Two-step Approach towards the Accelerated Synthesis of Dendritic Macromolecules

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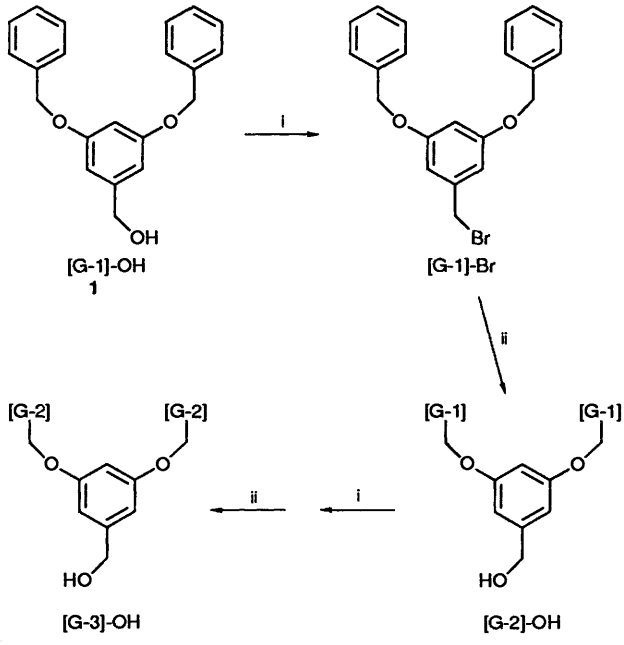
The accelerated synthesis of regular dendritic poly(ether-urethane) macromolecules through growth of two generations in a single synthetic operation has been explored. This procedure requires the use of two AB_2 monomers such as 3,5-diisocyanatobenzyl chloride and 3,5-dihydroxybenzyl alcohol that can react pairwise in a one-pot sequential addition procedure. The two monomers are added stepwise to a previously formed first-generation dendrimer to produce a third-generation dendritic molecule without any need for intermediate purification or activation procedures. When 3,5-dihydroxybenzyl alcohol is used as the second monomer, some irregular growth is seen due to the occurrence of a side reaction involving transesterification of the carbamic ester moiety. The side reaction can be avoided if 3,5-dihydroxybenzyl alcohol is replaced by methyl 3,5-dihydroxybenzoate.

