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Syntheses of dendritic branches based on L-lysine: is the stereochemistry preserved throughout the synthesis?

Malcolm Driffield, David M. Goodall and David K. Smith*
Department of Chemistry, University of York, Heslington, York, UK YO10 5DD.
E-mail: dks3@york.ac.uk

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This paper reports the syntheses of individual dendritic branches based on L-lysine and functionalised with either Boc or Bz surface groups. Convergent and divergent synthetic approaches were employed and the preservation of stereochemistry during the syntheses was monitored using polarimetry, NMR and HPLC. In addition, racemic dendritic branches based on D,L-lysine were synthesised for comparative purposes. It was observed that the preservation of stereochemistry in the dendritic peptide was dependent on the method of synthesis, with divergent methodology being preferred. The results are discussed in terms of the known stereochemical outcomes of traditional peptide coupling processes, and are generalised to the synthesis of other dendritic peptides. Such observations about the chirality of dendritic peptides are of relevance to chemists developing dendritic systems for applications where single enantiomer dendrimers would clearly be preferred, such as enantioselective catalysis or pharmaceutical chemistry.

Introduction

Chiral dendrimers have been widely exploited in recent years.[1] Their well-defined structures and molecular weights, low polydispersities and general topology make these molecules excellent candidates for studying the relationship between chirality and macroscopic structure. There are four different structural features which can give rise to chiral dendrimers: i) a chiral core, ii) chiral branching repeat units, iii) chiral surface groups, iv) an achiral core with four different branched groups attached. As such, chiral dendrimers have been shown to have a variety of uses; this article focuses on dendrimers in which the chirality is a consequence of the branched repeat unit. Dendrimers with chiral branches can closely resemble biological molecules, and are hence excellent candidate protein mimics.[2]

Many dendrimers with chiral branching rely on the use of building blocks related to the naturally occurring chiral pool, such as amino acids,[3] oligonucleotides,[4] bile acids,[5] tartaric acid [3a,b,6] and carbohydrates.[7] However, chiral branching has also been prepared from synthetic monomers allowing precise investigations into structure–property relationships, and enabling the study of subtle structural differences.[8]

Perhaps the most widely employed chiral dendritic branches are those based on L-lysine.[9] L-Lysine is cheap and can be readily functionalised using standard peptide methodology. This has led, for example, to the exploitation of L-lysine dendrimers in the development of novel catalysts,[10] modified silicas for chromatographic applications,[11] solubilisation and transport systems,[12] dendritic porphyrins for light harvesting,[13] dendritic assemblies[14] and gel phase materials.[15] Some of these applications rely on the inherent chirality of the L-lysine dendritic framework. In addition, given its use of naturally occurring building blocks, it is expected that this type of dendritic structure should be biocompatible. The search for useful dendritic biomaterials is currently of intense interest.[16] L-Lysine dendrimers have been functionalised with groups such as saccharides, capable of interacting with biological systems,[17] and furthermore they have also been used in a wide range of biologically inspired applications, from gene transfection to investigations of antimicrobial activity.[18] L-lysine dendrimers have recently been decorated with gadolinium complexes and shown to have potential as MRI agents, in particular providing effective angiographic images.[19] Clearly, for any *in vivo* applications such as this, it is desirable that the dendritic framework should firstly be monodisperse, but secondly that it should be a single enantiomer. This will avoid deleterious effects which might be caused by the presence of any diastereomeric/enantiomeric impurities. In principle, the potential number of diastereomers of dendritic lysine derivatives increases exponentially with each generation of growth.

This paper describes the synthesis of small functionalised dendritic L-lysine derivatives using two different synthetic approaches – convergent and divergent.[20] Crucially, the preservation of stereochemistry during the synthesis is investigated. It is found that the stereochemical information inherent within the L-lysine building block can be lost during the synthesis if the wrong strategy is applied. ^{1}H NMR studies and HPLC investigations support this analysis. There have been numerous previous studies of amino acid racemisation using techniques such as ^{1}H NMR,[21] HPLC,[22] X-ray diffraction and CD,[23] but this is the first time that the stereochemistry of lysine based dendritic branches has been investigated. Although this paper only reports small L-lysine derivatives, the results can be extended by analogy to the synthesis of higher generation dendritic structures. The results in this paper are therefore of significance to those who wish to exploit the easily synthesised L-lysine dendritic system for applications (*e.g.* catalysis, chromatography, *etc.*) in which stereochemical homogeneity is important. They are also of considerable significance for the potential biomedical application of any systems based on dendritic peptides.

Results and discussion

a) Synthesis and stereochemical investigation of Boc functionalised dendritic branches

Dendritic L-lysine derivatives with Boc protecting groups on the surface were synthesised according to Scheme 1 using a convergent coupling methodology previously reported.[14c] Dendritic growth was achieved in Scheme 1 using 1,3-dicyclohexylcarbodiimide (DCC) as a coupling agent with 1-hydroxybenzotriazole (HOBt) in order to suppress any racemisation of the chiral centres. Racemisation can occur in such peptide bond formation reactions *via* the oxazolone mechanism (Scheme 2).[24] The other key step was base-mediated deprotection of the

