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Synthesis of novel dendrimers incorporating a dye into the core

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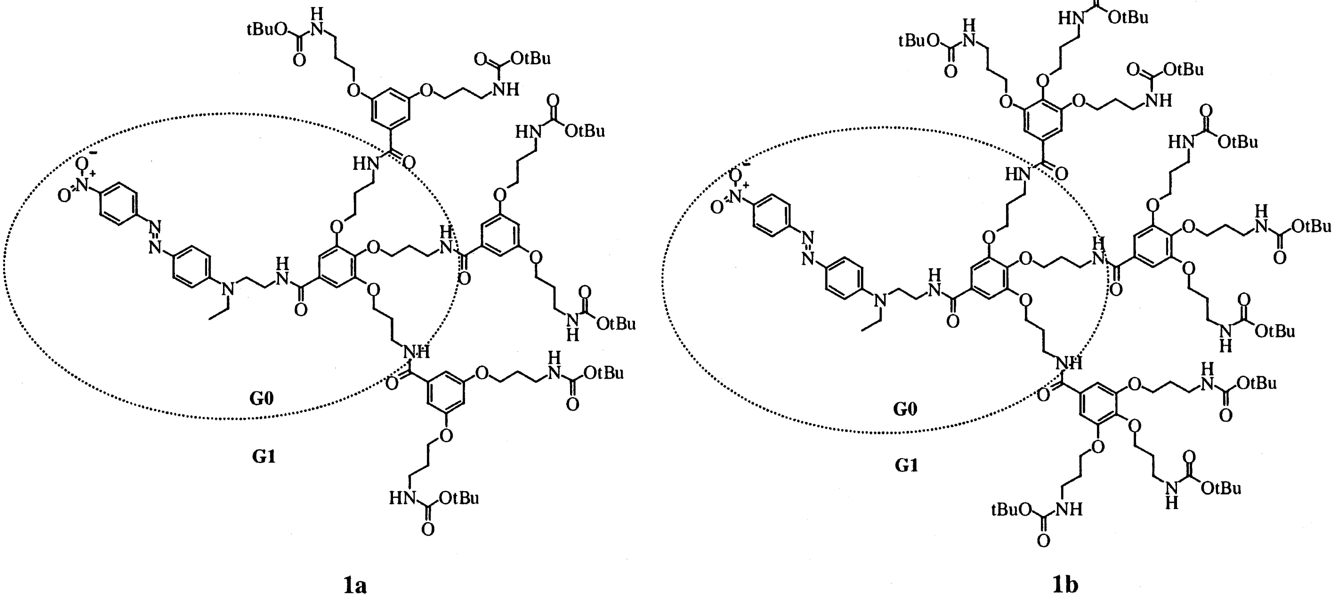
Abstract—Dendrimers **1a** and **1b**, with six and nine terminal *tert*-butyloxycarbonyl (*t*-Boc) protected amine groups, respectively, have been prepared by an efficient divergent synthetic approach. These novel dendrimers contain a dye Red-1 incorporated into the core, which adds to them, in addition to their physicochemical properties proper to dendrimers, an additional one that is the visibility perceptible to human eyes. This new property was particularly interesting in relation to our research of new carriers for active entities and/or antibodies. © 2001 Elsevier Science Ltd. All rights reserved.

Dendrimers are highly branched, globular, monodispersed macromolecules.[1] They comprise a core, branching units, and a large number of terminal groups. Unlike most synthetic linear macromolecules, dendrimers are believed to be essentially free of chain entanglement, and they possibly adopt defined morphologies which are known to influence the basic physical and chemical properties in solution, such as self-assembly,[2] liquid crystallinity,[3] intramolecular singlet energy transduction,[4] biological recognition,[5] and encapsulation.[6] Many possible and important applications of dendrimers have been postulated, including catalysis,[7] anion binding, biomimetics and, in particular, drug delivery offered by their usable 'surface' and their transport possibilities.[8] In relation to our research activities, we developed an efficient divergent synthetic route to the generation-1 (G1) dendrimers **1a** and **1b** (Fig. 1), which include dye Red-1 in the core and six and nine *t*-Boc-protected primary amines, respectively. The fact that the dye Red-1 was incorporated into the



1a

1b

Figure 1.

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dendrimer confers to them a particularity, which is the visibility perceptible to human eyes compared to most dendrimers. This new additional property, together with the chemically functionalizable terminal *t*-Boc-protected primary amines, make them interesting targets in our research of new carriers for, e.g. active entities and/or antibodies.

We would like to report here the synthesis of **1a** and **1b** starting from the readily available dye Red-1. Transformation of the primary alcohol of Red-1 to its amino analog **3** was carried out in three steps (Scheme 1). Mesylation of Red-1, performed quantitatively in the presence of TEA in CH_2Cl_2, was followed by substitution with sodium azide in DMSO at 50°C, to give azide derivative **2** in 95% yield. The azide group was then reduced quantitatively to the desired amino compound **3** with triphenylphosphine in THF in the presence of 1.1 equiv. of H_2O.

