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[13] Crystals of **1** were grown from [D_1]chloroform/toluene at $-35\,^{\circ}C$. $C_{10}H_{13}IO_3S\cdot CDCl_3$, $M_r = 460.54$, monoclinic, space group $P2_1/c$, $a = 11.379(5)$, $b = 5.674(2)$, $c = 25.220(11)$ Å, $b = 94.089(8)^{\circ}$, $V = 1624.0(11)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.884\ g\,cm^{-3}$, $T = 150(2)$ K, yellow block $0.22 \times 0.34 \times 0.40\ mm^3$, $2\theta_{max} = 59.82^{\circ}$, 10382 measured reflections, 4297 unique, R values ($I > 2\sigma(I)$): $R1 = 0.0655$, $wR2 = 0.1314$. Crystals of **2** were grown from dichloromethane at ambient temperature. $C_{10}H_{13}IO_4S\cdot CH_2Cl_2$, $M_r = 441.09$, monoclinic, space group $C2/c$, $a = 19.784(2)$, $b = 6.5461(6)$, $c = 24.647(2)$ Å, $b = 96.697(2)^{\circ}$, $V = 3170.2(5)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.848\ g\,cm^{-3}$, $T = 150(2)$ K, $2\theta_{max} = 60.02^{\circ}$, 17723 measured reflections, 4322 unique, R values ($I > 2\sigma(I)$): $R1 = 0.0345$, $wR2 = 0.0703$. Bruker SMART Platform with CCD detector, Mo radiation ($\lambda = 0.71073$ Å) with graphite monochromator, omega scans with 0.3° increments for the frames. Absorption corrections made with SADABS (G. M. Sheldrick, University of Göttingen, **1998**); structure solution and refinement with SHELXTL 5.10 (Bruker AXS, Inc., Madison, WI, **1997**) against F^2 (177 parameters for **1**, 173 parameters for **2**). All nonhydrogen atoms were refined with anisotropic temperature parameters, all hydrogen atoms (except $CDCl_3$ deuterium atom in **1**) were placed in calculated positions and refined isotropically. The $CDCl_3$ deuterium atom was located from the Fourier map and refined isotropically. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC–137694 and CCDC-137693. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)..CCDC

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A General Entry into Glycopeptide "Dendrons"**

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Dedicated to Professor Günter Wulff on the occasion of his 65th birthday

In order to study and manipulate carbohydrate–protein interactions, carbohydrate and dendrimer chemistries have been combined in order to design multivalent glycoconjugate mimetics.[1] Such carbohydrate dendrimers potentially influence carbohydrate–protein interactions strongly due to the multivalency or cluster effects.[2, 3] Moreover, they may combine the properties of drug binding and transport with other, still unknown, qualities of synthetic biomaterials. Two main entries into the synthesis of carbohydrate dendrimers have been utilized so far: by the glyco-coating of noncarbohydrate dendrimers to form glycodendrimers[4] or by the convergent combination of molecular wedges derived from carbohydrate clusters[5] to yield carbohydrate dendrimers of different architectures.[6] Both synthetic approaches do not allow enlargement of the carbohydrate-containing molecules by the formation of successive generations,[7] although some reported carbohydrate dendrimers possess a relatively high sugar density.

We now report on the synthesis of glycopeptide dendrons in which the peptide coupling of orthogonally protected AB_2-type carbohydrate units form the basis for an iterative

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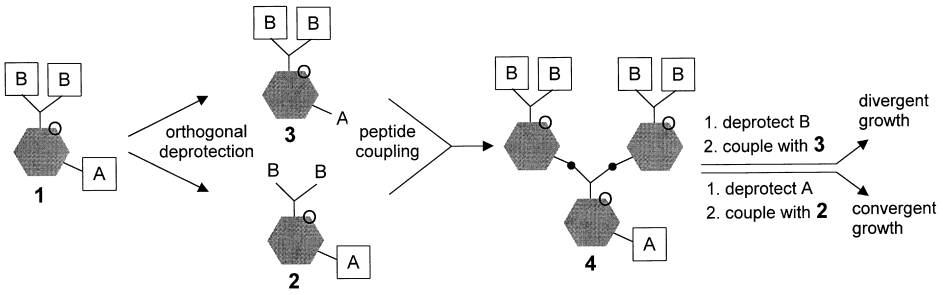
reaction sequence to lead to the various generations of carbohydrate-containing dendrons in either a divergent or convergent manner (Scheme 1). The use of peptide chemistry in the linking step avoids sophisticated glycosylation techniques for each coupling step. Furthermore, this synthetic protocol simplifies adaptation to solid-phase chemistry, which can be used for automated synthesis of glycopeptide dendrons as well as for combinatorial approaches of various kinds.



