Synthesis of a chiral dendrimer based on polyfunctional amino acids

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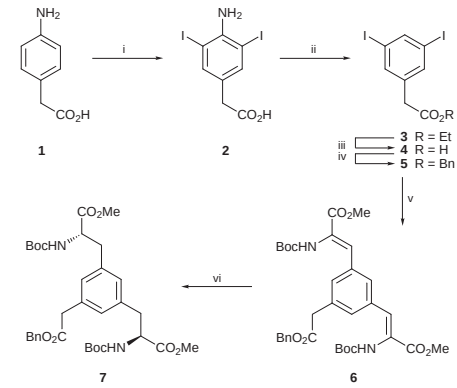
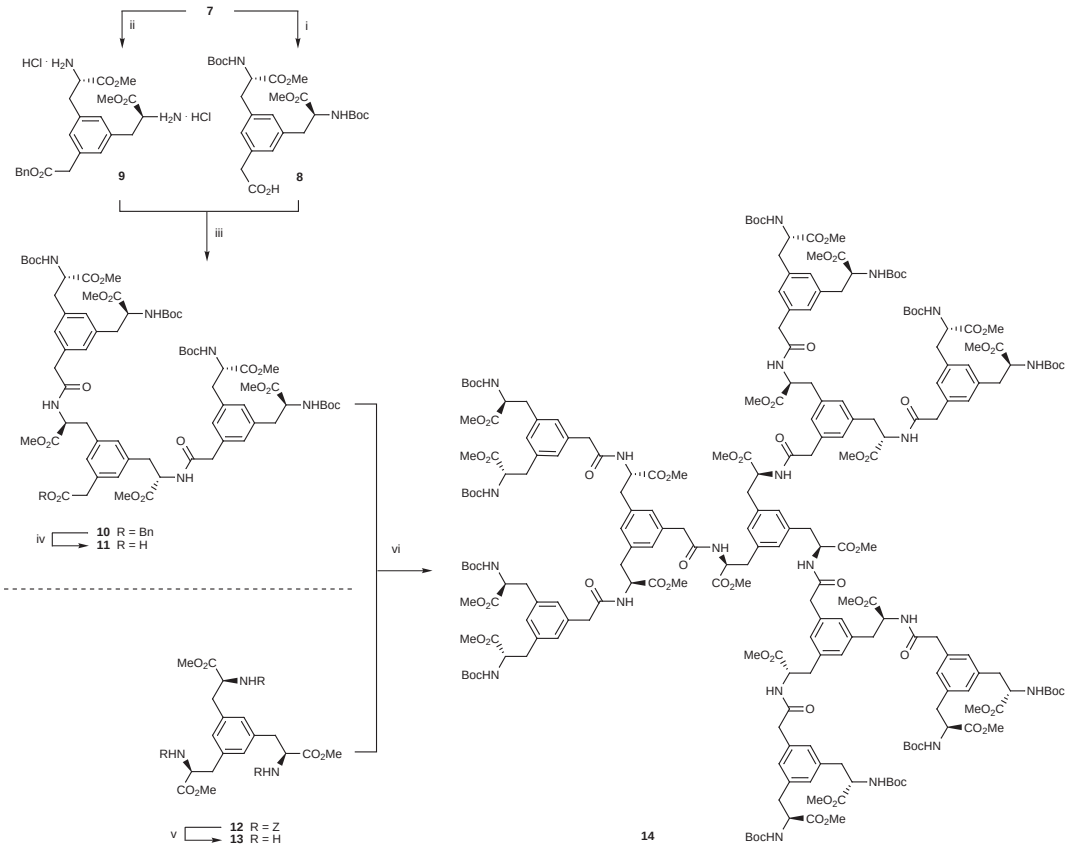
A chiral, nonracemic dendrimer of generation two based on aromatic bis- and tris-amino acids has been synthesised.

The design and synthesis of functional dendrimers has been the focus of much research during the last ten years.[1,2] Chiral, nonracemic dendrimers with well-defined stereochemistry are a particularly interesting subclass, with potential applications in asymmetric catalysis and chiral molecular recognition.[3] For biological applications, polyionic, water-soluble dendrimers will be of interest.[4] Here we report the synthesis of a chiral, nonracemic dendrimer **14** (see Scheme 2) based on synthetic, di- and tri-functional amino acids.

The dendrimer **14** is assembled from nine units of the bis-amino acid **7** and one unit of protected phenyltrisalanine **12**.[5] The synthesis of **7** is described in Scheme 1, and is based on a Heck coupling–hydrogenation protocol which has been used in our laboratory before.[5–7] Starting from 4-aminophenylacetic acid **1**, iodination with ICl gave **2**.[8] Removal of the amino group *via* stepwise diazotization and reduction proved difficult, and *in situ* generation of the diazonium salt in refluxing EtOH was the only satisfactory method found. Under these conditions, the diazonium salt was immediately reduced by EtOH giving **3** as



