Synthesis and characterisation of water-soluble poly(aryl ether) dendrimers for encapsulation of biomimetic active site analogues †

Michael J. Hannon,* Paul C. Mayers and Paul C. Taylor *

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, UK CV4 7AL. Fax: + 44 (0)24 7652 4112; E-mail: M.J.Hannon@warwick.ac.uk; P.C.Taylor@warwick.ac.uk

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Synthetic strategies to incorporate active site analogues of metalloenzymes at the core of water-soluble dendritic structures are explored. Synthesis of water-soluble aryl ether dendrimers containing tripyridyl metal-binding sites is successful when a convergent, but not a divergent, strategy is employed.

Introduction

In the last 10–15 years, the synthesis of dendritic structures and the investigation of their properties has been the subject of a major research effort worldwide.[1] Initial work focused on developing the principles behind dendrimer synthesis,[2] but more recently efforts have been directed towards the preparation of systems which have some function or exhibit novel properties, often at the borderline between polymer chemistry and supramolecular chemistry.[3] In particular, dendrimers containing metal ions—*metallodendrimers*[4]—have formed the basis of a good deal of work. Metal ion complexes have been incorporated in dendrimers in many ways: as surface groups,[5] as connectors and branching centres[6] and as dendrimer cores.[7]

We are interested in the development of dendritic systems which contain, at their core, ligands for the coordination of a variety of metal ions with the eventual goal of preparing systems containing active site analogues of metalloenzymes encapsulated inside a dendrimer. In the molecules we envisage, the coordinated metal ion will *not* play a structural role in forming the dendrimer but rather the dendrimer itself will provide a unique environment for the metal ion.[8] For example, coordination inside a dendrimer could prevent access by other ligands and lead to weakly solvated "vacant" coordination sites that would normally be occupied by other ligands. This is of particular interest in our development of enzyme models: nature often modifies the properties and coordination numbers of metal ions by burying them in a substrate binding pocket thus enabling them to play a catalytic role. Dendrimer systems of this type may thus be considered to provide a model for *functional* metal ion sites in proteins; most metallodendrimers containing metal ions in their interior reported to date mimic the *structural* role played by protein-bound metal ions.

A wide variety of dendrimer systems has been described in the literature. Given our biomimetic goals, we desired dendritic systems that would best model the relatively rigid microenvironment found in the interior of protein structures while maintaining a small degree of flexibility. For this reason, we discounted relatively flexible aliphatic dendrimers and very rigid alkyne and alkyne-aryl dendrimers and chose instead to focus on aryl dendrimers. Functionality placed on the exterior of a dendrimer is important for determining its solubility; clearly aqueous solubility is an important target in biomimetic design. Our target therefore is dendrimer systems with water-solubilising terminal groups and aryl-based interiors into the centre of which might be incorporated a variety of different active site mimics.

To investigate how we might prepare such systems we focused on the incorporation of a tripodal N_3-donor ligand, tri-2-pyridylmethanol,[9] although we envisage that the same techniques may readily be adapted to permit incorporation of a wide range of biomimetic sites. Tripodal N_3-donor ligands are of particular interest in the investigation of zinc enzymes such as carbonic anhydrase which contain a tetrahedral zinc(II) ion with three sites occupied by N-donor atoms from the protein framework and a vacant or weakly solvated fourth site in a pseudo-tetrahedral arrangement—a system that has proved extremely difficult to replicate in free solution due to either the coordination of a second ligand to give a hexadentate pseudo-octahedral ZnL_2 arrangement or the formation of hydroxy-bridged $LZn(OH)_nZnL$ species.[10]

Results and discussion

Divergent strategy

Our initial synthetic studies centered around divergent strategies: that is the growth of a dendrimer outwards from a central core molecule. Tri-2-pyridylmethanol has a hydroxy functionality which can act as a dendrimer growth point. Efficient synthetic procedures for the divergent growth of ester-linked dendrimers based upon an acid chloride or carbodiimide ester coupling and benzyl protection strategy that ultimately leads to hydroxy-terminated, water-soluble compounds have already been established in our laboratories.[11] However, the tertiary alcohol of the core molecule was found to be rather unreactive—tripyridylmethanol itself shows no reaction with either acid chloride **1** or the corresponding acid in the presence of dicyclohexylcarbodiimide (DCC) under a variety of reaction conditions.

If the sodium salt of tripyridylmethanol is prepared by treatment with sodium hydride in tetrahydrofuran, the reaction with acid chloride **1** then proceeds smoothly in DMF to give ester **2**. However, attempts to remove the benzyl protecting groups to give dihydroxy compound **3** were unsuccessful under a variety of conditions (Scheme 1). Under all conditions, the main product obtained was 3,5-dihydroxybenzoic acid, indicating cleavage of not only the protecting groups but also the ester function. When the reaction was carried out using transfer hydrogenation conditions,[12] the only nitrogen containing component found was tri-2-pyridylmethane[13] and when con-

† Synthetic procedures for compounds **1** to **13** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b002026p/

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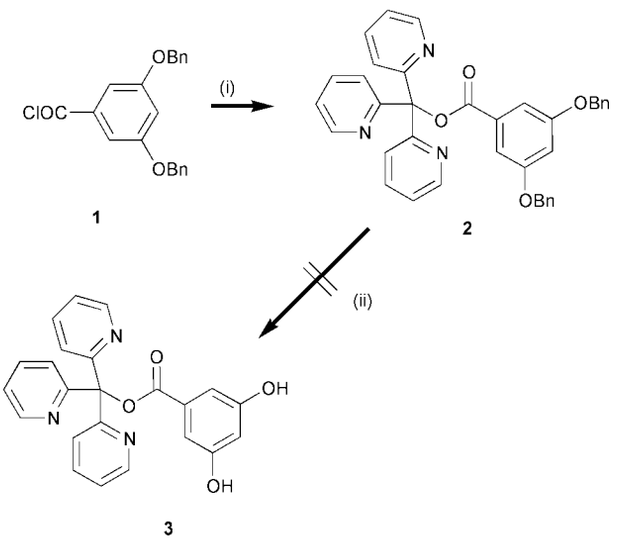
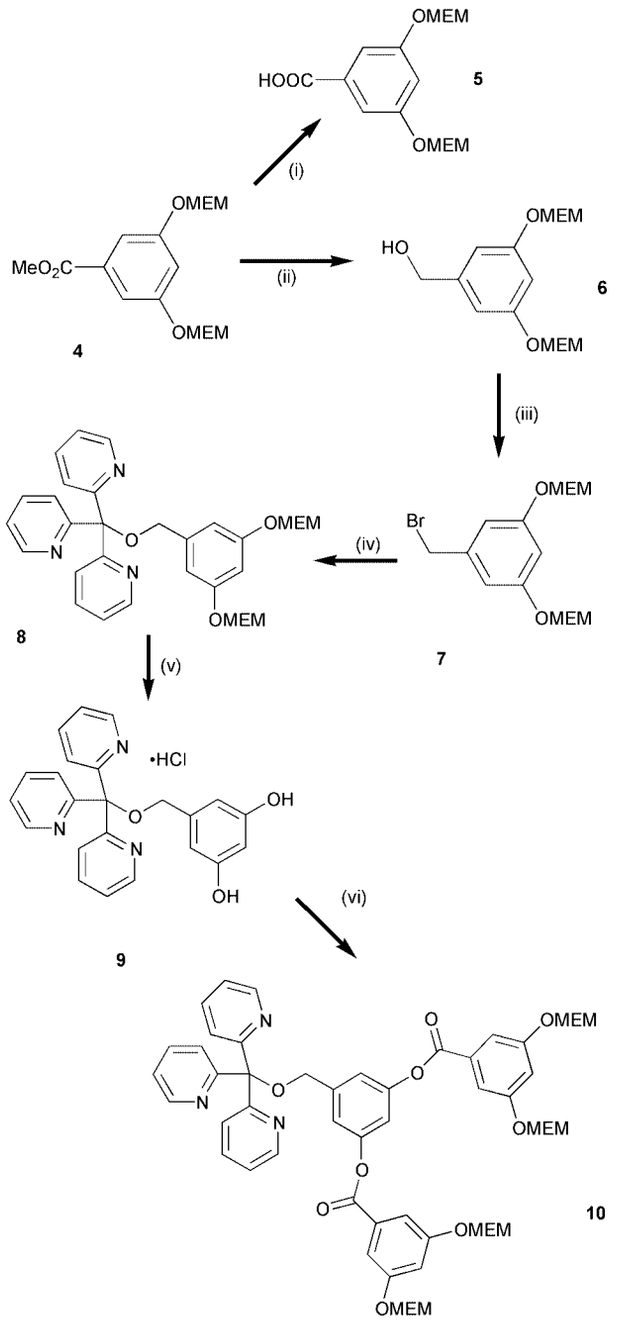


