# A Convergent Synthesis of Carbohydrate-Containing Dendrimers**

**Peter R. Ashton, Sue E. Boyd, Christopher L. Brown, Narayanaswamy Jayaraman, Sergey A. Nepogodiev, and J. Fraser Stoddart***

**Abstract**: The synthesis of carbohydrate-containing dendrimers has been achieved by a convergent growth approach. The synthetic strategy involves: 1) the synthesis of the triglucosylated derivative of tris(hydroxymethyl)methylamine (TRIS), 2) the introduction of a glycine-derived spacer and 3,3′-iminodipropionic acid derived branching units on to the TRIS derivative by amide bond formation, 3) condensation of the above saccharide-containing dendrons with a trifunctional 1,3,5-benzenetricarbonyl derivative, used as the core, by formation of amide bonds, and 4) deprotection of the saccharide units. A 9-mer and an 18-mer, carrying nine and eighteen saccharide units at the periphery, respectively, have been synthesized, in high yields at each step, by this synthetic strategy. By a variety of chromatographic and spectroscopic techniques, the dendrimers were shown to be structurally homogeneous, monodisperse, and error-free at all steps in their growth. These investigations were complemented by molecular modeling studies on the dendrimers. The presence of slightly distorted $C_3$ symmetry was noted in both the 9-mer and the 18-mer.

**Keywords**
carbohydrates · cluster glucosides · convergent syntheses · dendrimers · neoglycoconjugates

## Introduction

Dendrimers are a rapidly emerging class of macromolecules. During the past few years, dendrimer synthesis has evolved as a field of synthetic chemistry and has attracted considerable interest from organic, organometallic, and polymer chemists alike. Timely review articles have appeared on state-of-the-art approaches to dendrimer syntheses and their application.[1] The wide interest from a broad spectrum of synthetic chemists has resulted largely from the macromolecular characteristics of dendrimers. The architectural features of dendrimers include their precise constitutions with high overall symmetries, their well-defined internal cavities, and their nanometer dimensions.

Two approaches that are now well recognized for dendrimer synthesis are divergent[2] and convergent[3] growth. Recently, double exponential growth[4] and self-assembling[5] synthetic approaches have also been introduced. Based on these methods, organic[6] and organometallic[7] molecules and biomolecules, such as peptides[8] and nucleic acids,[9] have been built into dendritic compounds. The flexibility of dendrimer synthesis facilitates the incorporation of units other than structural ones, such as crown ethers,[10] porphyrins,[11] tartaric acid,[12] chiral tris(hydroxymethyl)methane derivatives,[13] and chiral 1,2-diols.[14] Promising applications relying upon the use of dendrimers are also beginning to be recognized.[15]

In their role as one of the major biomolecules, carbohydrates are very attractive building blocks for dendrimer synthesis. Nature produces dendritic structures in the form of branched polysaccharides: they are present in numerous glycoproteins[16] and a large number of plant polysaccharides, such as gum arabic,[17] and animal polysaccharides, such as glycogen.[18] Biomolecules containing multiple saccharide residues play a vital role in many cellular processes.[19] Indeed, there are a number of important biological phenomena that depend on carbohydrate/protein interactions, the study of which now forms the basis of glycobiology.[20] Moreover, the evolution of neoglycoconjugates as a powerful alternative to study the mechanisms of complex carbohydrate–protein interactions is now well established.[21] From extensive studies of the binding of neoglycoproteins with lectins, a class of carbohydrate-binding protein, Lee et al. have established the so-called "glycoside cluster effect".[22] With proper orientation and spacing of sugars in a multivalent ligand, strong binding between determinant carbohydrate residues and the lectins has been achieved in several studies involving cluster glycosides.[23] The so-called "glycodendrimers", reported by Roy et al.,[24] have also been shown to display a multivalent effect. Such avidity effects in carbohydrate–protein interactions by multivalent presentation of ligands may depend on the subtle changes in the structure of individual saccharides in a neoglycopolymer.[25] The synthesis of several saccharide residues attached at the periphery of preformed PAMAM dendritic cores has been repoted by Aoi et al.[26] These fully sugar-persubstituted dendrimers—called "sugar balls"—demonstrate increased binding affinity with certain proteins when compared with the individual monomeric sugar unit.

The choice of carbohydrates in dendrimer synthesis arises, not only from their potential biological relevance and impor-

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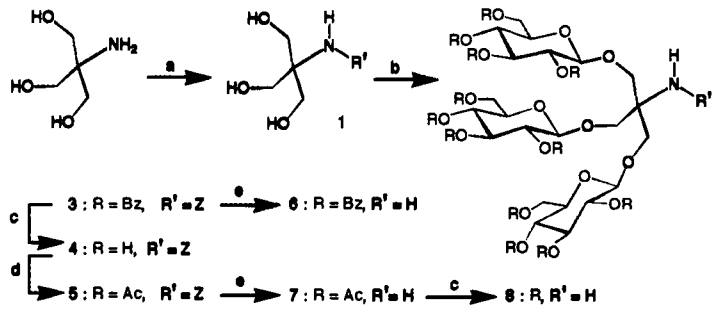
tance, but also from the well-known supramolecular character of oligosaccharides, exhibited in systems such as cyclodextrins.[27] Supramolecular phenomena have already been observed and discussed in dendrimers.[15f-i] Here, we report the syntheses of dendrimers in which carbohydrates are located at the peripheries of short peptidic chains emanating from a benzenoid central core. The general aim, at the outset of this research program, has been the delineation of synthetic sequences that will ultimately afford dendrimers with precisely defined molecular structures. The isolation and characterization of carbohydrate-containing dendrimers are described in this full paper.




Scheme 1. Syntheses of dendrons **6** and **7**. Reagents and conditions: a) Z-Cl, $Na_2CO_3$, $H_2O$, 0 °C, 5 h, 28%; b) 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**2**) (3.4 equiv), AgOTf (3.4 equiv), 2,4,6-collidine (3.0 equiv), $CH_2Cl_2/MeNO_2$, $-25 \rightarrow 0$ °C, 3 h, 77%; c) 0.05 M NaOMe/MeOH, 25 °C, **4**, 4.5 h, 92%, **8**, 15 h, 94%; d) $Ac_2O/C_5H_5N$, 25 °C, 15 h, 93%; e) $H_2$, 10% Pd/C, 25 °C, EtOAc/MeOH, **6**, 84%, **7**, 98%.

## Results and Discussion

**Synthetic Strategy:** We have adopted the convergent approach[3] for the synthesis of carbohydrate-containing dendrimers. In this approach, building blocks, called dendrons are constructed first of all and then these dendrons are attached to a multipodent core unit in the final steps of the dendrimer construction.

For the first steps in the dendron construction, tris(hydroxymethyl)methylamine (TRIS) was selected as the starting material on which to locate three carbohydrate units. Fortunately, glycosylation of the three primary hydroxyl groups of TRIS had already been investigated by several groups in the preparation of cluster glycosides and other glycoconjugates.[22, 23a-d] In addition, TRIS had been used previously as a building block in dendrimer synthesis.[1b] In the present study, we employed glucose as the source of the glycosyl donors toward the hydroxymethyl groups in TRIS and hence as the carbohydrate residue present in the final dendrimers. The availability of the free amino group in TRIS, after glycosylation, enables further elaboration through the formation of amide bonds with either branch-point synthons or, where steric problems arise, with spacer synthons possessing appropriate carboxyl functionalities. Since the use of amide-bond bridges forms the basis of our synthetic strategy, these branch-point and spacer synthons require, in turn, amine functionalities for their further elaboration. Accordingly, glycine (amino acetic acid) and 3,3'-iminodipropionic acid were chosen as the sources of the spacers and the interior branching residues, respectively. Upon completion of the synthesis of the saccharide-containing dendrons in this manner, the final step was envisaged to be the attachment of the dendrons to a multipodent core. A 1,3,5-benzenetricarbonyl-derived unit was selected in order to provide the final dendrimer with a triply branched core.

**Syntheses of the 9-mer (25) and 18-mer (37)**: The construction of the 9-mer (**25**) and the 18-mer (**37**) was initiated with the preparation of the respective dendrons from readily available starting materials.

*Synthesis of the Triglucosylated Dendrons of TRIS*: The amino group in TRIS was protected first of all with the benzyloxycarbonyl group (Z) under Schotten–Baumann conditions. In this manner, **1** was obtained[28] in moderate yield by treatment of TRIS in $H_2O$ with benzyloxycarbonyl chloride in the presence of $Na_2CO_3$ as base (Scheme 1). This compound was then glucosylated with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[29] (**2**) in $CH_2Cl_2/MeNO_2$ in the presence of AgOTf[30] as the promoter and 2,4,6-collidine as the base. The *O*-benzoylated product **3**—isolated in 77% yield—served as the starting material for further reactions leading to the construction of dendrimers. The corresponding *O*-acetylated dendron **5** was obtained in good yields by removal of the *O*-benzoyl groups in **3** under Zemplén's conditions to give **4** followed by acetylation with $Ac_2O$ in $C_5H_5N$. This deprotection–protection strategy was used to obtain **5** because a complex mixture of products was formed when the acceptor **1** was treated directly with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, as a result of random cleavage of the *O*-acetyl groups under the AgOTf-promoted conditions. Both dendrons **3** and **5** were then subjected to hydrogenolysis over 10% Pd/C in order to obtain the corresponding free amines **6** and **7**, respectively, in near quantitative yields. The bulkier *O*-benzoylated dendron **3** required a much longer time to complete its deprotection, compared with its *O*-acetylated analogue **5**. The de-*O*-acetylation of **7** to afford **8** was also achieved (94%) under Zemplén conditions.

The strategy was then to extend the dendron inwards with the use of simple peptide bond-coupling chemistry, since it offers a range of methodologies for the formation of amide bonds.[31] Thus, in a stepwise manner, reaction of the dendritic amines **6** and **7** with $N^{\alpha}$-BOC-Gly-OPFP (**9**) afforded the glycine-extended dendrons **10** and **11**, respectively, in high yields (Scheme 2). Again, the relative ease of the reaction of **9** with the *O*-acetylated dendron **7** can be appreciated when it is compared with the reaction of **9** with the corresponding *O*-benzoylated derivative **6**, which requires several days to go to completion. The de-*O*-acetylation of **11**, under alkaline conditions, afforded the deprotected dendron **12** (90% yield). The BOC protecting groups in **10** and **11** were removed by treatment with trifluoroacetic acid in $CH_2Cl_2$ to afford the protonated forms of the dendritic amines **13** and **14**, respectively, as their trifluoroacetate salts. A similar de-*O*-acetylation of **14** afforded the completely deprotected dendron **15**.

*Synthesis of Branched Dendrons*: The dipropionic acid **16** was chosen as the interior branching unit, since it has two carboxylic acid functionalities available for the ensuing condensation step, which provides a dendron carrying six saccharide units (**19** and **20**, Scheme 3). The corresponding bispentafluorophenyl ester of **16** was synthesized in three steps. Firstly, hydrolysis of the commercially available 3,3'-iminodipropionitrile with $Ba(OH)_2$ gave **16**. Then reaction of the amino group with benzyloxycarbonyl chloride under Schotten–Baumann conditions afforded **17**. The carboxylic acid functions in **17** were then activated by treatment with pentafluorophenol in the presence of DCC to give **18**. Reaction of **18** with both dendrons **13** and **14**—under the same reaction conditions as used for the synthesis of **10** and **11**—led to the desired dendrons **19** and **20**, respectively, in good yields.



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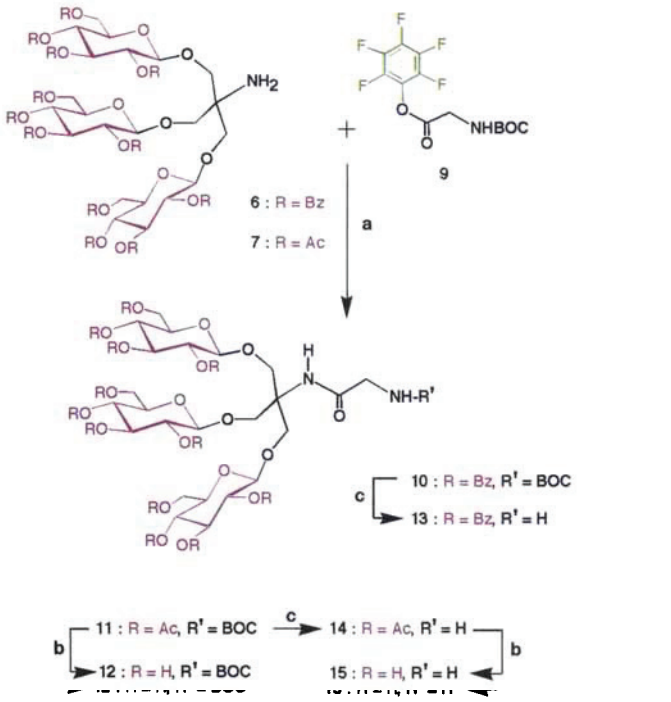
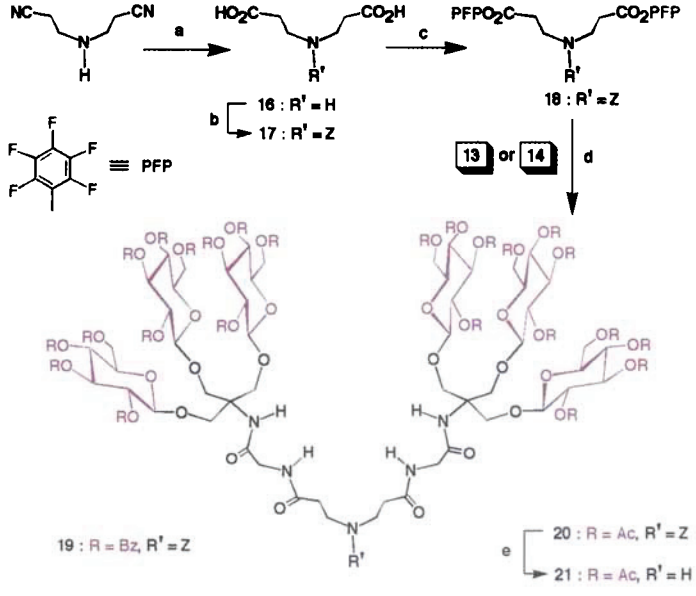



Scheme 2. Syntheses of dendrons **13** and **14** with extended linker. Reagents and conditions: a) $CH_2Cl_2$/DMF (2:1), 25 °C, **10**, 90%, **11**, 85%; b) 0.05 M NaOMe/MeOH, 25 °C, 6 h, **12**, 90%, **15**, 68%; c) TFA, $CH_2Cl_2$, 0 °C, 12 h, quantitative.

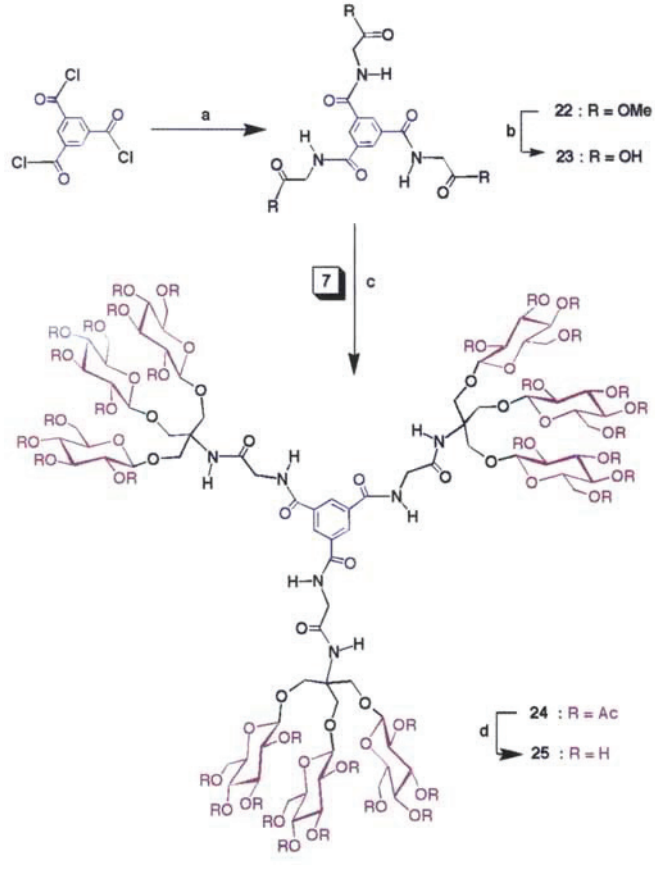



Scheme 3. Convergent syntheses of bisbranched dendrons **19** and **21**. Reagents and conditions: a) $Ba(OH)_2 \cdot 8H_2O/H_2O$, 70 °C, 18 h, then 50% aq. $H_2SO_4$, 48%; b) Z-Cl, satd. $NaHCO_3$, 0 °C, 16 h, 43%; c) DCC, $C_6F_5OH$, EtOAc/$CH_2Cl_2$ (1:1), 0 → 25 °C, 24 h, quantitative; d) $Et_3N$, $CH_2Cl_2$/DMF (2:1), 25 °C, **19**, quantitative, **20**, 67%; e) $H_2$, 10% Pd/C, EtOAc/MeOH, 25 °C, 12 h, 85%.

Hydrogenolysis of the benzyloxycarbonyl group present in **20** afforded the free amine **21** (85% yield).

