The Synthesis of Chiral Dendrimeric Molecules Based on Amino Acid Repeat Units

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The synthesis of hyperbranched poly-L-aspartic acid, poly-L-glutamic acid and poly-L-lysine is reported.

The field of dendrimer synthesis, particularly the production of chiral dendrimeric species is of growing importance. It is of note that the first dendrimer synthesised, by Denkewalter *et al.*, was in fact chiral.[1] However, little attention has been paid to these molecules, and their full characterisation has never been rigorously reported.

Analogues of this poly-(lysine) dendrimer, containing thiosialoside groups have been constructed *via* solid phase synthesis and reported by Roy.[3] Poly(lysine) dendrimers derivatised with poly(ethylene oxide) have also been reported by Chapman *et al.*[4]

Newkome and Lin reported the first synthesis of a series of dendritic molecules terminated with a chiral group, tryptophane.[5] These molecules were synthesised from a series of previously reported acid terminated dendrimers.[6] Seebach *et al.* have also reported their efforts toward the synthesis of fully chiral dendrimers using convergent procedures.[8a,b] Chow *et al.* have recently constructed chiral dendrimers using tartaric acid as the repeat unit.[9]

We reasoned that the simplest repeat unit for any *chiral* dendrimer would be natural products, in particular di-functionalised L-amino acids, or monosaccharides.[13] This work concentrates on the use of the L-amino acids, aspartic acid, glutamic acid and lysine, as repeat units for the synthesis of chiral dendrimers.

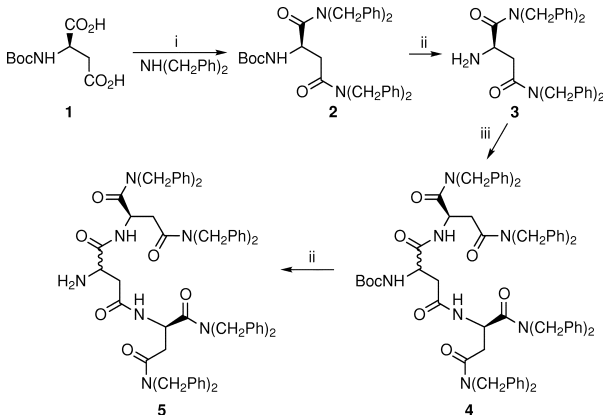
1. *Aspartic Acid Repeat Unit*.—*tert*-Boc-L-aspartic acid was reacted with an excess (2.25 equiv.) of dibenzylamine in the presence of 1,3-dicyclohexylcarbodimide (DCC) and 4-dimethylaminopyridine (DMAP). This afforded the first generation (*t*-Boc) dendron in good yield (Scheme 1).

The *t*-Boc protecting group was then easily removed by using a excess of trifluoracetic acid (TFA) giving the first generation dendron in 78% yield. The iterative process could then be continued by coupling of this new amine with a second molecule of the repeat unit, *tert*-Boc-L-aspartic acid, in the presence of DCC and DMAP to give the larger second generation (*t*-Boc) dendron in 84% crude yield.

The free amine dendrons were then condensed with a tri-acid chloride core, benzene-1,3,5-tricarbonyl trichloride, giving a small dendrimer in excellent yield.

Although the use of a central core allowed the synthesis of larger dendrimers, it had the effect of linking epimeric dendrons, and hence increasing the number of possible diastereoisomers. This led to confusion when attempting to identify these dendrimens using either ^{1}H or ^{13}C NMR spectroscopy. This difficulty, as well as the low yield of the condensation step for larger dendrimers, inhibited any further investigation of this system.

