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The synthesis of unsymmetrical PAMAM dendrimers using a divergent/divergent approach

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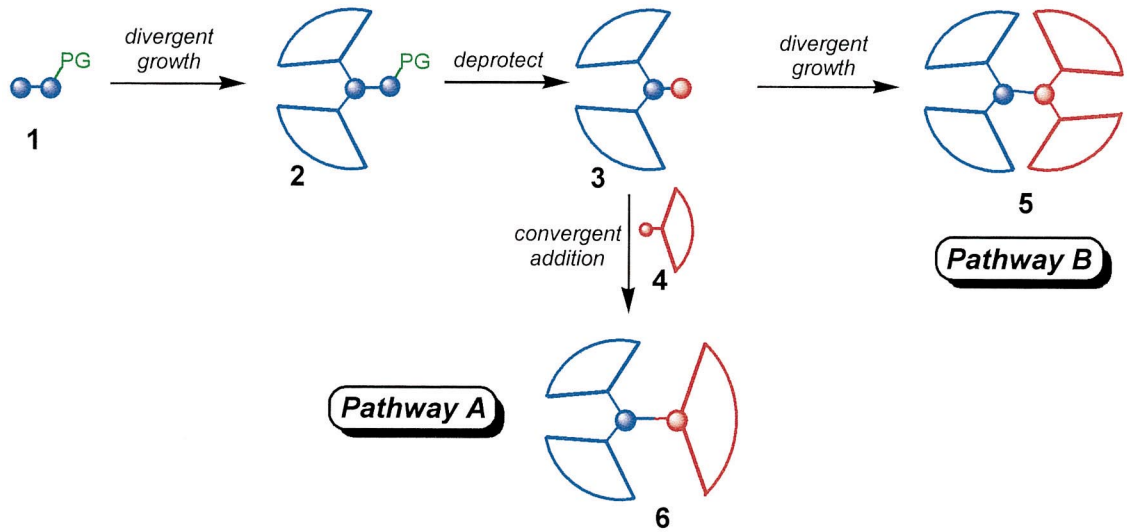
Abstract—The synthesis of unsymmetrical dendrimers possessing terminal methyl ester groups on one face, and *iso*-butylamide groups on the opposite face is reported. The final unsymmetrical dendrimers are obtained in high purity and therefore do not require complicated or excessive purification procedures. © 2001 Elsevier Science Ltd. All rights reserved.



Scheme 1. Schematic representation of the two general methods for the construction of unsymmetrical dendrimers, (i) the divergent/convergent approach, pathway A, and (ii) the divergent/divergent approach, pathway B.

Dendrimers synthesised using traditional methods produce multiple branched macromolecules that possess a regular 3D architecture. Although the potential applications for these symmetrical molecules are diverse, for some applications it would be more advantageous to use an unsymmetrical dendrimer (i.e. a dendrimer containing more than one terminal functional group). One such example, which is currently being studied in our laboratory, is the application of dendrimers to site-specific drug and gene delivery. For example, a dendrimer that contains drug moieties or DNA binding sites on one-surface, and cell recognition groups on the other, will result in a delivery system capable of targeting specific cells. Towards this end we have initiated a programme of research aimed at developing a convenient methodology for the synthesis of unsymmetrical poly(amidoamine) (PAMAM) dendrimers. (PAMAM dendrimers have shown much promise as gene binding,[1] gene delivery[2] and drug delivery[3] systems.) Two general methods for the synthesis of unsymmetrical PAMAM dendrimers are shown schematically in Scheme 1. The first method, developed by Okada[4] and referred to as the divergent/convergent approach, is shown in pathway A. Our proposed method (pathway B) would

