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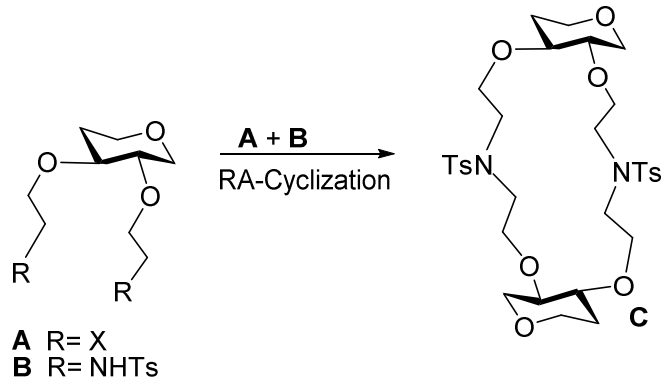

Graphical Abstract

Carbohydrate-Based Aza-Macrocycles by Richman-Atkins Cyclization of Glucopyranose Precursors

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A B S T R A C T

2, 3-Di-ω-halo- as well as 2, 3-di-ω-toluenesulfonamide-alkylated glucopyranoside derivatives were prepared. Their condensation with α,ω-bis-toluenesulfonamide components under varying Richman-Atkins conditions with alkali carbonate in DMF led to carbohydrate-linked aza-macrocycles displaying 14-, 17-, 18-, 21-, 24-, and 25-membered ring structures. Isomeric aza-macrocylic coronands of 20- as well as 30-membered ring size containing two saccharides could be obtained employing Richman-Atkins condensations of two functionalized sugar building units.

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1. Introduction

Supramolecular chemistry became en vogue with the synthesis of crown ethers by Pedersen et al., [1-3] which induced a plethora of studies with regard to synthesis and a large variety of different complexation properties. The application of crown ether structures in preparative chemistry such as by phase transfer catalysis and analytical chemistry e.g. in ion chromatography are well described. Aza-macrocycles [4] were reported as early as 1886 with tetra-aza quaterene by von Baeyer, [5] and already Curtis [6, 7] described interactions of aza coronands with Ni(II) salts. It is interesting to recall that transition metals are decisive in many biological processes, and further are ubiquitously used as catalysts. For decontamination of toxic metals or their derivatives aza macrocycles are under survey, [8] and more recently applications in medical diagnostics employing carbohydrate copper, gold, as well as silver complexes in tumor treatment were reported. [9,10] As an additional feature in supramolecular chemistry chirality is of particular relevance, [11-14] and thus the development and studies of carbohydrate-based crown ethers initiated by Stoddart et al. [15-20] was obvious and very successful in an array of different reactions e.g. asymmetrical Michael reactions. [21-23] The very advantageous formation of carbohydrate containing complex macrocycles employing metathesis was recently reported. [24]

Focus of the present study was on the preparation of carbohydrate-based nitrogen containing macrocycles employing easily obtained activated sugar precursor structures and a highly efficient ring closing procedure. The general formation of aza-cycles was first demonstrated by Richman and Atkins using alkali salts of sulfamide with primary halides, mesylates or tosylates. [25] More detailed studies confirmed the rather straightforward mechanism of the Richman-Atkins cyclization and the influence of solvents, temperature, bases and other reaction parameters. [26-32] Until to date there were only three reports employing this advantageous approach to obtain saccharide-based aza macrocycles. [33-35]

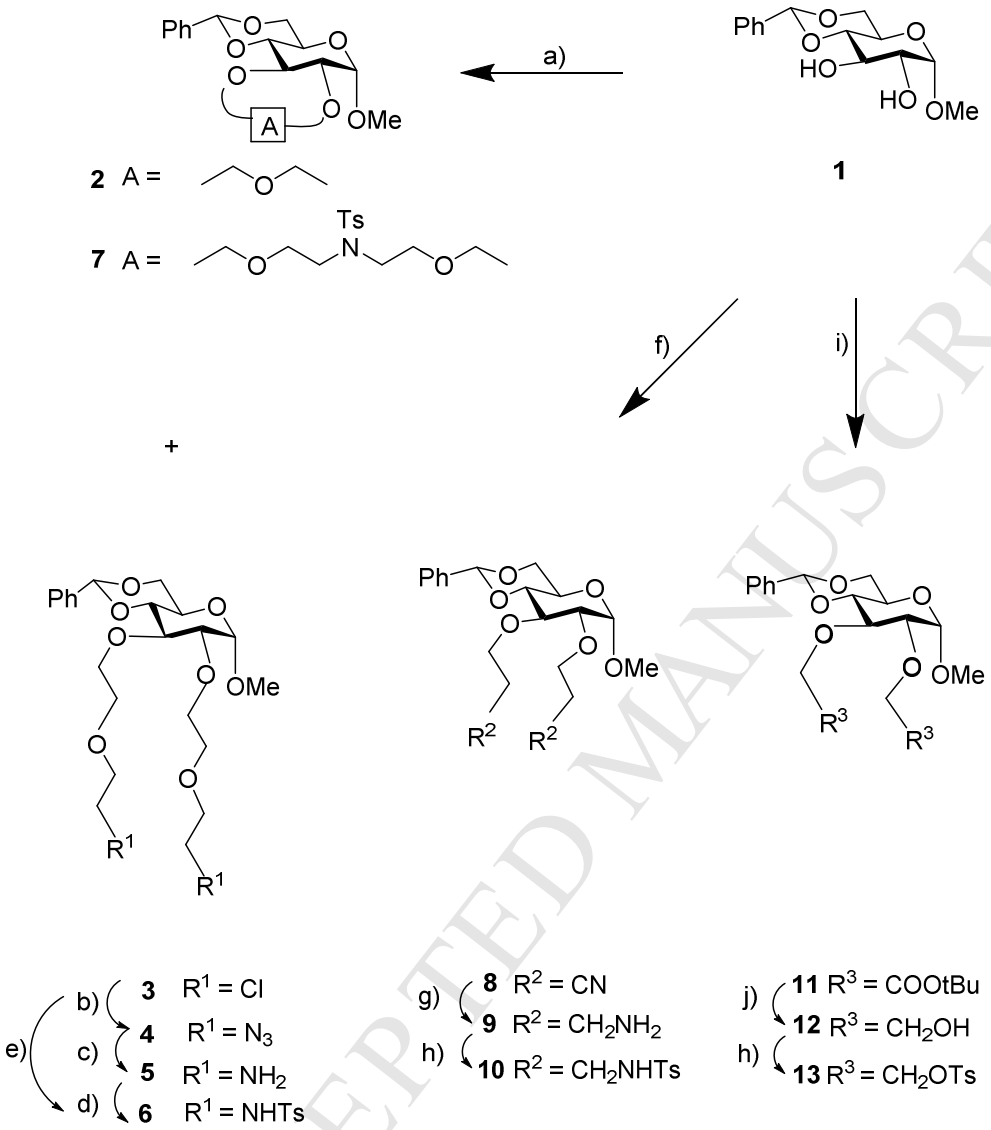
2. Results and discussion

2.1. Synthesis of monosaccharide models

Starting with commercially available methyl α-D-glucopyranoside the benzylidene acetal **1** [36] was obtained, which has two hydroxyl functions ready for etherification with a bifunctional spacer system. Thus treatment of **1** employing phase transfer catalysis (PTC) [37] with bis(2-chloroethyl)ether according to Gross et al. [38] gave equal amounts of the dialkylated product **3** and the crown ether **2**. This 9-crown-3 system apparently formed by intramolecular nucleophilic substitution was surprisingly not mentioned in reference38. By enhancing the concentration of the haloether the relative ratio of products could be largely shifted towards the desired compound **3**. Further straight forward transformations with sodium azide in DMF gave the diazido derivative **4** in 88 % yield, hydrogenation lead to the diamino compound **5** in 93 % yield, and a final tosylation resulted in formation of the bis-toluenesulfonamide **6**. By treatment of **3** with toluene sulfonamide in high excess [39] compound **6** was obtained directly in 47 % yield but accompanied by coronand **7** in 30 % yield. The latter could be obtained selectively in 74 % yield under stoichiometric conditions.

