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Macrocyclic derivatives with a sucrose scaffold: insertion of a long polyhydroxylated linker between the terminal 6,6′-positions†

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A series of five new macrocyclic hybrids with a sucrose scaffold were prepared by the reaction of activated 1′,2,3,3′,4,4′-hexa-*O*-methylsucrose with diversely functionalized D-mannitols. The 21-, 25-, and 31-membered representatives containing mannitol units were prepared by a macrocyclization of 6,6′-di-*O*-propargylated sucrose with protected 1,6-diazido-D-mannitol or 6,6′-di-azidosucrose with propargylated D-mannitol (a "click" approach), whereas 23-membered representatives were prepared by double *N*-alkylation of 1′,2,3,3′,4,4′-hexa-*O*-methyl-6,6′-di-aminosucrose with 1,6-di-bromoacyl D-mannitol. All sucrose derivatives were tested as putative hosts for chiral recognition of α-phenylethylammonium (α-PEA) cations. In one case, in striking contrast to all sucrose-based macrocyclic hosts previously reported by us, unexpected reverse preference for the R-enantiomer was observed (K_R/K_S = 1.5).

Introduction

Carbohydrates are important platforms for the preparation of a broad array of functionalized chiral crown, aza-, and thia-crown ethers and their analogs.[1,2] Monosaccharides are mostly used,[3] however, as such chiral scaffolds, whereas application of disaccharides is much less explored.[4]

During our studies on the preparation of functional materials from simple carbohydrates, we turned our attention to chiral crown and aza-crown ethers[5] incorporating the most common disaccharide – sucrose (Fig. 1, type **I**).

We observed that these relatively simple 16- and 19-membered macrocyclic systems could be employed for the demanding enantioselective recognition of chiral ammonium cations.[6] We have prepared also larger macrocyclic structures bearing one (*e.g.* **II**, Fig. 1)[7] or two sucrose units (**III**, Fig. 1).[8,9] Recently we have reported a new type of a 21-membered macrocyclic sucrose diamide (Fig. 1, type **III**) in which the terminal positions of this disaccharide are linked *via* a longer polyhydroxylated-bridge.[10]

In this paper we extend our studies to the synthesis of a series of five structurally related derivatives with the macrocyclic cavity ranging from 21 to 31 atoms. In addition, enantiodiscriminating properties of these macrocycles towards model phenylethyl ammonium (α-PEA) cations were also examined.

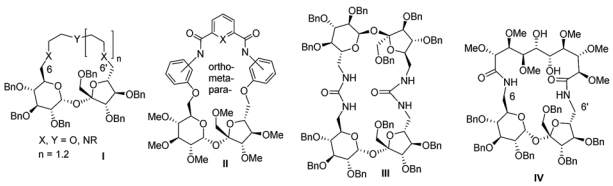

Fig. 1 Examples of the macrocyclic hosts incorporating a sucrose backbone developed in our group.

Results and discussion

Although most of the macrocyclic sucrose-derivatives prepared by us to date were built on benzylated sucrose, in this study we decided to employ their per-methylated analogues. The *O*-methyl protection offers lower molecular weight, reduced steric hindrance, and increased stability under a range of conditions (*e.g.* catalytic hydrogenation) as compared to benzyl protection. In addition, the ^{1}H NMR spectra of targeted macrocyclic products would be less complex; hence determination of their complexation properties by ^{1}H NMR titration experiments should be facilitated, in particular with the guest molecules containing protons resonating at 6–8 ppm.

Hexa-*O*-methyl-sucrose **1** and its di-amino analog **3** were thus chosen as suitable disaccharide backbones (Scheme 1).

Compound **1** was prepared as described previously[11] (Scheme 1, conditions a), whereas new diamine synthon **3** was prepared from free sucrose in the four-step synthesis, involving: selective chlorination under Appel conditions,[12] S_N2-type substitution of both chlorine atoms with sodium azide, methylation of the remaining free hydroxyl groups, and

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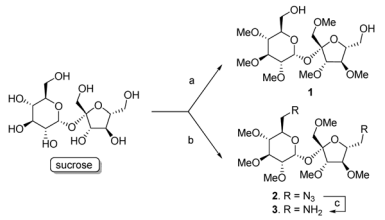


Scheme 1 Synthesis of sucrose intermediates **1–3**; conditions: (a) 1. TrCl, py; 2. MeI, KOH, TBAB, DMF; 3. Na, NH_3/THF, see ref. 11; (b) 1. PPh_3, CCl_4, py; 2. NaN_3, DMF; 3. MeI, KOH, TBAB, DMF; 4. H_2, Pd/C, MeOH.

subsequent hydrogenation of the azide groups (Scheme 1, conditions b).

Synthesis of sucrose macrocycles by azide–alkyne cycloaddition

From a variety of possible ways to link both terminal positions of glucose and fructose units (C6 and C6′), the 'click' approach was chosen. It was based on the reaction of di-azido-sucrose **2** with appropriate di-propargylic linkers: **4**, **6**, and **10** or the reaction performed in a reverse manner (the appropriate propargylic sucrose derivative and azido linker).

The model reaction of diazide **2** with *O*-propargylated derivative of D-mannitol **4** [13] allowed preparing macrocyclic sucrose-triazole-mannitol hybrid **5** in a satisfactory 28% yield (Scheme 2).

