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Synthesis of Selectively Functionalized Carbosilane Dendrimers with a Carbohydrate Core

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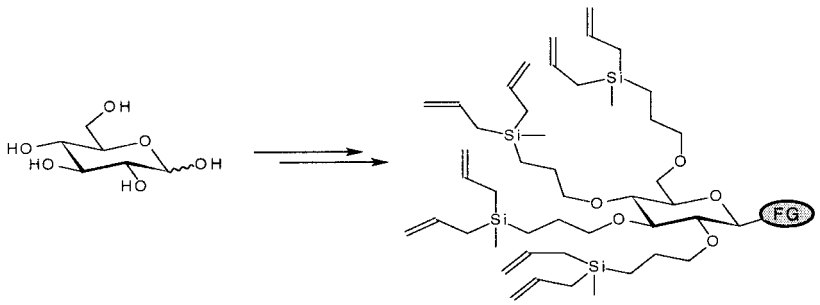
ABSTRACT



First-generation members of a novel family of dendrimers schematically shown above have been synthesized. They display carbohydrate-centered carbosilanes in which one functional group (FG) is discriminated from the others. This will eventually allow their utilization in the synthesis of labeled carbosilanes or as selectively functionalized scaffolds for the preparation of multivalent glycomimetics.

Dendrimers[1] combine the advantages of monodisperse molecules with an especially large number of functionalities of one kind, assembled in the periphery of the molecule. However, a major disadvantage of the principles of dendritic growth is that chemical discrimination of one functionality from the others present in a particular dendrimer is difficult.[2] Selectively functionalized dendrimers would allow a number of attractive options such as immobilization of the molecule or its labeling with a reporter group; therefore searching for synthetic avenues to selectively functionalized dendrimers is an important task.

We have been dealing with the preparation of dendrimers with carbohydrate cores for various purposes and introduced chiral glucose-based poly(amidoamine) (PAMAM) dendrimers.[3] Using carbohydrates as core molecules for dendrimer synthesis offers promising advantages for the preparation of selectively functionalized analogues, since the anomeric position of monosaccharides can be easily discriminated from the other ring hydroxyls by glycosidation prior to the construction of dendritic layers. Thus, glycosides can serve as core scaffolds for the synthesis of selectively functionalized dendrimers. This is the focus of our current work.

Because we are also utilizing this chemistry for the synthesis of multivalent glycomimetics, which are designed as inhibitors of bacterial adhesion,[4,5] the choice of the spacer characteristics being used in such a molecule is relevant. To design rather flexible glycodendrimer antennae and avoid intramolecular interactions of spacers, we have selected

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(2) (a) Hawker, C. J.; Fréchet, J. M. J. *Macromolecules* **1990**, *23*, 4726−4729. (b) Wooley, K.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1059−1076.

(3) Dubber, M.; Lindhorst, Th. K. *Chem. Commun.* **1998**, 1265−1266.

(4) (a) Beachey, E. H. *J. Infect. Dis.* **1981**, *143*, 325−345. (b) Krogfeld, K. A. *Rev. Infect. Dis.* **1991**, *13*, 721−735. (c) Karlsson, K.-A. *Curr. Opin. Struct. Biol.* **1991**, *1*, 732−740.

(5) For multivalency in biological systems, see: Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem.* **1998**, *110*, 2908−2953; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2754−2794.

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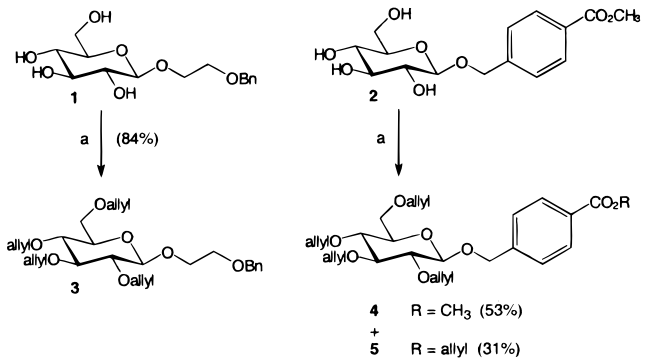
carbosilane dendrimers[6] for this program, rather than the nitrogen-based PAMAM dendrimers.

The applied synthetic route comprises per-allylation of suitable glucosides and subsequent application of a hydrosilylation−Grignard addition protocol, which is used for growing carbosilane dendrimer generations.

Compounds **1** and **2** were selected as the starting glucosides. They were obtained by glycosylation of the corresponding alcohols using glucosyl trichloroacetimidate as glycosyl donor under standard conditions.[7] Per-allylation of **1** under Williamson conditions afforded tetraallylated glycoside **3** (Scheme 1).

