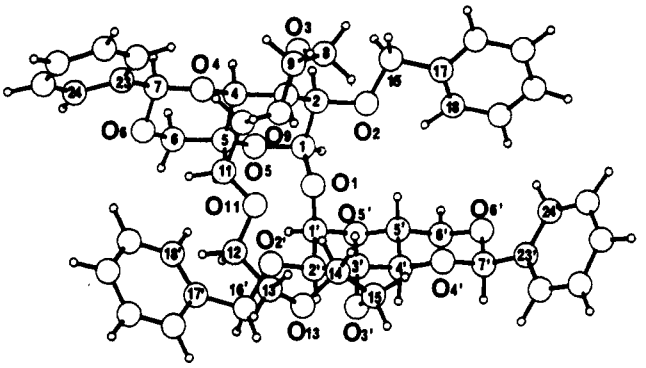

Figure 1. A PLUTO view of the structure of 1 as determined by X-ray diffraction.

The bis-*trehalo*-3,3′-tetraethylene glycol (3) showed peaks at m/z 1713 $(M)^+$ and 1736 $(M + Na)^+$. The water-soluble macrocycles 2, 4, 6, and 8 were obtained in good yield by hydrogenolysis of the corresponding protected derivatives 1, 3, 5, and 7.

The conformation in solution of the macrocycles was studied by NMR spectroscopy. The ^1H NMR parameters for 1, 3, 5, and 7 and their precursors 10–12 are shown in Table I. The spectra were analyzed using conventional COSY spectroscopy. Comparison of the ^1H NMR spectra of 1, 3, and 5 and those of their precursors 10 and 11 indicated that no important changes take place in the conformation of the disaccharide moiety upon cyclization, the main differences being those observed in the chemical shift of protons H3 and H2′ (Table I). In contrast, the signals for the anomeric protons and anomeric carbons of 7 and the corresponding deprotected derivative 8 were strongly deshielded (Table II) with regard to the cyclic isomers 1 and 5 and the acyclic precursor 12. This deshielding can be explained by the proximity of H1 to the oxygen atoms of the polyethylene glycol chain.[10] Thus, the conformation around the glycosidic bond of compound 7 seems to be different from that of its precursor 12. A NOE involving H1 and H5′ could be observed, with use of 1D-NOE and NOESY experiments, in compounds 1, 5, 10, and 12 (Table III) according to the expected conformation obtained by X-ray and MM2 calculations (see the following text). This effect could not be observed for compound 7. Although the absence of NOE should be treated very warily as evidence, the presence of a strong NOE between H1 and the protons of the polyethylene glycol chain in compound 7, not observed for macrocycles 1, 3, and 5, supports the proximity between them. Furthermore, molecular mechanics calculations[11] for 1, 5, and 7 using the crystallographic coordinates obtained for 1 as starting parameters (protective groups not included) gave a calculated MM2 geometry that accounted for the spectroscopic data observed for 1 and 5 but not for 7 (Table IV).

A PLUTO view of the solid-state conformation of 1 is given in Figure 1.[12] The molecule conforms with a quasibinary axis through O1 and O11 with torsion angles around the glycosidic linkages (Φ and Φ′) of 76° and 71° (Table IV), similar to those found for trehalose and trehalose derivatives,[13] the mean distance H1–H5′ being 2.8 Å. Molecular mechanics calculations provided, for 1, 5, and 7, a structure

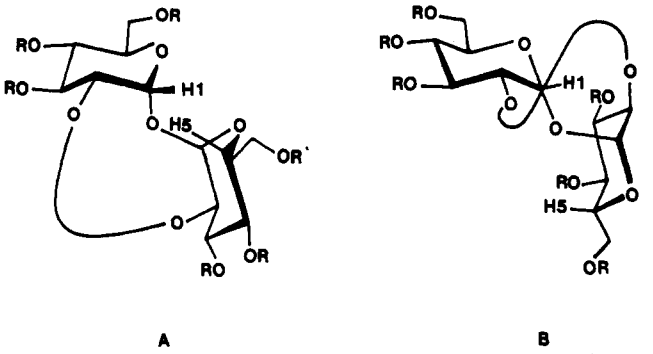

Figure 2. Schematic representation of isomers **A** and **B** for macrocycles 7 and 8.