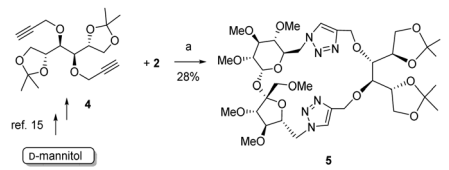
This encouraging result prompted us to perform a more detailed study on the preparation of other sucrose-containing macrocycles by this 'click' approach. The required propargylated intermediates **6** and **10**, as well as azide **9**, were obtained from hexa-*O*-methyl-sucrose **1** and tetra-*O*-methyl-D-mannitol **7** [14] as shown in Scheme 3.

Finally, the reaction between *O*-propargylated D-mannitol **10** and sucrose-azide **2** under the 'click' conditions, provided macrocycle **11** in 34% yield, while the reverse reaction between *O*-propargylated sucrose **6** and D-mannitol azide **9** furnished **12** in a 26% yield (Scheme 4).

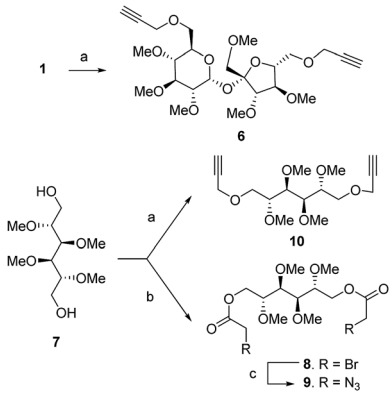
Synthesis of sucrose macrocycles by *N*-alkylation

Two macrocyclic hosts: **16** and **17** containing the amide and ester motifs were synthetized by the reaction of sucrose diamine **3** with the corresponding linker **8** or its nitrogen analog **15** (Scheme 5).

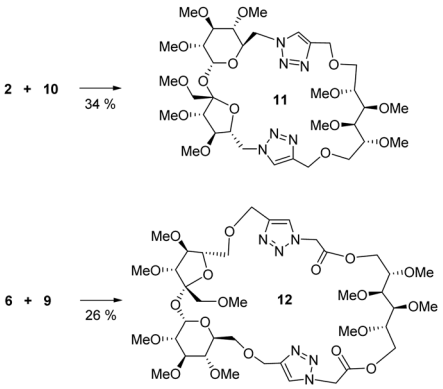
The required dibromo-linker **15** was readily prepared from diol **7** by an activation of both hydroxyl groups (as mesylates), the S_N2-type substitution with sodium azide, and subsequent hydrogenation to amines which were subjected to the reaction with bromoacetyl bromide. The macrocyclization between diamine **3**



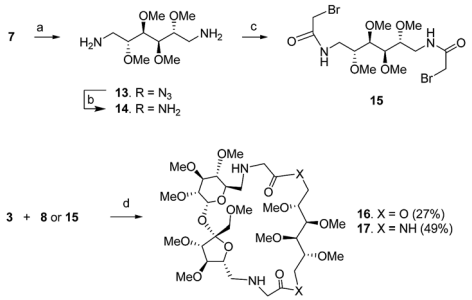
Scheme 2 Synthesis of the 21-membered sucrose-triazole-mannitol hybrid **5**; conditions: (a) $CuSO_4{\cdot}H_2O$, sodium ascorbate, *t*-BuOH/CH_2Cl_2/H_2O, 4 : 1 : 1 (v/v/v).



Scheme 3 Synthesis of acyclic sugar intermediates **6**, **8** and **9**, conditions: (a) propargyl bromide, KOH, TBAB DMF (65% for **6** and 69% for **10**); (b) $BrCH_2COBr$, K_2CO_3, CH_2Cl_2, 80%; (c) NaN_3, DMF, 65%.



Scheme 4 Synthesis of the 25- and 31-membered sucrose-triazole-mannitol hybrids **11** and **12**, respectively; conditions: (a) $CuSO_4{\cdot}H_2O$, sodium ascorbate, *t*-BuOH/CH_2Cl_2/H_2O, 4 : 1 : 1 (v/v/v).



Scheme 5 Synthesis of 23-membered sucrose-amide-mannitol hybrids **16** and **17**; conditions: (a) 1. MsCl/pyridine; 2. NaN_3; (b) Pd/C/H_2, MeOH; (c) $BrCH_2COBr$, DMAP, Et_3N, CH_2Cl_2, (65% over two steps); (d) DIPEA, MeCN.

and dibromide **8** performed in MeCN under high dilution conditions afforded macrocycle **16** in 27% yield. The analogous process carried out for compounds **3** and **15** furnished the corresponding macrocycle **17** in 49% yield. The near two times higher yield of the cyclization observed for **17**, as compared to **16**, suggests some kind of preorganization effect that favors the ring-closing in the former case. Presumably, the amide groups, which – in contrast to ester groups – are both hydrogen-bond

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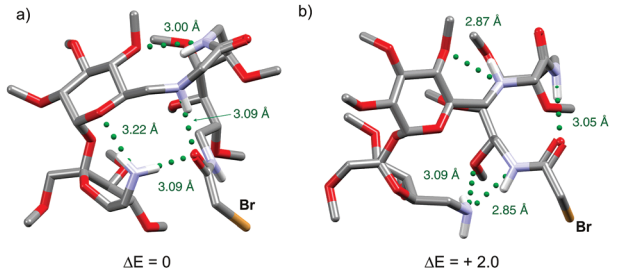

Fig. 2 The lowest-energy structures of the linear intermediate exemplifying facilitation of the ring-closure step by intramolecular hydrogen bonds; non-acidic protons have been omitted for clarity; energies are given in kcal mol^{-1}.

donors and acceptors, preorganize the linear intermediate as very recently observed for C_2-symmetric macrocyclic urea-sucrose derivatives.[9] This assumption is supported by DFT calculations (B3LYP-D3/6-31G(d)/C-PCM/MeCN, see Experimental section for details) which suggest that both amide groups actively participate in folding of the linear intermediate, hence facilitating the ring-closure step over oligomerization (Fig. 2).