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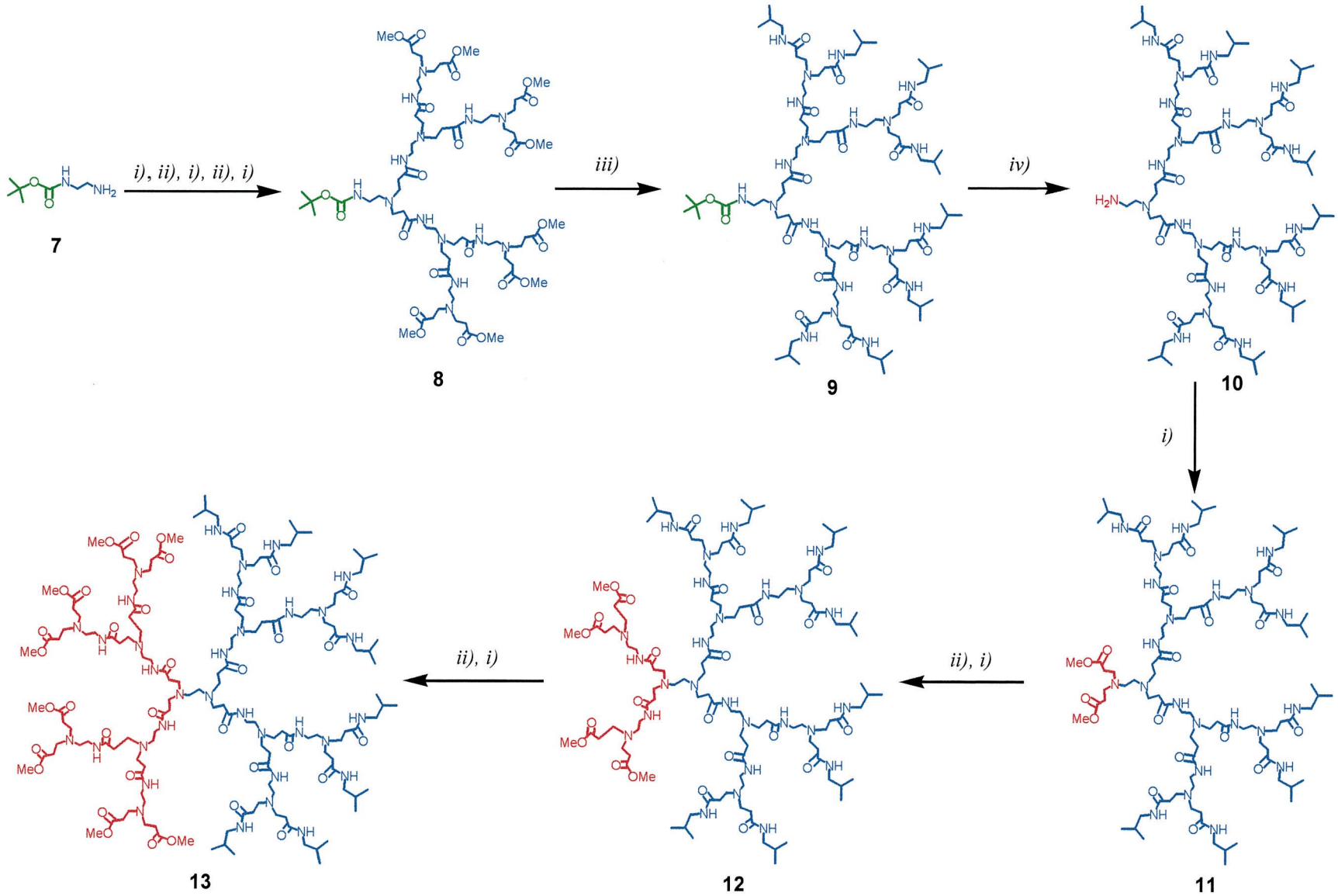

Scheme 2. Divergent/divergent synthesis of unsymmetrical PAMAM dendrimers. (i) Methyl acrylate/MeOH, (ii) excess ethylenediamine/MeOH, (iii) excess *iso*-butylamine/MeOH, (iv) trifluoroacetic acid/dichloromethane.

involve an identical divergent synthesis of the first dendron **3**, but in this case, the final unsymmetrical dendrimer **6** is also grown using a second divergent procedure (after suitable deprotection of the focal point of dendron **2**). This completely divergent PAMAM approach means that excess reagents and solvents can be removed using a rotary evaporator and/or simple distillation techniques. Therefore, complicated and costly separation/purification procedures are not required; this therefore offers a distinct advantage over the divergent/convergent and convergent/convergent methods.