Scheme 1 Attempted synthesis using benzyl protecting groups. *Reagents*, *conditions and yields*: (i) $(2\text{-Py})_3CO^-Na^+$, DMF, 18 h, RT (80%); (ii) 10% Pd/C, chloroform–methanol, 30 psi H_2, 18 h or 10% Pd/C, cyclohexene, ethanol, reflux 18 h.

ventional hydrogenation techniques[11] were used, to our surprise di-2-pyridyl(2-piperidyl)methane was the major product.[14]

Since the tri-2-pyridylmethanol core was clearly not stable to hydrogenation, we decided to investigate alternative protecting groups. The choice of suitable groups is somewhat limited since they must be removed in near quantitative yield under conditions that will enable the resulting hydroxy-terminated dendrimers to be readily purified despite their high polarity and relative insolubility in organic solvents (particularly at higher generations). We decided to investigate the methoxyethoxymethyl (MEM) group which can be removed in the presence of acid or Lewis acid. Ester **4**[15] was hydrolysed to acid **5** under basic conditions (Scheme 2), but attempts to prepare the acid chloride using thionyl chloride were unsuccessful presumably due to the sensitivity of the MEM protecting groups to hydrogen chloride generated in the reaction. We therefore decided to attach the core molecule *via* an ether link: ester **4** was reduced to alcohol **6** with lithium aluminium hydride and brominated with PPh_3–CBr_4 to give bromide **7**. Treatment of **7** with the sodium salt of tripyridylmethanol afforded ether-linked compound **8** which was readily deprotected with strong acid to give the core molecule **9** as its hydrochloride salt. DCC coupling[11] of **9** with 2 equivalents of acid **5** gave the second generation dendrimer **10** in good yield. However, attempts to deprotect **10** under similar conditions were unsuccessful due to the sensitivity to acid of the ester functions, so no larger dendrimers were prepared. A divergent preparation of ether-linked dendrimers was not pursued since the yields obtained in the ether synthesis are not high enough to allow the preparation of larger dendrimers in good yield and high purity.

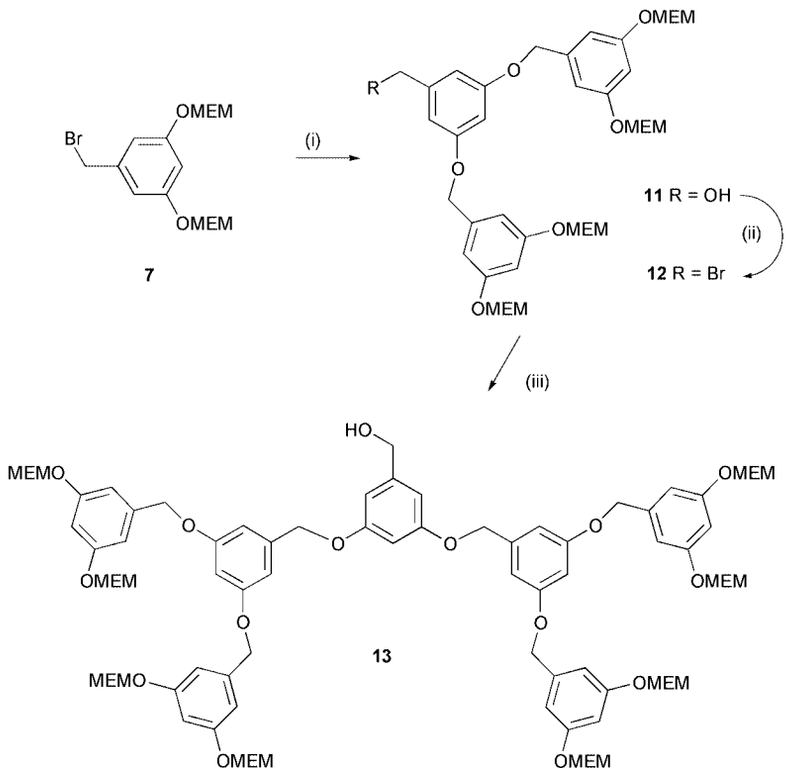


Scheme 2 Divergent synthesis using MEM protecting groups. *Reagents*, *conditions and yields*: (i) 40% KOH, ethanol, reflux 3 h (76%); (ii) $LiAlH_4$, Et_2O, 4 h, RT (100%); (iii) PPh_3, CBr_4, THF, 0 °C to RT, 0.25 h (49%); (iv) $(2\text{-Py})_3CO^-Na^+$, DMF, 18 h, RT (85%); (v) 36% HCl, MeOH, 3 h, RT (100%); (vi) acid **5**, DCC, dimethylpyridinium toluene-*p*-sulfonate, CH_2Cl_2, RT, 18 h (64%).

