Dendrimers are attracting growing interest for use in stereoselective synthesis,\textsuperscript{[1,11]} as a new type of material,\textsuperscript{[12]} and in biological studies, for example as DNA carriers.\textsuperscript{[3]} We now report on the first synthesis of monodisperse, enzymatically degradable, polyanionic dendrimers from \((R)-3\)-hydroxybutanoic acid (HB)\textsuperscript{[4]} and trimesic acid.

The convergent synthesis starts with the previously described\textsuperscript{[4]} benzyl esters 1a and 1b of the dimer and the tetramer of HB, respectively, which were used as elongation units. For the assembly of the dendritic core and the branching units we employed the commercially available trimesic acid trichloride 3 and the TBDPS-protected 5-hydroxymethyl-1,3,5-benzenedicarboxylic acid dichloride 4,\textsuperscript{[5]} which can be easily obtained from the corresponding trimethyl trimesate. Acylation of the HB-oligomers 1 with 3 gave the core structures 5, and debenzylation yielded the tricarboxylic acids 6. Branching unit 7 was obtained by acylation of 1 with 4. The branches 10 for the dendrimers of the second generation were synthesized starting from the silylated ester 7, followed by debenzylation (→ 8), then activation (→ 9),\textsuperscript{[5]} and subsequent acylation of the desilylated derivative of 7 with the acid chloride 9. The coupling of 6 with the desilylated branches 7 and 10 finally gave the dendrimers of the first (green circle in formula 11/12) and of the second generation (11), respectively. The selective hydrogenolysis of the terminal benzyl groups of the dendrimers was achieved by catalytic transfer hydrogenation\textsuperscript{[6]} and gave the polyanionic dendrimers of the first and second generation (12a).

The dendritic compounds were obtained in 150 mg (11b) to 450 mg (11a) quantities as viscous oils that were soluble in CH$_2$Cl$_2$. All compounds were fully characterized (optical rotation, IR, $^1$H and $^{13}$C NMR spectroscopy, MS, elemental analysis; see experimental part a); Figure 1 shows five MALDI-MS molecular peaks and proves the identity and the monodispersity of the corresponding compounds.

To study the biodegradability\textsuperscript{[7]} of the dendrimers, we tested their stability in the presence of various hydrolyses. Figure 2 depicts the degradation of three dendritic compounds 6a, 6b, and 11b with a PHB-depolymerase.\textsuperscript{[8]} The linear tetrameric HB 2b was used as the standard substrate for the depolymerase. The protected dendrimers with dimeric HB-elongation units were not degraded by the depolymerase, whereas the free acids were moderately good substrates for this enzyme.\textsuperscript{[9]} This observation is surprising as the simple dimeric HB 2a is not a substrate for the depolymerase. \(^1\)H NMR spectroscopic investigations of the degradation products of the deprotected, first-generation dendrimer with dimeric HB-elongation units (green circle in formula 11/12) revealed free HB, the triester of 1,3,5-benzenetricarboxylic acid with HB, and also compound 13.\textsuperscript{[10]} The enzymatic hydrolysis of the deprotected, first-generation dendrimer, which has dimeric HB-elongation units, was followed by ti-
tristatic experiments over 24 hours. More than five equivalents of base were consumed, which corresponds to a conversion of more than 55%. Like 2b, all dendrimers with tetrameric HB-elongation units are good substrates for the depolymerase (Fig. 2). Zero-order kinetics is observed for the first de-

![Fig. 1. Characterization of the dendrimers and the building blocks by mass spectrometry (MALDI-MS): a) first generation with dimeric HB-elongation units and free acid groups (C_{20}H_{33}O_{15}S, 2294.2 g mol^{-1}, 2317 [M+Na]+); b) second generation with dimeric HB-elongation units and R = Bn (11a: C_{33}H_{56}O_{18}S, 6510.7 g mol^{-1}, 6537 [M+Na]+); c) first generation with tetrameric HB-elongation units and free acid groups (C_{22}H_{33}O_{16}S, 4390.6 g mol^{-1}, 4412 [M+Na]+); d) protected branch of the second generation with tetrameric HB-elongation units (10b: C_{18}H_{32}O_{14}S, 3217.5 g mol^{-1}, 3240 [M+Na]+, 3256 [M+K]+); e) second generation with tetrameric HB-elongation units and R = Bn (11b: C_{33}H_{58}O_{21}S, 10130.5 g mol^{-1}, 10153 [M+Na]+).

