Cluster Mannosides as Inhibitors of Type 1 Fimbriae-Mediated Adhesion of *Escherichia coli*: Pentaerythritol Derivatives as Scaffolds

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Pentaerythritol derivatives were used as core molecules for the synthesis of two cluster α-D-mannosides, which were designed as oligomannoside mimetics. The problem of glycosyl orthoester formation, which frequently occurs in oligo-mannosylations, was solved. The clusters were tested for their capacity to block binding of *Escherichia coli* to yeast mannan in vitro and were found to be more than 200 times more potent in inhibiting mannose-specific adhesion than methyl α-D-mannoside.

Introduction

A most exciting feature of carbohydrates is their ability to encode biological information in the form of three-dimensional arrangements of atoms and functional groups, e.g. those represented by the complex oligosaccharide portions present in glycoproteins and glycolipids.[1] This information is translated into a biological effect by the formation of noncovalent complexes between segments of oligosaccharide structures and specialized proteins, the lectins and selectins,[2] respectively. Such carbohydrate-protein complexes are currently under investigation in order to elucidate their structural and functional details.[3] One of the tools optimally suited for the investigation and manipulation of carbohydrate-protein interactions consists of oligosaccharide mimetics that are structurally modeled on their naturally occurring counterparts. The design of oligosaccharide mimetics may allow both an easier synthetic access to the necessary ligands and the optimization of their affinities to the respective receptors.[4]

A rational approach to the synthesis of oligosaccharide mimetics involves subjecting the naturally occurring structures to a "molecular striptease" that substitutes the inner regions of an oligosaccharide by a simple, noncarbohydrate core molecule. The latter can then be functionalized with the carbohydrate epitopes, which are essential for receptor binding. In this way, oligoantennary oligosaccharides of naturally occurring glycoconjugates may be mimicked by so-called cluster glycosides.[5]

Such cluster glycosides are promising antiadhesives to block bacterial infection, as bacterial adhesion is often a prerequisite for infection. To adhere to the surface of their target cells, bacteria use multivalent contacts between their own lectins and parts of the host cell glycocalyx. Some bacterial lectin domains are assembled on long, proteinogenous appendages on the bacterial surface, which are called pili or fimbriae. Fimbriae are classified according to their sugar specificity and mannose-specific fimbriae are called "type 1 fimbriae". While type 1-fimbriated *E. coli* are normal inhabitants of the colon, they cause infections if they colonize the urinary tract. Type 1 fimbriae of *E. coli* substantially contribute to the adhesion and virulence of this microorganism.[6]

During our ongoing research program aimed at inhibiting the mannose-specific adhesion of *Escherichia coli* bacteria to their host cells,[7] we synthesized a number of different cluster mannosides to mimic structural ensembles present in high-mannose type *N*-glycans.[8] Some tri- and tetravalent glycoclusters turned out to be especially potent inhibitors of bacterial binding. We conclude from these results that the synthetic glycoclusters, completely or partially, fit into the carbohydrate recognition domain (CRD) of the bacterial lectin. This finding is in keeping with a structural model for the bacterial CRD used for mannose-specific adhesion, according to which the CRD consists of three subsites and may accommodate mannose-containing trisaccharides of a specific three-dimensional structure.[9] These findings make it an attractive scientific goal to improve the synthesis, yield and performance of cluster mannosides that can serve as oligomannoside mimetics and potentially inhibit mannose-specific bacterial adhesion.

In this context, we recently turned our attention to pentaerythritol as a scaffold for clustering. Pentaerythritol has been used successfully as a branched core molecule for the preparation of glycomimetics as well as dendrimers.[10] It was first used for sugar clustering with the goal of producing potentially megacaloric nutrients.[11] In this and other cases,[12] as well as for the synthesis of sugar-based clusters,[11] ester linkages were used for clustering. Peptide linkages were chosen to assemble tumor-associated saccharides en route to haptens for anti-tumor vaccine development.[13]

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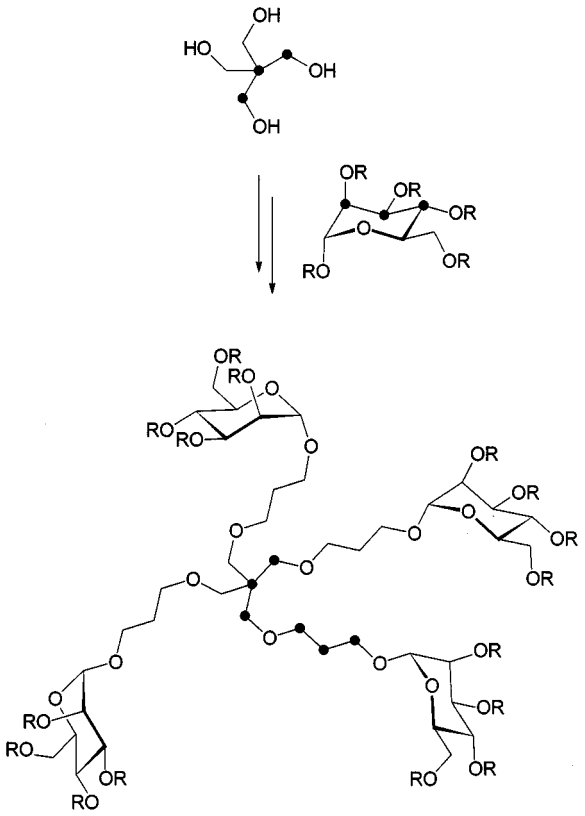
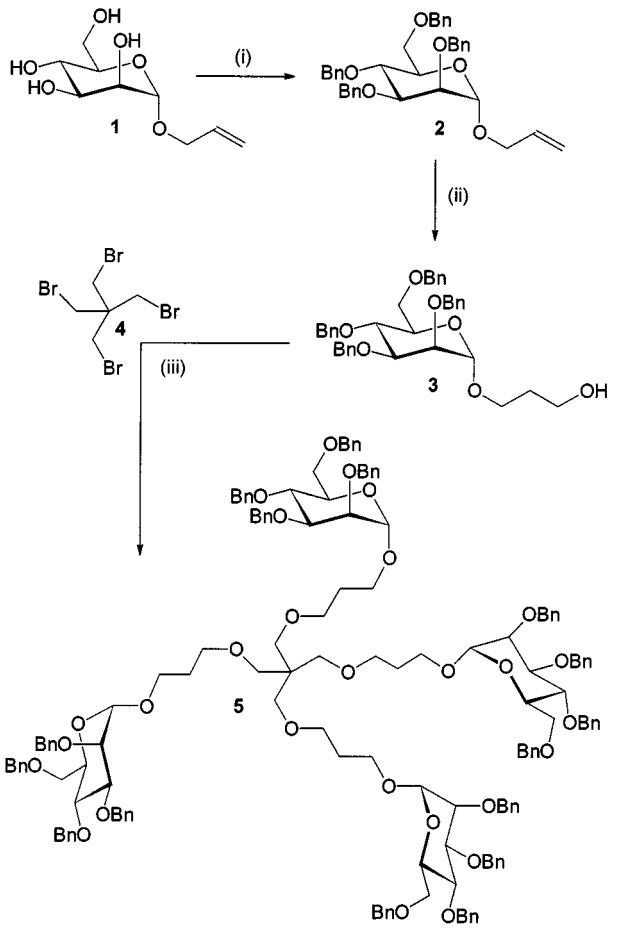