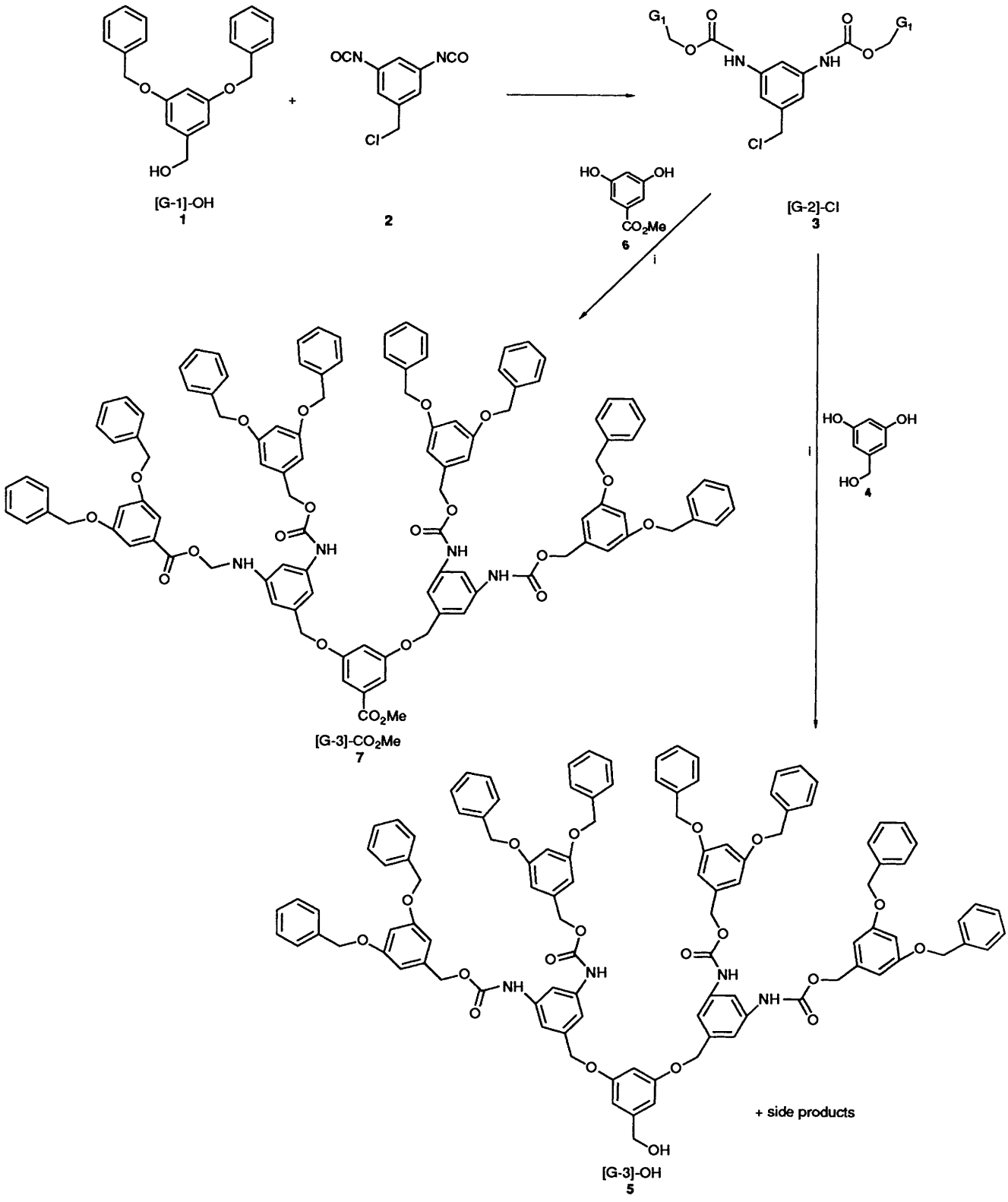
Since their first introduction in 1985,[1,2] regular dendritic macromolecules have been synthesized by either a convergent[3-7] or a divergent[1,2,8] procedure. In the stepwise synthesis of regular dendrimers each generation growth usually involves a sequence of steps such as activation of reactive groups, purification, coupling to a monomer, and finally a second purification in order to isolate the next higher generation. This method is tedious, but also powerful since, with the proper choice of chemistry, very unique macromolecular architectures can be prepared.[3,9] An additional way of preparing hyperbranched, dendritic-like macromolecules is *via* the one-pot polymerization of an AB_x monomer.[10-14] Although this method does not afford regular dendritic macromolecules, it is attractive as large quantities of high molecular weight polymers[14] with properties resembling those of their regular analogues can be prepared in a short period of time. However, the polymerization of AB_x monomers does not allow the unique control over molecular architecture that is provided by the stepwise convergent-growth approach.[3c,d] In order fully to explore and utilize the unique properties of regular dendritic macromolecules a more rapid method for their synthesis must be developed. This report focuses on a first synthetic strategy for the accelerated preparation of regular dendritic macromolecules.

Our approach to the accelerated synthesis of regular dendritic macromolecules is based on the concept that, with the proper choice of monomers, it should be possible to grow two generations in one synthetic operation without any intermediate purification or activation procedure. Hence, our target is the one-pot preparation of a third-generation dendrimer directly from the first-generation material with only a single purification step in comparison to the four purification and two activation steps required for the conventional growth of two generations shown in Scheme 1. This initial accelerated growth strategy requires the preparation of two monomers with four different functional groups that can only react pairwise as a result of their addition in sequential fashion. Furthermore, all the reactions must be free of side reactions and the functional groups formed during the reaction must be stable to the overall reaction conditions. Two reactions that appear to meet these criteria are the Williamson ether synthesis involving reaction of a phenolate with a benzylic halide, and the formation of a urethane from an isocyanate and an alcohol. These two reactions seem promising, as we have previously used the Williamson ether synthesis to prepare dendritic phenyl benzyl ethers either by the convergent route[3] or by the one-pot



Scheme 1 *Reagents:* i, CBr_4, PPh_3; ii, 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6

