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Synthesis of chiral carbohydrate-centered dendrimers

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D-Glucose was converted into its per-*O*-(2-aminoethyl)-functionalized derivative 4, which served as initiator core for the construction of the chiral, monodisperse PAMAM-type carbohydrate-centered hybrid dendrimer 7.

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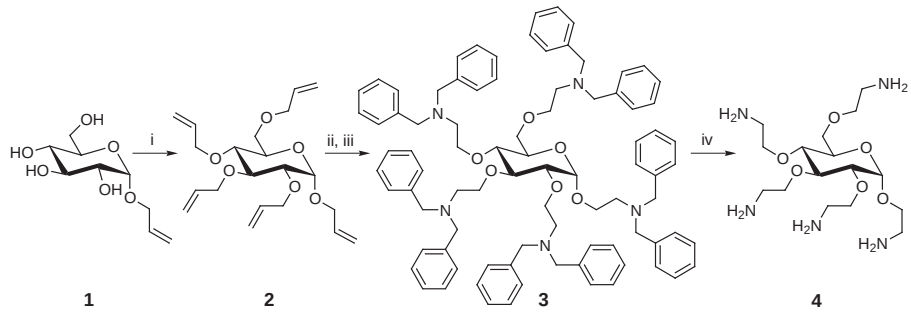
Dendrimer chemistry is a rapidly developing field of research.[1] Dendrimers offer the prospect of novel materials with advantagous properties, allowing them to serve as soluble catalysts,[2] dendritic boxes[3] or other supramolecular dendritic arrangements. Furthermore, new applications such as enantioselective synthesis with chiral dendrimers, or favourable bioapplications such as in transfection[4] and glycobiology, are currently being explored. Dendrimer chemistry has been combined with carbohydrate chemistry in order to form multivalent glycomimetics[5] (glycodendrimers) with antiadhesive properties or other carbohydrate containing dendrimers.[6] Other than from the point of view of glycobiology, the combination of carbohydrates and dendrimers is attractive for the manipulation of dendritic structures leading to modified properties of, as yet, unestimated value. Carbohydrate cores are especially appealing for the design of dendrimers due to their easy availibility from the chiral pool and renewable resources, biocompatibility, low toxicity and natural polyfunctionality. In addition, intrinsic chirality may be introduced into dendrimers by using carbohydrate cores.[7] Furthermore, the stereochemical shape of dendrimers may be easily manipulated by choosing differently configurated monosaccharides, and the core multiplicity may be altered by utilizing mono-, di- or even oligosaccharides as carbohydrate cores, such as trehalose or raffinose. This is of special interest as the shape and composition of dendrimers may dramatically affect their host–guest relationships.[8]

Here we report the first synthesis of a carbohydrate-centered Starburst® PAMAM dendrimer based on a reaction sequence which is suited to converting reducing sugars into carbohydrate derivatives which can serve as initiator cores for the development of PAMAM generations. This was exemplified with D-glucose. First, allyl α-D-glucoside **1**, which was obtained by Fischer glycosylation, was perallylated to **2** under phase transfer catalysis (Scheme 1). Partially allylated products were not formed as the allylation rate increases with the extent of allylation of the starting material under these conditions.[9] Ozonolysis of the resulting allyl 2,3,4,6-tetra-*O*-allyl-α-D-glucoside (**2**) was performed in a $NaHCO_3$-buffered CH_2Cl_2–MeOH reaction mixture[10] to yield the desired penta-hemiacetal after reduction with PPh_3. This was characterized as the corresponding pentahydrate by NMR spectroscopy in D_2O. The penta-hemiacetal was submitted to a reductive amination reaction: application of $BnNH_2$ led to nearly inseparable mixtures comprised of cyclic amines, due to intramolecular reactions. However, the use of Bn_2NH and sodium acetoxyborohydride[11] as the reducing agent gave the desired benzyl cluster **3** at −10 °C in high yields without purification problems. Then **3** was converted into the pentaamine **4** by heterogeneous catalytic transfer hydrogenation reaction[12] with ammonium formate and Pd (10% on charcoal) in MeOH in a clean reaction. Thus the target compound **4** could be synthesized starting from allyl glucoside (**1**) in 43% overall yield.