Convergent strategy

Further attempts to prepare hydroxy-terminated dendrimers utilised the MEM-bromide **7** in a convergent strategy. MEM-protected, benzyl ether-linked dendrimers were synthesised as outlined in Scheme 3. Treatment of bromide **7** with 3,5-dihydroxybenzyl alcohol, potassium carbonate and catalytic 18-crown-6 in a Fréchet-type synthesis[2c] gave the G_2-OH dendrimer **11** in good yield. However, bromination of **11** using CBr_4–PPh_3 gave G_2-Br **12** in a rather low yield (39%). Further investigations revealed that this low yield was due to partial cleavage of the MEM protecting groups presumably due to the formation of acidic by-products during the course of the reaction. A second coupling with dihydroxybenzyl alcohol gave G_3-OH dendrimer **13** in good yield but attempts to brominate **13** failed to give the corresponding bromide in a synthetically useful yield. The lower bromination yields at higher generations presumably reflect the increased number of surface MEM groups that are susceptible to acidic cleavage.

Rather than pursue other protecting group strategies, we decided to investigate whether we could develop a convergent synthesis using a non-removable surface group, but one which would ensure solubility in as wide a range of solvents as possible including, most importantly, water and aqueous solvent mixtures as well as organic solvents. This was prompted by recent reports which suggest that the triethylene glycol monomethyl ether group could afford the required solubility in aliphatic dendrimer systems[16] so we developed a synthesis based upon this terminal group as outlined in Scheme 4.[17] Triethylene glycol monomethyl ether was treated with toluene-*p*-sulfonyl chloride in pyridine to give tosylate **15**[18] which was used to



Scheme 3 Convergent synthesis using MEM protecting groups. *Reagents*, *conditions and yields*: (i) 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6, acetone, reflux 18 h (100%); (ii) PPh_3, CBr_4, THF, 0 °C to RT, 0.5 h (39%); (iii) 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6, acetone, reflux 18 h (88%).

alkylate the disodium salt of methyl 3,5-dihydroxybenzoate to give ester **16**. Reduction with lithium aluminium hydride followed by bromination with 1,2-bis(diphenylphosphino)-ethane (DPPE) and tetrabromomethane gave bromide **18**. The use of triphenylphosphine (TPP) in the bromination step was found to result in troublesome separation of the bromo dendrimers and the triphenylphosphine oxide by-product.[19] This problem is overcome by the use of DPPE as reported in the literature.[20]

Bromide **18** was elaborated to higher generation dendrimers *via* successive applications of the Fréchet-type cycle[2c] based upon alkylation of 3,5-dihydroxybenzyl alcohol and activation *via* bromination of the terminal hydroxy group. G_1-Br gave G_2-OH **19** in quantitative yield and bromination gave G_2-Br **20** (79%). A second application of the cycle gave G_3-OH **21** (93%) followed by G_3-Br **22** (81%). A final cycle gave G_4-OH **23** (84%) and G_4-Br **24** (80%). Treatment of G_1-Br **18**, G_2-Br **20**, G_3-Br **22** and G_4-Br **24** with sodium tripyridylmethoxide in DMF gave G_1-$OCPy_3$ **25** (62%), G_2-$OCPy_3$ **26** (60%), G_3-$OCPy_3$ **27** (55%) and G_4-$OCPy_3$ **28** (60%) respectively as shown in Scheme 5. The relatively low yield for the final step is consistent with the difficulty of alkylation of the hindered tertiary alcohol of tri-2-pyridylmethanol which we observed even in simple small molecule reactions.

To allow for the water solubility of all the compounds, the Fréchet methodology[2c] was modified and an aqueous work up procedure was avoided. The yields compare well with those reported by Fréchet in the organic soluble benzyl-terminated dendrimer series[2c] although purification was somewhat more difficult: the non-crystalline nature of the compounds meant that recrystallisations were not possible and purification was by flash chromatography on silica gel.

The series of compounds obtained do indeed have excellent solubility properties: this is well illustrated by our ability to use $CDCl_3$ and D_2O virtually interchangeably as solvents when recording NMR spectra of the dendrons and dendrimers, particularly for the lower generations. The ^1H NMR spectrum of G_2-OH dendron **19** is illustrated in both $CDCl_3$ and D_2O in Fig. 1. At higher generations, the water solubility is somewhat reduced thus making $CDCl_3$ a more practical choice for acquisition of NMR data, but the water solubility is still more than adequate for the types of biomimetic catalytic studies that we ultimately envisage. The ^1H NMR spectra are typically broader in D_2O than $CDCl_3$.

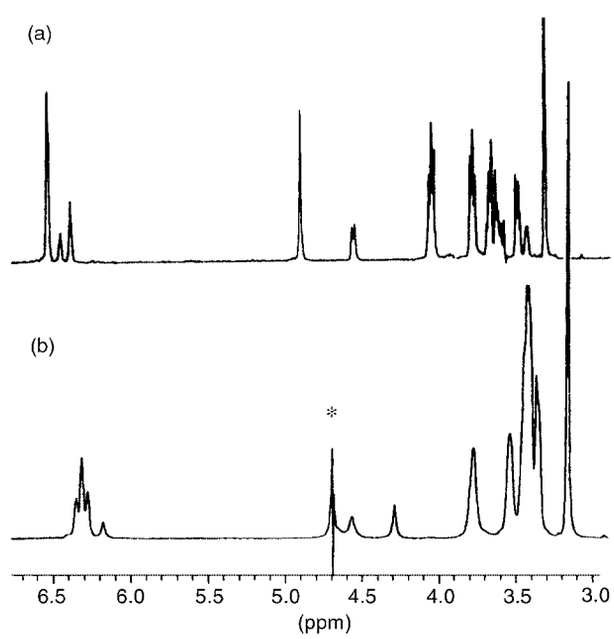
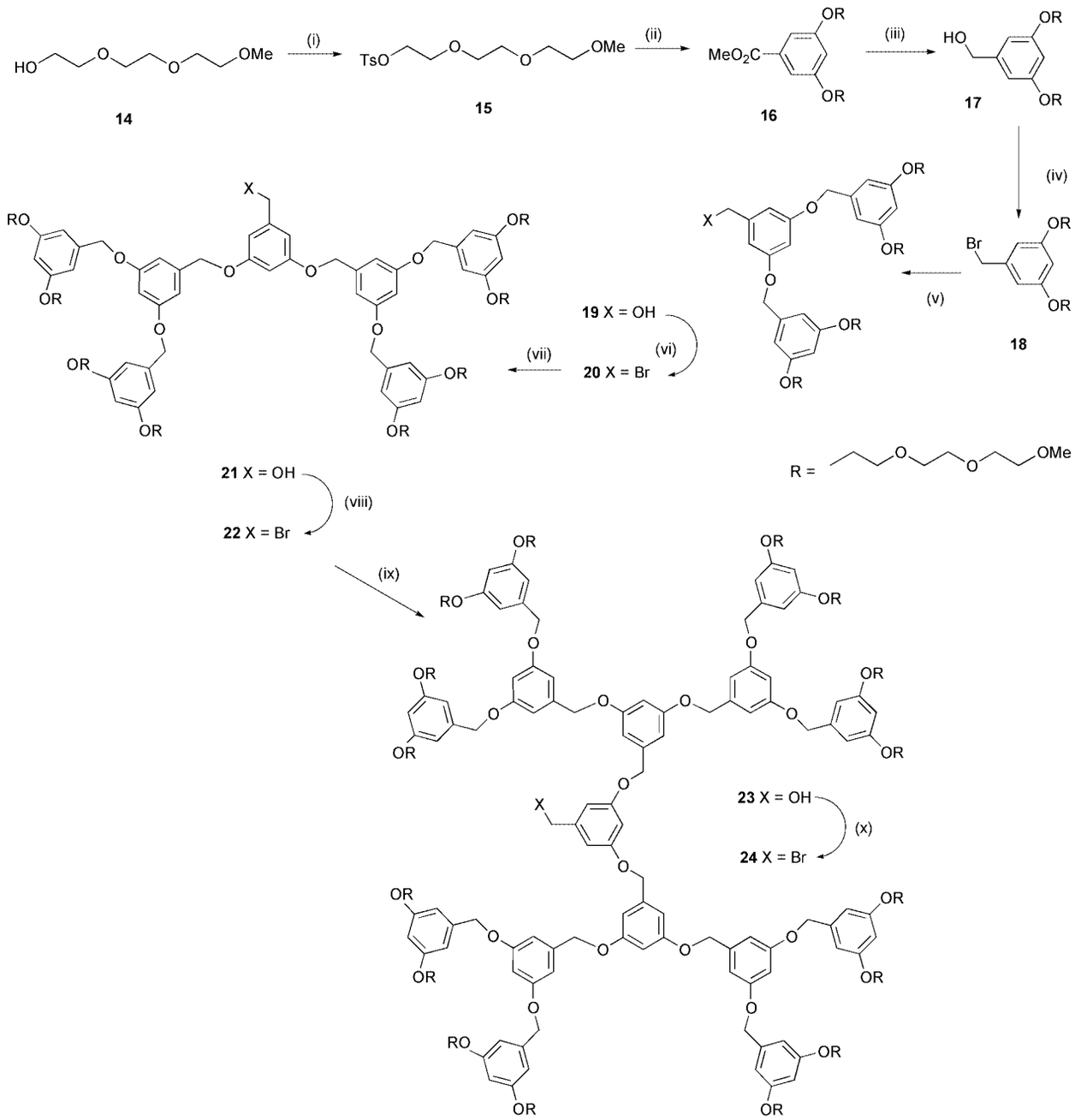