2. *Glutamic Acid Repeat Unit*.—L-glutamic acid was first protected as the benzyloxycarbamate, by reaction with benzyloxy chloroformate under Schotten–Baumann conditions, giving the protected amino acid (**8**) in 50% yield. Benzyloxy carbonyl-L-glutamic acid (*Z*-glutamic acid) was subsequently treated with dibenzylamine, DCC, and a catalytic amount of DMAP as before, to yield the *Z*-protected

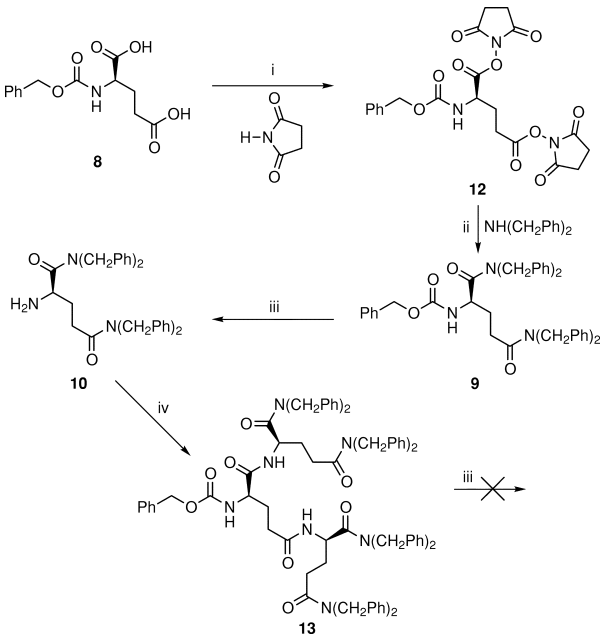


Scheme 1 *Reagents and conditions*: i, DCC, DMAP, CH_2Cl_2; ii, TFA; iii, DCC, CH_2Cl_2

dendron (**9**) in 72% yield (Scheme 4). The *Z*-protected dendron, was treated with iodotrimethylsilane in acetonitrile, at 0 °C, rapidly affording the first generation amine dendron (**10**), in 90% yield.

Reaction of this amine with a second molecule of the repeat unit, the *Su* active ester (**12**) of *Z*-glutamic acid (*Z*-glu*Su*$_2$), yielded the larger second generation protected dendron (**13**), as a *single* diastereoisomer, in 71% yield.

Unfortunately attempted deprotection of this larger dendron (**13**) using iodotrimethylsilane (as well as other Lewis acids) failed. Therefore, the dibenzylamine was replaced with the chiral group, L-glutamic acid diethyl ester. This simple substitution has the added advantage, of



Scheme 4 *Reagents and conditions*: i, DCC; ii, DME; iii, IMe_3Si; iv, DME

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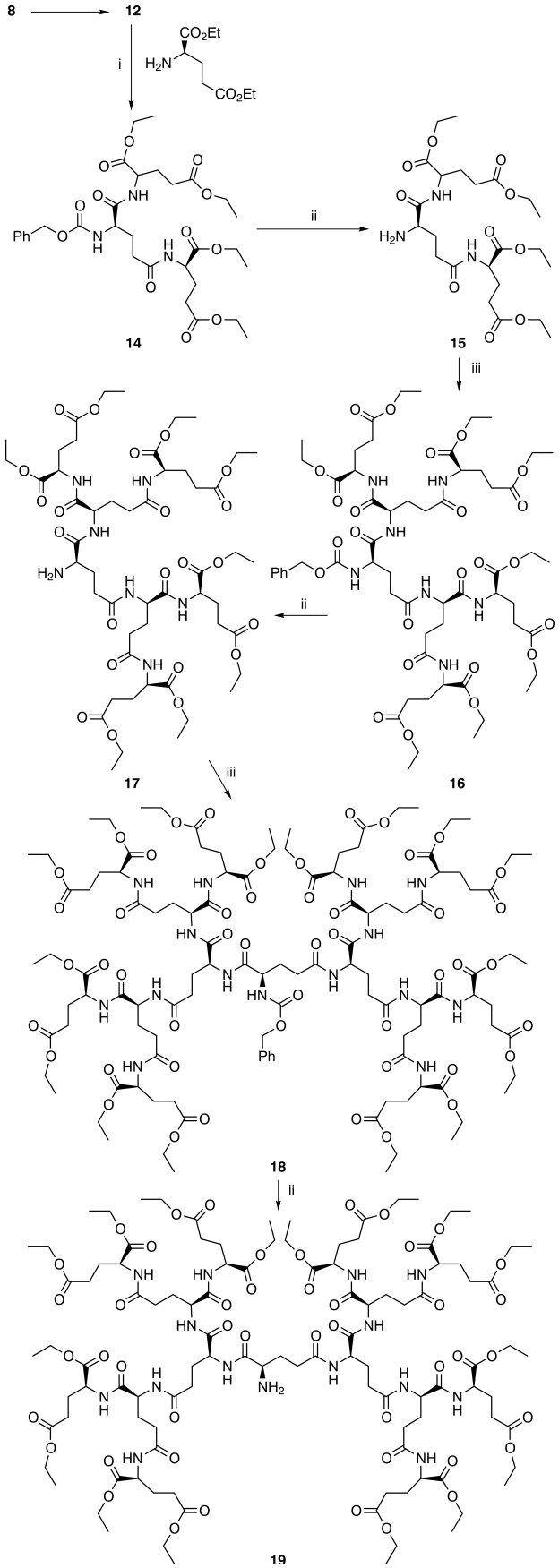