Scheme 1. Pentaerythritol-based cluster glycosides as depicted were designed to serve as high mannose-type glycan mimetics, in which C_3 spacers, highlighted by black dots, are thought to substitute monosaccharide units



Scheme 2. (i) BnBr, NaH, DMF, 86%; (ii) 9-BBN, THF, then NaOH and H_2O_2, 91%; (iii) NaH, diglyme, 62%

In addition, galabioside clusters were synthesised on the basis of pentaerythritol derivatives and proved to be excellent in vitro inhibitors of hemagglutination caused by *Streptococcus suis*.[14] Furthermore, pentaerythritol has been used as the skeleton molecule for the synthesis of sialyl Lewis-X mimetics,[15] for the synthesis of mono-, di- and tridentate galactose clusters carrying photoaffinity labels to block and label the hexose transport system in erythrocytes[16] and to synthesize α-D-mannosyl clusters as photoaffinity ligands for Concanavalin A.[17]

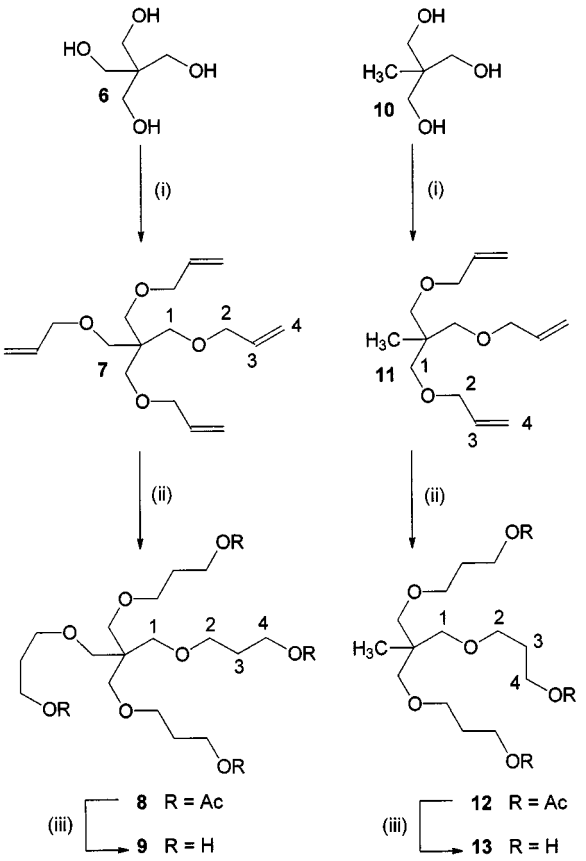
For the inhibition of mannose-specific bacterial adhesion, we designed a pentaerythritol-based cluster-mannoside as depicted in Scheme 1, in which pentaerythritol itself, as well as the included C_3 spacers, are used as structural substitutes of monosaccharide moieties. This principle was introduced by Lehmann and co-workers with the synthesis of so-called spacer-modified oligosaccharides to investigate the sugar binding site of α-amylase.[18] We now report on the synthesis of the target molecule **19** as well as its trivalent analogue **21**, and on their antiadhesive properties in inhibiting mannose-specific binding of type 1-fimbriated *E. coli*.

Results and Discussion

Synthesis

A retrosynthetic analysis reveals two possibilities for the synthesis of cluster mannoside **19**; (i) incorporating a C_3 chain as the aglycon part of the carbohydrate portion prior to clustering or (ii) realizing the required C_3 spacer moieties at the core molecule. In both synthetic routes, an allylation-hydroboration sequence would allow the necessary hydroxypropyl spacers to be established.

When we followed the first route, the spacer portion was introduced as the aglycon moiety in mannoside **3**, in order to perform the necessary glycosylation step at an early stage of the synthesis. For the synthesis of **3**, allyl α-D-mannoside (**1**) was prepared by Fischer glycosylation, benzylated to **2** under standard conditions, and **2** was eventually subjected to a hydroboration/oxidation reaction to obtain the primary alcohol **3**. Hydroboration of the allyl group in **2** proceeded strictly regioselectively when the sterically demanding hydroborane 9-BBN (9-borabicyclo[3.3.1]nonane) was used as the reagent. The structure of **3** could be unequivocally proved by ^{1}H-NMR spectroscopy after acetylation of a small sample. Mannoside **3** was then used as the alcohol component in a Williamson ether synthesis with pentaerythritol tetrabromide (**4**). This reaction, however, led to a mixture of mono-, di-, tri-, and tetradentate products, even when an eight-fold excess of alcohol and forced reaction conditions were used (Scheme 2). In the best cases, the tetra-cluster **5** could be isolated in 62% yield, although yields that were lower by approximately 10% were also of-



Scheme 3. (i) Allyl bromide, aq. NaOH, TBABr, 59% for **7**, 47% for **11**; (ii) 9-BBN, THF, then NaOH and H_2O_2, then Ac_2O, pyridine, 87% for **8**, 84% for **12**; (iii) NaOMe, MeOH, quant.

ten obtained. This result is in accordance with the known reluctance with which neopentyl positions, as present in **4**, react in substitution reactions.

Therefore, an alternative route to target cluster **19** was started, in which first pentaerythritol was modified to serve as spacer-equipped tetrafunctional core molecule in the subsequent glycosylation step. Derivatisation of pentaerythritol was accomplished by per-allylation of the poorly soluble pentaerythritol by reversed phase transfer catalysis according to a published procedure.[19] The resulting allyl ether **7** was then converted into pure tetra-alcohol **9** by a hydroboration/oxidation reaction of the double bonds using 9-BBN, acetylation of the product to form **8**, purification at this stage and then Zemplén deacetylation (Scheme 3). The analogous reaction sequence was carried out with 2,2,2-trihydroxymethylethane (**10**) to yield **13** and to allow the synthesis of the trivalent cluster analogue **21**, which we intended to compare to **19** in the biological studies. NMR data of core molecules **7**−**9** and **11**−**13** are listed in Table 1.

The subsequent mannosylation of **9** and **13** turned out to be more difficult than expected. With 2,3,4,6-tetra-*O*-acetyl-α-mannosyl bromide as the glycosyl donor, only glycosyl orthoesters were obtained and by using acetylated mannosyl trichloroacetimidate **14** as the glycosyl donor, no improvement was achieved in this regard (Scheme 4). With TMS triflate as the catalyst, as well as with $BF_3{\cdot}Et_2O$ used as the Lewis acid, orthoester clusters **15** and **16**, respectively, were isolated in significant yields. Attempts to isomerize **15** and **16** to the respective mannosides were not successful. 1,2-*O*-glycosyl orthoesters can be recognized in ^{1}H-NMR spectra by a typical high-field shift of 2-H ($\delta \approx 4.6$) and 5-H ($\delta \approx 3.7$) and, moreover, by the chemical shift of the orthoacetyl CH_3 group ($\delta = 1.78$), which is clearly separated from the acetyl CH_3 groups resonating at $\delta \approx 2$.

