Primary hydroxy-modified cyclomaltoheptaose derivatives with two kinds of substituents. Preparation of 6$^{\text{I}}$-(benzyloxycarbonylamino)-, 6$^{\text{I}}$-(*tert*-butoxycarbonylamino)- and 6$^{\text{I}}$-azido-6$^{\text{I}}$-deoxy-6$^{\text{II}}$,6$^{\text{III}}$,6$^{\text{IV}}$, 6$^{\text{V}}$,6$^{\text{VI}}$,6$^{\text{VII}}$-hexa-*O*-tosylcyclomaltoheptaose and their conversion to the hexakis-(3,6-anhydro) derivatives

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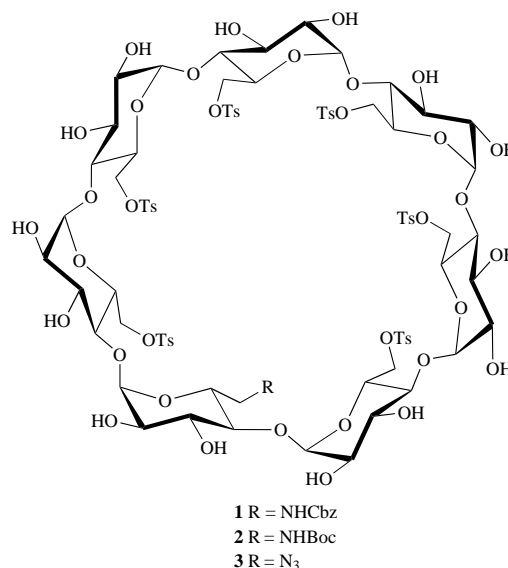^{b} *Central Research Laboratories, Tsumura & Co., 3586 Yoshiwara, Inashiki-gun, Ibaraki 300-11, Japan*

Three cyclomaltoheptaoses (1, 2 and 3) which possess a benzyloxycarbonylamino group, a *tert*-butoxycarbonylamino group or an azido group, and six tosyloxy groups, on their C-6 atoms have been prepared. These can be versatile intermediates for the synthesis of derivatives possessing an amino group as well as other functional groups. As an example of their derivatization, their conversion to compounds containing 3,6-anhydroglucoses, which possess cation-binding abilities, is also reported.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of α(1 ⟶ 4)-linked glucose units. They can include a variety of guest molecules.[1] Because of this feature, not only the CDs themselves but also their modified derivatives have been the subject of a great number of academic studies as well as industrial applications.[1] However, there have not been so many CD derivatives which possess two kinds of substituents. On highly specialized molecules such as enzymes, several functional groups work co-operatively. In the case of CD derivatives, Tabushi prepared cyclomaltoheptaose (β-cyclodextrin, β-CD) derivatives possessing a modified vitamin B$_6$ and an ω-amino group as an artificial B$_6$ enzyme and attained a chiral amino-transfer reaction.[2] Multifunctionalized CD derivatives are considered to be quite useful intermediates in the quest to generate highly sophisticated functions such as those of enzymes or antibodies.
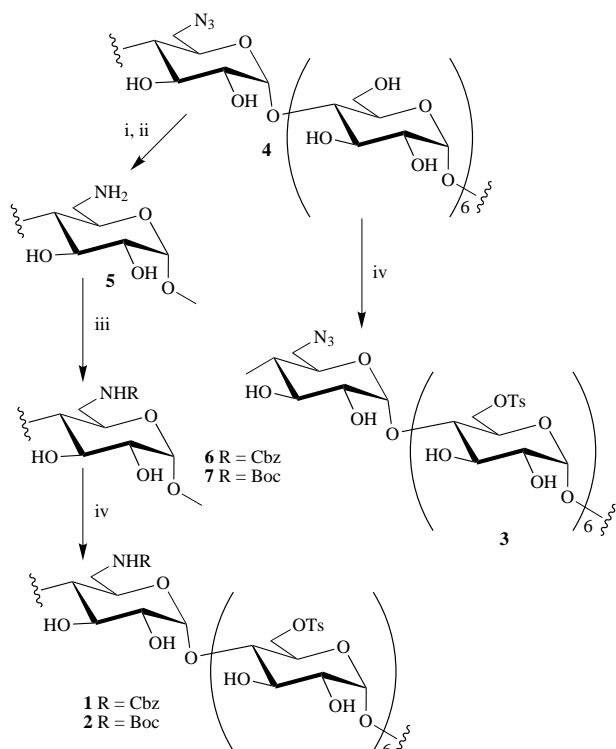
In our study of multiply modified CD derivatives, we here describe the preparation of three β-CDs possessing two kinds of substituents at their C(6) atoms, namely 6$^{\text{I}}$-Cbz-amino-, 6$^{\text{I}}$-Boc-amino- and 6$^{\text{I}}$-azido-6$^{\text{I}}$-deoxy-6$^{\text{II}}$,6$^{\text{III}}$,6$^{\text{IV}}$,6$^{\text{V}}$,6$^{\text{VI}}$,6$^{\text{VII}}$-hexa-*O*-Ts-β-CD (compounds 1, 2 and 3, respectively). They can be used as versatile intermediates for the synthesis of derivatives possessing a functional group such as an amino group at one C(6) position and also other kinds of functional groups at the other six C(6) atoms. The amino-protecting groups of compounds 1 and 2, a benzyloxycarbonyl (Cbz) group[3] and a Boc group,[4] have general use in peptide chemistry and are deprotected by hydrogenolysis and TFA treatment, respectively. The latter (TFA) treatment does not affect the glycosidic bonds of CDs.[5] An azido group in compound 3 is easily converted to an amino group[6] and also enables the introduction of various functional groups such as an aldehyde group[7] and a triazole moiety.[8] The six tosyloxy groups in compounds 1–3 can be converted to other functional groups in the conventional way. As a particular example, we will here describe the conversion of these three compounds to the respective derivatives containing 3,6-anhydroglucoses, which, unlike the usual CD derivatives, exhibit cation-binding abilities.