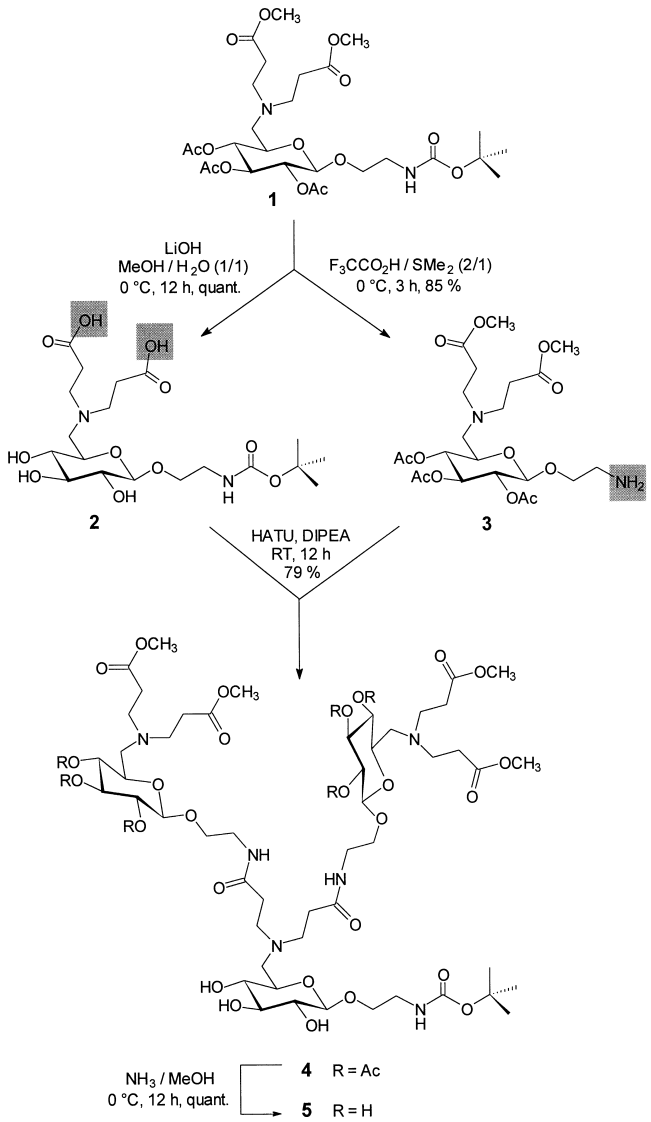
Scheme 1. The general approach to glycopeptide dendrons from orthogonally protected carbohydrate AB_2-type building blocks such as **1** (see Scheme 2). B is a carboxy group and A is an amino moiety, and the respective protected groups are boxed. This design allows an iterative synthetic sequence of deprotection and peptide-coupling reactions leading to successive generations of dendritic growth. The first-generation glycopeptide dendron **4** may be extended according to a divergent or convergent approach. Convergent growth led to second- and third-generation dendrons **7** and **8** (see Schemes 3 and 4). A gray-shaded hexagon represents a monosaccharide ring and a black circle represents an amide linkage.

The AB_2-type glucoside building block **1**[8] forms the basis for the preparation of glycopeptide dendrons **5**, **7**, and **8**. Mildly alkaline hydrolysis of the methyl ester groups in **1** with $LiOH \cdot H_2O$ in $MeOH/H_2O$ (1/1) leads to the unprotected biscarboxylic acid **2**, while removal of the *tert*-butoxycarbonyl (Boc) protecting group in **1** by a mixture of trifluoroacetic acid and dimethyl sulfide[9] gave the amino-functionalized glucoside **3** (Scheme 2). Thus, glucoside **1** gives both the complementary building blocks **2** and **3**, which were used in a peptide-coupling reaction.