*Attempted Reactions of Dendrons with 1,3,5-Benzenetricarbonyl Chloride*: Attempts to condense the dendrons **6/7**, **13/14**, and **21** with the core precursor, benzenetricarbonyl chloride—chosen for its high reactivity toward amines—failed either completely or in large measure to afford the expected dendritic macromolecules. Reaction of the dendron **13** (3.3 mol equiv) with benzenetricarbonyl chloride in $CH_2Cl_2$/DMF (2:1) led to significant amounts of mono- and disubstituted products, in addition to the desired trisubstituted product, at least as inferred from the MALDI-TOF spectra and also TLC, which revealed evidence for a number of products. Similarly, in the case of **14**, under the same reaction conditions, only the mono- and disubstituted derivatives were formed. With **6/7** and **21**, no reaction occurred even after several days. This outcome suggested that steric hindrance might be preventing the formation of the required dendrimers. Furthermore, isolation of pure compounds from these multicomponent mixtures proved to be a very difficult task. All these difficulties and more prompted us to explore the use of a core unit in which the reactive sites were located at the ends of extended spacer chains, in order to reduce the possibility of steric congestion. As anticipated, the core, when it was extended with spacer units, turned out to be very much better for the construction of dendritic macromolecules.

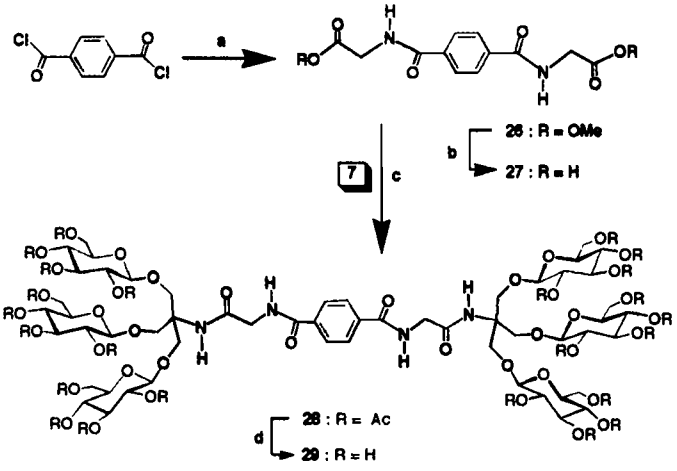
*Synthesis of the 9-mer (25) and the 6-mer (29)*: The triacid core **23** was obtained by first condensing Gly-OMe·HCl with benzenetricarbonyl chloride in the presence of $Et_3N$ to give the trimethyl ester **22** (Scheme 4). Hydrolysis of **22** with 2 M NaOH gave the triacid **23** (56% yield). The usual amide bond coupling reagents—DCC and HOBT—were effective in the condensation of the triacid **23** and the dendritic amines. Thus, reaction of the dendron **7** (3.3 mol equiv) with **23** in $CH_2Cl_2$/DMF (2:1), in the presence of DCC and HOBT, afforded the dendrimer **24**. With




Scheme 4. Synthesis of the first-generation dendrimer **24**. Reagents and conditions: a) $Et_3N$, Gly-OMe·HCl, $CH_2Cl_2$/DMF, 0 °C → 25 °C, 20 h, 56%; b) 2 M NaOH/$H_2O$/MeOH, 0 °C, 3 h, quantitative; c) **7** (3.3 equiv), DCC (3.2 equiv), HOBT (3.2 equiv), $CH_2Cl_2$/DMF (2:1), 18 h, quantitative; d) 0.05 M NaOMe/MeOH, 25 °C, 15 h, 48%.

the presence of one branching location derived from TRIS, **24** can be considered as a "first generation" dendrimer. No mono- and disubstituted products were isolated.

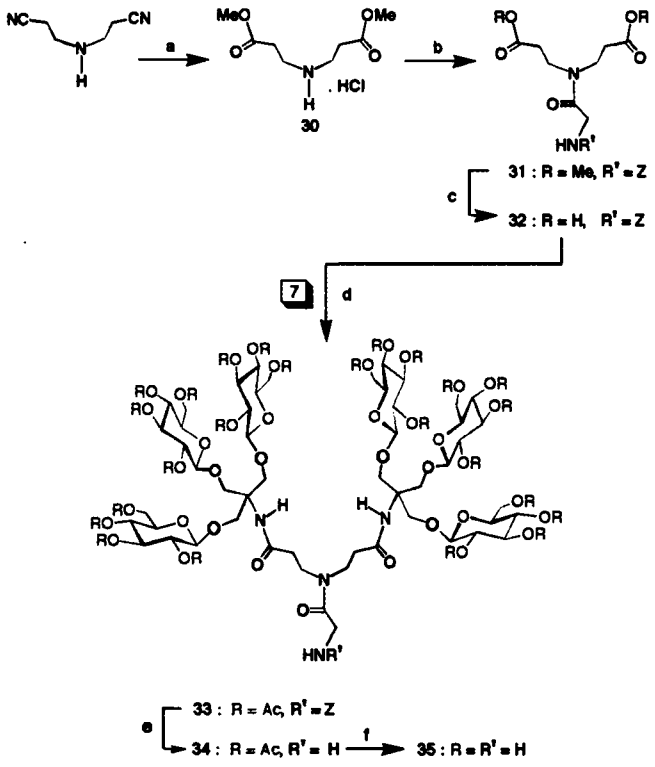
A similar methodology was followed for the preparation of the dendrimer-like 6-mer **28** (Scheme 5). Compound **26**, prepared by the condensation of Gly-OMe·HCl with terephthaloyl chloride in the presence of $Et_3N$, was hydrolyzed with 2M NaOH, giving the corresponding diacid **27**. Reaction of the dendron **7** with **27** in the presence of DCC and HOBT afforded **28** quantitatively. In both cases, the products were obtained in almost pure form. The removal of the protecting groups from **24** (Scheme 4) and **28** (Scheme 5) afforded the deprotected dendrimer **25** and the dendrimer-like **29**, respectively.




Scheme 5. Reaction of **7** with a terephthaloyl core unit. Reagents and conditions: a) Gly-OMe·HCl, $CH_2Cl_2$/DMF, satd. $NaHCO_3$, 0 → 25 °C, 15 h, 41% ; b) 2M NaOH/$H_2O$/MeOH, 0 °C, 3 h, 93%; c) **7** (2.2 equiv), DCC (2.1 equiv), HOBT (2.1 equiv), $CH_2Cl_2$/DMF (2:1), 15 h, 97%; d) 0.05M NaOMe/MeOH, 25 °C, 6 h, 65%.

This sequence of reactions for **7** could not be extended to the use of **21** as a dendron, however. Under the established reaction conditions, treatment of **21** with the core compound **23** did not yield the desired product, even after prolonged reaction times—again, presumably on account of increased steric crowding. In order to circumvent this problem, an additional spacer unit was attached to the focal point in the dendron **21**. It was apparent that the dendron **7** could be treated with the diacid **16**, in the presence of DCC and HOBT, to obtain the corresponding bisamide (vide infra), thereby effectively reducing the spacer length between the branches in the branched dendron. Accordingly, the preparation of the branched dendron was modified by the formal removal of glycine-derived spacers in **21** and the relocation of the spacers instead at the amine focal point to obtain **34**.

*Synthesis of the 18-mer (37)*: The preparation of the dendron **34** was achieved in four steps (Scheme 6). Firstly, the bis(methyl propionate) **30** was obtained by methanolysis of 3,3'-iminodipropionitrile in the presence of MeOH. Reaction of **30** with $N^2$-Z-Gly in the presence of DCC and HOBT afforded compound **31** with a glycine-extended branching unit. Hydrolysis of **31** with 2M NaOH gave the diacid **32**, which was then condensed with the amine **7** in the presence of DCC and HOBT to produce the branched dendron **33** in 63% overall yield. Hydrogenolysis of **33** to remove the amine protecting group on the glycine-derived spacer with 10% Pd/C as catalyst afforded the corresponding free amine **34**. De-*O*-acetylation of **34** under mild alkaline conditions gave the deprotected dendron **35**.




Scheme 6. Synthesis of the bisbranched dendron **34** for the second-generation dendrimer. Reagents and conditions: a) HCl/MeOH, reflux, 8 h, 93%; b) $Et_3N$, $N^2$-Z-Gly, DCC, HOBT, $CH_2Cl_2$, 0 → 25 °C, 34 h, 92% ; c) 2M NaOH/$H_2O$/MeOH, 0 °C, 3 h, quantitative; d) **7** (2.2 equiv), DCC (2.0 equiv), HOBT (2.0 equiv), $CH_2Cl_2$/DMF (2:1), 18 h, 73% ; e) $H_2$, 10% Pd/C, EtOAc, 25 °C, 22 h, 91%; f) 1M NaOMe/ MeOH:$H_2O$ (1:1), 18 h, 86%.

Reaction of **34** with **23**, using the established protocol (DCC and HOBT), produced the dendrimer **36** (Scheme 7), which can be regarded as a "second generation" dendrimer with the presence of two branching locations. This compound was purified by gel permeation chromatography. The efficiency of the coupling reaction was illustrated further by the exclusive production of the trisubstituted dendrimer and the absence of any of the corresponding mono- and disubstituted derivatives from the reaction mixture. Finally, complete de-*O*-acetylation of **36** afforded the dendrimer **37** (82% yield) with free hydroxyl groups on all the peripheral glucosidic units.

Clearly, it is critical that steric congestion is avoided at each stage in the synthesis in order to obtain dendrons or dendrimers in high yield when employing this particular convergent methodology. The steric congestion, which otherwise prevents coupling between reactive sites, is readily circumvented by locating reactive sites further apart from each other and well away from branching points. However, as noted already by Fréchet et al.,[32] there may sometimes be additional problems to overcome in strategies utilizing amide bond formations. Nevertheless, by the judicious choice of purpose-built dendrons, the assembly of dendritic macromolecules with complete constitutional homogeneity can be achieved, as a result of the faultless constitution of each growth component. This property is, of course, one of the main advantages in the convergent synthetic methodology.

**Structural Characterization**: Almost all of the dendrons and dendrimers described in this paper were purified by column chromatography on silica gel. Since the solubilities of all the compounds containing protecting groups were excellent in most



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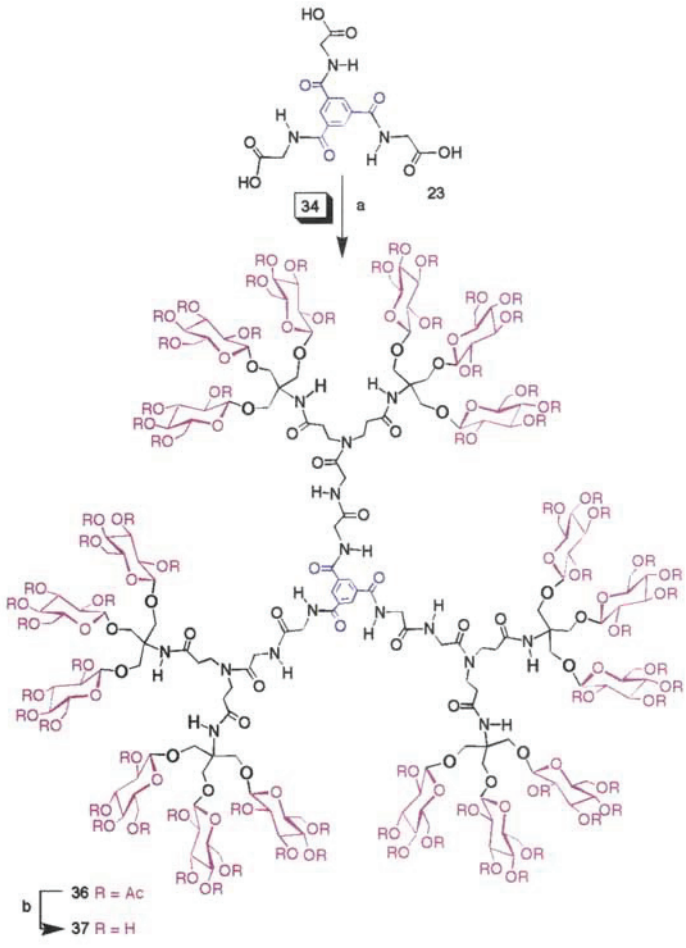


Scheme 7. Synthesis of the second-generation dendrimer **36**. Reagents and conditions: a) **34** (3.3 equiv), DCC (3.2 equiv), HOBT (3.2 equiv), $CH_2Cl_2$/DMF (2:1), 25 °C, 72 h, 71%; b) 1 M NaOMe/MeOH:$H_2O$ (1:1), 25 °C, 18 h, 82%.

organic solvents, the purification procedures were quite straightforward. The thin-layer chromatography (TLC) profiles of most of the dendrons and dendrimers were well-defined, although the beginnings of band broadening was observed for the second-generation dendrimers. For any particular coupling reaction, the products and the by-products have large differences in their molecular masses and—to some extent—in their mobilities on TLC. Purifications were therefore relatively straightforward. In some instances, the products only required purification for the purposes of characterization. In practice, many of the reactions can be performed without purification of compounds at an intermediate stage, since small amounts of impurities can be removed in the final step. The purification of 18-mer **36** was performed by gel permeation chromatography (GPC), with THF as the eluant. The chromatogram showed a narrow and symmetrically shaped elution curve for the product. Apart from this major peak, there were no other prominent peaks except for those corresponding to the unreacted starting materials and by-products at longer retention times. From the NMR spectroscopic studies, it was observed that the 18-mer **36** still contained a small amount of an impurity after the initial GPC run. Even after three additional runs through the GPC column, a slight trace of the impurity remained. It is possible that this 18-mer might occlude or encapsulate small molecules which are tenaciously retained within its dendritic structure. The deprotected dendrons and dendrimers were purified, once again by GPC with $H_2O$ as the eluant. A progressive trend was observed in the retention volumes at which each dendron or dendrimer could be separated. A comparison of the relative retention volumes for the smaller dendrons, such as **8**, **12**, and **15** with those for the larger ones, such as the dendrimers **25**, **29**, and **37**, shows a progressive decrease, as expected. A narrow and symmetrically shaped chromatogram was obtained for all the products. By performing GPC on all the deprotected compounds, we believe that any salts and/or impurities were removed.

The purified dendrons and dendrimers were characterized by all the commonly available techniques, such as elemental analysis, $^1H$ and $^{13}C$ NMR spectroscopies, and mass spectrometry. Also, their chiroptical properties were determined.

*Specific and Molecular Optical Rotations*: The optical rotations were, in general, measured in $CHCl_3$ for the *O*-acylated dendrons and dendrimers and in $H_2O$ for the deacylated derivatives. The optical rotation data are presented in Table 1.

Table 1. Optical rotation data [a] of dendrons and dendrimers.

| | [α] [b] | Molar rotation (°) | Molar rotation per saccharide unit (°) |
|---|---|---|---|
| **3** | +1.7 (*c* = 1.23) | +34 | +11 |
| **4** | −16.4 (*c* = 1.21) [c] | −122 | −41 |
| **5** | −19.7 (*c* = 1.03) | −245 | −82 |
| **6** | +21.5 (*c* = 1.65) | +399 | +125 |
| **7** | −12.1 (*c* = 1.02) | −135 | −45 |
| **8** | −21.1 (*c* = 0.91) [d] | −128 | −43 |
| **10** | +4.1 (*c* = 0.89) | +83 | +28 |
| **11** | −22.6 (*c* = 1.08) | −287 | −96 |
| **12** | −18.1 (*c* = 1.01) | −138 | −46 |
| **13** | +6.9 (*c* = 1.70) [c] | +138 | +46 |
| **14** | −19.7 (*c* = 1.04) [c] | −253 | −84 |
| **15** | −19.1 (*c* = 0.8) [d] | −122 | −41 |
| **19** | +3.9 (*c* = 1.32) | +161 | +27 |
| **20** | −24.0 (*c* = 1.15) | −623 | −104 |
| **21** | −25.3 (*c* = 0.7) | −622 | −103 |
| **24** | −30.7 (*c* = 0.76) | −1126 | −125 |
| **25** | −28.5(*c* = 1.4) [d] | −612 | −68 |
| **28** | −21.7 (*c* = 1.6) | −535 | −89 |
| **29** | −24.0 (*c* = 0.7) [d] | −350 | −58 |
| **33** | −19.3 (*c* = 0.94) | −490 | −82 |
| **34** | −19.0 (*c* = 1.18) | −456 | −76 |
| **35** | −16.0 (*c* = 0.90) [d] | −223 | −37 |
| **36** | −16.5 (*c* = 1.12) | −1245 | −69 |
| **37** | −21.8 (*c* = 1.17) [d] | −985 | −55 |

[a] The optical rotation was recorded at the D-line of Na. [b] In units of $10^{-1}$ °$cm^2 g^{-1}$ and in $CHCl_3$ unless otherwise specified. [c] In MeOH. [d] In $H_2O$.