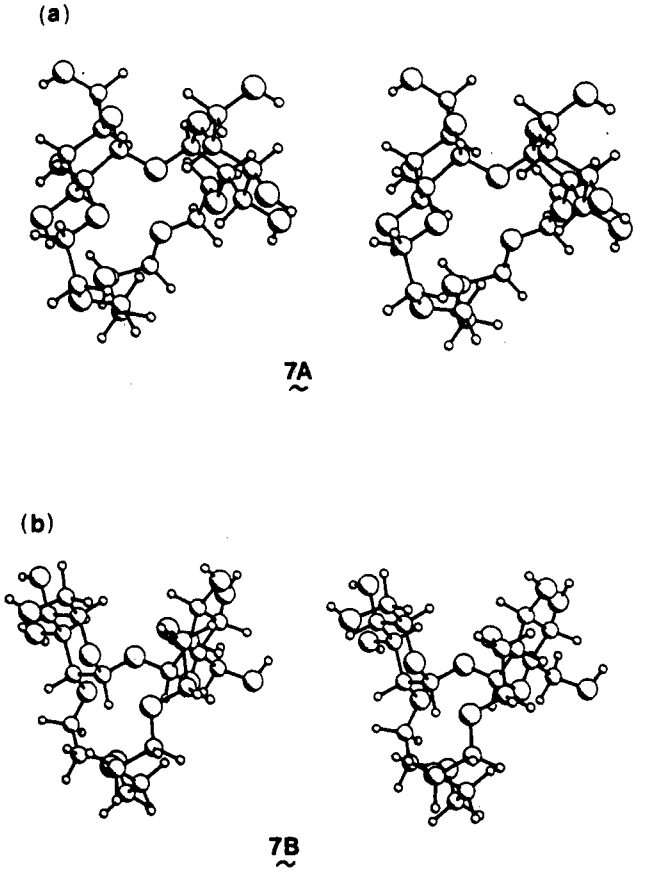

Figure 3. Stereoview of the MM2 calculated minimum conformation of isomers (a) **7A** and (b) **7B**.

quite similar to that found in the solid state for 1 with an average deviation of ca. 7° for the torsion angles of macrocycles 1 and 5 (Table IV) and proton–proton and proton–oxygen distances that agree with those observed in the solid state and correlate with the experimental NMR data. The calculated geometry for the 18-crown-6 7 gave values for Φ and Φ′ (Table IV, **7A**) smaller than those for 1 and 5, indicating that the linkage of positions O2 and O2′ with the tetraethylene glycol chain distorts the geometry around the glycosidic bond. This distortion makes the distances between H1 and H5′ shorter, and hence, strong NOE values should be expected in contrast to the experimental data (Table III). On other hand, the spectral changes upon complexation with organic ammonium salts were drastically different for macrocycles 1 and 5 on one side and for

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Table V. Relative Stabilities ($E_{\text{confor A}} - E_{\text{confor B}}$) of Conformers A and B of α,α-Trehalose and of the 3,3′ and 2,2′ Dianions

molecule	INDO (kcal/mol)	AM1 (kcal/mol)
α,α-trehalose	−9.8	−6.9
3,3′ dianion	−9.7	−6.6
2,2′ dianion	−4.9	−2.4

7 on the other. While in the case of 1 and 5 the signal for H3 was deshielded (δ 0.2) upon complexation, in the case of 7 the signal for H3 was unaffected and a deshielding was observed for H1 (δ 0.17).