Chiral recognition properties of sucrose-derived hosts

With macrocyclic hosts in hand we aimed to test their recognition properties toward a model chiral cationic guest, *i.e.* hydrochloride salt of 1-phenylethylamine (α-PEA).[15] We noticed, however, that addition of either the S- or R-enantiomer of α-PEA does not cause any significant changes of the chemical shifts in the NMR spectra of macrocycles: **5**, **11**, **12**, and **16** in $CDCl_3$. This experimental observation, surprisingly for us, indicates that these macrocyclic host molecules are unable to form sufficiently strong complexes with protonated α-PEA.

Comparison of the structures of hosts: **5**, **11**, **12**, and **16** with structurally related aza-crown hosts of type **I** (see Fig. 1) suggests that the macrocyclic cavity is too big to accommodate the α-PEA guest. In addition, good chiral recognition properties of sucrose-macrocycles reported earlier might result from the additional dispersion interaction between aromatic rings originating from the sugar *O*-benzyl protection and phenyl ring of the α-PEA guest, respectively. Moreover, the presence of triazole and ether groups in hosts **5**, **11**, and **12** introduces additional steric hindrance which might inhibit the binding of the guest within the macrocyclic cavity.

Fortunately, a considerable change of the chemical shift of an anomeric proton of sucrose was observed upon addition of 2.2 equiv. of chloride salt of either R- or S-α-PEA to a $CDCl_3$ solution of host **17** (Fig. 3).

The non-linear curve fitting algorithm (as implemented in HypNMR software)[16] allowed us to determine the following association constants for the 1 : 1 (host : guest) complexes of **17** with S-α-PEA (K_a = 79 ± 7 M^{-1}) and R-α-PEA (K_a = 119 ± 9 M^{-1}), respectively. This data indicates that host **17** exhibits a moderate preference toward the R-enantiomer of α-PEA ($K_{a,R}/K_{a,S}$ = 1.50 ± 0.24) (see Fig. 4a).

The validity of an assumed 1 : 1 binding model was confirmed by a random distribution of residuals, whereas a Job plot suggests a higher binding stoichiometry (Fig. 4b). The latter

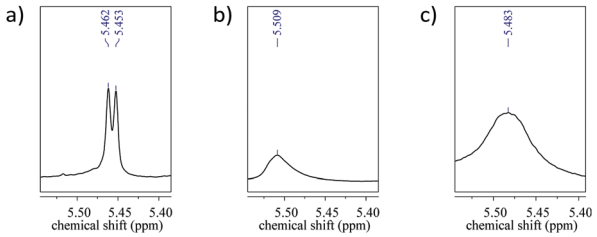

Fig. 3 Part of the ^{1}H NMR spectra of host **17** and its complexes with 2.2 equiv. of α-PEA-HCl in $CDCl_3$: free **17** (a), **17** + S-α-PEA-HCl (b), and **17** + R-α-PEA-HCl (c).

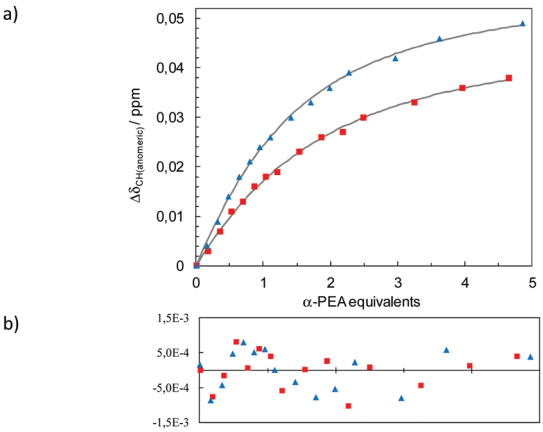

Fig. 4 Experimental chemical shift changes of the anomeric proton (a) and distribution of residual errors (b) for titration of host **17** with hydrochloride of S-α-PEA (red squares) and R-α-PEA (blue triangles) in $CDCl_3$ at 303 K; calculated binding isotherms (gray lines).

method is now, however, recognized as out-dated and erroneous, in particular for the analysis of host–guest complexes with moderate stability, such as observed here.[17]

To further test the recognition properties of host **17** towards α-PEA cations we conducted ESI-MS and computational studies (Fig. 5).

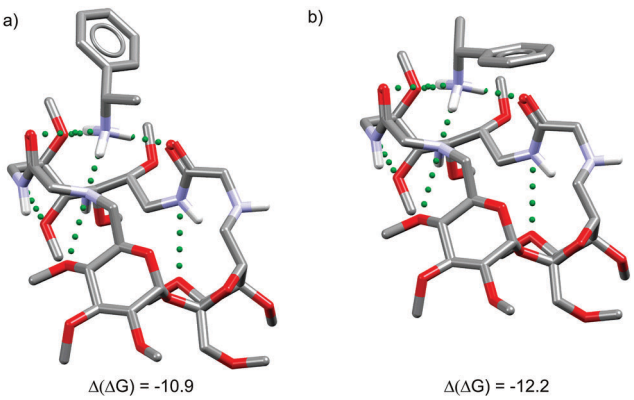

Fig. 5 Energy-minimized structures of complexes of host **17** with S-α-PEA (a) and R-α-PEA (b) calculated at the DFT/B3LYP-D3/6-31G(d)/C-PCM:$CHCl_3$ level of theory; non-acidic protons have been omitted for clarity; binding energies of complexes ($\Delta(\Delta(G) = \Delta G_{complex} - (\Delta G_{host} + \Delta G_{a\text{-}PEA+})$) are given in kcal mol^{-1}.

