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Synthesis of a Novel Amino Acid Based Dendrimer

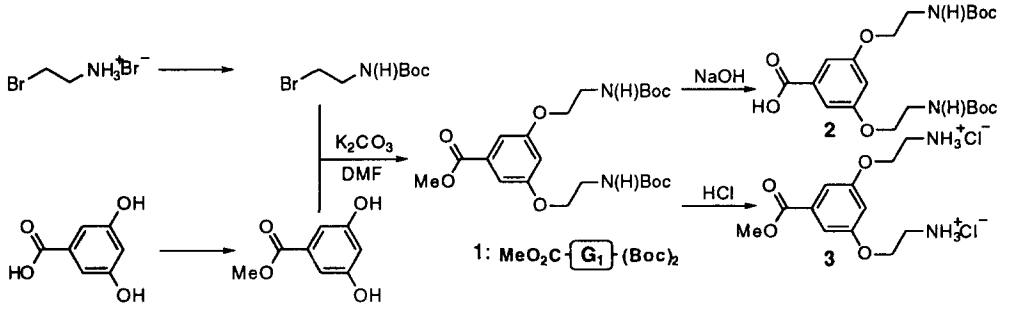
Suzanne J.E. Mulders, Arwin J. Brouwer, Peter G.J. van der Meer, and Rob M.J. Liskamp*

Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands

Abstract:: An easy accessible dendrimer monomer 3,5-bis(2-*tert*-butyloxycarbonyl aminoethoxy) benzoic acid methyl ester **1** was designed. The monomer was converted to both the "surface" and "braching" monomer in a versatile synthesis of a novel amino acid based dendrimer by the covergent method, using the well established and high-yielding BOP-peptide coupling method.

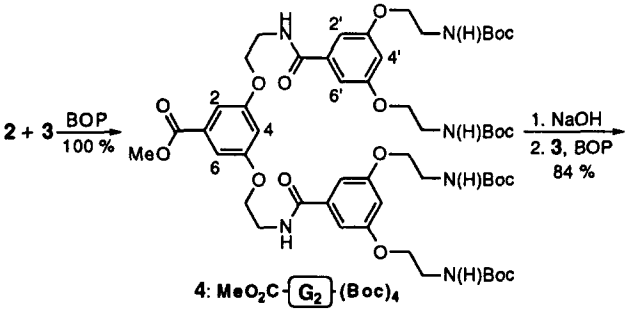
In the preparation of the first molecules to be named (star burst) dendrimers advantage was taken from the formation of the stable amide bond,[1] leading to defined macromolecules ultimately containing several hundreds of amide bonds, *i.e.* as many as there are present in proteins. In subsequent dendrimer syntheses, both by the divergent and the convergent method, formation of a variety of other bonds was employed to construct layers of repeating units, denoted as dendrimer generations.[2] A smaller, but still significant, number of dendrimer syntheses, feature the repeated formation of amide bonds in their construction.[3] The formation of amide bonds in the synthesis of peptides has been an extremely well-studied reaction of the past decades and has led to the development of excellent coupling reagents for the high-yielding and clean syntheses of peptides.[4] As a consequence large peptides or even proteins can be synthesized.[5] We thought that these features of peptide synthesis could be exploited in search for a reliable strategy for efficient construction of novel amino acid based dendrimers, which is reported in this communication.

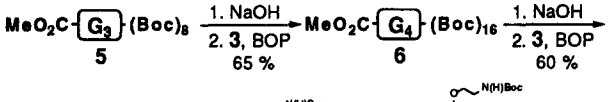
We embarked on the construction by the convergent method of amino acid dendrimers using 3,5-bis(2-*tert*-butyloxycarbonyl aminoethoxy) benzoic acid methyl ester **1**, which is easy accessible from 3,5-dihydroxybenzoic acid and 2-bromoethylamine hydrobromide. **1** is then converted to both the "surface" monomer **2** by saponification using Tesser's base[6] and the "branching" monomer **3** by removal of the Boc-group (Scheme 1).