The glucose derivative **4** represents a stereochemically well-defined, oligofunctional molecule with five uniformly functionalized spacers. It may serve as core molecule for the synthesis of carbohydrate-centered glycoclusters[13] or of carbohydrate-centered dendrimers. It was submitted to the reaction sequence leading to PAMAM dendrimer generations, consisting of the exhaustive Michael addition of the polyamine to methyl acrylate, followed by amidation of the resulting methyl esters with ethylenediamine.[14] Indeed reaction of **4** with methyl acrylate led to the decaester **5** in quantitative yield, which was quantitatively converted into the first generation hybrid PAMAM dendrimer **6** with ethylenediamine (Scheme 2). Further branching at the amino functions at the periphery of the molecule led to the eicosaester **7**, also in quantitative yield. The monodisperse structures of **5**–**7** could unequivocally be confirmed by NMR spectroscopy as ^1H–^{13}C HMBC NMR allowed the detection of each individual branch of every molecule.‡ All synthesized compounds are chiral.§ However, the specific rotation values of the carbohydrate-centered dendrimers decrease with increasing generation, according to observations made in the literature,[15] whereas the molar rotation values remain in the same range (*ca.* 400).

In conclusion, a reaction sequence has been elaborated which is generally applicable for the facile and uniform conversion of free saccharides into fully *O*-(2-aminoethyl)-functionalized derivatives such as **4**. These are suited for dendritic expansion, opening the door into a wide array of structurally diverse, but well-defined, carbohydrate-centered PAMAM dendrimers. The new hybrid dendrimers may be custom-designed by choice of the carbohydrate core giving rise to possible advantageous



Scheme 1 *Reagents and conditions*: i, allyl chloride (5 equiv.), 40% aq. NaOH, Bu_4NBr (1 equiv.), 35 °C, 16 h, 76%; ii, O_3, $NaHCO_3$, CH_2Cl_2–MeOH 6 : 1, work-up with PPh_3; iii, $Na(AcO)_3BH$, AcOH, Bn_2NH, THF, work-up with 1 M NaOH, 74% (2 steps); iv, Pd–C (10%), NH_4HCO_2, MeOH, 76%

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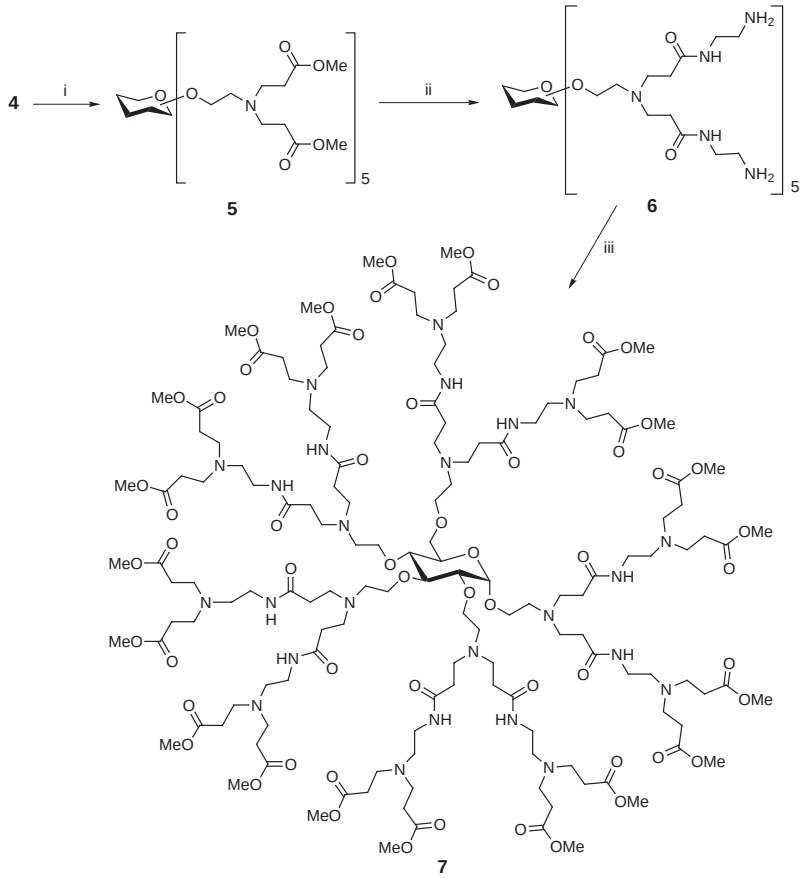

