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‘Sugaring’ carbosilane dendrimers via hydrosilylation

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Abstract—Two new pathways to introduce carbohydrate derivatives into dendritic carbosilane structures were explored. Pathway one utilised alcoholysis of a chlorosilane with a protected hydroxyethyl glycoside resulting in Si–O linkages. Pathway two proceeds via a hydrosilylation reaction of a protected allyl glycoside with a carbosilane containing Si–H end groups in the presence of a platinum catalyst, thus leading to Si–C linked structures.

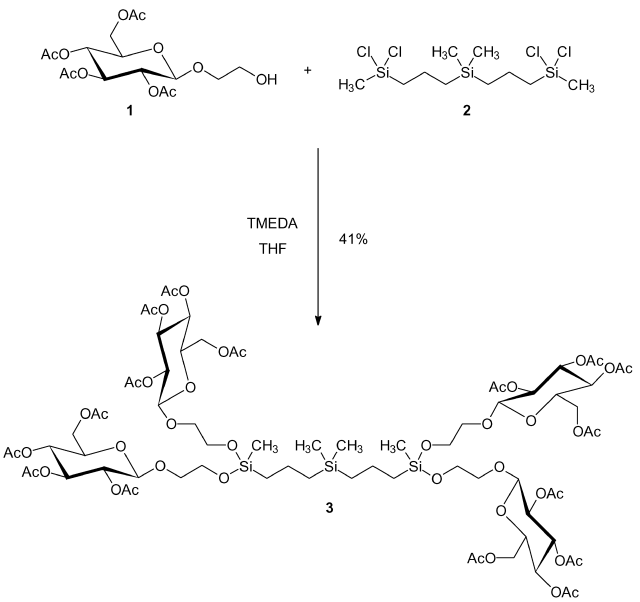
1. Introduction

Dendrimers[1,2] with their monodispersity and defined number of uniform functional surface groups present ideal scaffolds whenever a certain structural feature is to multiply displayed within one molecule. Utilising this strategy among other structures, organometallic complexes exhibiting catalytic[3] or redox[4] activity and carbohydrates[5] have been grafted on dendritic scaffolds of varying composition. The use of dendrimers in carbohydrate chemistry, which has led to a large number of glycodendrimers[6] is especially attractive, as such compounds can mimic multiantennary oligosaccharides from complex glycoconjugates.[7] In recent time our group has introduced several examples of dendrimers containing carbohydrates. Along with pure[8] and carbohydrate-centered[9] PAMAM and combined carbohydrate-peptide[10] backbones we have explored carbohydrate-centered carbosilanes[11] as dendritic scaffolds.

Carbosilanes bearing saccharide epitopes on their surface were first introduced by Matsuoka et al.[12–14] Coupling between the carbosilane scaffold and the carbohydrate counterpart was effected by nucleophilic displacement of a bromine leaving group on the dendritic scaffold by a thio nucleophile borne by the saccharide component. In this paper we now report our approach for glycodendrimer synthesis via carbosiloxane formation and a method for attaching carbohydrate derivatives to carbosilane backbones without using any hetero atoms.

2. Results and discussion

First we explored the reaction pathway to carbosiloxane based glycodendrimers. Carbosiloxanes are formed by treatment of a chloro silane compound with an alcohol component in the presence of base.[15] According to this general procedure we reacted the acetyl protected hydroxy ethyl glucoside **1** with the tetrafunctional chloro silane **2** prepared according to standard conditions[16] (Scheme 1). The resulting carbosiloxane glycodendrimer **3** was formed in 41% yield. This rather moderate yield is probably due to steric hindrance of the second reactive chlorine on one silicon atom after the initial attack of the first alcohol derivative. However, 35% of the originally used starting glucoside **1** could be recovered. Product **3** has been



Scheme 1.

Keywords: carbosilanes; carbosiloxanes; carbohydrates; glycodendrimers.