Reaction of **1** with 2-bromopropane nitril under PTC conditions gave both, the mono- and the bis-cyanoethylated compound **8.** High pressure [40] hydrogenolysis of the latter employing rhodium on aluminium oxide [41] gave the bis-3-aminopropyloxy derivative **9** quantitatively, and by final tosylation the crystalline starting material **10** for a Richman-Atkins cyclization was obtained.

As a third pathway alkylation of **1** was performed employing bromoacetic acid *tert*-butyl ester to give compound **11**. Reduction with lithium aluminium hydride resulted in formation of the corresponding diol **12,** [42] which was tosylated to give precursor derivative **13** [43] in 73 % yield (Scheme 1).



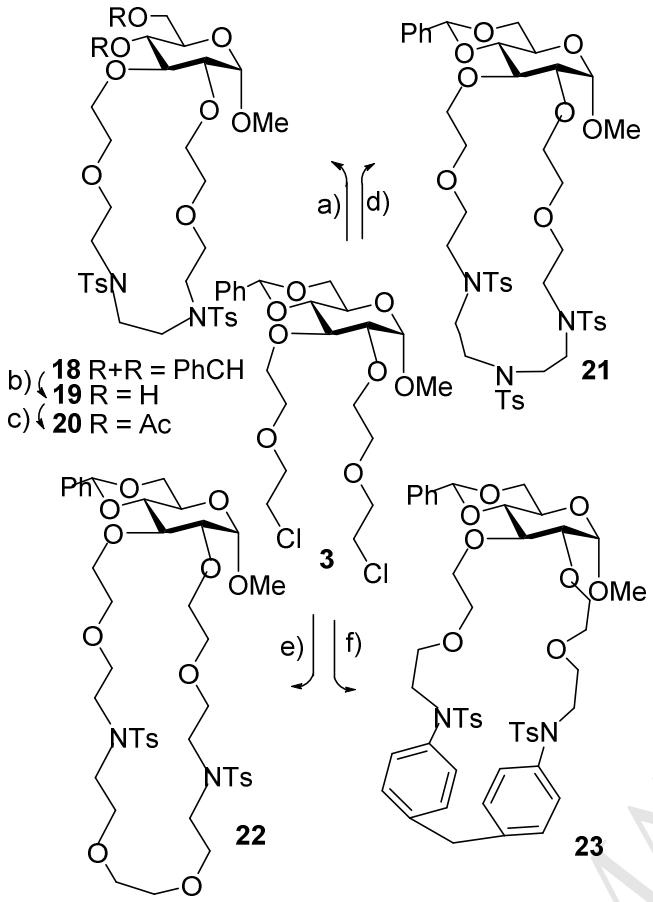
Scheme 1. *Synthesis of 2,3-di-O-alkylated glucopyranosides.* Reaction conditions: a) 50% aq. NaOH, $(ClCH_2CH_2)_2O$, Bu_4NBr, toluene, 60°C; b) NaN_3, DMF, TMEDA, 80°C; c) Pd/C-H_2,Et_3N MeOH; d) TsCl, pyridine ,-20°C; e)$TsNH_2$, K_2CO_3, DMF, 80°C; f) $BrCH_2CH_2CN$, 20% aq. NaOH, Bu_4NHSO_4, CH_2Cl_2; g) Rh/Al_2O_3-H_2, $MeOH/NH_3$; h) TsCl, pyridine, -20°C; i) 50% aq. NaOH, Bu_4NBr, CH_2Cl_2; j) $LiAlH_4$, THF, 70 °C.

2.2. Sugar-based 18- to 25-membered oxa-aza macrocycles by Richman-Atkins cyclization

For elaboration of advantageous reaction parameters macrocyclization reactions of the sugar dihalo precursor **3** with alkyl sulfonamide building units **14** - **16,** [44,45] and **17** were studied. Previously used solvents such as DMSO or HMPA were inferior to freshly prepared anhydrous DMF, both regarding reaction as well as workup. Potassium or cesium carbonate were much better bases than sodium carbonate and allowed the reaction to proceed under essentially milder conditions. Surprisingly the structure of the bis-sulfonamide reagenthas only little influence, and regardless of the resulting ring size yields were in the range of 40-70 % without optimization.

Treatment of compounds **3** and **14** in DMF at 80 °C with cesium carbonate resulted in formation of the 18-membered macrocycle **18** in 62 % yield. Mild methanolic acid treatment led to selective cleavage of the benzylidene ring in **19**, and further acetylation gave compound **20**. Interestingly, most of these macrocycles showed pronounced glass temperatures in the range of 60 – 80 °C.

The corresponding transformations of **3** and **15** gave the 21-membered component **21**, and that of **3** and **16** lead to the 24-membered compound **22.** Finally, condensation of **3** and **17** gave the 25-membered derivative **23** in around 50% yield with glass temperatures of 60-90 °C (Scheme 2).



Scheme 2. *Ring closing reactions of precursor **3***. Reaction conditions:

a) TsHN–NHTs (**14**), Cs_2CO_3, DMF, 80°C;

b) 10% aq. HCl, MeOH, 70 °C; c) Ac_2O, pyridine, 20°C;

d) TsHN–N(Ts)–NHTs (**15**), K_2CO_3, DMF, 80°C;

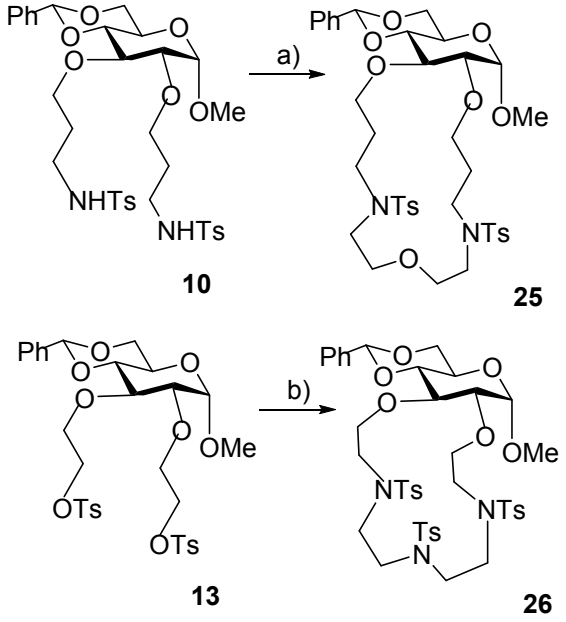
e) TsHN–O–O–NHTs (**16**), K_2CO_3, DMF, 80°C;

f) TsHN–C$_6$H$_4$–CH$_2$–C$_6$H$_4$–NHTs (**17**), Cs_2CO_3, DMF, 80°C.

2.3. Alternative Richman-Atkins cyclization for sugar-based oxa-aza macrocycles

Saccharides with two sulfonamide groups can be condensed under Richman-Atkins conditions with α, ω-bis-tosyloxy components. Thus, derivative **10** was reacted with **24** in DMF at 80 °C and cesium carbonate as base to give the 17-membered saccharide macrocycle **25** in 78 % yield. The corresponding reaction of **13** and the diethylene tris-sulfonamide **15** under similar conditions gave

the saccharide coronand **26** in 76 % yield. This 14-membered macrocycle contains three nitrogen functions and presents a structure en route to sugar-based cyclams (Scheme 3).



Scheme 3. *Ring closing reactions of compounds **10** and **13**.*

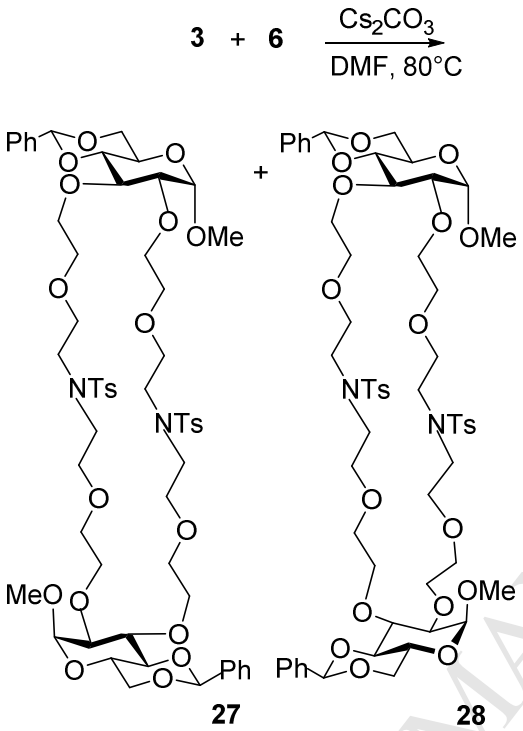
Reaction conditions:

a) TsO, O, Ts, OTs (**24**), Cs_2CO_3, DMF, 80°C;

b) TsHN, N, NHTs (**15**), Cs_2CO_3, DMF, 80°C.