1 R = NHCbz
2 R = NHBoc
3 R = N$_3$

Results and discussion

The synthetic procedure for the tosylated Cbz-amino derivative **1** was as follows (Scheme 1). An amino derivative **5**[6] was treated with CbzCl in aq. alkali. Reversed-phase (RP) chromatography with an increasing MeOH gradient elution gave the desired Cbz-amino derivative **6** (71.6%). The structure was confirmed by spectroscopy. In particular, the signal of NHCO (δ_{H} 7.05) on the ^{1}H NMR spectrum and its negative ninhydrin test suggested that its amino group was benzyloxycarbonylated. Compound **6** was subjected to tosylation by use of TsCl in pyridine. The reaction was monitored by RPHPLC analysis (Fig. 1), which showed that this reaction generated a major product **1** whose six 6-OHs were tosylated, and also by-products with larger t_{R}-values, whose 2-OH was also tosylated,† as in the case of

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† This is a regioisomeric mixture. The number of tosyl groups was determined by its ^{1}H NMR spectrum (data not shown).

Scheme 1 *Reagents*: i, PPh$_3$; ii, aq. NH$_3$; iii, CbzCl for **6** [(Boc)$_2$O for **7**]; iv, TsCl, pyridine

Fig. 1 RP-HPLC (A) and column chromatography (B) of the mixture obtained by reaction of the Cbz-amino derivative **6** with TsCl in pyridine. A linear gradient of MeCN was applied.

per-6-*O*-tosylation of native CDs.[9] The reaction mixture was applied to RP chromatography with increasing amounts of MeCN in water as gradient eluent, which accomplished the isolation of the desired product **1** (46.4%). In the ^{1}H NMR spectrum of product **1**, the signals for six Ts groups [δ 2.37 (Me) and 7.2–7.8 (ArH)] appeared in addition to those of a Cbz-amino group. Its elemental analysis and mass spectrum also supported the assigned structure. In a similar manner, the hexa-6-*O*-tosylated Boc-amino derivative **2** was prepared from amine **5** (Scheme 1). In this procedure, the Boc-amino derivative **7**, the product of *tert*-butoxycarbonylation of amine **5**, was not isolated because the reaction mixture was insoluble in the solvent for RP chromatography. After removal of the solvent, we subjected the reaction mixture to tosylation and then separated product **2** by RP chromatography. The ^{1}H NMR spectrum of compound **2** demonstrated the existence of a Boc group [δ 1.29 (CMe$_3$)] and also six Ts groups [δ 2.37 (C$_6$H$_4$*Me*), 7.31–7.46 and 7.63–7.90 (ArH)]. An azido derivative **4**‡ was also tosylated as in the case of compound **6** and the product was subjected to RP chromatography to give the hexa-6-*O*-tosylated azido-β-CD **3**. The structure of products **2** and **3** was also confirmed by their elemental analyses and mass spectra. These experiments suggested that substituents such as a Cbz-amino, a Boc-amino or an azido group enables further modification for multifunctionalization of a CD molecule.