Scheme 1 *Reagents and conditions*: i, ICl (2.0 equiv.), HCl (1 M), room temp. 18 h, 65%; ii, H_2SO_4, $NaNO_2$ (3.0 equiv.), EtOH (99.5%), reflux, 1 h, 55%; iii, NaOH (2 M), reflux, 3 h, then HCl, 92%; iv, $KHCO_3$ (1.1 equiv.), BnBr (1.1 equiv.), DMF, 60 °C, 2 h, 58%; v, H_2C=C(NHBoc)CO_2Me (2.0 equiv.), $Pd(OAc)_2$ (0.10 equiv.), $NaHCO_3$ (5.0 equiv.), $Bu_4N^+Cl^-$ (2.0 equiv.), DMF, 60 °C, 8 h, 43%; vi, {Rh(COD)[(S,S)-Et-DuPHOS]}$^+OTf^-$ (0.009 equiv.), H_2 (40 psi), MeOH, room temp., 6 h, > 99%, > 98%, ee dr > 99 : 1.



Scheme 2 *Reagents and conditions*: i, Pd/C (5%), EtOH (99.5%), H_2 (1 atm), room temp., 3 h; ii, 3 M HCl in EtOAc, 30 min, room temp.; iii, **8** (2.0 equiv.), TFFH (2.4 equiv.), DIEA (4.8 equiv.), DMF, room temp., 5 min, then **9** (1.0 equiv.), room temp., 1 h, then repeat acylation with **8** (1.0 equiv.), TFFH (1.2 equiv.), Pr^i_2NEt (2.4 equiv.), 57% overall from **7**; iv, Pd/C (5%), EtOH (99.5%), H_2 (1 atm), room temp., 3 h; v, Pd/C (5%), EtOH (99.5%), H_2 (1 atm), room temp., 6 h; vi, **11** (4.0 equiv.), TFFH (4.4 equiv.), Pr^i_2NEt (8.8 equiv.), DMF, room temp., 5 min, then **13** (1.0 equiv.), room temp., 1 h, 87% overall from **12**.

the ethyl ester, which had to be replaced by a benzyl ester to give **5**. Unfortunately, reduction of the diazonium salt of **2** with benzyl alcohol failed. Heck coupling with methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate[7] gave the unsaturated derivative **6**, which was hydrogenated with a chiral Rh^{I}-Et-DuPHOS† catalyst[9] to give **7**.

The convergent synthesis of dendrimer **14** from **7** and **12** is shown in Scheme 2. Since **14** is a polyamide related to a peptide, but possibly more sterically congested, an efficient peptide coupling reagent with minimum steric bulk and high reactivity was desired for the formation of the amide bonds. Based on these considerations, we chose to use TFFH[10]† for the amide bond formations. To this end, hydrogenolysis of **7** yielded **8**, while acidolysis of **7** with HCl in EtOAc (generated from AcCl and EtOH) gave **9**. Acylation of **9** with 2 equiv. of **8** using TFFH proved difficult, and a substantial amount of monoacylated material was recovered. To achieve satisfactory results, **9** had to be acylated twice, first with 2 equiv. of **8** and then with 1 equiv., in two consecutive operations. With this procedure, the dendritic wedge **10** was formed in 57% yield from **7**.

Hydrogenolysis of **10** yielded the free acid **11**, and similar treatment of **12** yielded triamine **13**. Acylation of **13** with 4 equiv. of **11** using TFFH finally yielded dendrimer **14** in 87% yield after a single acylation. This coupling thus proceeded with higher efficiency than that leading to the dendritic wedge **10** above. The reason for this counterintuitive outcome is unclear at present. The identity of **14** was confirmed by NMR and MALDI MS analyses (calc. 4488.9 [M + Na], found 4488.7).

While **14** was synthesised in fully protected form, deprotection of the methyl esters, the Boc groups, or both, will yield a polyionic compound with potentially interesting properties. Studies in this direction are in progress in our laboratory.

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Notes and references

† List of abbreviations: (*S*,*S*)-Et-DuPHOS = 1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene, TFFH = *N*,*N*,*N*′,*N*′-tetramethyl-2-fluoroformamidinium hexafluorophosphate.

1 H.-F. Chow, T. K.-K. Mong, M. F. Nongrum and C.-W. Wan, *Tetrahedron*, 1998, **54**, 8543.
2 G. R. Newkome, C. N. Moorefield and F. Vögtle, *Dendritic Molecules, Concepts, Syntheses, Perspectives*, VCH, Weinheim, 1996.
3 H. W. I. Peerlings and E. W. Meijer, *Chem. Eur. J.*, 1997, **3**, 1563.
4 D. K. Smith and F. Diederich, *Chem. Eur. J.*, 1998, **4**, 1353.
5 A. Ritzén and T. Frejd, *Tetrahedron: Asymmetry*, 1998, **9**, 3491.
6 A. Ritzén, B. Basu, S. K. Chattopadhyay, F. Dossa and T. Frejd, *Tetrahedron: Asymmetry*, 1998, **9**, 503.
7 A.-S. Carlström and T. Frejd, *Synthesis*, 1989, 414.
8 J. W. Barnett, F. A. Robinson and B. M. Wilson, *J. Chem. Soc.*, 1947, 202.
9 M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
10 L. A. Carpino and A. El-Faham, *J. Am. Chem. Soc.*, 1995, **117**, 5401.

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