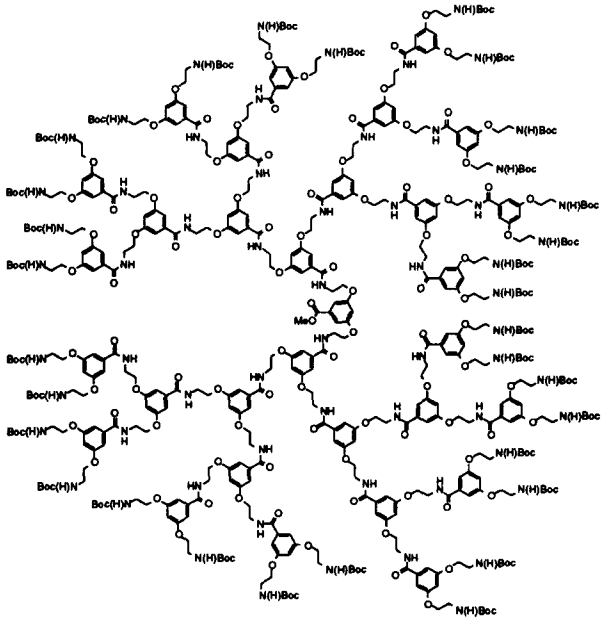


Scheme 1. Synthesis of "surface" dendrimer monomer **2** and "branching" dendrimer monomer **3**.

Counting from **1** as the first generation, the second generation dendrimer **4** was synthesized in a BOP coupling reaction in a quantitative yield.[4a] The preparation of higher generations consisted of repeating a two reaction cycle, *i.e.* saponification of the methyl ester and coupling to the branching monomer **3**. The yields were satisfactory to good and a fifth generation dendrimer **7** containing 32 end-groups (mw 10,125) was conveniently prepared in 60 % yield (Scheme 2). In order to obtain reproducible yields as of the third generation, couplings had to carried out in refluxing acetonitrile to ensure that the reaction mixtures remained homogeneous. Each dendrimer was purified by column chromatography and obtained pure according to TLC and HPLC.







7: MeO_2C-G5-$(Boc)_{32}$

Scheme 2. Synthesis by the convergent method of a fifth generation amino acid based dendrimer.[7]

It was possible to measure satisfactory FAB-mass spectra up to the fourth generation dendrimer *i.e.* **6**. For the fifth generation dendrimer **7** it was possible to record an electron spray mass spectrum giving rise to a distribution of pentapositive ions of which *e.g.* the presumed [M+5Na$^+$]-ion of m/z 2048.06 corresponds to a mw of 10,125.3.

The signals in the ^{13}C NMR spectra of the dendrimers are still relatively sharp in the fifth generation dendrimer **7**. Going from the first to the fifth generation, the decrease and concomitant increase of the ^{13}C signals of CO_2Me and Boc-groups, respectively, is nicely observed. The signals of CO_2Me, albeit weak, can still be distinguished in the ^{13}C spectrum of the fifth generation dendrimer **7** and are clearly visible in the ^{13}C spectrum of the fourth generation dendrimer **6** (Figure 1). Not unexpectedly, the signals in the ^{1}H-NMR spectra start already to broaden significantly at the third generation dendrimer **5** and are broad in the spectrum of **7**. Interestingly, the aromatic protons *viz.* C^{2}H, C^{4}H and C^{6}H of the first dendrimer layer are found separately from aromatic protons of subsequent dendrimer layers and are still visible in the ^{1}H-NMR spectrum of the fourth generation dendrimer **6** as well as the singlet of the methylester.