As an example of the derivatization of compounds **1**, **2** and **3**, their 6-*O*-Ts-glucose moieties were converted to 3,6-anhydroglucose residues by treatment with alkali. The derivatives containing 3,6-anhydroglucose moieties exhibit specific cation-binding characteristics.[11] The hexatosylated Cbz-amino CD **1** was treated with KOH in aq. MeOH. RP chromatographic separation by gradient elution with increasing MeOH in water gave a product with a very much lower R_f-value on TLC than that of compound **1**. It was ninhydrin-positive without acid treatment, and was not detected by UV, indicating the

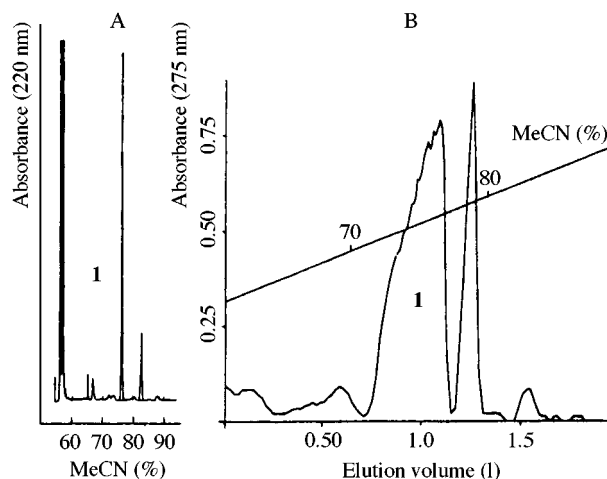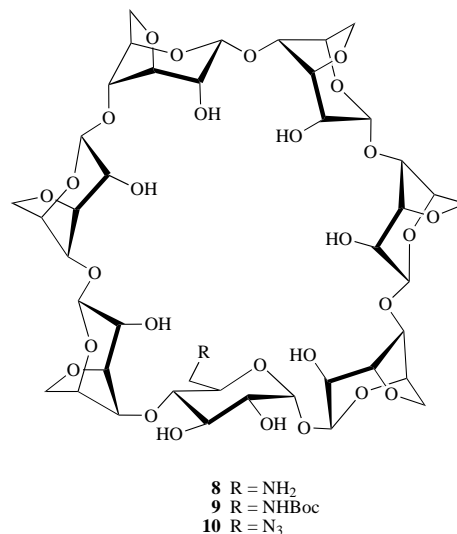‡ The azide **4** was synthesized from the tosyl compound according to the method in ref. 10.

absence of a UV-absorbing chromophoric group. The existence of signals due to a 6-amino-6-deoxyglucose[6] in addition to those of six 3,6-anhydroglucoses[11] in the ^{1}H NMR spectrum (Fig. 2) and also the corresponding molecular ion in the mass spectrum confirmed that an unexpected removal of the Cbz group occurred simultaneously with the 3,6-anhydration reaction, to give the hexakis-(3,6-anhydro) amino derivative **8**. It is usually assumed that alkali treatment for saponification does not deprotect any Cbz-protected amino group.[12] However, we found that cleavage of a Cbz group from Cbz-Phe and Cbz-Gly did indeed occur under conditions as strong as those applied in the case of reaction from **1** to **8** [Cbz-Phe or Cbz-Gly (5×10^{-5} mol) in 1 mol dm^{-3} KOH (2 cm^3); 70 °C]. Cbz-Gly was deprotected even at rt. Therefore, when dealing with Cbz-amino compounds, it is recommended that unnecessarily strong alkaline conditions be avoided. In our case of the synthesis of compound **8** from substrate **1**, this characteristic of the Cbz-amino group has saved us one step of deprotection and leads to a shorter route to compound **8**.

8 R = NH$_2$
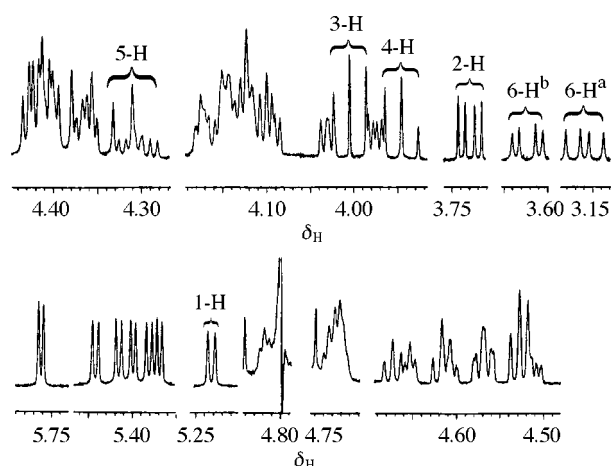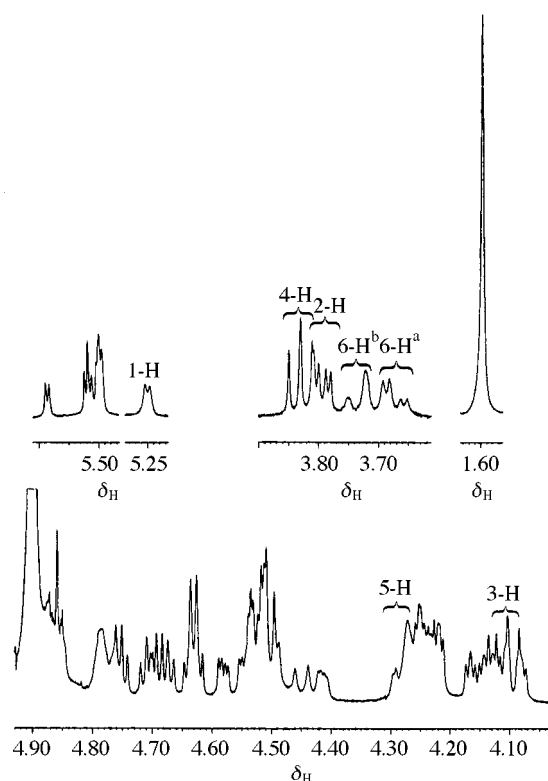**9** R = NHBoc
10 R = N$_3$