Fig. 1 300 MHz ^1H NMR spectra of G_2-OH dendrimer **19** in (a) $CDCl_3$ and (b) D_2O. * Denotes residual solvent peaks.

The presence of the ethylene glycol units on the exterior also affords another important property: unlike many other neutral dendrimers, the compounds are readily characterised by electrospray mass spectrometry. Addition of a small amount of alkali metal ions (Li^+, Na^+ or K^+) results in the formation of adducts with the dendrimers (presumably *via* binding to the triethylene



Scheme 4 Convergent synthesis of triethylene glycol terminated dendrimers. *Reagents, conditions and yields*: (i) toluene-*p*-sulfonyl chloride, DMAP, pyridine, 18 h, 0–5 °C (90%); (ii) methyl 3,5-dihydroxybenzoate (disodium salt), DMF, 55 °C, 18 h (76%); (iii) $LiAlH_4$, Et_2O, RT, 18 h (97%); (iv) DPPE, CBr_4, THF, 0 °C, 10 min (60%); (v) 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6, acetone, reflux, 18 h (100%); (vi) DPPE, CBr_4, THF, 0 °C, 10 min (79%); (vii) 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6, acetone, reflux, 18 h (93%); (viii) DPPE, CBr_4, THF, 0 °C, 10 min (81%); (ix) 3,5-dihydroxybenzyl alcohol, K_2CO_3, 18-crown-6, acetone, reflux, 18 h (84%); (x) DPPE, CBr_4, THF, 0 °C, 10 min (80%).

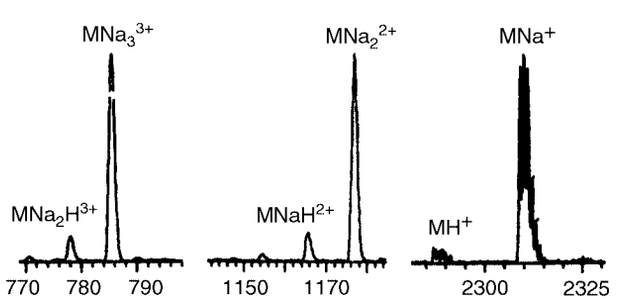
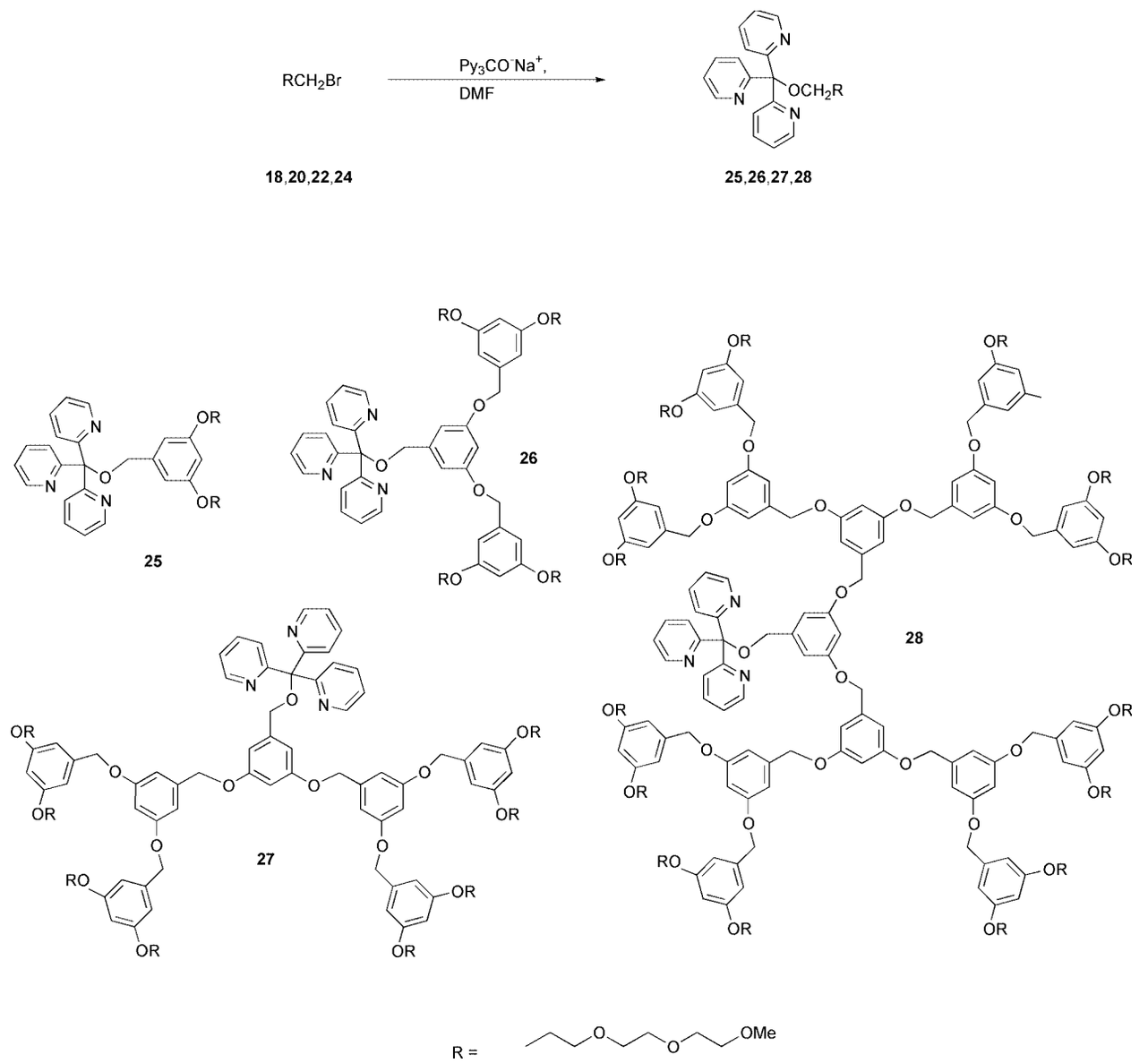