Table 1. ^{1}H-NMR data (400 MHz, $CDCl_3$) of core molecules **7**−**9** and **11**−**13**

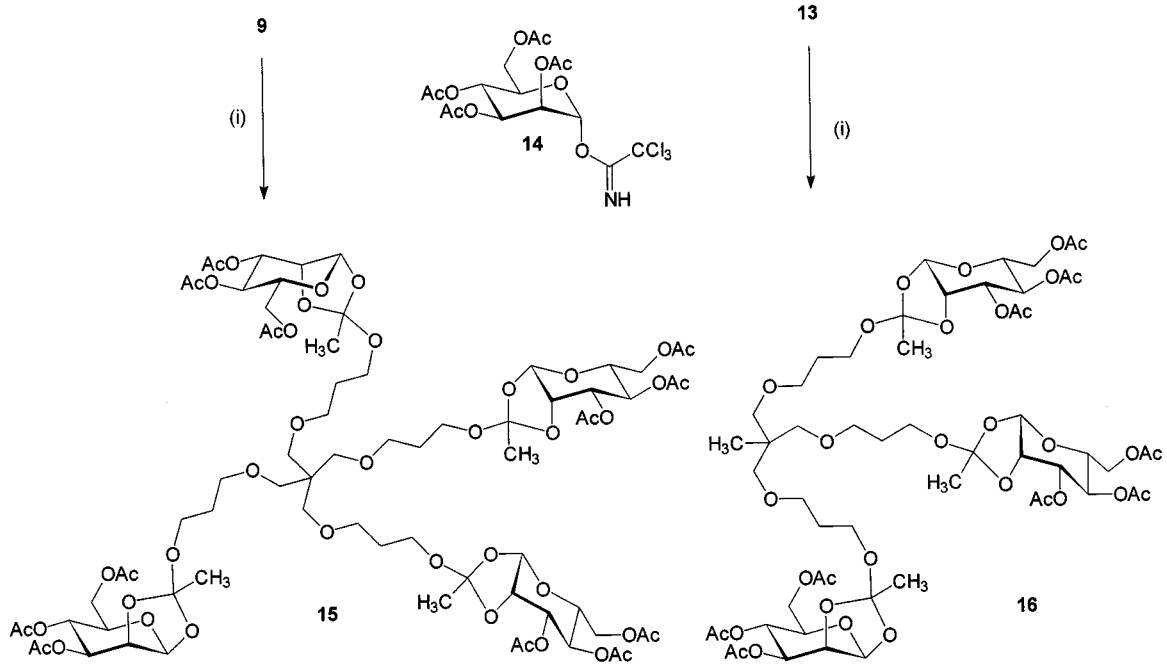
	Positions of recorded protons					
	1	2	3	4	$COCH_3$	CH_3
7	3.46 (s)	3.95 (dddd)	5.88 (m_c)	5.25 (ddd) 5.13 (ddd)	–	–
11	3.30 (s)	3.95 (m_c)	5.87 (m_c)	5.20 (m_c)	–	1.00 (s)
8	3.35 (s)	3.45 (t)	1.86 (m_c)	4.13 (t)	2.05 (s)	–
12	3.23 (s)	3.45 (t)	1.86 (m_c)	4.15 (t)	2.05 (s)	0.91 (s)
9	3.39 (s)	3.58 (t)	1.79 (m_c)	3.74 (t)	–	–
13	3.30 (s)	3.59 (t)	1.80 (m_c)	3.75 (t)	–	0.90 (s)

To circumvent orthoester formation, which was shown to be the dominant problem of the mannosylation reaction, benzoyl-protected mannosyl trichloroacetimidate **17**[20] was used as the glycosyl donor. No orthoester formation was observed in this case and, upon mannosylation of **9** and **13**, the protected cluster mannosides **18** and **20**, respectively, were isolated in excellent yields after purification on silica gel followed by gel permeation chromatography (Scheme 5). Thus, benzoylated trichloroacetimidate **17**, which is obtained in three steps from mannose is an excellent mannosyl donor in cluster mannoside synthesis and completely avoids the problem of orthoester formation. Deprotection to afford the target clusters **19** and **21**, respectively, was an easy and quantitative reaction under Zemplén conditions (using sodium methanolate in methanol).

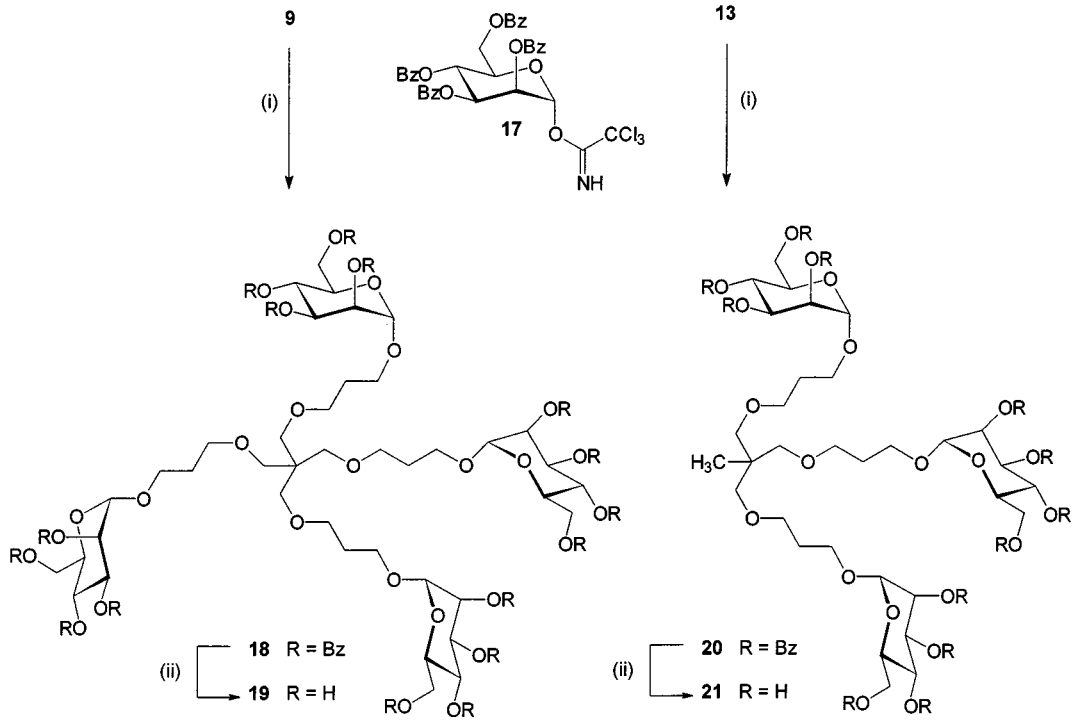
Clusters **18**−**21** show symmetrical well-resolved NMR spectra that exhibit the signal set for one "arm" of the clusters. MS analyses of the clusters give single peaks at the expected masses.