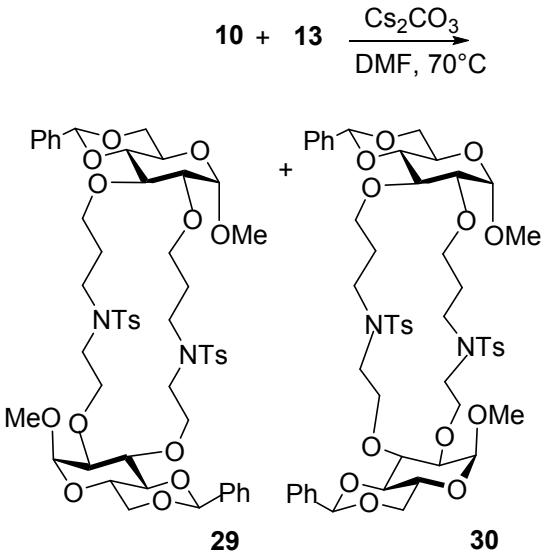
2.4. Formation of coronands with two saccharide units by Richman-Atkins cyclization

In line with the above discussed approach the formation of two sugar-based isomeric crown ethers could be realized. By reaction of the dichloro precursor **3** with the bis-toluene sulfonamide **6** the two isomeric 30-membered components **28** and **29** were obtained, which only differ in their bridging positions. Chromatographic separation was not feasible, and in ^{1}H-NMR all signals were largely on top of each other. However, the ^{13}C-NMR in combination with the DEPT spectrum confirmed the structure, which was further substantiated by FAB-MS (Scheme 4).



Scheme 4. *30-Membered macrocycles with two saccharide units.*

A corresponding transformation could be performed by reaction of the bis-sulfonamide **10** and the bis-tosyloxy derivative **13**, which led to both isomerically linked 20-membered bis-saccharide macrocycles **29** and **30** in 32



Scheme 5. *Synthesis of 20-membered macrocycles with two saccharide units.*

and 35 % yield, respectively. In contrast to the previous example, these compounds could be nicely separated. All NMR spectra were in keeping with their structures, however, an unequivocal assignment could not be realized. Since both samples are non-crystalline with glass temperatures of 89-95 °C and 84-88 °C, respectively, X-ray elucidations for asserting the absolute configurations could not be performed (Scheme 5).

3. Conclusion

Employing varying Richman-Atkins conditions with alkali carbonate in DMF proved to be a facile approach for the synthesis of saccharide-based aza-macrocycles. Thus, 2,3-ω-haloalkylated as well as ω- toluenesulfonamide-alkylated glucopyranoside derivatives could be successfully condensed with α,ω-bis-tosylsulfonamide components and gave sugar-based aza-macrocycles displaying 14-, 17-, 18-, 21-, 24-, and 25-membered rings in convincing yields. Corresponding condensations of two differently functionalized carbohydrate units led to isomeric aza-macrocyles of 20- as well as 30-membered rings

containing two saccharides. Studies regarding host as well as catalytic properties of representative components are presently under way.

4. Experimental

4.1. General methods

All reactions were monitored by thin layer chromatography on silica gel foils GF_{254} (Merck). Detection was by UV or spraying with 20 % ethanolic sulfuric acid and subsequent heating. Amines were detected with 10 % ninhydrin in ethanol and further heating to 200° C. Column chromatography was done on silica gel 60 (230-400 mesh, Merck) by the flash mode with the solvent mixture recorded. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (100 and 62 MHz) were done on Bruker AMX-400 and AC-250. Signal assignment was by ^{1}H,^{1}H- and ^{1}H,^{13}C-COSY measurements. $CDCl_3$ (δ 77.0 for ^{13}C) and TMS (δ 0.0 for ^{1}H) were used as internal standards. FAB mass spectra were recorded on double focussing mass spectrometer VG 70-250 S (VG Analytical) with *m*-nitrobenzyl alcohol as matrix material and xenon as ionisation gas. MALDI-TOF mass spectra were done on Bruker Biflex with nitrogen laser 337 nm, pulse width 5 ms and α-cyano-4-hydroxy- cinnamic acid as matrix. Melting points and glass temperatures are uncorrected and were taken with a Leitz heating microscope or with an Olympus BH polarising microscope and Mettler FP82 heating table. Optical rotations were measured with Perkin-Elmer polarimeters 241 and 243 using sodium D line (589 nm), cuvette length 10 cm, and temperature 20 °C. Elemental analysis was performed by the Microanalytical Section of the Department of Chemistry.

4.2. General procedures

4.2.1. Alkylation by Phase Transfer Catalysis (GP1)

The saccharide derivative was dissolved in the given solvent and alkylation reagent (0.55 eq) and phase transfer catalyst (1.5 eq) were added. Under vigorous stirring 20-50 % aqueous sodium hydroxide was added and the reaction performed as recorded. For workup the aqueous phase was thoroughly extracted by an organic solvent, combined with the organic phase, dried over sodium sulfate, and after evaporation the residue purified or separated by chromatography.

4.2.2. Tosylation of Amines and Alcohols (GP2)

The starting material was dissolved in anhydrous pyridine (5-15 mL per hydroxyl or amino group) and cooled to -20 °C. Under stirring tosyl chloride (1.15 eq per hydroxyl or amino group) added. After termination of the reaction (1-5 d) the solvent was evaporated in vacuo (temperature below 50 °C) and several times co-evaporated with toluene. The raw material was purified by chromatography.

4.2.3. Richman-Atkins Cyclization (GP3)

The ditosylate or dichloride (0.5-1.0 mmol) and the nucleophilic component (0.5-1.0 mmol) were dissolved in anhydrous dimethylformamide (10 mL). After addition of base (3-5 eq of Na_2CO_3, K_2CO_3 or Cs_2CO_3) the reaction was kept as 60-80 °C for several days. Workup was by filtration over silica gel and evaporation. The remainder was dissolved in toluene/ethyl acetate and treated by ultra sonification for 5 min followed by filtration over silica gel, evaporation and purification of the raw material by chromatography.

4.3. Syntheses

4.3.1. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(3-oxapentylene)-α-D-glucopyranoside (2) and Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(5-chloro-oxapentyl)-α-D-glucopyranoside (3)

Reaction of compound **1** (15.0 g, 53 mmol), bis(2-chloroethyl)-ether (37.8 g, 31 mL, 264 mmol), tetrabutylammonium bromide (5.0 g, 15.5 mmol) in toluene (400 mL) and sodium hydroxide (50 % aqueous solution, 200 mL) according to GP1 was done for 3 days at 60°C. Workup gave a mixture which was separated by column chromatography (dichloromethane/acetone 30 : 1 to 15 : 1).

Compound **2**: yield 3.6 g (19 %), mp 116 °C (from isopropanol), $[\alpha]_D^{20}$ = + 94.2 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.51-7.33 (m, 5H, Ph), 5.54 (s, 1H, PhC*H*), 4.80 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.49 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.87 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.51 (dd, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.73 (dd, 1H, $J_{5,6ax}$ 10.0, $J_{6ax,6eq}$ 10.5 Hz, H-6ax), 4.28 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.5 Hz, H-6eq), 3.44 (s, 3H, OCH_3), 4.14-4.02 (m, 2H, OCH_2), 3.84-3.74 (m, 7H, OCH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.53 (C-1), 82.40 (C-2), 79.59 (C-3), 80.70 (C-4), 62.41 (C-5), 69.07 (C-6), 55.22 (OCH_3), 74.95, 73.56, 71.10 (4C, OCH_2), 101.60 (Ph*C*H), 137.38, 129.26, 128.20, 126.24 (6C, Ph). Calcd. for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86. Found: C, 61.27; H, 6.85. FAB-MS found [M+H$^+$] 353 (100%); [M$^+$-OCH_3] 321 (40%).