The specific rotations observed for dendrons and dendrimers in the *O*-acetylated series are similar to that reported for methyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside ($[\alpha]_D = -18.2$, $CHCl_3$).[33] Likewise, no significant changes were observed for any of the *O*-benzoylated dendrons and the de-*O*-acylated dendrons and dendrimers. Furthermore, the molar rotations obtained within each series is roughly proportional to the number of saccharide units attached to the periphery of the dendrons and dendrimers. The contribution per saccharide unit is ca. +20° for the *O*-benzoylated derivatives, ca. −90° for the *O*-acetylated derivatives, and ca. −50° for the de-*O*-acylated derivatives. These observations are in accord with the conclusions of other researchers: the optical rotation of a dendrimer with chiral surface groups was found to be proportional to the number of chiral units located at the periphery of the dendrimer.[34, 12]

*Elemental Analyses*: This information was obtained by combustion analysis. The observed values for the elemental compositions were very close to the expected values. Although the

change in calculated compositions from one generation to the next becomes smaller and smaller, the data can be considered as evidence for their constitutional homogeneities—in conjunction with other methods of characterization.

*Mass Spectrometry*: In the case of all the compounds reported in this paper, the mass spectra produced by liquid secondary ion (LSI) and by matrix-assisted laser-desorption time-of-flight (MALDI-TOF) mass spectrometries show a strong molecular ion, generally as hydrogen, sodium, or potassium 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 to record their mass spectra. In the compounds with a protected amino group, the LSI mass spectra show the molecular ion as a sodium or potassium adduct, whereas the corresponding free amines produce a protonated molecular ion in high abundance. Thus, the dendron **7** affords a protonated molecular ion at $m/z = 1112$, whereas the dendron **5**, with a protected amino group, produces a molecular ion corresponding to an $[M+Na]^+$ ion at $m/z = 1268$.

The first-generation dendrimer **24** and the dendrimer-like compound **28** exhibit molecular ions at $m/z$ = 3685 and 2502, respectively, corresponding to their $[M+Na]^+$ and $[M+K]^+$ adducts, respectively. Similarly, dendrons in the series **10**, **11**, **19**, and **20** give rise to the molecular ion peak as their sodium adducts. When the amine protecting groups are removed, as in **13** and **14**, the protonated molecular ion is the dominant one. For the few compounds analyzed—especially the 9-mer **24** and 18-mer **36**—the isotopic distributions in the molecular ion regions obtained in the LSI mass spectra are in very good agreement with the theoretical isotopic distributions. The calculated and the observed masses of the protected and deprotected dendrons and dendrimers are presented in the Table 2.

LSI-MS also serves as a useful means to verify the completeness of reactions at all reaction sites in dendron and dendrimer production. The formation of incompletely terminated products, such as mono- and disubstituted derivatives, if present, can be identified very easily. The MALDI-TOF-MS technique produces spectra that are largely dominated by the molecular ion peak as a hydrogen, sodium, or potassium adduct and are devoid of fragmentation for the most part. The efficiencies of the coupling reactions can again be assessed routinely by the presence of only the molecular ion species of the dendron or dendrimer. Representative mass spectra recorded using the LSI and MALDI-TOF techniques for the 18-mer **36** are presented in Figure 1. Clearly, the MALDI-TOF technique is preferred for the analyses of the higher molecular weight dendrimers because of the much greater mass range of the time-of-flight analyzer.

Table 2. Molecular weight data of dendrons and dendrimers [a].

| | Molecular formula | Molecular weight calcd | Molecular weight obsd [b] |
|---|---|---|---|
| **3** | $C_{114}H_{95}NO_{32}$ | 1989.7 | 2012 (+Na) |
| **4** | $C_{30}H_{47}NO_{20}$ | 741.4 | 764 (+Na) |
| **5** | $C_{54}H_{71}NO_{32}$ | 1245.5 | 1268 (+Na) |
| **6** | $C_{106}H_{89}NO_{30}$ | 1855.7 | 1857 (+H) |
| **7** | $C_{46}H_{65}NO_{30}$ | 1111.5 | 1112 (+H) |
| **8** | $C_{22}H_{41}NO_{18}$ | 607.3 | 629 (+Na) [c] |
| **10** | $C_{113}H_{100}N_2O_{33}$ | 2012.8 | 2036 (+Na) |
| **11** | $C_{53}H_{76}N_2O_{33}$ | 1268.6 | 1291 (+Na) |
| **12** | $C_{29}H_{52}N_2O_{21}$ | 764.4 | 785 (+Na) [c] |
| **13** | $C_{110}H_{93}F_3N_2O_{33}$ | 2026.7 | 1913 (−TFA) |
| **14** | $C_{50}H_{69}F_3N_2O_{33}$ | 1282.5 | 1169 (−TFA) |
| **15** | $C_{24}H_{44}N_2O_{19}$ | 664.4 | 687 (+Na) [c] |
| **19** | $C_{230}H_{197}N_5O_{66}$ | 4084.6 | 4109 (+Na) |
| **20** | $C_{110}H_{149}N_5O_{66}$ | 2596.1 | 2620 (+Na) |
| **21** | $C_{102}H_{143}N_5O_{64}$ | 2462.1 | 2502 (+K) [c] |
| **24** | $C_{153}H_{204}N_6O_{96}$ | 3661.6 | 3685 (+Na) |
| **25** | $C_{81}H_{132}N_6O_{60}$ | 2149.0 | 2172 (+Na) |
| **28** | $C_{104}H_{138}N_4O_{64}$ | 2467.0 | 2502 (+K) [c] |
| **29** | $C_{56}H_{90}N_4O_{40}$ | 1458.7 | 1481 (+Na) |
| **33** | $C_{108}H_{146}N_4O_{65}$ | 2539.1 | 2563 (+Na) |
| **34** | $C_{100}H_{140}N_4O_{63}$ | 2405.1 | 2431 (+Na) [c] |
| **35** | $C_{52}H_{92}N_4O_{39}$ | 1396.7 | 1420 (+Na) [c] |
| **36** | $C_{315}H_{429}N_{15}O_{195}$ | 7542.3 | 7568 (+Na) |
| **37** | $C_{171}H_{285}N_{15}O_{123}$ | 4517.2 | 4539 (+Na) [c] |

[a] Nominal mass obtained from LSI-MS. [b] Only the most abundant peak in the molecular ion region is given. [c] Mass measured by MALDI-TOF-MS, using gentisic acid as the matrix and calibrated using either insulin (mw = 5734) or gramicidin s (mw = 1142); see Experimental Section for details of the mass spectrometric analysis.

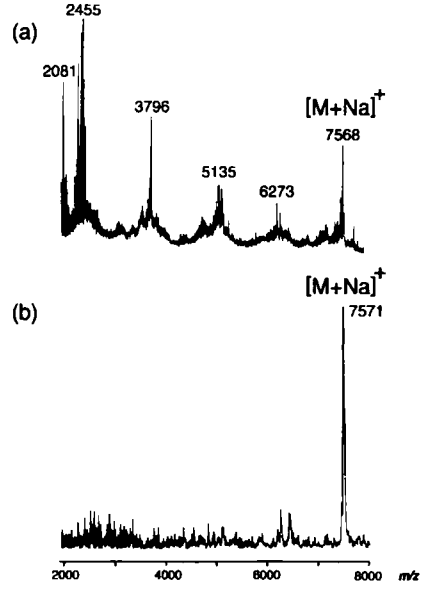


Fig. 1. Mass spectra obtained for **36** recorded using the a) LSI-MS and b) MALDI-TOF-MS techniques. The LSI-MS experiment results in a high degree of fragmentation of the macromolecule. Fragments arising from the cleavage of variable numbers of saccharide protecting groups and from cleavage at branching points are evident. The MALDI-TOF-MS, in contrast, is dominated by the molecular ion peak and provides an excellent indication of the homogeneity of the macromolecule.

*$^1H$ NMR Spectroscopy*: $^1H$ NMR spectroscopic investigations have been very useful for the characterization of all the new dendrons and dendrimers described in this paper. The $^1H$ chemical shifts are largely as expected. Obvious major characteristics of the spectra are their simple, sharp, and well-resolved resonances for the protons of the glucopyranosyl units and indeed for the non-carbohydrate protons. The integrated ratios of protons associated with the inner residues to the protons attached to the peripheral glucose units were helpful in monitoring the growth of the dendrons. The resonances for the amide protons are particularly useful in this respect. The coupling reactions of the dendrons **6** and **7** with the spacer **9**, with the branching unit **32**, or with the cores **23** and **27** could be monitored by the appearance of sharp singlets for the amide protons at around $\delta = 6.85$: their integrated ratios were always in accordance with the expected values. Because of the sharpness of the resonances associated with these protons, they could be observed clearly even in the case of higher-generation 18-mer **36**.

The simplicity of the $^1H$ NMR spectra—which extends from initial dendrons through to final dendrimers—points to both their highly symmetric structures and the monodisperse nature of the compounds. The distribution and multiplicities of the



0947-6539/96/0209-1120 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 9

signals for the D-glucopyranosyl residues contain a wealth of information. All protons associated with the D-glucopyranosyl residues and on the remaining structural units could be assigned unambiguously. The more polar solvent $CD_3COCD_3$ gave much better distributions of signals compared with $CDCl_3$. Accordingly, most of the dendrons and dendrimers were studied in $CD_3COCD_3$. The coupling constants observed between the protons of the D-glucopyranosyl residues were largely insensitive to the nature of the dendron or dendrimer. For example, the large coupling constant observed for H-1 and H-2 was always in excess of 7.5 Hz, in accordance with the $\beta$-anomeric configuration for the D-glucopyranosyl residues. The "carbohydrate regions" of the $^1$H NMR spectra for the series **7**, **24**, and **28** are illustrated in Figure 2. A $^1$H NMR spectrum of the corresponding resonances for the deprotected species **29** is provided as a sample illustration in Figure 3. It is interesting to note the behavior of the glycine-derived (or acetamido) protons. In many cases, the diastereotopic glycine methylene protons exhibited accidental chemical shift equivalence and resonated as an apparent doublet. However, in the cases **19**, **20**, **24**, and **28**, AX spin systems were observed with both the glycine methylene protons resonating as the expected double doublets ($J_{vic} \approx 2$–5 Hz and $J_{gem} \approx 16$ Hz).

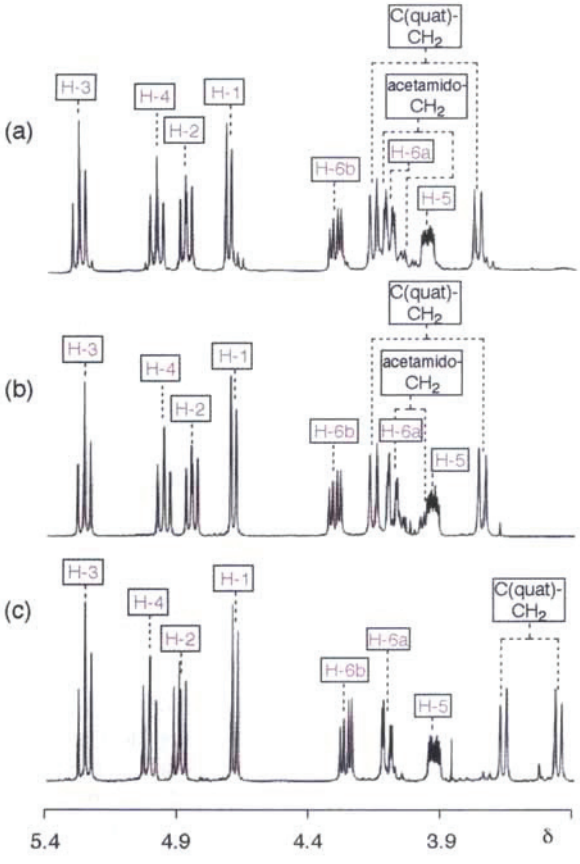


Fig. 2. The carbohydrate region of the $^1$H NMR spectra (400 MHz, 304 K, $CD_3COCD_3$) of the *O*-acetylated series a) **24**, b) **28**, and c) **7**. Assignments of the resonances are shown on the partial spectra.

The $^1$H NMR spectrum (400 MHz, $CD_3COCD_3$, 304 K) of the first-generation dendrimer **24** shows well-resolved resonances, which could be assigned unambiguously. The sharp singlet for the protons on the core benzene unit and the well-defined proton resonances for the peripheral D-glucopyranosyl residues and the remaining spacer regions are in accordance with the presence of averaged $C_3$ symmetry in the molecule. Molecular modeling studies suggest (vide infra) the same symmetry characteristics are present in this molecule.

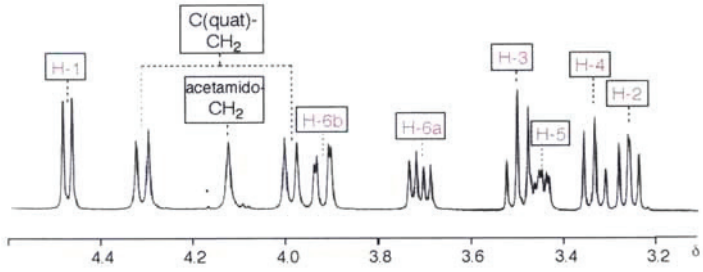


Fig. 3. The carbohydrate region of the $^1$H NMR spectrum (400 MHz, 304 K, $D_2O$) of the fully deacetylated species **29**. Assignments of the resonances are shown on the partial spectrum.

There is a substantial change in the behavior of the second-generation dendrimers **36** and **37** and their corresponding precursor dendrons **33** and **35** in comparison to all the remaining dendrons and dendrimers. The appearance of the $^1$H NMR spectra recorded at room temperature in a range of solvents ($CD_3COCD_3$, $CD_3SOCD_3$, and $CD_3NO_2$) showed resonances that were rather broad for both the glucopyranosidic protons and for the protons in the spacer regions. Subsequently, studies were performed at elevated temperatures (384 K) in $CD_3SOCD_3$. Under these conditions, where chemical exchange is fast on the $^1$H NMR timescale, the spectra simplified to those expected for highly symmetric compounds, similar to the spectra observed for the smaller dendrons and dendrimers at room temperature. The dynamic behavior exhibited by **36** and **37** is believed to be due to restricted rotation about the tertiary amide bonds[35] in the spacer arms, creating unique *cis* and *trans* environments near the peripheries of the dendrimers. The "carbohydrate regions" of the high-temperature $^1$H NMR spectra of the dendrimers **36** and **37** are illustrated in Figure 4.

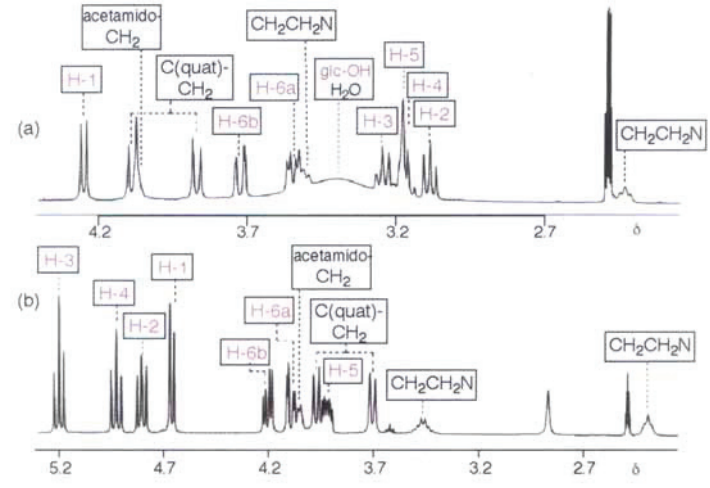


Fig. 4. The carbohydrate region of the $^1$H NMR spectra (400 MHz, $CD_3SOCD_3$) of the second-generation dendrimers. a) The spectrum of the deprotected species **37** (389 K). b) The spectrum of the protected analogue **36** (384 K). Assignments of the resonances are shown on the partial spectra.

In the spectrum of **36**, apart from the required resonances corresponding to the dendrimer, an impurity of unknown origin and constitution is evident. This impurity could be removed only after repeated purification by GPC; this may indicate the

occlusion or encapsulation of the impurity within the dendrimer. The impurity is notably absent in samples of the completely deprotected dendrimer **37**, obtained from **36** without need for the rigorous purification of the protected starting material.

*$^{13}C$ NMR Spectroscopy*: All the dendrons and dendrimers were analyzed by $^{13}C$ NMR spectroscopy. These broad-band decoupled spectra shared all the major features that characterized their analogous $^{1}H$ NMR spectra. Comparisons of the chemical shifts of particular carbons on the protected D-glucopyranosyl residues across the entire range of the dendrons and dendrimers reveal that the shifts are within $\pm 0.8$ ppm. In the case of the deprotected dendrons and dendrimers, the differences in chemical shift were even less, namely, within $\pm 0.2$ ppm. The only difference observed was that, in the de-*O*-acylated dendrons and dendrimers, the carbons were uniformly deshielded to the extent of ca. 4 ppm relative to the corresponding resonances in the protected analogues, with the exception of the glucopyranose C-6 carbons, which were hardly affected by the nearby protected or free hydroxyl group, and the core benzene ring carbons in **24**, **25**, **28**, **29**, **36**, and **37**. All these spectroscopic characteristics illustrate further the structural homogeneity confirmed by mass spectrometry and $^{1}H$ NMR spectroscopy. The very efficient stereoselective glycosylation of the hydroxymethyl groups in **1** with the glycosyl donor **2** and the stability of the anomeric $\beta$-configuration can easily be monitored from the appearance of anomeric carbon resonances at $\delta \approx 101$ in the presence of protecting groups and at $\delta \approx 105$ in the free saccharide analogues. The achievement of symmetrical functionalizations around the benzene cores in **24**, **25**, **28**, **29**, **36**, and **37** was demonstrated by the presence of only two kinds of carbons for the aromatic unit.