The hexatosylated Boc-amino derivative **2** was similarly treated with KOH. The product **9** showed the signals of 3,6-anhydroglucoses and also those of Boc-protected aminoglucose in its ^{1}H NMR spectrum (Fig. 3). The structure of product **9** was also supported by its mass spectrum. A Boc-amino group can withstand these alkaline conditions, unlike the case of a Cbz-amino group. Deprotection of the Boc group of compound **9** by TFA gave a complicated mixture due to cleavage of

Table 1 Relative abundances (%)[a] of the alkali metal-incorporating CD ions in the LSIMS spectra

	$[M + Li]^+$	$[M + Na]^+$	$[M + K]^+$	$[M + Rb]^+$	$[M + Cs]^+$	Others[b]
10	~0	3.7	25.2	26.3	40.8	4.0
11	~0	~0	29.3	40.7	20.2	9.8

[a] Abundances are shown as the relative intensity of the corresponding peak to the sum of the intensities of [CD + metal] peaks in the spectrum.
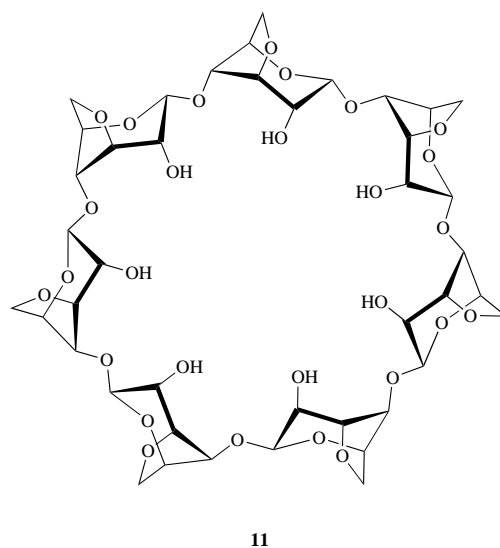[b] **10**, $[M + 2K - H]^+$; **11**, $[M + K + Rb - H]^+$ 5.1, $[M + K + Cs - H]^+$ 4.7.

Fig. 2 ¹H NMR (500 MHz; D₂O) spectrum of the hexa-(3,6-anhydro) amino derivative **8**. Signals of the aminoglucose moiety are marked.

Fig. 3 ¹H NMR (500 MHz; D₂O) spectrum of the hexa-(3,6-anhydro) Boc-amino derivative **9**. Signals of the Boc-aminoglucose moiety are marked.

glycosidic bonds. This demonstrated that a glycosidic bond of a 3,6-anhydroglucose residue is severed even by neat TFA treatment because of the activated C-1 of the residue.[13] All six Ts-glucoses of the azido tosyl ester **3** were also converted to 3,6-anhydroglucoses upon alkali treatment to give the azido anhydride **10**. The azido group of compound **10** was reduced to an amino group by use of Ph₃P–aq. NH₃ to give the amino

anhydride **8**. The product was indistinguishable from that synthesized from compound **1** in both chromatographic behaviour and ¹H NMR and mass spectral properties.

The molecular cavity of compounds **8**, **9** and **10** was constructed from one glucose and six 3,6-anhydroglucoses. In order to estimate the inclusion ability of this kind of molecular cavity, a preliminary binding analysis§ of compound **10**¶ by use of liquid secondary-ion mass spectrometry (LSIMS) was performed. The results are shown in Table 1. The observed abundances of the [CD + metal] ion peaks are assumed to be proportional to the affinities of the CDs for the metal cation. Compound **10** bound Cs⁺ most strongly, in contrast to the β-CD derivative **11**¶,[14] composed of seven 3,6-anhydroglucoses,

11

which exhibited specificity for the smaller Rb⁺. This situation is analogous to the relationship between the cyclomaltohexaose derivative composed of one glucose and five 3,6-anhydroglucoses and the one composed of six 3,6-anhydroglucoses, which exhibited their highest affinity for Rb⁺ and K⁺, respectively.[11c] By use of compounds **8**, **9** and **10**, we can construct a novel compound containing the moiety which best binds Cs⁺. Application to a stationary phase of chromatography or an electrode should also be possible. Compound **8** itself can act as a ditopic host,[15] because its amino group is considered to function as a second binding site. More detailed study of further structural modifications and their binding ability are in progress.

