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Molecular Diversity of Novel Amino Acid Based Dendrimers

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Abstract: We have expanded the recently introduced methodology for the preparation of a novel amino acid based dendrimer in order to be able to synthesize a diversity of dendrimers. For this purpose different hydroxybenzoic acids and amino alcohols were used to prepare the required monomers, necessary for construction of the respective dendrimers. © 1997 Elsevier Science Ltd.

In the preparation of the first molecules to be named (starbust) dendrimers advantage was taken from the formation of the stable amide bond,[1] leading to defined macromolecules ultimately containing several hundreds of amide bonds, *i.e.* as many as there are present in proteins. Not surprisingly, a significant number of subsequent dendrimer syntheses featured the repeated formation of amide bonds in their construction.[2]

In a previous communication we have described the efficient synthesis of a novel amino acid based dendrimer[3]. The BOP coupling reagent,[4] normally used in high-yielding and clean syntheses of peptides, was employed for the preparation of this particular dendrimer.

In addition to the development of a reliable strategy for efficient construction of novel amino acid based dendrimers, it was our wish to introduce a considerable degree of molecular diversity in our dendrimer synthetic strategy, so that it could be employed for the preparation - in the future also by combinatorial methods - of dendrimers with a variety of branching patterns, interior cavity size, interior and surface functionality.

We realized that a significant molecular diversity of dendrimers could be generated by using aromatic residues bearing varying numbers of amino and carboxylic acid functions. On their turn, these amino acid building blocks can be derived from various commercially available hydroxy benzoic acid derivatives and amino alcohol derivatives, which are either commercially available or easily synthetically accessible. A few representative examples of amino acid based dendrimer monomers containing a substituted aromatic residue are schematically depicted in Figure 1. From this figure it also follows that already twelve different (homo)dendrimer monomers are possible by combination of the four depicted hydroxy benzoic acid derivatives and the three shown amino alcohols.

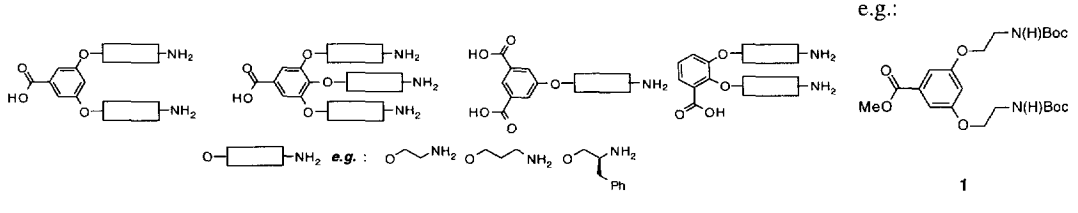
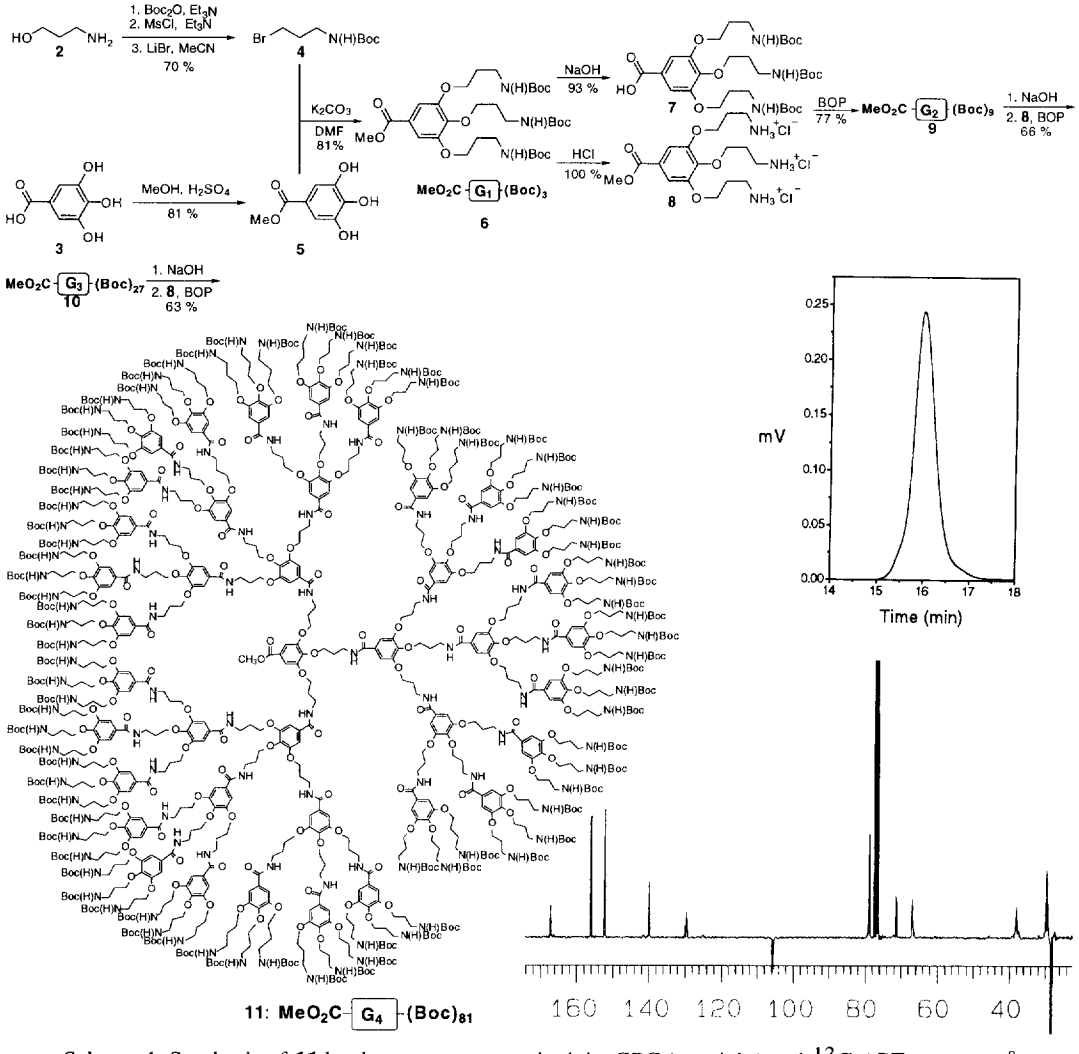