An inspection of the space-filling molecular models (CPK) showed that the cyclization of diol 12 with tetraethylene glycol ditosylate can take place following two different paths to give two isomeric macrocycles schematically represented as **A** and **B** in Figure 2.

For isomer **A** the Φ and Φ′ angles should be in the range of those found for trehalose and trehalose derivatives,[13] while for **B** one of these angles has to adopt a larger value. This latter conformation could resemble one of the local minima predicted for α,α'-2-(tetrahydropyran-2-yloxy)-tetrahydropyran (Φ = 147°, Φ′ = 67°).[14] A view of the conformation of isomers **7A** and **7B**, according to MM2 calculations, is given in Figure 3. Both isomers are local minima in the conformational map, the corresponding calculated Φ and Φ′ torsion angles being 53°, 53° for the expected **7A** and 89°, 123° for **7B** (Table IV). The approximate steric energy differences between both structures, ignoring entropic factors, is 3.9 kcal/mol if favor of **7A**, and the averaged H1/H5′ distances are 2.30 Å for **7A** and 4.13 Å for **7B**.

A structure like **B** could explain all spectroscopic data observed for macrocycles 7 and 8. Isomers **A** and **B** of 7 and 8 are not interconvertible due to the small size of the crown ether cavity. The phenomenon reminds one of a type of atropoisomerism similar to that described for ansa compounds.[15a,b] A similar phenomenon has recently been described in the literature.[15c]

In the case of diols 10 and 11 the cyclization to give isomer **B** is not possible because the distance between the free hydroxyl groups is longer than the length of the tetraethylene glycol chain. It is interesting to note that in the cyclization of 12 only one isomer was isolated and traces of neither any other cyclization product nor monoalkylated derivatives were detected. A possible explanation of this fact could be that the formation of a dianion in positions 2 and 2′ may force the trehalose moiety to change its conformation in order to minimize the electrostatic repulsion between the two negatively charged oxygens.[16] Semiempirical calculations by INDO[17] and AM1[18] methods using the coordinates obtained by force field calculations for both conformers[19] of α,α-trehalose with the interglycosidic angles as in **A** (Φ = Φ′ ≈ 70) and **B** (Φ 147, Φ′ 67) and for the corresponding two conformers of the 2,2′ and the 3,3′ dianions predicted the energy differences given in Table V.

As expected, conformer **B** of trehalose is higher in energy (6.9 and 9.8 kcal/mol, according to INDO and AM1, respectively) than conformer **A**, and the same holds true for the 3,3′ dianion (see Table V). In contrast, the stability of conformer **A** of the 2,2′ dianion strongly decreases, its energy being only 4.9 (INDO) and 2.4 kcal/mol (AM1) lower than that of conformer **B**. The different values obtained by both semiempirical methods may be explained by the known fact that the AM1 method understimates the vicinal lone-pair repulsion.[20] Such a change in conformational preferences of the 2,2′ dianion could be attributed to the repulsion between the two negatively charged oxygens atoms closer in conformer **A** than in **B**.[16] This repulsion may not be expected for the 3,3′ dianion because the distances between the oxygen atoms in both conformations are similar and higher than in the 2,2′ dianion. However, other factors, probably stereoelectronic in origin, may not be completely excluded since monoalkylation in positions 2 or 2′, or dialkylation in both with ethylene glycol derivatives, seems to cause a conformational change of the trehalose moiety as indicated by NOE experiments.

The observed conformational change in the disaccharidic structure of macrocycles 7 and 8 constitutes a case in which one of the glycosidic angles violates the generally holding exo anomeric effect.[8]

The synthesis of the conformer **A** of 7 by a stepwise strategy is now being attempted in our laboratory. Attempts to crystallize macrocycle 7 and the synthesis of mono-*trehalo*-2,2′-crown ethers where the length of the polyethylene glycol chain will allow the interconversion between the two possible isomers are underway.