*Molecular Modeling Studies*: In the absence of any X-ray crystallographic evidence for structures in the solid state and in an attempt to gain some insight into the nature of the three-dimensional structures for the dendrimers **24** and **36** and the de-*O*-acylated dendrimers **25** and **37**, we modeled these compounds using the Macromodel program.[36] The structural data obtained from these preliminary studies are provided in Table 3. The measured structural parameters are defined in Figure 5. This computational approach has allowed us 1) to visualize several feasible low-energy conformations for the dendrimers, 2) to produce approximate locations of the monosaccharide units with respect to the central core units, and 3) to afford the approximate sizes and volumes of the dendrimers. The features pertinent to the dendritic nature of these compounds, with and without protecting groups, obtained from molecular modeling, can be summarized as follows:

1) There is an overall increase in average molecular radius (measured through the plane of the benzene ring) of about 50% in progressing from the first- to the second-generation systems.
2) The average distance between monosaccharide units that radiate from the same quaternary carbon center on a single dendron is compressed by only about 6–8% on going from the first- to the second-generation dendrimers; this suggests that there is considerable scope for further elaboration to higher-generation dendrimers.
3) There is an "easing" of steric compression (measured as a change in the molecular radius) of between 10 and 15% upon deprotection of **24** and **36** to give **25** and **37**, respectively.
4) The calculated molecular volumes of **25** and **37** are approximately half those of their protected analogues **24** and **36**, and the second-generation dendrimers have roughly twice the volumes of the first-generation dendrimers. Also, the packing density increases, on going from one generation to the next one.

Figure 6 shows the computer-generated CPK space-filling representations for the 9-mer **24** and the 18-mer **36**. The computer-visualized structures of both these compounds exhibit features that are broadly consistent with their $^{1}H$ NMR spectra in that they are highly symmetrical (the results of the calculations suggest both molecules adopt very slightly distorted $C_3$ arrangements) with the dendrimer branches radiating symmetrically in space from the central benzene cores. Other general features observed in these modeling studies include:

1) In the dendrimers **25** and **37**, there is extensive hydrogen bonding networks between adjacent D-glucopyranosyl residues in the individual dendrons, between amide groups within the spacer units and the proximal dendrons, and, in the case of **37**, extensive communication between individual dendrons.
2) All the D-glucopyranosyl residues adopt near perfect $^{4}C_{1}$ conformations.
3) Overall, there is a gradual change in morphology from a highly spacious and dynamically open structure in **24** (Fig. 6a) to a more densely packed annular arrangement in **36** (Fig. 6b).

Although molecular modeling of systems of this size is, at best, an approximation, we are confident that this foray has given us an insight into some of the possible three-dimensional surfaces of these carbohydrate-containing dendrimers.

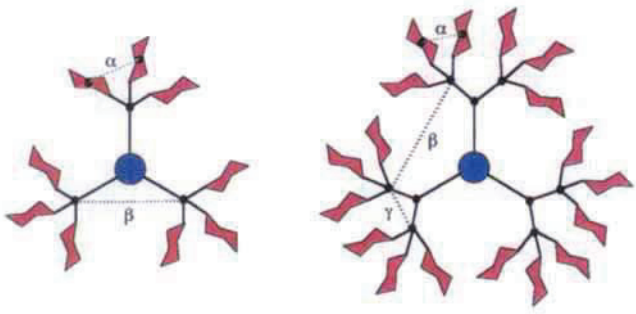


Fig. 5. Cartoons showing the parameters employed in the molecular modeling studies. The core is blue. The spacers are gray. The branching points are filled circles. The carbohydrate residues are pink.

Table 3. Structural data calculated for the saccharide dendrimers **24**, **25**, **36**, and **37** [a].

| | **24** (**25**) | **36** (**37**) |
|---|---|---|
| no. of saccharide units | 9 | 18 |
| approx. radius (Å) [b] | 12.5 (10.5) | 18 (17) |
| approx. spacer length (Å) [c] | 8.0 (8.0) | 13.5 (13.5) |
| $\alpha$ (Å) [d] | 8.0 (8.0) | 7.5 (7.5) |
| $\beta$ (Å) [e] | 13.5 | 16.5 (17.5) |
| $\gamma$ (Å) [f] | – | 10.0 |
| total molecular vol. (Å$^3$) [g] | 3416 (1933) | 7272 (4120) |

[a] See Experimental Section for the details of molecular modeling. [b] Measured from the centroid of the benzene core to the furthest point on the periphery of the dendrimer surface that resides in the plane described by the benzene core. [c] Distance through space between the centroid of the benzene core to the quaternary carbon atom that supports the saccharide units. [d] Average distance between the centroids of adjacent sugar units within the same dendron (see Fig. 5). [e] Average distance between quaternary carbons of adjacent dendrons (see Fig. 5). [f] Average distance between quaternary carbons in adjacent dendrons within a single arm (see Fig. 5). [g] Obtained from the Polygen program Quanta.



0947-6539/96/0209-1122 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 9

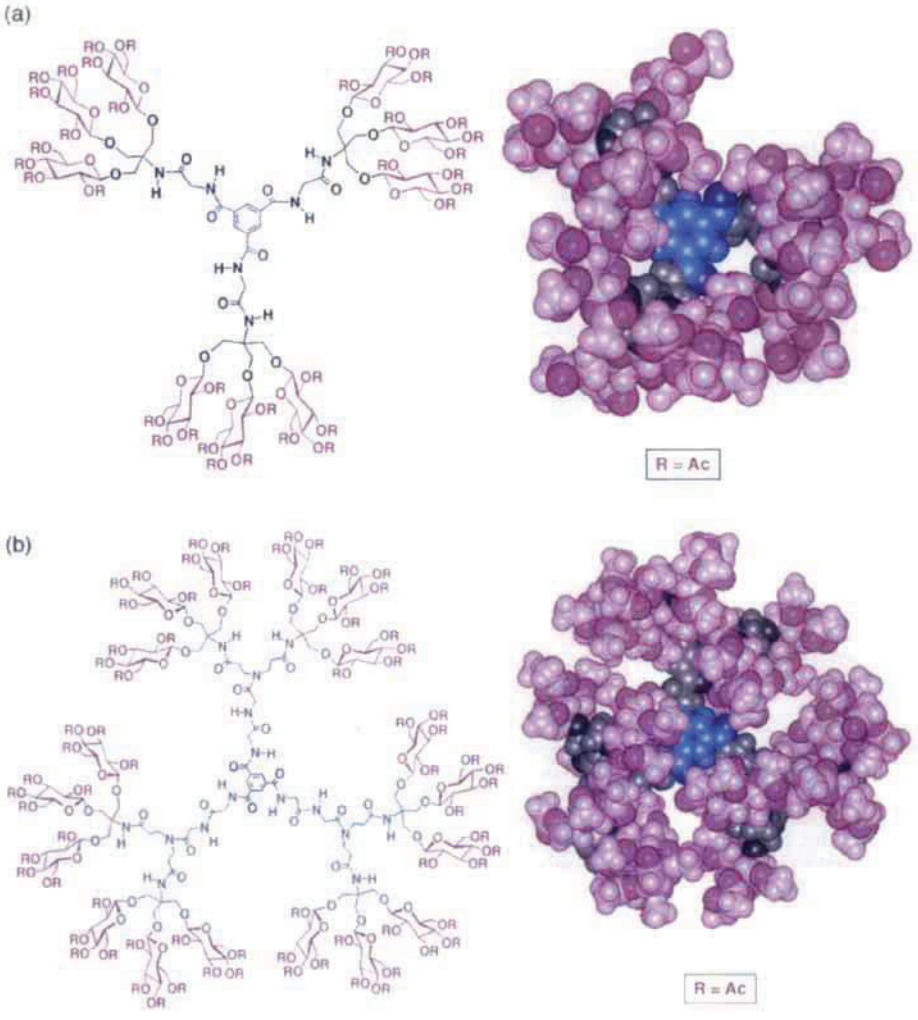


Fig. 6. Computer-generated CPK space-filling representations of the *O*-acetylated dendrimers a) **24** and b) **36**.

## Conclusion

We have devised a convergent synthetic strategy for the preparation of dendrimers possessing glucose units at their peripheries, based upon known synthetic methods. The three-step procedure, involving 1) glycosylation of the hydroxymethyl groups in TRIS with carbohydrate moieties, 2) successive amide bond formation to give dendrons and then dendrimers, and 3) removal of the protecting groups on the saccharides, was optimized. In several instances, yields in excess of 70% were obtained. The uniform attachment of the dendrons to the trifunctional 1,3,5-benzenetricarbonyl-derived cores was achieved by using glycine-derived spacers at either the focal point of the dendrons or at the core molecule, or at both. Characterization of all the dendrons and dendrimers by mass spectrometry, by $^1H$ and $^{13}C$ NMR spectroscopy, and by elemental analysis proved their high structural homogeneities and supported their assigned constitutions. Molecular modeling studies allowed the dendrimer molecules to be visualized. It also indicated the extent of the packing of the saccharide residues at the peripheries, which gives us some idea of the scope remaining for the further growth in these dendrimers.

The reliability of this general approach should permit the extension of the synthetic methodology to the synthesis of higher-generation dendrimers by the incorporation of additional building blocks with similar functionalities into the synthetic regime, provided reduced reactivities at the focal points resulting from steric inhibition can be avoided. The concept of including dendritic synthetic principles for the construction of neoglycoconjugates is relatively new and highly attractive. One of the advantages of the present synthetic methodology is its simplicity. It will permit ready access to potentially large numbers of dendritic neoglycomers of varying constitutions and sizes. At present, we are carrying out further syntheses and studies on the basis of the initial encouraging findings reported in this paper.

## Experimental Section

**General Methods:** Chemicals were purchased from Aldrich and used as received except 1) tris(hydroxymethyl)methylamine (TRIS), purchased from Fisons (England) and 2) 1,3,5-benzenetricarbonyl chloride, purchased from Lancaster (England). Reactions were carried out under an $N_2$ blanket with dry, freshly distilled solvents, which were prepared as described in literature procedures: DMF and $CH_2Cl_2$ by treatment with $CaH_2$, MeOH by treatment with Mg in the presence of catalytic amount of $I_2$, and $C_5H_5N$ by treatment with $P_2O_5$. Yields refer to chromatographically pure products. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60F (Merck 5554) in the following mobile phases: A) PhMe/EtOAc (80:20, *v/v*); B) PhMe/EtOAc (60:40, *v/v*); C) PhMe/EtOAc (40:60, *v/v*); D) EtOAc/MeOH (95:5, *v/v*); E) nBuOH/AcOH/$C_5H_5N$/$H_2O$ (15:5:10:12, *v/v*). The plates were inspected by UV light and developed either with iodine vapor or by charring with 5% $H_2SO_4$ in EtOH. Preparative TLC was performed on silica gel 60F (Merck 5717). Column chromatography was carried out using silica gel 60F (Merck 9385, 230–400 mesh). Gel permeation chromatography (GPC) of the fully protected dendrimer **36** was performed on a Phenogel (500 Å) (Phenomenex, Cheshire, England) semipreparative column (300 × 7.80 mm) attached on a Gilson 714 high-performance liquid chromatography system fitted with a UV detector. Detection was carried out at 260 nm, and GPC grade THF (Fisons) was used for elutions. The fully deprotected dendrons and dendrimers were purified on a Fractogel (25–40 μm) (Fractogel® TSK HW-40 (S), Merck 14983) column (100 × 0.25 cm), fitted with a differential refractometer (Waters Associates), with deionized and degassed $H_2O$ as eluant. Melting points were determined on a Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed by the University of North London Microanalytical Service. Low-resolution electron impact and chemical ionization mass spectra (EI-MS, and CI-MS) were obtained from a VG Prospec mass spectrometer. Liquid secondary ion mass spectra (LSI-MS) were recorded on a VG ZabSpec mass spectrometer, using a *m*-nitrobenzyl alcohol matrix and a scan speed of 10 s per decade. Matrix-assisted laser desorption ionisation–time-of-flight mass spectra (MALDI-TOF-MS) was performed on a Kratos Kompact MALDI-III instrument using gentisic acid (2,5-dihydroxy benzoic acid) and an average of 50 laser shots per sample. Optical rotations were performed at 23 °C on a Perkin Elmer 457 polarimeter. IR Spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. $^1H$ NMR Spectra were recorded on either a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX400 (400 MHz) spectrometer with either the residual solvent or TMS as internal standards. For studies in $D_2O$, TSP was used as the external reference. $^{13}C$ NMR spectra were recorded on a Bruker AC300 (75.5 MHz) spectrometer or a Bruker AMX400 (100.6 MHz) spectrometer. $^1H$ and $^{13}C$ assignments were verified by two-dimensional HMQC experiments in several instances. The chemical shifts are expressed in ppm and the coupling constants from the $^1H$ NMR spectra in Hertz (Hz) and are within a ca. ±0.2 Hz error range. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet; app. d, apparent doublet; app. t, apparent triplet; band, several overlapping signals; br, broad.

***N*-(Benzyloxycarbonyl)tris(hydroxymethyl)methylamine** (**1**): Benzyloxycarbonyl chloride (11.60 mL, 81.2 mmol) was added to a stirred solution of TRIS (6.55 g, 54.1 mmol) in $H_2O$ (30 mL) at 0 °C over 0.5 h. The pH of the medium was main-

tained at ca. 8–10 by the addition of small amounts of $Na_2CO_3$ (s). After 1 h of stirring, a thick mass separated. The reaction mixture was allowed to warm up to room temperature and left for 4 h. The slurry was filtered, washed with $H_2O$ (2 × 30 mL), dried, again washed with warm PhMe (2 × 25 mL), and the resulting white powder was dried for several hours to obtain **1** (3.90 g, 28%) as a white solid. TLC, $R_f$ ($CHCl_3$/MeOH, 9:1) = 0.50 (UV); M.p. 102–104 °C; CI-MS: *m/z* 256 $[M+1]^+$; $^1$H NMR (300 MHz, $CD_3CN$): $\delta$ = 3.35 (3H, t, $^3J$ = 6.0 Hz, OH), 3.62 (6H, d, $^3J$ = 6.0 Hz, C(quat)$CH_2$), 5.07 (2H, s, urethane $CH_2$), 5.13 (1H, br, urethane NH), 7.36 (5H, s, Ph); $^{13}$C NMR (75.5 MHz, $CD_3CN$): $\delta$ = 61.7 (C(quat)), 63.0 (C(quat)$CH_2$), 67.0 ($CH_2$Ph), 128.9, 129.0, 129.5, 138.2 (Ph ring carbons), 157.4 (CO). Anal. calcd for $C_{12}H_{17}NO_5$ (255.27): C, 56.47; H, 6.71; N, 5.49. Found: C, 56.41; H, 6.52; N, 5.48.

***N*-(Benzyloxycarbonyl)tris(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxymethyl)-methylamine (3)**: A mixture of **1** (0.38 g, 1.51 mmol), AgOTf (1.35 g, 5.25 mmol), and 2,4,6-collidine (0.55 g, 4.53 mmol) in $CH_2Cl_2$ (20 mL) and $MeNO_2$ (10 mL) was stirred at −25 to −30 °C. A solution of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide [29] (**2**) (3.46 g, 5.25 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise over 0.5 h to this suspension. Stirring was continued for 0.5 h at the same temperature and then the reaction mixture was allowed to reach 0 °C and left stirring for 2.5 h. After completion of the reaction (TLC), $C_5H_5N$ (1.0 mL) was added to the reaction mixture and it was diluted with $CH_2Cl_2$ (30 mL) before being filtered over Celite. The filtrate was washed successively with a 1 M aqueous $Na_2S_2O_3$ solution (3 × 20 mL), a 1 M aqueous $NaHCO_3$ solution (3 × 20 mL), and $H_2O$ (3 × 20 mL). Then, it was dried and the solvents were evaporated off in vacuo. The residue was dried thoroughly to obtain a crude mixture (3.80 g), the TLC of which showed a main product ($R_f$ (A) = 0.65; $H_2SO_4$), in addition to a few other minor products ($R_f$ (A) = 0.20, 0.40, 0.58, 0.78; $H_2SO_4$). The main product was separated by column chromatography ($SiO_2$, PhMe/EtOAc, 93:7). The solvents were evaporated off and dried thoroughly to yield **3** (2.29 g, 77%) as a white foamy solid. TLC, $R_f$ (A) = 0.65 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 3.60 (3H, d, $^2J_{Ha,Hb}$ = 11.0 Hz, C(quat)C$H_a$H$_b$), 3.87 (3H, m, H-5), 4.21 (3H, d, $^2J_{Ha,Hb}$ = 11.0 Hz, C(quat)CH$_a$H$_b$), 4.31 (3H, d, $^3J_{1,2}$ = 9.0 Hz, H-1), 4.44 (3H, dd, $^3J_{5,6a}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.0 Hz, H-6a), 4.57 (3H, dd, $^3J_{5,6b}$ = 3.0 Hz, $^2J_{6a,6b}$ = 12.0 Hz, H-6b), 4.71 (1H, d, $^2J_{Ha,Hb}$ = 12.0 Hz, C$H_a$H$_b$Ph), 4.81 (1H, d, $^2J_{Ha,Hb}$ = 12.0 Hz, CH$_a$H$_b$Ph), 5.41 (3H, dd, $^3J_{1,2}$ = 9.0 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 5.63 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.5 Hz, H-4), 5.76 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.5 Hz, H-3), 5.94 (1H, s, urethane NH), 7.26–8.12 (65H, band, 13 × Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 58.9 (C(quat)), 63.1 (C-6), 66.2 ($CH_2$Ph), 68.5 (C(quat)$CH_2$), 69.6 (C-4), 71.9 (C-2), 72.0 (C-5), 72.6 (C-3), 101.5 (C-1), 128.4–133.7 (Ph ring carbons), 154.9 (urethane CO), 164.7, 165.1, 165.7, 166.1 (COPh). Anal. calcd. for: $C_{114}H_{95}NO_{32}$ (1990.99): C, 68.77; H, 4.81; N, 0.70. Found: C, 68.60; H, 4.83; N, 0.66.