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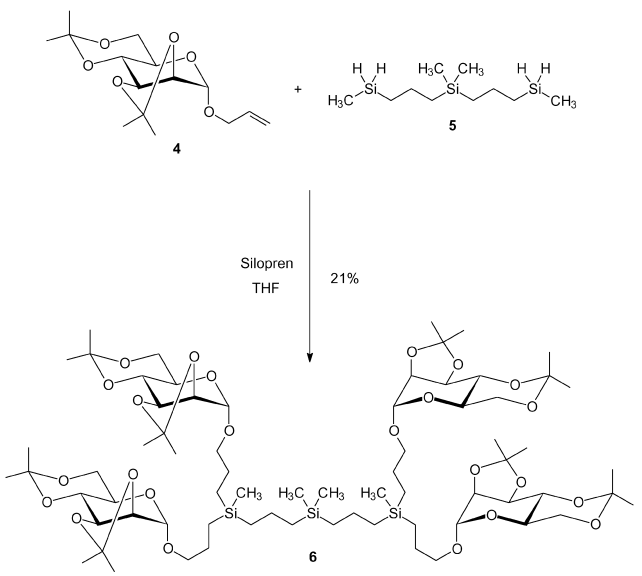
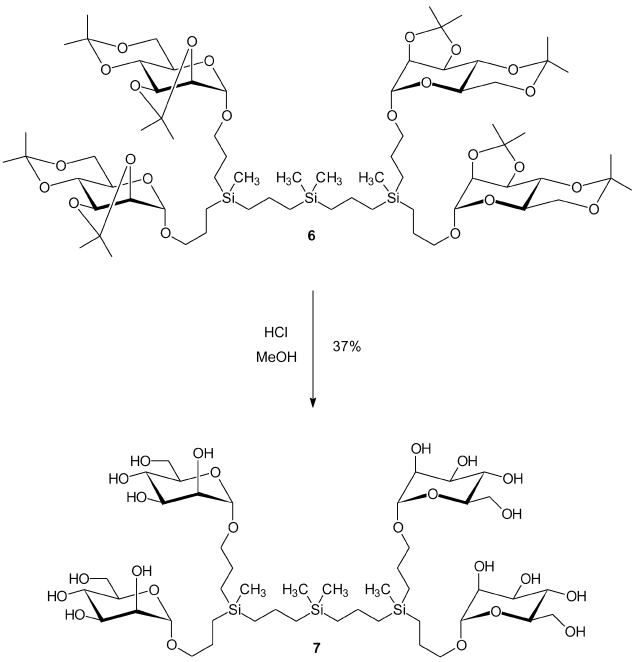
characterised by NMR and MALDI-TOF studies. However, significant decomposition, giving the starting glucoside, was observed in chloroform solution at room temperature after a few days. An attempt at deacetylation of the hydroxy functions under Zemplèn conditions[17] led to complete decomposition of the glycodendrimer **3**.

Our approach to hetero atom free connection of carbohydrates to carbosilane scaffolds proceeded by the well known platinum catalysed hydrosilylation reaction of alkenes with suitable hydrosilane compounds.[18] In dendrimer chemistry this reaction has first been utilised by van der Made et al[19] in a divergent synthesis, where the dendritic moiety contained the alkene functions and the hydrosilane component was added in excess. For our purposes however, synthesis via a dendritic hydrosilane and an allyl glycoside was much more feasible. This 'reverse' approach to functionalised carbosilane dendrimers is known in the literature,[20,21] although more rarely than the normal one. Thus we reacted the di-isopropylidene protected allyl mannoside **4** with the tetrafunctional hydrosilane **5**, prepared according to standard procedures,[22] in the presence of Silopren™ (Bayer AG, platinum–siloxane-complex 67–69%, 2-propanol 16–18%) (Scheme 2). The desired Si–C linked glycodendrimer **6** was obtained in 21% yield. Unfortunately, all attempts to improve the rather low yield of the reaction leading to **6** were thus far unsuccessful. The 'reverse' approach to carbosilanes was reported to be successful in the literature in cases where either small alkenes were reacted with dendrimers containing di- or trihydrosilane surface groups[20] or monohydrosilanes and more bulky alkenes were converted to the desired products.[21] On the other hand, the reaction of bulky alkenes with dihydro silane terminated dendrimers was reported to proceed incompletely.[21] Thus, the synthesis of the tetra-antennary carbosilane dendrimer **6** can be regarded as a success, even more so as a sterically demanding tricyclic carbohydrate derivative (**4**) with a rather short alkene aglycon has been used. Even though our attempts to change the isopropylidene protective groups in **4** and use the acetylated analogue did not lead to an improved yield, there



Scheme 2.



Scheme 3.

are still possibilities for variation, e.g. length of the alkene aglycon, that may lead to improved yields.

Finally the isopropylidene protected glycodendrimer **6** was deprotected with HCl in methanol to give the free-OH compound **7** in 37% yield (Scheme 3). Minor impurities in the form of a mono isopropylidinated species could be detected in the MALDI-TOF mass spectrum.

In summary we were able to introduce a new strategy to attach carbohydrates to dendritic carbosilane cores that can dispense with hetero atoms.

