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The Synthesis of Chiral Dendritic Molecules Based on The Repeat Unit L-Glutamic Acid

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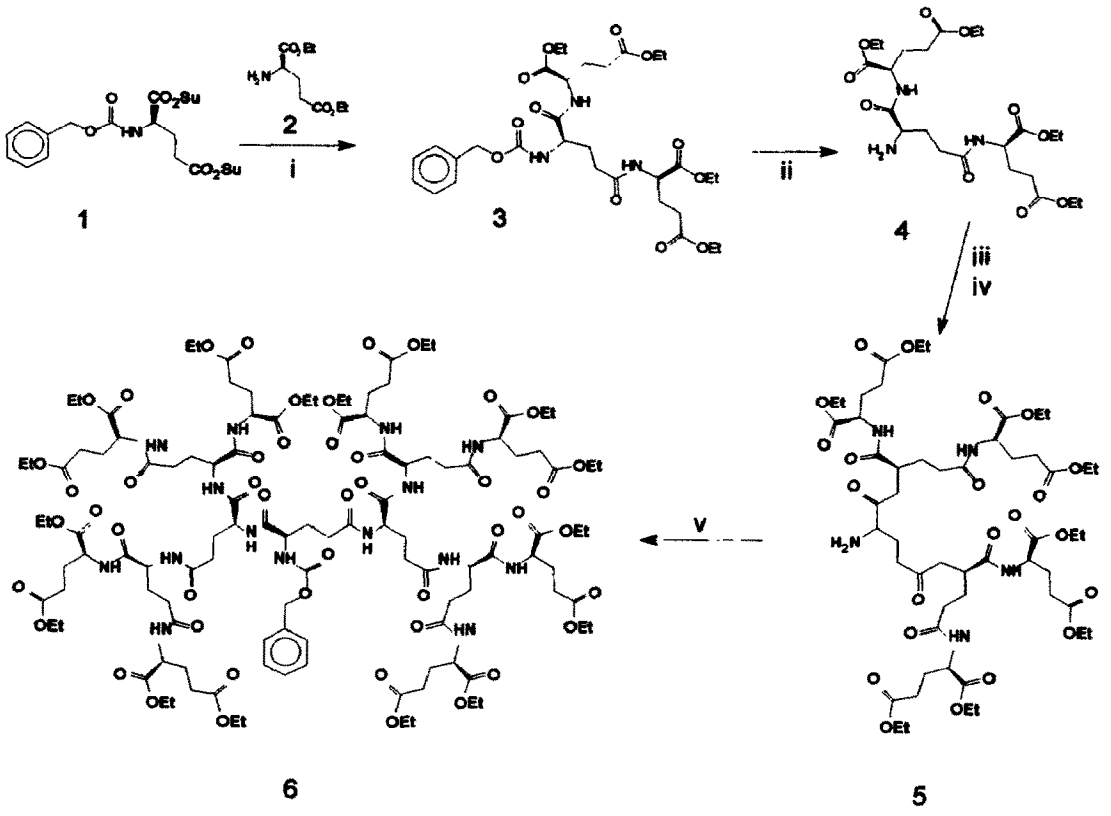
Abstract: The convenient synthesis of a glutamate based dendrimeric molecule is reported. This chiral unsymmetrical dendrimer, contains 15 chiral centres all with identical configurations (L).

The recent paper by Seebach [1], reporting the synthesis of chiral *cores* for dendrimeric molecules, has prompted us to report our initial efforts towards the synthesis of a fully *chiral dendritic molecule*. Dendrimers first appeared in 1985 [2] and many different types have now been described [3]. Denkewalter reported the first synthesis of a chiral (polylysine) dendrimeric molecule as early as 1983 [4], however these were never thoroughly characterised. We can now report the synthesis and full characterisation of the chiral dendrimer **6**, based on the repeat unit L-glutamic acid, using a convergent growth strategy [5]. Benzyloxycarbonyl protected L-glutamic acid was treated with N-hydroxy succinimide, DCC and a catalytic amount of dimethylamino pyridine in dichloromethane, to give the active ester **1** in 91% yield. Treatment of this active ester with L-glutamicacid-diethylester **2** in dimethoxycthane gave the branched molecule **3** [6] in 89 % yield. Initial attempts to remove the benzyloxycarbonyl protecting group using a conventional procedure (HBr in acetic acid) failed and an alternative procedure was required. Iodotrimethylsilane in acetonitrile is reported to be an excellent reagent for the deprotection of benzyloxycarbonyl esters [7], however it is also a good reagent for the cleavage of other esters. It was hoped that by careful monitoring of the reaction it would be possible to selectively remove the single benzyloxycarbonyl ester without cleaving any of the external esters. The reaction was subsequently carried out at -5°C and was immediately quenched when no more starting material could be seen by TLC (5mins). After purification amine **4** was isolated as a single diastereoisomer in 94% yield. The next tier was introduced after treatment of amine **4** with a second molecule of the active ester **1**, to give the larger protected dendron in 84% yield. Attempted de-protection of this larger dendron was undertaken using the same procedure as before (iodotrimethylsilane in acetonitrile). Unfortunately TLC analysis indicated that a number of other products were also being formed, presumably as a result of terminal ethyl ester cleavage, and the desired amine **5** could only be isolated in low yield. It was assumed that the reason for this resulted from *masking* of the reactive site by this larger dendron, all attempts to increase this yield failed and a third deprotection method was sought. Catalytic hydrogenation seemed the most attractive alternative and several methods were investigated, hydrogen transfer (Pd-C, cyclohexene [8]; and Pd-C, 1,4 cyclohexadiene [9]) failed to give better yields, whilst direct hydrogenation (Pd-C, H_2 1atm) increased the yield of amine **5** to a satisfactory 73%. The aromatic protons of the benzyloxycarbonyl protecting group resonate as a distinct singlet in the ^1H NMR spectrum, and the disappearance of this peak was used to monitor the success of the various deprotction methods.

The final dendrimer **6**, was then constructed after reaction of amine **5** with a third molecule of the active ester **1**, to give the final product as a single diastereoisomer in 51% yield. Although the non symmetrical nature of these dendrimers makes structural verification very difficult, ^{13}C NMR and FAB MS, along with size exclusion chromatography (SEC) [10], proved to be excellent techniques for the analysis of the structure and purity of these dendrimers. Thus chiral dendrimer **6** was synthesised in six steps and possess fifteen chiral centres (all L), with a relative molecular weight of 2537. Work is proceeding in our laboratory to further extend the branching of this dendrimer, as well as to study the formation, and binding, of chiral specific inclusion complexes.



i, DME; ii, Me_3SiI, MeCN; iii, I, DME; iv, H_2/Pd-C; v, I, DME.

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10. a) Selected spectroscopic and elemental data; *m/z* (FAB) 2537 (M^+) and 2560 (M^+Na); Found C, 54.4; H, 7.4; N, 8.0. $C_{115}H_{177}N_{15}O_{48}$ requires C, 54.4; H, 7.03; N, 8.3. δ_C 14.093, 14.190 ($OCH_2\underline{C}H_3$). 51.637, 51.783 ($O\underline{C}H_2CH_3$). b) SEC was carried out on a Polymer Laboratories PL gel mixed E column, with tetrahydrofuran as eluent. The column was calibrated using narrow dispersity linear polystyrene standards.

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