***N*-(Benzyloxycarbonyl)tris(β-D-glucopyranosyloxymethyl)methylamine (4)**: A solution of **3** (1.0 g, 0.50 mmol) in 0.05 M methanolic NaOMe (60.2 mL) was stirred at room temperature for 4.5 h, before being neutralized with Amberlite IR-120 ($H^+$ form) ion-exchange resin and filtered. The solvents were removed in vacuo. The resulting white powder was washed with hexane and $Et_2O$ (3 × 15 mL each) and dried thoroughly to obtain **4** (0.37 g, 92%); $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 3.10 (3H, t, $^3J_{1,2}$ = 7.0 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 3.21 (6H, band, H-4 and H-5), 3.28 (3H, app. t, $^3J_{2,3}$ = 9.5 Hz, H-3), 3.50 (3H, m, $^2J_{6a,6b}$ = 13.5 Hz, H-6a), 3.71 (6H, band, H-6b and C(quat)C$H_a$H$_b$), 4.0 (3H, d, $^2J_{Ha,Hb}$ = 11.0 Hz, C(quat)CH$_a$H$_b$), 4.23 (3H, d, $^3J_{1,2}$ = 7.0 Hz, H-1), 4.92 (2H, s, C$H_2$Ph), 7.27 (5H, s, Ph); $^{13}$C NMR (75.5 MHz, $D_2O$): $\delta$ = 61.2 (C(quat)), 63.5 (C-6), 70.1 ($CH_2$Ph), 70.4 (C(quat)$CH_2$), 72.2 (C-4), 75.6 (C-2), 78.1 (C-3), 78.4 (C-5), 105.6 (C-1), 130.4–135.8 (Ph ring carbons), 158.0 (urethane CO).

***N*-(Benzyloxycarbonyl)tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)-methylamine (5)**: Acetic anhydride (3.69 mL) was added to a stirred solution of **4** (0.77 g, 1.04 mmol) in $C_5H_5N$ (5.38 mL), and the reaction mixture was left at room temperature for 6 h, before being evaporated in vacuo. The resulting residue was dissolved in EtOAc (45 mL), washed with 5% aqueous $NaHCO_3$ solution (3 × 20 mL) and $H_2O$ (2 × 20 mL), before being dried. Solvents were evaporated off in vacuo and the residue was dried thoroughly to obtain **5** (1.21 g, 93%) as a white foamy residue. TLC, $R_f$ (B) = 0.34 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02, 2.03 (36H, 4s, COMe), 3.79 (3H, d, $^2J_{Ha,Hb}$ = 10.5 Hz, C(quat)C$H_a$H$_b$), 3.93 (3H, m, $^3J_{5,6a}$ = 2.6 Hz, $^3J_{5,6b}$ = 5.0 Hz, $^3J_{4,5}$ = 10.3 Hz, H-5), 4.10 (6H, band, H-6a, C(quat)CH$_a$H$_b$), 4.29 (3H, dd, $^3J_{5,6b}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.5 Hz, H-6b), 4.70 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.91 (3H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.7 Hz, H-2), 5.03 (5H, brt, 4-H and CH$_2$Ph), 5.28 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.7 Hz, H-3), 5.92 (1H, band, urethane NH), 7.38 (5H, m, Ph); $^{13}$C NMR (75.5 MHz, $CD_3COCD_3$): $\delta$ = 20.4, 20.5, 20.6 (CO*Me*) 59.4 (C(quat)), 62.6 (C 6), 66.5 ($CH_2$Ph), 69.0 (C(quat)$CH_2$), 69.3 (C-4), 72.1 (C-2), 72.4 (C-5), 73.2 (C-3), 101.9 (C-1), 128.7, 128.8, 129.2, 137.9 (Ph ring carbons), 155.6 (urethane CO), 169.7, 169.9, 170.2, 170.7 (COMe). Anal. calcd. for: $C_{54}H_{71}NO_{32}$ (1246.14): C, 52.05; H, 5.74; N, 1.12. Found: C, 52.07; H, 5.82; N, 1.02.

**Tris(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxymethyl)methylamine (6)**: A suspension of **3** (1.50 g, 0.75 mmol) in EtOAc/MeOH (2:1) (45 mL) and 10% Pd/C (0.750 g) was hydrogenolyzed by using a balloon filled with $H_2$ gas, at 35–40 °C for 5 d. The reaction mixture was then filtered over Celite and washed with EtOAc, and the solvents were removed in vacuo to yield impure **6** (0.97 g), which was purified from unreacted starting material by column chromatography ($SiO_2$, PhMe/EtOAc, 80:20) to afford pure **6** (0.78 g, 84%) as a white foamy solid. TLC, $R_f$ (A) = 0.19 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 3.24 (3H, d, $^2J_{Ha,Hb}$ = 9.6 Hz, C(quat)C$H_a$H$_b$), 3.63 (3H, d, $^2J_{Ha,Hb}$ = 9.6 Hz, C(quat)CH$_a$H$_b$), 3.77 (3H, m, H-5), 4.33 (3H, d, $^3J_{1,2}$ = 7.9 Hz, H-1), 4.49 (6H, band, H-6a, H-6b), 5.42 (3H, dd, $^3J_{1,2}$ = 7.9 Hz, $^3J_{2,3}$ = 9.5 Hz, H-2), 5.67 (3H, app. t, $^3J_{3,4}$ = 9.5 Hz, H-4 ), 5.79 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.5 Hz, H-3), 7.32–8.17 (60H, m, 12 × Ph). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 56.0 (C(quat)), 63.4 (C-6), 70.2 (C(quat)$CH_2$), 72.1 (C-4), 72.4 (C-2), 72.7 (C-5), 73.6 (C-3), 102.1 (C-1), 126.6–134.5 (Ph ring carbons), 165.2, 165.5, 165.9 and 166.1 (COPh). Anal. calcd. for $C_{106}H_{89}NO_{30}$ (1856.85): C, 68.56; H, 4.83; N, 0.75. Found: C, 68.46; H, 4.75; N, 0.71.

**Tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methylamine (7)**: A suspension of **5** (1.20 g, 0.96 mmol) in EtOAc/MeOH (2:1) (15 mL) and 10% Pd/C (0.35 g) was hydrogenolyzed by using a balloon filled with $H_2$ gas for 8 h. The reaction mixture was filtered over Celite and washed with EtOAc. The solvents were evaporated in vacuo, and the residue was dried to obtain **7** (1.05 g, 98%) as a foamy white powder. TLC, $R_f$ (EtOAc) = 0.17 ($H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02, 2.03 (36H, 4s, CO*Me*), 3.40 (3H, d, $^2J_{Ha,Hb}$ = 9.9 Hz, C(quat)C$H_a$H$_b$), 3.62 (3H, d, $^2J_{Ha,Hb}$ = 9.9 Hz, C(quat)CH$_a$H$_b$), 3.87 (3H, m, $^3J_{5,6a}$ = 2.5 Hz, $^3J_{5,6b}$ = 5.0 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 4.04 (3H, dd, $^3J_{5,6a}$ = 2.5 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6a), 4.20 (3H, dd, $^3J_{5,6b}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.3 Hz H-6b), 4.62 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.84 (3H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 4.95 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.09 (3H, app. t, $^3J_{3,4} \approx {}^3J_{2,3}$ = 9.8 Hz, H-3); $^{13}$C NMR (100.6 MHz, $CD_3COCD_3$): $\delta$ = 20.4, 20.5, 20.6 (CO*Me*), 54.8 (C(quat)), 61.0 (C-6), 67.7 (C-4), 70.6 (C-2), 70.8 (C-5), 71.1 (C$H_2$C(quat)), 71.6 (C-3), 100.3 (C-1), 168.2, 168.3, 168.6, 169.1 (COMe). Anal. calcd. for: $C_{46}H_{65}NO_{30}$ (1112.0): C, 49.69; H, 5.89; N, 1.26. Found: C, 49.67; H, 5.94; N, 1.22.

**General Procedure for the De-*O*-acylations under Zemplén's Conditions**: The *O*-acylated dendrons or dendrimers already dissolved in MeOH were treated with the required amount of a methanolic solution of 1 M NaOMe such that the final solution concentration was 0.05 M. Alternatively, the dendrons or dendrimers in MeOH:$H_2O$ (1:1) were treated with a methanolic solution of 1 M NaOMe, and the pH of the solution was adjusted to ca. 9. The reaction mixture was left stirring at room temperature, and precipitated material, if any, was dissolved in the minimum amount of $H_2O$, neutralized with Amberlite IR-120 ($H^+$ form) resin, filtered, and washed, and the solvents were removed in vacuo. Purification by GPC afforded the fully de-*O*-acylated dendrons or dendrimers.

**Tris(β-D-glucopyranosyloxymethyl)methylamine (8)**: The de-*O*-acetylation of **7** (250 mg, 0.225 mmol) was carried out in 0.05 M methanolic NaOMe solution (25 mL) for 15 h, followed by workup and purification as given in the general procedure to afford **8** (128 mg, 94%) as a glassy solid. Retention volume (GPC): 118 mL; TLC, $R_f$ (E) = 0.27 ($H_2SO_4$); $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 3.37 (3H, dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.0 Hz, H-2), 3.43 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.0 Hz, H-4), 3.50 (3H, m, $^3J_{5,6b}$ = 2.3 Hz, $^3J_{5,6a}$ = 5.9 Hz, $^3J_{4,5}$ = 9.0 Hz, H-5), 3.53 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.0 Hz, H-3), 3.76 (3H, dd, $^3J_{5,6a}$ = 5.9 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6a), 3.83 (3H, d, $^2J_{Ha,Hb}$ = 10.7 Hz, C(quat)C$H_a$H$_b$), 3.95 (3H, dd, $^3J_{5,6b}$ = 2.3 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6b), 4.06 (3H, d, $^2J_{Ha,Hb}$ = 10.7 Hz, C(quat)CH$_a$H$_b$), 4.52 (3H, d, $^3J_{1,2}$ = 7.8 Hz, H-1); $^{13}$C NMR (100.6 MHz, $CD_3COCD_3$): $\delta$ = 51.7 (C(quat)), 63.5 (C-6), 72.2 (C(quat)$CH_2$), 72.5 (C-4), 75.9 (C-2), 78.4 (C-3), 78.8 (C-5), 105.6 (C-1).

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl Glycine Pentafluorophenyl Ester (9)**: Dicyclohexylcarbodiimide (DCC) (0.87 g, 4.20 mmol) was added to a stirred solution of *N*$^{\alpha}$-BOC-Gly (0.70 g, 4.0 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. After 0.25 h, a solution of pentafluorophenol (0.77 g, 4.20 mmol) in $CH_2Cl_2$ (15 mL) was added. The reaction mixture was stirred at room temperature for 24 h, before being filtered to remove the precipitated materials. The filtrate was diluted with $CH_2Cl_2$ (25 mL), washed successively with 5% aqueous $NaHCO_3$ (3 × 20 mL) and $H_2O$ (3 × 15 mL), before being dried ($MgSO_4$). Removal of the solvent and drying in vacuo afforded the product **9**, as a yellow microcrystalline solid (1.36 g, 100%). LSI-MS: *m/z*: 342 $[M+1]^+$, 286 $[M - Me_3C]^+$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.48 (9H, s, $CMe_3$), 4.30 (2H, d, Gly-$CH_2$), 5.12 (1H, br, urethane NH).

**General Procedure for the Preparation of Amides Using Pentafluorophenyl Esters**: The pentafluorophenyl ester (1.0–1.1 molequiv) was added to a stirred solution of the amine (1.0 molequiv) in $CH_2Cl_2$/DMF (2:1) at 0 °C and under an $N_2$ blanket. The reaction mixture was allowed to stir at room temperature until the amine component had disappeared (TLC). The solvents were then evaporated off and the resulting residue was dissolved in EtOAc, washed with 5% aqueous $NaHCO_3$ solution (50 mL), $H_2O$ (25 mL), and dried, before the solvents were completely evaporated off to afford the crude product, which was purified by column chromatography ($SiO_2$).

***N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*-[tris(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxymethyl)methyl]glycinamide (10)**: A solution of **6** (0.50 g, 0.27 mmol) in $CH_2Cl_2$/



0947-6539/96/0209-1124 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 9

DMF (15 mL) was added to **9** (0.10 g, 0.30 mmol) at 0 °C under an $N_2$ blanket. The reaction mixture was allowed to stir at room temperature for 96 h. It was then subjected to column chromatography ($SiO_2$, PhMe/EtOAc, 85:15) to obtain **10** (0.49 g, 90%) as a white foamy powder. TLC, $R_f$ (B) = 0.60 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.48 (9H, s, $CMe_3$), 3.53 (2H, brd, Gly-$CH_2$), 3.57 (3H, d, $^2J_{H_a,H_b}$ = 10.2 Hz, C(quat)$CH_aH_b$), 3.84 (3H, m, $^3J_{5,6a}$ = 3.0 Hz, $^3J_{5,6b}$ = 7.4 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 4.30 (3H, d, $^2J_{H_a,H_b}$ = 10.2 Hz, C(quat)-$CH_aH_b$), 4.45 (6H, band, H-1 and H-6a), 4.46 (3H, dd, $^3J_{5,6b}$ = 3.0 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6b), 5.38 (3H, dd, $^3J_{1,2}$ = 7.9 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 5.62 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.79 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.8 Hz, H-3), 5.91 (1H, brt, Gly-NH), 6.63 (1H, s, C(quat)NH), 7.31–8.12 (60H, m, 12 × Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 28.4 ($CMe_3$), 44.2 (Gly-$CH_2$), 49.8 ($CMe_3$), 59.4 (C(quat)), 63.0 (C-6), 68.0 (C(quat)$CH_2$), 69.6 (C-4), 71.9 (C-2, C-5), 72.5 (C-3), 101.3 (C-1), 128.3–133.7 (Ph ring carbons), 162.7 (urethane CO), 164.7, 165.1, 165.7, 166.1 (COPh), 169.5 (Gly-CO). Anal. calcd. for: $C_{113}H_{100}N_2O_{33}$ (2014.02): C, 67.39; H, 5.01; N, 1.39. Found: C, 67.21; H, 4.94; N, 1.91.

**$N^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]glycinamide (11)**: A solution of **7** (0.834 g, 0.750 mmol) in $CH_2Cl_2$/DMF (15 mL) was added to **9** (0.38 g, 1.12 mmol) at 0 °C, under an $N_2$ blanket. The reaction mixture was allowed to stir at room temperature for 80 h. It was then subjected to column chromatography ($SiO_2$, PhMe/EtOAc, 85:15) to obtain **11** (0.82 g, 85%) as a white foamy powder. TLC, $R_f$ (D) = 0.62 ($H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.48 (9H, s, $CMe_3$), 1.95, 1.99, 2.02, 2.03 (36H, 4s, COMe), 3.71 (2H, brd, Gly-$CH_2$), 3.77 (3H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 3.95 (3H, m, $^3J_{5,6a}$ = 2.4 Hz, $^3J_{5,6b}$ = 5.0 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 4.12 (3H, dd, $^3J_{5,6a}$ = 2.4 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 4.18 (3H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)-$CH_aH_b$), 4.35 (3H, dd, $^3J_{5,6b}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 4.72 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.92 (3H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 5.05 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.30 (3H, app. t, $^3J_{3,4} \approx {}^3J_{2,3}$ = 9.8 Hz, H-3), 6.02 (1H, brt, Gly-NH), 6.68 (1H, s, C(quat)NH); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 20.3, 20.5, 20.6 (COMe), 28.3 ($CMe_3$), 44.2 (Gly-$CH_2$), 49.0 ($CMe_3$), 59.1 (C(quat)), 61.6 (C-6), 68.2 (C(quat)$CH_2$), 71.4 (C-4), 71.9 (C-2 and C-5), 72.6 (C-3), 100.9 (C-1), 155.8 (urethane CO), 169.3, 169.4, 169.7, 170.0, 170.6 (COMe and Gly-CO). Anal. calcd. for: $C_{53}H_{76}N_2O_{33}$ (1269.17): C, 50.16; H, 6.04; N, 2.21. Found: C, 50.18; H, 5.97; N, 2.15.