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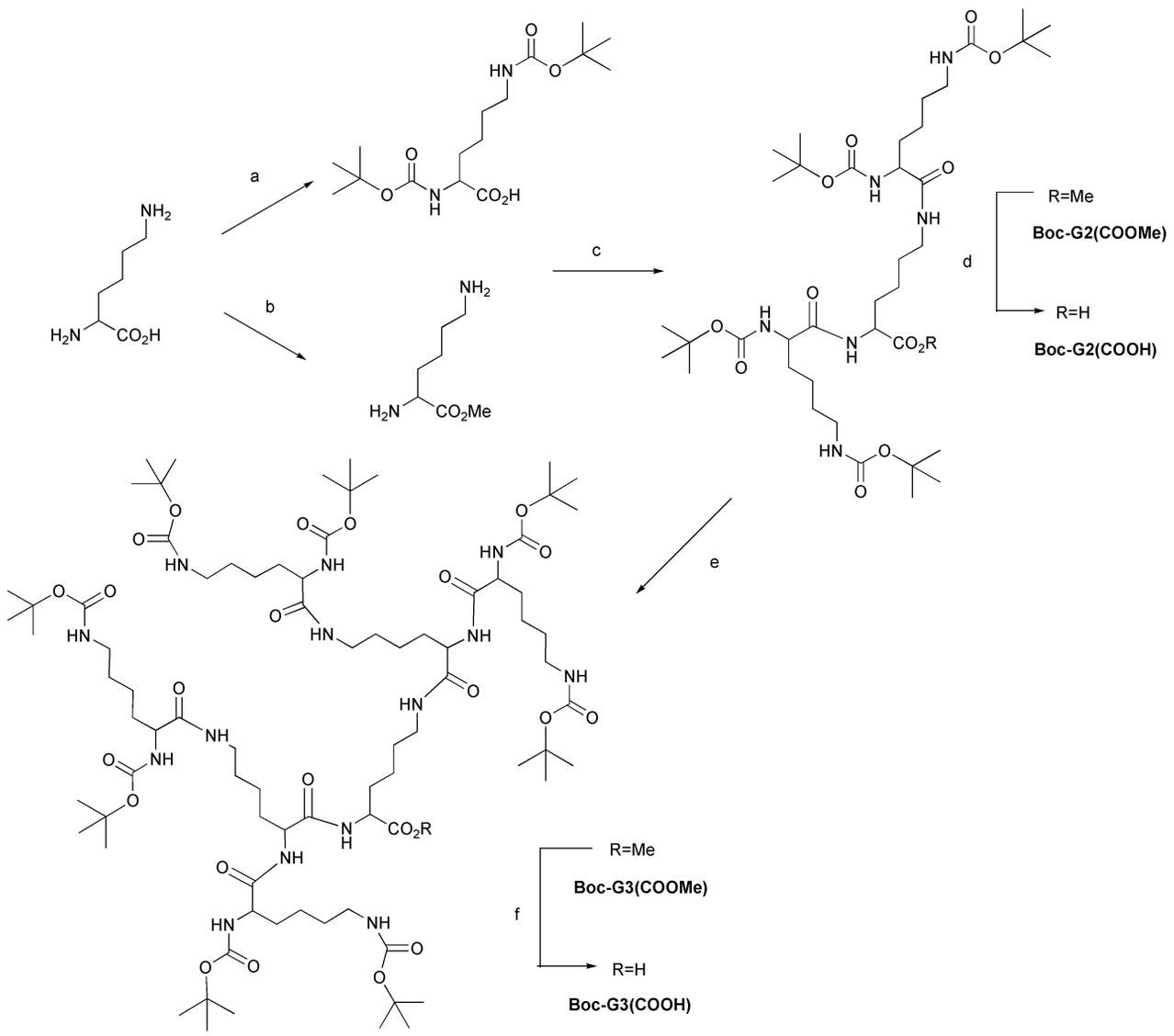
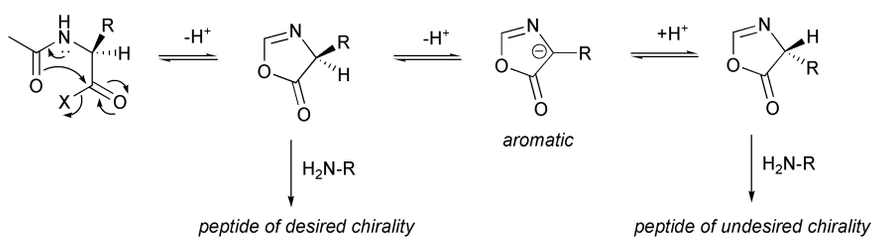


Scheme 1 Convergent synthesis of **Boc-G$_n$(COOH)** (n = 1–3): a) Boc_2O, NaOH, H_2O, dioxane, 97%; b) 2,2-dimethoxypropanone, MeOH, HCl, 93%; c) DCC, HOBt, Et_3N, EtOAc, 82%; d) NaOH, MeOH, H_2O, 90%; e) **Lys(COOMe)**, DCC, HOBt, Et_3N, EtOAc, 86%; f) NaOH, MeOH, H_2O, 92%.



Scheme 2 Racemisation during peptide synthesis *via* the oxazolone mechanism.

methyl ester protecting group at the focal point of the dendritic branch. It is known that such reactions can give rise to loss of stereochemistry, a process which is proposed to occur *via* direct enolisation.[25] During the synthesis, the quantity of base used was limited and the temperature was controlled in order to minimise the chance of enolisation occurring.

As the branches were being developed for use in chiral stationary phases,[11a,b] we monitored the stereochemistry of the branches to ensure that stereochemical information was retained throughout the synthesis. In order for the stereochemical problem to be tractable, we focused on the stereochemistry of relatively small second generation dendritic branches – **Boc-G2(COOMe)** and **Boc-G2(COOH)**. It was also decided to synthesise second generation dendritic branches using racemic D,L-lysine as a building block. These dendritic branches were synthesised in a manner directly analogous to that used with L-lysine building blocks. The racemic dendritic material could then be directly compared with the dendritic branches synthesised from L-lysine to check whether the stereochemical information is conserved in the latter case.

The second generation dendritic branches have three chiral centres and no plane of symmetry. Hence there is the possibility of eight (2^3) stereoisomers – four pairs of enantiomers. It should be pointed out that the dendritic material synthesised using D,L-lysine may not be an equal mixture of all stereoisomers, as it has previously been observed in dendrimer syntheses that the formation of certain diastereomers can sometimes be favoured in the synthetic pathway.[26]

^{1}H NMR spectroscopy was a key technique in determining the stereochemical outcomes of these reactions. The ^{1}H NMR

Table 1 ^{1}H NMR (CD_3OD) chemical shifts (δ, ppm) and coupling constants (J, Hz) for the CH peaks of dendritic derivatives **Boc-G2(COOMe)** and **Boc-G2(COOH)** synthesised from L-lysine and D,L-lysine

Compound	δ	Multiplicity	J	Compound	δ	Multiplicity	J
Boc-G2(COOMe) (L)	4.41	dd	5.0, 9.0	Boc-G2(COOMe) (D,L)	4.40	m	—
	4.10	br t	—		4.08	br	—
	3.99	br t	—		3.99	br	—
Boc-G2(COOH) (L)	4.39	dd	4.5, 9.0	Boc-G2(COOH) (D,L)	4.40	m	—
	4.10	brt	—		4.07	br	—
	3.99	br t	—		3.98	br	—

spectra of the different diastereomeric lysine based dendritic branches would be expected to be different. If the stereochemistry of all three chiral centres is preserved, each CH should appear as a doublet of doublets (or apparent triplet), due to the coupling of each with the two adjacent diastereotopic CH_2 protons.[27] If different diastereomers are present, however, each CH peak might be expected to be a more complex multiplet due to overlapping of the CH dd (or t) peaks associated with each diastereoisomer.

Table 1 summarises the results obtained. For the dendritic branches synthesised using L-lysine, the three CH protons appear as a sharp doublet of doublets and two slightly broadened triplets. This is the case for both **Boc-G2(COOMe)** and **Boc-G2(COOH)**. For the dendritic branches synthesised using D,L-lysine, however, the three CH protons appear as one complex multiplet and two very broadened unresolved peaks. This result, although not by itself conclusive, provides strong evidence that the chiral centres in the dendritic branch derived from L-lysine are still intact, and that in this case, neither amide coupling conditions nor base-induced deprotection of the methyl ester cause significant loss of stereochemical information.

In order to confirm the stereochemical homogeneity of the dendritic branches based on L-lysine, an achiral HPLC investigation was carried out. Although this will not discriminate between enantiomers, it should in principle be possible to distinguish the four diastereomeric pairs of enantiomers.