![Fig. 2. Enzymatic degradation of the tetrameric HB 2b, the core unit 6, and the second-generation dendrimer 11b with the PHB-depolymerase (0.25 mg mL^{-1} substrate in H_{2}O, 4.25 U mL^{-1} depolymerase from Alcaligenes faecalis) [8]. pH = 7.5, 30 °C). x = "acid equivalents" formed, in arbitrary units.

gradation step. The reaction is about one hundred times faster than the degradation of dendrimers with dimeric HB-elongation units. In the second degradation step (also zero order), the kinetics is comparable with that of dendrimers with dimeric HB-elongation units. Furthermore, the dendritic compounds were degraded by an esterase, a lipase, and a protease.\textsuperscript{[11]}

In conclusion, we have described the first examples of biodegradable\textsuperscript{[7]} dendrimers, which may have applications in materials science (for example, for the construction of defined nanocavities\textsuperscript{[2h1]} that are similar to those for chemically degradable dendritic and hyperbranched organosilicon compounds.\textsuperscript{[12]} Furthermore, they could possibly be used as drug carriers.\textsuperscript{[3]}

**Experimental Procedure**

a) Analytical data of two selected compounds [13]:

11a (6510.7 g mol^{-1}): 48% yield (450 mg of material purified on 75 g silica gel, eluent CHCl_{3}/EtOAc 4:1) for the coupling of 6a and 3 equiv. desilylated 10a.

\[ \text{IR (CHCl}_{3}, \text{cm}^{-1}): v = 3035, 2986, 1735, 1607, 1498, 1455, 1388, 1248, 1135, 1100, 1057, 973 \text{ cm}^{-1}; \text{H NMR (500 MHz, CDCl}_{3}): \delta = 8.75 (s, 3H, areneH), 8.53 (t, J = 1.57 Hz, 9H, areneH), 8.15 (d, J = 1.58 Hz, 6H, areneH), 8.14 (d, J = 1.60 Hz, 12H, areneH), 7.34-7.27 (m, 60H, areneH), 5.55-5.44 (m, 2H, areneH). \]

10b (3217.48 g mol^{-1}): 69% yield (900 mg of material purified on 80 g silica gel, eluent CHCl_{3}/EtOAc 8:1) for the coupling of 9b and 2 equiv. desilylated 7b.

\[ \text{IR (CHCl}_{3}, \text{cm}^{-1}): v = 3032, 2986, 1736, 1607, 1498, 1456, 1405, 1383, 1302, 1171, 1134, 1101, 1056, 976 \text{ cm}^{-1}; \text{H NMR (400 MHz, CDCl}_{3}): \delta = 8.54 (t, J = 1.63 Hz, 2H, areneH), 8.48 (s, 1H, areneH), 8.17 (s, 2H, areneH). \]
arene H). 7.67–7.65 (d), 7.62–7.60 (m, 6H, H2C), 7.50–7.53 (m, 18H, H2C), 5.17 (d, J = 1.13 Hz, 4H, H2C), 5.10 (s, 8H, H2C), 4.82 (s, 2H, H2C), 2.81–2.35 (m, 48H, H2C), 4.12 (d, J = 6.31 Hz, 9H, H2C), 1.41 (d, J = 6.26 Hz, 9H, H2C), 1.28–1.20 (m, 54H, H2C), 1.11 (s, 9H, H2C). 13C NMR (100 MHz, CDCl3): 169.88, 169.71, 169.14, 169.11, 169.07, 164.46, 136.76, 135.69, 135.51, 135.23, 131.22, 130.39, 129.86, 128.92, 128.80, 76.29, 76.67, 67.63, 67.56, 67.49, 66.44, 65.23, 40.96, 40.75, 40.64, 40.39, 28.61, 19.89, 19.78, 19.75, 19.69. MALDI-MS (see Fig. 1d): 3250 [M + K]+; 3240 [M + Na]+. Analysis calcd for C116H60OSi: C 61.73, H 6.39; found: C 61.80, H 6.39.