3. Experimental

3.1. General

Reactions requiring dry or oxygen free conditions were carried out under an atmosphere of argon (Schlenk conditions). THF was dried by distillation from sodium/potassium ketyl, TMEDA was distilled from sodium, each under an atmosphere of argon. TLC was performed on silica gel plates GF_{254} (Merck), detection was effected by charring with 10% sulphuric acid in ethanol followed by heat treatment. Flash chromatography was performed on silica gel 60 (230–400 mesh, particle size 0.040–0.063 mm, Merck). SEC was performed on Sephadex LH 20 (Pharmacia). Optical rotations were measured on Perkin–Elmer polarimeters 241 or 243 (sodium-D-line: 589 nm, length of cell 1 dm) in the solvents given respectively. NMR spectra were recorded on Bruker AMX 400 (400.13 MHz for ^1H) and DRX 500 (500.13 MHz for ^1H, 125.47 MHz for ^{13}C) instruments. The spectra were calibrated on the solvent peak ($CDCl_3$: 7.24 ppm for ^1H and 77.0 ppm for ^{13}C; MeOH-d_4: 3.35 ppm for ^1H and 49.30 ppm for ^{13}C). Assignment of the peaks was achieved with aid of 2D NMR techniques

(^{1}H–^{1}H-COSY and HSQC). In the reported data, the abbreviation 'Su' denotes a sugar moiety. MALDI-TOF mass spectra were recorded on a Bruker Biflex III 19 kV instrument, DHB (2,4-dihydroxy benzoic acid) in acetonitrile/water 1:2 with 0.1% TFA was used as matrix. Microanalyses of the compounds did not lead to accurate values. This is probably due to residual traces of solvent that could not be removed from the samples due to the syrupy character of the compounds.

3.2. Reactions

3.2.1. 1,15-Di-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4,12-di-[2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-ethyl]-4,8,8,12-tetramethyl-3,13-dioxa-4,8,12-trisilapentadecane (3). Under Schlenk conditions 2,2,10,10-tetrachloro-6,6-dimethyl-2,6,10-trisila-undecane (115 mg, 311 μmol) was dissolved in dry THF (5 ml). Subsequent addition of TMEDA (0.19 ml, 1.24 mmol) resulted in the formation of a thick white precipitate. A solution of the acetyl protected hydroxyethyl glucoside (488 mg, 1.24 mmol) in dry THF (3 ml) was added dropwise to the reaction mixture, that afterwards was stirred under reflux for 1.5 days. Progress of the reaction was monitored by TLC (petroleum ether/acetone 1:3, product R_f=0.90). The mixture was allowed to cool to room temperature and the precipitate was filtered off. Concentration of the filtrate in vacuo led to a yellow oil together with further precipitation. The crude product was purified by flash chromatography on silica gel (petroleum ether/acetone 4:3, R_f=0.20) to yield the title compound (228 mg, 127 μmol, 41%) as a thick yellow syrup; $[\alpha]_D^{20}=-18.8$ (c=0.65, $CHCl_3$); MALDI-TOF-MS: m/z=1815.8, $[M+Na]^+$ (calcd 1815.6); m/z=1831.8, $[M+K]^+$ (calcd 1831.6); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.14–5.23 (4H, 2 t ≈ m, H-3), 4.92–5.10 (8H, m, H-4, H-2), 4.50–4.60 (4H, 2 d, H-1, $^3J_{1,2}$=7.7 Hz), 4.07–4.29 (8H, m, H-6, H-6′), 3.54–3.93 (20H, m, H-5, SuO–CH_2–CH_2–O–Si), 2.07, 2.06, 2.03, 2.01, 2.00, 1.98 (48H, each s, OAc), 1.26–1.42 (4H, m, Si–CH$_2$–CH_2–CH$_2$–Si), 0.46–0.49 (8H, m, Si–CH_2–CH$_2$–CH_2–Si), −0.06, −0.07 (12H, each s, SiCH_3, Si(CH_3)$_2$) ppm.