Samples of the branches prepared from L-lysine were compared with those prepared from D,L-lysine using a Hypercarb column. The chromatograms obtained are shown in Figs 1a and 1b. The diastereoisomers of **Boc-G2(COOMe)** (D,L) were not fully resolved under the chromatographic conditions, and only three components were evident in the time range of interest (> 20 min) (Fig. 1a). The material constructed using L-lysine, however, only shows a single peak corresponding to one of the peaks from the racemic material. This would imply that the stereocentres are all intact after the peptide coupling reaction. Furthermore, after NaOH mediated deprotection, **Boc-G2(COOH)** generated from L-lysine also gave a single peak, whereas the material generated from D,L-lysine again clearly showed different diastereoisomers (Fig. 1b). This indicates that the stereochemistry of the dendritic branch probably survives the basic conditions.

In combination, therefore, the ^{1}H NMR and HPLC results indicate that, as expected, the second generation dendritic branches with peripheral Boc groups have maintained their stereochemical integrity during the synthetic procedures utilised. To develop novel stationary phases, we desired aromatic rings on the dendritic surface in order to enhance interactions with analytes *via* π–π interactions. The influence of the surface groups on the stereochemical outcome of the dendrimer synthesis was therefore investigated.

b) Convergent synthesis and stereochemical investigation of benzamide functionalised dendritic branches

An analogous convergent synthetic procedure was applied to the synthesis of novel branched molecules, **Bz-G2(COOMe)** and **Bz-G2(COOH)** (Scheme 3). The only difference between

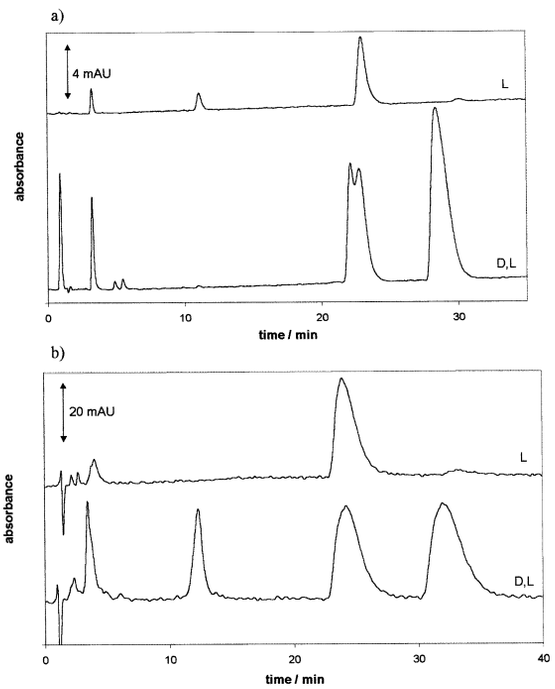


Fig. 1 HPLC chromatograms for a) **Boc-G2(COOMe)**, b) **Boc-G2(COOH)**. *Conditions*: Hypercarb column 100 × 4.6 mm, 5 μm particles, 1 ml min^{-1}, 200 nm; a) mobile phase gradient of acetonitrile : water 50 : 50 (v/v) to 70 : 30 (v/v) over 60 min, for (L) 5 μl injection, c = 1.4 mM, for (D,L) 5 μl injection, c = 1.4 mM; b) mobile phase of acetonitrile : water : acetic acid 50 : 50 : 0.1 (v/v/v), for (L) 50 μl injection, c = 0.6 mM, for (D,L) 50 μl injection, c = 0.6 mM.

the dendritic branches is that the surface groups are connected *via* an amide linkage, rather than one based on a carbamate. It transpires that this has a profound effect on the stereochemical outcome of the dendrimer synthesis.

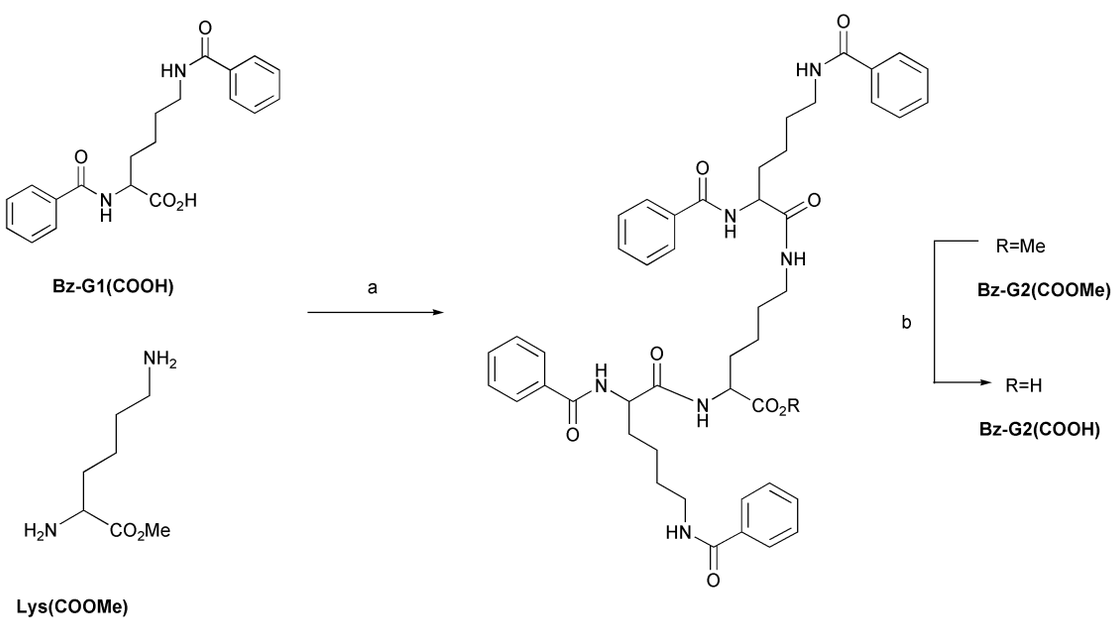
Initially these dendrimers were synthesised using enantiopure L-lysine building blocks. The synthesis of **Bz-G1(COOH)** was achieved using an adaptation of literature methodology,[28] and standard DCC, HOBt coupling conditions were then used to synthesise **Bz-G2(COOMe)**. This reaction proceeded in low yield due to solubility problems. The methyl ester at the focal point was efficiently hydrolysed using NaOH to give **Bz-G2(COOH)**. The same synthetic procedure was also applied to D,L-lysine in order to generate a mixture of all possible stereoisomers of the dendritic structures.

In the case of these benzamide protected dendritic branches the ^{1}H NMR analysis was very interesting (Fig. 2). For **Bz-G2(COOMe)** synthesised using L-lysine, the ^{1}H NMR spectrum (Fig. 2b) had a similar appearance to the material synthesised using D,L-lysine (Fig. 2a), with each of the CH peaks appearing as a complex multiplet, rather than the expected doublet of doublets (Table 2). This provides evidence that some of the stereochemical information was lost during the peptide coupling step. Similarly for **Bz-G2(COOH)**, all the CH peaks appeared as multiplets, irrespective of the stereochemical origin of the dendrimer.