Scheme 8 *Reagents and conditions*: i, DME; ii, H_2, Pd–C, EtOH; iii, DME

allowing other hydrogenation techniques to be used, and would also give us a first generation dendron with three chiral centres.

Z-glu*Su*$_2$ was treated with the hydrogen chloride salt of L-glutamic acid diethyl ester and triethylamine in dimethoxyethane giving the first generation, protected, ester terminated dendron (**14**) in 84% yield (Scheme 8). Deprotection of the small dendron (**14**) using iodotrimethylsilane in acetonitrile produces the first generation amine (**15**) in 94% yield.

The next tier could then be introduced after treatment of amine (**15**) with a second molecule of the repeat unit *Z*-glu*Su*$_2$ (**12**), giving the larger protected ester dendron, as a single diastereoisomer (**16**), in 84% yield. Catalytic hydrogenation (H_2/Pd–C in ethanol) produced the larger deprotected dendron (**17**) in a satisfactory 73% yield. The third generation (protected) dendron (**18**) was then constructed, in 51% yield, after reaction with a third molecule of the repeat unit *Z*-glu*Su*$_2$ (**12**). Hydrogenation (H_2/Pd–C in ethanol) produced the deprotected dendron (**19**) in a reasonable 53% yield.

Although hydrogenation at this sterically hindered site was successful, attempted coupling with a fourth molecule of the repeat unit (*Z*-glu*Su*$_2$) failed.

3. *Lysine Repeat Unit*.—L-lysine is reacted with methylacrylate, *via* an exhaustive Michael addition, giving the tetra-ester substituted acid in an excellent 98% yield (Scheme 6). This acid was then converted to the active ester, after treatment with *N*-hydroxysuccinimide, DCC and DMAP in CH_2Cl_2, giving the desired product in 45% yield. When the active ester, was treated with L-lysine in dimethoxyethane, only starting materials could be recovered. The unreactivity of the active ester, may be due to early masking of the reactive site. Interestingly though, reaction of the same core molecule (ethylenediamine), with the tetra-ester substituted acid, and DCC in CH_2Cl_2, successfully yielded the desired dendrimer in a satisfactory 50% yield. Further effort is currently being directed towards understanding and overcoming these problems.

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Techniques used: ^{1}H NMR, ^{13}C NMR, IR, SEC, FAB MS, poloragraphy

References: 24

Tables: 1 (MS, specific rotations, and SEC of products)

Schemes: 6 (complete synthetic pathways)

Figures: 1 (NMR *vs.* dendrimer generation)

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