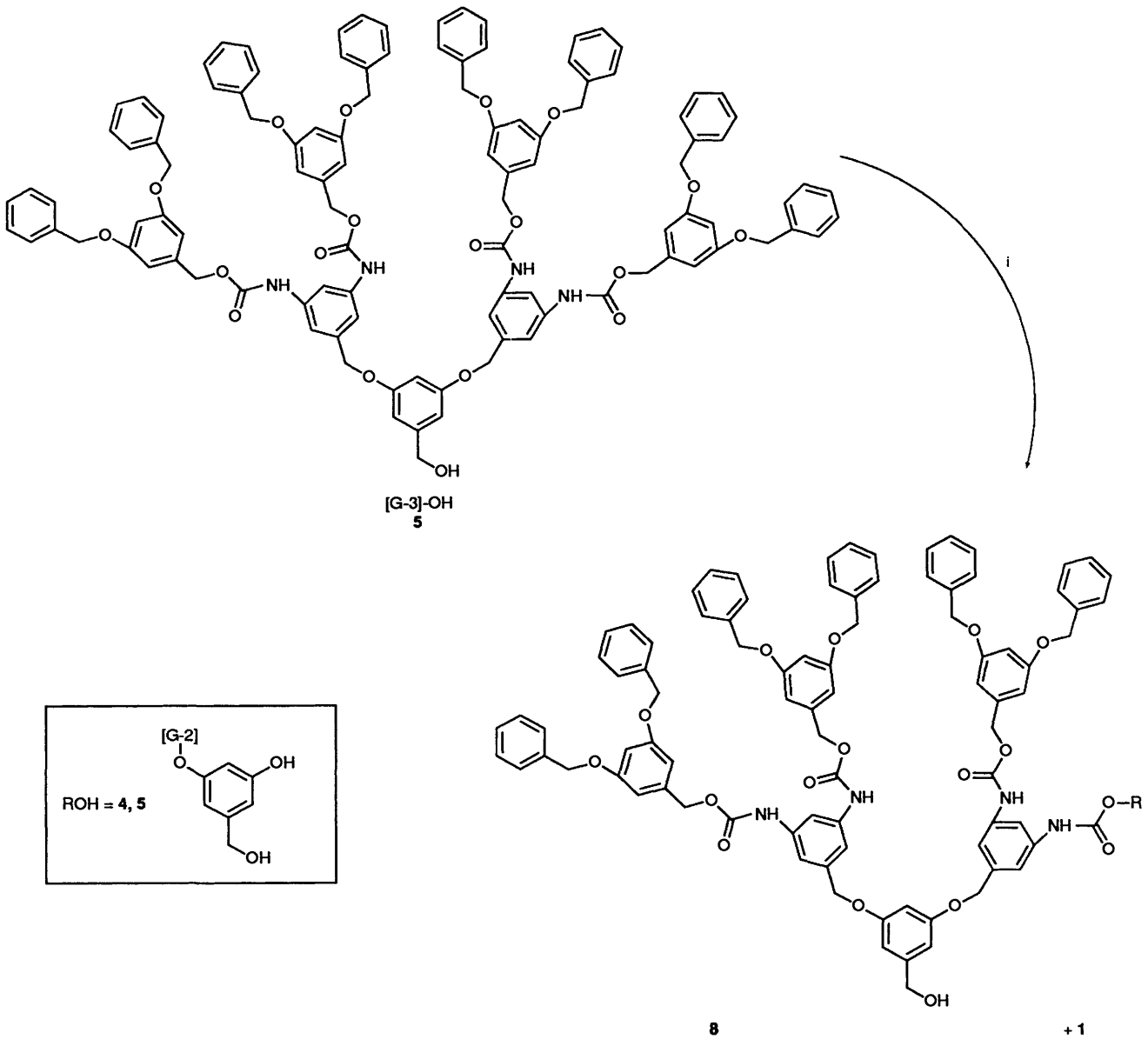
polymerization of an AB_2 monomer.[10a] Also, the reaction of diisocyanates with diols has been widely used by polymer chemists to form polyurethanes. The reaction is advantageous in the preparation of high molecular weight materials as it proceeds rapidly, with no release of by-products, and with few side reactions if the proper conditions are chosen.[15] Scheme 2 outlines our one-pot multistep approach. In the first step preformed first-generation alcohol [G-1]–OH **1**, is allowed to react with 3,5-diisocyanatobenzyl chloride, **2**, to form the second-generation biscarbamate [G-2]–Cl **3** with a benzylic chloride group at its focal point. Without any purification of this intermediate product, 3,5-dihydroxybenzyl alcohol **4** is added to the same reaction flask along with the reagents that are necessary for the Williamson ether synthesis to afford compound **5**, the third-generation alcohol, [G-3]–OH. In principle, the procedure could be used to transform any low-generation dendrimer to the corresponding dendritic molecule two generations higher.