In conclusion, three CD derivatives which possess a protected amino group or an azido group in addition to six Ts groups were prepared. By chemical conversion of the two kinds of substituents, they can be transformed into a novel derivative such as that composed of an aminoglucose and six 3,6-anhydroglucoses.

§ See ref. 11(b)–(d) and the references cited therein.
¶ Na and K salts are often included by CD derivatives possessing 3,6-anhydroglucose moieties during their preparation. Flame atomic emission spectrometry determined that compounds **10** and **11** contained less than 0.05% (w/w) of included Na and K.

Experimental

IR spectra were run on a JASCO-A102 spectrometer. ^{1}H NMR (200, 400 or 500 MHz) spectra were recorded on a Varian Gemini 200, a Varian UNITY plus 400 or a Bruker AM 500 spectrometer. J-Values are given in Hz. Mass measurements were carried out with an Hitachi M-2000 (LSIMS) or a Shimadzu-Kratos CONCEPT 32IH (FAB) spectrometer. TLC was run on precoated silica-gel plates (Art 5554, Merck) with the following solvent systems: PrOH–AcOEt–water [7:7:2 (v/v/v)] (solvent 1), [1:1:1 (v/v/v)] (solvent 2), [7:7:5 (v/v/v)] (solvent 3), or PrOH–AcOEt–water–28% aq. NH$_3$ [5:3:2:1 (v/v/v/v)] (solvent 4). Spot detection was carried out by UV light and/or staining with 0.1% naphthalene-1,3-diol in EtOH–water–H$_2$SO$_4$ [200:157:43 (v/v/v)]. A prepacked ODS column [LiChroprep RP-18, size B (25 × 310 mm), Merck] was used for low-pressure RP column chromatography. RP HPLC was carried out with a TSK gel ODS-80Ts (5 µm; 4.6 × 120 mm, TOSOH) or a J'sphere ODS-M80 (4 µm; 4.6 × 120 mm, YMC Inc.) column. Flame atomic emission spectrometry was performed with SAS/727 AAS (Seiko).

6^I-Cbz-amino-6^I-deoxycyclomaltoheptaose 6

The amine 5 (1.00 g, 8.57 × 10^{-4} mol) was treated with aq. Cbz chloride (1.28 g, 8.13 × 10^{-3} mol in 30 cm^3) containing NaHCO$_3$ (769 mg, 9.46 × 10^{-3} mol) for 1 h. The reaction mixture was washed with diethyl ether, and concentrated *in vacuo*. The residue was dissolved in 5% aq. MeOH (1 dm^3) and subjected to a low-pressure RP chromatography. After elution with 7% aq. MeOH (500 cm^3), gradient elution from 7% aq. MeOH (700 cm^3) to 20% aq. MeOH (700 cm^3) gave the Cbz-amino derivative 6 (778 mg, 71.6%); R_f (solvent 2) 0.16 (Found: C, 42.15; H, 6.25; N, 1.0. Calc. for C$_{50}$H$_{77}$NO$_{36}$·8H$_2$O: C, 42.5; H, 6.65; N, 1.0%); δ_H(200 MHz; [^{2}H$_6$]DMSO) 4.30–4.72 (6 H, 6-OH), 4.82 (6 H, br d, 1-H glucose), 4.90 (1 H, d, 1-H Cbz-aminoglucose), 4.98 (2 H, br d, CH_2Ph), 5.60–5.95 (14 H, 2- and 3-OH), 7.05 (br t, 1 H, NH) and 7.35 (5 H, br s, Ph); m/z (LSIMS) 1268.5 [(M + H)$^+$].

6^I-Cbz-amino-6^I-deoxy-6^{II},6^{III},6^{IV},6^V,6^{VI},6^{VII}-hexa-*O*-Ts-cyclomaltoheptaose 1

The lyophilized Cbz-amino derivative 6 (301 mg, 2.37 × 10^{-4} mol) was treated with TsCl (1.65 g, 8.65 × 10^{-3} mol) in dry pyridine (15 cm^3) at 10 °C for 3 h. After addition of water, the pyridine was evaporated off and the residue was dissolved in 55% aq. MeCN (500 cm^3), and this solution was subjected to low-pressure RP chromatography using (i) elution with 60% aq. MeCN (500 cm^3) and (ii) gradient elution from 60% aq. MeCN (1 dm^3) to 90% aq. MeCN (1 dm^3) to give the tosyl derivative 1 (242 mg, 46.4%); R_f (solvent 1) 0.45; t_R [column: J'sphere ODS-M80; gradient: 60–90% aq. MeCN (30 min); flow rate: 1.0 cm^3 min^{-1}] 19.5 min (Found: C, 48.5; H, 5.05; N, 0.7; S, 8.65. Calc. for C$_{92}$H$_{113}$NO$_{48}$S$_6$·4H$_2$O: C, 48.8; H, 5.4; N, 0.6; S, 8.5%); δ_H(200 MHz; [^{2}H$_6$]DMSO) 2.37 (18 H, br s, Me), 4.58 (6 H, 1-H of Ts-glucose), 4.80–5.15 (3 H, 1-H of Cbz-aminoglucose and CH_2Ph), 7.22–7.42 (12 H, ArH) and 7.55–7.81 (12 H, ArH); m/z (LSIMS) 2214.9 [(M + Na)$^+$].