Scheme 2 *Reagents and conditions*: i, methyl acrylate (22 equivs.), MeOH, 3 d, room temp., quant.; ii, ethylendiamine (600 equivs.), MeOH, 5 d, +5 °C, quant. iii, methyl acrylate (60 equivs.), MeOH, 3 d, room temp., quant.

properties compared to classical PAMAMs, such as altered solubilities and overall shapes, better biodegradibility, lower toxicity and chirality.

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Notes and References

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‡ All compounds showed consistent NMR and mass spectral data. *Selected data* for **7**: MALDI-TOF (positive) [Calc. for $C_{146}H_{257}N_{25}O_{56}$: 3258.8. Found 3261.0 (M + 1)]; δ_H(500 MHz, CD_3OD) 5.02 (d, 1 H, $J_{1,2}$ 3.2, H-1), 4.03–3.93 (m, 2 H, OCH_2CH_2N), 3.88–3.59 (m, 73 H, H-5, H-6, H-6′, 4 OCH_2CH_2N, 20 OCH_3), 3.54 (dd ≈ t, 1 H, $J_{2,3}$ 9.2, $J_{3,4}$ 9.2, H-3), 3.34–3.27 [m, 21 H, H-2, 10 $C(O)NCH_2CH_2N$], 3.26 (dd ≈ t, 1 H, $J_{4,5}$ 9.2, H-4), 3.0–2.89 [m, 20 H, 10 $NCH_2CH_2C(O)N$], 2.89–2.76 (dd ≈ t, 50 H, 5 OCH_2CH_2N, 20 $NCH_2CH_2CO_2Me$), 2.64–2.57 [dd ≈ t, 20 H, 10 $C(O)NCH_2CH_2N$], 2.54–2.49 (dd ≈ t, 40 H, 20 $NCH_2CH_2CO_2Me$), 2.49–2.41 [dd ≈ t, 20 H, 10 $NCH_2CH_2C(O)N$]; δ_C 175.9 (20 CO_2Me), 175.7–175.5 (10 CO_2N), 99.2 (C-1), 84.5 (C-3), 83.2 (C-2), 80.9 (C-4), 73.1 (C-5), 73.0, 72.9, 72.5, 71.8, 70.7, 68.3 (C-6, 5 OCH_2CH_2N), 55.7, 55.6, 55.5, 55.0, 54.7 (5 OCH_2CH_2N), 55.0 [20 $C(O)NCH_2CH_2N$], 53.4 (20 CO_2CH_3), 52.7, 52.6, 52.6, 52.5, 52.5 [10 $NCH_2CH_2C(O)N$], 51.7 (20 $NCH_2CH_2CO_2Me$), 39.7 [10 $C(O)NCH_2CH_2N$], 35.8, 35.7, 35.6, 35.6, 35.5 [10 $NCH_2CH_2C(O)N$], 34.8 (20 NCH_2CH_2 CO_2Me).

§ Selected specific optical rotations: **1** $[\alpha]_D^{20}$ +160.5 (*c* 1.09, MeOH); **3** $[\alpha]_D^{27}$ +35.2 (*c* 1.18, $CHCl_3$); **5** $[\alpha]_D^{27}$ +34.6 (*c* 0.96, MeOH); **7** $[\alpha]_D^{25}$ +13.1 (*c* 0.38, MeOH).

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