Synthesis of Oligosaccharide Dendrimers**

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Abstract: Two β-D-glucopyranoside-based dendrimers, one incorporating three tetra- and the other three hepta-saccharide wedges attached to a central trisfunctionalized nonsaccharide core component, have been synthesized. Branching at designated saccharide units of the tetra- and of the heptasaccharide wedges arises from $(1\rightarrow2)/(1\rightarrow3)/(1\rightarrow6)$ and from $(1\rightarrow3)/(1\rightarrow6)$ intersaccharide linkages, respectively, with the 1,2-*trans* configuration at all anomeric centers. Both oligosaccharide wedges were constructed by stepwise glycosylation strategies and have reactive primary amino groups at their focal points located at the termini of spacer arms connected to the reducing glucose residues. Amide bond formation between these amino groups and appropriate core components carrying three carboxylic acid functions afforded two dendrimers incorporating a total of 12 and 21 monosaccharide units when the tetra- and the heptasaccharide wedges were employed, respectively. These nanosized highly branched macromolecules possess molecular diameters of 5–6 nm and molecular weights of 6195 and 10008 Daltons for the 12-mer and 21-mer, respectively. The wedges and dendrimers were characterized and the intersaccharide connectivity elucidated by extensive mono- and bidimensional ^{1}H and ^{13}C NMR spectroscopic investigations. In addition, LSIMS and MALDI-TOFMS investigations were also performed and revealed molecular ion peaks generally as H, Na, or K adducts for all oligosaccharides.

Keywords: carbohydrates · dendrimers · glycosylations · nanostructures · oligosaccharides

Introduction

The iterative assembly of monodisperse, highly branched, polyfunctionalized macromolecules in the form of so-called *dendrimers*[1] that relies upon the use of strictly abiotic synthetic methods has recently assumed considerable importance. One of the reasons for this development is that these synthetic dendrimers can be created in many different forms with precise molecular structures comparable, in their sizes and shapes, to biomolecules. On account of their multifunctionalities, saccharides can be utilized easily as building blocks for the construction of carbohydrate-containing dendritic molecules—so-called *glycodendrimers*[2]—giving rise to new kinds of glycoconjugate derivatives and polysaccharide mimics. Indeed, the syntheses and the evaluations of the biological activities of a number of carbohydrate-coated dendrimers, in which sugar residues are attached to the termini of noncarbohydrate dendritic skeleton, has been accomplished by Roy[3] and Lindhorst,[4] as well as by ourselves.[5] This research activity is directed at developing the concept of the multivalent or cluster effect[6] exhibited by multiantennary saccharides in some particular carbohydrate–protein interactions. However, it is not unreasonable to speculate that the range of possible applications for carbohydrate-containing dendrimers could be much more extensive. Saccharides can also be considered as suitable building blocks for controlling various characteristics of dendrimers, such as their sizes, shapes, topologies, flexibilities, and surface properties, and are likely to confer biocompatibility upon the molecules. For example, given certain combinations of sizes and structures for particular generations, carbohydrate dendrimers could possess internal void volumes similar to the cavities present in cyclodextrins[7] or to the channels formed in some polysaccharides,[8] and hence be capable of solubilizing hydrophobic organic molecules in aqueous media. Recently, we have described two different approaches to the production of dendrimers coated with carbohydrates on their exterior

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[**] Part 7 of the series Synthetic Carbohydrate Dendrimers: for Part 6, see ref. [5].

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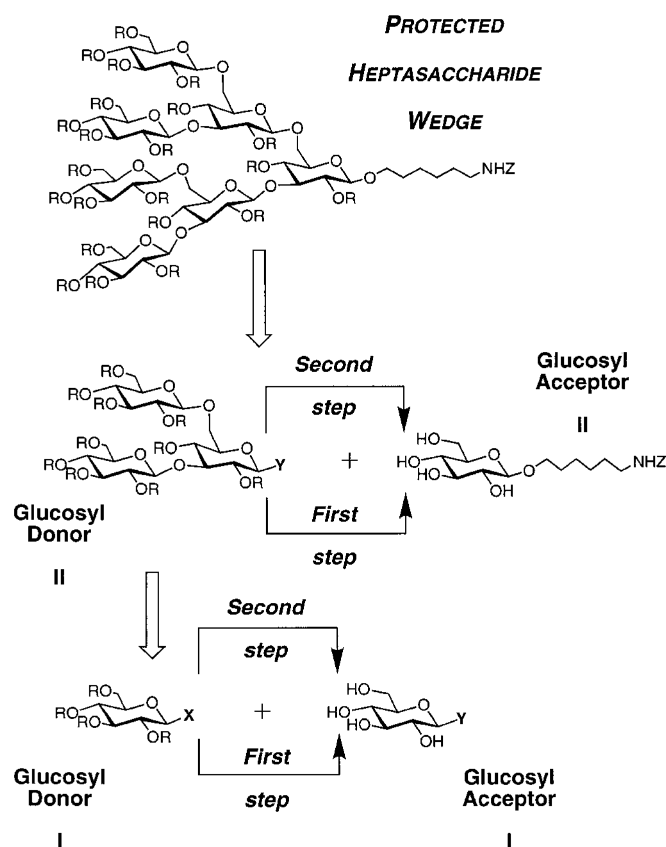
surfaces—namely, a convergent[9] and a divergent[10] one. Here, we report on a synthetic strategy for assembling carbohydrate dendrimers based on a combination of branched oligosaccharides as dendritic components and noncarbohydrate units as trivalent cores. From the numerous possible structures of branched oligosaccharides, we have chosen one based on β-D-glucopyranose residues with (1→3) and (1→6) glycosidic linkages. Our synthetic efforts for preparing branched glucans were inspired by the well-documented syntheses of both linear (1→6)-linked[11] and (1→3)-linked[12] β-D-gluco-oligosaccharides, as well as of (1→3)/(1→6)-branched[13] β-D-gluco-oligosaccharides.

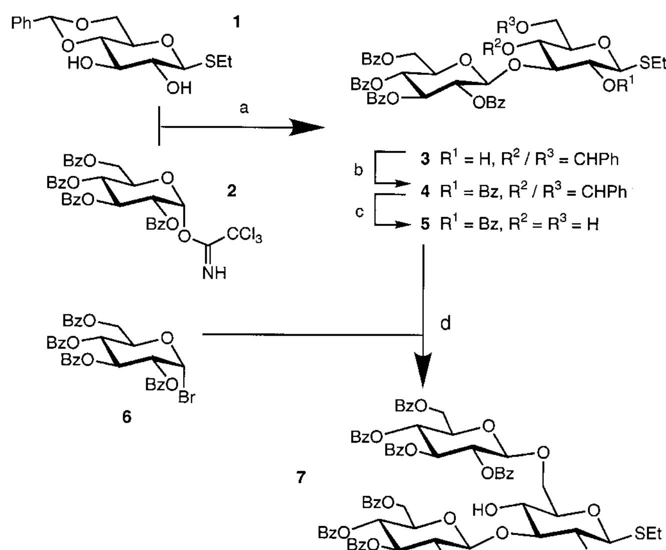
Results and Discussion

Synthesis: The synthesis of carbohydrate dendrimers requires the preparation of two types of building blocks, namely 1) a branched oligosaccharide bearing a spacer arm with, at its terminus, a reactive group which can couple efficiently to 2) a trivalent core component. Thus, our first synthetic target was a functionalized heptasaccharide containing a 6-aminohexyl aglycone and appropriate protecting groups. The retrosynthetic analysis of such a heptasaccharide derivative is outlined in Scheme 1. This scheme relies on an approach which involves glycosylations at positions 3 and 6 of a monosaccharide glucosyl acceptor with a 3,6-branched glucotriosyl donor. In turn, the latter can be constructed by a similar glycosylation route, starting from its monosaccharide components. The use of two different leaving groups **X** and **Y** which exhibit different reactivities in coupling reactions allows us to carry out the direct glycosylation by the trisaccharide without having to evoke additional steps for the activation of its reactive anomeric center.[14]



Scheme 1. Retrosynthetic scheme for the assembly of the 3,6-branched glucoheptaoside, outlining the order of the glycosylation steps, without specifying the nature of the protecting groups and their precise positions.

The synthetic route commences with the synthesis of the disaccharide derivative **3**, which was obtained by regioselective coupling of the diol **1**[13b] with the trichloroacetimidate **2**[13b, 15] under conditions previously developed by van Boom[13b] involving catalysis by TMSOTf at −20 °C in CH_2Cl_2 (Scheme 2). Benzoylation of **3** gave the fully protected derivative **4**,[13b] which was treated with 90% CF_3CO_2H in CH_2Cl_2 in order to remove the benzylidene group, affording a new glucosyl acceptor, the diol **5**. On account of the much higher reactivity of the primary hydroxyl group in **5**, it was possible to carry out 6-*O*-glucosylation with total regioselectivity. This reaction was carried out between **5** and a slight excess of the glucosyl bromide **6**[16] in the presence of AgOTf as a promoter and molecular sieves 4 Å as an acid scavenger, resulting in the formation of only one glycosylation product, the trisaccharide derivative **7** in 79% yield. In the presence of a base such as collidine, the yield of the glycoside **7** was much lower as a result of a competing reaction leading to the formation of a considerable amount of the corresponding orthoester.



Scheme 2. Synthesis of the trisaccharide **7**. Reagents and conditions: a) $TMSOTf/CH_2Cl_2$, mol. sieves 4 Å, −20 °C, 1 h, 63%; b) $BzCl/C_5H_5N$, 23 °C, 24 h, 98%; c) 90% CF_3CO_2H/CH_2Cl_2, 23 °C, 10 min, 80%; d) AgOTf/mol. sieves 4 Å/CH_2Cl_2, −30 to −5 °C, 1 h, 79%.

Assuming that we might exploit the different reactivities of the 2-OH and 3-OH groups of 4,6-*O*-benzylidene glucosides in glycosylation reactions, we have identified the glucosyl acceptor **11** (Scheme 3), similar to the glucosyl acceptor **1**. The monosaccharide residue of the glycosyl acceptor **11** represents the focal portion of the target dendritic heptasaccharide. Thus, it should contain a spacer arm, which was introduced when the glucosyl bromide **6** was coupled with *N*-benzyloxycarbonyl-

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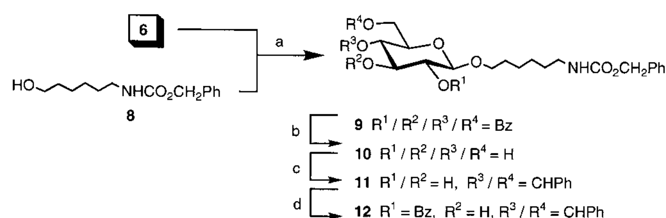
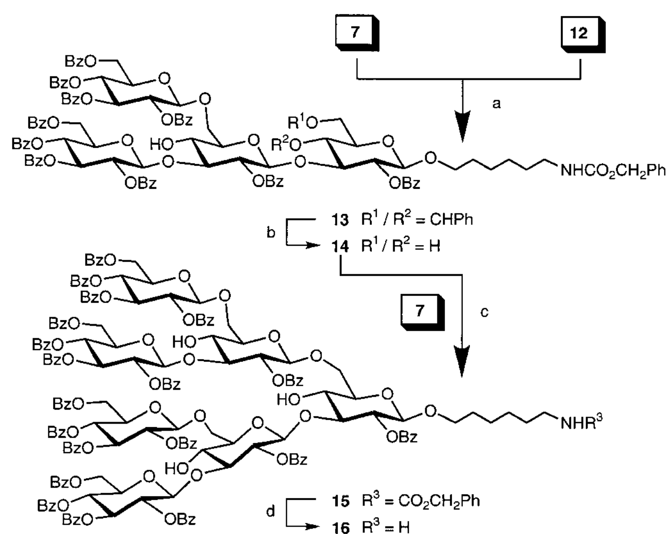


Scheme 3. Synthesis of the spacer-armed glucopyranoside **12**. Reagents and conditions: a) $HgBr_2/Hg(CN)_2$, mol. sieves 4 Å, 23 °C, 12 h, 69%; b) NaOMe/MeOH, 23 °C, 5 h, 100%; c) $PhCH(OMe)_2$/10-camphorsulfonic acid/DMF, 50 °C, 5 Torr, 4 h, 90%; d) $BzCl/Bu_4NI/K_2CO_3/CH_2Cl_2$, 25 °C, 3 days, 58%.

aminohexanol[17] (**8**) under standard Helferich conditions ($HgBr_2/Hg(CN)_2$ in CH_2Cl_2) to give the β-glucoside **9** in 69% yield. Debenzoylation of **9** (MeONa in MeOH) afforded quantitatively the tetraol **10**, which was converted into the 4,6-*O*-benzylidene acetal **11** in 90% yield by the treatment of **10** with $PhCH(OMe)_2$ in the presence of a catalytic amount of (+)-camphorsulfonic acid.

