Convergent Synthesis of $1 \rightarrow 3$ C-Branched Polyamide Dendrons

Michael Brettreich and Andreas Hirsch*

Institut für Organische Chemie der Universität Erlangen-Nürnberg, Henkestr. 42, D-91054 Erlangen, Germany Fax: +49 9131 8526864; e-mail: hirsch@organik.uni-erlangen.de

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Abstract: A convergent synthesis of $1 \rightarrow 3$ *C*-branched polyamide dendrons was developed providing a facile access to defined monodisperse dendritic building blocks.

Dendrons are increasingly used as versatile building blocks in organic chemistry in order to design stereochemically defined macromolecules with attractive solubility-, polarity-, amphiphilic-, molecular aggregation-, biological activity-, reactivity-, catalytical- and photochemical properties¹. Among the various types of dendritic building blocks $1 \rightarrow 3$ *C*-branched polyamide dendrimers, developed by Newkome et al.² are of interest due to their high branching multiplicity and bulkiness as well as the hydrophilicity of their corresponding unprotected polyacids. So far, only divergent syntheses involving the problem of incomplete transformation³ of the multiple termini have been applied for these dendrimers bearing cores like adamantane², anthraquinone derivatives⁴, metal complexes⁵, porphyrines and cyclophanes⁶.

In a project aimed at the synthesis of dendrimers involving C_{60} as a very versatile structure determining core^{7,8} we became interested in the development of water soluble and superamphiphilic dendrimers containing Newkome type $1 \rightarrow 3$ *C*-branched polyamide dendrons as hydrophilic moieties. For this purpose it is desirable to have a series of defined dendrons in hand and to elaborate a convergent synthesis of dendrons like **1** which can easily be attached to the fullerene core either after the introduction of a functional group allowing for a direct coupling with C_{60} or *via* coupling to suitable precursor adducts.

The convergent synthesis of **1** (Scheme 1) is based on the use of the nitro tricarboxylic acid **2** and the amino tricarboxylate **3** as starting materials^{2,9}. At the same time **2** was employed as the trifunctional coupling component in each branching step. For the synthesis of the second generation dendrons **4** and **5** the two components were subjected to a standard amide formation procedure using 1-hydroxy-benzotriazole [HOBT] and dicyclohexylcarbodiimide [DCC] in DMF as condensing agents. Triscarboxamide **4** was isolated in 71 % yield after flash chromatography on silica gel. The reduction of the nitro group in **4** was achieved with hydrogenation using Raney-nickel as catalyst affording the 2nd generation amine **5** in 90 % yield. After a second cycle using the same procedures for the coupling reaction the 3rd generation nitro compound **6** was obtained in 21 % yield after flash chromatography on silica gel. Finally, hydrogenation of **6** afforded the dendritic 3rd generation amine **1** in 75 % yield.¹⁰

With the development of the 2nd and 3rd generation amines **1** and **6** we provided building blocks susceptible to a variety of subsequent coupling reactions. The attachment to various central cores should be straightforward for example if they contain carboxylic acid functionalities (e.g. *via* peptide-coupling) or any other functionality that readily reacts with primary amines. We have already published a successful coupling of the 2nd generation amine to C₆₀ as a core molecule (see ref. ⁸).

The newly synthesized compounds were fully characterized by IR- and NMR-spectroscopy, by FAB-mass spectrometry as well as by elemental analysis (experimental datails and spectroscopic data are given in ref.¹⁰).

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References and Footnotes

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- (10) 9-Cascade:nitromethane[3]:(2-aza-3-oxopentylidyne):propionicacid-tert-butylester 4: A solution of 160 mg (0.58 mmol) 4-nitro-4-[2-(carboxyethyl)]heptanediacid 2, 800 mg (1.93 mmol) 4-amino-4-[2-(tert-butoxycarbonyl)ethyl)]-heptanedioate 3, 234 mg (1.73 mmol) HOBT and 357 mg (1.73 mmol) DCC in 15 ml DMF was stirred for 48 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuum. The residue was disolved in 25 ml ethyl acetate and this solution was washed with 10% HCl, water, saturated aqueous NaHCO₃ and brine solutions. After drying the organic phase over MgSO₄ and concentration in vacuum the product was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate 2:1) to give 605 mg (71 %) of **4**. ¹H-NMR (400 MHz, CDCl₂, 25 °C): δ [ppm] = 1.44 (s, H-10, 81 H), 1.95 (m, H-6, 18 H), 2.11 (m, H-2 and H-3, 12 H), 2.20 (m, H-7, 18 H), 6.23 (s, NH, 3 H); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ[ppm] = 28.10 (C-10), 29.82, 29.93, 31.32 and 31.35 (C-2, C-3, C-6, C-7), 57.64 (C-5), 80.72 (C-9), 92.56 (C-1), 170.57 (C-4), 172.82 (C-8); FAB-MS: m/z = 1470 (M⁺; calc. for ${}^{13}C^{12}C_{75}H_{132}N_4O_{23}$: 1470); IR(KBr): v (cm⁻¹) = 3367, 2979, 2936, 1731, 1683, 1665, 1538, 1456, 1368, 1317, 1255, 1155, 953, 848, 757. Anal. calc. for C76H132N4O23.0.5 C₆H₁₂ (1512.0): C 62.76, H 9.20, N 3.71; found: C 62.39, H 9.60, N 3.61.