Compound **3**: yield 5.3 g (20 %), colorless syrup, $[\alpha]_D^{20}$ = + 43.1 (*c* =1.0, $CHCl_3$); ref.[37]: mp 62-63 °C, $[\alpha]_D$ = + 42.2 (*c* =1.4, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.49-7.35 (m, 5H, Ph), 5.53 (s1H, PhC*H*), 4.86 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.43 (s, 3H, OCH_3), 3.96-3.63 and 3.54-3.49 (m, 21H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2Cl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.64 (C-1), 82.27, 81.23, 79.60 (C-2, C-3, C-4), 62.87 (C-5), 55.81

(OCH_3), 72.76, 71.74, 71.56, 71.24, 69.62 (7C, C-6, OCH_2), 43.37, 43.21 (2C, CH_2Cl), 101.99 (Ph*C*H), 137.93, 129.50, 128.74, 126.61 (6C, Ph).

4.3.2. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(5-azido-3-oxapentyl)-α-D-glucopyranoside (4)

Compound **3** (2.5 g, 5.0 mmol) and sodium azide (1.95 g, 30 mmol) were dissolved in DMF (50 mL), tetramethylenediamine (TMEDA, 1 mL) added and heated to 80 °C for 24 hours. The cooled suspension was filtered over silica, the solvent removed by distillation and the raw material purified by flash chromatography with dichloromethane/acetone 30 : 1 to give 2.23 g (88 %) of **4** as slightly yellow syrup; $[\alpha]_D^{20}$ = + 44.7 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.49-7.35 (m, 5H, Ph), 5.52 (s, 1H, PhC*H*), 4.85 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.51 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.79 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.57 (dd, 1H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.5 Hz, H-4), 3.72 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.44 (s, 3H, OCH_3), 4.00-3.55 (m, 13H, H-5, OCH_2), 3.40-3.21 (m, 4H, CH_2N_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 99.15 (C-1), 81.74, 80.73, 79.10 (C-2, C-3, C-4), 62.39 (C-5), 55.29 (OCH_3), 72.23, 71.49, 70.75, 70.04, 69.66, 69.12 (7C, C-6, OCH_2), 50.83, 50.67 (2C, CH_2N_3), 101.48 (Ph*C*H), 137.47, 128.99, 128.22, 126.13 (6C, Ph).

4.3.3. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(5-amino-3-oxapentyl)-α-D-glucopyranoside (5)

Compound **4** (2.16 g, 4.25 mmol) was dissolved in methanol (50 mL) and triethylamine (2 mL) as well as palladium/charcoal (5 %, 500 mg) added. The mixture was hydrogenated at normal pressure and room temperature for 24

hours. Filtration over Celite and evaporation gave 1.8 g (93 %) of **5** as colorless syrup; $[\alpha]_D^{20}$ = + 43.4 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.49-7.34 (m, 5H, Ph), 5.52 (s, 1H, PhC*H*), 4.84 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.00-3.23 (m, 19 H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2NH_2), 4.27 (dd, 1H, $J_{5,6eq}$ 4.0, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.43 (s, 3H, OCH_3), 2.88-2.73 (m, 2H, CH_2NH_2), 1.60 (m, 4H, NH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 99.16 (C-1), 81.82, 80.69, 78.94 (C-2, C-3, C-4), 62.39 (C-5), 55.32 (OCH_3), 73.03, 72.20, 71.09, 70.62, 70.03, 69.11 (7C, C-6, OCH_2), 41.90, 41.83 (2C, CH_2NH_2), 101.46 (Ph*C*H), 137.47, 128.98, 128.22, 126.13 (6C, Ph).

4.3.4. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(5-tosylamino-3-oxapentyl)-α-D-glucopyranoside (6)

a) Compound **3** (424 mg, 0.86 mmol), *p*-toluenesulfonamide (3.46 g, 20.2 mmol), and potassium carbonate (2.8 g, 20.2 mmol) in DMF (20 mL) were treated according to GP3 for 24 h at 80°C. Workup as in GP 3 and separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave 330 mg (47 %) of compound **6** and 154 mg (30 %) of compound **7**.

b) Compound **5** (1.76 g, 3.86 mmol), *p*-toluenesulfonyl chloride (1.62 g, 8.5 mmol) dissolved in anhydrous pyridine (50 mL) were treated according to GP2 for 48 h at -20°C. Workup as in GP 2 and separation by flash chromatography (dichloromethane/acetone 10 : 1) gave 1.61 g (54 %) of compound **6.** Glass temperature 51-53 °C; $[\alpha]_D^{20}$ = + 33.9 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.75-7.24 (m, 13H, Ph), 5.56 (s, 1H, PhC*H*), 4.83 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.55 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.81 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ 9.0 Hz, H-3), 3.62 (dd, 1H, $J_{3,4}$ = 9.0 $J_{4,5}$ 9.5 Hz, H-4), 3.80 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6ax}$ 10.0 $J_{5,6eq}$ 4.5 Hz, H-5), 3.74 (dd, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.43 (s, 3H, OCH_3), 5.75, 5.71 (d, 2H, $J_{CH,NH}$ 6.0

Hz, NHTs), 3.90-3.36 (m, 12H, OCH_2), 3.13-2.99 (m, 4H, CH_2NTs), 2.39 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.66 (C-1), 80.21 (C-2), 81.65 (C-3), 78.67 (C-4), 62.47 (C-5), 69.05 (C-6), 55.31 (OCH_3), 72.17, 70.99, 70.69, 70.47, 69.71, 69.30 (6C, OCH_2), 43.00 (2C, CH_2NHTs), 21.48 (2C, CH_3Ts), 101.44 (Ph*C*H), 143.17-137.32 and 129.65-126.17 (18C, Ph). Calcd. for $C_{36}H_{48}O_{12}S_2$ (764.9): C, 56.53; H, 6.33; N, 3.66; S, 8.38. Found: C, 56.53; H, 6.43; N, 3.73; S, 8.37.

4.3.5Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(6-tosyl-3,9-dioxa-6-aza-undecylene)-α-D-glucopyranoside (7)

Compound **3** (755 mg, 1.52 mmol), *p*-toluenesulfonamide (287 g, 1.67 mmol), and cesium carbonate (2.48 g, 7.6 mmol) in DMF (10 mL) were treated according to GP3 for 24 h at 80°C. Workup as in GP 3 and separation by flash chromatography (toluene/ethyl acetate 2 : 1) gave 671 mg (74 %) of compound **7**. Mp 107 °C; $[\alpha]_D^{20}$ = + 18.3 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.70-7.27 (m, 9H, Ph), 5.52 (s, 1H, PhC*H*), 4.83 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.48 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.56 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 4.00-3.60 (m, 15H, H-4, -5, -6ax, OCH_2), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.43 (s, 3H, OCH_3), 3.45-3.35 and 3.29-3.16 (m, 2H, $J_{CH,NH}$ 6.0 Hz, CH_2NTs), 2.42 (s, 4H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.14 (C-1), 79.70 (C-2), 82.21 (C-3), 77.73 (C-4), 62.29 (C-5), 69.07 (C-6), 55.23 (OCH_3), 72.26, 70.90, 70.45, 70.36, 70.28 (6C, OCH_2), 50.38 (2C, CH_2NTs), 21.49 (2C, CH_3Ts), 101.37 (Ph*C*H), 143.26-136.25 and 129.70-126.05 (12C, Ph). Calcd. for $C_{29}H_{39}NO_{10}S$ (593.7): C, 58.67; H, 6.62; N, 2.36; S, 5.40. Found: C, 58.72; H, 6.70; N, 2.33; S, 5.25. FAB-MS found [M+Cs^+] 726 (40%), M+Rb^+] 678 (35%), [M + Na^+] 616 (25%), [M + H^+] 594 (70%).

4.3.6Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(2-cyanoethyl)-α-D-glucopyrano-side (8)

Reaction of compound **1** (1.0 g, 3.5 mmol), 2-bromopropane nitril (950 mg, 0.6 mL, 7.1 mmol), tetrabutylammonium hydrogensulfate (600 mg, 1.8 mmol) in DMF (15 mL) and sodium hydroxide (20 % aqueous solution, 10 mL) according to GP1 was done for 24 hour at 20°C. Workup gave a mixture of 567 mg (42 %) compound **8** and 536 mg (46 %) of methyl 4, 6-*O*-benzylidene-2-*O*-(2-cyanoethyl)-α-D-glucopyranoside which were separated by column chromatography (dichloromethane/acetone 10 : 1).