Antiadhesive Properties

Bacteria use specific fimbrial lectins to adhere to the glycocalyx of their host cells. Since adhesion is often the first step in bacterial pathogenesis, an anti-adhesive intervention may effectively prevent bacterial infection. Mimetics of the oligosaccharides that bind to the bacterial carbohydrate recognition domains are likely candidates for inhibiting bacterial adhesion. The antiadhesive potencies of cluster mannosides **19** and **21** were tested in an ELISA-microplate format using a genetically engineered *E. coli* strain, HB101 (pPKl4),[21] which expresses only type 1 fimbriae on its surface. Serially diluted aqueous solutions of clusters **19** and **21** were included in the adhesion reaction and the cluster concentration that inhibits binding by 50% was determined (IC_{50}). Both clusters worked as inhibitors of bacterial adhe-



Scheme 4. (i) TMSOTf; for **15** in acetonitrile, 64%; for **16** in toluene, 54%



Scheme 5. (i) CH_2Cl_2, TMSOTf, 92% for **18**, 95% for **20**; (ii) NaOMe, MeOH, quant.

sion at concentrations in the low micromolar range, with the tetravalent cluster **19** surpassing the inhibitory potency of methyl mannoside by 257 and its trivalent analogue **21** by 200. On a valency-corrected basis, **19** and **21** performed almost equally well. These results demonstrate that cluster **19** and also **21** can serve as oligomannoside mimetics, displaying a significantly elevated inhibitory potency compared to methyl α-D-mannoside, which was used as monovalent reference compound (Table 2).

Conclusion

A number of conclusions can be drawn concerning the synthesis and biological effects with type 1 fimbriae CRDs

Table 2. Antiadhesive properties of the examined cluster mannosides obtained in ELISA inhibition assays, in comparison to methyl α-D-mannopyranoside (MeMan); inhibition values obtained in four independently performed assays were averaged

	MeMan	19 (tetravalent)	21 (trivalent)
IC_{50} [a] [μM] (assay 1)	3000	12.5	12.5
IC_{50} [a] [μM] (assay 2)	3500	15	12.5
IC_{50} [a] [μM] (assay 3)	4000	11	24
IC_{50} [a] [μM] (assay 4)	2500	12	16
average IC_{50} [μM]	3250	12.63	16.25
standard deviation	645.5	5.4	1.7
RIC_{50} [b]	1	257	200
valency-corrected RIC_{50} [c]	1	64	67

[a] IC_{50}: 50% of binding inhibited. – [b] RIC_{50}: Relative IC_{50} based on MeMan (≡1). – [c] Relative IC_{50} based on moles mannoside contained in one mole cluster.

of cluster mannosides such as **19** and **21**. (i) The C_3 spacer-equipped branched oligofunctional alcohols **9** and **13** used as glycosyl donor scaffolds can be readily prepared by an allylation-hydroboration sequence starting from the sterically more hindered alcohols **6** and **10**, respectively. (ii) These oligoalcohols can be quantitatively α-mannosylated using benzoylated mannosyl trichloroactetimidate **17** as the glycosyl donor without orthoester formation. (iii) Cluster mannosides **19** and **21** are potent inhibitors of mannose-specific adhesion of *E. coli* in the ELISA.

The observed inhibition of bacterial adhesion is most likely explained by binding of cluster glycosides **19** and **21** to single carbohydrate recognition domains (CRDs), which are distributed along type 1 fimbriae, rather than by multivalent binding, which would reflect interaction of the sugar clusters with more than one CRD.[22]

Experimental Section

General Methods: Flash chromatography was performed using Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh). – TLC was performed on Kieselgel 60 F_{254} plates from Merck. Detection was carried out under UV light or by spraying with 20% ethanolic sulfuric acid followed by heating. Core molecules were visualized with anisaldehyde reagent[23] and subsequent heating. – Size exclusion chromatography was performed on Sephadex LH-20 from Pharmacia. – NMR spectra were measured with a Bruker AMX 400 (400 MHz for ^{1}H and 100.67 MHz for ^{13}C NMR) or a DRX 500 (500 MHz for ^{1}H and 125.84 MHz for ^{13}C NMR) spectrometer. Chemical shifts are in ppm, relative to internal TMS (δ = 0.00 for ^{1}H and ^{13}C NMR) or solvent peaks, which were calibrated as follows: $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.00 for ^{13}C NMR), [D_4]methanol (δ = 3.35 for ^{1}H and δ = 49.30 for ^{13}C NMR). Where necessary, two-dimensional ^{1}H-^{1}H or ^{1}H-^{13}C COSY experiments were performed for complete signal assignments. – Optical rotation values were obtained using a 341 or 243 Perkin–Elmer polarimeter (Na-D line, 589 nm, cell length 10 cm). – Mass spectra were measured with a VG Analytical 70–250S (FAB MS) or Bruker Biflex III (MALDI-TOF MS) instrument. The matrix used for MALDI was dihydroxybenzoic acid (DHB) in water/acetonitrile (2:1) with 0.1% trifluoroacetic acid was used. Optical densities (ODs) were measured with a Dynatech 5000 ELISA reader at 405 nm with the reference read at 490 nm.

Materials: Methyl α-D-mannoside was purchased from Merck, pentaerythritol tetrabromide from Aldrich, and TMSOTf (Fluka) was used without further purification. F-shaped polystyrene plates from Sarsted (with a lid) were used for inhibition tests. A recombinant type 1 fimbriated *E. coli* strain, *E. coli* HB101 (pPKl4),[21] was used and cultured as described in the literature.[8a] Mannan from *Saccharomyces cerevisiae* was obtained from Sigma and was used in 50 mM Na_2CO_3 solution (1 mg/mL, pH = 9.6). A polyclonal anti fimA antibody was used as the first ELISA antibody. The second antibody was a goat-anti-rabbit peroxidase conjugated antibody (IgG, H+L) and was purchased from Dianova. Skimmed milk was obtained from Glücksklee, Tween 20 from Roth, ABTS [2,2′-azidobis(3-ethylbenzthiazoline-6-sulfonic acid)] from Sigma and thimerosal {2-[(ethylmercurio)thio]benzoic acid, sodium salt} from Merck.

Buffers: PBS (phosphate buffer saline) was prepared by dissolving 8 g of NaCl, 0.2 g of KCl, 1.44 g of $Na_2HPO_4 \times 2\ H_2O$ and 0.2 g of KH_2PO_4 in 1000 mL of distilled deionised water (pH = 7.2). PBSE (PBS buffer used for ELISA) was used as a 150 mM solution [pH = 7.2, NaCl (136.90 mM), KCl (2.68 mM), Na_2HPO_4 (8.0 mM), KH_2PO_4 (2.4 mM), 0.01% thimerosal]. PBSET was PBSE buffer + 0.05% Tween 20. Substrate buffer was 0.1 M sodium citrate dihydrate, adjusted to pH = 4.5 with citric acid. The ABTS solution was prepared by dissolving ABTS (1 mg) in substrate buffer (1 mL) by sonication followed by the addition of 0.1% H_2O_2 (25 μL per mL).