Fig. 2 Positive electrospray mass spectrum of G_3-$OCPy_3$ dendrimer **27** in the presence of NaCl.

glycol groups). These adducts give extremely intense signals in the positive electrospray mass spectrum. Several signals are observed corresponding to the binding of different numbers of metal ions as illustrated for the G_3-CPy_3 dendrimer **27** in the presence of Na^+ ions in Fig. 2. The formation of highly charged species allows the characterisation of very high molecular weight dendrimers on a mass spectrometer with a relatively modest *m*/*z* range: for example, we have characterised dendrimers with a molecular weight approaching 10 kDa on an instrument where the *m*/*z* detection range is limited to 4000. This is not dissimilar to the mass spectrometric characterisation of large, multiply charged protein molecules.[21] A great advantage of the electrospray technique is the mild nature of the ionisation method. Because of the low cone voltages used in the ionisation process, we can assume that we see no significant fragmentation of the molecule. We can therefore assign any signals corresponding to partial dendrimer units as being due to the presence of impurities rather than fragmentation in the spectrometer and thus indicative that further purification is required. Because the electrospray technique is very sensitive as



Scheme 5 Preparation of tri-2-pyridylmethanol dendrimers. *Reagents*, *conditions and yields*: $(2\text{-Py})_3CO^-Na^+$, DMF, RT, 18 h (62% for **25**, 60% for **26**, 55% for **27**, 60% for **28**).

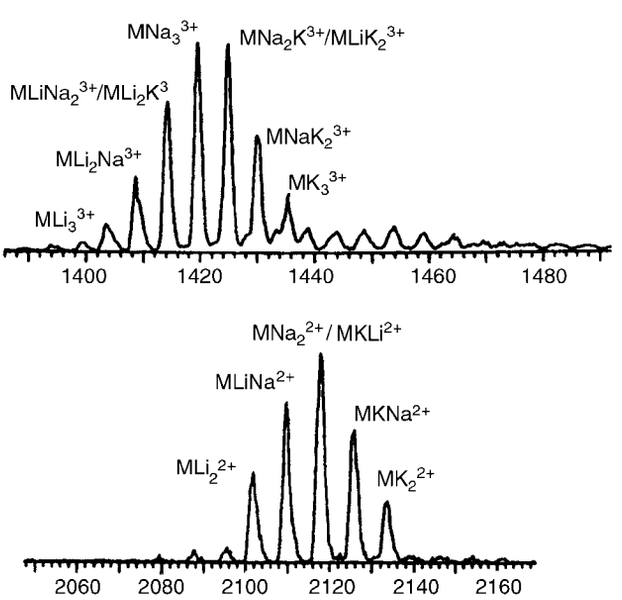


Fig. 3 Positive electrospray mass spectrum of G_4-OH dendrimer **23** in the presence of equimolar amounts of LiCl, NaCl and KCl.

well as very mild, it will detect the presence of extremely small amounts of impurity that may not be detected by other techniques—for example, ^{1}H NMR spectroscopy—particularly at higher generations. Electrospray compatibility is also an especially important feature for our future biomimetic studies since metal–ligand coordination complexes are rarely compatible with the harsher MALDI technique traditionally favoured by dendrimer chemists.

Although the best spectra are obtained in the presence of Na^+ ions, similar results can also be achieved using Li^+ or K^+ ions. The relative binding affinities have been investigated in a qualitative manner by the addition of equimolar amounts of lithium, sodium and potassium chlorides to G_4-OH dendron **23** and acquisition of the electrospray spectrum illustrated in Fig. 3. By considering the signals corresponding to the 2+ ions, the MNa_2^{2+} signal is most intense (although this signal is presumably a superimposition of MNa_2^{2+} and the much weaker $MLiK^{2+}$ which have the same *m*/*z* value) followed by MLi_2^{2+} and MK_2^{2+} which are of approximately equal intensity. This suggests a binding affinity thus: $Na^+ > Li^+ \sim K^+$.

Conclusions

In conclusion, we have utilised a Fréchet-type methodology to

prepare, in high yield, a series of water-soluble aryl ether dendrimers containing a potentially biomimetic metal ion binding site at their core. This convergent strategy is far more versatile and straightforward than similar divergent approaches and allows the rapid preparation of relatively large amounts of dendrimers. The triethylene glycol functionality reproduces in our aryl dendrimers the excellent solubility properties reported by other workers in aliphatic dendrimer systems.[16] Binding of alkali metal ions by the triethylene glycol groups affords an excellent means of characterisation and purity determination *via* electrospray mass spectrometry. Preliminary studies confirm that the tripyridyl containing dendrimers bind a range of metal ions including zinc(II). The preparation and investigation of these complexes are currently underway in our laboratories and will be reported elsewhere.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ACF250 or AMX 300 spectrometers operated in Fourier transform mode. Chemical shifts were referenced to TMS as an internal standard or to residual solvent peaks ($CHCl_3$ at 7.25 ppm in d-chloroform and $CD_3S(O)CHD_2$ at 2.52 ppm in d_6-DMSO). Positive electrospray spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer at the EPSRC National Mass Spectrometry Centre, Swansea. Samples were injected as a solution in methanol and typical cone voltages were in the range 30–50 V. Samples containing additional Na^+ were prepared by treatment of the sample with a small volume of a saturated methanolic solution of sodium chloride. Other mass spectra were recorded on a Kratos MS80 instrument. FAB^+ spectra were recorded using a matrix of *m*-nitrobenzyl alcohol (NOBA). Microanalyses were performed on a Leeman Labs Inc. CE440 Elemental Analyser. Analytical TLC was performed on aluminium plates precoated with Merck silica gel 60 (F_{254}). Flash chromatography was carried out using Merck 9385 Kieselgel 60 silica (0.040–0.063 mm, 230–400 mesh).