b) Determination of the biodegradability: The substrate (1.0 mg) was dissolved or suspended in 4 ml H2O. The pH was adjusted to 7.5 after which the hydrolysis was added. The pH was kept constant throughout the addition of the first generation and the consumption of base was recorded (1 U = 1 mol acid formed per min−1).

Enzymes used for the experiments: 35 mg of a PHB-depolymerase [8] (from Alcaligenes faecalis, 486 U mg−1) [14]. 1 mg of an esterase (from pig liver, 220 U mg−1) [14]. 1 mg of a lipase (from Pseudomonas fluorescens, 42 U mg−1) [14] and 1.25 mg of a protease (trypsin, from bovine pancreas).

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[3] for the entrance of the tricarboxylic acid 6 for the coupling with desilylated singly and doubly reduced compounds, followed by silylation of the hydroxyl group and saponification of the ester group, and subsequent conversion to the acid chloride with (COCl)2 (this reagent was also used for the synthesis of 9 and 10).

[4] for the activation of the tricarboxylic acid 6 for the coupling with desilylated doubly reduced compounds.

[5] As a critical role for the carbohydrate sector in receptor contact is that of the enediyne antibiotics [21] such as calicheamicin γ1 (Fig. 1) [3]. Work from our laboratories [4] as well as from Nicolaou et al. [5] and others [6–8] has established that contacts between the pentacyclic carbohydrate region and the minor groove of DNA provide much of the remarkable sequence selectivity of calicheamicin γ1. Similarly, such interactions also foster the molecular contacts between esperimicin A and its target DNA [9]. Though the aglycones such as calicheamicinone (2) retain cytotoxicity and some double-strand cleaving ability, sequence selectivity requires the existence of the carbohydrate domain. [10, 11]. Indeed, moderate sequence selectivity can be realized through co-incubation of non-

**Synthesis and a Preliminary DNA Binding Study of Hybrids of the Carbohydrate Domain of Calicheamicin γ1 and the Aglycone of Daunorubicin: Calichearubinics A and B**

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Many important medicinal agents of natural origin contain a sugar or sugarlike moiety. From a chemical standpoint, such agents can be divided into aglycones and carbohydrate components. In most instances, both components in themselves are totally lacking in useful biological activity. [11] Traditionally, considerations about the mechanism of action of the drug have been directed to the aglycone, with the carbohydrate viewed as a necessary appendage for biotransport or for other factors related to drug availability.

While the nature of interplay of the aglycone and carbohydrate components in various drugs presumably varies from case to case, it is now apparent that in some important instances the carbohydrate domain may play a critical role in drug receptor recognition. One example of such a critical role for the carbohydrate sector in receptor contact is that of the enediyne antibiotics [21] such as calicheamicin γ1 (Fig. 1) [3]. Work from our laboratories [4] as well as from Nicolaou et al. [5] and others [6–8] has established that contacts between the pentacyclic carbohydrate region and the minor groove of DNA provide much of the remarkable sequence selectivity of calicheamicin γ1. Similarly, such interactions also foster the molecular contacts between esperimicin A and its target DNA [9]. Though the aglycones such as calicheamicinone (2) retain cytotoxicity and some double-strand cleaving ability, sequence selectivity requires the existence of the carbohydrate domain. [10, 11]. Indeed, moderate sequence selectivity can be realized through co-incubation of non-

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