Scheme 2 *Reagents:* i, Cs_2CO_3, KI, 18-crown-6

Results and Discussion

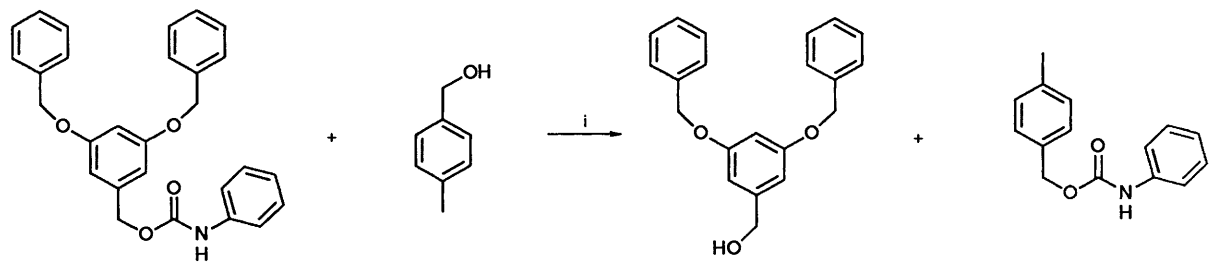
The preparation[16] of monomer **2** in 22% yield has been reported by the direct reaction of phosgene with 3,5-diaminobenzyl alcohol, the rest of the starting material being consumed to afford a polyurethane. Our first attempt at the phosgenation of the hydrochloride salt of 3,5-diaminobenzyl alcohol gave compound **2** in 33% yield. This reaction, carried out in a heterogeneous medium, affords the desired product in solution while a major by-product remains in the solid phase. This by-product is thought to be a crosslinked polyurethane as it is insoluble in both organic and aqueous solvents. Sayigh and Ulrich have reported[17] that the addition of a catalytic amount of dimethylformamide (DMF) during the synthesis of isocyanates greatly improved the yield and reduced the amount of



Scheme 3 *Reagent:* i, ROH

phosgene that is required. Therefore, the yield of compound **2** was increased to 50–60% by the addition of 10 mol% DMF to the reaction mixture, and, in contrast to the uncatalysed reaction, some unchanged 3,5-diaminobenzyl alcohol dihydrochloride salt (20–30%) was recovered and it was reused in subsequent reactions. The proposed catalytic species for this reaction is chlorodimethylforminium chloride which activates phosgene for the subsequent reaction with an aromatic amine.[18] Monomer **4** and the first-generation dendrimer **1** were prepared as described in the literature.[3]

The first synthetic step for the one-pot conversion of first-generation dendrimer [G-1]–OH into third-generation [G-3]–OH is the formation of the intermediate, second-generation chloride [G-2]–Cl, **3**. Monomer **2** was allowed to react with a slight excess of compound **1** to ensure that no free isocyanate moieties remained after reaction. [G-2]–Cl formed cleanly with no visible by-products as confirmed by TLC, FTIR, ^{1}H NMR, and size-exclusion chromatography. The next step in the one-pot sequence is the *O*-alkylation of the phenolic groups of compound **4** with [G-2]–Cl. A number of parameters were optimized during the study of this reaction including the choice of solvent [acetone, tetrahydrofuran (THF) and DMF], base (Cs_2CO_3 and K_2CO_3), halide-exchange agents (R_4NI, KBr and KI), phase-transfer agent (18-crown-6) and temperature (room temperature to 67 °C). The best conditions, both in terms of limiting the occurrence of side reactions during etherification and reducing the time required for the reaction, involved the use of Cs_2CO_3, KI, 18-crown-6 and THF at reflux. Typically the reaction was over in approximately six hours. As the product is amorphous and cannot be isolated by crystallization, flash chromatography was used to remove the small excess of first- and second-generation materials [G-1]–OH and [G-2]–Cl. However, even after removal of the starting material, chromatographic analysis showed that the product was still impure, slightly contaminated by impurities with very similar R_f-values that could not be separated cleanly. The amount of impurity was initially small but it was shown to increase with the reaction time. For example, a long reaction time of 24 h led to a product that showed a multiplicity of by-products in addition to the desired major product, [G-3]–OH, when examined by chromatography. Additional examination of the crude product by ^{1}H NMR spectroscopy showed a number of unassignable resonances in the benzyl proton region of the spectrum in addition to the predominant resonances of the desired product [G-3]–OH.