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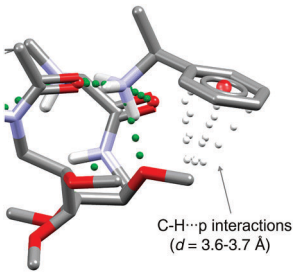

Fig. 6 Exemplification of the CH···π interactions in the **17**⊃S-α-PEA complex.

Seemingly, in the positive (+) ion mode, we were unable to observe the signals corresponding to the complexes of **17** with R- and S-enantiomers of α-PEA. This might indicate that under ESI-MS experimental conditions (high dilution of the sample in competitive methanol used as the carrier solvent) these complexes are at the undetectable level since in considerably less polar and competitive $CDCl_3$ the K_as derived from the ^{1}H NMR titration experiments are rather small.

Nevertheless, in line with the titration experiments in solution, the DFT calculations suggest a preference for the R- over S-enantiomer of α-PEA ($\Delta(\Delta G) = -12.2$ *vs.* -10.9 kcal mol^{-1}). The energy-minimized structures of both complexes demonstrate a similar binding mode in which the guest molecule is bound above the macrocyclic cavity by three $O_{host}\cdots$H–N (d = 2.75–2.87 Å) and one $N_{host}\cdots$H–N (d = 3.00 Å) hydrogen bonds, respectively (Fig. 5). In addition, in both cases the conformation of the complex is stabilized by three albeit rather weak intramolecular hydrogen bonds (d = 2.91–3.25 Å).

The analysis of the complex of **17** with S-α-PEA indicates that one OMe group from a mannitol linker and a phenyl ring from a PEA guest are positioned in close proximity. This, in turn, might generate a steric hindrance resulting in a lower stability of a complex, as compared to the R-α-PEA guest in which the phenyl ring is positioned above a macrocyclic cavity (Fig. 6).

Conclusion

We have prepared five new macrocyclic hosts with a sucrose scaffold in which the terminal positions of the disaccharide are connected *via* a mannitol bridge of various lengths. Only one 21-membered host, bearing two amide groups (**17**), has shown complexing ability towards α-PEA cations, the model chiral ammonium guest. In striking contrast to all sucrose-based macrocyclic hosts previously prepared by us, this host shows the unexpected reverse preference for the R-enantiomer of α-PEA (K_R/K_S = 1.5 in $CDCl_3$).

Experimental section

Materials and methods

NMR spectra were recorded in $CDCl_3$, DMSO-d_6, acetone-d_6, and benzene-d_6 with a Varian AM 500 or AM-600 spectrometer at 303 K. Chemical shifts (δ) are reported in ppm as relative to TMS (δ 0.00) for ^{1}H NMR spectra and residual solvent ($CDCl_3$: δ 77.23; DMSO-d_6: δ 39.51; acetone-d_6: δ 206.7; benzene-d_6: δ 128.4) for the ^{13}C NMR spectra. All resonances for the carbon skeletons were assigned by COSY (^{1}H–^{1}H), HSQC (^{1}H–^{13}C), and HMBC (^{1}H–^{13}C) correlations. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or ABCR, and were used without purification. Hexanes (65–80 °C fraction from petroleum) and EA were purified by distillation. TLC was carried out on silica gel 60 F254 (Merck). Chromatography was performed on Buchi glass columns packed with silica gel 60 (230–400 mesh, Merck), or GraceResolv™ (40 μm) columns and Reveleris® from GRACE. Specific rotation was measured with a Jasco DIP-360 digital polarimeter for solutions in CH_2Cl_2 ($c \sim 0.5$ M) at rt.

DFT calculations

All calculations were performed using the Spartan'16 Parallel Suite[18] program at the B3LYP-D3/6-31G(d) level of theory. The C-PCM implicit solvent model was used to simulate the MeCN or $CHCl_3$ environment. A DFT functional with dispersion (B3LYP-D3)[19] was chosen for a better description of noncovalent interactions. The detailed calculation procedure is similar to that described in ref. 20.

General procedure A for macrocyclization *via* 1,3-dipolar cycloaddition. The corresponding di-azide (0.4 mmol) was dissolved in a mixture of solvents: *t*-BuOH : CH_2Cl_2 : H_2O (4 : 1 : 1, v/v/v) to make a final concentration of 0.01 M. To this solution were added $CuSO_4{\cdot}5H_2O$ (0.8 mmol, 2 equiv.) and sodium ascorbate (1.6 mmol, 1.4 equiv.). The di-propargyl partner (0.4 mmol) in the same mixture of solvents (c = 0.01 M) was then added dropwise within 2 h and the reaction was stirred for an additional 12 h at rt. After this time the solvent was evaporated under vacuum and the crude product was purified by column chromatography.

General procedure B for macrocyclization *via* double *N*-alkylation. To a solution of diamine **3** (170 mg, 0.4 mmol, 1 equiv.) in ACN (40 mL, c = 0.01 M) was added DIPEA (4.2 equiv.), followed by dropwise addition of a solution of either dibromide **8** or **15** (0.4 mmol, 1 equiv.) in ACN (40 mL, c = 0.01 M) over 1 h. The reaction was then stirred for 18 h at 60 °C and the solvent was evaporated under vacuum yielding the crude product as an oil which was purified by column chromatography.