ELISA: The ELISA protocol used to determine the inhibitory potencies of the cluster mannosides towards type 1 fimbriated *E. coli* was carried out according to a published procedure.[8c] ELISA plates were incubated at 37 °C. In preliminary experiments, the optimal concentrations for mannan, bacteria and antibody solutions were determined. Microtiter plates were coated with mannan solution (100 μL per well) and dried overnight at 37 °C. The plates were washed once with PBS (150 μL per well) and then blocked with 5% skimmed milk in PBSE for 30 min at 37 °C. The wells were washed with PBSE (150 μL) and then PBSE (50 μL) and inhibitor solution (50 μL) were added. Inhibitor solutions were diluted serially twofold in PBSE. Bacterial suspension (50 μL per well) was added and the plate was left at 37 °C for 1 h to allow sedimentation of the bacteria. Each well was then washed four times with PBSE (150 μL) and then 50 μL of the first antibody (anti fimA antibody, solution as optimized prior to the experiments) in 2% skimmed milk was added. The plates were incubated for 30 min and then washed twice with PBSET and the second antibody was added (50 μL). The plates were incubated for 30 min and subsequently washed three times with PBSET, PBSE and substrate buffer. ABTS solution (50 μL) was added, the mixture incubated for 30 min at 37 °C and the reaction was stopped by adding 2% oxalic acid (50 μL). IC_{50} values reflect the inhibitor concentration that causes 50% inhibition of bacterial binding to yeast mannan. The percentage inhibition was calculated as $[OD(nI) - OD(I)] \times 100 \times [OD(nI)]^{-1}$. Duplicate results were used for the construction of the inhibition curves for each individual ELISA experiment. Typically, the intra-assay variation of an individual ELISA is very small, whereas the IC_{50} values obtained from several independently performed ELISAs differ significantly. However, when relative inhibition potencies were used to determine the inhibitory potencies of the cluster mannosides towards type 1 fimbriated *E. coli* the results are highly reproducible. For ELISA controls, the bacterial adhesion to blocked, uncoated microtiter plates was

checked, and the reaction of antibodies with carbohydrate derivatives as well as the reaction of the employed antibodies with yeast mannan was tested and found to be negligible. The low background obtained from these control experiments was subtracted when calculating the IC_{50} values.

3-Hydroxypropyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (3): To a solution of benzylated allyl mannoside **2** (4.0 g, 6.89 mmol) in dry dioxane (40 mL) was added 9-BBN (30 mL of a 0.5 M solution in THF) dropwise at 0 °C under argon. The reaction mixture was stirred at room temp. for 20 h, cooled to 0 °C and 3 M aq. NaOH (80 mL) and 30% H_2O_2 (8 mL) were added. The reaction mixture was stirred at room temp. for 2 d, the phases were separated and the aqueous phase was extracted three times with ethyl acetate (100 mL each). The organic phases were combined, washed with satd. NaCl solution, and dried with $MgSO_4$. The solution was filtered and the filtrate concentrated in vacuo to give an almost colorless syrup, which was purified by flash chromatography (toluene/ethyl acetate, 1:1) to yield the title alcohol (3.72 g, 6.2 mmol, 91%) as a colorless syrup. − To facilitate the structural characterization by NMR, a small amount of **3** was acetylated at room temp. in acetic anhydride/pyridine, coevaporated with toluene after complete conversion and filtered through a short silica gel column to yield 3-acetoxypropyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside. − **3:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (m, 2 H, C−CH_2−C), 3.50 (m, 1 H, man-O−CH*H*), 3.63−3.79 (m, 6 H, CH*H*−OH, man-O−C*H*H, 2-H, 5-H, 6-H, 6-H′), 3.93 (t, 1 H, 4-H), 3.85 (m, 2 H, 3-H, C*H*H−OH), 4.47−4.77 (m, 7 H, 3 CH_2-benzyl, CH*H*-benzyl), 4.85 (d, 1 H, *J* = 2.0 Hz, 1-H), 4.86 (d, 1 H, C*H*H-benzyl), 7.10−7.40 (m, 20 H, aryl-H). − **3-Acetoxypropyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (m_c, 2 H, C−CH_2−C), 2.00 (s, 3 H, OAc), 3.42 (m, 1 H, O−CH*H*−CH_2), 3.70−3.80 (m, 5 H, OC*H*H−CH, 2-H, 5-H, 6-H, 6-H′), 3.89 (dd, *J* = 3.1, 10.1 Hz, 1 H, 3-H), 3.98 (t, *J* = 10.1 Hz, 1 H, 4-H), 4.10 (m, 2 H, CH_2OAc), 4.48−4.57 (m, 2 H, CH_2-benzyl), 4.62−4.79 (m, 5 H, 2 × CH_2-benzyl, CH*H*-benzyl), 4.84 (d, *J* = 1.5 Hz, 1 H, 1-H,), 4.87 (d, 1 H, C*H*H-benzyl), 7.10−7.40 (m, 20 H, aryl-H).

Benzyl-Protected Tetravalent Cluster Mannoside 5: Mannoside **3** (500 mg, 0.835 mmol) was dissolved in diglyme (diethylene glycol dimethyl ether, 10 mL) and stirred with sodium hydride (100 mg) for 1 h at room temp. under exclusion of moisture (N_2). A solution of pentaerythritol tetrabromide (**4**, 40 mg, 0.103 mmol) in diglyme (5 mL) was added dropwise at reflux temperature and the reaction mixture was stirred under reflux for 30 h. MeOH (10 mL) was added at room temp., the mixture was filtered through a Celite bed and the filtrate was concentrated in vacuo. Flash-chromatographic purification of the residue (toluene/ethyl acetate, 10:1) afforded the title cluster (157 mg, 0.063 mmol, 62%) as colorless syrup. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (m, 8 H, CH_2−O−CH_2−CH_2−CH_2−O-man), 3.43 (m, 12 H, 4 × CHH−O-man, 4 × C−CH_2−O), 3.73 (m_c, 20 H, 4 × 2-H, 4 × 3-H, 4 × 5-H, 4 × 6-H′, 4 × CHH−O-man), 3.89 (dd, 4 H, 6-H), 3.98 (t, 4 H, 4-H), 4.05 (m, 8 H, CH_2−O−CH_2−CH_2−CH_2−O-man), 4.44−4.85 (m, 32 H, benzyl−CH_2), 4.83 (dd, 4 H, 1-H), 7.12−7.40 (m, 80 H, aryl-H). − ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 35.1 (O−CH_2−CH_2−CH_2−O), 44.1 (C_q, core-C), 68.0, 69.2 (O−CH_2−CH_2−CH_2−O), 69.3 (C_q−CH_2−O), 72.0, 72.4, 73.2, 75.0 (benzyl−CH_2), 64.3 (C-6), 71.7, 74.7, 74.8, 80.1 (C-2, C-3, C-4, C-5), 97.8 (C-1), 127.3−138.3 (aryl-C). − (FAB-MS); *m*/*z*: 2460.3 [M + H$^+$]; 2459.025 calcd. for $C_{153}H_{172}O_{28}$.