**$N^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*-[tris(β-D-glucopyranosyloxymethyl)methyl]glycinamide (12)**: The de-*O*-acetylation of **11** (250 mg, 0.197 mmol) was carried out in 0.05 M methanolic NaOMe solution (20 mL) during 6 h, followed by workup and purification as outlined in the general procedure, to afford **12** (140 mg, 90%) as a glassy solid. Retention volume (GPC) 110 mL; TLC, $R_f$ (E) = 0.45 ($H_2SO_4$); $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 1.49 (9H, s, $CMe_3$), 3.34 (3H, dd, $^3J_{1,2}$ = 7.7 Hz, $^3J_{2,3}$ = 9.9 Hz, H-2), 3.43 (3H, dd, $^3J_{4,5}$ = 7.7 Hz, $^3J_{3,4}$ = 9.9 Hz, H-4), 3.48 (3H, m, H-5), 3.53 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.9 Hz, H-3), 3.76 (5H, band, H-6a and Gly-$CH_2$), 3.96 (3H, dd, $^3J_{5,6b}$ = 2.0 Hz, $^2J_{6a,6b}$ = 12.2 Hz, H-6b), 3.99 (3H, d, $^2J_{H_a,H_b}$ = 10.7 Hz, C(quat)$CH_aH_b$), 4.31 (3H, d, $^2J_{H_a,H_b}$ = 10.7 Hz, C(quat)$CH_aH_b$), 4.50 (3H, d, $^3J_{1,2}$ = 7.7 Hz, H-1); $^{13}$C NMR (75.5 MHz, $D_2O$): $\delta$ = 30.4 ($CMe_3$), 46.6 ($CMe_3$), 48.3 (Gly-$CH_2$), 62.4 (C(quat)), 63.5 (C-6), 70.5 (C(quat)$CH_2$), 72.4 (C-4), 75.8 (C-2), 78.3 (C-3), 78.7 (C-5), 105.6 (C-1), 160.8 (urethane CO), 174.9 (Gly-CO).

***N*-[Tris(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxymethyl)methyl]glycinamide Trifluoroacetate Salt (13·TFA)**: The removal of the BOC protecting group was carried out by treatment of a solution of **10** (0.68 g, 0.34 mmol) in $CH_2Cl_2$ (30 mL) with trifluoroacetic acid (2.0 mL). The mixture was refrigerated for 15 h, and the solvents were then evaporated off. The resulting residue was triturated with hexane (15 mL) and $Et_2O$ (15 mL) before being completely dried, to obtain **13**·TFA (0.70 g, 100%) as a white glassy solid. $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 3.50 (3H, d, $^2J_{H_a,H_b}$ = 10.0 Hz, C(quat)$CH_aH_b$), 3.76 (3H, m, H-5), 4.28 (3H, d, $^2J_{H_a,H_b}$ = 10.0 Hz, C(quat)$CH_aH_b$), 4.46 (9H, band, H-1, H-6a, H-6b), 4.54 (2H, d, Gly-$CH_2$), 5.39 (3H, dd, $^3J_{1,2}$ = 7.9 Hz, $^3J_{2,3}$ = 9.6 Hz, H-2), 5.68 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.6 Hz, H-4), 5.78 (3H, app. t, $^3J_{3,4} \approx {}^3J_{2,3}$ = 9.6 Hz, H-3), 7.30–8.14 (60H, m, 12 × Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 60.6 (C(quat)), 63.6 (C-6), 68.2 (C(quat)$CH_2$), 68.5 (Gly-$CH_2$), 70.2 (C-4), 72.6 (C-2), 72.8 (C-5), 73.7 (C-3), 102.0 (C-1), 129.3–134.8 (Ph ring carbons), 165.4, 165.7, 166.1, 166.4 (COPh and Gly-CO). Anal. calcd. for: $C_{110}H_{93}N_2O_{33}F_3$ (2027.94): C, 65.15; H, 4.62; N, 1.38. Found: C, 65.17; H, 4.67; N, 1.48.

***N*-[Tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]glycinamide Trifluoroacetate Salt (14·TFA)**: The removal of the BOC protecting group was carried out by treatment of a solution of **11** (0.50 g, 0.39 mmol) in $CH_2Cl_2$ (15 mL) with trifluoroacetic acid (1.5 mL) using the procedure already described for **13**·TFA The product **14**·TFA (0.50 g, 100%) was obtained as a white glassy powder. $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02, 2.03 (36H, 4s, COMe), 3.77 (3H, d, $^2J_{H_a,H_b}$ = 10.2 Hz, C(quat)$CH_aH_b$), 3.96 (3H, m, H-5), 4.10 (3H, dd, $^3J_{5,6a}$ = 2.34 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6a), 4.21 (3H, d, $^2J_{H_a,H_b}$ = 10.2 Hz, C(quat)-$CH_aH_b$), 4.34 (3H, dd, $^3J_{5,6b}$ = 4.98 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6b), 4.41 (2H, m, Gly-$CH_2$), 4.70 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.88 (3H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.6 Hz, H-2), 5.03 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.6 Hz, H-4), 5.28 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.6 Hz, H-3); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 20.5, 20.6, 20.8 (COMe), 61.0 (C(quat)), 62.6 (C-6), 68.7 (C(quat)$CH_2$), 69.0 (Gly-$CH_2$), 69.4 (C-4), 72.3 (C-2), 72.5 (C-5), 73.3 (C-3), 101.7 (C-1), 170.0, 170.3, 170.9 (MeCO and Gly-CO).

***N*-[Tris(β-D-glucopyranosyloxymethyl)methyl]glycinamide (15)**: The de-*O*-acetylation of **14**·TFA (0.108 g, 0.144 mmol) was carried out in 0.05 M methanolic NaOMe solution (10 mL) during 6 h, followed by workup and purification as outlined in the general procedure, to afford **15** (0.042 g, 68%) as a glassy solid. Retention volume (GPC) 110 mL; $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 3.14 (3H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.3 Hz, H-2), 3.23 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.3 Hz, H-4), 3.31 (3H, m, $^3J_{5,6b}$ = 2.0 Hz, $^3J_{5,6a}$ = 5.9 Hz, $^3J_{4,5}$ = 9.3 Hz, H-5), 3.46 (3H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.3 Hz, H-3), 3.56 (3H, dd, $^3J_{5,6a}$ = 5.9 Hz, $^2J_{6a,6b}$ = 12.5 Hz, H-6a), 3.65 (2H, m, Gly-$CH_2$), 3.77 (3H, dd, $^3J_{5,6b}$ = 2.0 Hz, $^2J_{6a,6b}$ = 12.5 Hz, H-6b), 3.80 (3H, d, $^2J_{H_a,H_b}$ = 10.7 Hz, C(quat)$CH_aH_b$), 4.13 (3H, d, $^2J_{H_a,H_b}$ = 10.7 Hz, C(quat)$CH_aH_b$), 4.32 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1); $^{13}$C NMR (75.5 MHz, $D_2O$): $\delta$ = 43.4 (Gly-$CH_2$), 70.2 (C(quat)), 63.3 (C-6), 70.2 (C(quat)$CH_2$), 72.3 (C-4), 75.7 (C-2), 78.2 (C-3), 78.6 (C-5), 105.6 (C-1), 168.8 (Gly-CO).

**3,3′-Iminodipropionic acid (16)**: A mixture of 3,3′-iminodipropionitrile (5.0 g, 40.65 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (27.0 g, 86 mmol) in $H_2O$ (60 mL) was heated at 70 °C, with stirring, for 18 h. The mixture was adjusted to 40–50 °C, treated with 50% aqueous $H_2SO_4$ (8 mL), and stirred for 0.5 h, before being filtered over Celite. In order to ensure complete precipitation of all the inorganic material, a further 8 mL of 50% aqueous $H_2SO_4$ was added, and the mixture was filtered through Celite again. The filtrate was then evaporated off and dried to obtain **16** as its hydrogen sulfate salt (5.0 g, 48%). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 2.79 (4H, m, $NCH_2$), 3.30 (4H, t, $COCH_2$).

***N*-(Benzyloxycarbonyl)-imino-3,3′-bis(propionic acid) (17)**: Benzyloxycarbonyl chloride (2.0 mL, 14.0 mmol) was added dropwise to a stirred aqueous solution of **16** (2.0 g, 12.42 mmol) in saturated aqueous $NaHCO_3$ solution (25 mL) at 0 °C. The pH of the reaction mixture was kept alkaline by adding the required amount of $NaHCO_3$ solution. It was left to stir for 4 h before being refrigerated for 12 h. The reaction mixture was warmed up to room temperature, washed with $Et_2O$ (2 × 20 mL), neutralized with dilute HCl, and extracted with EtOAc (3 × 30 mL). The organic portion was washed with $H_2O$ (20 mL), dried, evaporated in vacuo and dried thoroughly to obtain **17**, m.p. 113–115 °C (1.58 g, 43%). MALDI-TOF-MS: $m/z$ 317 $[M+Na]^+$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.66 (4H, dd, $CH_2N$), 3.61 (4H, m, $CH_2CH_2N$), 5.13 (2H, s, $CH_2Ph$), 7.35 (5H, s, Ph), 8.88 (2H, br, COOH); $^{13}$C NMR (75.5 MHz, $CD_3CN/CD_3SOCD_3$): $\delta$ = 33.1, 33.8 ($CH_2N$), 43.9, 44.4 ($CH_2CH_2N$), 66.9 ($CH_2Ph$), 127.6, 127.9, 128.4, 136.6 (Ph ring carbons), 155.7 (CON), 172.3, 173.5 (COOH).

***N*-(Benzyloxycarbonyl)imino-3,3′-bis(pentafluorophenyl propionate) (18)**: This compound was prepared, following a similar protocol to that described for the preparation of **9**, except that the reaction was carried out in EtOAc/$CH_2Cl_2$ (1:1). A solution of **17** (1.0 g, 3.38 mmol) in EtOAc/$CH_2Cl_2$ (1:1) (15 mL) was added to a solution of DCC (1.53 g, 7.44 mmol) and pentafluorophenol (1.37 g, 7.44 mmol) in $CH_2Cl_2$ (10 mL) to afford the corresponding bis(pentafluorophenyl ester) **18** as a white powder (2.10 g, 100%). LSI-MS: $m/z$: 628 $[M+1]^+$.

***N*-(Benzyloxycarbonyl)imino-3,3′-bis[*N*-[*N*-[tris(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxymethyl)methyl]acetamido]propionamide] (19)**: A solution of the pentafluorophenyl ester **18** (0.039 g, 0.062 mmol) in $CH_2Cl_2$ (5 mL) was added, dropwise, to a stirred mixture of **13**·TFA (0.28 g, 0.138 mmol) and $Et_3N$ (0.02 mL, 0.144 mmol) in $CH_2Cl_2$/DMF (12 mL) at 0 °C and under an $N_2$ blanket. After 24 h of stirring at room temperature, the reaction mixture was worked up as described in the general procedure. The product **19** was purified by column chromatography ($SiO_2$, PhMe/EtOAc, 1:1) and isolated as a white foamy powder (0.30 g, quantitative). TLC, $R_f$ (C) = 0.77 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 2.53 (4H, brt, $CH_2N$), 3.58 (6H, d, $^2J_{H_a,H_b}$ = 10.1 Hz, C(quat)$CH_aH_b$), 3.67 (8H, band, $CH_2CH_2N$ and acetamido $CH_2$), 3.83 (6H, m, H-5), 4.25 (6H, d, $^2J_{H_a,H_b}$ = 10.1 Hz, C(quat)$CH_aH_b$), 4.45 (12H, band, H-1 and H-6a), 4.54 (6H, dd, $^3J_{5,6b}$ = 2.9 Hz, $^2J_{6a,6b}$ = 12.0 Hz, H-6b), 5.13 (2H, s, $CH_2Ph$), 5.42 (6H, dd, $^3J_{1,2}$ = 7.6 Hz, $^3J_{2,3}$ = 9.7 Hz, H-2), 5.67 (6H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.7 Hz, H-4), 5.81 (6H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.7 Hz, H-3), 6.69 (2H, s, C(quat)NH), 7.29–8.18 (≈122H, band, 24 × Ph and 2 × acetamido NH); $^{13}$C NMR (100.6 MHz, $CD_3COCD_3$): $\delta$ = 34.8 ($NCH_2$), 43.8 ($NCH_2CH_2$), 40.5 (acetamido $CH_2$), 60.3 (C(quat)), 63.6 (C-6), 68.2 (C(quat)$CH_2$), 70.3 (C-4), 72.6 (C-2), 72.9 (C-5), 73.8 (C-3), 102.0 (C-1), 128.4–134.7 (Ph ring carbons), 161.0 (propionamido CO), 166.6 (acetamido CO), 165.4 (urethane CO), 165.4, 165.7, 166.1, 166.4 (COPh).

***N*-(Benzyloxycarbonyl)imino-3,3′-bis[*N*-[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]acetamido]propionamide] (20)**: A solution of the pentafluorophenyl ester **18** (0.14 g, 0.22 mmol) in $CH_2Cl_2$ (5 mL) was added, dropwise, to a stirred mixture of **14**·TFA (0.62 g, 0.48 mmol) and $Et_3N$ (0.14 mL, 1.0 mmol) in $CH_2Cl_2$/DMF (12 mL) at 0 °C and under an $N_2$ blanket. After 72 h of stirring at room temperature, the reaction mixture was worked up as described in the general procedure. The product **20** was purified by column chromatography ($SiO_2$, EtOAc/PhMe, 97:3) and was obtained as a white foamy powder (0.42 g, 67%). TLC, $R_f$ (D) = 0.60 (UV, $H_2SO_4$); $^1$H NMR (400 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02,

2.03 (72H, 4s, COMe), 2.48 (4H, brt, $CH_2N$), 3.30 (4H, brt, $CH_2CH_2N$), 3.65 (2H, d, $^3J_{NH,CH_a}$ = 2.0 Hz, acetamido $CH_aH_b$), 3.71 (6H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 3.78 (2H, d, $^3J_{NH,CH_b}$ = 5.5 Hz, $^2J_{H_a,H_b}$ = 16.5 Hz, acetamido $CH_aH_b$), 3.87 (6H, m, $^3J_{5,6a}$ = 2.5 Hz, $^3J_{5,6b}$ = 4.9 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 4.04 (12H, band, H-6a and C(quat)$CH_aH_b$), 4.24 (6H, dd, $^3J_{5,6b}$ = 4.9 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 4.63 (6H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.82 (6H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 4.96 (6H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.08 (2H, s, $CH_2Ph$), 5.20 (6H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.8 Hz, H-3), 6.52 (2H, s, C(quat)NH), 7.14 (2H, br, acetamido NH), 7.22–7.38 (5H, m, Ph); $^{13}C$ NMR (100.6 MHz, $CD_3COCD_3$): $\delta$ = 20.4, 20.5, 20.6 (*COMe*), 35.0 ($NCH_2$), 44.1 ($NCH_2CH_2$), 42.7 (acetamido $CH_2$), 59.9 (C(quat)), 62.0 (C-6), 68.0 (C(quat)$CH_2$), 68.7 (C-4), 71.7 (C-2), 71.8 (C-5), 72.7 (C-3), 101.1 (C-1), 127.9, 128.6, 137.7 (Ph ring carbons), 155.8 (propionamido CO), 169.4 (acetamido CO), 170.3 (urethane *CO*), 169.4, 169.7, 170.3 (*COMe*). Anal. calcd. for: $C_{110}H_{149}N_5O_{66}$ (2597.37): C, 50.87; H, 5.74; N, 2.70. Found: C, 50.83; H, 5.67; N, 2.61.

**Imino-3,3′-bis[*N*-[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]acetamido]propionamide] (21)**: The removal of the Z group in **20** (0.60 g, 0.23 mmol) was carried out by hydrogenolysis over 10% Pd/C (0.30 g), using a balloon filled with $H_2$ gas, for 12 h. The reaction mixture was filtered over Celite and the solvents were evaporated off to obtain the product as a foamy white solid (0.48 g, 85%). TLC, $R_f$ (D) = 0.12 ($H_2SO_4$); $^1H$ NMR (300 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02, 2.03 (72H, 4s, COMe), 2.95 (4H, brt, $CH_2N$), 3.40 (b, $CH_2NCH_2N + H_2O$) 3.76 (6H, d, $^2J_{H_a,H_b}$ = 10.4 Hz, C(quat)$CH_aH_b$), 3.89 (4H, d, $^3J_{NH,CH_a}$ = 3.6 Hz, acetamido $CH_2$), 3.96 (6H, m, $^3J_{4,5}$ = 9.8 Hz, $^3J_{5,6b}$ = 4.7 Hz, $^3J_{5,6a}$ = 2.4 Hz, H-5), 4.14 (12H, band, H-6a and C(quat)$CH_aH_b$), 4.32 (6H, dd, $^3J_{5,6b}$ = 4.7 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 4.72 (6H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.90 (6H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 5.04 (6H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.29 (6H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.8 Hz, H-3), 6.92 (2H, s, C(quat)NH), 7.82 (2H, br, acetamido NH); $^{13}C$ NMR (75.5 MHz, $CD_3COCD_3$): $\delta$ = 20.4, 20.6, 20.7 (*COMe*), 34.1 ($NCH_2$), 44.0 ($NCH_2CH_2$), 41.8 (acetamido $CH_2$), 60.1 (C(quat)), 62.5 (C-6), 68.6 (C(quat)$CH_2$), 69.2 (C-4), 72.2 (C-2), 72.3 (C-5), 73.2 (C-3), 101.7 (C-1), 156.0 (propionamido CO), 169.9 (acetamido CO), 169.9, 170.2, 170.8 (*COMe*). Anal. calcd. for: $C_{102}H_{143}N_5O_{64}$ (2463.24): C, 49.70; H, 5.85; N, 2.84. Found: C, 49.85; H, 5.89; N, 2.93.