The uronium-based salt HATU,[10] together with DIPEA,[10, 11] proved to be a suitable promoter for the peptide coupling which gave the first generation glycopeptide dendron **4** in 79% yield. Dendron **4** was purified by gel-permeation chromatography (GPC) using a Sephadex LH-20 column and methanol as the eluent. The NMR spectra of **4** showed one set of signals for the acetyl-protected glucose moiety and another set for the core glucose moiety in both the ^1H and ^{13}C NMR spectra (Table 1). Deacetylation of **4** with saturated methanolic ammonia gave the unprotected tetramethyl ester **5** in quantitative yield. Compound **5** was purified by GPC using a bio-gel P-6 packed column and an ammonium hydrogen carbonate buffer as the eluent.

Using the Boc-deprotection and peptide-coupling reaction sequence, the synthesis of higher generations of glycopeptide dendrons was carried out in a convergent manner. Thus, the Boc-protected first generation dendron **4** was converted to the respective amine, which coupled with **2** to lead to the protected second generation glycopeptide dendron **6** in 60% yield (Scheme 3). Compound **6** was purified by GPC as per compound **4**. The NMR spectra of **6** displayed two sets of signals for the carbohydrate moieties (Table 1). The deacetylation of **6** could not, unlike **4**, be fully completed with saturated methanolic ammonia due to solubility problems. However, when aqueous ammonia was used for the deprotection step, saponification of the methyl esters occured with concomitant removal of the acetate protective groups. In this way the octacarboxylic acid **7** was obtained and purified as per **5**.

Analogous to the preparation of **6**, the third-generation dendron **8**, containing 15 sugar moieties, was obtained after Boc deprotection of **6** and peptide coupling of the resulting amine to **2** (Scheme 4). However, as the high molecular mass glycopeptide mimetic obtained was poorly soluble in methanol, an aqueous carbonate buffer was used as the eluent during gel filtration through bio-gel P-6. The ^1H NMR of the product fractions



Scheme 2. Synthesis of first-generation glycopeptide dendron.

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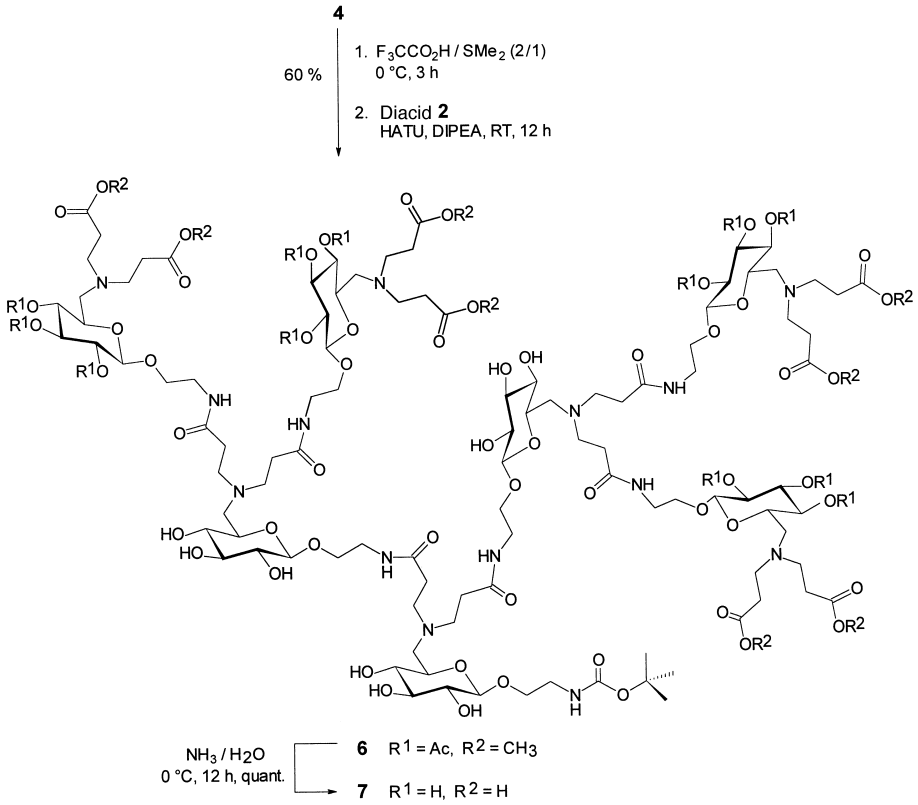
Table 1. Selected ^{1}H (500 MHz) and ^{13}C (125.75 MHz) NMR data for compounds **4**–**8**.