Figure 1. Illustration of the molecular diversity of amino acid based dendrimer monomers

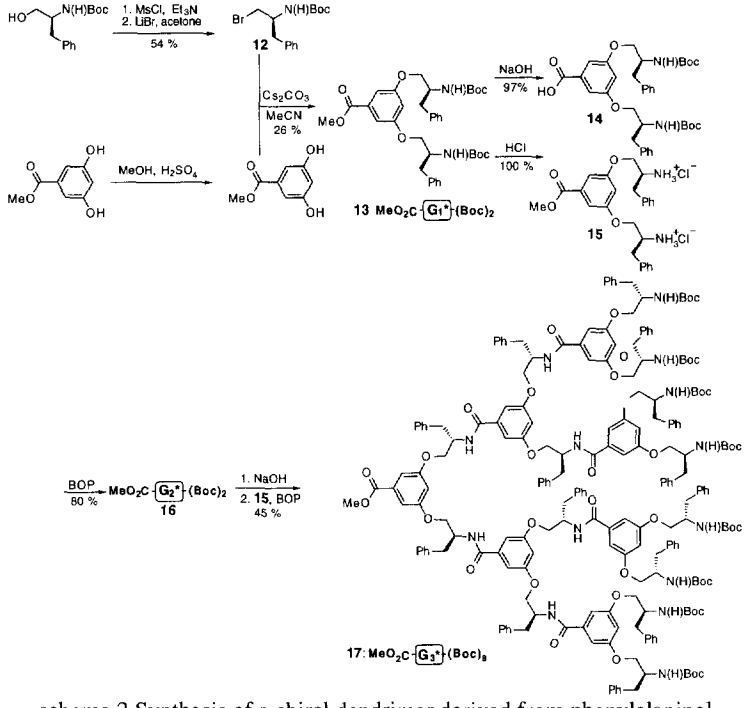
Previously,[3] the easy accessible dendrimer monomer 3,5-bis(2-*tert*-butyloxycarbonyl aminoethoxy) benzoic acid methyl ester **1** was converted to both the "surface" and "branching" monomer in a versatile synthesis of a novel amino acid based dendrimer by the convergent method, using the well established and high-yielding BOP-peptide coupling method. To illustrate the potential molecular diversity of this class of amino acid based dendrimers we have now prepared up to a fourth generation dendrimer (81 endgroups, mw 21,077) based on dendrimer monomer **6** as well as a third generation chiral dendrimer assembled from monomer **13**.[5]