**Benzene-1,3,5-tricarbamido-*N*,*N*,*N*-tris(methyl acetate) (22)**: A solution of benzene-1,3,5-tricarbonyl chloride (0.80 g, 3 mmol) in $CH_2Cl_2$ (10 mL) and DMF (4 mL) was slowly added, over a period of 2 h, to a stirred mixture of Gly-OMe·HCl (1.50 g, 12 mmol) and $Et_3N$ (4.17 mL, 30 mmol) in $CH_2Cl_2$/DMF (2:1) (15 mL) at 0 °C. The stirring was continued at the same temperature for 4 h and at room temperature for 16 h. The reaction mixture was then filtered and solvents were evaporated off in vacuo. The resulting residue was dissolved in $CHCl_3$ (120 mL) and washed successively with 5% aqueous HCl solution (2 × 25 mL), saturated aqueous $NaHCO_3$ solution (2 × 25 mL) and $H_2O$ (15 mL), dried, evaporated and dried thoroughly to obtain **22** as a white powder (0.75 g, 56%). M.p. 181–183 °C; LSI-MS: *m/z*: 424 $[M+1]^+$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 3.82 (9H, s, OMe), 4.20 (6H, d, $^3J$ = 6.5 Hz, $CH_2$), 8.04 (3H, t, $^3J$ = 6.5 Hz, CONH), 8.24 (3H, s, Ph); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 41.9 ($NHCH_2$), 52.5 (OMe), 128.6, 134.5 (Ph ring carbons), 166.6 (COOMe), 171.1 (CONH). Anal. calcd. for: $C_{18}H_{21}N_3O_9$ (423.38): C, 51.11; H, 4.99; N, 9.93. Found: C, 51.13; H, 4.95; N, 9.97.

**Benzene-1,3,5-tricarbamido-*N*,*N*,*N*-tris(acetic acid) (23)**: To a stirred solution of the triester **22** (0.50 g, 1.18 mmol) in MeOH (10 mL) at 0 °C, 2 M aqueous NaOH solution (5 mL, 10 mmol) was added. The solution was left to stir for 3 h. The resultant precipitate was dissolved by addition of $H_2O$ (5 mL), neutralized with Amberlite IR-120 ($H^+$ form) ion-exchange resin, filtered, evaporated, and dried thoroughly to afford **23** as a white powder (0.47 g, 100%). M.p. 224–226 °C; LSI-MS: *m/z*: 380 for $[M-1]^+$; $^1H$ NMR (300 MHz, $CD_3COCD_3/CD_3SOCD_3$ (1:1)): $\delta$ = 3.98 (6H, d, $^3J$ = 6.0 Hz, $CH_2$), 8.52 (3H, s, Ph), 9.12 (3H, t, $^3J$ = 6.0 Hz, CONH), 12.67 (3H, brs, COOH). $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 41.5 ($CH_2$), 129.2, 134.3 (Ph ring carbons), 166.0 (CONH), 171.4 (COOH). Anal. calcd. for: $C_{15}H_{15}N_3O_9$ (381.30): C, 47.25; H, 3.97; N, 11.02. Found: C, 47.37; H, 3.98; N, 11.03.

**General Procedure for the Preparation of Amides Using DCC and HOBT**: A solution of amine (1.0–1.1 equiv) in $CH_2Cl_2$ was added to a stirred solution of triacid **23** (0.3 equiv), DCC (1.0 equiv), and HOBT (1.0 equiv) in $CH_2Cl_2$/DMF (2:1) at 0 °C and under an $N_2$ blanket. The reaction mixture was stirred at room temperature until the amine component had disappeared (TLC). After filtering the precipitated material, the solvents were completely evaporated off. The resulting residue was dissolved in EtOAc, washed successively with 5% aqueous HCl solution (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and $H_2O$ (25 mL), and dried. The solvents were evaporated in vacuo to afford the crude product which was purified either by column chromatography or by size-exclusion chromatography.

**1,3,5-Tris-[*N*-[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl oxymethyl)methyl]acetamido]carbamido]benzene (24**, 9-mer): A solution of **7** (1.0 g, 0.90 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to a stirred solution of **23** (0.10 g, 0.27 mmol), DCC (0.18 g, 0.87 mmol), and HOBT (0.12 g, 0.87 mmol) in $CH_2Cl_2$/DMF (15 mL) at 0 °C, under an $N_2$ blanket. The reaction mixture was left to stir at room temperature for 18 h, then filtered and worked up to obtain the 9-mer **24** (1.20 g, ≈100%) in almost pure form as a foamy solid. For analytical purposes, this material was further purified by preparative TLC (solvent system D). TLC, $R_f$ (D) = 0.74 (UV, $H_2SO_4$); $^1H$ NMR (400 MHz, $CD_3COCD_3$): $\delta$ = 1.94, 1.97, 2.03, 2.07 (108H, 4s, COMe), 3.77 (9H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 3.96 (9H, m, $^3J_{5,6a}$ = 2.4 Hz, $^3J_{5,6b}$ = 5.0 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 4.03 (3H, dd, $^2J_{H_a,H_b}$ = 16.7 Hz, $^3J_{H_a,NH}$ = 5.3 Hz, acetamido $CH_aH_b$), 4.11 (12H, band, H-6a and acetamido $CH_aH_b$), 4.17 (9H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 4.31 (9H, dd, $^3J_{5,6b}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.3 Hz H-6b), 4.71 (9H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.88 (9H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 4.99 (9H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.28 (9H, app. t, $^3J_{3,4} \approx {}^3J_{2,3}$ = 9.8 Hz, H-3); 6.86 (3H, s, acetamido NH), 8.10 (3H, brt, carbamido NH), 8.60 (3H, s, Ph); $^{13}C$ NMR (100 MHz, $CD_3COCD_3$): $\delta$ = 20.4, 20.5, 20.6 (*COMe*), 44.2 (acetamido $CH_2$), 60.4 (C(quat)), 62.6 (C-6), 68.7 ($CH_2$C(quat)), 69.0 (C-4), 72.3 (C-2), 72.4 (C-5), 73.3 (C-3), 101.8 (C-1), 129.8, 135.8 (Ph ring carbons), 166.5 (acetamido CO), 166.8–171.0 (*COMe* and carbamido CO). Anal. calcd. for: $C_{153}H_{204}N_6O_{96}$ (3663.26): C, 50.16; H, 5.61; N, 2.29. Found: C, 50.12; H, 5.65; N, 2.27.

**1,3,5-Tris[*N*-[*N*-[tris-(β-D-glucopyranosyloxymethyl)methyl]acetamido]carbamido]-benzene (25)**: The de-*O*-acetylation of **24** (0.25 g, 0.07 mmol) was carried out in 0.05 M methanolic NaOMe solution (48 mL) for 15 h, followed by workup and purification as described in the general procedure for de-*O*-acetylations under Zemplén's conditions to afford **25** (0.070 g, 48%) as a glassy solid. Retention volume (GPC): 80 mL; $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.21 (9H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.4 Hz, H-2), 3.29 (9H, dd, $^3J_{3,4}$ = 9.4 Hz, $^3J_{4,5}$ = 9.6 Hz, H-4), 3.38 (9H, m, $^3J_{5,6b}$ = 2.2 Hz, $^3J_{5,6a}$ = 6.0 Hz, $^3J_{4,5}$ = 9.6 Hz, H-5), 3.44 (9H, app. t, $^3J_{3,4} \approx {}^3J_{2,3}$ = 9.4 Hz, H-3), 3.65 (9H, dd, $^3J_{5,6a}$ = 6.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 3.86 (9H, dd, $^3J_{5,6b}$ = 2.2 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 3.94 (9H, d, $^2J_{H_a,H_b}$ = 10.6 Hz, C(quat)$CH_aH_b$), 4.10 (6H, s, acetamido $CH_2$), 4.24 (9H, d, $^2J_{H_a,H_b}$ = 10.6 Hz, C(quat)$CH_aH_b$), 4.42 (9H, d, $^3J_{1,2}$ = 8.0 Hz, H-1); 8.42 (3H, s, Ph); $^{13}C$ NMR (100.6 MHz, $D_2O$): $\delta$ = 46.5 (acetamido $CH_2$), 62.7 (C(quat)), 63.6 (C-6), 70.6 (C(quat)$CH_2$), 72.6 (C-4), 76.0 (C-2), 78.4 (C-3), 78.8 (C-5), 105.8 (C-1), 132.5, 137.2 (Ph ring carbons), 171.6 (acetamido CO), 173.8 (carbamido CO).

**Terephthalamido-*N*,*N*-bis(methyl acetate) (26)**: A solution of terephthaloyl chloride (1.0 g, 4.93 mmol) in $CH_2Cl_2$ (25 mL) and DMF (5 mL) was added to a stirred solution of Gly-OMe·HCl (1.25 g, 10 mmol) in saturated aqueous $NaHCO_3$ solution (25 mL) at 0 °C. Additional amounts of $NaHCO_3$ solution were added to keep the reaction mixture alkaline. The stirring was continued at the same temperature for 3 h and at room temperature for 12 h. The reaction mixture was then extracted with $CHCl_3$ (60 mL). The organic portion was washed with $H_2O$ (30 mL), dried, evaporated in vacuo and dried thoroughly to afford **26** (0.62 g, 41%) as a white spongy powder. M.p. 159–161 °C. EI-MS: *m/z*: 308 for $[M]^+$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 3.82 (6H, s, OMe), 4.24 (4H, d, $CH_2$), 6.90 (2H, brt, CONH), 7.83 (4H, s, Ph); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 41.6 ($COCH_2$), 52.3 (OMe), 127.5, 136.5 (Ph ring carbons), 167.0 (*COOMe*), 170.5 (CONH). Anal. calcd. for: $C_{14}H_{16}N_2O_6$ (308.29): C, 54.55; H, 5.23; N, 9.09. Found: C, 54.74; H, 5.11; N, 8.91.

**Terephthalamido-*N*,*N*-bis(acetic acid) (27)**: To a stirred solution of the diester **26** (0.25 g, 0.81 mmol) in MeOH (6 mL) at 0 °C, 2 M aqueous NaOH solution (2.30 mL, 4.59 mmol) was added. The solution was left to stir for 3 h. The precipitated material was dissolved by addition of $H_2O$ (5 mL), the mixture neutralized with Amberlite IR-120 ($H^+$ form) ion-exchange resin, filtered, evaporated, and dried thoroughly to afford **27** (0.21 g, 93%) as a white powder. M.p. 256–258 °C (decomp.). MALDI-TOF-MS: *m/z*: 302 $[M+Na]^+$; $^1H$ NMR (300 MHz, $CD_3SOCD_3$): $\delta$ = 3.95 (4H, d, $CH_2$), 7.95 (4H, s, Ph), 9.0 (2H, t, CONH), 12.66 (2H, brs, COOH); $^{13}C$ NMR (75.5 MHz, $CD_3SOCD_3$): $\delta$ = 41.3 ($CH_2$), 127.4, 136.4 (Ph ring carbons), 165.9 (CONH), 171.2 (COOH). Anal. calcd. for: $C_{12}H_{12}N_2O_6$ (280.24): C, 51.43; H, 4.32; N, 10.0. Found: C, 51.41; H, 4.28; N, 10.01.

***N*,*N*-[*N*-[Tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]acetamido]terephthalamide (28)**: A solution of **7** (0.45 g, 0.41 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to a stirred solution of **27** (0.054 g, 0.19 mmol), DCC (0.082 g, 0.40 mmol), and HOBT (0.054 g, 0.40 mmol) in $CH_2Cl_2$/DMF (15 mL) at 0 °C, under an $N_2$ blanket. The reaction mixture was left to stir at room temperature for 15 h, then filtered and worked up as described in the general procedure for amide bond formation using DCC and HOBT, to obtain **28** (0.42 g, 97%) in almost pure form as a foamy solid. It was further purified by column chromatography ($CH_2Cl_2$/MeOH, 97:3). TLC, $R_f$ (D) = 0.71 (UV, $H_2SO_4$); $^1H$ NMR (400 MHz, $CD_3COCD_3$): $\delta$ = 1.95, 1.99, 2.02, 2.03 (72H, 4s, COMe), 3.75 (6H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 3.94 (6H, m, $^3J_{5,6a}$ = 2.4 Hz, $^3J_{5,6b}$ = 5.0 Hz, $^3J_{4,5}$ = 9.8 Hz, H-5), 3.98 (2H, d, $^2J_{H_a,H_b}$ = 16.5 Hz, $^3J_{H_a,NH}$ = 5.4 Hz, acetamido $CH_aH_b$), 4.06 (2H, d, $^2J_{H_a,H_b}$ = 16.5 Hz, $^3J_{H_b,NH}$ = 6.0 Hz, acetamido $CH_aH_b$), 4.09 (6H, dd, $^3J_{5,6a}$ = 2.4 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 4.17 (6H, d, $^2J_{H_a,H_b}$ = 10.3 Hz, C(quat)$CH_aH_b$), 4.31 (6H, dd, $^3J_{5,6b}$ = 5.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 4.69 (6H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 4.85 (6H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, H-2), 4.96 (6H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.8 Hz, H-4), 5.26 (6H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.8 Hz, H-3); 6.77 (2H, s, acetamido NH), 7.85 (2H, dd, $^3J_{H_a,NH}$ = 5.4 Hz, $^3J_{H_b,NH}$ = 6.0Hz, terephthalamide NH), 8.05 (4H, s, Ph); $^{13}C$ NMR (100.6 MHz, $CD_3COCD_3$): $\delta$ = 19.9, 20.0, 20.1, 20.2 (*COMe*), 43.7 (acetamido $CH_2$), 59.7 (C(quat)), 62.0 (C-6), 68.0 (C(quat)$CH_2$), 68.8 (C-4), 71.7 (C-2), 71.9 (C-5), 72.7 (C-3), 101.1 (C-1), 127.8, 137.2 (Ph ring carbons), 166.5 (acetamido CO), 169.3 to 169.7 (*COMe* and



0947-6539/96/0209-1126 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 9

terephthalamide CO). Anal. calcd. for: $C_{104}H_{138}N_4O_{64}$ (2468.21): C, 50.61; H, 5.64; N, 2.27. Found: C, 50.59; H, 5.76; N, 2.15.

***N,N*-[*N*-[Tris(β-D-glucopyranosyloxymethyl)methyl]acetamido]terephthalamide (29)**: The de-*O*-acetylation of **28** (0.225 g, 0.091 mmol) in 0.05 M methanolic NaOMe solution (37 mL) for 6 h, followed by workup and purification as described in the general procedure afforded **29** (0.086 g 65%) as a glassy solid. Retention volume (GPC): 87 mL; $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 3.27 (6H, dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.4 Hz, H-2), 3.33 (6H, dd, $^3J_{3,4}$ = 9.2 Hz, $^3J_{4,5}$ = 9.7 Hz, H-4), 3.46 (6H, m, $^3J_{5,6b}$ = 2.4 Hz, $^3J_{5,6a}$ = 6.0 Hz, $^3J_{4,5}$ = 9.7 Hz, H-5), 3.51 (6H, dd, $^3J_{3,4}$ = 9.2 Hz, $^3J_{2,3}$ = 9.4 Hz, H-3), 3.71 (6H, dd, $^3J_{5,6a}$ = 6.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 3.92 (6H, dd, $^3J_{5,6b}$ = 2.4 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6b), 3.99 (6H, d, $^2J_{Ha,Hb}$ = 10.6 Hz, C(quat)C$H_a$H$_b$), 4.13 (4H, s, acetamido CH$_2$), 4.32 (6H, d, $^2J_{Ha,Hb}$ = 10.6 Hz, C(quat)CH$_a$$H_b$), 4.48 (6H, d, $^3J_{1,2}$ = 8.0 Hz, H-1); 7.98 (4H, s, Ph); $^{13}$C NMR (75.5 MHz, $D_2O$): $\delta$ = 46.4 (acetamido CH$_2$), 62.5 (C(quat)), 63.5 (C-6), 70.4 (C(quat)*C*H$_2$), 72.4 (C-4), 75.8 (C-2), 78.3 (C-3), 78.6 (C-5), 105.6 (C-1), 130.6, 139.0 (Ph ring carbons), 172.7 (acetamido CO), 173.7 (terephthalamide CO).

**3,3′-Iminobis(methyl propionate) (30)**: A slow stream of dry HCl gas was passed through a solution of 3,3′-iminodipropionitrile (5.0 g) in MeOH (70 mL) with heating under reflux for 8 h. The reaction mixture was left at room temperature overnight and filtered, before the solvent was evaporated off in vacuo to afford the hydrochloride salt of **30** (8.50 g, 93%) as a white granular solid. $^{13}$C NMR (75.5 MHz, $D_2O$): $\delta$ = 32.8 (*C*H$_2$CH$_2$N), 45.9 (CH$_2$N), 55.5 (COO*Me*) and 175.7 (*C*OOMe).