Experimental Section

General Procedures. Cyclization reactions were carried out under argon and in rigorously anhydrous conditions. TLC was performed on aluminium sheets coated with silica gel 60 F_{254} (Merck) with detection by charring with sulfuric acid. NMR spectra were recorded at 30 °C in $CDCl_3$. The bidimensional experiments were recorded at 300 MHz with matrix data of 256 × 1K. Samples for both NOEDIFF and NOESY experiments were prepared after degasification under argon. The NOEDIFF experiments were performed in the steady-state conditions (preirradiation time 5–7 s). The 2D-COSY experiments used the pulse sequence 90°-t_1-90° acquisition and/or 90°-t_1-90°-90° acquisition. The NOESY experiments were performed in phase-sensitive mode and used the pulse sequence 90°-t_1-90°-t_m-90° acquisition with a mixing time t_m of 0.5–1 s. The characteristics of the X-ray analysis, the final atomic coordinates, structure factors, thermal components and hydrogen parameters are given as supplementary material.[12] Crystals suitable for X-ray investigation were grown by slow diffusion of hexane in a solution of 1 in ethyl acetate. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. The FAB mass spectra were obtained in a nitrobenzyl alcohol matrix with a MS-50 Kratos instrument fitted with a 1.2 T magnet using a FAB 11 WF Ion Tech atom gun and with a ZAB instrument.

Cyclization Reactions. A solution of the diol precursor (0.6 mmol) in dry THF (40 mL) was added under argon atmosphere to a suspension of potassium hydroxide (10 equiv) in THF (2 mL), and the mixture was heated at 70 °C for 30 min. A solution of tetraethylene glycol ditosylate (1.5 equiv) in dry THF (15 mL) was added dropwise during 3 h. The stirring and heating were

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continued for 10–24 h (TLC). After being cooled, the mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (hexane:acetone = 7:3).

Mono- and Bis-*trehalo*-3,3′-tetraethylene Glycol (1 and 3). A solution of 2,2′-di-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (10;[9] 431 mg, 0.167 mmol) in dry THF (40 mL) was treated with KOH (760 mg, 13.6 mmol) in THF (2 mL) and then with a solution of tetraethylene glycol ditosylate (465 mg, 0.926 mmol) as described previously. Column chromatography (hexane:acetone = 7:3) of the residue eluted first the **mono-*trehalo*-3,3′-tetraethylene glycol** (1; 80 mg, 0.093 mmol, 15%) as a white solid: mp 132 °C; $[\alpha]_D$ 61° (*c* 0.47, chloroform); ^{1}H NMR see Table I; ^{13}C NMR δ 138.3 (C ipso), 137.6 (C ipso), 128.7–126.2 (Ar), 101.3 (PhCH), 94.2 (C1), 82.0, 79.2, 78.1, 73.7, 72.5, 71.0, 70.6, 68.9, 63.0 (C6); FAB-MS *m/z* 879 $(M + Na)^+$. Anal. Calcd for $C_{48}H_{56}O_{14}$: C, 67.27; H, 6.59. Found: C, 67.29; H, 6.63.

Further elution gave **bis-*trehalo*-3,3′-tetraethylene glycol** (3; 110 mg, 0.064 mmol, 10%) as a syrup: $[\alpha]_D$ 48.4° (*c* 0.31, chloroform); ^{1}H NMR see Table I; ^{13}C NMR (C_6D_6) δ 139.11 (C ipso), 138.4 (C ipso), 129.8–126.8 (Ar), 101.7 (PhCH), 94.5 (C1), 82.8, 79.6, 79.1, 74.3, 72.3, 71.1, 70.9, 70.6, 69.2, 68.7, 63.3; ($CDCl_3$) 138.2, 137.5, 129.8–126.2, 101.4, 94.5, 81.9, 79.1, 78.4, 73.9, 71.4, 70.6, 70.5, 70.2, 68.9, 62.9; FAB-MS *m/z* 1713 $(M)^+$, 1736 $(M + Na)^+$. Anal. Calcd for $C_{96}H_{112}O_{28}$: C, 67.27; H, 6.59. Found: 67.30; H, 6.62.