Initially, this appeared to be a surprising result, given that peptide coupling had been performed using HOBt as an

Table 2 ^{1}H NMR (CD_3OD) chemical shifts (δ, ppm) and coupling constants (J, Hz) for the CH peaks of dendritic derivatives **Bz-G2(COOMe)** and **Bz-G2(COOH)** and synthesised from L-lysine and D,L-lysine

Compound	δ	Multiplicity	J	Compound	δ	Multiplicity	J
Bz-G2(COOMe) (L) convergently prepared	4.63	m	—	Bz-G2(COOMe) (D,L)	4.64	m	—
	4.53	m	—		4.53	m	—
	4.43	m	—		4.43	m	—
Bz-G2(COOMe) (L) divergently prepared	4.65	dd	5.0, 9.0				
	4.53	dd	6.0, 8.0				
	4.45	dd	6.0, 8.0				
Bz-G2(COOH) (L) convergently prepared	4.64	m	—	Bz-G2(COOH) (D,L)	4.64	m	—
	4.53	m	—		4.53	m	—
	4.44	m	—		4.43	m	—
Bz-G2(COOH) (L) divergently prepared	4.65	dd	4.5, 9.0				
	4.54	dd	6.0, 8.0				
	4.44	dd	5.0, 9.0				



Scheme 3 Synthesis of **Bz-G2(COOH)**: a) DCC, HOBt, Et_3N, EtOAc, 13%; b) NaOH, H_2O, MeOH, 24 h, 70%.

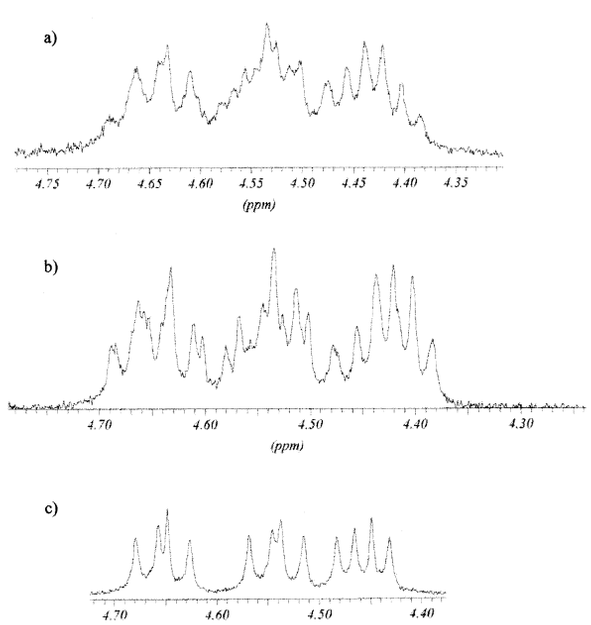


Fig. 2 The CH peaks from the ^{1}H NMR spectra for a) **Bz-G2-(COOMe)** (D,L), b) **Bz-G2(COOMe)** (L) convergently prepared, c) **Bz-G2(COOMe)** (L) divergently prepared.

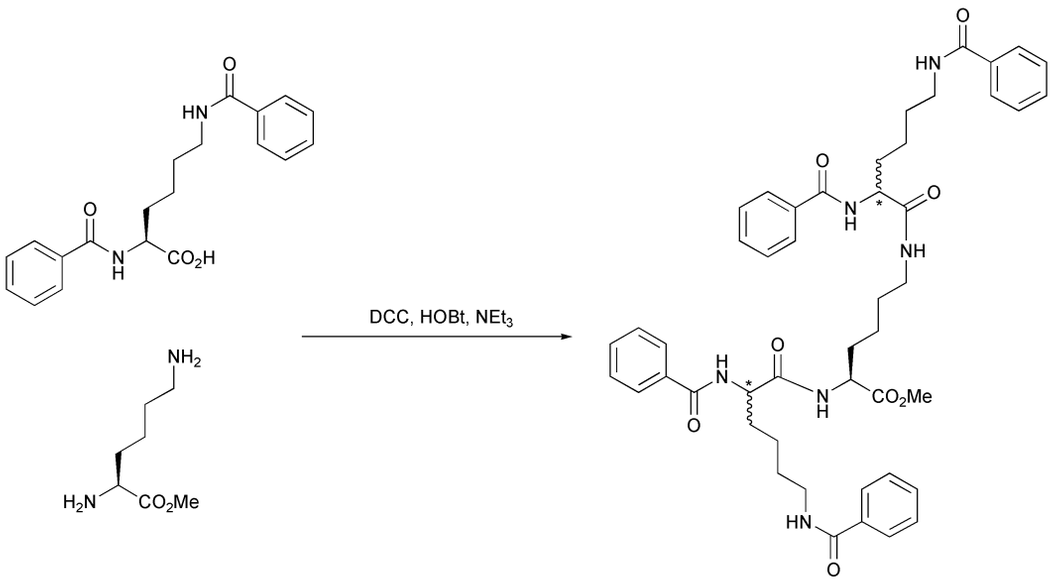
additive in order to suppress racemisation of the chiral centres. However, in contrast to the Boc protected dendrimers, the surface groups are acyl groups rather than carbamates. It is known that racemisation during peptide coupling is more likely to occur *via* the oxazolone mechanism (Scheme 2) if the amino group of the amino acid is connected to a simple acyl group, whereas with carbamate groups in place, racemisation is less likely.[25] It therefore appears that in the synthesis of **Bz-G2(COOMe)** the acyl surface groups mean that the presence of HOBt is unable to prevent the loss of stereochemistry. This process would result in the stereochemical scrambling of two of the chiral centres in the dendritic branch (Scheme 4), producing all four possible diastereoisomers.

Unfortunately, we were unable to separate the diastereoisomers of **Bz-G2(COOMe)** or **Bz-G2(COOH)** by HPLC in order to confirm this analysis, and it was therefore decided to synthesise these dendritic branches using another approach in an attempt to preserve the stereochemical information.