Synthesis of 1,6-dipropargyl-2,3,4,5-tetra-*O*-methyl-D-mannitol (10). To a solution of **7** (650 mg, 2.73 mmol, 1 equiv.) and propargyl bromide (0.35 mL, 3 equiv.) in toluene (40 mL), was added 50% aqueous NaOH (30 mL) followed by TBAB (50 mg). The heterogeneous mixture was vigorously stirred for 4 h at rt. Then it was partitioned between water (50 mL) and ether (30 mL). The layers were separated, and the aqueous one extracted with ether (2 × 20 mL). Combined organic solutions were washed with water (30 mL) and brine (30 mL), dried and concentrated, and the crude product was purified by column chromatography (hexanes : EA, 1 : 1 v/v) to give **10** (592 mg, 69%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (dd, J = 2.4, 1.8 Hz, 4H), 3.93 (dd, J = 10.7, 2.4 Hz, 2H), 3.70 (dd, J = 10.7, 4.0 Hz, 2H), 3.58 (dt, J = 1.9, 1.2 Hz, 2H), 3.51 (dd, J = 5.3, 4.3 Hz, 2H), 3.49 (s, 6H), 3.43 (s, 6H), 2.44 (t, J = 2.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.66, 79.62,

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79.01, 74.54, 67.20, 60.60, 58.41, 56.92. HR-MS ESI (*m*/*z*): calc. for [M($C_{16}H_{26}O_6$) + Na^+]: 337.1627, found: 337.1629. Anal.: calc. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.24; O, 30.53, found: 61.03, H 8.16. $[\alpha]_{20}$ = +5.7. IR (film): 3453, 2938, 2833, 2115, 1724, 1643, 1464, 1446, 1137, 1220, 1186, 1104, 848, 770, 665, 639, 507 cm^{-1}.

1,6-Di-*O*-(2-bromoacetyl)-2,3,4,5-tetra-*O*-methyl-D-mannitol (8). To a stirred solution of **7** (185 mg, 0.78 mmol, 1 equiv.) in CH_2Cl_2 (15 mL) containing powdered K_2CO_3 (430 mg, 3.12 mmol, 4 equiv.), bromoacetyl bromide (0.35 mL, 2.34 mmol, 3 equiv.) was added dropwise within 15 min and the mixture was stirred for 18 h at rt. Then, it was partitioned between 10% citric acid (50 mL) and CH_2Cl_2 (30 mL), the layers were separated, and the aqueous one extracted with CH_2Cl_2 (2 × 15 mL). Combined organic solutions were washed with H_2O (30 mL) and brine (30 mL), dried and concentrated, and the crude product was purified by column chromatography using a gradient of hexanes and EA (1 : 0 → 1 : 1 v/v) to afford **8** (296 mg, 80%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (dd, J = 12.2, 2.2 Hz, 1H), 4.18 (dd, J = 12.2, 3.4 Hz, 1H), 3.90 (d, J = 1.7 Hz, 2H), 3.59–3.55 (m, 1H), 3.52 (dd, J = 8.2, 3.0 Hz, 1H), 3.49 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.07, 78.78, 78.08, 62.84, 60.80, 57.11, 25.65. HR-MS ESI (*m*/*z*): calc. for [M($C_{14}H_{24}Br_2O_8$) + Na^+]: 500.9736, found: 500.9730. Anal.: calc. for $C_{14}H_{24}Br_2O_8$: C, 35.02; H, 5.04; Br, 33.28, found: C, 35.04; H, 5.04; Br, 33.13. $[\alpha]_D$ = +27.0. IR (film): 3501, 2939, 2833, 1739, 1460, 1424, 1365, 1336, 1284, 1184, 1171, 1111, 1090, 1023, 937, 890, 849, 713, 665, 621, 548, 512 cm^{-1}.

1,6-Di-*O*-(2-azido-acetyl)-2,3,4,5-tetra-*O*-methyl-D-mannitol (9). To a solution of dibromide **8** (135 mg, 0.28 mmol, 1 equiv.) in DMF (5 mL) NaN_3 (55 mg, 0.84 mmol, 3 equiv.) was added and the mixture was stirred for 2 h at rt. It was then partitioned between water (15 mL) and ether (15 mL), the layers were separated, and the aqueous one extracted with ether (2 × 10 mL). Combined organic solutions were washed with water (30 mL) and brine (30 mL), dried and concentrated, and the crude product was purified by column chromatography (hexanes : EA, 1 : 1 v/v) to afford **9** (74 mg, 65%) as a transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.92 (dd, J = 12.2, 2.2 Hz, 1H), 4.17 (dd, J = 12.2, 3.1 Hz, 1H), 3.94 (d, J = 2.4 Hz, 2H), 3.54 (d, J = 8.4 Hz, 1H), 3.51 (ddd, J = 8.3, 3.0, 2.3 Hz, 1H), 3.48 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.13, 78.68, 77.95, 62.06, 60.75, 57.02, 50.36. HR-MS ESI (*m*/*z*): calc. for [M($C_{14}H_{24}N_6O_8$) + Na^+]: 427.1553; found: 427.1540. Anal.: calc. for $C_{14}H_{24}N_6O_8$: C, 41.57; H, 5.98; N, 20.78, found: C, 41.58; H, 5.91; N, 20.55. $[\alpha]_{20}$ = +23.7. IR (film): 2981, 2938, 2835, 2108, 1747, 1460, 1426, 1367, 1346, 1292, 1239, 1190, 1112, 1089, 1038, 1023, 944, 839, 771, 733, 648, 553, 512 cm^{-1}.