Mono-*trehalo*-2,3′-tetraethylene Glycol (5). A solution of 3,2′-di-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (11;[9] 70 mg, 0.1 mmol) in dry THF (12 mL) was treated with KOH (123 mg, 2.2 mmol) in THF (1 mL) and then with tetraethylene glycol ditosylate (75.5 mg, 0.15 mmol) as described previously. Column chromatography (hexane:acetone = 7:3) of the residue gave the **mono-*trehalo*-2,3′-ethylene glycol** (3; 46.6 mg, 43%) as a syrup: $[\alpha]_D$ 56.0° (*c* 1.2, chloroform); ^{1}H NMR see Table I; ^{13}C NMR δ 138.2, 137.5, 134.4, 128.9–125.5, 101.2 (double intensity, PhCH), 92.4 (double intensity, C1), 82.5, 81.9, 80.0, 78.7, 75.1, 73.1, 71.5, 71.3, 70.9, 70.3 (double intensity), 70.3 (double intensity), 70.1 (double intensity), 69.7, 69.0, 63.5, 62.8; FAB-MS *m/z* 879 $(M + Na)^+$. Anal. Calcd for $C_{48}H_{56}O_{14}$: C, 67.27; H, 6.59. Found: C, 67.30; H, 6.62.

Mono-*trehalo*-2,2′-tetraethylene Glycol (7). A solution of 3,3′-di-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (12;[9] 170 mg, 0.24 mmol) in dry THF (21 mL) was treated with KOH (300 mg, 5.5 mmol) and then with tetraethylene glycol ditosylate (183 mg, 0.365 mmol) as described previously. Column chromatography (hexane:acetone = 7:3) of the residue gave the **mono-*trehalo*-2,2′-tetraethylene glycol** (7; 100 mg, 70%) as a syrup: $[\alpha]_D$ 44° (*c* 1.33, chloroform); ^{1}H NMR see Table I; ^{13}C NMR δ 138.2, 136.7, 127.7–125.1 (Ar), 100.2 (PhCH), 99.4 (C1), 84.3, 81.2, 77.7, 74.0, 73.5, 71.8, 69.5, 68.4, 61.5; FAB-MS *m/z* 879 $(M + Na)^+$. Anal. Calcd for $C_{48}H_{56}O_{14}$: C, 67.27; H, 6.59. Found: C, 67.31; H, 6.63.

General Method of Deprotection. The protected macrocycle (1, 3, 5, or 7, 0.1 mmol) was dissolved in 10 mL of methanol–ethyl acetate (9:1). A catalytic amount of Pd/C and two drops of acetic acid were added, and the mixture was hydrogenated under pressure (40 psi) for 15–28 h. The suspension was filtered, washed, and evaporated to dryness. The residue was purified by column chromatography (chloroform–methanol).

Preparation of Mono-*trehalo*-3,3′-tetraethylene Glycol (2). Following the general method of deprotection, 90 mg (0.105 mmol) of 1 were dissolved in methanol–ethyl acetate (9:1, 10 mL). The mixture was hydrogenated for 15 h. Compound 2 was obtained in 60% yield (30 mg, 0.06 mmol) as a syrup and purified by column chromatography (chloroform:methanol = 2:1): $[\alpha]_D$ +10 (*c* 0.1, MeOH); ^{1}H NMR (D_2O) δ 5.18 (d, *J* = 12 Hz, H1), 4.13 (m, Etg), 3.97 (t, H3), 4.00–3.94 (m, Etg), 3.85 (m, H5), 3.80 (m, Etg), 3.65 (dd, H2), 3.47 (t, H4); ^{13}C NMR (D_2O) δ 94.1 (C1), 84.4 (CH), 73.9 (CH), 73.6 (CH_2), 73.3 (CH_2), 72.7 (double intensity, CH), 71.09 (CH_2), 61.7 (C6). Anal. Calcd for $C_{20}H_{36}O_{14}$: C, 47.88; H, 7.25. Found: C, 48.02; H, 7.45.