9 10 1 11

Scheme 4 *Reagents:* i, Cs_2CO_3, THF

In order to achieve the preparation of a pure, third-generation dendrimer by this accelerated route, it is necessary to understand the origin of the side reactions to minimize their occurrence. Previous work[3] having shown that the ether bond is stable to reaction conditions[3] similar to those used in this work, it was suspected that the less stable urethane linkage, rather than the ether linkage, was at the origin of the side reactions. One possible pathway, shown in Scheme 3, involves the transesterification of one of the carbamic acid ester groups of compound **5** with the benzyl alcohol moieties that are found in compound **5** itself as well as in unchanged monomer **4**, or even in the intermediate ether initially obtained by monoalkylation of triol **4** with chloride **3**. All of these transesterifications would liberate [G-1]–OH and produce undesired side products such as compound **8** that are difficult to separate from substrate **5**. Of course, excess of [G-1]–OH may also undergo the same transesterification, but this reaction would produce no net change. The transesterification of carbamates has been well documented,[19] and the reaction is known to be catalysed by both acids and bases.

The stability of the carbamate linkage to the reaction conditions was probed using the model reaction outlined in Scheme 4. After heating of a mixture of a first-generation carbamate **9** with caesium carbonate and *p*-methylbenzyl alcohol **10** for 22 h at reflux temperature, the exchange products, *p*-methylbenzyl *N*-phenylcarbamate **11** and [G-1]–OH together with the starting materials were observed both by chromatography and by ^{1}H NMR spectroscopy. In the absence of *p*-methylbenzyl alcohol no reaction took place. This model reaction confirms that transesterification is indeed a possible pathway for the formation of the side products shown in Scheme 3. As tin compounds are known to catalyse the transesterification of carboxylic acid esters,[20] dibutyltin dilaurate was replaced with 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst used in the formation of dendritic urethane [G-2]–Cl. This replacement did not have any effect on the purity of the final product, suggesting that the side reactions that occur in this sequential procedure are dominated by the base-catalysed transesterification of the carbamate linkage occurring during the second-stage etherification.

Since a free alcohol moiety is required for the exchange reaction to take place, an alternative procedure involving methyl 3,5-dihydroxybenzoate **6** instead of the alcohol **4** was investigated. This alternative procedure proved satisfactory, as the third-generation dendrimer [G-3]–CO_2Me **7** was obtained free of side products by reaction of the alcohol **1** with chloride **2**, then ester **6**, followed by rapid purification by flash chromatography. The structure of the third-generation dendrimer [G-3]–CO_2Me was easily confirmed by ^{1}H NMR spectroscopy since, in this case, the assignments are simplified by the distinct chemical shift of the three different 1,3,5-substituted aromatic rings and the three signals of the different benzyl groups (Fig. 1).