Tetra-*O*-allyl-pentaerythritol (7): Pentaerythritol (**6**, 3 g, 22 mmol) was dissolved in 33% aqueous NaOH solution (50 mL). Tetrabutylammonium bromide (2 g, 6.2 mmol) was added, the temperature was raised to 40 °C and then allyl bromide (10 mL, 118 mmol) was added dropwise over 1 h. The reaction mixture was stirred for 12 h at room temp. so vigorously that it appeared to be homogeneous. Toluene (100 mL) was added, the organic phase was washed with water, concentrated in vacuo and purified by flash chromatography (toluene/ethyl acetate, 20:1) to yield the per-allylated product (3.84 g, 13 mmol, 59%) as a colorless syrup; for NMR data see Table 1.

Tetra-*O*-(3-acetoxypropyl)pentaerythritol (8): Allylated pentaerythritol **7** (240 mg, 0.8 mmol) was dissolved in dry THF (50 mL), 9-BBN (14 mL, 7 mmol) was added and the reaction mixture was stirred under reflux for 1 h. The excess hydride was destroyed by adding a small amount of water. The mixture was cooled to 0 °C, 3 M aq. NaOH (7 mL) was added, followed by dropwise addition of 30% H_2O_2 (7 mL). The reaction mixture was stirred overnight at room temp., the aqueous phase was carefully saturated with K_2CO_3 and the organic phase was separated. The K_2CO_3-saturated aqueous phase was extracted twice with THF (40 mL each) and the combined organic phases were dried with $MgSO_4$. After filtration, the filtrate was concentrated in vacuo, the residual syrup dissolved in pyridine (6 mL) and acetic anhydride (6 mL, 63 mmol) and stirred at room temp. for 2 h. The mixture was coevaporated with toluene on the rotary evaporator and purified on silica gel by flash chromatography (petroleum ether/ethyl acetate, 3:2) to yield the title compound (378 mg, 0.7 mmol, 87%) as a colorless syrup; for NMR data see Table 1.

Tetra-*O*-(3-hydroxypropyl)pentaerythritol (9): The acetylated derivative **8** (430 mg, 0.68 mmol) was dissolved in dry MeOH (20 mL), a little sodium was added to afford a catalytic amount of sodium methoxide and the reaction mixture was stirred overnight at room temp. The mixture was neutralized with ion exchange resin (Dowex W50 H$^+$), filtered and the filtrate was concentrated in vacuo to afford tetraol **9** (290 mg, 0.69 mmol, quant.) as a colorless syrup; for NMR data see Table 1.

2,2,2-Tris(allyloxymethyl)ethane (11): 2,2,2-Tris(hydroxymethyl)-ethane (**10**, 2 g, 16.6 mmol) was dissolved in 33% aqueous NaOH solution (50 mL) at 40 °C. Allyl bromide (7.5 g, 62 mmol) and tetrabutylammonium bromide (2 g, 6.2 mmol) were added and the reaction mixture was stirred vigorously for 7 h at 40 °C. Water was added, the aqueous phase was extracted three times with CH_2Cl_2 (100 mL each) and the combined organic phases were dried ($MgSO_4$). After filtration, the solvent was removed in vacuo. Flash-chromatographic purification (toluene/ethyl acetate, 20:1) afforded the title compound (1.87 g, 7.8 mmol, 47%) as a colorless syrup; for NMR data see Table 1.

2,2,2-Tris(acetoxypropyloxymethyl)ethane (12): The allylated core molecule **11** (0.67 g, 2.79 mmol) was dissolved in dry dioxane (20 mL) under N_2 and the solution was cooled to 0 °C. 9-BBN (51 mL of a 50% solution in THF, 25.5 mmol) was added dropwise and the reaction mixture was stirred at room temp. for 24 h. The mixture was cooled to 0 °C and 3 M aq. NaOH (50 mL) was added followed by the dropwise addition of 30% H_2O_2 (8 mL). The reaction mixture was stirred overnight at room temp., the aqueous phase was carefully saturated with K_2CO_3, and the organic layer was separated. The K_2CO_3-saturated aqueous phase was extracted twice with THF (40 mL each) and the combined organic phases were dried with $MgSO_4$. The solution was filtered and the filtrate concentrated in vacuo. The residue was dissolved in pyridine (25 mL), acetic anhydride (20 mL) was added and the solution was stirred at room temp. for 2 h. The mixture was coevaporated with toluene in the rotary evaporator and purified on silica gel by flash

chromatography (toluene/ethyl acetate, 4:1) to yield the title compound (680 mg, 1.62 mmol, 58%) as a colorless syrup; for NMR data see Table 1.

2,2,2-Tris(hydroxypropyloxymethyl)ethane (13): The acetylated derivative **12** (600 mg, 1.42 mmol) was dissolved in dry MeOH (30 mL), a catalytic amount of sodium was added and the reaction mixture was stirred overnight at room temp. The mixture was neutralized with ion exchange resin (Dowex W50 H^+), filtered and the filtrate was concentrated in vacuo to afford triol **13** (420 mg, quant.) as colorless syrup; for NMR data see Table 1.

Tetravalent 1,2-*O*-(Orthoacetyl)-β-D-mannopyranose Cluster 15: The branched tetraol **9** (0.099 g, 0.275 mmol) and the trichloroacetimidate **14** (0.89 g, 1.82 mmol) were combined and coevaporated three times with dry toluene (15 mL each) to remove traces of moisture. This mixture was then dissolved in dry acetonitrile under nitrogen and TMSOTf (0.5 mL of a 0.02 M solution in CH_2Cl_2) was added at 0 °C. The reaction temperature was allowed to rise to room temp. and after 2 h of stirring at ambient temperature more TMSOTf (0.5 mL of a 0.02 M solution in CH_2Cl_2) was added. The reaction mixture was stirred at room temp. overnight, triethylamine (100 μL) was added and the mixture was concentrated in vacuo. Repeated flash chromatography (*n*-hexane/acetone, 4:5) gave the title compound (0.298 g, 0.176 mmol, 64%) as colorless syrup. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (s, 12 H, 4 × orthoacetyl-CH_3), 1.78 (m_c, 8 H, 4 × O−CH_2−CH_2−CH_2−O), 2.04, 2.06, 2.10 [3 × s, each 12 H, each 4 × C(O)CH_3], 3.31 (m, 8 H, 4 × C−CH_2−O), 3.41 (m_c, 8 H, 4 × CCH_2OCH_2), 3.55 (m_c, 8 H, 4 × manOCH_2), 3.68 (ddd, 4 H, 4 × 5-H), 4.14 (dd, *J* = 2.5, 12.0 Hz, 4 H, 4 × 6-H), 4.22 (dd, *J* = 5.0, 12.0 Hz, 4 H, 4 × 6-H′), 4.58 (dd ≈ t, 4 H, 4 × 2-H), 5.16 (dd, *J* = 4.0, 9.5 Hz, 4 H, 4 × 3-H), 5.28 (dd ≈ t, *J* = 9.5 Hz, 4 H, 4 × 4-H), 5.47 (d, *J* = 2.5 Hz, 4 H, 4 × 1-H). − ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.7, 20.7, 20.7 [3 × C(O)CH_3], 24.7 (orthoacetyl-CH_3), 29.8, (O−CH_2−CH_2−CH_2−O), 45.4 (C_q, core-C), 59.8* (O−CH_2−CH_2−CH_2−O), 62.4 (C-6), 65.7 (C-4), 68.0* (O−CH_2−CH_2−CH_2−O), 69.6 (C−CH_2−O), 70.6 (C-3), 71.4 (C-5), 76.5 (C-2), 97.4 (C-1), 124.3 [orthoacetyl-C$(OR)_3$], 169.4, 170.3, 170.6 [3 × C(O)CH_3]; assignments of signals denoted by * may be interchanged. − FAB-MS; $C_{73}H_{108}O_{44}$ [M^+]: calcd. 1689.63 ; found 1689.45.