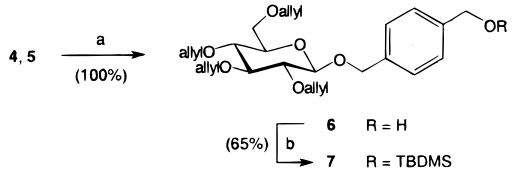
Scheme 1[a]



[a] (a) NaH, allyl bromide, DMF.

The analogous procedure applied to **2** gave a mixture of esters **4** and **5**,[8] which can be separated by means of flash chromatography. However, they are better used as a mixture, since they yield the same product in the following step (Scheme 2).

Scheme 2[a]

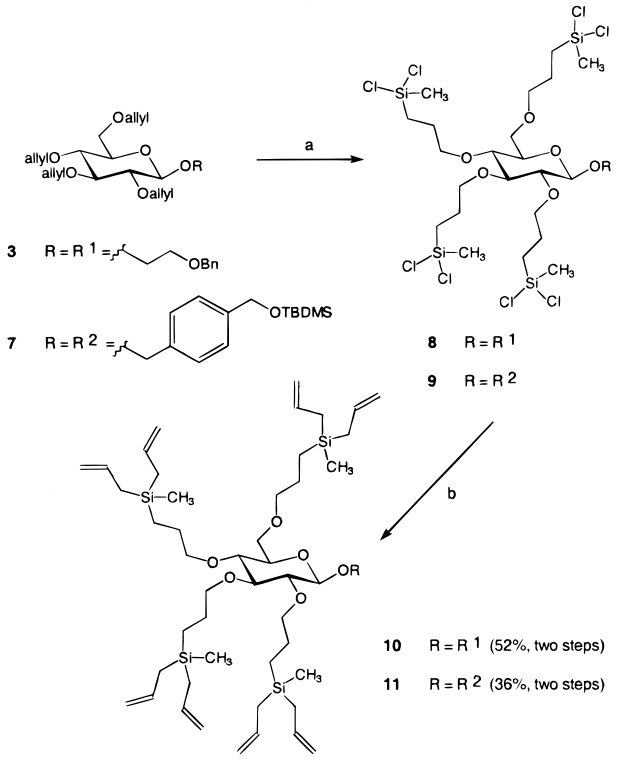


[a] (a) $LiAlH_4$, Et_2O; (b). TBDMS-OTf, MeCN.

The aglycon moiety of glucoside **3** can be directly submitted to the hydrosilylation−Grignard addition sequence. Esters **4** and **5**, on the other hand, first must be reduced to alcohol **6**, which was subsequently protected as the silyl ether **7** using TBDMS-OTf (Scheme 2). Glucoside **7** can now also survive the reaction conditions necessary for build up of carbosilane generations.

For construction of the carbosilane dendrimers, dichloromethylsilane and allylmagnesium bromide were chosen as reagents. Hydrosilylation[9] of the allylic groups was effectively catalyzed by hexachloroplatinic acid in 2-propanol (Speier's catalyst[10]) to afford chlorosilanes **8** and **9**. These were submitted to the Grignard reaction without purification, which finally led to the first-generation carbosilane dendrimers **10** and **11** (Scheme 3).[11]

Scheme 3[a]



[a] (a) $HSiMeCl_2$, $H_2PtCl_6 \cdot 6\ H_2O$/*i*-PrOH, THF; (b) allylMgBr, Et_2O.

Proton NMR spectra of **10** and **11** display large areas of overlapping signals due to the asymmetric character of these carbohydrate-centered representatives of carbosilane dendrimers. However, key signals for the allylic protons, the silyl-methyl groups, and the benzylic protons as well as the anomeric H-1 clearly allow the determination of integration ratios which confirm complete conversion of four allyl functions in **3** and **7**. ^{13}C NMR spectra, on the other hand, are well-resolved and allow the assignment of each peak.

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(8) Boysen, M. M. K.; Lindhorst, Th. K. *J. Carbohydr. Chem.*, in press.

(9) (a) Muslof, M. C.; Speier, J. L. *J. Org. Chem.* **1964**, *29*, 2519−2524. (b) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 16−21. (c) Ojima I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; pp 1479−1526. (d) Marciniec, B.; Gulinski, J. *J. Organomet. Chem.* **1993**, *446*, 15−23.

(10) (a) Benkeser, R. A.; Kang, J. *J. Organomet. Chem.* **1980**, *185*, C9−C12. (b) Lewis, L. N.; Lewis, N. *J. Am. Chem. Soc.* **1986**, *108*, 7228−7232. (c) Lewis, L. N. *J. Am. Chem. Soc.* **1990**, *112*, 5998−6004.

Structures of **10** and **11** were furthermore approved by MALDI-TOF analysis.[12]

In summary, we have introduced the first carbosilane dendrimers with carbohydrate cores, exemplified by the first-generation representatives **10** and **11**. Our synthetic strategy allows for selective functionalization of these molecules at the glucoside aglycon moiety. Further research will be directed toward the preparation of higher generations within this dendrimer family and the modification of their peripheral functions.