Compound **8**: mp 125 °C, ref.[40] 126-127 °C; $[\alpha]_D^{20}$ = + 53.9 (*c* =1.0, $CHCl_3$), ref.[39] + 58.0 (*c*=1.2 in $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.48-7.36 (m, 5H, Ph), 5.54 (s, 1H, PhC*H*), 4.86 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.45 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.80 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.57 (dd, 1H, $J_{3,4}$ = 9.5, $J_{4,5}$ 10.0 Hz, H-4), 3.86 (ddd, 1H, $J_{4,5}$ 10.0, $J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.5 Hz, H-5), 3.73 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.29 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.46 (s, 3H, OCH_3), 4.04-4.01 (m, 2H, OCH_2), 3.93-3.79 (m, 2H, OCH_2), 2.65 and 2.58 (each dd, 2H, $J_{CH,CH}$ 6.1 Hz, CH_2CN).

4.3.7 Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(3-aminopropyl)-α-D-glucopyranoside (9)

Compound **8** (4.1 g, 10.5 mmol) was dissolved in ammonia-saturated methanol (50 mL). Rhodium on Al_2O_3 (5 %, 500 mg) were added, and the mixture was hydrogenated in an autoclave at 50 bar and 20 °C for 3 days.

Filtration over Celite and evaporation gave 3.9 g (93 %) of **9** as a colorless syrup; $[\alpha]_D^{20}$ = + 90.4 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$ + D_2O): δ=7.49-7.32 (m, 5H, Ph), 5.54 (s, 1H, PhC*H*), 4.83 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.54 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.98-3.60 (m, 7H, H-3, -5, -6ax, OCH_2), 3.52 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ 9.5 Hz, H-4), 4.28 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.44 (s, 3H, OCH_3), 2.84-2.69 (m, 4H, CH_2NH_2), 1.81-1.67 (m, 4H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.77 (C-1), 82.11, 80.35, 78.23 (C-2, C-3, C-4), 62.34 (C-5), 69.03 (C-6), 55.31 (OCH_3), 71.19, 69.51 (2C, OCH_2), 39.69, 39.39 (2C, CH_2NH_2), 33.98, 33.56 (2C, CH_2), 101.42 (Ph*C*H), 137.41, 128.98, 128.25, 126.06 (6C, Ph).

4.3.8 Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-[3-*N*-tosylaminopropyl]-α-D-glucopyranoside (10)

Compound **9** (3.9 g, 9.8 mmol), *p*-toluenesulfonyl chloride (4.4 g, 23.3 mmol) dissolved in anhydrous pyridine (150 mL) were treated according to GP2 for 48 h at -20°C. Workup as in GP2 and separation by chromatography (dichloromethane/acetone 17 : 1) gave 2.8 g (41 %) of compound **10.** Mp 126 °C; $[\alpha]_D^{20}$ = + 29.5 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.76-7.20 (m, 13H, Ph), 5.52 (s, 1H, PhC*H*), 4.85 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.35 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.66 (dd, 1H, $J_{2,3}$ = 9.0, $J_{3,4}$ 9.5 Hz, H-3), 3.49 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ 9.5 Hz, H-4), 3.86-3.65 (m, 6H, H-5, -6ax, OCH_2), 4.27 (dd, 1H, $J_{5,6eq}$ 4.0, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.45 (s, 3H, OCH_3), 5.51, 5.25 (dd, 2H, $J_{CH,NH}$ 5.5 and 6.0 Hz, NHTs), 3.10-2.99 (m, 4H, CH_2NHTs), 1.80-1.62 (m, 4H, CH_2), 2.40, 2.38 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.05 (C-1), 79.63 (C-2), 78.21 (C-3), 81.95 (C-4), 62.27 (C-5), 69.13 (C-6), 55.29 (OCH_3), 71.80, 68.98 (2C, OCH_2), 41.80, 41.45 (2C, CH_2NHTs), 29.28, 28.93 (2C, CH_2), 21.49 (2C, CH_3Ts), 101.47 (Ph*C*H), 143.15-137.24 and 129.72-126.09 (18C, Ph).

4.3.9. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(*tert*-butyloxycarbonylmethyl)-α-D-glucopyranoside (11)

Reaction of compound **1** (1.5 g, 5.3 mmol), *tert*-butyl bromoacetate (2.27 g, 1.7 mL, 11.7 mmol), tetrabutylammonium bromide (1.7 g, 5.3 mmol) in dichloromethane (30 mL) and sodium hydroxide (50 % aqueous solution, 10 mL) according to GP1 was done for 1 hour at 20°C. Workup and column chromatography (dichloromethane/acetone 40 : 1) gave 1.47 g (54%) of compound **11** as colorless syrup; $[\alpha]_D^{20}$ = - 4.0 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.47-7.35 (m, 5H, Ph), 5.50 (s, 1H, PhC*H*), 5.08 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.58 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.93 (dd, 1H, $J_{2,3}$ 9.0, $J_{3,4}$ 9.5 Hz, H-3), 3.64 (dd, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.81 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.5 Hz, H-5), 3.74 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.46 (s, 3H, OCH_3), 4.49 and 4.30 (each d, each 1H, *J* 17.5 Hz, OCH_a), 4.35 and 4.18 (each d, each 1H, *J* 16.0 Hz, OCH_b), 1.47, 1.39 (s, 18H, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.73 (C-1), 82.20, 80.25, 79.21 (C-2, C-3, C-4), 61.98 (C-5), 70.63 (C-6), 55.36 (OCH_3), 170.30, 169.33 (2C, CO), 81.84, 81.51 (2C, q, *t*-Bu),70.07, 69.12 (2C, OCH_2), 28.16, 28.11 (6C, CH_3-*t*Bu), 101.29 (Ph*C*H), 137.31, 128.98, 128.23, 126.12 (6C, Ph). Calcd. for $C_{18}H_{26}O_8$ (370.4): C, 58.37; H, 7.08. Found: C, 58.09; H, 7.18.

4.3.10. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(2-hydroxyethyl)-α-D-glucopyranoside (12)

Compound **11** (4.4 g, 8.6 mmol) dissolved in anhydrous tetrahydrofuran (100 mL) was treated with lithium aluminium hydride (1.64 g, 43.1 mmol) and

refluxed for 24 h. Following addition of methanol filtration over Celite and evaporation of solvents gave the raw material which was purified by chromatography (ethyl acetate/ ethanol 12: 1). Yield: 2.54 g (80 %) of compound **12.** Mp 107 °C, ref.[42] 114 °C; $[\alpha]_D^{20}$ = + 73.4 (*c* =1.0, $CHCl_3$), ref.[42] $[\alpha]_D^{20}$ = + 12.1 (*c* =0.13, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.48-7.35 (m, 5H, Ph), 5.55 (s, 1H, PhC*H*), 4.86 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.53 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.88 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.57 (dd, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.73 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.5 Hz, H-5), 3.97-3.66 (m, 9H, H-6ax, OCH_2), 4.28 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.45 (s, 3H, OCH_3), 4.20-4.12 (m, 4H, CH_2OTs), 4.07-3.98 and 3.90-3.79 (each m, each 2C, OCH_2), 3.17 and 3.05 (b, each 1H, OH), . ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.41 (C-1), 81.92, 80.57, 78.10 (C-2, C-3, C-4), 62.41 (C-5), 69.02 (C-6), 55.31 (OCH_3), 74.56, 72.92 (2C, OCH_2), 62.07, 61.86 (2C, CH_2OH), 101.61 (Ph*C*H), 137.05-126.04 (6C, Ph).