The two benzoic acid branching units possessing three and two *tert*-butyloxycarbonyl aminopropyloxy side chains, respectively, were prepared from 3-bromopropylamine hydrobromide, methyl gallate and methyl 3,5-dihydroxybenzoate (Scheme 2). The bromopropylamine hydrobromide **4** was protected as *t*-Boc derivative **5** with $(Boc)_2O$ in CH_2Cl_2 in the presence of TEA in 95% yield. A PTBD resin (1,5,7-triazabicyclo-[4,4,0]dec-5-ene bound to polystyrene with 2% DVB)[9] was used as base in acetonitrile for the alkylation of **6** and **7** with **5**, to afford the tri- and bi-branched derivatives **8** and **9**, respectively, in good yields. Their corresponding acids **10** and **11** were then obtained under normal saponification conditions.

The coupling of amine **3** with acid **10** was performed with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) at 50°C in acetonitrile in the presence of diisopropylethylamine (DIEA) for 12 h (Scheme 3). At the end of the reaction, the mixture was heated to 80°C to get a homogeneous solution, and after cooling to room temperature, the generation-zero (G0) dendrimer **12** was obtained in 84% yield as a red solid.[10] The deprotection of the three *t*-Boc protecting groups was carried out easily with gaseous HCl in EtOAc at 0°C for 1 h. The amine intermediate **13** was allowed to react with acids **11** and **10**, respectively, under the same conditions as in the previous coupling reaction. The G1 dendrimer **1a**, which did not precipitate after cooling the solution to room temperature, was obtained after purification by chromatography on silica gel as red solid (75%), while the G1 dendrimer **1b** was obtained as a red solid by crystallization in EtOAc. All of the compounds gave satisfactory analysis spectra (^{1}H NMR, MS and IR).[11]

In conclusion, we have developed a divergent synthetic route for the efficient preparation of two novel dendrimers (**1a** and **1b**). Incorporation of the dye Red 1 into the core confers to these dendrimers the visibility perceptible to human eyes, and the six or nine terminal *t*-Boc-protected amine groups provide the possibility for further chemical elaboration: for example, attachments of active molecules, antibodies, etc. We are currently studying their potential uses in the pharmaceutical domain and the results will be communicated in the future.

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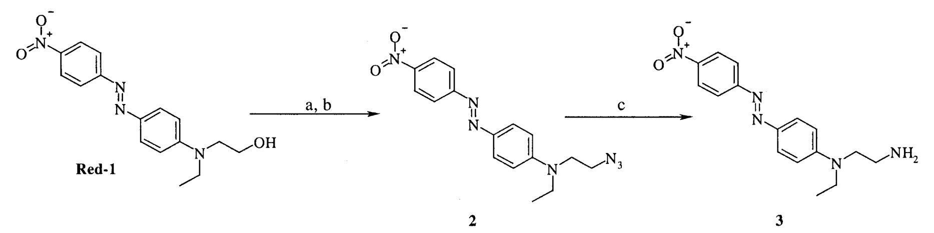
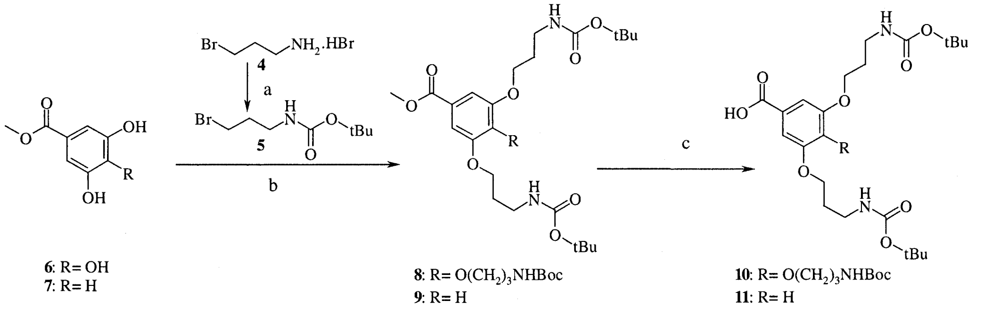
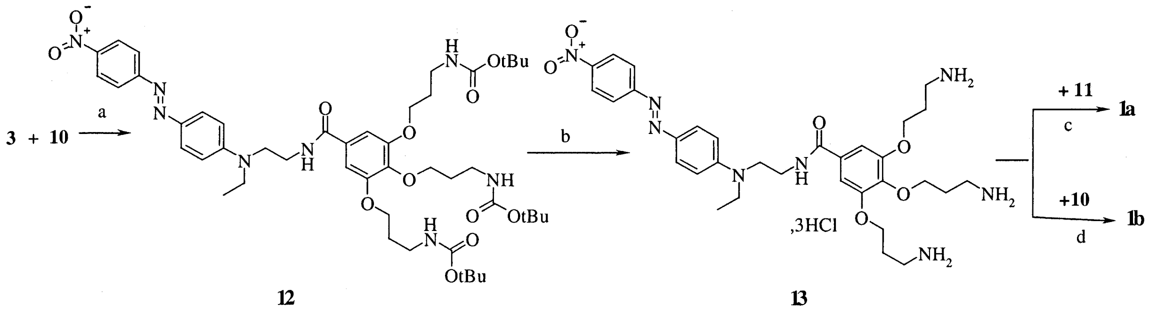