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Supporting Information Available: Full experimental details and ^{1}H NMR as well as ^{13}C NMR spectroscopic data for compounds **3**−**7**, **10**, and **11** and MALDI-TOF spectrometric data for compounds **10** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **General Procedure for the Preparation of Carbosilan Dendrimers from Tetraallylated Glucosides.** For both reactions in this two-step protocol, except for the final workup, the Schlenk technique is required. **Hydrosilylation.** The tetraallylated compound (**3** or **7**) was dissolved in dry THF (0.11−0.37 mol/L). After addition of dichloromethylsilane (6 equiv) and 1−4 drops of Speier's catalyst, the mixture was stirred at rt for 1 h and then under reflux for another 10 h. After cooling to rt, the solvent and excess dichloromethylsilane were removed under vacuum as completely as possible. The resulting oily crude product (chlorosilane **8** or **9**) which still contained residual solvent and silane reagent was used in the next synthetic step without any further purification. **Grignard Addition of Allylmagnesiumbromide to Si−Cl Bonds.** The crude chlorosilane (**8** or **9**) was dissolved in dry diethyl ether under an atmosphere of nitrogen (0.11−0.22 mol/L). To this solution was added dropwise allylmagnesiumbromide in diethyl ether (1 mol/L, 1.5 equiv per Si−Cl bond; a larger excess of Grignard reagent should be used because of residual dichloromethylsilane in the crude product). Precipitation of magnesium salts resulted instantly. After the addition was finished, the mixture was stirred under reflux for 12 h and then cooled to rt and poured onto an ice-cold saturated ammonium chloride solution. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were then twice washed with water and finally once with brine. Drying over magnesium sulfate, filtration, and evaporation of the solvent yielded the crude product which was purified by flash chromatography on silica gel.

(12) Detailed analytical data for target compound **10**, also representative for compound **11**: yield 52% (1.13 g, 1.15 mmol, two steps); ^{1}H NMR ($CDCl_3$) δ = 7.25−7.34 (5H, m, 5 aryl-H), 5.67−5.81 (8H, m, 8 CH_2═C*H*CH_2), 4.78−4.88 (16H, m, 8 C*H*$_2$═$CHCH_2$), 4.50−4.58 (2H, m, CH_2Ph), 4.26 (1H, d, H-1), 3.96−4.03 (1H, ddd ≈ m, su (= sugar moiety) OC*H*$_A$H$_B$), 3.14−3.84 (16H, m, H-3, H-4, H-5, H-6, H-6′, 4 OC*H*$_2$$CH_2$-$CH_2$Si, C*H*$_2$$OCH_2$Ph, su OCH_AH_B), 3.07 (1H, dd ≈ t, H-2), 1.46−1.61 (24H, m, 8 CH_2═CHC*H*$_2$, 4 OCH_2C*H*$_2$$CH_2$Si), 0.42−0.56 (8H, m, 4 OCH_2-CH_2C*H*$_2$Si), −0.02, −0.03, −0.05 (12H, each s, 4 $SiCH_3$) ppm; $^3J_{1,2} \approx {}^3J_{2,3}$ = 8.1 Hz; ^{13}C NMR ($CDCl_3$) δ = 138.3 (C, aryl-C), 134.6, 134.5 (CH, 8 CH_2═*C*HCH_2), 128.3, 127.6, 127.5 (CH, 4 aryl-C), 113.3, 113.2 (CH_2, 8 *C*H$_2$═$CHCH_2$), 103.7 (CH, C-1), 84.8, 78.1, 75.0 (CH, C-3, -4, -5), 82.3 (CH, C-2), 76.4, 75.8, 75.6, 74.6 (CH_2, 4 O*C*H$_2$$CH_2$$CH_2$Si), 73.1 ($CH_2$, *C*H$_2$Ph), 69.8, 69.3, 68.9 ($CH_2$, C-6, *C*H$_2$$OCH_2$Ph, su OCH_2), 24.6, 24.5, 24.4, 23.8 (CH_2, 4 OCH_2*C*H$_2$$CH_2$Si), 21.2 ($CH_2$, 8 CH_2═CH*C*H$_2$), 9.1, (CH_2, 4 OCH_2CH_2*C*H$_2$Si), −5.9 (CH_3, $SiCH_3$) ppm; MALDI-TOF MS *m*/*z* 1001.7 ((M + Na)$^+$, calcd 1001.6), 1017.7 ((M + K)$^+$, calcd 1017.6) for $C_{55}H_{94}O_7Si_4$ (M = 978.6), 875.6 (($C_{48}H_{80}O_7Si_3Na$)$^+$, calcd 876.1).