4.3.11. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-(*p*-toluenesulfonyloxyethyl)-α-D-glucopyranoside (13)

Compound **12** (2.2 g, 6.0 mmol) and *p*-toluenesulfonyl chloride (2.9 g, 15.1 mmol) dissolved in anhydrous pyridine (50 mL) were treated according to GP2 for 24 h at -20°C. Workup as in GP2 and purification by chromatography (dichloromethane) gave 2.0 g (73 %) of compound **13.** Mp 121 °C, ref.[43] 127-128 °C; $[\alpha]_D^{20}$ = + 31.6 (*c* =1.0, $CHCl_3$), ref.[43] $[\alpha]_D^{20}$ = + 25.6 (*c* =1.5, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ=7.75-7.21 (m, 13H, Ph), 5.49 (s, 1H, PhC*H*), 4.82(d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.41 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.74 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.48 (dd, 1H, $J_{3,4}$ 9.5, $J_{4,5}$ 10.0 Hz, H-4), 3.77 (ddd, 1H, $J_{4,5} = J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.5 Hz, H-5), 3.71 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.27 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.44 (s, 3H, OCH_3), 4.20-4.12 (m, 4H, CH_2OTs), 4.07-

3.98 and 3.90-3.79 (each m, each 2C, OCH_2), 2.42, 2.40 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.01 (C-1), 80.46 (C-2), 79.24 (C-3), 81.93 (C-4), 62.19 (C-5), 69.40 (C-6), 55.37 (OCH_3), 78.84, 72.64 (2C, OCH_2), 70.07, 69.04 (2C, CH_2OTs), 21.63 (2C, CH_3Ts), 101.25 (Ph*C*H), 143.51-132.99 and 129.89-126.01 (18C, Ph).

4.3.12. 4 ,4´-Ditosylamino-diphenylmethane (**17**)

4, 4´-Diamino-diphenylmethane (15.0 g, 75.7 mmol) dissolved in anhydrous pyridine (250 mL) was cooled to – 20°C and portion wise treated with *p*-toluenesulfonyl chloride (33.2 g, 174 mmol). After 3 days the solution was poured onto ice water (250 mL), extracted twice with diethyl ether (each 300 mL), the organic solvent successively washed with cold HCl (2N, 300 mL) and ice water (300 mL), dried over Na_2SO_4, decolorized with active charcoal and evaporated. The residue was recrystallized from dichloromethane/methanol 1 : 1 to give 23.9 g (62 %) of compound **17**. Mp 167 °C; ^{1}H-NMR (400 MHz, DMSO): δ = 10.10 (s, 2H, NHTs), 7.63and 7.34 (m, each 4H, Ph), 7.03-6.98 (m, 8H, Ph), 2.55 (s, 6H, CH_3Ts). Calcd. for $C_{27}H_{26}N_2O_4S_2$ (506.7): C, 64.01; H, 5.17; N, 5.53; S, 12.66. Found: C, 63.60; H, 5.15; N, 5.42; S, 12.66.

4.3.13. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(6, 9-ditosyl-3, 12-dioxa-6, 9-diaza-tetradecanylene)-α-D-glucopyranoside (18)

Compound **3** (2.75 g, 5.57 mmol), ethylene bis-toluenesulfonamide (**14**) (2.05 g, 5.57 mmol), and cesium carbonate (5.3 g, 16.5 mmol) in DMF (40 mL) were treated according to GP3 for 2 days at 80°C. Workup as in GP3 and

separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave 2.72 g (62 %) of compound **18**. Glass temperature 81 °C; $[\alpha]_D^{20}$ = + 21.4 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.75-7.18 (m, 13H, Ph), 5.52 (s, 1H, PhC*H*), 4.75 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 3.89-3.23 (m, 25H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2NTs), 4.26 (dd, 1H, $J_{5,6eq}$ 4.0, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.38 (s, 3H, OCH_3), 2.43, 2.42 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.95 (C-1), 82.01, 80.36, 79.02 (C-2, C-3, C-4), 62.30 (C-5), 55.28 (OCH_3), 71.92, 71.71, 70.94, 70.77, 70.63, 69.12 (7C, C-6, OCH_2), 50.31, 50.22, 49.74, 49.58 (4C, CH_2NTs), 21.58 (2C, CH_3Ts), 101.39 (Ph*C*H), 143.37-136.15 and 129.79-126.10 (18C, Ph). Calcd. for $C_{38}H_{50}N_2O_{12}S_2$ (791.0): C, 57.71; H, 6.37; N, 3.54; S, 8.11. Found: C, 58.51; H, 6.52; N, 3.38; S, 8.36. FAB-MS found [M+H^+] 791 (40%), [M^+-OCH_3] 759 (20%), [M^+-$CH_3C_6H_4SO_2$] 635 (100%).

4.3.14. Methyl 2, 3-*O*-(6, 9-ditosyl-3, 12-dioxa-6, 9-diaza-tetradecanylene)-α-D-glucopyranoside (19)

Compound **18** (1.13 g, 1.43 mmol) was dissolved in methanol (100 mL), HCl (0.5 M, 5 mL) added and heated to 70 °C for 1h. The mixture was neutralized with Na_2CO_3, evaporated to dryness, and the residue extracted with dichloromethane (200 mL). The organic phase was washed twice with water (each 50 mL) then dried over Na_2SO_4 and evaporated to give 902 mg (90 %) of compound **19**. Glass temperature 72-75 °C, $[\alpha]_D^{20}$ = + 32.1 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.74-7.32 (m, 8H, Ph), 4.75 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.21-3.20 (m, 26H, H-2, -3, -4, -5, -6a, -6b, OCH_2, CH_2NTs), 3.40(s, 3H, OCH_3), 2.43 (s, 6H, CH_3Ts), 2.77 (d, 1H, $J_{4,OH}$ 1.5 Hz, OH-4), 2.11 (dd, 1H, $J_{6,OH}$ 6.1 Hz, OH-6). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 97.78 (C-1), 81.82, 80.43, 70.64, 70.49 (C-2, C-3, C-4, C-5), 62.49 (C-6), 55.17 (OCH_3), 72.06, 71.38, 71.16, 70.86, 70.33,

69.63 (6C, OCH_2), 50.53, 49.91, 49.68, 49.66 (4C, CH_2NTs), 21.53 (2C, CH_3Ts), 143.45-135.79 and 129.73-127.32 (8C, Ph). Calcd. for $C_{31}H_{46}N_2O_{12}S_2$ (702.8): C, 52.98; H, 6.60; N, 3.99; S, 9.12. Found: C, 52.70; H, 6.65; N, 3.90; S, 9.12. FAB-MS found [M+Na^+] 725 (100%), [M +H^+] 703 (10%), [M^+-$CH_3C_6H_4SO_2$] 672 (40%).

4.3.15. Methyl 4, 6-di-*O*-acetyl-2, 3-*O*-(6, 9-ditosyl-3, 12-dioxa-6, 9-diaza-tetradecanylene)-α-D-glucopyranoside (20)

Compound **19** (63 mg, 90 μmol) dissolved in pyridine (5 mL) was treated with acetic acid anhydride (64 mg, 0.6 mmol) for 24h at 20 °C. Co-distillation with toluene and purification by flash chromatography (toluene/ethyl acetate 1:1) gave 65 mg (92 %) of compound **20**. Glass temperature 63-68 °C, $[\alpha]_D^{20}$ = + 37.8 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.76-7.32 (m, 8H, Ph), 4.78 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.41 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 3.67 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ 9.5 Hz, H-3), 4.95 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ 9.5 Hz, H-4), 3.77 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6a}$ 5.0, $J_{5,6b}$ 2.0 Hz, H-5), 4.21 (dd, 1H, $J_{5,6a}$ 5.0, = $J_{6a,6b}$ 12.0 Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.40 (s, 3H, OCH_3), 4.05-3.98, 3.81-3.75 and 3.72-3.68 (each m, each 1H, OCH_2), 3.63-3.18 (m, 17H, OCH_2, CH_2NTs), 2.44 (s, 6H, CH_3Ts), 2.07, 2.05 (s, 6H, CH_3CO). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 97.90 (C-1), 80.31 (C-2), 79.71 (C-3), 69.91 (C-4), 67.46 (C-5), 62.492 (C-6), 55.39 (OCH_3), 72.07, 71.63, 71.18, 71.00, 70.57, 70.47 (6C, OCH_2), 50.46, 50.31, 49.99, 49.78 (4C, CH_2NTs), 21.57 (2C, CH_3Ts), 20.86, 20.80 (2C, *C*H_3CO), 170.77, 169.50 (2C, CH_3*C*O), 143.39-136.19 and 129.80-127.39 (12C, Ph). $C_{35}H_{50}N_2O_{14}S_2$ (786.9): FAB-MS found [M+Na^+] 809 (100%), [M +H^+] 787 (30%), [M^+-$CH_3C_6H_4SO_2$] 631 (40%).