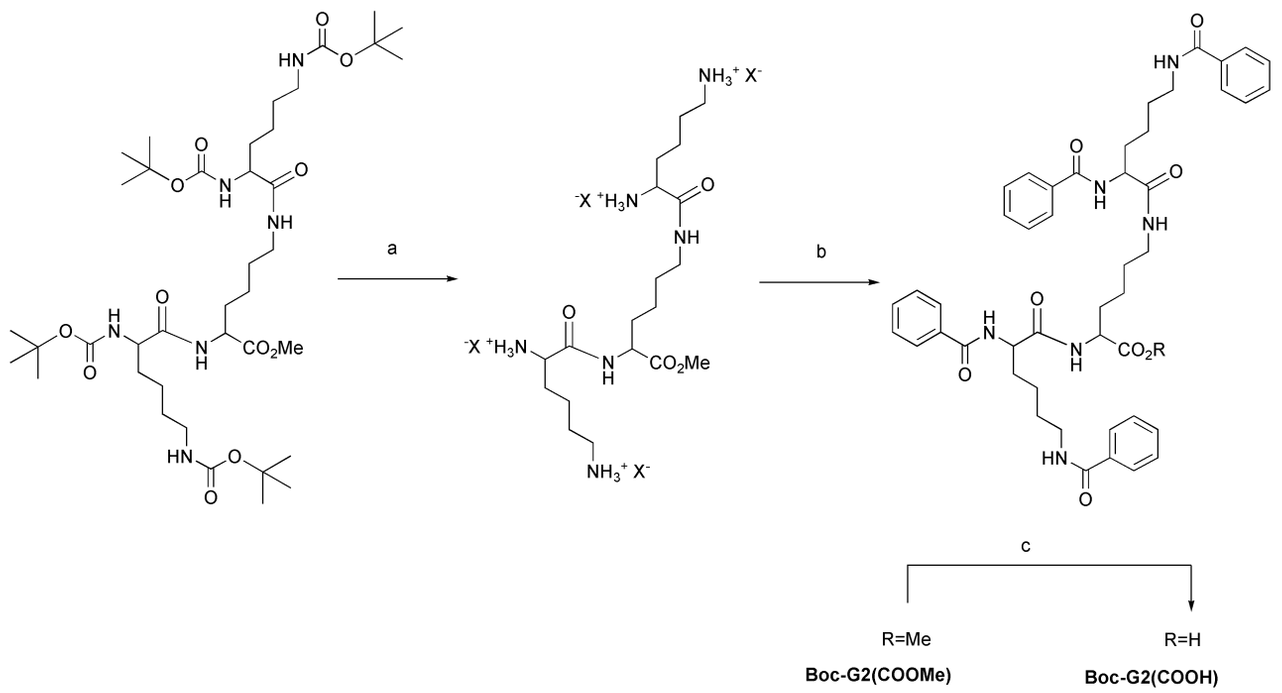
c) Divergent synthesis and stereochemical investigation of benzamide functionalised dendritic branches

Due to the apparent loss of stereochemical information described above, a divergent strategy was employed for the synthesis of **Bz-G2(COOMe)** and **Bz-G2(COOH)** from L-lysine building blocks (Scheme 5). This involved the synthesis of **Boc-G2(COOMe)** *via* the usual method, which is known to give rise to single enantiomer material (see above).

Initially, the Boc groups were then removed by deprotection with trifluoroacetic acid, and the product trifluoroacetate salt was deprotonated with triethylamine and reacted with benzoyl chloride with the aim of divergently generating the desired product. Unfortunately, mass spectrometry of the reaction



Scheme 4 Proposed loss of stereochemistry at two of the chiral carbon atom in the convergent synthesis of **Bz-G2(COOMe)**. The carbon atoms which lose their stereochemical homogeneity are marked with an asterisk (*).

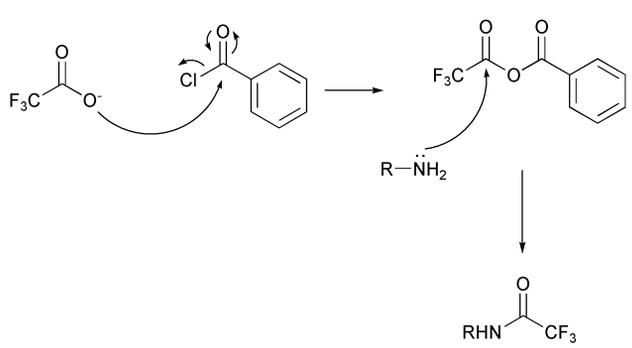


Scheme 5 a) HCl, Et_2O, quant.; b) i) Et_3N, CH_2Cl_2, ii) BzCl, 60%; c) NaOH, H_2O, MeOH, 24 h, 70%.

product indicated that a mixture of products had been synthesised, in which some amines were converted into benzamides, but others to trifluoroacetamides. It is proposed that the trifluoroacetate counter ion present in the benzoylation reaction is capable of acting as a nucleophile to form a mixed anhydride on reaction with benzoyl chloride (Scheme 6), and that this can react with the dendritic amine giving rise to the observed trifluoroacetamide impurities.

In order to avoid this unusual problem, we used hydrochloric acid in diethyl ether to remove the protecting groups from **Boc-G2(COOMe)**,[29] and the resultant chloride salt was deprotonated with triethylamine and reacted *in situ* with benzoyl chloride. This gave rise to **Bz-G2(COOMe)** in good yield. Simple deprotection of the methyl ester with NaOH again generated **Bz-G2(COOH)**.

In contrast to the convergently-synthesised material or the material synthesised using racemic D,L-lysine, the material synthesised using the divergent route proceeding through the Boc protected intermediates gave ^{1}H NMR spectra indicating that



Scheme 6 Proposed mechanism for formation of mixed trifluoroacetamide/benzamide products.

the stereochemical integrity had been maintained. All CH peaks appeared as sharp, well resolved doublets of doublets, as would be expected for a dendritic branch which existed as a single enantiomer (Table 2, Fig. 2c).