3.2.2. 1,15-Di-(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyloxy)-4,12-di-[3-(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyloxy)-propyl]-4,8,8,12-tetramethyl-4,8,12-trisilapentadecane (6). Under Schlenk conditions 6,6-dimethyl-2,6,10-trisilaundecane (144 mg, 619 μmol) and isopropylidene protected allyl mannoside (2.97 g, 9.90 mmol) were dissolved in dry THF (10 ml) and two drops of Silopren were added to the resulting mixture which was subsequently refluxed for two days. After the mixture had cooled to room temperature, it was diluted with a little dichloromethane and filtered over a pad of silica gel to remove insoluble degradation products of the platinum catalyst. Purification was effected by SEC on Sephadex LH-20 (methanol). The title compound (182 mg, 127 μmol, 21%) was isolated as a thick light yellow syrup; $[\alpha]_D^{20}$=6.1 (c=5.8, MeOH); MALDI-TOF-MS: m/z=1455.8, $[M+Na]^+$ (calcd 1455.8); m/z=1471.8, $[M+K]^+$ (calcd 1471.7); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.99 (4H, d ≈ s, H-1, $^3J_{1,2}$ ≈0 Hz), 4.10–4.17 (8H, m, H-2, H-3), 3.84 (4H, dd, H-6, $^3J_{5,6}$=5.7, $^2J_{6,6'}$=10.8 Hz), 3.68–3.76 (8H, m, H-4, H-6′), 3.51–3.64 (8H, m, SuO–CH_aH–CH$_2$–CH$_2$–Si, H-5), 3.27–3.40 (4H, m, SuO–CHH_b–CH$_2$–CH$_2$–Si), 1.46–1.60 (32H, SuO–CH$_2$–CH_2–CH$_2$–Si, CH_3 isopropylidene), 1.40 (12H, s, CH_3 isopropylidene), 1.24–1.36 (16H, m, CH_3 isopropylidene, Si–CH$_2$–CH_2–CH$_2$–Si), 0.42–0.61 (16H, m, Si–CH_2–CH$_2$–CH_2–Si, SuO–CH$_2$–CH$_2$–CH_2–Si), −0.05, −0.07 (12H, je s, SiCH_3, Si(CH_3)$_2$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=109.4, 99.7 (C, CH_3CCH_3 isopropylidene), 97.8 (CH, C-1), 76.2 (CH, C-2), 74.9 (CH, C-3), 72.8 (CH, C-4), 70.8 (CH_2, SuO–CH_2–CH$_2$–CH$_2$–Si), 62.1 (CH_2, C-6), 61.3 (CH, C-5), 29.1, 28.2, 26.2, 18.8 (CH_3, CH_3 isopropylidene), 23.9 (CH_2, SuO–CH$_2$–CH_2–CH$_2$–Si), 20.2, 18.3 (CH_2, Si–CH_2–CH_2–CH_2–Si), 18.8 (CH_3, CH_3 isopropylidene), 9.7 (CH_2, SuO–CH$_2$–CH$_2$–CH_2–Si), −3.2, −5.3 (SiCH_3, Si(CH_3)$_2$) ppm.

3.2.3. 1,15-Di-(α-D-mannopyranosyloxy)-4,12-di-[3-(α-D-mannopyranosyloxy)-propyl]-4,8,8,12-tetramethyl-4,8,12-trisilapentadecane (7). The isopropylidene protected compound **6** (66 mg, 46 μmol) was dissolved in methanol (2 ml). Five drops of concentrated hydrochloric acid were added and the mixture was stirred for 12–15 h at room temperature. Progress of the deprotection was monitored by TLC (methanol/ethyl acetate 1:1). To neutralise ion-exchange resin III (strongly basic anion exchange resin, Merck) was added. The title compound (19 mg, 17 μmol, 37%), was obtained after filtration, evaporation of the solvent and drying in vacuo as a thick light yellow syrup; $[\alpha]_D^{20}$=42.5 (c=0.95, MeOH); MALDI-TOF-MS: m/z=1135.6, $[M+Na]^+$ (calcd 1135.5); m/z=1151.5, $[M+K]^+$ (calcd 1151.5); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.80 (4H, d, H-1, $^3J_{1,2}$=1.5 Hz), 3.81–3.90 (8H, m, H-2, H-6′, $^2J_{5,6'}$=2.2 Hz), 3.55–3.79 (20H, m, H-3, H-4, H-6, SuO–CH_aH–CH$_2$–CH$_2$–Si, H–5, $^3J_{4,5}$=9.7, $^3J_{5,6}$=5.5 Hz), 3.39–3.84 (4H, m, SuO–CHH_b–CH$_2$–CH$_2$–Si), 1.58–1.71 (8H, m, SuO–CH$_2$–CH_2–CH$_2$–Si), 1.37–1.48 (4H, m, Si–CH$_2$–CH_2–CH$_2$–Si), 0.52–0.77 (16H, m, Si–CH_2–CH$_2$–CH_2–Si, SuO–CH$_2$–CH$_2$–CH_2–Si), 0.03, 0.01 (12H, each s, SiCH_3, Si(CH_3)$_2$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=101.8 (CH, C-1), 74.8 (CH, C-5), 73.0 (CH, C-4), 72.6 (CH, C-2), 71.7 (CH_2, SuO–CH_2–CH$_2$–CH$_2$–Si), 68.9 (CH, C-3), 63.2 (CH_2, C-6), 25.5 (CH_2, SuO–CH$_2$–CH_2–CH$_2$–Si), 21.4, 20.0, 19.7 (CH_2, Si–CH_2–CH_2–CH_2–Si), 11.2 (CH_2, SuO–CH$_2$–CH$_2$–CH_2–Si), −2.6, −4.7 (SiCH_3, Si(CH_3)$_2$) ppm.

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