4.3.16. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(6, 9, 12-tritosyl-3, 15-dioxa-6, 9, 12-triaza-heptadecanylene)-α-D-glucopyranoside (21)

Compound **3** (760 mg, 1.53 mmol), diethylenetriamino tris-toluenesulfonamide (**15**)[44,45] (868 mg, 1.53 mmol), and potassium carbonate (1.1 g, 7.7 mmol) in DMF (10 mL) were treated according to GP3 for 4 days at 80°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave 625 mg (41 %) of compound **21**. Glass temperature 81-86 °C; $[\alpha]_D^{20}$ = + 6.0 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.77-7.16 (m, 17H, Ph), 5.54 (s, 1H, PhC*H*), 4.69 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.73-3.32 (m, 29H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2NTs), 4.25 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.40 (s, 3H, OCH_3), 2.42, 2.41 (s, 9H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.40 (C-1), 81.50, 79.69, 78.64 (C-2, C-3, C-4), 61.86 (C-5), 54.75 (OCH_3), 71.33, 70.83, 70.46, 70.29, 69.89, 69.67, 68.50 (7C, C-6, OCH_2), 49.75, 49.46, 49.32, 49.22, 48.92, 48.77 (6C, CH_2NTs), 21.06 (3C, CH_3Ts), 100.80 (Ph*C*H), 143.05-135.31 and 129.35-125.66 (24C, Ph). Calcd. for $C_{47}H_{61}N_3O_{14}S_3$ (988.2): C, 57.13; H, 6.22; N, 4.25; S, 9.73. Found: C, 58.00; H, 6.35; N, 4.00; S, 9.16. FAB-MS found [$M+H^+$] 988 (20%), [M^+-OCH_3] 956 (20%), [M^+-$CH_3C_6H_4SO_2$] 832 (100%).

4.3.17. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(6, 15-ditosyl-3, 9, 12, 18-tetraoxa-6, 15-diaza-icosanylene)-α-D-glucopyranoside (22)

Compound **3** (700 mg, 1.41 mmol), 1, 8-ditosylamino-3, 6-dioxaoctane (**16**)[44,45] (645 mg, 1.41 mmol), and potassium carbonate (976 mg, 7.1 mmol) in DMF (10 mL) were treated according to GP3 for 3 days at 80°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 2 : 1) gave 553 mg (45 %) of compound **22**. Glass temperature 60-63 °C; $[\alpha]_D^{20}$ = + 18.7 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.71-7.18 (m, 13H, Ph), 5.52 (s, 1H,

PhC*H*), 4.78 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.90-3.30 (m, 33H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2NTs), 4.26 (dd, 1H, $J_{5,6eq}$ 4.0, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.41 (s, 3H, OCH_3), 2.42, 2.39 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.09 (C-1), 81.87, 80.37, 79.00 (C-2, C-3, C-4), 62.33 (C-5), 55.25 (OCH_3), 72.26, 71.09, 70.70, 70.45, 70.35, 70.20, 69.08 (11C, C-6, OCH_2), 49.36, 49.18, 49.15 (4C, CH_2NTs), 21.49, 21.46 (2C, CH_3Ts), 101.33 (Ph*C*H), 143.22-136.82 and 129.67-125.30 (18C, Ph). Calcd. for $C_{42}H_{58}N_2O_{14}S_2$ (879.1): C, 57.39; H, 6.65; N, 3.19; S, 7.29. Found: C, 57.27; H, 6.57; N, 3.02; S, 7.21. FAB-MS found [M+Cs^+] 1012 (70%), [M+Rb^+] 964 (45%), [M+H^+] 880 (25%), [M^+-OCH_3] 847 (35%), [M^+-$CH_3C_6H_4SO_2$] 723 (90%).

4.3.18. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-[bis-*N*-(4, 4´-ditosylamino-diphenylmethane)-3-oxapentyl]-α-D-glucopyranoside (23)

Compound **3** (500 mg, 1.0 mmol), 4, 4´-ditosylamino-diphenylmethane (**17**)[44,45] (562 mg, 1.1 mmol), and cesium carbonate (1.62 g, 5.0 mmol) in DMF (10 mL) were treated according to GP3 for 2 days at 80°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave 479 mg (52 %) of compound **23**. Glass temperature 79-87 °C; $[\alpha]_D^{20}$ = + 24.9 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.52-6.92 (m, 21H, Ph), 5.48 (s, 1H, PhC*H*), 4.73 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.21 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0 Hz, H-2), 3.58 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ 9.0 Hz, H-3), 3.43 (dd, 1H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.5 Hz, H-4), 3.71 (ddd, 1H, $J_{4,5}$ = 9.5. $J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.5 Hz, H-5), 3.69 (dd, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.25 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.38 (s, 3H, OCH_3), 3.90 (s, 2H, $PhCH_2Ph$), 3.75-3.14 (m, 16H, OCH_2, CH_2NTs), 2.42, 2.40 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.04 (C-1), 80.82 (C-2), 78.91 (C-3), 81.55 (C-4), 62.37 (C-5), 69.05 (C-6), 55.29 (OCH_3), 72.84, 71.01, 70.39, 70.11, 69.82, 69.42

(6C, OCH_2), 50.52, 50.39 (2C, CH_2NTs), 41.31 (Ph*C*H_2Ph), 21.55 (2C, CH_3Ts), 101.43 (Ph*C*H), 143.37-135.92 and 129.43-125.30 (30C, Ph). Calcd. for $C_{49}H_{56}N_2O_{12}S_2$ (929.1): C, 63.34; H, 6.08; N, 3.02; S, 6.90. Found: C, 64.11; H, 6.25; N, 2.84; S, 6.69. FAB-MS found [M+H^+] 929 (100%), [M^+-OCH_3] 897 (30%), [M^+-$CH_3C_6H_4SO_2$] 774 (100%).

4.3.19. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(4, 10-ditosyl-7-oxa-4, 10-diazatri-decanylene)-α-D-glucopyranoside (25)

Compound **10** (262 mg, 0.63 mmol), diethyleneglycol ditosylate (**24**)[44,45] (262 mg, 0.63 mmol), and cesium carbonate (977 mg, 3.0 mmol) in DMF (10 mL) were treated according to GP3 for 3 days at 80°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave 383 mg (78 %) of compound **25**. Glass temperature 66-71 °C; $[\alpha]_D^{20}$ = + 25.8 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.70-7.14 (m, 13H, Ph), 5.51 (s, 1H, PhC*H*), 4.84 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.90-3.13 (m, 18H, H-2, -4, OCH_2, CH_2NTs), 3.65 (dd, 1H, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.76 (ddd, 1H, $J_{4,5}$ = 9.5. $J_{5,6ax}$ 10.0, $J_{5,6eq}$ 4.0 Hz, H-5), 3.71 (dd, 1H, $J_{5,6ax} = J_{6ax,6eq}$ 10.0 Hz, H-6ax), 4.26 (dd, 1H, $J_{5,6eq}$ 4.0, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.41 (s, 3H, OCH_3), 1.99-1.78 (m, 4H, CH_2), 2.42, 2.38 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.01 (C-1), 82.63, 79.64, 77.56 (C-2, C-3, C-4), 62.20 (C-5), 55.24 (OCH_3), 71.00, 70.80, 70.28, 69.05, 68.03 (5C, C-6, OCH_2), 49.23, 48.71, 47.76, 47.61 (4C, CH_2NTs), 29.64, 29.32 (2C, *C*H_2), 21.49, 21.45 (2C, CH_3Ts), 101.23 (Ph*C*H), 143.29-137.03 and 129.71-125.30 (18C, Ph). Calcd. for $C_{38}H_{50}N_2O_{11}S_2$ (775.0): C, 58.90; H, 6.50; N, 3.61; S, 8.27. Found: C, 59.87; H, 6.75; N, 3.48; S, 8.71. FAB-MS found [M+Na^+] 797 (100%), [M+H^+] 775 (90%).