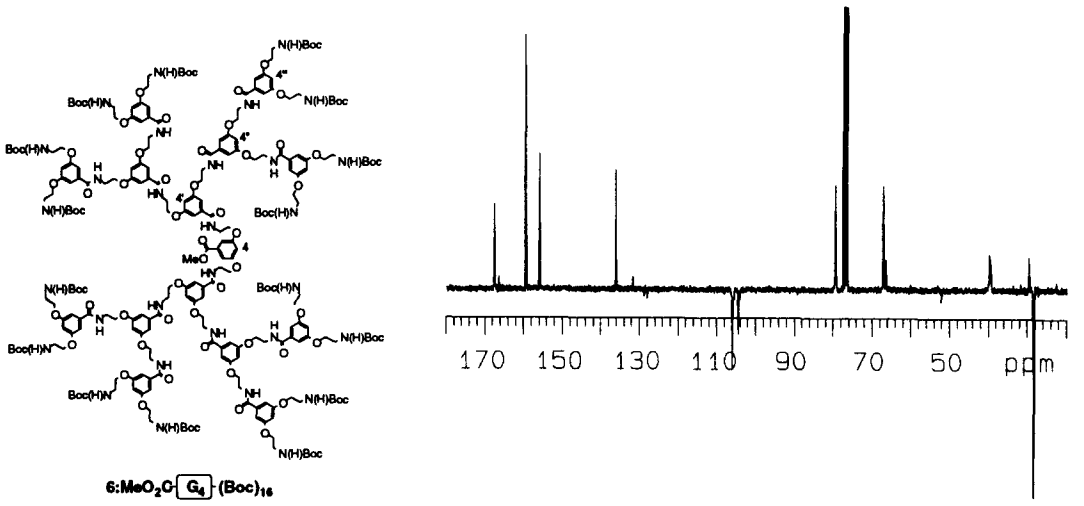


Figure 1. ^{13}C-APT spectrum of MeO_2C-[G4]-$(Boc)_{16}$ (mw 4967.5): δ 28.4 (C($\underline{C}H_3$)$_3$), 39.6, 39.9 (CH_2NH, C'H_2NH, C''H_2NH, C'''H_2NH), 52.2 (OCH_3), 66.5 (OCH_2), 67.2 (OC'H_2, OC''H_2, OC'''H_2), 79.5 ($\underline{C}$(CH$_3$)$_3$), 104.4, 106.0 (Ph-C$^{2,6,2',6',2'',6'',2''',6'''}$, Ph-C$^{4,4',4'',4'''}$), 131.8 (Ph-C^1), 136.2 (Ph-C$^{1',1'',1'''}$), 156.0 (N'''HC=O), 159.5, 159.6 (Ph-C$^{3,5,3',5',3'',5'',3''',5'''}$), 166.6 ($\underline{C}O_2Me$), 167.6, 167.7 (NHC=O, N'HC=O, N''HC=O).

We have developed an efficient strategy for the synthesis of a novel amino acid based dendrimer containing an aromatic residue. By varying the aromatic residue and/or the amino alcohol part in the dendrimer monomers a considerable diversity of dendrimers, with *e.g.* a variety of branching patterns, interior cavity size, interior and surface functionality, will become synthetically accessible.[8] Combinatorial approaches can then be used to synthesize libraries of dendrimers directed towards the selection of optimization of desired molecular properties *e.g.* with respect to possible binding of guest-molecules.

Although we have used the convergent method for the construction of dendrimers, the coupling results and purity of the dendrimers have convinced us that these dendrimers will also be accessible by the divergent method using solid-phase synthesis, which is under present investigation.

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7. **7 (MeO2C-[G5]-(Boc)32):** R_f= 0.39 (eluent: DCM/MeOH, 9/1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 288H, $C(CH_3)_3$), 3.40 (bs, 64H, $CH_2N''''H$), 3.65 (bs, 60H, CH_2NH, $C'H_2NH$, $C''H_2NH$, $C'''H_2NH$), 3.87 (bs, 124H, OCH_2, $OC'H_2$, $OC''H_2$, $OC'''H_2$, $OC''''H_2$), 5.41 (bs, 32H, $N''''H$), 6.32, 6.40 (bs(twice), 31H, Ph-$C^{4,4',4'',4''',4''''}$H), 6.81, 6.89 (bs(twice), 62H, Ph-$C^{2,6,2',6',2'',6'',2''',6''',2'''',6''''}$H), 7.68 (bs, 30H, NH, N'H, N''H, NH'''); ^{13}C NMR (75.5 MHz, CD_3OD) δ 27.9 ($C(\underline{C}H_3)_3$), 40.0 (CH_2NH, $C'H_2NH$, $C''H_2NH$, $C'''H_2NH$, $C''''H_2NH$), 52.0 (OCH_3), 66.7, 67.3 (OCH_2, $OC'H_2$, $OC''H_2$, $OC'''H_2$, $OC''''H_2$), 79.3 ($\underline{C}(CH_3)_3$), 104.9, 106.3 (Ph-$C^{2,6,2',6',2'',6'',2''',6''',2'''',6''''}$, Ph-$C^{4,4',4'',4''',4''''}$), 132.0 (Ph-$C^{1}$), 136.4 (Ph-$C^{1',1'',1''',1''''}$), 157.3 ($N''''HC{=}O$), 160.2 (Ph-$C^{3,5,3',5',3'',5'',3''',5''',3'''',5''''}$), 167.1 ($CO_2Me$), 168.8 (NHC=O, N'HC=O, N''HC=O, N'''HC=O). C^4H: denotes a proton of a first generation; $C^{4'}$H: denotes a proton of a second generation etc. ; $C^{4',4'',4''',4''''}$: carbon signals from the second to the fifth generation.
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