Scheme 1. *Reagents and conditions*: (a) MsCl, TEA, CH_2Cl_2, rt, 100%; (b) NaN_3, DMSO, 50°C, 95%; (c) PPh_3, THF–H_2O, 100%.



Scheme 2. *Reagents and conditions*: (a) $(Boc)_2O$, TEA, CH_2Cl_2, rt, 95%; (b) PTDB resin, CH_3CN, 50°C, 80%; (c) NaOH (2N), EtOH, 100%.



Scheme 3. *Reagents and conditions*: (a) BOP, DIEA, CH_3CN, 50°C, 84%; (b) HCl, EtOAc, 0°C, 100%; (c) **11**, BOP, DIEA, CH_3CN, 50°C, 75% (d) **10**, BOP, DIEA, CH_3CN, 50°C, 85%.

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10. General coupling procedure—an example of the preparation of G0 dendrimer **12**: To a solution of CH_3CN (80 ml), under nitrogen, at room temperature, was added successively 0.5 g (1.6 mmol) of amine **3**, 1.23 g (1.92 mmol) of acid **10**, 0.85 g (1.92 mmol) of BOP and 0.833 ml (4.8 mmol) of diisopropylethylamine, and the mixture was heated at 50°C for 12 h. At the end of the reaction, a red suspension was obtained, which was further heated at 80°C in order to obtain an homogeneous solution. After cooling to room temperature, a red solid was obtained, which was filtered, washed with Et_2O, and dried under vacuum to afford 1.28 g of **12** (84%). Data of **12**: $R_f=0.55$ (eluent: CH_2Cl_2/MeOH, 9/1, v/v); ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, $J=7$ Hz, 3H), 1.43 (s, 27H), 1.97 (m, 6H), 3.38 (m, 6H), 3.56 (q, $J=7$ Hz, 2H), 3.71 (br s, 4H), 4.05 (m, 6H), 5.04 (br s, 2H), 5.31 (br s, 1H), 6.71 (br s, 1H), 7.00 (s, 2H), 6.88 (app.d, $J=9$ Hz, 2H), 7.91 (app.d, $J=9$ Hz, 2H), 7.93 (app.d, $J=9$ Hz, 2H), 8.32 (app.d, $J=9$ Hz, 2H); MS (ESI): $[M+H]^+=937^+$, $[M+Na]^+=959^+$; IR ($CHCl_3$): 3453, 1706, 1659, 1601, 1588, 1559, 1516, 1493 cm^{-1}.
11. Data of **1a**: $R_f=0.50$ (eluent: CH_2Cl_2/MeOH, 9/1, v/v); ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, $J=7$ Hz, 3H), 1.42 (s, 54H), 1.70–1.0 (m, 18H), 3.14–3.25 (m, 18H), 3.53 (m, 2H), 3.64 (br s, 4H), 3.77–3.94 (m, 18H), 4.91–5.09 (br s, 10H), 6.49 (br s, 3H), 6.89 (br s, 6H), 7.04 (s, 2H), 6.87 (app.d, $J=9$ Hz, 2H), 7.87 (app.d, $J=9$ Hz, 2H), 7.89 (app.d, $J=9$ Hz, 2H), 8.29 (app.d, $J=9$ Hz, 2H); MS (LSIMS): $[M+H]^+=1988.4^+$; IR ($CHCl_3$): 3448, 1708, 1653, 1595, 1515 cm^{-1}. Data of **1b**: $R_f=0.58$ (eluent: CH_2Cl_2/MeOH, 8/2, v/v); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J=7$ Hz, 3H), 1.42 (s, 81H), 1.75–2.10 (m, 24H), 3.56 (m, 2H), 3.10–3.80 (m, 28H), 4.05 (m, 24H), 5.20–5.40 (br s, 10H), 6.88 (app.d, $J=9$ Hz, 2H), 7.87 (app.d, $J=9$ Hz, 4H), 7.08(s, 2H), 7.06 (s, 4H), 6.97 (s, 2H), 8.29 (app.d, $J=9$ Hz, 2H); MS (LSIMS): $[M+H]^+=2508.9^+$, $[M+K]^+=2547.9^+$; IR ($CHCl_3$): 3452, 1701, 1653, 1600, 1587, 1514, 1498 cm^{-1}.