6^I-Boc-amino-6^I-deoxy-6^{II},6^{III},6^{IV},6^V,6^{VI},6^{VII}-hexa-*O*-Ts-cyclomaltoheptaose 2

The amine 5 (995 mg, 8.50 × 10^{-4} mol) was treated with (Boc)$_2$O (315 mg, 1.45 × 10^{-3} mol) in 50% aq. 1,4-dioxane (60 cm^3) at pH 8.5 for 3 h. The solution was concentrated *in vacuo* and lyophilized. The reaction mixture was subsequently treated with TsCl (6.03 g, 3.16 × 10^{-2} mol) in dry pyridine (50 cm^3) at 10 °C for 2.5 h. The work-up procedure gave the product in a 55% aq. MeCN solution (600 cm^3), which was divided into two fractions. Each of them was applied to a low-pressure RP chromatography column with elution by 55% aq. MeCN (600 cm^3) followed by linear gradient elution from 55% aq. MeCN

(800 cm^3) to 85% aq. MeCN (800 cm^3). This treatment gave the tosyl derivative 2 (586 mg, 32.0%); R_f (solvent 1) 0.53; t_R [column: ODS-80Ts; gradient: 70–100% aq. MeCN (40 min); flow rate: 1.0 cm^3 min^{-1}] 11.8 min (Found: C, 47.85; H, 5.3; N, 0.8; S, 8.9. Calc. for C$_{89}$H$_{115}$NO$_{48}$S$_6$·4H$_2$O: C, 47.9; H, 5.55; N, 0.65; S, 8.6%); δ_H(200 MHz; [^{2}H$_6$]DMSO) 1.29 (9 H, s, CMe$_3$), 2.37 (18 H, br s, Ar*Me*), 4.60 (6 H, br s, 1-H of Ts-glucose), 4.82 (1 H, br s, 1-H of Boc-aminoglucose), 7.31–7.46 (12 H, ArH) and 7.63–7.90 (12 H, ArH); m/z (LSIMS) 2180.9 [(M + Na)$^+$] and 2198.3 [(M + K)$^+$].

6^I-Azido-6^I-deoxy-6^{II},6^{III},6^{IV},6^V,6^{VI},6^{VII}-hexa-*O*-Ts-cyclomaltoheptaose 3

The lyophilized azide 4 (400 mg, 3.45 × 10^{-4} mol) was treated with TsCl (1.98 g, 1.03 × 10^{-1} mol) in dry pyridine (20 cm^3) at 10 °C for 2 h. The work-up procedure gave the product in a 50% aq. MeCN solution (400 cm^3), which was applied to a low-pressure RP chromatography column by use of 60% aq. MeCN (200 cm^3) and gradient elution from 60% aq. MeCN (500 cm^3) to 100% MeCN (500 cm^3) to give the tosyl derivative 3 (179 mg, 24.9%); R_f (solvent 1) 0.51; t_R [column: J'sphere ODS-M80; gradient: 60–90% aq. MeCN (30 min); flow rate: 1.0 cm^3 min^{-1}] 16.2 min (Found: C, 46.7; H, 5.05; N, 1.95; S, 9.25. Calc. for C$_{84}$H$_{105}$N$_3$O$_{46}$S$_6$·4H$_2$O: C, 46.75; H, 5.3; N, 1.95; S, 9.2%); ν_{max}(KBr)/cm^{-1} 2060 (azido), 1160 and 1340 (sulfonyl); δ_H(200 MHz; [^{2}H$_6$]DMSO) 2.39 (18 H, br s, Me), 4.58–4.80 (7 H, 1-H), 5.68–5.98 (14 H, 2- and 3-OH), 7.36–7.50 (12 H, ArH), 7.65–7.83 (12 H, ArH); m/z (LSIMS) 2107.1 [(M + Na)$^+$] and 2122.1 [(M + K)$^+$].