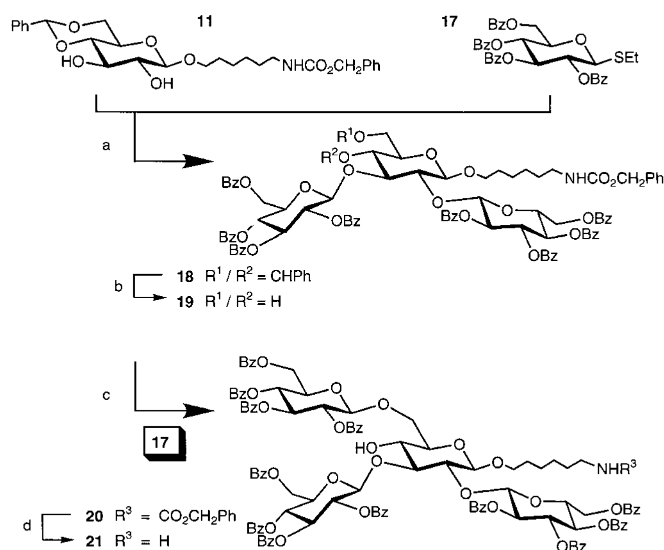
In order to investigate the possibility of carrying out regioselective 3-*O*-glycosylation of the diol **11** with thioglycoside donors, we employed a monosaccharide analogue of the triglycosyl donor **7**, namely, ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside.[18] The reaction was carried out in the presence of the NIS/TfOH catalytic system.[19] However, no regioselectivity was observed in this case and the isolation of individual products of the glycosylation was not easy. Therefore, selective protection of the 2-OH group in **11** was necessary. This protection was achieved by partial benzoylation of **11** under phase-transfer conditions[20] ($BzCl/Bu_4NI/K_2CO_3$ in CH_2Cl_2) which affords the monobenzoate **12** in 58% yield. Glycosylation of this compound with the thioglucotrioside **7**, promoted by NIS/TfOH in CH_2Cl_2 at room temperature, afforded the tetrasaccharide derivative **13** in 39% yield (Scheme 4). Debenzylidenation (90% CF_3CO_2H in CH_2Cl_2) of **13** gave the diol **14** (61% yield), which was once again



Scheme 4. Synthesis of the heptasaccharide wedge **16**. Reagents and conditions: a) TfOH/NIS, 23 °C, 5 min, 39%; b) 90% CF_3CO_2H/CH_2Cl_2, 23 °C, 10 min, 61%; c) TfOH/NIS, 0 to 23 °C, 1 h, 28%; d) H_2, 10% Pd/C, $MeOH/CH_2Cl_2$, 35 °C, 18 h, 20%.

subjected to condensation with the glycosyl donor **7** under the same conditions as those used for the glycosylation of **11**, but at a lower temperature (0 °C). These conditions allowed us to accomplish the coupling with an excellent 6-*O*-regioselectivity, affording the heptasaccharide **15** in the modest yield of 28%. Notably, only very small amounts of self-condensation products of **7** were detected in both reactions (Scheme 4) when this compound was used as a glycosyl donor despite the presence of a free 4-OH group in the molecule. Removal of the Z-protecting group from **15** by conventional hydrogenolysis led to the free amine **16**, which could act as a dendron in the subsequent assembly of a carbohydrate dendrimer.

In addition to the synthesis of the heptasaccharide **16**, other branched oligoglucoside dendrons have been prepared. Although the iodonium-ion-promoted (NIS/TfOH in CH_2Cl_2 at 25 °C) monoglycosylation of the diol **11** with the perbenzoylated thioglycoside **17** was completely unsuccessful, the same reaction carried out with two molar equivalents of the donor **17**, gave the trisaccharide **18** (Scheme 5) in 55% yield as



Scheme 5. Synthesis of the tetrasaccharide wedge **21**. Reagents and conditions: a) TfOH/NIS, 23 °C, 10 min, 55%; b) 90% CF_3CO_2H/CH_2Cl_2, 23 °C, 10 min, 96%; c) TfOH/NIS, 23 °C, 10 min, 30%; d) H_2, 10% Pd/C, $EtOH/CH_2Cl_2$, 35 °C, 4 h.

the major product. Debenzylidenation of **18** (90% CF_3CO_2H in CH_2Cl_2) afforded the diol **19**, which was glycosylated yet again with the glycosyl donor **17** catalyzed by NIS/TfOH. On this occasion, the reaction proved to be 6-*O*-regioselective as expected, leading to the tetrasaccharide derivative **20**. Indeed, no glycosylation of the unreactive 4-OH group was observed. The synthesis of the dendron **21** was completed with the deprotection of the amino group, as described above in the preparation of the amine **16**. Both amines **16** and **21** were used directly in the final steps to form dendrimers without further purification.

The target dendrimers containing glucooligosaccharide wedges were synthesized by employing the approach previously elaborated[9] for the construction of some carbohydrate-coated dendrimers. This approach involves the creation of three amide bonds between a tricarboxylic acid core and

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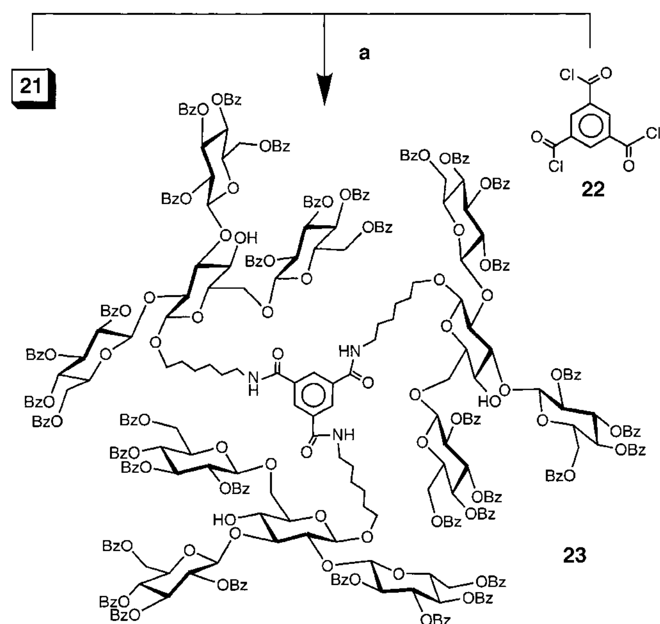
saccharide dendrons bearing free amino groups. Thus, the condensation of 3.3 molar equivalents of the tetrasaccharide derivative **21** with benzene tricarbonyl trichloride (**22**) gave the dendrimer **23** (Scheme 6) incorporating 12 β-D-glucopyranosidic residues in 20% yield after the purification by column chromatography on silica gel.



Scheme 6. Synthesis of the oligosaccharide dendrimer **23**. Reagents and conditions: a) CH_2Cl_2/Et_3N, 23 °C,6 h, 20%.

In contrast, no trace of the dendrimer incorporating the trisubstituted core was detected when the heptasaccharide derivative **16** was treated with the trisacid chloride **22**. In order to encourage the formation of a three-directional dendrimer in this case, the extended core **24**[9a] had to be employed (Scheme 7). The reaction of the bulky heptasaccharide dendron **16** with **24** used the standard coupling methodology,[21] involving the use of DCC/HOBT. The pure dendrimer **25** was isolated in a yield of 8% after extensive purification by gel permeation chromatography performed with THF as the eluant. This purification procedure allowed us to separate **25** from substantial amounts of 1) a compound incorporating two wedges attached to the core component, 2) the starting heptasaccharide wedge **16**, and 3) low molecular weight side-products and reagents (Figure 1).

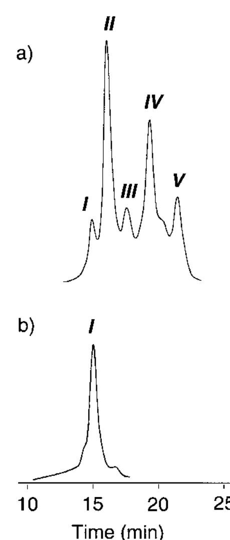
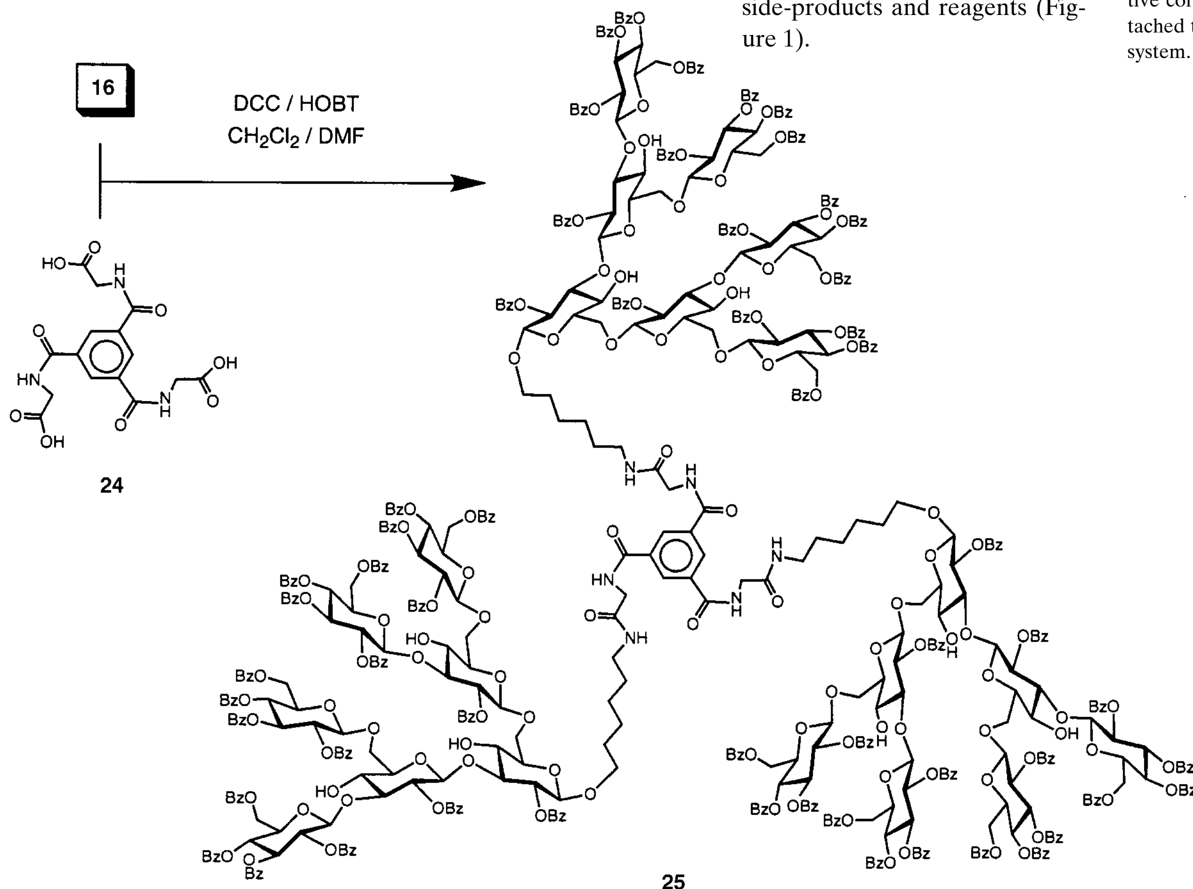