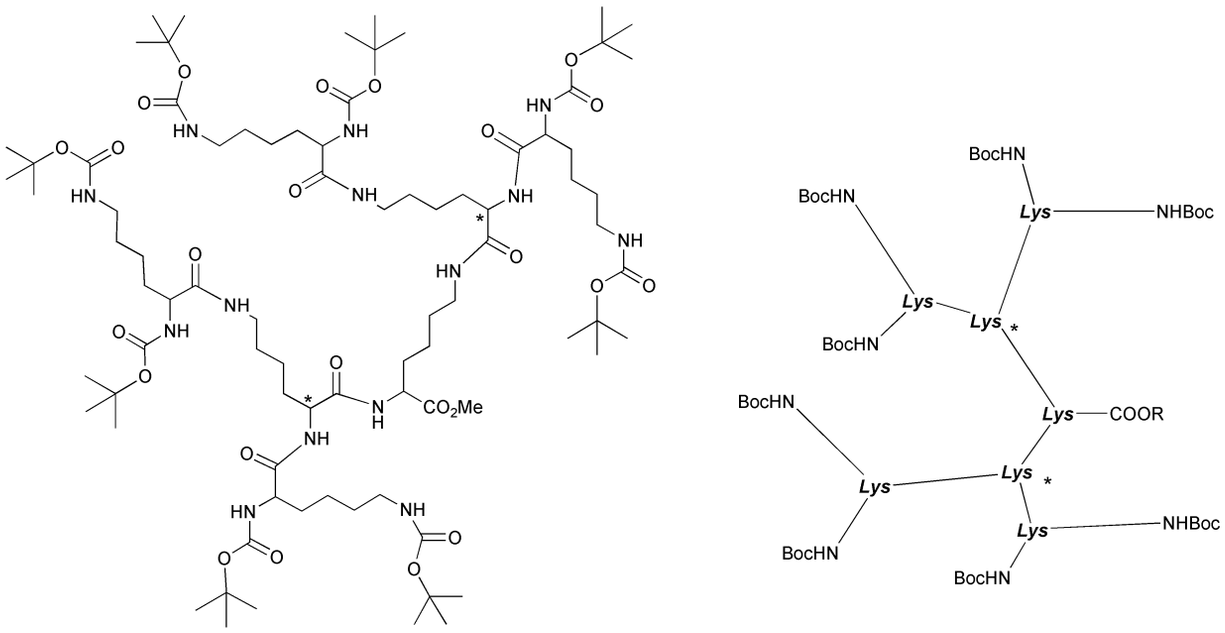


Fig. 3 Convergent synthesis of **Boc-G3(COOR)** would be expected to cause loss of stereochemistry at the chiral centres marked with *.

Table 3 Specific rotation measurements, $[\alpha]_D$ (c = 1, MeOH)/deg cm^3 g^{-1} dm^{-1}.

Compound	$[\alpha]_D$ from L lysine	$[\alpha]_D$ from D,L lysine
Bz-G2(COOMe) convergent	−3.6	−0.5
Bz-G2(COOMe) divergent	+3.6	
Bz-G2(COOH) convergent	+2.5	−0.8
Bz-G2(COOH) divergent	+5.6	

Polarimetry provides supporting evidence for these ^{1}H NMR observations. Table 3 provides $[\alpha]_D$ values for the different benzamide protected dendritic branches. Values for those prepared *via* the divergent approach are significantly different to those prepared convergently (in fact, for **Bz-G2(COOMe)** the $[\alpha]_D$ value has the opposite sign). It is noteworthy that unlike the racemic material constructed from D,L-lysine, for which the $[\alpha]_D$ value is near zero, the $[\alpha]_D$ values for the branches constructed convergently using L-lysine are non-zero. This is consistent with our proposal that two of the three possible chiral centres will be scrambled using this approach, with the third chiral centre being left intact.

Conclusions

This paper shows that the synthetic approach to dendritic peptides plays a key role in controlling the stereochemical information they contain. Divergent synthetic approaches should maintain the enantiopurity of the individual L-lysine building blocks in the final dendritic structure. Although only performed with low generation dendritic L-lysine and D,L-lysine derivatives, these studies have significant implications for the construction of homochiral dendritic systems.

Firstly, for the synthesis of higher generation dendrimers, by extrapolating our results, it would be expected that the convergent coupling of **Boc-G2(COOH)** with lysine methyl ester to give **Boc-G3(COOMe)** (Scheme 1) will not yield a homochiral product. Although the surface groups are Boc carbamate groups, the groups closest to the reactive carboxylic acids are acyl (peptide) groups. As this paper shows, the proximate presence of such functionalities may cause loss of stereochemical information, presumably *via* the oxazolone mechanism. This would generate dendritic structures in which five chiral centres would be maintained and two would be scrambled (Fig. 3). At each subsequent level of convergent coupling, stereochemical information would again be lost. Due to the complexity of the analysis, however, we did not explicitly study these higher generation systems. From the systems that were studied, we suggest that for applications where homochirality of the dendritic branches is an important consideration, it is preferable to synthesise these dendritic structures divergently using carbamate based protecting groups (such as Boc or Fmoc) during the synthetic procedure. Surface groups other than carbamates, which will be connected *via* a simple amide bond, should be attached in the final step of the synthesis.

There are also implications of these observations on the synthesis of focal point functionalised dendritic L-lysine derivatives. If the functionality at the focal point is attached in the final step of the synthesis it is possible that epimerisation of the dendritic structure may occur, with the focal point amino acid building block being racemised *via* the oxazolone mechanism. The steric bulk of the dendritic branches may hinder this process, however, it should clearly be considered as a possibility. This is of importance where active groups are to be attached to the focal point of such branches for use in applications such as enantioselective catalysis, where stereochemistry is of key importance.

Furthermore, such observations have implications for the synthesis of other chiral dendritic peptides.[3] For example, when using glutamic acid as a dendrimer building block, amine and carboxylic acid units are effectively inverted compared to L-lysine, and therefore a consideration of the oxazolone mechanism would indicate that convergent coupling using carbamate-based protecting groups will be more likely to maintain the stereochemical integrity of the structures. This was indeed the strategy originally applied for the synthesis of this type of dendritic structure.[3g] However, an analysis of previously reported synthetic routes used for the synthesis of other chiral peptides indicates that in some cases, stereochemical integrity may have been compromised. This may account for some of the surprising reports in the literature in which molar rotation per chiral residue has actually been observed to decrease on increasing dendrimer size. (*e.g.* ref. 3*d*.)

Obviously, stereochemical considerations will be of key importance in the development of bioactive dendritic systems, for which the existence of the dendritic molecule as a single enantiomer will be desirable. As indicated earlier, dendrimers based on amino acids have particular potential in this area due

to their reliance on naturally occurring building blocks for their construction.

Experimental

Silica column chromatography was carried out using silica gel provided by Fluorochem Ltd. (35–70 μ). Thin layer chromatography was performed on commercially available Merck aluminium backed silica plates. Preparative gel permeation chromatography was carried out using a 2 m glass column packed with Biobeads SX-1, supplied by Biorad. Analytical gel permeation chromatograms were recorded using a Waters instrument incorporating a Waters Styragel guard column (200 Å styrene-DVB co-polymer packing material) and two Shodex columns in series (KF-802.5 and KF-803) using THF as eluent. Column temperature was regulated at 40 °C for all analyses. ^{1}H and ^{13}C NMR spectra were recorded on either a Jeol EX-270 (^{1}H 270 MHz, ^{13}C 67.9 MHz) or a Bruker AMX-500 (^{1}H 500 MHz, ^{13}C 125 MHz) at 25 °C. Chemical shifts (δ) are quoted in parts per million, referenced to residual solvent. Coupling constant values (J) are given in Hz. DEPT experiments were used to assist in the assignment of ^{13}C NMR spectra. HPLC analysis was carried out using a HP 1090 liquid chromatography instrument (Agilent Technologies, Stockport, UK) with standard HP 1090 solvent delivery system, autosampler and autoinjector. UV absorbance detection was carried out with a Spectroflow 757 abs detector (ABI Analytical, Ramsey, NJ, USA) with an 8 mm pathlength flow cell. Hypercarb columns, provided by Hypersil (Runcorn, Cheshire, UK) were used. Chromatographic conditions are given with specific examples. Optical rotations were measured as $[a]_D$ on a JASCO DIP-370 digital polarimeter at 298 K. Positive ion electrospray mass spectra were recorded on a Finnigan LCQ mass spectrometer. Positive ion fast atom bombardment mass spectra were recorded on a Fisons Instruments Autospec mass spectrometer. The isotope distribution observed for mass spectral ions of the larger molecules is consistent with data calculated from isotopic abundances. Infra-red spectra were recorded using an ATI Mattson Research Series 1 FTIR spectrometer.