***N*-(*N*$^{\alpha}$-Benzyloxycarbonylglycinamido)-3,3′-bis(methyl propionate) (31)**: Et$_3$N (0.76 mL, 5.5 mmol) was added to a stirred suspension of **30** (1.0 g, 4.44 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. After 0.75 h, Et$_2$O was added, the reaction mixture filtered, and the solvents were evaporated off to obtain 3,3′-iminobis(methyl propionate) as an oil (0.73 g, 87%). This was dissolved in $CH_2Cl_2$ (20 mL) before DCC (0.99 g, 4.80 mmol) and HOBT (0.65 g, 4.80 mmol) were added at 0 °C. A solution of *N*$^{\alpha}$-Z-Gly (1.0 g, 4.80 mmol) in $CH_2Cl_2$ (8 mL) was then added dropwise, stirring was continued at the same temperature for 4 h and at room temperature for 30 h. The precipitate was filtered out, the solvents evaporated off, and the resulting residue dissolved in EtOAc (40 mL), washed successively with 10% aqueous HCl solution (2 × 15 mL), saturated aqueous NaHCO$_3$ solution (2 × 20 mL), and $H_2O$ (2 × 15 mL), and dried. The solvents were evaporated off and dried thoroughly to obtain **31** (1.34 g, 92%) as an oil. FT-IR = 3392, 2953, 1746, 1734, 1714, 1684, 1653, 1203, 1178 and 1047; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.61 (4H, t, $^3J$ = 7.5 Hz, CH$_2$N), 3.59 (4H, t, $^3J$ = 7.5 Hz, C$H_2$CH$_2$N), 3.65, 3.69 (6H, s, s, OMe), 4.05 (2H, d, Gly-CH$_2$), 5.12 (2H, s, C$H_2$Ph), 5.73 (1H, brt, Gly-NH), 7.33 (5H, m, Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 32.3, 33.1 (*C*H$_2$CH$_2$N), 42.2, 42.6, (CH$_2$N), 43.0 (Gly-CH$_2$), 51.8, 52.0 (COO*Me*), 66.8 (*C*H$_2$Ph), 127.9, 128.0, 128.5, 136.5 (Ph ring carbons), 156.3 (CONH), 168.4 (CON), 171.0 and 172.2 (*C*OOMe).

***N*-(*N*$^{\alpha}$-(Benzyloxycarbonyl)glycinamido)-3,3′-bis(propionic acid) (32)**: To a stirred solution of the diester **31** (0.40 g, 1.05 mmol) in MeOH (5 mL) at 0 °C, 2 M aqueous NaOH solution (2.25 mL, 4.50 mmol) was added and the reaction mixture left to stir for 3 h. The precipitated material was dissolved in $H_2O$ (5 mL), neutralized with Amberlite IR-120 ($H^+$ form) ion-exchange resin, filtered, evaporated and dried thoroughly to afford **32** as an oil (0.38 g, 100%), which solidified on standing after several days. FT-IR: $\tilde{\nu}$ = 3333, 2934, 1732, 1716, 1699, 1683, 1652, 1634, 1258, 1047 cm$^{-1}$; MALDI-TOF-MS: *m/z*: 374 $[M+Na]^+$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 2.52 (4H, t, $^3J$ = 7.50 Hz, CH$_2$N), 3.53 (4H, t, $^3J$ = 7.5 Hz, C$H_2$CH$_2$N), 4.04 (2H, d, Gly-CH$_2$), 5.04 (2H, s, C$H_2$Ph), 5.88 (1H, brt, Gly-NH), 7.28 (5H, m, Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 32.3, 33.2 (*C*H$_2$CH$_2$N), 42.0, 42.4 (CH$_2$N), 43.0 (Gly-CH$_2$), 66.4 (*C*H$_2$Ph), 127.8, 127.9, 128.3, 136.5 (Ph ring carbons), 156.3 (CONH), 168.3 (CON), 172.6 and 173.5 (COOH). Anal. calcd. for: $C_{16}H_{20}N_2O_7$ (352.34): C, 54.55; H, 5.72; N, 7.95. Found: C, 54.63; H, 5.64; N, 8.02.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-*N,N*-bis[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]propionamido]glycinamide (33)**: A solution of **7** (0.60g, 0.54 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to a stirred solution of **32** (0.084 g, 0.24 mmol), DCC (0.100 g, 0.48 mmol), and HOBT (0.065 g, 0.48 mmol) in $CH_2Cl_2$/DMF (15 mL) at 0 °C, under an $N_2$ blanket. The reaction mixture was left stirring at room temperature for 18 h, before being worked up as described in the general procedure to obtain **33** (0.663 g, 73%) as a semi-solid powder. TLC, $R_f$ (D) = 0.68 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$) [37]: $\delta$ = 1.95, 1.99, 2.02, 2.03 (72H, 4s, COMe), 2.56 (4H, br, CH$_2$N), 3.55 (4H, br, C$H_2$CH$_2$N), 3.74 (6H, d, C(quat)C$H_a$H$_b$), 3.97 (6H, m, H-5), 4.18 (14H, band, C(quat)CH$_a$$H_b$, H-6a and Gly-CH$_2$), 4.35 (6H, m, H-6b), 4.70 (6H, d, H-1), 4.93 (6H, dd, H-2), 5.06 (6H, app. t, H-4), 5.13 (2H, s, C$H_2$Ph), 5.30 (6H, app. t, H-3), 6.17 (1H, brt, urethane NH), 6.71, 6.88 (2H, s, s, propionamido NH), 7.40 (5H, m, Ph); $^{13}$C NMR (75.5 MHz, $CD_3COCD_3$): $\delta$ = 20.5, 20.6, 20.8, 20.9 (CO*Me*), 35.4, 35.9 (CH$_2$N), 42.6, 43.2 (*C*H$_2$CH$_2$N), 43.8 (Gly-CH$_2$), 60.2, 60.3 (C(quat)), 62.5, 62.6 (C-6), 69.0 (C(quat)*C*H$_2$), 69.3 (C-4), 72.3 (C-2), 72.5 (C-5), 73.3 (C-3), 101.8 (C-1), 126.1–138.4 (Ph ring carbons), 157.1 (propionamido CO), 169.2–172.1 (*C*OMe, urethane CO and Gly-CO). Anal. calcd. for: $C_{108}H_{146}N_4O_{65}$ (2540.32): C, 51.06; H, 5.75; N, 2.21. Found: C, 51.10; H, 5.72; N, 2.19.

***N,N*-Bis-[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy methyl)methyl]propionamido]glycinamide (34)**: A solution of **33** (0.660g, 0.26 mmol) in EtOAc (10 mL) was hydrogenolyzed over 10% Pd/C using a balloon filled with $H_2$ gas, for 22 h. The reaction mixture was filtered over Celite, the solvents were dried and evaporated off in vacuo to obtain **34** (0.570 g, 91%) as a white foamy powder. TLC, $R_f$ (D) = 0.33 (UV, $H_2SO_4$); $^1$H NMR (300 MHz, $CD_3COCD_3$) [37]: $\delta$ = 1.95, 1.99, 2.02, 2.03 (72H, 4s, COMe), 2.52 (4H, br, CH$_2$N), 3.53 (4H, br, C$H_2$CH$_2$N), 3.78 (6H, d, C(quat)C$H_a$H$_b$), 4.0 (6H, m, H-5), 4.18 (14H, band, C(quat)CH$_a$$H_b$, H-6a and Gly-CH$_2$), 4.38 (6H, m, H-6b), 4.72 (6H, d, H-1), 4.94 (6H, dd, H-2), 5.05 (6H, app. t, H-4), 5.31 (6H, app. t, H-3), 6.80 (2H, br, propionamido NH); $^{13}$C NMR (75.5 MHz, $CD_3COCD_3$): $\delta$ = 19.9, 20.1, 20.4 (CO*Me*), 37.1 (CH$_2$N), 41.0 (*C*H$_2$CH$_2$N), 45.8 (Gly-CH$_2$), 69.0 (C(quat)), 62.6 (C-6), 69.0 (C(quat)*C*H$_2$), 69.2 (C-4), 72.2 (C-2), 72.4 (C-5), 73.2 (C-3), 101.8 (C-1), 157.4 (propionamido CO), 169.9–170.8 (*C*OMe, Gly-CO). Anal. calcd. for: $C_{100}H_{140}N_4O_{63}$ (2406.19): C, 49.92; H, 5.86; N, 2.33. Found: C, 50.07; H, 5.79; N, 2.29.

***N,N*-Bis[*N*-[tris(β-D-glucopyranosyloxymethyl)methyl]propionamido]glycinamide (35)**: The de-*O*-acetylation of a solution of **34** (0.100g, 0.240 mmol) in MeOH:$H_2O$ (1:1) (10 mL) was performed using 1 M methanolic NaOMe (0.1 mL) for 18 h, followed by workup and purification as described in the general procedure for de-*O*-acetylation, to afford **35** (0.050 g, 86%). Retention volume (GPC) 111 mL; $^1$H NMR (400 MHz, 385 K, $CD_3SOCD_3$): $\delta$ = 2.46 (4H, br, CH$_2$N), 3.15 (6H, m, H-2), 3.17 (8H, band, C$H_2$CH$_2$N and H-4), 3.23 (6H, m, H-5), 3.53 (6H, m, H-6a), 3.69 (12H, band, H-3, H-6b), 3.85 (6H, d, C(quat)C$H_a$H$_b$), 3.86 (2H, s, Gly-CH$_2$), 4.08 (6H, d, C(quat)CH$_a$$H_b$), 4.24 (6H, d, H-1); $^{13}$C NMR (100 MHz, 355 K, $CD_3SOCD_3$): $\delta$ = 33.7–34.3 (CH$_2$N), 41.2–42.5 (*C*H$_2$CH$_2$N and Gly-CH$_2$), 59.2, 59.4 (C(quat)), 60.8 (C-6), 67.0, 67.4 (C(quat)*C*H$_2$), 69.9 (C-4), 73.1 (C-2), 76.2 (C-3), 76.4 (C-3), 103.3 (C-1), 165.2 (propionamido CO), 169.5, 170.3 (Gly-CO).

**1,3,5-Tris[*N*-[*N*-[*N,N*-bis[*N*-[tris(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)methyl]propionamido]acetamido]acetamido]carbamido]benzene (36**, 18-mer): A solution of **34** (0.50 g, 0.208 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to a stirred solution of **23** (0.024 g, 0.063 mmol), DCC (0.041 g, 0.20 mmol), and HOBT (0.027 g, 0.20 mmol) in $CH_2Cl_2$/DMF (15 mL) at 0 °C, under an $N_2$ blanket. The reaction mixture was left to stir at room temperature for 72 h, before being filtered and worked up as described in the general procedure for amide bond formation using DCC and HOBT. The crude product (0.459 g) was purified by GPC to obtain **36** (0.370 g, 71%) as a white powder. A small amount of an impurity was noticed in the $^1$H NMR spectrum of this product. In order to remove this impurity, a small portion of the sample was purified three more times by GPC. TLC, $R_f$ (EtOAc/MeOH, 85:15) = 0.71 (UV, $H_2SO_4$); $^1$H NMR (400 MHz, 385 K, $CD_3SOCD_3$): $\delta$ = 1.94, 1.98, 2.02, 2.03 (≈216H, 4s, COMe), 2.39 (12H, m, CH$_2$N), 3.46 (12H, m, C$H_2$CH$_2$N), 3.70 (18H, d, $^2J_{Ha,Hb}$ = 10.4 Hz, C(quat)C$H_a$H$_b$), 3.92 (18H, m, $^3J_{5,6a}$ = 3.0 Hz, $^3J_{5,6b}$ = 5.1 Hz, $^3J_{4,5}$ = 9.4 Hz, H-5), 3.97 (18H, d, $^2J_{Ha,Hb}$ = 10.4 Hz, C(quat)CH$_a$$H_b$), 4.04, 4.06 (12H, brs, acetamido CH$_2$), 4.09 (18H, dd, $^3J_{5,6a}$ = 3.0 Hz, $^2J_{6a,6b}$ = 12.3 Hz H-6a), 4.20 (18H, dd, $^3J_{5,6b}$ = 5.1 Hz, $^2J_{6a,6b}$ = 12.3 Hz, H-6b), 4.66 (18H, d, $^3J_{1,2}$ = 7.8 Hz, H-1), 4.80 (18H, dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.4 Hz, H-2), 4.92 (18H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 9.4 Hz, H-4), 5.20 (18H, app. t, $^3J_{2,3} \approx {}^3J_{3,4}$ = 9.4 Hz, H-3), 6.73 (6H, s, propionamido NH), 7.49, 8.47 (6H, br, acetamido NH and carbamido NH), 8.50 (3H, s, Ph); $^{13}$C NMR (100.6 MHz, 385 K, $CD_3SOCD_3$): $\delta$ = 19.6, 19.7, 19.8 (CO*Me*), 39.0–42.0 (band, CH$_2$N, *C*H$_2$CH$_2$N, acetamido CH$_2$ and $CD_3SOCD_3$), 59.0 (C(quat)), 61.7 (C-6), 67.5 (*C*H$_2$C(quat)), 68.5 (C-4), 71.1 (C-2), 71.2 (C-5), 72.2 (C-3), 100.4 (C-1), 128.0, 138.4 (Ph ring carbons), 151.3 (propionamido CO), 168.9–169.8 (*C*OMe, carbamido CO and acetamido CO). Anal. calcd. for: $C_{315}H_{420}N_{15}O_{195}$ (7545.81): C, 50.14; H, 5.73; N, 2.78. Found: C, 50.18; H, 5.79; N, 2.65.

**1,3,5-Tris[*N*-[*N*-[*N,N*-bis[*N*-[tris(β-D-glucopyranosyloxymethyl)methyl]propionamido]acetamido]acetamido]carbamido]benzene (37)**: The de-*O*-acetylation of a solution of **36** (0.146 g, 0.019 mmol) in MeOH:$H_2O$ (1:1) (20 mL) was performed using 1 M methanolic NaOMe solution (0.8 mL) for 18 h, followed by workup and purification as described in the general procedure for de-*O*-acetylations under Zemplén's conditions, to afford **37** (0.072 g, 82%) as a glassy solid. Retention volume (GPC): 75 mL; $^1$H NMR (400 MHz, 389 K, $CD_3SOCD_3$): $\delta$ = 2.43 (12H, brt, CH$_2$N), 3.08 (18H, dd, $^3J_{1,2}$ = 7.7 Hz, $^3J_{2,3}$ = 8.5 Hz, H-2), 3.18 (36H, band, H-4 and H-5), 3.25 (18H, app. t, $^3J_{2,3}$ = 8.5 Hz, H-3), 3.51 (12H, brt, C$H_2$CH$_2$N), 3.55 (18H, dd, $^3J_{5,6a}$ = 5.0 Hz, $^2J_{6a,6b}$ = 11.3 Hz, H-6a), 3.72 (18H, dd, $^3J_{5,6b}$ = 2.3 Hz, $^2J_{6a,6b}$ = 11.3 Hz, H-6b), 3.87 (18H, d, $^2J_{Ha,Hb}$ = 10.3 Hz, C(quat)C$H_a$H$_b$), 4.08 (30H, app. d, C(quat)CH$_a$$H_b$ and acetamido CH$_2$), 4.25 (18H, d, $^3J_{1,2}$ = 7.7 Hz, H-1), 6.85 (6H, s, propionamido NH), 7.58 (6H, m, acetamido NH and carbamido NH), 8.50 (3H, s, Ph); $^{13}$C NMR (100.6 MHz, 355 K, $CD_3SOCD_3$): $\delta$ = 39.0–41.0 (band, CH$_2$N, *C*H$_2$CH$_2$N, and $CD_3SOCD_3$), 42.5 (acetamido CH$_2$), 59.4 (C(quat)), 60.9 (C-6), 67.4 (C(quat)*C*H$_2$), 70.0 (C-4), 73.2 (C-2), 76.3 (C-3), 76.4 (C-5), 103.3 (C-1), 128.5, 134.3 (Ph ring carbons), 165.4 (propionamido CO), 167.5 (acetamido CO), 168.5 (carbamido CO).

**Molecular Simulation:** Simulations were carried out using the AMBER force field as implemented in Macromodel [38] (V. 4.5) running on a Silicon Graphics Indigo 2 Workstation. The dendrons were assembled within the Macromodel INPUT submode and then fully minimized (final gradient < 0.5 kJ Å$^{-1}$) using the Polak Ribiere Conjugate Gradient (PRCG) algorithm with extended cut-offs (8 Å for VDW and

20 Å for charge/charge electrostatic interactions). Solvation was included in the form of the GB/SA solvation model [38] for either $CHCl_3$ or $H_2O$. The individual dendron units were then attached to the central core, and the angle between the dendron and the core was adjusted manually to minimize steric clashes between separate dendrons. The whole assembly was then fully minimized using the above method (final gradient < 0.5 kJ $Å^{-1}$). Molecular dynamics, using the AUTO set-up mode (SAMPLE off) within Macromodel (timestep 1.5 fs for 10 ps at 300 K), afforded structures removed from the starting geometry which were then fully minimized (AMBER, PRCG, extended cut-offs, GB/SA solvation) until the RMS deviation was less than 0.5 kcal $Å^{-1}$. Molecular volume calculations were performed using the Polygen Quanta [39] software, running on a Silicon Graphics Indigo XS 24 workstation.

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[40] Ac = acetyl; $Ac_2O$ = acetic anhydride; app. = apparent; BOC = *tert*-butyloxycarbonyl; Bz = benzoyl; DCC = 1,3-dicyclohexylcarbodiimide; Glc = glucose; Gly = glycine; HOBT = 1-hydroxybenzotriazole; PFP = pentafluorophenyl; TRIS = tris(hydroxymethyl)methylamine; Z = benzyloxycarbonyl.



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