Figure 1. GPC traces of a) the crude reaction mixture and of b) the pure 21-mer dendrimer **25** after its isolation from the reaction mixture. Peaks ***I***, ***II***, and ***III*** correspond to tri- (**25**) and disubstituted core molecules and the starting heptasaccharide **16**, respectively. Peaks ***IV*** and ***V*** correspond to unidentified low molecular weight compounds. GPC was performed in THF on a Phenogel (500 Å) semipreparative column (30 × 7.8 mm) attached to a Gilson 714 HPLC system.



Scheme 7. Synthesis of the oligosaccharide dendrimer **25**. Reagents and conditions: DCC/HOBT/ CH_2Cl_2/DMF, 23 °C,14 days, 8%.

Mass spectrometry: For all the compounds reported in this paper, the mass spectra produced by the liquid secondary ion (LSI) and the matrix-assisted laser-desorption ionization/time-of-flight (MALDI-TOF) mass spectrometric techniques show large peaks for molecular ions, generally as H, Na, or K adducts. In many cases, the molecular ion is the base peak in the spectrum, indicating the high stability of these macromolecules under the conditions used for mass spectrometry. The calculated and observed masses of the various saccharide derivatives are listed in Table 1. The MALDI-TOF technique was also employed to analyze the reaction mixtures in order to monitor the progress of the glycosylations. The spectra produced are dominated by H, Na, and K adducts and are largely devoid of fragmentation.

Table 1. Mass spectrometric data[a] of the oligosaccharides **3–7**, **9–16**, and **18–21**, and of the dendrimers **23** and **25**.

Compound	Molecular formula	Molecular weight calcd	Molecular weight observed	Technique
3	$C_{49}H_{46}O_{14}S$	890	911 [*M*+Na]	MALDI-TOF[b,c]
4	$C_{56}H_{50}O_{15}S$	994	1017 [*M*+Na]	LSIMS
5	$C_{49}H_{46}O_{15}S$	906	929 [*M*+Na]	LSIMS
7	$C_{83}H_{72}O_{24}S$	1484	1507 [*M*+Na]	LSIMS
9	$C_{48}H_{47}O_{12}N$	829	829 [*M*]	LSIMS
10	$C_{20}H_{31}O_{8}N$	413	414 [*M*+H]	LSIMS
11	$C_{27}H_{35}O_{8}N$	501	524 [*M*+Na]	LSIMS
12	$C_{34}H_{39}O_{9}N$	605	627 [*M*+Na]	MALDI-TOF[b,c]
13	$C_{115}H_{105}O_{33}N$	2027	2051 [*M*+Na]	LSIMS
14	$C_{108}H_{101}O_{33}N$	1939	1963 [*M*+Na]	LSIMS
15	$C_{189}H_{167}O_{57}N$	3361	3387 [*M*+Na]	LSIMS
16	$C_{181}H_{161}O_{55}N$	3227	3252 [*M*+Na]	MALDI-TOF[c,d]
18	$C_{95}H_{87}O_{26}N$	1657	1681 [*M*+Na]	MALDI-TOF[b,c]
19	$C_{88}H_{83}O_{26}N$	1569	1592 [*M*+Na]	MALDI-TOF[b,c]
20	$C_{122}H_{109}O_{35}N$	2147	2172 [*M*+Na]	LSIMS
21	$C_{114}H_{103}O_{33}N$	2013	2039 [*M*+Na]	MALDI-TOF[b,c]
23	$C_{351}H_{309}O_{102}N_3$	6195	6230 [*M*+Na]	MALDI-TOF[c,d]
25	$C_{558}H_{492}O_{171}N_6$	10008	10042 [*M*+Na]	MALDI-TOF[c,e]

[a] The masses given are the centroids of the isotopic distributions. [b] Gentisic acid was employed as the matrix. [c] Insulin (MW 5734), gramicidin (MW1142), or lysozyme C (MW 14305) were used for calibration. [d] *trans*-3-Indoleacrylic acid was employed as the matrix. [e] Retinoic acid was employed as the matrix.

^{1}H NMR spectroscopy: ^{1}H NMR spectroscopic investigations were indispensable to the characterization of the oligosaccharides. The unambiguous assignments of the signals in the ^{1}H NMR spectra were achieved by means of a variety of two-dimensional NMR spectroscopic methods. Correlation spectroscopy experiments (COSY 45) were sufficient to assign the resonances for all the disaccharides. For systems with larger numbers of monosaccharide residues, however, the complexity of the spectra increases rapidly, since the protons of the glucosidic units all resonate characteristically in narrow regions of the spectra. Hence, for the medium to high molecular weight saccharides, further, more sophisticated experiments were needed to delineate fully the spin systems of the individual monosaccharide residues. To this end, a combination of double-quantum-filtered correlation spectroscopy (dqf-COSY),[22] two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY),[23] homonuclear Hartmann–Hahn spectroscopy (HOHAHA)[24] and rotating-frame Overhauser enhancement spectroscopy (ROESY)[25] were employed successfully.

In the case of trisaccharide **7**, complete assignment of all the peaks in the spectra was achieved after the analysis of dqf-COSY and NOESY experiments. The dqf-COSY spectrum (Figure 2a) enabled the identification of the chemical shifts of the ring protons in each of the three different D-glucopyranosidic residues. Intersaccharide connectivities were confirmed (Figure 2b) by a NOESY experiment. Clear cross-

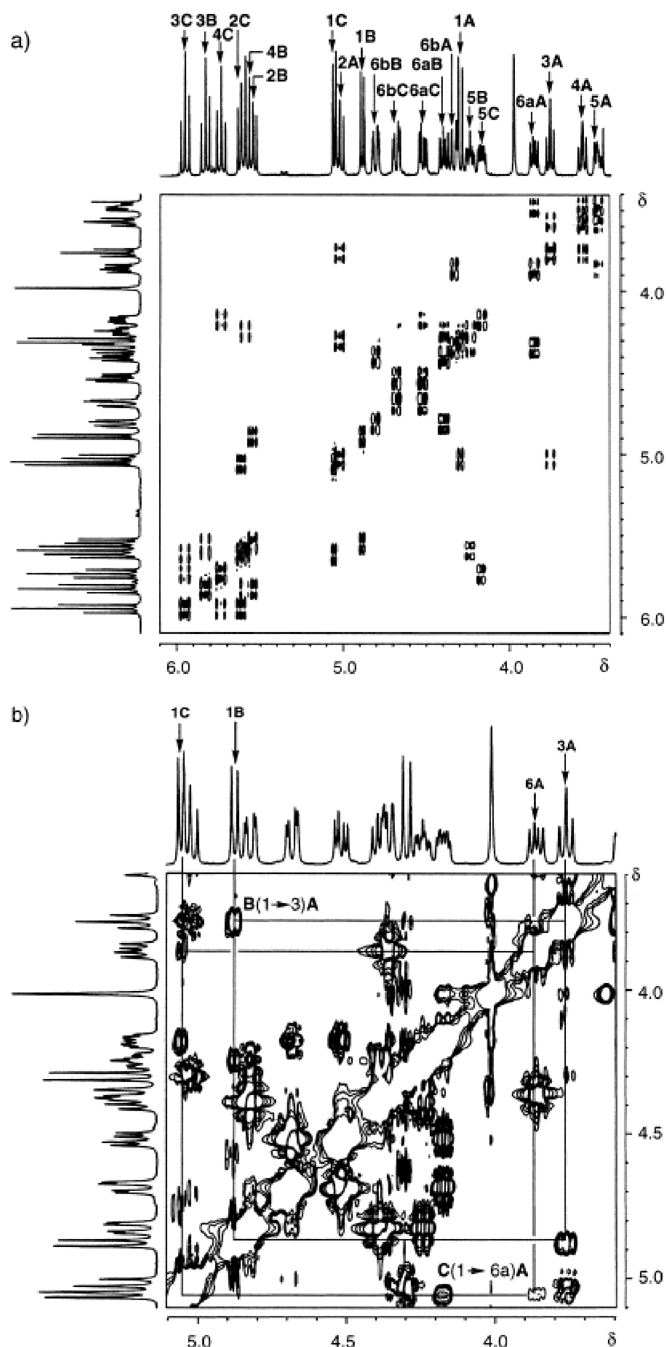


Figure 2. Saccharide region of the 2D-transformed data matrix from experiments (400 MHz, $CDCl_3$ 28°C) conducted on the trisaccharide **7**: a) dqf-COSY experiment with the complete assignment of the glucopyranosidic protons of **7** indicated, and b) NOESY experiment ($\tau m = 400$ ms), with the intersaccharide connectivities highlighted. The glucopyranose residues of **7** are marked **A**, **B**, **C** as illustrated in Table 2.

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peaks, indicating magnetization transfer between the anomeric proton of the **B** unit and the H-3 proton of **A**, and between the anomeric proton of **C** and the H-6 proton of the same **A** residue confirm that the three D-glucopyranose rings are linked in a **B**(1→3)**A** and **C**(1→6)**A** fashion. The overall structure of the trisaccharide can thus be fully established. The values observed for the vicinal coupling constants between the protons on H-1 and H-2 associated with the residues **A**, **B**, and **C**—that is, $^3J_{1,2} > 8$ Hz—confirm 1,2-*trans* configurations at all the newly-formed intersaccharide linkages.