	δ(**4**) in CD_3OD	δ(**5**) in D_2O	δ(**6**) in CD_3OD	δ(**7**) in D_2O	δ(**8**) in D_2O
^{1}H NMR:					
H-1[a]	4.40 (d, 1H)	4.44 (m_c, 3H)	4.21 (m_c, 3H)	4.51–4.38 (m, 7H)	4.41 (m_c, 15H)
H-1[b]	4.65 (d, 2H)	–	4.56 (d, 4H)	–	–
NCH_2	2.89 (m_c, 12H)	3.43 (m_c, 2H), 3.28 (m_c, 2H), 3.17–2.96 (m, 8H)	2.80 (m_c, 12H), 2.76 (m, 16H)	3.48 (m_c, 6H), 3.27 (m_c, 6H), 3.16–2.92 (m, 16H)	3.53–3.10 (m, 60H)
$CH_2C(O)$	2.48 (m, 12H)	2.64–2.46 (m, 12H)	2.37 (m, 16H), 2.35 (m, 12H)	2.67–2.45 (m, 28H)	2.76–2.44 (m, 60H)
$H_3COC(O)$	3.68 (s, 6H)	3.29 (s, 12H)	3.56 (s, 24H)	–	–
$H_3CC(O)O$	2.05 (s, 6H), 2.03 (s, 6H), 1.95 (s, 6H)	–	1.95 (s, 12H), 1.93 (s, 12H), 1.86 (s, 12H)	–	–
*t*Bu	1.44 (s, 9H)	1.38 (s, 9H)	1.34 (s, 9H)	1.37 (s, 9H)	1.31 (s, 9H)
^{13}C NMR:					
C-1	104.35, 101.94	102.94, 102.84	104.54, 101.94	102.39, 102.30	102.41, 102.27

[a] H-1 of OH-free glucose moieties. [b] H-1 of acetylated glucose moieties.



Scheme 3. Synthesis of second-generation glycopeptide dendron.

indicated partial deprotection of the *O*-acetate groups and, therefore, deprotection with saturated aqueous ammonia was perfomed subsequent to peptide coupling and prior to purification. As in the case of the deprotection of **6**, aqueous ammonia effected deacetylation as well as saponification of the methyl ester groups and consequently the hexadecaacid **8** was isolated as its ammonium salt.

In addition to the NMR analysis, the structures of all of the described compounds were confirmed by MALDI-TOF mass spectrometry (Table 2) and, in most cases, reasonable elemental analyses were obtained. Thus, all the glycopeptide dendrons proved to be monodisperse compounds without structural defects. The described route was superior over alternative strategies for the assembly of the described dendrons, including the divergent approach.

Stability against glycosidases of this new type of multivalent neoglycoconjugates was tested with glycopeptide dendron **5**. No degradation, according to HPLC analysis, was observed when **5** was incubated with β-glucosidase from almonds over several hours.