Thionyl chloride was redistilled before use. Tetrahydrofuran, diethyl ether and dimethylformamide used in reactions were the best available commercial anhydrous grades. Other solvents and reagents were standard grades available from commercial suppliers and were used without any further purification.

Tripyridylmethanol[9] and tosylate **15**[18] were prepared as reported in the literature. Synthetic procedures for compounds **1** through to **13** are available in the electronic supplementary information.

Methyl 3,5-bis(methoxyethoxyethoxyethoxy)benzoate 16

To an ice-cooled suspension of sodium hydride (60% suspension in oil, 1.31 g, 32.7 mmol) in dry dimethylformamide (3 cm^3) was added methyl 3,5-dihydroxybenzoate (2.50 g, 14.9 mmol) in dimethylformamide (8 cm^3) with stirring over 5 minutes. The mixture was heated at 60 °C for 2 hours before cooling in ice. A solution of tosylate **15** (11.83 g, 37.2 mmol) in dimethylformamide (8 cm^3) was added dropwise over 10 minutes and the resulting mixture then heated at 55 °C for 18 hours. After cooling, ethyl acetate (150 cm^3) and water (25 cm^3) were added to the product to give a clear 2-phase solution. The ethyl acetate layer was separated and washed with further water (2 × 25 cm^3), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (4 × 20 cm) using 4% methanol in dichloromethane as eluant to give ester **16** (5.20 g, 76%) as a colourless oil (Found C, 57.0; H, 7.3. $C_{22}H_{36}O_{10}$ requires C, 57.4; H, 7.9%); δ_H(250 MHz; $CDCl_3$) 3.35 (6H, s, OMe), 3.50–3.75 (16H, m, CH_2), 3.84 (4H, t, *J* 4.8, CH_2), 4.12 (4H, t, *J* 4.7, CH_2), 6.67 (1H, t, *J* 2.3, 4-Ar), 7.16 (2H, d, *J* 2.3, 2-Ar); δ_C(75.5 MHz; $CDCl_3$) 52.3, 59.1, 67.9, 69.7, 70.7, 70.8, 70.9, 72.1, 106.9, 108.1, 132.1, 160.0, 166.7; *m*/*z* (EI$^+$) 460 (8%, M$^+$), 238 (10), 103 (25), 91 (37), 59 (100), 45 (45).

3,5-Bis(methoxyethoxyethoxyethoxy)benzyl alcohol 17

To a mechanically stirred, ice-cooled suspension of lithium aluminium hydride (3.29 g, 86.7 mmol) in dry ether (40 cm^3) was added a solution of ester **16** (20.0 g, 46.2 mmol) in dry ether (200 cm^3) dropwise over 1 hour. The resulting mixture was stirred at room temperature for 2 hours and then gently refluxed for 3 hours. After cooling, the reaction was quenched by the sequential addition of water (3.3 cm^3), 15% aqueous sodium hydroxide (3.3 cm^3) and water (10 cm^3). The precipitate formed was removed by filtration and washed well with tetrahydrofuran. The combined filtrate and tetrahydrofuran washings were dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give alcohol **17** (18.2 g, 97%) as a pale oil (Found: C, 58.3; H, 8.5. $C_{21}H_{36}O_9$ requires C, 58.3; H, 8.4%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3600w, 3461br, 3060s, 2881vs, 1955w, 1597vs, 1450vs, 1351vs, 1275vs and 1104vs; δ_H(300 MHz; $CDCl_3$) 2.04 (1H, t, *J* 5.8, OH), 3.35 (6H, s, OMe), 3.50–3.75 (16H, m, CH_2), 3.81 (4H, t, *J* 4.9, CH_2), 4.08 (4H, t, *J* 4.8, CH_2), 6.39 (1H, t, *J* 2.3, 4-Ar), 6.51 (2H, d, *J* 2.3, 2-Ar); δ_C(75.5 MHz; $CDCl_3$) 59.2, 64.9, 67.7, 70.0, 70.7, 70.9, 71.0, 72.1, 100.8, 105.5, 144.3, 160.2; *m*/*z* (EI$^+$) 432 (100%, M$^+$), 286 (45), 183 (72), 140 (72), 103 (66), 59 (100).

3,5-Bis(methoxyethoxyethoxyethoxy)benzyl bromide 18

To an ice-cooled solution of alcohol **17** (2.68 g, 6.20 mmol) and tetrabromomethane (3.08 g, 9.30 mmol) in dry tetrahydrofuran (6 cm^3) was added a solution of 1,2-bis(diphenylphosphino)-ethane (1.85 g, 4.65 mmol) in dry tetrahydrofuran (6 cm^3) dropwise over 10 minutes. The resulting mixture was stirred in ice for 10 minutes and at room temperature for 10 minutes before quenching by the addition of water (0.25 cm^3). The solvent was removed under reduced pressure and the product purified by flash chromatography on silica gel (2 × 20 cm) using 2–3% methanol in dichloromethane as eluant to give bromide 18 (1.85 g, 60%) as a colourless oil (Found: C, 50.7; H, 7.1. $C_{21}H_{35}O_8Br$ requires C, 50.9; H, 7.1%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3060s, 2882vs, 2827s, 1955w, 1596vs, 1450vs, 1351vs, 1296vs and 1104vs; δ_H(300 MHz; $CDCl_3$) 3.37 (6H, s, OMe), 3.53 (4H, m, –CH_2–), 3.65–3.70 (12H, m, 3 × –CH_2–), 3.82 (4H, t, *J* 4.7, –CH_2–), 4.09 (4H, t, *J* 4.7, –CH_2–), 4.38 (2H, s, -CH_2Br), 6.41 (1H, t, *J* 2.2, 4-ArH), 6.53 (2H, d, *J* 2.2, 2-ArH); δ_C(75.5 MHz; $CDCl_3$) 33.9 (CH_2Br), 59.4 (OMe), 67.9, 70.0, 70.9, 71.0, 71.4, 72.2 (6 × CH_2), 102.0 (4-Ar), 108.2 (2-Ar), 140.0 (C1), 160.3 (C3); *m*/*z* (EI$^+$) 494/496 (100%, M$^+$), 416 (80), 383 (55), 295 (80).

General procedure for the preparation of dendritic benzyl alcohols

A mixture of the required benzyl bromide (2.05 equivalents), 3,5-dihydroxybenzyl alcohol (1.0 equivalents), dry potassium carbonate (2.5 equivalents) and 18-crown-6 (0.2 equivalents) were heated at reflux under nitrogen in dry acetone for 18 hours. The product was diluted with dichloromethane, filtered and the solvent removed under reduced pressure to yield the crude product which was purified by flash chromatography on silica gel.