While [G-3]–CO_2Me itself **7** or its trichloroethyl ester

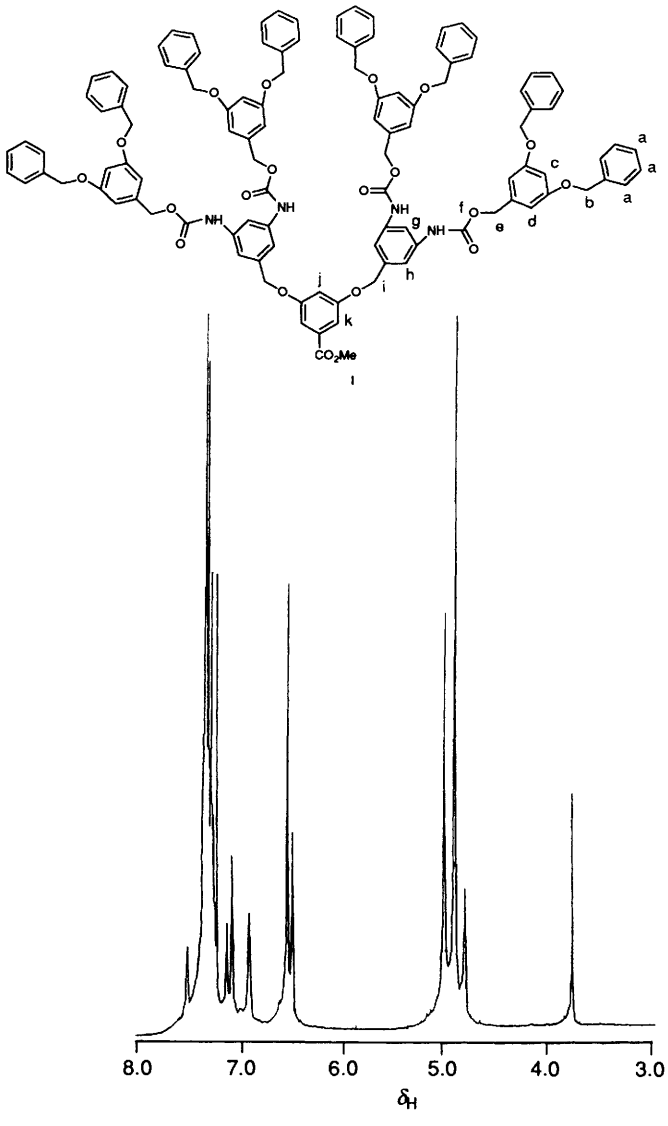


Fig. 1 ^{1}H NMR spectrum of third-generation dendrimer **7**

analogue are useful in the elaboration of higher dendrimers with ester linkages,[21] its conversion into the third-generation alcohol **5**, which could be used again in a similar reaction scheme to afford a fifth-generation urethane-ether dendrimer, was explored. This transformation was found to be difficult, as a strong reducing agent, such as lithium aluminium hydride, reduced both the ester and the carbamate, while a weaker reducing agent, such as $LiBH_4$–methanol,[22] was able only partially to reduce the dendrimer **7** (~30% conversion). Alternative procedures to obtain compound **5** might involve the replacement of ester **6** by 3,5-dihydroxybenzaldehyde which we

have used previously[3d] in the preparation of other dendritic macromolecules containing groups sensitive to strong reducing agents, or protection of the benzyl group of the triol **4** with a readily removed moiety such as a *tert*-butyldimethylsilyl or a *tert*-butyldiphenylsilyl ether. Both of these pathways would prevent the transesterification that is responsible for the formation of side products.

Conclusions.—The concept of accelerated dendrimer synthesis through a multistep one-pot approach has been demonstrated using two different AB_2 monomers, such as 3,5-diisocyanatobenzyl chloride and methyl 3,5-dihydroxybenzoate, that contain reactive groups capable of pairwise reaction. This approach reduces the large number of purification steps that are required for the synthesis of regular, narrow polydispersity dendritic molecules. The choice of monomers is critical, as undesired side reactions must be avoided in order to preserve the structural regularity of the final dendrimers. We are currently testing a second accelerated approach to regular dendritic macromolecules through the use of dendritic macromonomers.

Experimental

IR spectra were recorded on a Nicolet IR/44 spectrometer as thin films on KBr plates. ^{1}H NMR spectra were recorded with $CDCl_3$ solutions on a Bruker WM 300 (300 MHz) spectrometer using the residual proton signal as an internal standard. THF was distilled from sodium benzophenone ketyl. DMF was distilled from CaH_2 with the middle fraction being collected. Methanol was distilled and stored over activated 4 Å molecular sieves. K_2CO_3 and Cs_2CO_3 were dried at 125 °C for 24 h in the presence of P_2O_5. [G-1]–OH **1** and 3,5-dihydroxybenzyl alcohol **4** were prepared as described previously.[3] For the ^{1}H NMR assignments of [G-3]–CO_2Me **7** and [G-3]–OH see Fig. 1.