Trivalent 1,2-*O*-(Orthoacetyl)-β-D-mannopyranose Cluster 16: Triol **13** (50 mg, 0.25 mmol) and trichloroacetimidate **14** (1.0 g, 2.0 mmol) were combined and coevaporated three times with dry toluene to remove traces of moisture. The mixture was kept under nitrogen and dry toluene (20 mL) was added to dissolve the starting materials. The solution was cooled to 0 °C and TMSOTf (0.5 mL of a 0.02 M solution in CH_2Cl_2) was added to start the reaction. The reaction mixture was stirred overnight at room temp. Triethylamine (100 μL) was added and the mixture was concentrated in vacuo. Flash-chromatographic purification (toluene/acetone, 4:1) gave the tris(orthoester) **16** (161 mg, 0.13 mmol, 54%) as a white foam. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, C−CH_3), 1.73 (s, 9 H, 3 × orthoacetyl-CH_3), 1.78 (m_c, 6 H, OCH_2−CH_2−CH_2O), 2.04, 2.07, 2.10 (3 × s, each 9 H, each 3 × $COCH_3$), 3.20 (s, 6 H, 3 × CCH_2O), 3.40 (m_c, 6 H, 3 × CCH_2OCH_2), 3.56 (m_c, 6 H, 3 × manOCH_2), 3.70 (ddd, *J* = 2.5, 5.1, 9.7 Hz, 3 H, 3 × 5-H), 4.17 (dd, *J* = 2.5, 12.2 Hz, 3 H, 3 × 6-H′), 4.21 (dd, *J* = 5.1, 12.2 Hz, 3 H, 3 × 6-H), 4.60 (dd, *J* = 2.5, 4.1 Hz, 3 H, 3 × 2-H), 5.18 (dd, *J* = 4.1, 9.7 Hz, 3 H, 3 × 3-H), 5.30 (dd ≈ t, *J* = 9.7 Hz, 3 H, 3 × 4-H), 5.48 (d, *J* = 2.5 Hz, 3 H, 3 × 1-H). − ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.5, 20.6, 20.6 (3 × $COCH_3$), 24.5 ($OCCH_3$), 29.6 (C−CH_2−C), 40.8 (C_q, core-C), 62.3 (C-6), 59.6, 67.8 (OCH_2−CH_2−CH_2−O), 65.5, 70.4, 71.2, 76.3 (C-2, C-3, C-4, C-5), 77.3 (H_3C−C−CH_2), 97.2 (C-1), 124.8 (orthoacetyl-C), 169.0, 169.8, 170.2 (C=O). − FAB-MS; $C_{53}H_{78}O_{30}$ [M^+]: calcd.1194.45; found 1193.98.

Benzoyl-Protected Tetravalent Cluster Mannoside 18: Tetraol **9** (14 mg, 0.038 mmol) and the benzoylated mannosyl trichloroacetimidate **17** (0.91 g, 1.2 mmol) were dissolved in dry CH_2Cl_2 (8 mL) under N_2. TMSOTf (5% solution in CH_2Cl_2, 0.5 mL) was added and the reaction mixture was stirred overnight at room temp. $NaHCO_3$ (5 g) was added and the suspension was quantitatively transferred (rinse with CH_2Cl_2) to a silica gel column and purified by flash chromatography (light petroleum ether/ethyl acetate, 2:1 → 1:2). This was followed by a second purification step on Sephadex LH-20 (elution with CH_2Cl_2/MeOH, 1:1) to yield the title cluster (95 mg, 0.035 mmol, 92%) as a white amorphous solid. − $[\alpha]_D^{21}$ = −47.2 (*c* = 0.63 in CH_2Cl_2) − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (m_c, 8 H, 4 × $OCH_2CH_2CH_2O$), 3.48 [br. s, 8 H, $(ROCH_2)_4C$], 3.56 [m_c, 8 H, $(RCH_2OCH_2)_4C$], 3.69 (m_c, 4 H, 4 × manOCHH), 3.91 (m_c, 4 H, 4 × manOCHH), 4.44 (dddd ≈ m, 4 H, 4 × 5-H), 4.47 (dd, *J* = 4.1, 11.2 Hz, 4 H, 4 × 6-H′), 4.69 (dd, *J* = 1.5, 11.2 Hz, 4 H, 4 × 6-H), 5.09 (d, *J* = 1.5 Hz, 4 H, 4 × 1-H), 5.70 (dd, *J* = 1.5, 3.6 Hz, 4 H, 4 × 2-H), 5.92 (dd, *J* = 3.6, 10.2 Hz, 4 H, 4 × 3-H), 6.13 (dd ≈ t, *J* = 10.2 Hz, 4 H, 4 × 4-H), 7.19−7.47, (m, 40 H + $CHCl_3$, 40 × aryl-H), 7.55 (m, 8 H, 8 × aryl-H), 7.82, 7.93, 8.03, 8.09 (each 8 H, each m≈d, 32 × *o*-aryl-H). − ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 30.2 (CH_2, $OCH_2CH_2CH_2O$), 46.0 (C_q), 63.3 (CH_2, C-6), 66.3 [CH_2, (man)-OCH_2], 67.4 (CH, C-4), 68.4 [CH_2, $(RCH_2OCH_2)_4C$], 69.2 (CH, C-5), 70.4 [CH_2, $(ROCH_2)_4C$], 70.6 (CH, C-3), 71.0 (CH, C-2), 98.2 (CH, C-1), 128.7, 128.8, 128.9, 129.0, 129.4, 129.6, 129.8, 130.1, 130.2, 130.3, 130.4, 133.4, 133.5, 133.8 (CH, aryl-C), 165.7, 165.8, 165.9, 166.5 (C, 16 × C=O). − MALDI-TOF-MS; $C_{153}H_{140}O_{44}$ [M + Na]$^+$: calcd. 2680.87; found 2703.83 .