The dqf-COSY spectrum (Figure 3a) was insufficient to allow a complete assignment of the intraresidue connectivities of the tetrasaccharide **21** to be made. An additional HOHAHA experiment (Figure 3b) was necessary in order to isolate

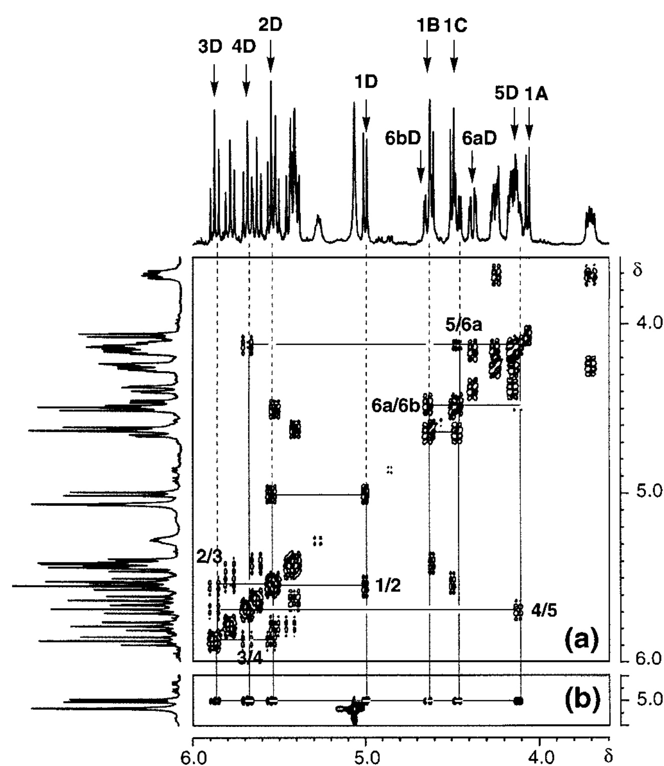

Figure 3. Saccharide region of the 2D-transformed data matrices from experiments (400 MHz, $CDCl_3$, 28 °C) conducted on the tetrasaccharide **20.** a) dqf-COSY experiment illustrating the spin system for the residue **D**, along with the anomeric protons of the residues **A**, **B**, and **C**. b) A fragment of the data from the HOHAHA experiment ($\tau m = 150$ ms) centered on the anomeric proton of residue **D**. The mode of the **A/B/C/D** assignment of the D-glucopyranose residues in **20** is as illustrated in Table 2.

the contributing individual spin systems for the four D-glucopyranosidic residues. The dqf-COSY spectrum could then be used to delineate the coupled pairs of vicinal and geminal protons within each residue. The intraresidue connectivities were thus established by a joint analysis following both experiments. Interresidue connectivities could be deciphered unambiguously by analysis of the NOESY experiment confirming the **B**(1→2)**A**/**C**(1→3)**A**/**D**(1→6)**A** connections.

In the case of the final heptasaccharide **16**, the ^{1}H NMR spectrum is exceptionally complex. Experiments were conducted in an effort to distinguish the protons associated with the six glycosidic linkages, as these were considered the most relevant in relation to a complete structural analysis. Studies of the dqf-COSY and HOHAHA spectra and, in particular, a ^{1}H/^{13}C gradient selected heteronuclear multiple quantum correlation (HMQC)[26] experiment (Figure 4b), enabled the assignment of all of the anomeric protons, as well as of the H-3 and H-6 protons of the internal D-glucopyranosidic residues. The anomeric protons of the four residues located at the

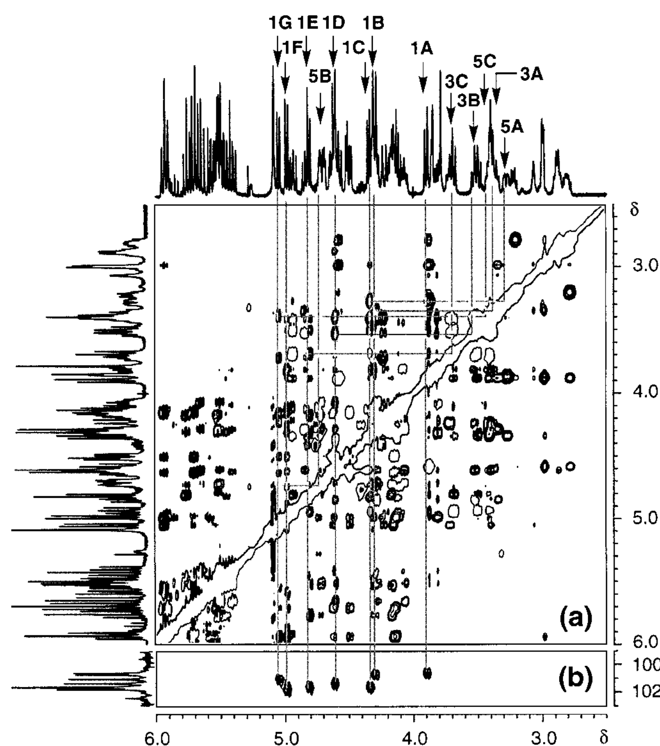

Figure 4. Saccharide region of the 2D-transformed data matrices from experiments conducted on the heptasaccharide **15** (400 MHz, 100 MHz, $CDCl_3$, 28 °C). a) A ROESY experiment (spin-lock field 2 kHz) illustrating the intersaccharide connectivities. b) The anomeric region (ω1) of the gradient-selected HMQC revealing the seven ^{1}H/^{13}C anomeric connectivities.

periphery of the heptasaccharide (i.e., those bearing four benzoyl protecting groups) could be readily distinguished from those of the partially deprotected internal monobenzoylated bisglycosylated residues and from the one at the reducing end by considerations of their relative chemical shifts. Specifically, all the protons on the fully protected peripheral monosaccharide residues are expected to resonate at lower field with respect to those on the internal residues. Unlike previous examples, NOESY experiments performed using a number of mixing intervals (300–900 ms) proved ineffective at defining the interresidue connectivities in this instance. Numerous antiphase cross peaks, arising as a result of zero quantum coherence between *J* coupled pairs, were observed in the matrix, even at very extended mixing times. Thus, the unambiguous distinction of the expected in-phase cross-peaks arising from dipolar coupled pairs (i.e., nOe) was not possible. In this case, the use of a different experiment—namely a ROESY experiment (Figure 4a)—was necessary to establish the connectivities across the glycosidic linkages. The

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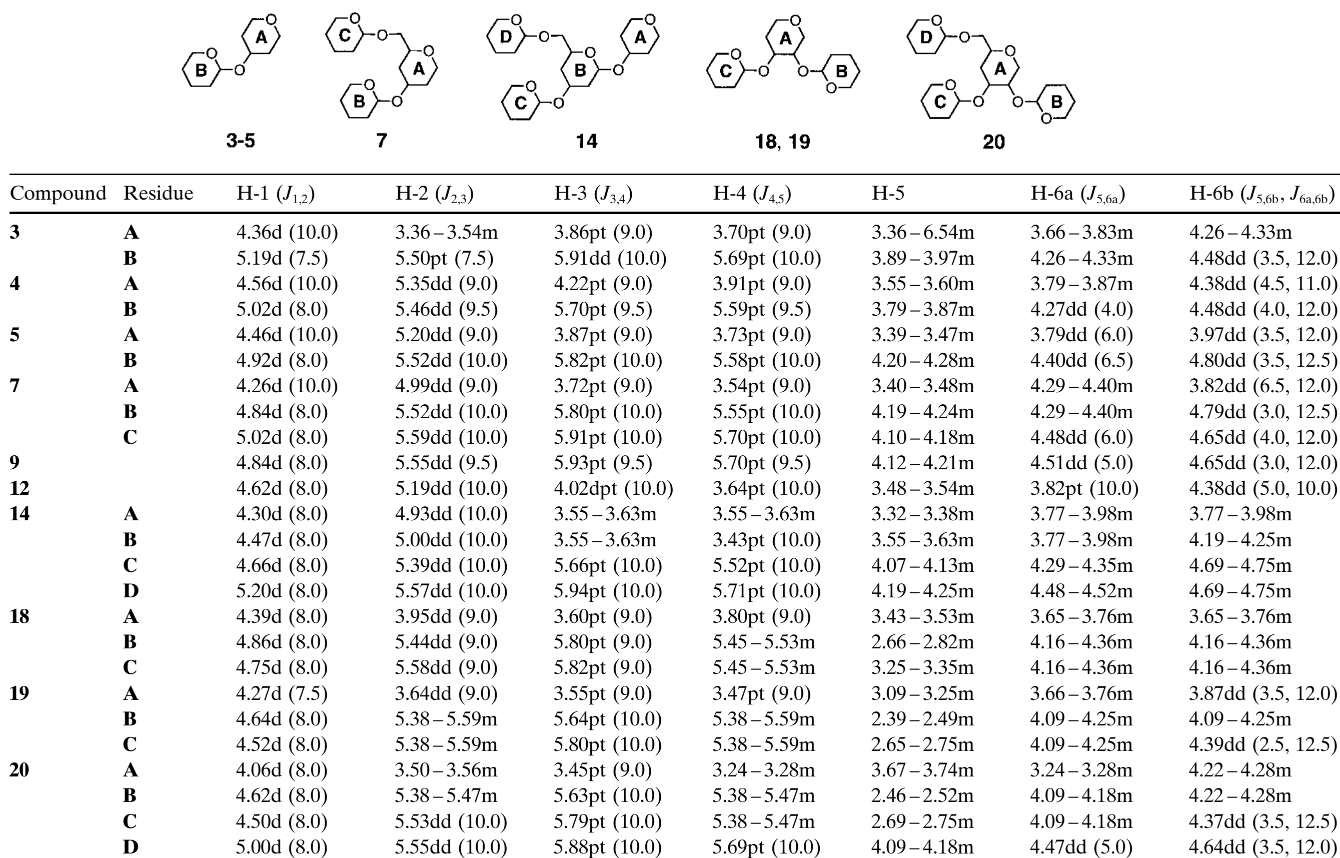
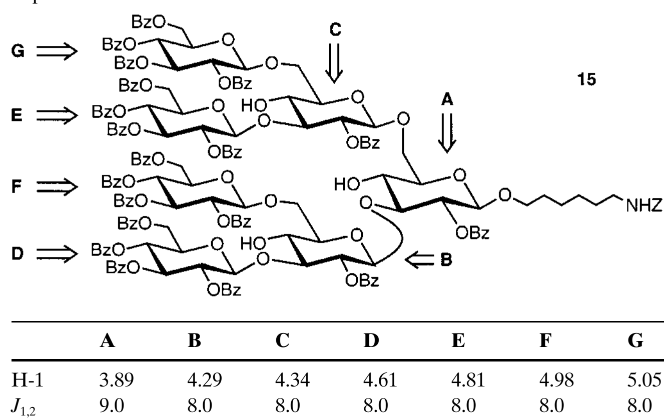
Table 2. Chemical shifts (δ values) and coupling constants (J in Hz) of the glucopyranosidic protons in the ^{1}H NMR spectra ($CDCl_3$, 25 °C) of compounds **3**–**5**, **7**, **9**, **12**, **14**, and **18**–**20**. The individual D-glucopyranose residues in the frameworks of the oligosaccharides are identified below.