Preparation of Bis-*trehalo*-3,3′-tetraethylene Glycol (4). Following the general method of deprotection, 153 mg (0.09 mmol) of 3 were dissolved in methanol–ethyl acetate (20 mL, 9:1). The mixture was hydrogenated for 48 h. Compound 4 was obtained in 65% yield (58 mg, 0.058 mmol) as a syrup and purified by column chromatography (chloroform:methanol = 7:4): $[\alpha]_D$ +75° (*c* 0.05, methanol); ^{1}H NMR (DMSO-d_6) δ 4.87 (d, H1), 4.85 (d, OH4), 4.66 (d, OH2), 4.37 (broad singlet, OH6), 3.85–3.56 (m, Etg), 3.64 (m, H5), 3.60–3.30 (m, Etg, H6ab), 3.52 (t, H3), 3.30 (dd, H2), 3.22 (t, H4); ^{13}C NMR (DMSO-d_6) δ 92.7 (C1), 82.3, 72.4, 71.0, 70.7, 70.0, 69.7, 69.6, 69.4, 60.5. Anal. Calcd for $C_{40}H_{72}O_{28}$: C, 47.98; H, 7.25. Found: C, 48.15; H, 7.70.

Preparation of Mono-*trehalo*-3,2′-tetraethylene Glycol (6). Following the general method of deprotection, 150 mg (0.175 mmol) of 5 were dissolved in methanol–ethyl acetate (9:1, 20 mL). The mixture was hydrogenated for 24 h. Compound 6 was obtained in 94% yield (80 mg, 0.16 mmol) as a syrup and purified by column chromatography (chloroform:methanol = 2:1): $[\alpha]_D$ +108° (*c* 0.19, methanol); ^{1}H NMR (D_2O) δ 5.41 (d, H1), 5.16 (d, H1′), 4.11–3.58 (m), 4.07 (t, H3), 3.45 (dd, H2′); ^{13}C NMR (D_2O) δ 95.3 (C1), 92.5 (C1′), 89.6, 82.1, 75.4, 75.1, 74.6, 74.5, 74.4, 74.2, 73.1, 72.5 (double intensity), 72.3, 72.1 (3 carbons), 61.5 (double intensity). Anal. Calcd for $C_{20}H_{36}O_{14}$: C, 47.98; H, 7.25. Found: C, 47.38; H, 7.00.

Preparation of Mono-*trehalo*-2,2′-tetraethylene Glycol (8). Following the general method of deprotection, 250 mg (0.292 mmol) of 7 were dissolved in methanol–ethyl acetate (9:1, 20 mL). The mixture was hydrogenated for 24 h. Compound 8 was obtained in 81% yield (119, 0.23 mmol) as a syrup and purified by column chromatography (chloroform:methanol = 2:1): $[\alpha]_D$ +100° (*c* 0.35, methanol); ^{1}H NMR (D_2O) δ 5.83 (d, H1), 4.12 (m, Etg), 3.87 (m, H5), 3.81 (m, Etg), 3.73 (t, H3), 3.66 (m, H6ab, Etg), 3.60 (m, Etg), 3.48 (t, H4), 3.24 (dd, H2); ^{13}C NMR (D_2O) δ 100.2 (C1), 84.5, 74.6, 73.7, 73.2, 72.9, 71.6, 70.9, 70.8, 61.4. Anal. Calcd for $C_{20}H_{36}O_{14}$: C, 47.98; H, 7.25. Found: C, 48.20; H, 7.62.

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Supplementary Material Available: Tables of atomic coordinates, isotropic thermal parameters, bond distances and angles and X-ray crystallographic data for compound 1 (19 pages); observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.