1,6-*N*-di-(2-bromoacetylo)-2,3,4,5-tetra-*O*-methyl-D-mannitol (15)

This reaction was carried out under Ar atmosphere. To a stirred and cooled to −78 °C solution of 1,6-diamino-2,3,4,5-tetra-*O*-methyl-D-mannitol **14** (120 mg, 0.52 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) containing DMAP (3 mg) and Et_3N (0.151 mL, 1.08 mmol, 2.1 equiv.), bromoacetyl bromide (0.092 mL, 1.06 mmol, 2.06 equiv.) was added dropwise within 1 h. The cooling bath was removed and the solution was stirred until all starting material disappeared (TLC monitoring in hexanes : ethyl acetate, 3 : 1). Water (10 mL) and saturated $NaHCO_3$ solution (10 mL) were added, the layers were separated, and the aqueous one extracted with CH_2Cl_2 (2 × 10 mL). Combined organic solutions were washed with H_2O (30 mL) and brine (30 mL), dried and concentrated, and the product was purified by column chromatography (hexanes : EA, 4 : 1 to 100% EA) to give **15** (170 mg, 0.35 mmol, 69%) as a transparent oil. ^{1}H NMR (600 MHz, C_6D_6) δ 6.67 (s, 2H), 3.60–3.55 (m, 2H), 3.45 (dd, J = 3.8, 1.4 Hz, 2H), 3.41 (s, 6H), 3.39 (s, 4H), 3.34 (td, J = 5.0, 1.2 Hz, 2H), 3.12 (s, 6H). ^{13}C NMR (150 MHz, C_6D_6) δ 164.89, 81.11, 79.36, 60.42, 56.47, 38.69, 28.97. MS (ESI): calcd for *m*/*z* = 499.0055 [M($C_{14}H_{26}N_2O_6Br_2$) + Na^+]; found: 499.0048 [M($C_{14}H_{26}N_2O_6Br_2$) + Na^+]; anal. calcd for $C_{14}H_{26}N_2O_6$: C, 35.17; H, 5.48; N, 5.86; Br, 33.42. Found: C, 35.18; H, 5.66; N, 5.90; Br, 33.45. $[\alpha]_{20}$ = −19.0; IRr (film) = 3076, 2980, 2935, 2830, 1657, 1538, 14 62, 1442, 1333, 1302, 1211, 1188, 1105, 1008, 886, 845, 754, 697, 664, 545 cm^{-1}.

Synthesis of 6.6′-di-*O*-propargyl-2,3,4,1′,3′,4′-hexa-*O*-methyl-sucrose (6). To a solution of 1′,2,3,3′,4,4′-hexa-*O*-methylsucrose (**1**; 628 mg, 1.47 mmol, 1 equiv.) in toluene (15 mL) containing TBAB (50 mg), aqueous 50% NaOH was added followed by propargyl bromide (0.35 mL, 4.41 mmol, 3 equiv.), and the mixture was vigorously stirred for 6 h at rt. Then it was partitioned between water (15 mL) and Et_2O (15 mL), the layers were separated, and the aqueous one extracted with Et_2O (2 × 10 mL). Combined organic solutions were washed with H_2O (30 mL) and brine (30 mL), dried and concentrated, and the product was purified by column chromatography (100% hexane to hexanes : EA, 1 : 1 v/v) to give **6** (480 mg, 0.96 mmol, 65%) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.54 (d, J = 3.7 Hz, 1H), 4.28 (dd, J = 15.9, 2.4 Hz, 1H), 4.24 (dd, J = 15.9, 2.4 Hz, 1H), 4.20 (dd, J = 4.4, 2.4 Hz, 2H), 4.18 (dd, J = 4.4, 2.4 Hz, 1H), 4.04 (d, J = 7.8 Hz, 1H), 3.99–3.95 (m, 2H), 3.85 (d, J = 7.7 Hz, 1H), 3.81 (dd, J = 10.2, 3.8 Hz, 1H), 3.79–3.74 (m, 2H), 3.67 (dd, J = 10.4, 2.0 Hz, 1H), 3.62 (s, 3H), 3.58 (dd, J = 10.6, 2.6 Hz, 2H), 3.47 (d, J = 2.5 Hz, 3H), 3.46 (s, 3H), 3.45 (d, J = 7.0 Hz, 1H), 3.44 (s, 3H), 3.39 (dd, J = 10.9, 4.6 Hz, 5H), 3.21 (dd, J = 10.2, 9.0 Hz, 1H), 3.14 (dd, J = 9.7, 3.7 Hz, 1H), 2.43 (t, J = 2.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 104.16, 89.25, 85.07, 83.73, 83.09, 81.55, 79.68, 79.58, 79.32, 79.22, 77.00, 74.65, 74.63, 73.95, 71.16, 70.20, 68.25, 60.64, 60.48, 59.37, 58.52, 58.50, 58.47, 58.41, 58.24. HR-MS ESI (*m*/*z*): calc. for [M($C_{24}H_{38}O_{11}$) + Na^+]: 525.2312, found: 525.23070. Anal.: calc. for M($C_{24}H_{38}O_{11}$) + H_2O: C, 55.37; H, 7.75, found: C, 55.37; H, 7.51. $[\alpha]_{20}$ = +43.7; IR (film): 3454, 3263, 2981, 2935, 2833, 2117, 1724, 1643, 1450, 1374, 1270, 1185, 1148, 1099, 1018, 982, 873, 836, 736, 701, 562 cm^{-1}.