Unprotected Tetravalent Cluster Mannoside 19: The protected cluster **18** (94 mg, 0.035 mmol) was dissolved in dry MeOH (100 mL). Sodium methoxide (1 M in MeOH, 1 mL) was added and the reaction mixture was stirred at room temp. for 14 d. The mixture was neutralized with ion exchange resin (Amberlite IR 120 H^+), filtered and the filtrate concentrated in vacuo. The residue was purified by size exclusion chromatography on Sephadex LH-20 (elution with MeOH) to yield the unprotected title cluster (38 mg, 0.037 mmol, quant.) as a colorless amorphous solid. − $[\alpha]_D^{19}$ = +60.2 (*c* = 1.04, $CHCl_3$). − ^{1}H NMR (400 MHz, [D_4]MeOH): δ = 1.88 (m_c, 8 H, 4 × $OCH_2CH_2CH_2O$), 3.42 [dd, 8 H, $(ROCH_2)_4C$], 3.50−3.59 [m, 16 H, 4 × 5-H, 4 × manOCHH, $(RCH_2OCH_2)_4C$], 3.67 (dd ≈ t, *J* = 9.2 Hz, 4 H, 4 × 4-H), 3.74 (dd, *J* = 3.6, 9.2 Hz, 4 H, 4 × 3-H), 3.77 (dd, *J* = 5.1, 12.2 Hz, 4 H, 4 × 6-H′), 3.81−3.90 (m, 12 H, 4 × 6-H, 4 × 2-H, 4 × manOCHH), 4.79 (d, *J* = 1.2 Hz, 1 H, 4 × 1-H). − ^{13}C NMR (100.67 MHz, [D]$_4$MeOH): δ = 32.0 (CH_2, $OCH_2CH_2CH_2O$), 47.8 (C_q), 64.0 (CH_2, C-6), 66.7 (CH_2, man-$OCH_2CH_2CH_2OCH_2$), 69.7 (CH, C-4), 70.4 (CH_2, $OCH_2CH_2CH_2$-OCH_2), 72.0 [CH_2, $(ROCH_2)_4C$], 73.4 (CH, C-2), 73.8 (CH, C-3), 75.3 (CH, C-5), 102.8 (CH, C-1). − MALDI-TOF-MS; $C_{41}H_{76}O_{28}$ [M + Na]$^+$: calcd. 1016.45; found 1139.36 .

Benzoyl-Protected Trivalent Cluster Mannoside (20): Triol **13** (58 mg, 0.20 mmol) and the benzoylated mannosyl trichloroacetimidate **17** (4.45 g, 6.0 mmol) were dissolved in dry CH_2Cl_2 (6 mL) under N_2. TMSOTf (5% solution in CH_2Cl_2, 0.1 mL) was added and the reaction mixture was stirred overnight at room temp. $NaHCO_3$ (5 g) was added and the suspension was quantitatively transferred (rinse with CH_2Cl_2) to a silica gel column and purified by flash chromatography (light petroleum ether/ethyl acetate, 2:1 → 1:1). This was followed by a second purification step on Se-

phadex LH-20 (elution with CH_2Cl_2/MeOH, 1:1) to yield the protected title cluster (389 mg, 0.19 mmol, 95%) as a white amorphous solid. − $[\alpha]_D^{24}$ = −41.9 (*c* = 0.97 in CH_2Cl_2). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.96 (m_c, 6 H, 3 × $OCH_2CH_2CH_2O$), 3.33 [s, 6 H, $(ROCH_2)_3CCH_3$], 3.55 (t, 6 H, 3 × $manOCH_2CH_2CH_2OCH_2$), 3.68 (m_c, 3 H, 3 × manOCHH), 3.92 (m_c, 3 H, 3 × manOCHH), 4.44 (ddd ≈ m, 3 H, 3 × 5-H), 4.48 (dd, *J* = 4.1, 12.2 Hz, 3 H, 3 × 6-H′), 4.70 (dd, *J* = 2.0, 12.2 Hz, 3 H, 3 × 6-H), 5.09 (d, *J* = 1.5 Hz, 3 H, 3 × 1-H), 5.70 (dd, *J* = 1.5, 3.6 Hz, 3 H, 3 × 2-H), 5.92 (dd, *J* = 3.6, 10.2 Hz, 3 H, 3 × 3-H), 6.13 (dd ≈ t, *J* = 10.2 Hz, 3 H, 3 × 4-H), 7.22−7.60 (m, 36 H, aryl-H), 7.83, 7.94, 8.04, 8.10 (each m≈d, each 6 H, *o*-aryl-H). − ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 17.9 (CH_3, CH_3), 30.1 (CH_2, $OCH_2CH_2CH_2O$), 41.4 (C, CCH_3), 63.3 (CH_2, C-6), 66.2 (CH_2, $manOCH_2CH_2CH_2OCH_2$), 67.4 (CH, C-4), 68.3 (CH_2, $manOCH_2CH_2CH_2OCH_2$), 69.2 (CH, C-5), 70.6 (CH, C-3), 71.0 (CH, C-2), 74.1 [CH_2, $(ROCH_2)_3CCH_3$], 98.1 (CH, C-1), 128.7, 128.8, 128.9, 129.4, 129.5, 129.8, 130.1, 130.2, 133.3, 133.4, 133.5, 133.8 (CH, aryl-C), 165.9, 166.5 (C, 12 C=O). − MALDI-TOF-MS; $C_{116}H_{108}O_{33}$ $[M + Na]^+$: calcd. 2028.68; found 2051.70.

Unprotected Trivalent Cluster Mannoside (21): The benzoylated cluster **20** (333 mg, 0.164 mmol) was dissolved in dry MeOH (100 mL), sodium methoxide (1 M in MeOH, 1 mL) was added and the reaction mixture was stirred at room temp. for 48 h. The mixture was neutralized with ion exchange resin (Amberlite IR 120 H^+), filtered and the filtrate concentrated in vacuo. The residue was purified by size exclusion chromatography on Sephadex LH-20 (elution with MeOH) to yield the unprotected title cluster (128 mg, 0.164 mmol, quant.) as a white amorphous solid. − $[\alpha]_D^{23}$ = +36.1 (*c* = 2.24 in MeOH). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 3 H, CH_3), 1.87 (m_c, 6 H, 3 × $OCH_2CH_2CH_2O$), 3.31 [br. s, 6 H, $(ROCH_2)_3CCH_3$], 3.50−3.59 (m, 12 H, 3 × 5-H, 3 × manOCHH, 3 × $manOCH_2CH_2-CH_2OCH_2$), 3.65−3.89 (m, 18 H, 3 × 3-H, 3 × 2-H, 3 × 4-H, 3 × 6-H, 3 × 6-H′, 3 × manOCHH), 4.80 (d ≈ s, 3 H, 3 × 1-H). − ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 19.2 (CH_3, CH_3), 32.0 (CH_2, $OCH_2CH_2CH_2O$), 43.1 (C_q, CCH_3), 63.9 (CH_2, C-6), 66.7 (CH_2, $manOCH_2CH_2CH_2OCH_2$), 69.7 (CH, C-4), 70.3 (CH_2, $manOCH_2CH_2CH_2OCH_2$), 73.3 (CH, C-2), 73.8 (CH, C-3), 75.6 (CH, C-5), 75.7 [CH_2, $(ROCH_2)_3CCH_3$], 102.7 (CH, C-1). − MALDI-TOF-MS; $C_{32}H_{60}O_{21}$ $[M + Na]^+$: calcd.780.36; found 803.43 .

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