Compound	Residue	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5	H-6a ($J_{5,6a}$)	H-6b ($J_{5,6b}$, $J_{6a,6b}$)
3	**A**	4.36d (10.0)	3.36–3.54m	3.86pt (9.0)	3.70pt (9.0)	3.36–6.54m	3.66–3.83m	4.26–4.33m
	B	5.19d (7.5)	5.50pt (7.5)	5.91dd (10.0)	5.69pt (10.0)	3.89–3.97m	4.26–4.33m	4.48dd (3.5, 12.0)
4	**A**	4.56d (10.0)	5.35dd (9.0)	4.22pt (9.0)	3.91pt (9.0)	3.55–3.60m	3.79–3.87m	4.38dd (4.5, 11.0)
	B	5.02d (8.0)	5.46dd (9.5)	5.70pt (9.5)	5.59pt (9.5)	3.79–3.87m	4.27dd (4.0)	4.48dd (4.0, 12.0)
5	**A**	4.46d (10.0)	5.20dd (9.0)	3.87pt (9.0)	3.73pt (9.0)	3.39–3.47m	3.79dd (6.0)	3.97dd (3.5, 12.0)
	B	4.92d (8.0)	5.52dd (10.0)	5.82pt (10.0)	5.58pt (10.0)	4.20–4.28m	4.40dd (6.5)	4.80dd (3.5, 12.5)
7	**A**	4.26d (10.0)	4.99dd (9.0)	3.72pt (9.0)	3.54pt (9.0)	3.40–3.48m	4.29–4.40m	3.82dd (6.5, 12.0)
	B	4.84d (8.0)	5.52dd (10.0)	5.80pt (10.0)	5.55pt (10.0)	4.19–4.24m	4.29–4.40m	4.79dd (3.0, 12.5)
	C	5.02d (8.0)	5.59dd (10.0)	5.91pt (10.0)	5.70pt (10.0)	4.10–4.18m	4.48dd (6.0)	4.65dd (4.0, 12.0)
9		4.84d (8.0)	5.55dd (9.5)	5.93pt (9.5)	5.70pt (9.5)	4.12–4.21m	4.51dd (5.0)	4.65dd (3.0, 12.0)
12		4.62d (8.0)	5.19dd (10.0)	4.02dpt (10.0)	3.64pt (10.0)	3.48–3.54m	3.82pt (10.0)	4.38dd (5.0, 10.0)
14	**A**	4.30d (8.0)	4.93dd (10.0)	3.55–3.63m	3.55–3.63m	3.32–3.38m	3.77–3.98m	3.77–3.98m
	B	4.47d (8.0)	5.00dd (10.0)	3.55–3.63m	3.43pt (10.0)	3.55–3.63m	3.77–3.98m	4.19–4.25m
	C	4.66d (8.0)	5.39dd (10.0)	5.66pt (10.0)	5.52pt (10.0)	4.07–4.13m	4.29–4.35m	4.69–4.75m
	D	5.20d (8.0)	5.57dd (10.0)	5.94pt (10.0)	5.71pt (10.0)	4.19–4.25m	4.48–4.52m	4.69–4.75m
18	**A**	4.39d (8.0)	3.95dd (9.0)	3.60pt (9.0)	3.80pt (9.0)	3.43–3.53m	3.65–3.76m	3.65–3.76m
	B	4.86d (8.0)	5.44dd (9.0)	5.80pt (9.0)	5.45–5.53m	2.66–2.82m	4.16–4.36m	4.16–4.36m
	C	4.75d (8.0)	5.58dd (9.0)	5.82pt (9.0)	5.45–5.53m	3.25–3.35m	4.16–4.36m	4.16–4.36m
19	**A**	4.27d (7.5)	3.64dd (9.0)	3.55pt (9.0)	3.47pt (9.0)	3.09–3.25m	3.66–3.76m	3.87dd (3.5, 12.0)
	B	4.64d (8.0)	5.38–5.59m	5.64pt (10.0)	5.38–5.59m	2.39–2.49m	4.09–4.25m	4.09–4.25m
	C	4.52d (8.0)	5.38–5.59m	5.80pt (10.0)	5.38–5.59m	2.65–2.75m	4.09–4.25m	4.39dd (2.5, 12.5)
20	**A**	4.06d (8.0)	3.50–3.56m	3.45pt (9.0)	3.24–3.28m	3.67–3.74m	3.24–3.28m	4.22–4.28m
	B	4.62d (8.0)	5.38–5.47m	5.63pt (10.0)	5.38–5.47m	2.46–2.52m	4.09–4.18m	4.22–4.28m
	C	4.50d (8.0)	5.53dd (10.0)	5.79pt (10.0)	5.38–5.47m	2.69–2.75m	4.09–4.18m	4.37dd (3.5, 12.5)
	D	5.00d (8.0)	5.55dd (10.0)	5.88pt (10.0)	5.69pt (10.0)	4.09–4.18m	4.47dd (5.0)	4.64dd (3.5, 12.0)

assignment of the protons of the D-glucopyranosidic residues of a number of key intermediate compounds is presented in Tables 2 and 3.

Table 3. Chemical shifts (δ values) and coupling constants (J in Hz) of the anomeric protons in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C) of the heptasaccharide **15**.



	A	B	C	D	E	F	G
H-1	3.89	4.29	4.34	4.61	4.81	4.98	5.05
$J_{1,2}$	9.0	8.0	8.0	8.0	8.0	8.0	8.0

Molecular modeling: In order to visualize the three-dimensional structures associated with the 12-mer and the 21-mer dendrimers **23** and **25**, respectively, a computational investigation was carried out on these highly branched molecules. They were constructed within the input mode of Macromodel5.0[27] and their geometries were optimized by energy minimization. The resulting structures were subjected to simulated annealing employing the AMBER* forcefield,[28] the generalized Born surface-area solvation model[29] for $CHCl_3$, and the Polak–Ribiere conjugate gradient algorithm[30] to afford the global minima shown in Figures 5 and 6. The approximate maximum radius (the maximum distance measured between the ring centroid of the core and the surface of the dendrimer) correspond to 25 and 28 Å for **23**

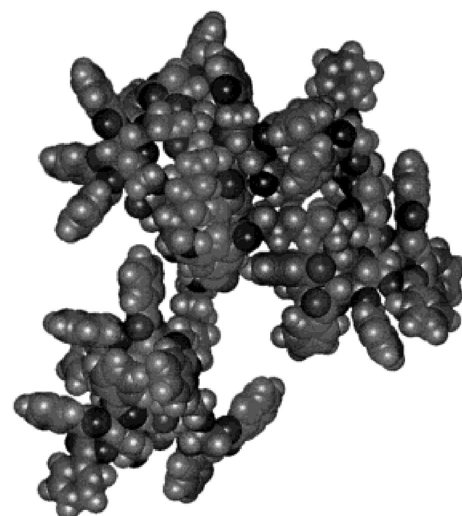


Figure 5. Computer-generated space-filling representation of the global minimum found for the 12-mer dendrimer **23**.

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0947-6539/98/0407-1250 $ 17.50+.50/0

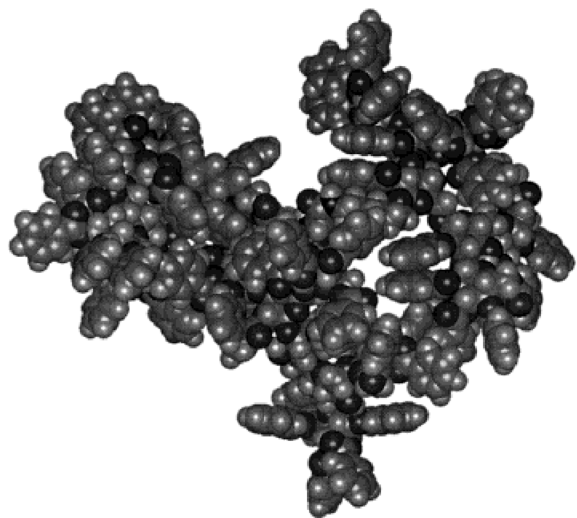

Figure 6. Computer-generated space-filling representation of the global minimum found for the 21-mer dendrimer **25**.

and **25**, respectively. Larger differences are observed in the total molecular van der Waals surfaces (6143 and 9845 Å^2 for **23** and **25**, respectively), as well as in the molecular volumes (4537 and 7270 Å^3 for **23** and **25**, respectively).

Conclusion

The syntheses of **23** and **25**, representatives of a new class of carbohydrate-containing dendritic molecule, have been realized. The distinctive feature of this class of glycodendrimers is that it incorporates branched oligosaccharides as dendritic components (dendrons) into their structures. In the case of the dendrimer **23**, such dendrons are exemplified by the glucotetraoside having glycosidic linkages at positions 2, 3, and 6 of the branching residue. The larger dendrimer **25** contains three heptasaccharide dendrons composed of glucopyranose residues, interconnected by β-(1 →3)- and β-(1 →6)-glycosidic bonds. The principles involved in assembling these carbohydrate dendrimers are similar to those reported earlier[9] for the construction of glycodendrimers possessing monosacharide units only on their peripheries. This approach involves the attachment of three dendrons to a central core component as the final step in the synthesis. The oligosaccharide dendrons were obtained using a combination of various glycosylation techniques in a stepwise manner. In the case of the construction of the branched heptasaccharide components of the larger dendrimer, a convergent scheme utilizing trisaccharide building blocks and repetitive 3-*O*- and 6-*O*-glycosylation has been developed. Further extensions of this general synthetic approach for constructing much more complex glycodendrimers are possible.

Experimental Section

General methods: Chemicals were purchased from Aldrich and used as received. Solvents were dried according to literature procedures.[31] 1,8-Diazabicyclo[5.4.0]undec-7-ene, dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, *N*-iodosuccinimide, trifluoromethanesulfonic acid, and trimethylsilyl trifluoromethanesulfonate are indicated by the acronyms DBU, DCC, HOBT, NIS, TfOH, and TMSOTf, respectively. The benzoyl and benzyloxycarbonyl groups are identified by the abbreviations Bz and Z, respectively. Yields refer to chromatographically pure products. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 (Merck 5554). Column chromatography and medium-pressure liquid chromatography were performed on silica gel 60 (Merck, 40–63 nm) and (Merck, 15–40 nm), respectively. Gel permeation chromatography (GPC) was carried out on a Phenogel semipreparative column (500 Å, 300 × 7.80 mm, Phenomenex, England) attached to a Gilson 714 high-performance liquid chromatographic system in THF (GPC grade, Fisons) using a variable UV detector set at 260 nm. Melting points were determined on an Electrothermal 9200 melting point apparatus. Microanalyses were performed by the University of North London Microanalytical Services. LSIMS were recorded on a VG ZabSpec mass spectrometer equipped with a cesium ion source using *m*-nitrobenzyl alcohol containing a trace amount of NaOAc. For accurate mass measurements using high-resolution LSIMS (HRLSIMS), the instrument was operated at a resolution of ca. 6000 by narrow-range voltage scanning along with polyethylene glycol or CsI as reference compounds. MALDI-TOF MS was performed on a Kratos Kompact MALDI-III instrument, with either gentisic acid, *trans*-3-indoleacrylic acid, or retinoic acid as matrices. Optical rotation measurements were measured at 23 °C on a Perkin–Elmer 457 polarimeter. ^{1}H NMR spectra were recorded on either a Bruker AC300 (300 MHz) or a Bruker AMX400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on either a Bruker AC300 (75.5 MHz) spectrometer or a Bruker AMX400 (100.6 MHz) spectrometer. All NMR experiments were carried out in $CDCl_3$ solution (with the exception of compound **10** which was analyzed in D_2O solution), at room temperature with the residual $CHCl_3$ (or HOD in the case of **10**) as an internal standard. All 2D experiments were recorded with the sample nonspinning. NMR spectroscopic data processing was carried out on a Bruker ASPECT station 1 offline processing facility with standard UXNMR software. HOHAHA[24] spectra were obtained by means of a MLEV-17 sequence for isotropic mixing and in-phase sensitive mode using time-proportional phase incrementation (TPPI). A 10 kHz spin-lock was used and 438–512 increments of 2 K data points were acquired. dqf-COSY,[22] ROESY,[25] and NOESY[23] spectra were obtained with similar spectral widths and digitization to those described above for the HOHAHA experiments. For NOESY experiments, a range of mixing times covering 300–900 ms was explored. For ROESY, a CW spin-lock field of 2 kHz was used and 512 increments of 2 K data points were acquired. The chemical shift values are expressed as δ values and the coupling constant values (J) are in Hertz. The following abbreviations are used for the signal multiplicities or characteristics: s, singlet; d, doublet; dd, double doublet; t, triplet; pt, pseudotriplet; dpt, double pseudotriplet; m, multiplet; br, broad.