3^I,6^I:3^{II},6^{II}:3^{III},6^{III}:3^{IV},6^{IV}:3^V,6^V:3^{VI},6^{VI}-Hexaanhydro-6^{VII}-Boc-amino-6^{VII}-deoxycyclomaltoheptaose 9

A solution of the Boc-amino tosyl ester 2 (593 mg, 2.75 × 10^{-4} mol) in 1 mol dm^{-3} KOH–75% aq. MeOH (150 cm^3) was kept at 65 °C for 2 days. The solution was neutralized, and concentrated *in vacuo*. The residue was dissolved in 15% aq. MeOH (400 cm^3) and subjected to low-pressure RP chromatography. After stepwise gradient elution with 15% aq. MeOH (800 cm^3), 20% aq. MeOH (1 dm^3) and 25% aq. MeOH (100 cm^3), gradient elution from 25% aq. MeOH (800 dm^3) to 65% aq. MeOH (800 cm^3) gave the anhydride 9 (251 mg, 81%); R_f (solvent 2) 0.22 (Found: C, 45.0; H, 5.9; N, 1.25. Calc. for C$_{47}$H$_{67}$NO$_{30}$·7H$_2$O: C, 45.1; H, 6.5; N, 1.1%); δ_H(500 MHz; D$_2$O) 1.60 (9 H, s, Me), 3.67 (1 H, dd, J 5.5 and 14.7, 6-H^a of Boc-aminoglucose), 3.74 (1 H, br d, 6-H^b of Boc-aminoglucose), 3.79 (1 H, dd, J 4.1 and 10.0, 2-H of Boc-aminoglucose), 3.83 (1 H, t, J 9.7, 4-H of Boc-aminoglucose), 4.10 (1 H, 3-H of Boc-aminoglucose), 4.28 (1 H, 5-H of Boc-aminoglucose) and 5.25 (1 H, br d, 1-H of Boc-aminoglucose); δ_H(400 MHz; [^{2}H$_6$]DMSO–D$_2$O) 1.31 (9 H, s, Me), 3.00 (1 H, br s, 6-H^a of Boc-aminoglucose), 3.30 (2 H, br d, 2- and 4-H of Boc-aminoglucose), 3.43 (1 H, br d, 6-H^b of Boc-aminoglucose), 3.51 (1 H, br t, 3-H of Boc-aminoglucose), 3.80 (1 H, br s, 5-H of Boc-aminoglucose), 4.85 (1 H, br s, 1-H of Boc-aminoglucose) and 5.10 (6 H, br d, 1-H of anhydroglucose); δ_H(400 MHz; [^{2}H$_6$]DMSO) 6.59 (1 H, br s, BocN*H*); m/z (LSIMS) 1164.4 [(M + K)$^+$]; (+FAB) 1126.383 77 [(M + H)$^+$. C$_{47}$H$_{68}$NO$_{30}$ requires m/z, 1126.382 62], 1148.366 07 [(M + Na)$^+$. C$_{47}$H$_{67}$NNaO$_{30}$ requires m/z, 1148.364 59] and 1164.339 09 [(M + K)$^+$. C$_{47}$H$_{67}$KNO$_{30}$ requires m/z, 1164.338 50]; (−FAB) 1124.367 29 [(M − H)$^-$. C$_{47}$H$_{66}$NO$_{30}$ requires m/z, 1124.366 97].

3^I,6^I:3^{II},6^{II}:3^{III},6^{III}:3^{IV},6^{IV}:3^V,6^V:3^{VI},6^{VI}-Hexaanhydro-6^{VII}-azido-6^{VII}-deoxycyclomaltoheptaose 10

A solution of the azido tosyl ester 3 (100 mg, 4.81 × 10^{-5} mol) in 1 mol dm^{-3} KOH–75% aq. MeOH (20 cm^3) was kept at 60 °C for 3 days. After a work-up procedure, the aq. solution (40 cm^3) was subjected to low-pressure RP chromatography. Stepwise gradient elution with 5% aq. MeCN (200 cm^3) and 20% aq.

MeCN (200 cm³), followed by gradient elution from 20% aq. MeCN (500 cm³) to 60% aq. MeCN (500 cm³), gave the anhydride **10** (38.9 mg, 76.9%); R_f (solvent 3) 0.06; t_R [column: J'sphere ODS-M80; gradient: 5–40% aq. MeCN (35 min); flow rate: 1.0 cm³ min⁻¹] 19.9 min (Found: C, 42.8; H, 5.4; N, 3.5. Calc. for $C_{42}H_{57}N_3O_{28} \cdot 7H_2O$: C, 42.8; H, 6.05; N, 3.55%); ν_{max}(KBr)/cm⁻¹ 2100 (azido); δ_H(500 MHz; D₂O) 3.71 (1 H, dd, J 4.0 and 10.0, 2-H of azidoglucose), 3.79 (1 H, t, J 9.5, 4-H of azidoglucose), 3.89 (1 H, dd, J 2.9 and 13.5, 6-Hᵃ of azidoglucose), 3.94 (1 H, dd, J 4.3 and 13.5, 6-Hᵇ of azidoglucose), 4.01 (1 H, 3-H of azidoglucose), 4.26 (1 H, ddd, J 2.9, 4.3 and 9.5, 5-H of azidoglucose), 5.22 (1 H, d, J 4.0, 1-H of azidoglucose) and 5.39–5.43 (6 H, 1-H of anhydroglucose); m/z (LSIMS) 1074.7 [(M + Na)⁺] and 1090.6 [(M + K)⁺]; (+FAB) 1026.328 36 [(M − N₂ + H₃)⁺. $C_{42}H_{60}NO_{28}$ requires m/z, 1026.330 19], 1052.322 74 [(M + H)⁺. $C_{42}H_{58}N_3O_{28}$ requires m/z, 1052.320 68], 1074.302 17 [(M + Na)⁺. $C_{42}H_{57}N_3NaO_{28}$ requires m/z, 1074.302 66], 1090.276 53 [(M + K)⁺. $C_{42}H_{57}KN_3O_{28}$ requires m/z, 1090.276 57]; (−FAB) 1050.306 43 [(M − H)⁻. $C_{42}H_{56}N_3O_{28}$ requires m/z, 1050.305 03].