Preparation of 3,5-*Diaminobenzyl Alcohol Dihydrochloride.*—A Parr pressure bottle was charged with 3,5-dinitrobenzyl alcohol (20 g, 101 mmol), 5% Pd on carbon (600 mg) and 95% ethanol (200 cm^3), and brought to 40 psi with hydrogen. After the mixture had been shaken for 2 h the reaction was deemed to be complete as hydrogen was no longer taken up. The reaction mixture was filtered through a bed of Celite into 95% ethanol (50 cm^3), which was acidified with conc. HCl (16.8 cm^3, 202 mmol). Orange needles precipitated out and were collected on a frit, and were then washed with absolute ethanol. Two additional crops of product were collected by reduction of the volume of the solution and cooling to give a total yield of title compound of 19.32 g (91%); δ_H 7.15 (3 H, s, ArH) and 4.49 (2 H, s, CH_2).

Preparation of 3,5-*Diisocyanatobenzyl Chloride* **2**.—3,5-Diaminobenzyl alcohol dihydrochloride (4.04 g, 19.1 mmol) was weighed into a dry 3-neck flask in a nitrogen-filled glove box. The stoppered flask was fitted with a reflux condenser, and kept under a positive pressure of Ar, which was introduced through the top of the reflux condenser *via* a needle in a septum. The exhaust gas was bubbled through a 20 wt% aq. NaOH. Freshly distilled 1,2-dichlorobenzene (60 cm^3) was added to the flask. The slurry was heated to 165 °C and $COCl_2$ was introduced into the reaction mixture for 20 min. After the flow of $COCl_2$ was stopped, one of the stoppers was replaced with a septum, and a DMF–1,2-dichlorobenzene solution [DMF (0.15 cm^3, 1.9 mmol) in 1,2-dichlorobenzene (10 cm^3)] was transferred by syringe into the reaction mixture over a period of 30 min. The flow of $COCl_2$ was resumed for an additional 3 h. The reaction mixture was then purged with N_2 for 30 min to remove the excess of $COCl_2$ (as monitored by FTIR, CO band at 1805 cm^{-1}). After cooling of the mixture to room temperature, the solvent was removed by vaccum distillation. Kugelrohr distillation of the brown residue (165 °C; 0.5 mmHg) gave compound **2** (2.22 g, 56%) as a clear liquid; ν_{max}/cm^{-1} 2265 (NCO); δ_H($CDCl_3$) 6.95 (2 H, d, ArH), 6.77 (1 H, t, ArH) and 4.48 (2 H, s, CH_2). The yield of compound **2** adjusted for starting material recovered by filtration was 84%.

One-pot Synthesis of the Third-generation Dendrimer **7** [G-3]–CO_2Me.—3,5-Diisocyanatobenzyl chloride **2** (200 mg, 0.959 mmol) was weighed into a dry 2-neck flask inside a nitrogen-filled glove box. The stopped flask was transferred out of the box and placed under a positive pressure of Ar. [G-1]–OH **1** (630 mg, 1.97 mmol), freshly distilled THF (10 cm^3) and dibutyltin dilaurate (5 mm^3, 8.4 μmol) were added, and the solution was stirred at room temperature. The reaction was followed by TLC and FTIR, and when the isocyanate band (2265 cm^{-1}) decreased to the baseline, methyl 3,5-dihydroxybenzoate **6** (81 mg, 0.479 mmol), Cs_2CO_3 (391 mg, 1.20 mmol), KI (16 mg, 96 μmol) and 18-crown-6 (25 mg, 96 μmol) were added. The reaction was brought to reflux for 20 h. The reaction mixture was thrown into water and then extracted with CH_2Cl_2. After drying, the product was purified by flash chromatography [eluted first with (2:1) hexanes–ethyl acetate and then with (1:1.25) hexanes–ethyl acetate] to give compound **7** (534 mg, 62%) as a solid; δ_H($CDCl_3$) 7.45 (2 H, s, g), 7.36–7.24 (40 H, m, a), 7.13 (2 H, d, k), 7.10 (4 H, d, h), 6.96 (4 H, s, f), 6.56 (8 H, d, d), 6.45 (1 H, t, j), 6.51 (4 H, t, c), 5.04 (8 H, s, e), 4.94 (16 H, s, b), 4.83 (4 H, s, i) and 3.81 (3 H, s, l).