Ethyl 2-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (5): A solution of **4** (1.40 g, 1.4 mmol) in CH_2Cl_2 (100 mL) was treated with 90% aqueous CF_3CO_2H (13 mL) at room temperature (RT) for 10 min, after which time TLC analysis (SiO_2:PhMe/EtOAc 3:2) showed the reaction to be complete. The solution was then washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and H_2O (3 × 100 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2:PhMe/EtOAc, 7:3) to give the title compound **5** (1.00 g, 80%). M.p. 215–216 °C; $[\alpha]_D = -5.5$ ($c = 1$ in $CHCl_3$); LSIMS: $m/z = 929$ $[M+Na]^+$; ^{1}H NMR ($CDCl_3$, 25 °C): $\delta = 1.13$ (t, 3H, $J = 7.5$ Hz), 2.55–2.69 (m, 2H), 3.39–3.47 (m, 1H), 3.73 (pt, 1H, $J = 9.0$ Hz), 3.79 (dd, 1H, $J = 6.0$, 12.0 Hz), 3.87 (pt, 1H, $J = 9.0$ Hz), 3.97 (dd, 1H, $J = 3.5$, 12.0 Hz), 4.20–4.28 (m, 1H), 4.40 (dd, 1H, $J = 6.5$, 12.5 Hz), 4.46 (d, 1H, $J = 10.0$ Hz), 4.80 (dd, 1H, $J = 3.5$, 12.5 Hz), 4.92 (d, 1H, $J = 8.0$ Hz), 5.20 (dd, 1H, $J = 9.0$, 10.0 Hz), 5.52 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.58 (pt, 1H, $J = 10.0$), 5.82 (pt, 1H, $J = 10.0$ Hz), 7.18–8.18 (m, 25H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta = 14.7$, 23.9, 62.8, 63.1, 69.4, 69.8, 70.8, 71.6, 72.6, 72.7, 80.1, 83.7, 86.8, 101.8, 128.1–133.7, 164.5, 165.0, 165.1, 165.7, 166.2; $C_{49}H_{46}O_{15}S$: calcd C 64.89, H 5.11, S 3.53; found C 64.95, H 5.13.

Ethyl 2-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (7): A solution of AgOTf (390 mg, 1.50 mmol) in freshly distilled PhMe (30 mL) was added dropwise over 30 min to a stirred mixture of the diol **5** (980 mg, 1.10 mmol), 2,3,4,6-*O*-tetrabenzoyl-α-D-glucopyranosyl bromide[16] (**6**; 990 mg, 1.50 mmol) and ground 4 Å

molecular sieves (2 g) in dry CH_2Cl_2 (50 mL) under Ar at $-30\,^\circ C$. After 30 min, another portion of AgOTf (390 mg, 1.50 mmol) in PhMe (30 mL) was added, following the same procedure. The temperature was then allowed to rise to $-5\,^\circ C$ over 1 h and the reaction mixture was neutralized with C_5H_5N and filtered through Celite®. The residue was washed with CH_2Cl_2 (50 mL) and the combined filtrates were washed with 10% aqueous $Na_2S_2O_3$ (2×100 mL), H_2O (1×100 mL), H_2SO_4 (1M, 2×100 mL), and aqueous $NaHCO_3$ (2×100mL). The organic solution was dried and concentrated to give a residue which was subjected to medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 95:5 to 9:1) to afforded **7** (1.27 g, 79%). $[\alpha]_D = +1$ ($c = 2$ in $CHCl_3$); LSIMS: $m/z = 1507$ $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 0.96$ (t, 3H, $J = 7.5$ Hz), 2.20–2.39 (m, 2H), 3.40–3.48 (m, 1H), 3.54 (pt, 1H, $J = 9.0$ Hz), 3.72 (pt, 1H, $J = 9.0$ Hz), 3.82 (dd, 1H, $J = 6.5$, 12.0 Hz), 4.10–4.18 (m, 1H), 4.19–4.24 (m, 1H), 4.26 (d, 1H, $J = 10.0$ Hz), 4.29–4.40 (m, 2H), 4.48 (dd, 1H, $J = 6.0$, 12.0 Hz), 4.65 (dd, 1H, $J = 4.0$, 12.0 Hz), 4.79 (dd, 1H, $J = 3.0$, 12.5 Hz), 4.84 (d, 1H, $J = 8.0$ Hz), 4.99 (dd, 1H, $J = 9.0$, 10.0 Hz), 5.02 (d, 1H, $J = 8.0$ Hz), 5.52 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.55 (pt, 1H, $J = 10.0$ Hz), 5.59 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.70 (pt, 1H, $J = 10.0$ Hz), 5.80 (pt, 1H, $J = 10.0$ Hz), 5.91 (pt, 1H, $J = 10.0$ Hz), 7.06–8.15 (m, 45H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta =$ 14.4, 23.3, 62.6, 62.9, 68.5, 69.0, 69.3, 70.4, 71.3, 71.8, 72.0, 72.4, 72.5, 72.9, 79.7, 83.1, 86.7, 101.5, 128.0–133.5, 164.2, 164.8, 164.9, 165.4, 165.5, 165.7, 166.0; $C_{83}H_{72}O_{24}S$: calcd C 67.11, H 4.89, S 2.16; found C 67.19, H 4.93.

6-Benzyloxycarbonylaminohexyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranoside (9): A solution of **8** (3.36 g, 13.4 mmol), $HgBr_2$ (2.60 g, 7.20 mmol), $Hg(CN)_2$ (3.40 g, 13.5 mmol), and ground 4 Å molecular sieves (20 g) in dry CH_2Cl_2 (50 mL) was stirred for 2 h at RT under N_2. Next, a solution of the glycosyl bromide **6** (9.20 g, 13.9 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise over 30 min and the mixture was stirred for a further 12 h until TLC analysis (SiO_2:hexane/EtOAc, 3:2) showed an almost complete conversion of the starting bromide **6** to products. The mixture was filtered through a layer of Celite and the residue was washed with CH_2Cl_2 (100 mL). The washings were combined with the filtrate. The solution was then washed with 10% aqueous NaBr (3×100 mL) and H_2O (3×100 mL), dried and concentrated. Column chromatography (SiO_2:hexane/EtOAc, 4:1) of the residue gave the title compound **9** (7.60 g, 69%). $[\alpha]_D = +15$ ($c = 1$ in $CHCl_3$); LSIMS: $m/z = 829$ $[M]^+$, 852 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 1.05$–1.38 (brm, 6H), 1.40–1.61 (brm, 2H), 2.95–3.06 (brm, 2H), 3.47–3.58 (m, 1H), 3.86–3.96 (m, 1H), 4.12–4.21 (m, 1H), 4.51 (dd, 1H, $J = 5.0$, 12.0 Hz), 4.65 (dd, 1H, $J = 3.0$, 12.0 Hz), 4.84 (d, 1H, $J = 8.0$ Hz), 5.10 (s, 2H), 5.55 (dd, 1H, $J = 8.0$, 9.5 Hz), 5.70 (pt, 1H, $J = 9.5$ Hz), 5.93 (pt, 1H, $J = 9.5$ Hz), 7.21–8.07 (m, 25H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta = 25.5$, 26.2, 29.2, 29.7, 40.9, 63.2, 66.5, 69.9, 70.2, 72.0, 72.2, 73.0, 101.3, 128.1–133.5, 165.1, 165.2, 165.9, 166.2; $C_{48}H_{47}O_{12}N$: calcd C 69.47, H 5.71, N 1.69; found C 69.83, H 5.52, N 1.59.

6-Benzyloxycarbonylaminohexyl *β*-D-glucopyranoside (10): A solution of the protected glucoside **9** (5.47 g, 6.60 mmol) in dry MeOH (50 mL) was treated with NaOMe (1M) in MeOH (0.2 mmol) at RT until TLC (SiO_2:hexane/EtOAc, 3:2) showed that the reaction was complete (5 h). The mixture was neutralized with Amberlyst 15 (H^+ form), filtered and concentrated to give compound **10** as a white solid (2.73 g, 100%). M.p. 110–112 °C; $[\alpha]_D = -11$ ($c = 1$ in H_2O); LSIMS: $m/z = 414$ $[M+H]^+$, 436 $[M+Na]^+$; ^1H NMR (D_2O, 25 °C): $\delta = 0.95$–1.50 (brm, 8H), 2.75–2.95 (brm, 2H), 3.16–3.48 (m, 5H), 3.50 (s, 2H), 3.62–3.84 (m, 3H), 4.26 (d, 1H, $J = 8.0$ Hz), 6.91–7.10 (m, 5H); ^{13}C NMR (D_2O, 25 °C): $\delta = 27.7$, 28.8, 31.7, 32.0, 43.3, 54.6, 63.5, 68.8, 72.2, 72.8, 75.8, 78.5, 105.1, 130.3, 130.9, 131.9, 139.3, 159.9; HRLSIMS: calcd for $C_{20}H_{31}NNaO_8$ $[M+Na]^+$ 436.1947, observed $m/z = 436.1948$.

6-Benzyloxycarbonylaminohexyl 4,6-*O*-benzylidene-*β*-D-glucopyranoside (11): A catalytic amount of 10-camphorsulfonic acid was added to a solution of the deprotected glucoside **10** (2.40 g, 5.8 mmol) and $PhCH(OMe)_2$ (1.2 mL, 7.7 mmol) in dry DMF (20 mL) and the mixture was stirred under reduced pressure (≈ 5 Torr) for 4 h at 50 °C until no trace of the starting material was detected by TLC (SiO_2:PhMe/EtOAc, 1:1). The reaction mixture was then neutralized with Et_3N and solvent was removed by evaporation in vacuo. The residue was dissolved in EtOAc (150 mL) and washed with aqueous $NaHCO_3$ (3×100 mL) and H_2O (2×100 mL), and the organic layer was dried and concentrated. Column chromatography (SiO_2:PhMe/EtOAc, 1:1) of the residue gave compound **11** (2.60 g, 90%). $[\alpha]_D = -30$ ($c = 1$, $CHCl_3$); LSIMS: $m/z = 524$ $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 1.29$–1.70 (brm, 8H), 2.87 (s, 1H), 2.98 (s, 1H), 3.12–3.24 (m, 2H), 3.40–3.57 (m, 4H), 3.74–3.82 (m, 2H), 3.85–3.92 (m, 1H), 4.32 (dd, 1H, $J = 5.0$, 11.0 Hz), 4.37 (d, 1H, $J = 8.0$ Hz), 4.78 (brs, 1H), 5.09 (s, 2H), 5.51 (s, 1H), 7.25–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta = 25.4$, 26.2, 29.3, 29.7, 40.7, 66.4, 66.7, 68.7, 70.3, 73.2, 74.6, 80.6, 101.9, 103.2, 126.3–129.3, 136.8, 137.0, 156.0; $C_{27}H_{35}O_8N$: calcd C 64.66, H 7.03, N 2.79; found C 64.52, H 7.17, N 2.62.