6ᴵ-Amino-3ᴵᴵ,6ᴵᴵ:3ᴵᴵᴵ,6ᴵᴵᴵ:3ᴵⱽ,6ᴵⱽ:3ⱽ,6ⱽ:3ⱽᴵ,6ⱽᴵ:3ⱽᴵᴵ,6ⱽᴵᴵ-hexaanhydro-6ᴵ-dexoxycyclomaltoheptaose 8

Alkali treatment of compound 1. A solution of the Cbz-amino tosyl ester **1** (72.9 mg, 3.33×10^{-5} mol) in 1 mol dm⁻³ KOH–75% aq. MeOH (20 cm³) was kept at 65 °C for 2 days. The workup procedure gave the product in a 15% aq. MeOH solution (200 cm³), which was subjected to low-pressure RP chromatography. After stepwise gradient elution with 15% aq. MeOH (800 cm³), 20% aq. MeOH (1 dm³) and 25% aq. MeOH (1 dm³), and also gradient elution from 25% aq. MeOH (500 cm³) to 70% aq. MeOH (500 cm³), gradient elution from 70% aq. MeOH (300 cm³) to 100% MeOH (300 cm³) gave the amino anhydride **11** (24.2 mg, 71%); R_f (solvent 2) 0.03 (Found: C, 41.85; H, 5.8; N, 1.2. Calc. for $C_{42}H_{59}NO_{28} \cdot HCl \cdot 8H_2O$: C, 41.8; H, 6.35; N, 1.15%); δ_H(500 MHz; D₂O) 3.16 (1 H, dd, J 8.4 and 13.5, 6-Hᵃ of aminoglucose), 3.62 (1 H, dd, J 4.1 and 13.5, 6-Hᵇ of aminoglucose), 3.73 (1 H, dd, J 4.1 and 9.5, 2-H of aminoglucose), 3.95 (1 H, t, J 9.5, 4-H of aminoglucose), 4.00 (1 H, t, J 9.5, 3-H of aminoglucose), 4.30 (1 H, ddd, J 4.1, 8.4 and 9.5, 5-H of aminoglucose), 5.23 (1 H, d, J 4.1, 1 H of aminoglucose) and 5.369, 5.375, 5.40, 5.42, 5.44 and 5.76 (6 H, all d, J 2.8, 3.1, 2.9, 3.2, 3.4 and 2.7, respectively, 1-H of 3,6-anhydroglucose); m/z (LSIMS) 1026.8 [(M + H)⁺], 1048.3 [(M + Na)⁺] and 1064.6 [(M + K)⁺]; (+FAB) 1026.329 89 [(M + H)⁺. $C_{42}H_{60}NO_{28}$ requires m/z, 1026.330 19]; (−FAB) 1024.311 26 [(M − H)⁻. $C_{42}H_{58}NO_{28}$ requires m/z, 1024.314 54].

Reduction of compound 10. The azido anhydride **10** (50.6 mg, 4.81×10^{-5} mol) was treated with triphenylphosphine (379 mg, 1.45×10^{-3} mol) in dry pyridine (5 cm³) for 4 h. After the addition of 28% aq. NH₃, the reaction mixture was stirred for 25 h under Ar. The solution was concentrated *in vacuo* and the residue was dissolved in water, the solution was adjusted to pH 4, washed with benzene, and lyophilized to give crude compound **8**, which was dissolved in water (20 cm³) and applied to a low-

pressure RP chromatography column. After elution with water (100 cm³), gradient elution from water (500 cm³) to 60% aq. MeOH (500 cm³), followed by 60% aq. MeOH (300 cm³) to 100% MeOH (300 cm³), gave the amino anhydride **8** (17.1 mg, 34.7%).

Cation-binding analysis by use of LSIMS

Aqueous solutions containing each of macrocycles **10** and **11** (1.0×10^{-2} M) and all of the alkali metal chlorides (2.3×10^{-2} M) were used as analytical samples.[11b]

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