4.3.20. Methyl 4, 6-*O*-benzylidene-2, 3-*O*-(3, 6, 9-tritosyl-3, 6, 9-triiaza-undecylene)-α-D-glucopyranoside (26)

Compound **13** (778 mg, 1.15 mmol), diethylenetriamino tris-tuoluenesulfonamide (**15**)[44,45] (650 mg, 1.15 mmol), and cesium carbonate (1.5 g, 4.6 mmol) in DMF (10 mL) were treated according to GP3 for 24 h at 80°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 4 : 1) gave 782 mg (76 %) of compound **26**. Glass temperature 98 °C; $[\alpha]_D^{20}$ = + 11.4 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.73-7.16 (m, 17H, Ph), 5.52 (s, 1H, PhC*H*), 4.85 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.07-3.14 (m, 21H, H-2, -3, -4, -5, -6ax, OCH_2, CH_2NTs), 4.25 (dd, 1H, $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10.0 Hz, H-6eq), 3.39 (s, 3H, OCH_3), 2.45, 2.44, 2.39 (s, 9H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 97.77 (C-1), 82.50, 78.49, 77.57 (C-2, C-3, C-4), 62.13 (C-5), 55.19 (OCH_3), 71.82, 68.99, 68.08 (3C, C-6, OCH_2), 50.98, 50.37, 49.75, 49.33 (6C, CH_2NTs), 21.55 (3C, CH_3Ts), 101.28 (PhCH), 143.67-137.25 and 129.85-125.99 (24C, Ph). Calcd. for $C_{43}H_{53}N_3O_{12}S_3$ (900.1): FAB-MS found [M+Na^+] 922(100%).

4.3.21. 2, 3´: 3, 2´-Bis-di-*O*-tosyl-(6-tosyl-3, 9-dioxa-6-aza-undecanylene)-bis-[methyl 4, 6-*O*-benzylidene-α-D-glucopyranoside] (27) and 2, 2´: 3, 3´-Bis-di-*O*-tosyl-(6-tosyl-3, 9-dioxa-6-aza-undecanylene)-bis-[methyl 4, 6-*O*-benzylidene-α-D-glucopyranoside] (28)

Compounds **3** (224 mg, 0.44 mmol), **6** (334 mg, 0.44 mmol) and cesium carbonate (1.4 g, 4.3 mmol) in DMF (10 mL) were treated according to GP3 for 4 days at 80°C. Workup as in GP3 and purification by flash chromatography (toluene/ethyl acetate 3 : 1) gave 270 mg (52 %) of a mixture **27** + **28**, which could not be separated. Data of this mixture: ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.71-7.24 (m, 18H, Ph), 5.50 (s, 2H, PhC*H,* PhC*H´*), 4.82 (d, 2H, $J_{1,2} = J_{1',2'}$ 3.5

Hz, H-1, -1´), 3.90-3.24 (m, 42H, H-2, -2´, -3, -3´, -4, -4´, -5, -5´, -6ax, -6ax´, OCH_2, CH_2NTs), 4.28-4.25 (m, 2H, H-6eq, -6eq´), 3.41 (s, 6H, OCH_3 ,OCH_3´), 2.42, 2.34 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 99.15 (C-1, -1´), 81.88, 81.84, 80.49, 80.43, 79.11 (6 C, C-2, -2´, C-3, -3´, C-4, -4´), 62.32 (2C, C-5, -5´), 55.28 (2C, OCH_3, OCH_3´), 72.22, 71.22, 71.15, 70.82, 70.74, 70.63, 70.46, 70.36, 70.22, 70.14, 69.07 (14C, C-6, -6´, OCH_2), 49.28, 49.11, 49.02, 48.96 (4C, CH_2NTs), 21.48 (2C, CH_3Ts), 101.32 (2C, Ph*C*H, Ph*C*H´), 143.42-137.47 and 129.69-126.08 (24C, Ph). Calcd. for $C_{58}H_{72}N_2O_{20}S_2$ (1187.4): FAB-MS found [M+Na^+] 1210 (100%).

4.3.22. 2, 3´: 3, 2´-Bis-di-*O*-(3-tosyl-3-aza-hexylene)-bis-[methyl 4, 6-*O*-benzylidene-α-D-glucopyranoside] (29) and 2, 2´: 3, 3´-Bis-di-*O*-(3-tosyl-3-aza-hexylene)-bis-[methyl 4, 6-*O*-benzylidene-α-D-glucopyranoside] (30)

Compounds **10** (585 mg, 0.83 mmol), **13** (563 mg, 0.83 mmol) and cesium carbonate (1.35 g, 4.15 mmol) in DMF (10 mL) were treated according to GP3 for 2 days at 70°C. Workup as in GP3 and separation by flash chromatography (toluene/ethyl acetate 1 : 1) gave compounds **29** and **30**, the assignment of which was ambiguous.

Eluting first compound **29** (or **30**): 283 mg (33 %); glass temperature 89-95 °C; $[\alpha]_D^{20}$ = + 40.7 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.66-7.16 (m, 18H, Ph), 5.53 (s, 2H, PhC*H,* PhC*H´*), 4.80 (d, 2H, $J_{1,2} = J_{1',2'}$ 3.5 Hz, H-1, -1´), 3.90-3.11 (m, 26H, H-2, -2´, -3, -3´, -4, -4´, -5, -5´, -6ax, -6ax´, OCH_2, CH_2NTs), 4.27 (dd, 2H, $J_{5,6eq} = J_{5',6eq'}$ 3.5, $J_{6ax,6eq} = J_{6ax',6eq'}$ 10.0 Hz, H-6eq, -6eq´), 3.40 (s, 6H, OCH_3, OCH_3´), 1.89-1.72 (m, 4H, CH_2), 2.38, 2.34 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.35 (C-1, -1´), 82.43, 81.92, 80.10, 80.01, 78.68, 77.85 (6 C, C-2, -2´, C-3, -3´, C-4, -4´), 62.32, 62.19 (2C, C-5, -5´), 55.34, 55.25 (2C, OCH_3,

OCH_3´), 70.73, 70.34, 69.07, 68.39, 67.46 (6C, C-6, -6´, OCH_2), 48.29, 48.28, 47.24, 45.53 (4C, CH_2NTs), 29.63, 29.35 (2C, CH_2), 21.47 (2C, CH_3Ts), 101.39, 101.26 (2C, Ph*C*H, Ph*C*H´), 143.23-137.34 and 129.70-125.30 (18C, Ph). Calcd. for $C_{52}H_{66}N_2O_{16}S_2$ (1039.2): C, 60.10; H, 6.40; N, 2.70; S, 6.17. Found: C, 60.28; H, 6.54; N, 2.75; S, 6.09. FAB-MS found [M+Cs^+] 1171 (80%), [M+Na^+] 1061 (100%).

Eluting second compound **30** (or **29**): 297 mg (35 %); glass temperature 84-88 °C; $[\alpha]_D^{20}$ = + 34.1 (*c* =1.0, $CHCl_3$); ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 7.70-7.14 (m, 18H, Ph), 5.49, 5.44 (s, 2H, PhC*H,* PhC*H´*), 4.84, 4.83 (d, 2H, $J_{1,2} = J_{1´,2´}$ 3.5 Hz, H-1, -1´), 3.90-3.05 (m, 26H, H-2, -2´, -3, -3´, -4, -4´, -5, -5´, -6ax, -6ax´, OCH_2, CH_2NTs), 4.29-4.24 (m, 2H, H-6eq, -6eq´), 3.44, 3.43 (s, 6H, OCH_3, OCH_3´), 1.97-1.90 and 1.78-1.69 (m, 4H, CH_2), 2.42, 2.35 (s, 6H, CH_3Ts). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 98.44 (2C, C-1, -1´), 82.25, 81.79, 80.19, 79.76, 78.70, 77.92 (6 C, C-2, -2´, C-3, -3´, C-4, -4´), 62.31, 62.30 (2C, C-5, -5´), 55.39, 55.31 (2C, OCH_3, OCH_3´), 71.32, 70.18, 69.06, 68.27 (6C, C-6, -6´, OCH_2), 49.00, 48.28, 47.12, 46.30 (4C, CH_2NTs), 29.36, 29.35 (2C, CH_2), 21.51 (2C, CH_3Ts), 101.32, 101.23 (2C, Ph*C*H, Ph*C*H´), 143.32-137.36 and 129.78-125.98 (18C, Ph). Calcd. for $C_{52}H_{66}N_2O_{16}S_2$ (1039.2): FAB-MS found [M+Na^+] 1061 (100%).

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Highlight

The efficient synthesis of novel carbohydrate-based macrocyclic nitrogen-containing crown ethers by Richman-Atkins cyclization is reported.