6-Benzyloxycarbonylaminohexyl 2-*O*-benzoyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (12): n-Bu_4NI (550 mg, 1.5 mmol) and dry K_2CO_3 (690 mg, 5.00 mmol) were added to a stirred solution of the diol **11** (503 mg, 1.00 mmol) in dry CH_2Cl_2 (6 mL), followed by slow addition of a solution of benzoyl chloride (140 µL, 1.20 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 3 days at 25 °C and diluted with CH_2Cl_2 (55 mL) before the precepitate was removed by filtration and the solution was washed with H_2O (5×25 mL), dried, and concentrated. Subjecting the residue to medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 7:3) gave **12** (351 mg, 58%). $[\alpha]_D = -28$ ($c = 0.6$ in $CHCl_3$); MALDI-TOF: $m/z = 627$ $[M+Na]^+$, 642 $[M+K]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 1.02$–1.23 (brm, 6H), 1.36–1.57 (m, 2H), 2.92–3.00 (m, 2H), 3.11 (d, 1H, $J = 3.5$ Hz), 3.42–3.48 (m, 1H), 3.49–3.52 (m, 1H), 3.64 (pt, 1H, $J = 10.0$ Hz), 3.82 (pt, 1H, $J = 10.0$ Hz), 3.84–3.91 (m, 1H), 4.02 (dpt, 1H, $J = 3.5$, 10.0 Hz), 4.38 (dd, 1H, $J = 5.0$, 10.0 Hz), 4.62 (d, 1H, $J = 8.0$ Hz), 4.71 (brs, 1H), 5.07 (s, 2H), 5.19 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.29 (s, 1H), 7.25–8.10 (m, 15H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta = 25.5$, 26.2, 29.3, 29.7, 40.9, 66.3, 66.6, 68.7, 70.2, 72.3, 74.9, 81.0, 101.7, 101.9, 126.4–133.3, 136.7, 137.0, 156.4, 165.8; $C_{34}H_{39}NO_9$: calcd C 67.42, H 6.49, N 2.31; found C 67.43, H 6.49, N 2.17.

6-Benzyloxycarbonylaminohexyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-[2-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-gluco-pyranosyl)-*β*-D-glucopyranosyl]-*β*-D-glucopyranoside (13): A catalytic amount of TfOH (7 µL, 0.07 mmol) was added very slowly to a stirred mixture of **12** (112 mg, 0.18 mmol), **7** (316 mg, 0.20 mmol) and NIS (90 mg, 0.4 mmol) in dry CH_2Cl_2 (20 mL) under an atmosphere of N_2 at RT. After 5 min, the reaction mixture was neutralized with C_5H_5N, diluted with CH_2Cl_2 (50 mL), and washed with 10% aqueous NaS_2O_3 (2×50 mL), aqueous $NaHCO_3$ (2×50 mL), and H_2O (1×50 mL) before the organic layer was dried and concentrated. Medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 7:1) of the residue afforded the pure tetrasaccharide **13** (135 mg, 39%). $[\alpha]_D = -2$ ($c = 1$ in $CHCl_3$); LSIMS: $m/z = 2051$ $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 0.96$–1.48 (m, 8H), 2.91–3.04 (m, 2H), 3.25–3.32 (m, 1H), 3.38–3.58 (m, 5H), 3.69–4.02 (m, 8H), 4.05–4.13 (m, 1H), 4.20–4.32 (m, 2H), 4.28 (d, 1H, $J = 10.0$ Hz), 4.48–4.55 (m, 1H), 4.56 (d, 1H, $J = 8.0$ Hz), 4.62 (d, 1H, $J = 8.0$ Hz), 4.72–4.80 (m, 2H), 5.08 (s, 2H), 5.12 (d, 1H, $J = 9.0$ Hz), 5.36 (pt, 1H, $J = 10.0$ Hz), 5.39–5.47 (m, 1H), 5.51 (pt, 1H, $J = 10.0$ Hz), 5.63 (s, 1H), 5.64 (pt, 1H, $J = 10.0$ Hz), 5.70 (pt, 1H, 10.0 Hz), 5.84 (pt, 1H, 10.0 Hz), 7.01–8.12 (m, 60H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta =$ 25.2, 25.3, 25.9, 29.3, 40.6, 61.6, 62.2, 66.2, 66.4, 67.8, 68.4, 68.6, 68.7, 69.0, 69.7, 71.0, 71.1, 72.0, 72.3 72.9, 73.5, 76.3, 77.0, 79.1, 85.4, 100.2, 100.3, 100.7, 101.4, 125.6–137.2, 163.6, 163.8, 164.4, 164.7, 164.8, 165.1, 165.4, 165.8, 165.9; HRLSIMS: calcd for $C_{115}H_{105}NNaO_{33}$ $[M+Na]^+$ 2050.6467, observed $m/z = 2050.6488$.

6-Benzyloxycarbonylaminohexyl 2-*O*-benzoyl-3-*O*-[2-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-*β*-D-gluco-pyranosyl]-*β*-D-glucopyranoside (14): A solution of the tetrasaccharide **13** (161 mg, 0.08 mmol) in dry CH_2Cl_2 (5 mL) was treated with 90% aqueous CF_3CO_2H (0.5 mL) at RT. After 10 min, TLC monitoring (SiO_2:PhMe/EtOAc, 1:1) showed that the reaction had almost gone to completion. The mixture was diluted with CH_2Cl_2 (40 mL) and then washed with aqueous $NaHCO_3$ (3×30 mL), and H_2O (2×30 mL), after which the organic layer was dried and concentrated to give a crude product, which was subjected to medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 7:3 to 1:1), affording the title compound **14** (93 mg, 61%). $[\alpha]_D = 9$ ($c = 2$ in $CHCl_3$); LSIMS: $m/z = 1963$ $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): $\delta = 0.94$–1.37 (m, 8H), 1.80 (brs, 1H), 2.50 (brs, 1H), 2.89–2.96 (m, 2H), 3.22–3.30 (m, 1H), 3.32–3.38 (m, 1H), 3.43 (pt, 1H, $J = 10.0$ Hz), 3.55–3.63 (m, 4H), 3.70–3.76 (m, 1H), 3.77–3.98 (m, 3H), 4.07–4.13 (m, 1H), 4.19–4.25 (m, 2H), 4.30 (d, 1H, $J = 8.0$ Hz), 4.29–4.35 (m, 1H), 4.47 (d, 1H, $J = 8.0$ Hz), 4.48–4.52 (m, 1H), 4.60 (brs, 1H), 4.66 (d, 1H, $J = 8.0$ Hz), 4.69–4.75 (m, 2H), 4.93 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.00 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.07 (s, 2H), 5.20 (d, 1H, $J = 8.0$ Hz), 5.39 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.52 (pt, 1H, $J = 10.0$ Hz), 5.57 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.66 (pt, 1H, $J = 10$ Hz), 5.71 (pt, 1H, $J = 10.0$ Hz), 5.94 (pt, 1H, $J = 10.0$ Hz), 6.95–8.09 (m, 55H); ^{13}C NMR

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($CDCl_3$, 25 °C): δ = 25.3, 26.0, 29.0, 29.4, 40.7, 62.5, 62.7, 66.4, 68.9, 69.1, 69.4, 71.2, 71.8, 72.2, 72.4, 72.8, 75.6, 84.1, 84.9, 101.2, 128.0–133.4, 163.7, 163.9, 164.8, 165.1, 165.5, 166.0; HRLSIMS: calcd for $C_{108}H_{101}NNaO_{33}$ $[M+Na]^+$ 1962.6154; observed m/z = 1962.6172.

6-Benzyloxycarbonylaminohexyl 2-*O*-benzoyl-3,6-di-*O*-[2-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-*β*-*D*-gluco-pyranosyl]-*β*-D-glucopyranoside (**15**): A catalytic amount of TfOH (1.6 μL, 0.017 mmol) was added to a mixture of the tetrasaccharide **14** (93 mg, 0.048 mmol), the trisaccharide **7** (83 mg, 0.052 mmol), and NIS (23 mg, 0.104 mmol) in dry CH_2Cl_2 (5 mL) under an atmosphere of N_2 at 0 °C. The reaction micture was allowed to warm up to RT, before being neutralized with C_5H_5N and worked up as described for the preparation of **13**. Repeated medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 85:15) on the crude product afforded the pure heptasaccharide **15** (56 mg, 28 %). $[\alpha]_D$ = −7.5 (c = 2 in $CHCl_3$); LSIMS: m/z = 3387 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 3.89 (d, J = 9.0 Hz), 4.29 (d, J = 8.0 Hz), 4.34 (d, J = 8.0 Hz), 4.61 (d, J = 8.0 Hz), 4.81 (d, J = 8.0 Hz), 4.98 (d, J = 8.0 Hz), 5.05 (d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 24.3, 25.2, 28.0, 28.5, 28.8, 39.8, 59.4, 61.6, 62.0, 65.5, 67.2, 67.4, 67.7, 68.2, 68.4, 68.5, 68.9, 69.4, 69.7, 70.3, 70.4, 70.9, 71.0, 71.1, 71.2, 71.5, 71.6, 71.5, 71.9, 72.0, 73.6, 74.3, 74.5, 82.7, 84.1, 84.8, 99.6, 99.8, 100.1, 100.4, 100.7, 100.8, 126.2–133.0, 136.8, 155.3, 162.7, 162.8, 163.1, 163.9, 164.0, 164.1, 164.2, 164.3, 164.6, 164.8, 165.0, 165.1, 165.2; HRLSIMS: calcd for $C_{189}H_{167}NNaO_{57}$ $[M+Na]^+$ 3385.0098; observed m/z = 3385.0103.

6-Benzyloxycarbonylaminohexyl 4,6-*O*-benzylidene-2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (**18**): A catalytic amount of TfOH (105 μL, 1.2 mmol) was added slowly to a solution of the diol **11** (740 mg, 1.48 mmol), and the thioglycoside **17** (2.23 g, 3.58 mmol) and NIS (1.6 g, 7.1 mmol) in dry CH_2Cl_2 (80 mL) under a N_2 atmosphere at RT. The reaction mixture was neutralized after 10 min with C_5H_5N before being worked up as described for the tetrasaccharide derivative **13**. The trisaccharide **18** was isolated (1.35 g, 55 %) following medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc 95:5 to 88:12). $[\alpha]_D$ = +33 (c = 1 in $CHCl_3$); MALDI-TOF: m/z = 1681 $[M+Na]^+$,1696 $[M+K]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 1.20–1.55 (br m, 8 H), 2.66–2.82 (m, 2 H), 3.13–3.24 (m, 2 H), 3.25–3.35 (m, 1 H), 3.43–3.53 (m, 1 H), 3.60 (pt, 1 H, J = 9.0 Hz), 3.65–3.76 (m, 2 H), 3.80 (pt, 1 H, J = 9.0 Hz), 3.95 (dd, 1 H, J = 8.0, 9.0 Hz), 4.16–4.36 (m, 5 H), 4.39 (d, 1 H, J = 8.0 Hz), 4.75 (d, 1 H, J = 8.0 Hz), 4.86 (d, 1 H, J = 8.0 Hz), 5.08 (s, 2 H), 5.19 (br s, 1 H), 5.44 (dd, 1 H, J = 8.0, 9.0 Hz), 5.45–5.53 (m, 3 H), 5.58 (dd, 1 H, J = 8.0, 9.0 Hz), 5.80 (pt, 1 H, J = 9.0 Hz), 5.82 (pt, 1 H, J = 9.0 Hz), 7.12–8.28 (m, 50 H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 25.7, 26.5, 29.4, 30.0, 41.1, 63.0, 63.4, 66.0. 66.6, 68.7, 69.7, 70.0, 70.1, 71.1, 72.3, 72.5, 72.6, 72.9, 78.4, 78.7, 80.0, 99.8, 100.0, 101.1, 101.8, 125.2–137.2, 156.4, 164.9, 165.0, 165.1, 165.2, 165.7, 165.8, 165.9; $C_{95}H_{87}NO_{26}$: calcd C 68.79, H 5.29, N 0.84; found C 68.79, H 5.26, N 0.67.