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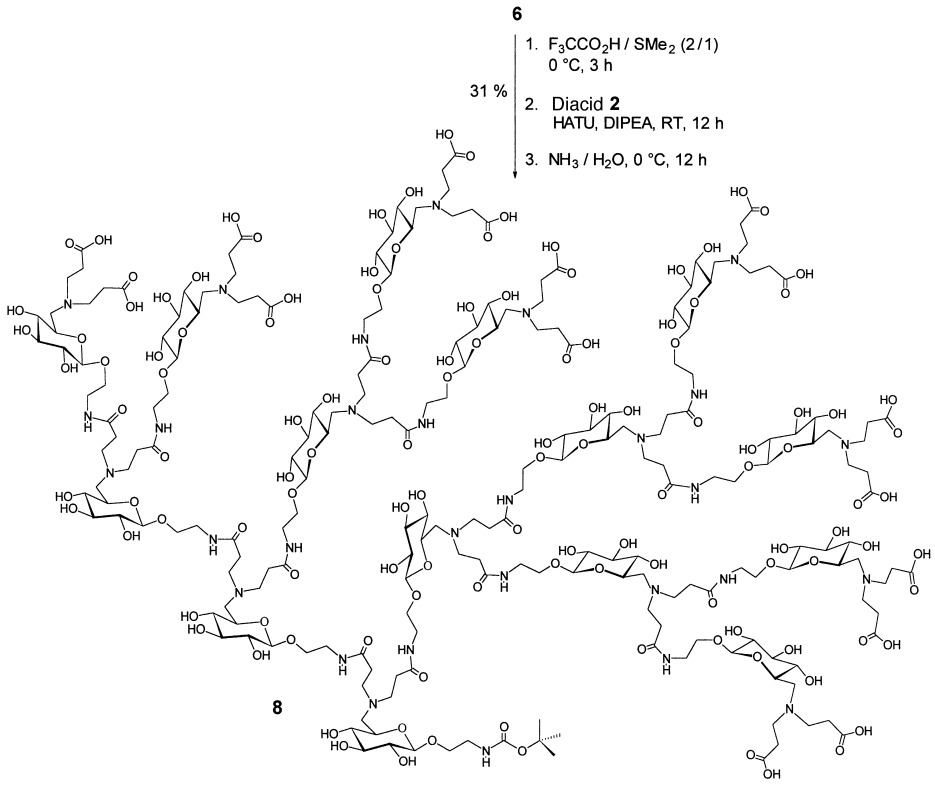

Scheme 4. Synthesis of third-generation glycopeptide dendron.

Table 2. Peaks obtained in MALDI-TOF mass spectrometry[a] of glycopeptide dendrons **4**–**8**.

Compound	Molecular formula	Calcd. mol. mass[b] [g mol^{-1}]	Observed mass peaks
4	$C_{63}H_{102}N_6O_{33}$	1470.65	1471.58 $[M+H]^+$, 1494.60 $[M+Na]^+$, 1509.53 $[M+K]^+$
5	$C_{51}H_{90}N_6O_{27}$	1218.58	1219.63 $[M+H]^+$, 1243.61 $[M+Na]^+$
6	$C_{135}H_{218}N_{14}O_{71}$	3171.38	3172.14 $[M+H]^+$, 3195.11 $[M+Na]^+$, 3208.10 $[M+K]^+$
7	$C_{103}H_{178}N_{14}O_{59}$	2555.13	2556.45 $[M+H]^+$, 2670.08 $[M+6NH_3+3H]^+$
8	$C_{215}H_{370}N_{30}O_{123}$	5340.36	5341.24 $[M+H]^+$, 5606.15 $[M+16NH_3-6H]^+$

[a] Dihydroxybenzoic acid (DHB) was employed as matrix in acetonitrile/water/TFA (2/1/0.1) for the co-crystallization of compounds **4**–**8**. The calibration of the mass peaks in a linear mode was made with 4-cyanocinamic acid (190.05 $[M+H]^+$), angiotensin II ($[M+H]^+$ 1046.54), bombesin ($[M+H]^+$ 1619.82), and bovine insulin (5734.56 $[M+H]^+$). [b] Main isotopes were used for the calculation of the molecular masses.

In conclusion, we have described a novel approach to the synthesis of hyperbranched carbohydrate-containing molecules, which can be grown in successive generations, in the form of glycopeptide dendrons. The three-dimensional structure of the compounds may represent elements present in natural glycopeptides and may be developed to a new class of glycocalyx mimetics by further enlargement. Currently we are extending the presented strategy with the aim to prepare hyperbranched molecules with antiadhesive properties.

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[10] Abbreviations used: HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphate; DIPEA = diisopropylethylamine.

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