9-Cascade:aminomethane[3]:(2-aza-3-oxopentylidyne):propanoicacid-*tert*-butylester **5**: To a solution of 163 mg (0.11 mmol)



Scheme 1

4 in 15 ml dry ethanol 150 mg Raney-nickel [Aldrich] were added and hydrogenated under normal pressure and room temperature for 24 hours. After filtering the solution on celite and removing the solvent the product was purified by flash chromatography on silica gel using first cyclohexane:ethyl acetate 1:2 and then cyclohexane:ethyl acetate: methanol 1:2:1 as eluent to give 143 mg (90 %) of **5**. ¹H-NMR (400 MHz, CDCl₃, 25 °C) [ppm]: δ = 1.43 (s, H-10, 81 H), 1.61 (m, H-1, 6 H), 1.95 (m, H-6, 18 H), 2.17 (m, H-3, 6 H), 2.21 (m, H-7, 18 H), 6.04 (s, NH, 3 H); ¹³C-NMR $\begin{array}{l} (100 \ MHz, \ CDCl_3, \ 25 \ ^{\circ}C) \ [ppm]: \\ \delta = 27.98 \ (C-10), \ 29.70, \ 29.79, \\ 31.45 \ and \ 35.02 \ (C-2, \ C-3, \ C-6, \ C-7), \ 52.68 \ (C-5), \ 57.29 \ (C-1), \\ 80.45 \ (C-9), \ 172.35 \ (C-4), \ 172.64 \ (C-8); \ FAB-MS: \ m/z \ = \ 1440 \\ (M^+; \ calc. \ for \ ^{13}C^{12}C_{75}H_{134}N_4O_{21}: \ 1440); \ IR(KBr): \nu \ (cm^{-1}) \ = \\ 3359, \ 2978, \ 2935, \ 1731, \ 1680. \ 1655, \ 1542, \ 1457, \ 1420, \ 1392, \\ 1368, \ 1317, \ 1255, \ 1154, \ 1102, \ 1037, \ 954, \ 848, \ 758, \ 590; \ Anal. \\ calc. \ for \ C_{76}H_{134}N_4O_{21}. \ EtOH \ (1486.0): \ C \ 63.05, \ H \ 9.50, \ N \ 3.77; \\ found: C \ 63.11, \ H \ 9.87, \ N \ 3.71. \end{array}$

27-Cascade:nitromethane[3]:(2-aza-3-oxopentylidyne)²:propanoicacid-tert-butylester 6: The third generation nitro compound 6 was prepared in yield 21 % using the same procedure applied for the synthesis of 4. However, instead of DMF, THF was used as solvent. The purification was achieved by flash chromatography (silica gel; cyclohexane:ethyl acetate = 3:2.). ¹H-NMR (400 MHz, $CDCl_3, 25 \text{ °C})$ [ppm]: $\delta = 1.43$ (s, H-14, 243 H), 1.95 (m, H-6, H-10, 72 H), 2.15 (m, H-2, H-3, 12 H), 2.19 (m, H-7, H-11, 72 H), 6.35 (s, NH, 9 H), 7.04 (s. NH, 3 H); ¹³C-NMR (100 MHz, CDCl₃, 25 °C) [ppm]: δ = 28.14 (C-14), 29.80, 31.11, 31.22 (C-2, C-3, C-6, C-7, C-10, C11), 57.38 (C-9), 57.97 (C-5), 80.42 (C-13), 92.97 (C-1), 171.06 (C-4), 172.65 (C-12), 172.69 (C-8); FAB-MS: m/z = 4674 ([M+Cs]⁺; calc. for ${}^{13}C_2{}^{12}C_{236}H_{411}N_{13}$ O₆₈Cs: 4675); IR(KBr): v (cm⁻¹) = 3376, 2980, 2934, 1735, 1681, 1656, 1539, 1457, 1393, 1368, 1319, 1256, 1213, 1166, 1147, 1102, 956, 848, 758; Anal. calc. for $C_{238}H_{411}N_{13}O_{68}C_6H_{12}$ (4627.1): C 63.34, H 9.21, N 3.94; found: C 62.95, H 9.64, N 3.82.

27-Cascade:aminomethane[3]:(2-aza-3-oxopentylidyne)²:propanoicacid-tert-butylester 1: The third generation dendron 1 was synthesized in 75 % yield analoguously to 6 by reduction with hydrogen. ¹H-NMR (400 MHz, CDCl₃, 25 °C) [ppm]: δ = 1.43 (s, H-14, 81 H), 1.59 (m, H-2, 6 H), 1.94 (m, C-6, C-10, 72 H), 2.14 (m, H-3, 6 H), 2.19 (m, H-7, H-11, 72 H), 6.24 (s, NH, 9H), 6.91 (s, NH, 3 H); ¹³C-NMR (100 MHz, CDCl₃, 25 °C) [ppm]: δ = 28.01 (C-14), 29.72, 31.22, 31.47, 35.24 (C-2, C-3, C-6, C-7, C10, C-11), 52.98 (C-1), 57.29 (C-9), 57.71 (C-5), 80.31 (C-13), 172.64 (C-8, C-12), 173.25 (C-4); FAB-MS: m/z = 4513 (M⁺; calc. for ${}^{13}C_2{}^{12}C_{236}H_{413}N_{13}O_{66}$: 4512), 4535 ([M+Na]⁺); IR(KBr): v (cm⁻¹) =3437, 3378, 3327, 2979, 2935, 1736, 1681, 1652, 1540, 1457, 1421, 1392, 1368, 1316, 1255, 1215, 1155, 1103, 1035, 955, 921, 848, 758, 592, 758, 592, 465, 433; Anal. calc. for $C_{238}H_{413}N_{13}O_{66}$.2 EtOH (4605.1): C 63.12, H 9.30, N 3.95; found: C 62.95, H 9.64, N 3.82.