General procedure for the preparation of dendritic benzyl bromides

To an ice-cooled solution of the required benzylic alcohol dendrimer (1.0 equivalents) and tetrabromomethane (1.5 equivalents) in dry tetrahydrofuran was added a solution of 1,2-bis(diphenylphosphino)ethane (0.75 equivalents) in dry tetrahydrofuran over several minutes. The resulting mixture was

stirred at 0 °C for 10 minutes and then allowed to warm to room temperature over 20 minutes. The reaction was quenched by the addition of water (0.25 cm^3) and the solvent removed under reduced pressure to yield the crude product which was purified by flash chromatography on silica gel.

G_2-OH Dendrimer 19

Dendrimer **19** was prepared from bromide **18** (1.85 g, 3.73 mmol), 3,5-dihydroxybenzyl alcohol (0.249 g, 1.776 mmol), 18-crown-6 (94 mg, 0.355 mmol) and dry potassium carbonate (0.613 g, 4.44 mmol) in dry acetone (20 cm^3). The crude product was purified by flash chromatography using 3–4% methanol in dichloromethane as eluant to give dendrimer **19** (1.73 g, 100%) as a colourless oil (Found: C, 59.8; H, 7.7. $C_{49}H_{76}O_{19}\cdot H_2O$ requires C, 59.6; H, 8.0%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3600w, 3463br, 3060s, 2881vs, 1956w, 1712w, 1597vs, 1450vs, 1350vs, 1296vs and 1105vs; δ_H(300 MHz; $CDCl_3$) 3.35 (12H, s, OMe), 3.53 (8H, m, $-CH_2-$), 3.60–3.75 (24H, m, 3 × $-CH_2-$), 3.82 (8H, t, *J* 4.8, $-CH_2-$), 4.09 (8H, t, *J* 4.8, $-CH_2-$), 4.59 (2H, d, *J* 5.5, -C*H*$_2$OH), 4.94 (4H, s, CH_2'), 6.42 (2H, t, *J* 2.3, 4-Ar′), 6.48 (1H, t, *J* 2.3, 4-Ar), 6.57 (6H, m, 2-Ar and 2-Ar′); δ_C(300 MHz; $CDCl_3$) 59.2 (OMe), 64.8 (CH_2), 67.7 (CH_2'), 69.9, 70.0, 70.8, 70.9, 71.0 and 72.1 (3 × OCH_2CH_2O), 101.2 (C4 and C4′), 105.7 (C2), 106.2 (C2′), 139.6 (C1′), 144.6 (C1), 160.0 and 160.3 (C3 and C3′); *m*/*z* (ES^+ with added Na^+) 991 (52%, MNa^+), 507 (100%, MNa_2^{2+}).

G_2-Br Dendrimer 20

Dendrimer **20** was prepared from **19** (1.70 g, 1.75 mmol), tetrabromomethane (0.873 g, 2.63 mmol) and 1,2-bis(diphenylphosphino)ethane (0.526 g, 1.32 mmol) in dry tetrahydrofuran (2 cm^3 + 2 cm^3). Flash chromatography using 2–3% methanol in dichloromethane as eluant gave dendrimer **20** (1.42 g, 79%) as a pale oil (Found: C, 56.8; H, 7.3. $C_{49}H_{75}O_{18}Br$ requires C, 57.0; H, 7.3%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3060w, 2882vs, 1964w, 1736w, 1596vs, 1450vs, 1322s and 1105vs; δ_H(300 MHz; $CDCl_3$) 3.36 (12H, s, OMe), 3.53 (8H, m, $-CH_2-$), 3.60–3.75 (24H, m, 3 × $-CH_2-$), 3.83 (8H, t, *J* 4.9, $-CH_2-$), 4.09 (8H, t, *J* 4.9, $-CH_2-$), 4.39 (2H, s, -CH_2Br), 4.93 (4H, s, CH_2'), 6.43 (2H, t, *J* 2.1, 4-Ar′), 6.50 (1H, t, *J* 2.1, 4-Ar), 6.56 (4H, d, *J* 2.1, 2-Ar′), 6.59 (2H, d, *J* 2.1, 2-Ar); δ_C(75.5 MHz; $CDCl_3$) 34.0 (CH_2Br), 59.3 (OMe), 67.6, 70.0 (2 × CH_2), 70.3 (O*C*H_2Ar), 70.9, 71.0, 71.1, 72.2 (4 × CH_2), 101.4 (C4′), 102.5 (C4), 106.3 (C2′), 108.5 (C2), 139.3 (C1′), 140.1 (C1), 160.3 (C3), 160.4 (C3′); *m*/*z* (ES^+ with added Na^+) 1056 (90%, MNa^+), 539 (100%, MNa_2^{2+}).

G_3-OH Dendrimer 21

Dendrimer **21** was prepared from **20** (1.42 g, 1.38 mmol), 3,5-dihydroxybenzyl alcohol (0.0964 g, 0.688 mmol), 18-crown-6 (0.036 g, 0.138 mmol) and potassium carbonate (0.238 g, 1.72 mmol) in dry acetone (10 cm^3). Flash chromatography using 2–4% methanol in dichloromethane as eluant gave dendrimer **21** (1.31 g, 93%) as a colourless oil (Found: C, 60.0; H, 7.4. $C_{105}H_{156}O_{39}\cdot CH_2Cl_2$ requires C, 59.9; H, 7.5%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3600w, 3463br, 3060s, 2881vs, 1955w, 1596vs, 1450vs, 1350vs, 1296vs and 1130vs; δ_H(300 MHz; $CDCl_3$) 2.37 (1H, t, *J* 5.5, OH), 3.34 (24H, s, OMe), 3.52 (16H, m, $-CH_2-$), 3.60–3.75 (48H, m, 3 × $-CH_2-$), 3.81 (16H, t, *J* 4.8, $-CH_2-$), 4.08 (16H, t, *J* 4.8, $-CH_2-$), 4.58 (2H, d, *J* 5.5, -C*H*$_2$OH), 4.93 and 4.95 (12H, 2s, CH_2' and CH_2''), 6.42 (4H, t, *J* 2.3, 4-Ar″), 6.49 (3H, m, 4-Ar and 4-Ar′), 6.56 (10H, m, 2-Ar and 2-Ar″), 6.62 (4H, d, *J* 2.1, 2-Ar′); δ_C(300 MHz; $CDCl_3$) 59.2 (OMe), 64.7 (G_1 CH_2), 67.7 (OCH_2CH_2O), 69.9 (G_3 CH_2), 70.1 (G_2 CH_2), 70.7, 70.8, 71.0, 72.1 (OCH_2CH_2O), 101.0 (C4), 101.3 (C4″), 101.7 (C4′), 105.7 (C2), 106.2 (C2″), 106.5 (C2′), 139.5 (C1″), 139.8 (C1′), 144.8 (C1), 160.1, 160.2 and 160.3 (C3, C3′ and C3″); *m*/*z* (ES^+ with added Na^+) 2065 (0.5%, MNa^+), 1044 (100%, MNa_2^{2+}), 704 (100%, MNa_3^{3+}).