Macrocyclic host 11. Following the general procedure A the crude product was purified by flash chromatography using EA : MeOH (9 : 1 v/v) to afford **11** (102 mg, 34%) as a white amorphous foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.88 (s, 1H), 5.25 (d, J = 3.4 Hz, 1H), 4.68 (dd, J = 14.7, 5.2 Hz, 1H), 4.63 (d, J = 12.7 Hz, 1H), 4.57 (dd, J = 14.7, 2.8 Hz, 1H), 4.49 (d, J = 12.7 Hz, 1H), 4.42 (dd, J = 14.4, 2.5 Hz, 1H), 4.17 (dd, J = 14.4, 9.3 Hz, 1H), 4.11 (ddd, J = 10.0, 5.1, 3.0 Hz, 1H), 4.03 (dd, J = 16.7, 2.6 Hz, 1H), 3.95–3.91 (m, 1H), 3.82 (t, J = 7.6 Hz, 1H), 3.60–3.56 (m, 2H), 3.54 (d, J = 11.0 Hz, 3H), 3.49–3.43

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(m, 7H), 3.41 (s, 3H), 3.39 (dt, J = 7.9, 2.6 Hz, 2H), 3.36–3.34 (m, 4H), 3.32 (d, J = 1.7 Hz, 3H), 3.30–3.27 (m, 4H), 3.26 (d, J = 5.3 Hz, 3H), 3.25 (s, 3H), 3.24–3.20 (m, 5H), 2.91 (dd, J = 9.8, 3.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 144.74, 144.50, 125.41, 125.03, 104.29, 89.52, 84.39, 83.97, 83.06, 81.14 (double intensity), 81.09, 81.07, 80.49, 79.41, 78.47, 73.04, 69.57, 69.33, 68.63, 64.64, 63.90, 60.39, 60.25, 60.06, 59.93, 59.07, 58.69, 58.40, 58.38, 57.57, 57.36, 53.24, 50.32. HR-MS ESI (m/z): calc. for [M($C_{34}H_{58}O_{15}N_6$) + Na^+]: 813.3858, found: 813.3832. Anal.: calc. for M($C_{34}H_{58}O_{15}N_6$) + H_2O: C, 50.49; H, 7.48; N, 10.39, found: C, 50.32; H, 7.40; N 10.16. $[\alpha]_D$ = +29.7.

Macrocyclic host 5. Following the general procedure A the crude product was purified by flash chromatography (EA : MeOH 9 : 1, v/v) to afford **5** (91 mg, 28%) as a white amorphous foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.74 (s, 1H), 4.90 (d, J = 13.0 Hz, 1H), 4.87 (d, J = 3.7 Hz, 1H), 4.71 (dd, J = 14.7, 2.5 Hz, 1H), 4.50 (dd, J = 13.9, 5.4 Hz, 1H), 4.38 (dd, J = 14.7, 3.3 Hz, 1H), 4.07 (dd, J = 11.5, 6.4 Hz, 1H), 4.04–3.95 (m, 5H), 3.93–3.83 (m, 4H), 3.94–3.82 (m, 4H), 3.62–3.59 (m, 1H), 3.51 (s, J = 7.6 Hz, 2H), 3.50–3.47 (m, 4H), 3.43 (s, 3H), 3.41 (s, 3H), 3.40–3.37 (m, 2H), 3.30 (s, 3H), 3.28 (s, 3H), 3.24–3.17 (m, 2H), 2.75 (dd, J = 9.8, 3.8 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d6) δ 145.10, 126.15, 125.78, 108.72, 108.57, 104.21, 88.88, 84.55, 83.17, 83.07, 80.50, 78.70, 78.55, 77.90, 77.68, 76.43, 75.92, 74.43, 69.09, 65.89, 65.50, 65.46, 65.25, 60.46, 60.19, 59.27, 58.47, 58.42, 58.06, 51.73, 49.38, 26.62, 25.69, 25.06, 21.19, 14.52. HR-MS ESI (m/z): calc. for [M($C_{36}H_{58}O_{15}N_6$) + Na^+]: 837.3858, found: 837.3826. Anal.: calc. for M($C_{36}H_{58}O_{15}N_6$) + H_2O: C, 51.91; H, 7.26; N, 10.09, found: C, 52.07; H, 7.24; N, 9.91. $[\alpha]_D$ = +33.9.