Compounds **Lys(COOMe)**[30] and **Boc-G1(COOH)**[31] were prepared according to literature methods, as were dendritic branches **Boc-G2(COOMe)** and **Boc-G2(COOH)**.[14c] Solvents and reagents were used as supplied. Compound **Bz-G1(COOH)** was prepared using an adaptation of a literature method.[28] All data for these compounds were in agreement with those reported in the literature. In all cases, syntheses for dendrimers derived from D,L-lysine were directly analogous to those reported for L-lysine based dendrimers. Experimental data was analogous for the two series, except for those points described in detail in the results and discussion (*i.e.* ^{1}H NMR, polarimetry and HPLC).

Synthesis of Bz-G2(COOMe)

(i) Convergent approach. Lys(COOMe) (6.60 g, 28 mmol) was suspended in dichloromethane (50 mL) and triethylamine (3 g, 30 mmol) was added. This was followed by the addition of **Bz-G1(COOH)** (21.3 g, 60 mmol) and the mixture was stirred under a nitrogen atmosphere for 2 min. The mixture was cooled to 0 °C and HOBt (7.60 g, 60 mmol) and DCC (11.80 g, 60 mmol) were added as a mixture of solids. The mixture was allowed to warm to room temperature and stirred for 96 h. The precipitate was removed by filtration and the filtrate was washed with $NaHCO_3$ (sat.), $NaHSO_4$ (8 g in 50 mL H_2O), $NaHCO_3$ (sat.) and water. The solution was dried ($MgSO_4$) and concentrated on a rotary evaporator to yield a white solid. This was dissolved in a minimum of DCM : MeOH (9 : 1, v/v) and diethylether was added until the solution was cloudy. After standing for 2 h, the product was collected by filtration, and dried for 24 h under high vacuum. Yield 3.0 g (3.6 mmol, 13%). For data see below.

(ii) Divergent approach. ^+H_3N-G2(COOMe) Cl$^-$ (see below for synthesis) (1.50 g, 2.7 mmol) was suspended in dichloromethane (100 ml), and triethylamine (1.78 g, 17.60 mmol) was added and stirred under a nitrogen atmosphere for 1 h. Benzoyl chloride (3.44 g, 24 mmol) was added and the solution was stirred for 7 d. The solvent was removed by rotary evaporation, water (100 mL) and DCM (100 mL) were added, and the mixture shaken well. The water was removed and the DCM solution was washed with $NaHCO_3$ (sat.), $NaHSO_4$ (8 g in 50 mL water), $NaHCO_3$ (sat.) and then water and brine. The solution was dried over $MgSO_4$ and concentrated on a rotary evaporator to give a white solid. This was dissolved in a minimum of DCM : MeOH (9 : 1, v/v) and diethylether was added until the solution was cloudy. After standing for 2 h at 0 °C, the product was collected by filtration. After 24 h under high vacuum a white solid was collected with a yield of 1.36 g (1.6 mmol, 60%). *Data for divergently synthesised material.* ^{1}H NMR: δ_H (500 MHz; CD_3OD) 7.70–7.90 (8H, m, Ar–H), 7.40–7.50 (12H, m, Ar–H), 4.61 (1H, dd, 6.0, 8.0, COC*H*(CH_2)NH), 4.48 (1H, dd, 6.0, 8.0, COC*H*(CH_2)NH), 4.41 (1H, dd, 5.0, 9.0, COC*H*(CH_2)NH), 3.65 (3H, s, CH_3O), 3.37 (4H, m, C*H*$_2$NH), 3.11 (2H, m, C*H*$_2$NH), 1.40–2.00 (18H, m, CH_2); ^{13}C NMR: δ_C (125 MHz; CD_3OD) 173.6 (*C*OOMe), 173.5, 173.3 (both CONH), 169.4, 169.4, 169.1, 169.0 (all Ar–*C*=O), 134.9, 134.8, 134.1, 134.0 (all Ar*C*–C), 132.3, 131.9, 128.9, 128.9, 128.8, 127.7, 127.7, 127.5, 127.5 (all ArC–H), 54.4, 54.0, 52.8 (all CO*C*H(CH_2)NH), 52.6 (OCH_3), 40.0, 39.9, 39.0 (all CH_2NH), 32.3, 32.1, 31.1, 29.3, 29.2, 28.7, 23.5, 23.3 (all CH_2); MS: EI *m*/*z* 856.4 (15), 855.4 ([M + Na]$^+$, 25), 834.2 (45), 833.2 ([M + H]$^+$, 100); HR FAB MS: $C_{47}H_{56}N_6O_8Na$ requires 855.4057, measured 855.4052; TLC (90 : 10 : 0.1, DCM–MeOH–triethylamine): R_f = 0.47; IR: ν_{max} (KBr discs)/cm^{-1} 3300*s*, 3064*m*, 3033*w*, 2937*m*, 2862*m*, 1743*m*, 1637*s*, 1577*w*, 1537*s*, 1489*m*, 1439*w*, 1309*m*, 1213*w*, 1180*w*, 1157*w*, 1076*w*, 1028*w*, 930*w*, 849*w*, 802*w*, 694*s*; $[a]_D$ +3.6 (c = 1, MeOH). *Significant differences in data for convergently synthesised material.* ^{1}H NMR: δ_H (500 MHz; CD_3OD) 7.90–8.00 (8H, m, Ar–H), 7.40–7.60 (12H, m, Ar–H), 4.64 (1H, m, COC*H*(CH_2)NH), 4.52 (1H, m, COC*H*(CH_2)NH), 4.42 (1H, m, COC*H*(CH_2)NH), 3.70 (3H, s, CH_3O), 3.42 (4H, m, C*H*$_2$NH), 3.21 (2H, m, C*H*$_2$NH), 1.30–2.10 (18H, m, CH_2); $[a]_D$ −3.6 (c = 1, MeOH).