6-Benzyloxycarbonylaminohexyl 2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (**19**): The trisaccharide derivative **18** (1.35 g, 0.81 mmol) was treated with 90 % aqueous CF_3CO_2H (5 mL) in CH_2Cl_2 (25 mL) for 10 min at RT. The reaction mixture was then diluted with CH_2Cl_2 (75 mL), washed with an aqueous $NaHCO_3$ (3 × 75 mL) and H_2O (2 × 50 mL) before the organic layer was dried and concentrated. Column chromatography of the residue (SiO_2:PhMe/EtOAc, 7:3 to 6:4) afforded the diol **19** (1.23 g, 96 %). $[\alpha]_D$ = +59 (c = 1 in $CHCl_3$); MALDI-TOF: m/z = 1592 $[M+Na]^+$,1607 $[M+K]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 1.12–1.55 (br m, 8 H), 2.39–2.49 (m, 1 H), 2.65–2.75 (m, 1 H), 3.09–3.25 (br m, 3 H), 3.39–3.45 (m, 1 H), 3.47 (pt, 1 H, J = 9.0 Hz), 3.55 (pt, 1 H, J = 9.0 Hz), 3.64 (dd, 1 H, J = 7.5, 9.0 Hz), 3.66–3.76 (m, 2 H), 3.87 (dd, 1 H, J = 3.5, 12.0 Hz), 4.09–4.25 (m, 3 H), 4.27 (d, 1 H, J = 7.5 Hz), 4.39 (dd, 1 H, J = 2.5, 12.5 Hz), 4.52 (d, 1 H, J = 8.0 Hz), 4.64 (d, 1 H, J = 8.0 Hz), 5.08 (s, 2 H), 5.14 (br s, 1 H), 5.38–5.59 (m, 4 H), 5.64 (pt, 1 H, J = 10.0 Hz), 5.80 (pt, 1 H, J = 10.0 Hz), 7.22–8.33 (m, 45 H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 25.9, 26.7, 29.6, 30.2, 41.4, 62.3, 63.0, 63.1, 66.5, 69.3, 69.7, 69.9, 71.3, 72.3, 72.8, 73.3, 75.5, 78.0, 85.7, 100.2, 100.4, 101.5, 128.1–137.1, 156.8, 165.0, 165.2, 165.4, 166.0, 166.1; $C_{88}H_{83}NO_{26}$: calcd C 67.30, H 5.33, N 0.89; found C 67.13, H 5.32, N 0.63.

6-Benzyloxycarbonylaminohexyl 2,3,6-tri-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (**20**): A catalytic amount of TfOH (15 μL, 0.17 mmol) was added to a solution of the diol **19** (330 mg, 0.21 mmol), the thioglycoside **12** (314 mg, 0.50 mmol), and NIS (225 mg, 1.00 mmol) in dry CH_2Cl_2 (30 mL) under an atmosphere of N_2 at RT. After 10 min, the reaction mixture was neutralized with C_5H_5N, diluted with CH_2Cl_2 (20 mL) and worked up according to the procedure already described for **13**. Purification of the crude product by medium-pressure liquid chromatography (SiO_2:PhMe/EtOAc, 9:1–85:15) gave the tetrasaccharide **20** (135 mg, 30 %). $[\alpha]_D$ = +43 (c = 1 in $CHCl_3$); LSIMS: m/z = 2172 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 1.15–1.55 (br m, 8 H), 2.46–2.52 (m, 1 H), 2.69–2.75 (m, 1 H), 3.15–3.21 (m, 3 H), 3.24–3.28 (m, 2 H), 3.45 (pt, 1 H, J = 9.0 Hz), 3.50–3.56 (m, 2 H), 3.67–3.74 (m, 1 H), 4.06 (d, 1 H, J = 8.0 Hz), 4.09–4.18 (m, 3 H), 4.22–4.28 (m, 2 H), 4.37 (dd, 1 H, J = 3.5, 12.5 Hz), 4.47 (dd, 1 H, J = 5.0, 12.0 Hz), 4.50 (d, 1 H, J = 8.0 Hz), 4.62 (d, 1 H, J = 8.0 Hz), 4.64 (dd, 1 H, J = 3.5, 12.0 Hz), 5.00 (d, 1 H, J = 8.0 Hz), 5.07 (s, 2 H), 5.28 (br s, 1 H), 5.38–5.47 (m, 3 H), 5.53 (dd, 1 H, J = 8.0, 10.0 Hz), 5.55 (dd, 1 H, J = 8.0, 10.0 Hz), 5.63 (pt, 1 H, J = 10.0 Hz), 5.69 (pt, 1 H, J = 10.0 Hz), 5.79 (pt, 1 H, J = 10.0 Hz), 5.88 (pt, 1 H, J = 10.0 Hz), 7.14–8.31 (m, 65 H); ^{13}C NMR ($CDCl_3$, 25 °C): δ = 25.8, 26.5, 29.3, 30.0, 41.2, 62.0, 63.0, 68.5, 69.1, 69.2, 69.6, 69.7, 70.9, 72.0, 72.1, 72.5, 73.0, 75.3, 77.3, 85.5, 99.9, 100.1, 101.0, 101.7, 127.9–136.9, 156.5, 164.7, 164.9, 165.0, 165.2, 165.7, 165.8, 165.9, 166.1; HRLSIMS: calcd for $C_{122}H_{109}NNaO_{35}$ $[M+Na]^+$ 2170.6678; observed m/z = 2170.6789.

Dendrimer 23: The *N*-benzyloxycarbonyl derivative **20** (93 mg, 0.043 mmol) was subjected to hydrogenolysis over 10 % Pd/C (25 mg) in $EtOH/CH_2Cl_2$, 2:1 (25 mL) at 35 °C for 4 days. The catalyst was filtered off through a layer of Celite and the filtrate was concentrated to afford **21** (73 mg, 84 %), a portion of which (46 mg, 0.023 mmol) was then added to a solution of 1,3,5-benzenetricarbonyl chloride (**22**; 1.9 mg, 0.007 mmol) and Et_3N (3.3 μL, 0.023 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of N_2. The reaction mixture was stirred at RT for 6 h and then subjected to column chromatography (SiO_2:PhMe/EtOAc, 7:3) to afford the dendrimer **23** (9 mg, 20 %). MALDI-TOF m/z = 6230 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 1.05–1.70 (br m, 24 H), 2.47–2.53 (m, 3 H), 2.66–2.72 (m, 3 H), 3.12–3.16 (m, 3 H), 3.24–3.28 (m, 12 H), 3.44 (pt, 3 H, J = 9.0 Hz), 3.48–3.55 (m, 6 H), 3.67–3.72 (m, 3 H), 4.07 (d, 3 H, J = 8.0 Hz), 4.10–4.18 (m, 9 H), 4.22–4.28 (m, 6 H), 4.36 (dd, 3 H, J = 3.5, 12.5 Hz), 4.46 (pt, 3 H, J = 5.0 Hz), 4.49 (d, 3 H, J = 8.0 Hz), 4.61 (d, 3 H, J = 8.0 Hz), 4.63 (dd, 3 H, J = 3.5, 12.0 Hz), 4.99 (d, 3 H, J = 8.0 Hz), 5.30 (s, 3 H), 5.38–5.44 (m, 9 H), 5.52 (dd, 3 H, J = 8.0, 10.0 Hz), 5.54 (dd, 3 H, J = 8.0, 10.0 Hz), 5.62 (pt, 3 H, J = 10.0 Hz), 5.67 (pt, 3 H, J = 10.0 Hz), 5.77 (pt, 3 H, J = 10.0 Hz), 5.87 (pt, 3 H, J = 10.0 Hz), 7.13–8.01 (m, 180 H), 8.23 (t, 3 H, J = 8.0 Hz), 8.29 (s, 3 H).

Dendrimer 25: Hydrogenolysis of the heptasaccharide **15** (56 mg, 0.017 mmol) in the presence of 10 % Pd/C (50 mg) in $MeOH/CH_2Cl_2$, 2:1 (30 mL) at 35 °C over 18 hours afforded the amine **16** (42 mg, 77 %, MALDI-TOF: m/z = 3252 $[M+Na]^+$), which was isolated as described for **21**. Compound **16** (42 mg, 0.013 mmol) was then added to a solution of DCC (2.62 mg, 0.013 mmol), HOBT (1.71 mg 0.013 mmol), and **24**[9a] (1.51 mg, 0.004 mmol) in CH_2Cl_2/DMF, 2:1 (30 mL) under an atmosphere of N_2 at RT. After 14 days, the solvent was evaporated in vacuo and the residue was subjected to GPC (Phenomenex column, THF); this resulted in isolation of three compounds (Figure 1): ***I***) the 21-mer **25** (10.1 mg, 8 %), GPC retention time 15.0 min, ***II***) the product corresponding to bisfunctionalization of the core, GPC retention time 16.1 min, and ***III***) the starting compound **16**, GPC retention time 17.7 min. Dendrimer **25**: MALDI-TOF: m/z = 10042 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 25 °C): δ = 3.90 (d, J = 9.0 Hz), 4.29 (d, J = 8.0 Hz), 4.35 (d, J = 8.0 Hz), 4.61 (d, J = 8.0 Hz), 4.82 (d, J = 8.0 Hz), 4.98 (d, J = 8.0 Hz), 5.06 (d, J = 8.0 Hz). Bisfunctionalized core derivative: MALDI-TOF: m/z = 6833 $[M+Na]^+$; the starting compound **16** MALDI-TOF: m/z = 3268 $[M+Na]^+$.

Molecular modeling: The 12-mer and 21-mer dendrimers **23** and **25**, respectively, were constructed individually within the input mode of Macromodel 5.0.[27] Subsequently, the geometries were optimized by energy minimization performed on each structure using the Polak–Ribiere conjugate gradient (PRCG) algorithm,[30] the AMBER* forcefield,[28] and the generalized Born surface area (GB/SA) solvation model[29] for $CHCl_3$, as implemented in Macromodel 5.0. Then the lowest energy conformations were searched for by molecular dynamics with stepwise simulated annealing performed on each individual structure in one step of 10 ps, followed by two steps of 20 ps in conjunction with the PRCG method, the AMBER* forcefield, and the GB/SA for $CHCl_3$. The simulated temperature was decreased from 300 to 150, and finally to 50 K, with a bath constant of 5.0 ps applied at all steps. The time step was maintained at 1.5 fs in the first two steps and increased to 2.0 fs in the final step.

Acknowledgements: This research was supported in the UK by Pfizer, by the Engineering and Physical Sciences Research Council, and by the University of Birmingham.

Received: October 27, 1997 [F863]

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