Macrocyclic host 12. Following the general procedure A the crude product was purified by flash chromatography (EA : MeOH 9 : 1, v/v) to afford **12** (83 mg, 23%) as a white amorphous foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.07 (s, 1H), 8.06 (s, 1H), 5.48–5.45 (m, 1H), 5.44 (d, J = 7.5 Hz, 2H), 5.42 (s, 2H), 5.39 (d, J = 3.5 Hz, 1H), 4.71 (dd, J = 12.2, 1.9 Hz, 1H), 4.67 (dd, J = 12.1, 2.0 Hz, 1H), 4.62 (t, J = 9.9 Hz, 2H), 4.54 (d, J = 12.0 Hz, 2H), 4.48 (d, J = 12.3 Hz, 1H), 3.90 (ddd, J = 16.9, 10.6, 5.8 Hz, 4H), 3.83–3.68 (m, 6H), 3.65–3.56 (m, 4H), 3.44 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.32 (s, 3H), 3.36–3.28 (m, 3H), 3.28–3.22 (m, 6H), 3.23–3.18 (m, 9H), 3.16 (s, 3H), 3.09–3.06 (m, 1H), 3.04–2.97 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.22, 167.09, 144.57, 144.43, 125.65, 125.57, 103.93, 88.75, 84.53, 83.63, 83.10, 81.24, 79.39, 79.09, 78.92, 78.74, 78.59, 73.85, 71.56, 70.44, 69.29, 64.18, 63.99, 62.85, 62.66, 60.30, 60.26, 60.23, 60.18, 60.14, 59.20, 58.25, 58.08, 57.05, 51.09, 50.98, 21.19, 14.52. HR-MS ESI (m/z): calc. for [M($C_{38}H_{62}O_{19}N_6$) + Na^+]: 929.3967, found: 929.3950. Anal.: calc. for M($C_{38}H_{62}O_{16}N_6$) + H_2O: C, 49.35; H, 6.97; N, 9.09, found: C, 49.38; H, 7.02; N, 8.82. $[\alpha]_D$ = +56.0.

Macrocyclic host 16. Following the general procedure B the crude product was purified by flash chromatography (CH_2Cl_2 : MeOH, 9 : 1 v/v) to afford **16** (81 mg, 27%) as a white amorphous foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.29 (d, J = 3.4 Hz, 1H), 4.42–4.38 (m, 2H), 3.90 (dd, J = 12.1, 4.4 Hz, 1H), 3.86 (dd, J = 12.2, 5.3 Hz, 1H), 3.82 (d, J = 7.3 Hz, 1H), 3.71 (dd, J = 9.7, 5.2 Hz, 2H), 3.67–3.63 (m, 1H), 3.47–3.43 (m, 2H), 3.41 (s, 4H), 3.40 (d, J = 2.3 Hz, 2H), 3.38 (t, J = 3.2 Hz, 6H), 3.37 (s, 3H), 3.34 (s, 4H), 3.32 (s, 3H), 3.32 (s, 3H), 3.30 (d, J = 3.8 Hz, 1H), 3.28 (s, 5H), 3.27 (d, J = 2.2 Hz, 5H), 3.26–3.20 (m, 3H), 3.07 (t, J = 9.4 Hz, 2H), 2.97 (dd, J = 9.7, 3.5 Hz, 1H), 2.83–2.63 (m, 5H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.59, 172.01, 103.16, 88.53, 84.31, 84.17, 82.53, 81.00, 80.32, 79.74, 79.62, 79.42, 79.33, 79.18, 73.63, 70.69, 62.22, 61.36, 59.98, 59.93, 59.71, 59.66, 58.77, 57.84, 57.76, 57.68, 56.91, 56.84, 51.18, 50.72, 50.03, 48.82. HR-MS ESI (m/z): calc. for [M($C_{32}H_{58}O_{17}N_2$) + H^+]: 743.3774, found: 743.3799. Anal.: calc. for M($C_{32}H_{58}O_{17}N_2$) + H_2O: C, 50.52; H, 7.95; O, 37.85; N, 3.68, found: C, 50.67; H, 7.88; N, 3.66. $[\alpha]_D$ = +50.4.

Macrocyclic host 17. Following the general procedure B the crude product was purified by flash chromatography (EA : MeOH, 9 : 1 v/v) to afford **17** (138.6 mg, 47%) as a white amorphous foam. ^{1}H NMR (600 MHz, acetone-d_6) δ 7.72 (s, 1H), 7.55 (s, 1H), 5.55 (d, J = 3.5 Hz, 1H), 4.02–3.94 (m, 2H), 3.92–3.87 (m, 2H), 3.66 (d, J = 11.1 Hz, 1H), 3.61–3.55 (m, 2H), 3.53 (s, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 3.46 (d, J = 3.7 Hz, 1H), 3.45 (s, 3H), 3.44 (s, 5H), 3.42 (d, J = 9.1 Hz, 3H), 3.40 (d, J = 1.9 Hz, 4H), 3.40 (s, 3H), 3.39 (s, 4H), 3.37 (dd, J = 6.3, 2.9 Hz, 2H), 3.33 (dd, J = 15.2, 5.1 Hz, 3H), 3.21 (d, J = 16.1 Hz, 2H), 3.08 (dd, J = 9.6, 3.6 Hz, 2H), 2.98 (dd, J = 11.3, 7.6 Hz, 4H), 2.70 (dd, J = 12.0, 8.0 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 170.48, 170.40, 104.48, 89.47, 85.62, 85.00, 83.21, 81.91, 81.28, 81.20, 80.91, 80.25, 80.10, 79.17, 73.57, 70.25, 59.85, 59.77, 59.75, 59.59, 58.52, 57.86, 57.54, 57.50, 56.43, 56.35, 52.39, 52.01, 51.77, 50.19, 37.02, 36.84. MS HR-MS ESI (m/z): calc. for [M($C_{32}H_{60}O_{15}N_4$) + H^+]: 741.4133, found: 741.4142. Elemental analysis indicated that **17** formed a strong complex with methylene chloride: anal: calc. for M($C_{32}H_{60}O_{15}N_4$) + CH_2Cl_2: C, 48.00; H, 7.57; N, 6.78, found: C, 47.86; H, 7.57; N, 6.64. $[\alpha]_{20}$ = +23.1.

Conflicts of interest

There are no conflicts to declare.

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