Synthesis of Bz-G2(COOH)

Bz-G2(COOMe) (from either the divergent or convergent approach) (0.44 g, 0.53 mmol) was dissolved in MeOH (30 ml) and cooled to 0 °C. NaOH (aq.) (2.5 ml, 1 M, 2.5 mmol) was added and the solution was stirred under a nitrogen atmosphere for 24 h. The solvent was removed by rotary evaporation and water was added (20 ml). This was then acidified to pH 2 with $NaHSO_4$ (8 g in 50 ml water) and the product was collected by filtration. This was washed with dilute HCl and diethyl ether and dried overnight under a high vacuum to produce a white solid (0.30 g, 0.37 mmol, 70%). *Data for divergently synthesised material:* ^{1}H NMR: δ_H (500 MHz; CD_3OD) 7.80–8.10 (8H, m, Ar–H), 7.40–7.60 (12H, m, Ar–H), 4.65 (1H, dd, 5.0, 8.0, COC*H*(CH_2)NH), 4.53 (1H, dd, 6.0, 8.0, COC*H*(CH_2)NH), 4.44 (1H, dd, 4.5, 9.0, COC*H*(CH_2)NH), 3.40 (4H, m, C*H*$_2$NH), 3.20 (2H, m, C*H*$_2$NH), 1.40–2.10 (18H, m, CH_2); ^{13}C NMR: δ_C (125 MHz; CD_3OD) 175.3 (COOH), 174.9, 174.8 (CONH), 174.7, 174.6, 170.4, 170.3 (all Ar–*C*=O), 135.9, 135.4, (Ar*C*–C), 132.8, 132.6, 128.7, 128.6, 128.3 (all ArC–H), 55.6, 55.3, 53.6 (all CO*C*H(CH_2)NH), 40.7, 40.6, 40.2, 40.0 (all CH_2NH), 33.0, 32.9, 32.1, 30.2, 29.7, 28.9, 24.6, 24.5, 23.9 (all CH_2); MS: EI *m*/*z* 818.5 ([M + H]$^+$, 50), 817.4 (100), 801 (95); HR FAB MS $C_{46}H_{54}N_6O_8Na$ requires 841.3901, measured 841.3908; TLC (90 : 10 : 0.1, DCM–MeOH–triethylamine):

$R_f = 0$; IR: ν_{max} (KBr discs)/cm^{-1} 3700*w*, 3456*s*, 3301*m*, 3074*w*, 2954*w*, 2928*m*, 2859*m*, 1723*m*, 1646*s*, 1575*m*, 1533*m*, 1490*w*, 1447*m*, 1312*w*, 1261*m*, 1185*w*, 1101*w*, 1026*w*, 800*w*, 694*m*, 667*w*; $[\alpha]_D$ +5.6 (*c* = 1, MeOH). *Significant differences in data for convergently synthesised material:* ^{1}H NMR: δ_H (500 MHz; CD_3OD) 7.80–8.00 (8H, m, Ar–H), 7.40–7.60 (12H, m, Ar–H), 4.65 (1H, m, COC*H*(CH_2)NH), 4.53 (1H, m, COC*H*(CH_2)NH), 4.44 (1H, m, COC*H*(CH_2)NH), 3.40 (4H, m, C*H*$_2$NH), 3.20 (2H, m, C*H*$_2$NH), 1.40–2.10 (18H, m, CH_2); $[\alpha]_D$ +2.5 (*c* = 1, MeOH).

Synthesis of $^+H_3$N-G2(COOMe) TFA$^-$

Boc-G2(COOMe) (0.69 g, 0.8 mmol) was dissolved in a minimum of dichloromethane (5 ml), and trifluoroacetic acid (4.0 g, 2.75 ml, 35 mmol) was added. This was stirred under a nitrogen atmosphere for 24 h and the solvent and excess trifluoracetic acid were removed by rotary evaporation. Acetonitrile (3 × 50 ml) and diethylether (3 × 50 ml) were added separately and removed by rotary evaporation and the product was dried under high vacuum to produce a hygroscopic white solid in quantitative yield. ^{1}H NMR: δ_H (270 MHz; D_2O) 4.40 (1H, m, COC*H*(CH_2)NH), 4.02 (1H, t, 6.5, COC*H*(CH_2)NH), 3.90 (1H, t, 6.5, COC*H*(CH_2)NH), 3.73 (3H, s, CH_3O), 3.20 (2H, t, 6.5, C*H*$_2$NH), 2.97 (4H, m, C*H*$_2$NH), 1.40–2.00 (18H, m, CH_2); ^{13}C NMR: δ_C (67.9 MHz; D_2O) 174.5 (*C*OOCH$_3$), 170.3, 169.8 (CH*C*ONH), 163.4 (q, 36, CF_3*C*OO–), 116.0 (q, 290, CF_3), 53.6, 53.5, 53.4 (all CO*C*H(CH_2)NH), 53.3 (CH_3O), 39.7, 39.5 (both CH_2NH), 30.9, 30.4, 28.2, 26.9, 23.7, 23.0, 21.9, 21.5 (all CH_2); MS: EI *m*/*z* 439.3 ([M + Na − 4CF_3CO_2H]$^+$, 100), 417.2 ([M + H − 4CF_3CO_2H]$^+$, 45), 289.1 (37); TLC (90 : 10 : 0.1, DCM–MeOH–triethylamine): $R_f = 0$.

Synthesis of $^+H_3$N-G2(COOMe) Cl$^-$

Boc-G2COOMe (2.15 g, 2.6 mmol) was dissolved in a minimum of dichloromethane (10 ml), and HCl in diethylether (10 ml, 1 M, 10 mmol) was added. This was stirred under a nitrogen atmosphere for 48 h and the solvent and excess reagents were removed by rotary evaporation. The product could be isolated using the following procedure: acetonitrile (2 × 10 ml) and diethylether (2 × 10 ml) were added separately and removed by rotary evaporation and the product was dried under high vacuum to produce a white powder (0.66 g, 1.17 mmol, 45%). δ_H (270 MHz; D_2O) 4.47 (1H, dd, 5.0, 9.0, COC*H*(CH_2)NH), 4.10 (1H, t, 6.5, COC*H*(CH_2)NH), 3.96 (1H, t, 6.5, COC*H*(CH_2)NH), 3.76 (3H, s, CH_3O), 3.28 (2H, m, C*H*$_2$NH), 3.00 (4H, m, C*H*$_2$NH), 1.40–2.00 (18H, m, CH_2); ^{13}C NMR: δ_C (67.9 MHz; D_2O) 173.9 (*C*OOCH$_3$), 170.3, 170.1 (CH*C*ONH), 54.3, 54.1, 53.9 (all CO*C*H(CH_2)NH), 53.0 (CH_3O), 40.5, 40.3, 40.2 (all CH_2NH), 34.9, 34.7, 32.3, 32.1, 28.1, 23.1, 22.6, 15.5, 14.2 (all CH_2); MS: EI *m*/*z* 417 ([M + H − 4HCl]$^+$, 100%), 209 (23). HR FAB MS $C_{19}H_{14}N_6O_4Na$ requires 417.3189, measured 417.3188; TLC (90 : 10 : 0.1, DCM–MeOH–triethylamine): $R_f = 0$; IR: ν_{max} (KBr disc)/cm^{-1} 3444*s*, 3242*m*, 3068*w*, 2931*s*, 1734*m*, 1674*s*, 1628*m*, 1571*m*, 1502*w*, 1271*w*, 1227*w*, 1178*w*, 1140*w*, 800*w*, 735*w*, 667*w*, 552*w*, 484*w*; $[\alpha]_D$ +14.8 (*c* = 1, MeOH).

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