Preparation of [G-3]–OH **5**.—(a) *By reduction of compound* **7**. [G-3]–CO_2Me **7** (300 mg, 0.167 mmol) was dissolved in freshly distilled diethyl ether. $LiBH_4$ (5.5 mg, 0.251 mmol) was added to the solution and then methanol (10 cm^3) was added slowly. The reaction mixture was refluxed for 10 h, and then quenched by dropwise addition of water and 10% HCl. The product precipitated in water and was then extracted with CH_2Cl_2. The crude product was purified by flash chromatography [eluted first with (2:1) hexanes–ethyl acetate and then with (1:1.25) hexanes–ethyl acetate] to afford compound **5** as a solid; δ_H($CDCl_3$) 7.44 (2 H, s, g), 7.35–7.24 (40 H, m, a), 7.06 (4 H, d, h), 6.96 (4 H, s, f), 6.56 (8 H, d, d), 6.51 (4 H, t, c), 6.42 (2 H, d, k), 6.24 (1 H, t, j), 5.04 (8 H, s, e), 4.94 (16 H, s, b), 4.83 (4 H, s, i) and 4.45 (2 H, s, l).

(b) *Attempted one-pot synthesis using compounds* **1**, **2** *and* **4**. 3,5-Diisocyanatobenzyl chloride **2** (96 mg, 0.46 mmol) was weighed into a dry 2-neck flask inside a nitrogen-filled glove box. After addition of [G-1]–OH **1** (309 mg, 0.97 mmol), dry THF (5 cm^3) and dibutyltin dilaurate (8.4 μmol) the solution was stirred at room temperature for 2 h. TLC showed that the reaction had gone to completion and so 3,5-dihydroxybenzyl alcohol **4** (29 mg, 0.207 mmol), caesium carbonate (150 mg, 0.460 mmol), potassium iodide (76 mg, 0.460 mmol) and 18-crown-6 (122 mg, 0.460 mmol) were added and the mixture was heated under reflux for 6 h. After precipitation in water and extraction in dichloromethane, the crude product was purified by flash chromatography with hexane–ethyl acetate (gradient from 2:1 to 1:2) to afford a solid (264 mg) consisting mainly of the desired product but from which contaminants could not be removed.

Preparation of 3,5-*Dibenzyloxybenzyl* N-*Phenylcarbamate* **9**.—[G-1]–OH **1** (513 mg, 1.60 mmol) was dissolved in freshly distilled THF (5 cm^3). Phenyl isocyanate (0.16 cm^3, 1.52 mmol) and dibutyltin dilaurate (10 cm^3, 17 mmol) were added to the solution, which was then stirred at room temperature under

nitrogen. After FTIR monitoring had confirmed that all of the isocyanate had been consumed, the solvent was removed under reduced pressure, and the product was purified by flash chromatography [(2:1) hexanes–ethyl acetate] to afford the title carbamate as a solid (480 mg, 72%); $\delta_H(CDCl_3)$ 7.44–7.05 (15 H, m, 3 × Ph), 6.76 (1 H, t, NH), 6.65 (2 H, d, ArH 2- and 6-H), 6.59 (1 H, t, ArH 4-H), 5.13 (2 H, s, $ArCH_2$) and 5.03 (4 H, s, $ArCH_2$).

Evidence for the Transesterification Side Reaction.—3,5-Dibenzyloxybenzyl *N*-phenylcarbamate **9** (105 mg, 0.239 mmol), *p*-methylbenzyl alcohol **10** (30 mg, 0.246 mmol) and Cs_2CO_3 (41 mg, 0.126 mmol) were weighed into a 2-neck flask. After addition of freshly distilled THF (3 cm^3), the mixture was refluxed for 22 h. At this point chromatographic analysis showed that free [G-1]–OH **1**, a new high-R_f spot, and the starting materials were present. ^1H NMR analysis of the reaction mixture showed that a new benzyl carbamate **11** had formed, which correlated to an authentic sample of *p*-methylbenzyl *N*-phenylcarbamate.

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