For the preparation of **11** we started from N-*tert*-butyloxycarbonyl-3-bromo-1-aminopropane **4** which was prepared from 3-amino-1-propanol **2** and gallic acid **3**, respectively, of which the corresponding methyl ester **5** was prepared (Scheme 1). Subsequently, both the "surface" monomer **7** and the "branching" monomer **8** were prepared from **6**. Using these monomers we were able to prepare the fourth generation dendrimer **11** in a convenient and straightforward way (Scheme 1).



Scheme 1. Synthesis of **11** by the convergent method, its GPC (top right) and ^{13}C-APT spectrum.[8]

For the preparation of monomer **13** of a chiral dendrimer, we used bromide **12**, derived from Boc-phenylalaninol, which was prepared from phenylalanine. In a substitution reaction with 3,5-dihydroxy benzoic acid methyl ester, previously employed in the synthesis of dendrimer monomer **1**, the chiral monomer **13** was prepared - unfortunately in a low yield (26%) - and converted to the "surface" and "branching" monomer **14** and **15**, respectively (Scheme 2). The purification by column chromatography of these dendrimers was tedious and only a third generation (eight end groups, mw 3650) chiral dendrimer **17** was prepared. Interestingly, the optical activity of the chiral dendrimer did not increase significantly going from the first generation dendrimer **13** (-6.5°) to the second generation dendrimer **16** (-10.4°) and even decreased at the third generation dendrimer **17** (-5.0°). This is in agreement with data obtained for other chiral dendrimers.[6,7] Each dendrimer was purified by column chromatography and analyzed by TLC, GPC and HPLC.[8]



scheme 2 Synthesis of a chiral dendrimer derived from phenylalaninol

By varying the aromatic residue and/or the amino alcohol part in dendrimer monomers we have developed a strategy for the synthesis of a considerable diversity of novel amino acid based dendrimers. In this way dendrimers with *e.g.* a variety of branching patterns, interior cavity size, interior and surface functionality, are accessible. Under present investigation is the use of combinatorial approaches for the synthesis of libraries of dendrimers directed towards the selection or optimization of desired molecular properties *e.g.* with respect to possible binding of guest-molecules. In addition, the synthesis of dendrimers containing surface NLO-groups is under study as well as deprotection of the surface amino groups followed by introduction of *e.g.* catalytic groups.