Our synthesis is shown in Scheme 2 and begins with the BOC-protected ethylene diamine unit **7**,[5] this was subjected to a standard PAMAM synthesis[6] eventually furnishing us with the ester-terminated dendrimer **8**, in an overall yield of 80% (five steps from **7**).[7] *iso*-Butylamine terminal groups were then added to give the first half of the unsymmetrical dendrimer **9**[8] in a reasonable 93% yield (*iso*-butylamine groups were chosen so as to prevent the terminal ester groups of **8** being involved in unwanted side reactions during future treatments with ethylenediamine). Removal of the BOC-protecting group was achieved under standard conditions[9] using trifluoroacetic acid in DCM to give the free amine dendron **10** in an *unoptimised* 38% yield. Finally, the unsymmetrical dendrimers **11**, **12** and **13**[10] were obtained in quantitative yields (requiring little or no purification), after subjecting the new amine group at the focus of **10** to a second PAMAM synthesis.

In conclusion, we have demonstrated that unsymmetrical dendrimers can be conveniently synthesised using a divergent/divergent approach (in conjunction with a protection/deprotection strategy). All dendrimers were obtained in excellent yields requiring little or no purification. We are currently developing this approach further and constructing unsymmetrical dendrimers with terminal groups suitable for target specific gene and drug delivery. Financial support from the Royal Society (small equipment grant) and the EPSRC a (QUOTA award), is gratefully acknowledged.

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7. In order to obtain the dendrimers in high yield and high purity great care must be taken to ensure that *all* remaining traces of ethylenediamine are removed after each amidation step (this can be most conveniently monitored using gas chromatography). If this is not done, small symmetrical dendrimers will form and reduce the purity and homogeneity of the final unsymmetrical dendrimers. Although these impurities can be removed using preparative GPC (biobeads, see Ref. 10), it adds an extra and undesirable level of complication.
8. *Experimental for dendritic wedge **9**.* A methanolic solution (30 ml) of the ester terminated dendron, $G=2.5$ (2.24 g, 1.46 mmol), was added dropwise to a stirred methanolic solution (15 ml) of *iso*-butylamine (15 ml, 0.151 mol) at 0°C over 20 minutes. The reaction mixture was stirred at room temperature for 20 days. The solvent and excess reagents were then removed under vacuum to give a thick honey coloured oil in 93% yield. ν_{max} cm^{-1} 3300 (b), 1670, 1683, 1652 and 1635. δ_C ppm (50 MHz, $CDCl_3$); 20.0, 20.4, 28.3, 31.0, 33.7, 37.1, 37.3, 37.4, 46.6, 49.4, 49.7, 50.1, 50.2, 51.6, 52.3, 57.2, 155.9, 172.3, 172.4, 172.5. δ_H ppm (200 MHz, $CDCl_3$); 0.91 (48H, d, $CHC\underline{H}_3$), 1.39 (9H, s, $C(C\underline{H}_3)_3$), 1.78 (8H, septet, $C\underline{H}CH_3$), 2.10–2.83 (70H, series of broad multiplets, all remaining $C\underline{H}_2$'s), 3.00 (16H, bt, $CONHC\underline{H}_2CH(CH_3)_2$), 3.1–3.4 (14H, broad multiplet, $CONHC\underline{H}_2$), 5.70 (1H, bt, $OCON\underline{H}$), 6.98–8.25 (14H, broad series of triplets, $CON\underline{H}$).
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10. The final dendrimers, **11**, **12** and **13**, were isolated in quantitative yield, analytical samples were purified by filtration through a biobead SX-1 column. All samples gave excellent spectroscopic data. Selected data for dendrimer **13**. ν_{max} cm^{-1} 3283 (b), 1733, 1699, 1653. δ_C ppm (50 MHz, $CDCl_3$); 20.3, 28.5, 32.7, 33.7, 34.1, 37.2, 37.3, 46.8, 49.0, 49.2, 49.7, 50.3, 51.6, 52.3, 52.8, 53.3, 171.9, 172.1, 172.3, 172.7. δ_H ppm (200 MHz, $CDCl_3$); 0.91 (48H, d, $CHC\underline{H}_3$), 1.78 (8H, septet, $C\underline{H}CH_3$), 2.25–2.92 (140H, series of broad multiplets, all remaining CH_2's), 3.02 (16H, bt, $CONHC\underline{H}_2CH(CH_3)_2$), 3.26 (24H, m, $CONHC\underline{H}_2$), 3.67 (24H, s, $OC\underline{H}_3$), 7.00–8.20 (20H, series of broad peaks, $CON\underline{H}$).