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6. see reference 5a, 5b and 5e
7. For comparison: the $[\alpha]^{20}$ of Boc-phenylalaninol is -24.0°.
8. **10** (**MeO$_2$C-[G4]-(Boc)8**)1);**17** (**MeO$_2$C-[G3*]-(Boc)8**); **10**: obtained as a white solid in 63%; R_f= 0.79 (eluent: DCM/MeOH, 9/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39, 1.41 (bs (twice), 729H, C(CH_3)$_3$), 1.89 (bs, 240H, OCH$_2$C$\underline{H}_2$, OC'H$_2$C'$\underline{H}_2$, OC"H$_2$C"$\underline{H}_2$, OC'"H$_2$C'"$\underline{H}_2$), 3.20-3.49 (m, 240H, NHC$\underline{H}_2$, N'HC'$\underline{H}_2$, N"HC"$\underline{H}_2$, N'"HC'"$\underline{H}_2$), 3.79, 3.92-4.01 (m (twice), 243H, OC$\underline{H}_3$,OC$\underline{H}_2$, OC'H$_2$, OC"H$_2$, OC'"$\underline{H}_2$), 5.46 (bs, 81H, N'"H), 7.00, 7.13, 7.26 (bs (3 times), 80H, Ph-C^{2,6}-H, Ph-C$^{2',6'}$-H, Ph-C$^{2",6"}$-H, Ph-C$^{2'",6'"}$-H), 7.87, 7.99, 8.09 (bs (3 times), 39H, NH, N'H, N"H); ^{13}C NMR ($CDCl_3$) δ 28.4 (C($\underline{C}H_3$)$_3$), 29.6, 30.1 (OCH$_2\underline{C}$H$_2$, OC'H$_2\underline{C}$'H$_2$, OC"H$_2\underline{C}$"H$_2$, OC'"H$_2\underline{C}$'"H$_2$), 37.5, 38.0, 38.2 (NHCH$_2$, N'HC'H$_2$, N"HC"H$_2$, N'"HC'"H$_2$), 67.0, 71.5, 72.3(OCH$_2$, OC'H$_2$, OC"H$_2$, OC'"H$_2$), 78.9 (C(CH$_3$)$_3$), 105.8 (Ph-C^{2,6}, Ph-C$^{2',6'}$, Ph-C$^{2",6"}$, Ph-C$^{2'",6'"}$), 129.5, 129.6, 129.7, 130.1 (Ph-C$^{1'}$, Ph-C$^{1"}$, Ph-C$^{1'"}$), 140.0 (Ph-C$^{4'}$, Ph-C$^{4"}$, Ph-C$^{4'"}$), 152.3, 152.4 (Ph-C^{3,5}, Ph-C$^{3',5'}$, Ph-C$^{3",5"}$, Ph-C$^{3'",5'"}$), 156.1 (N'"HC'"=O), 167.3 (two signals), 167.4, 167.5 (NHC=O, N'HC'=O, N"HC"=O)
17: obtained as a white solid in 47%; R_f= 0.91 (eluent: DCM/MeOH, 9/1, v/v); R_f= 0.67 (eluent: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ1.40 (s, 72H, C(CH$_3$)$_3$), 2.93 (bd, 16H, C"$_6$H$_5$-C"$\underline{H}_2$), 3.09 (bd, 12H, C$_6$H$_5$-C$\underline{H}_2$, C'$_6$H$_5$-C'$\underline{H}_2$), 3.81, 3.84, (s (twice), 19H, OCH$_3$, OC"H$_2$), 4.02 (m, 12H, OCH$_2$, OC'H$_2$), 4.13 (bs, 8H, C"H), 4.67 (bs, 6H, CH, C'H), 4.92 (bs, 8H, N"H), 6.50 (bs, 8H, Ph-C$^{4"}$-H, N'H), 6.59 (bs, 2H, Ph-C$^{4'}$-H), 6.66 (s, 1H, Ph-C^{4}-H), 6.78 (bs, 2H, NH), 6.86 (bs, 8H, Ph-C$^{2",6"}$), 7.02 (s, 2H, Ph-C^{2,6}-H), 7.17-7.26 (m, 74H, C$_6$H$_5$, C'$_6$H$_5$, C"$_6$H$_5$, Ph-C$^{2',6'}$-H); ^{13}C NMR ($CDCl_3$): δ 28.1 (C($\underline{C}$H$_3$)$_3$), 36.9, 37.4 (C$_6$H$_5$-$\underline{C}$H$_2$, C'$_6$H$_5$-$\underline{C}$'H$_2$, C"$_6$H$_5$-$\underline{C}$"H$_2$), 50.1, 50.4, 50.8 (CH, C'H, C"H), 52.1 (OCH$_3$) 68.2 (OCH$_2$, OC'H$_2$, OC"H$_2$), 79.6 (C(CH$_3$)$_3$), 104.5, 105.9, 106.1, 106.3, 108.3 (Ph-C^{4}, Ph-C$^{4'}$, Ph-C$^{4"}$, Ph-C^{2,6}, Ph-C$^{2',6'}$, Ph-C$^{2",6"}$), 126.4, 126.5, 128.4, 128.5, 128.7, 128.8, 129.2 (C$_6$H$_5$-C^{2,3,4}, C'$_6$H$_5$-C$^{2',3',4'}$, C"$_6$H$_5$-C$^{2",3",4"}$), 131.9 (Ph-C^{1}), 136.3, 137.0, 137.3, 137.4 (Ph-C$^{1'}$, Ph-C$^{1"}$, C$_6$H$_5$-C^{1}, C'$_6$H$_5$-C$^{1'}$, C"$_6$H$_5$-C$^{1"}$), 155.4 (N"HC=O), 159.0, 159.6 (Ph-C^{3,5}, Ph-C$^{3',5'}$, Ph-C$^{3",5"}$), 166.6, 167.0, 167.1 (NHC=O, N'HC=O, $\underline{C}$O$_2$CH$_3$) C^{4}H: denotes a proton of a first generation; C^{4}H: denotes a proton of a second generation etc. ; C$^{4,4"}$ carbon signals from the second and third generation.

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