G_3-Br Dendrimer 22

Dendrimer **22** was prepared from **21** (1.19 g, 0.583 mmol), tetrabromomethane (0.290 g, 0.874 mmol) and 1,2-bis(diphenylphosphino)ethane (0.174 g, 0.437 mmol) in dry tetrahydrofuran (1.6 cm^3 + 0.7 cm^3). Flash chromatography using 2–3% methanol in dichloromethane as eluant gave bromide **22** (1.00 g, 81%) as a pale oil (Found: C, 59.8; H, 7.4. $C_{105}H_{155}O_{38}Br$ requires C, 59.9; H, 7.4%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3060w, 2881s, 1596vs, 1450vs, 1372s, 1273s, 1173vs, 1104vs, 1070s; δ_H(300 MHz; $CDCl_3$) 3.35 (24H, s, OMe), 3.53 (16H, m, $-CH_2-$), 3.60–3.75 (48H, m, 3 × $-CH_2-$), 3.81 (16H, t, *J* 4.9, $-CH_2-$), 4.09 (16H, t, *J* 4.9, $-CH_2-$), 4.40 (2H, s, CH_2Br), 4.93 (12H, s, CH_2' and CH_2''), 6.42 (4H, t, *J* 2.3, 4-Ar″), 6.52 (3H, m, 4-Ar and 4-Ar′), 6.57 (8H, d, *J* 2.1, 2-Ar″), 6.61 (2H, d, *J* 2.1, 2-Ar), 6.64 (4H, d, *J* 2.1, 2-Ar′); δ_C(300 MHz; $CDCl_3$) 59.2 (OMe), 67.7 (OCH_2CH_2O), 69.9 (CH_2''), 70.2 (CH_2'), 70.8, 70.9, 71.1 (OCH_2CH_2O), 101.3 (C4″), 101.9 (C4′), 102.3 (C4), 106.2 (C2″), 106.7 (C2′), 108.5 (C2), 139.4 (C1 and C1″), 140.2 (C1′), 160.2, 160.3 and 160.4 (C3, C3′ and C3″); *m*/*z* (ES^+ with added K^+) 2144 (2%, MK^+), 1091 (100%, MK_2^{2+}), 741 (35%, MK_3^{3+}).

G_4-OH Dendrimer 23

Dendrimer **23** was prepared from **22** (0.780 g, 0.371 mmol), 3,5-dihydroxybenzyl alcohol (0.026 g, 0.185 mmol), 18-crown-6 (9.8 mg, 0.037 mmol) and potassium carbonate (0.064 g, 0.463 mmol) in dry acetone (3 cm^3). Flash chromatography using 2–5% methanol in dichloromethane as eluant gave dendrimer **26** (0.650 g, 84%) as a colourless oil (Found: C, 61.2; H, 7.5. $C_{217}H_{316}O_{79}\cdot 4H_2O$ requires C, 61.2; H, 7.7%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3502w, 3060s, 2881vs, 1955w, 1596vs, 1450vs, 1372s, 1296s, 1245w, 1145vs and 1070vs; δ_H(300 MHz; $CDCl_3$) 2.58 (1H, t, *J* 5.2, OH), 3.33 (48H, s, OMe), 3.51 (32H, m, $-CH_2-$), 3.60–3.75 (96H, m, 3 × $-CH_2-$), 3.80 (32H, t, *J* 4.7, $-CH_2-$), 4.07 (32H, t, *J* 4.7, $-CH_2-$), 4.57 (2H, d, *J* 5.2, -C*H*$_2$OH), 4.92 and 4.95 (28H, 2s, CH_2', CH_2'' and CH_3'''), 6.41 (8H, t, *J* 2.1, 4-Ar‴), 6.51 (7H, m, 4-Ar, 4-Ar′ and 4-Ar″), 6.56 (16H, d, *J* 2.1, 2-Ar‴), 6.60 (2H, d, *J* 2.1, 2-Ar), 6.64 (8H, d, *J* 2.1, 2-Ar″), 6.66 (4H, d, *J* 2.1, 2-Ar′); δ_C(75.5 MHz; $CDCl_3$) 59.3 (OMe), 64.8, 67.8, 69.9, 70.2, 70.8, 70.9, 71.1, 72.2 (CH_2), 101.4 and 101.8 (C4, 4′, 4″, 4‴), 105.9, 106.43 and 106.7 (C2, C2′, C2″, C2‴), 139.4 (C1‴), 139.6 (C1″), 139.8 (C1′), 144.8 (C1), 160.2, 160.3 and 160.4 (C3, C3′, C3″, C3‴); *m*/*z* (ES^+ with added Na^+) 2118 (5%, MNa_2^{2+}), 1420 (82%, MNa_3^{3+}), 1070 (100%, MNa_4^{4+}).

G_4-Br Dendrimer 24

Dendrimer **24** was prepared from **23** (0.590 g, 0.141 mmol), tetrabromomethane (0.233 g, 0.705 mmol) and 1,2-bis(diphenylphosphino)ethane (0.140 g, 0.353 mmol) in dry tetrahydrofuran (1.0 cm^3 + 0.5 cm^3). Flash chromatography using 2–4% methanol in dichloromethane as eluant gave dendrimer **24** (0.480 g, 80%) as a colourless oil (Found: C, 59.6; H, 7.2. $C_{217}H_{315}O_{78}Br\cdot 6H_2O$ requires C, 59.8; H, 7.5%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3060w, 2881vs, 1596vs, 1450vs, 1371s, 1297s, 1245w, 1173vs, 1146vs and 1070s; δ_H(300 MHz; $CDCl_3$) 3.31 (48H, s, OMe), 3.50 (32H, m, $-CH_2-$), 3.58–3.75 (96H, m, 3 × $-CH_2-$), 3.81 (32H, t, *J* 4.7, $-CH_2-$), 4.07 (32H, t, *J* 4.7, $-CH_2-$), 4.35 (2H, s, $-CH_2$Br), 4.91 and 4.95 (28H, 2s, CH_2', CH_2'' and CH_3'''), 6.38 (8H, t, *J* 2.1, 4-Ar‴), 6.48 (6H, m, 4-Ar′ and 4-Ar″), 6.53 (18H, m, 2-Ar‴ and 4-Ar), 6.58 (2H, d, *J* 2.1, 2-Ar), 6.62 (8H, d, *J* 2.1, 2-Ar″), 6.64 (4H, d, *J* 2.1, 2-Ar′); δ_C(75.5 MHz; $CDCl_3$) 34.0 (CH_2Br), 59.2 (OMe), 67.8, 70.0, 70.3, 70.9, 71.0, 71.1, 72.0, 72.3 (CH_2), 100.9 (C4‴), 101.4 (C4″ and C4′), 101.9 (C4), 105.9 (C2‴), 106.4 (C2″ and C2′), 108.6 (C2), 139.4 and 139.5 (C1‴, C1″ and C1′), 140.2 (C1), 160.3 and 160.4 (C3‴, C3″, C3′, C3); *m*/*z* (ES^+ with added K^+) 2164 (15%, MK_2^{2+}), 1456 (12%, MK_3^{3+}), 1101 (5%, MK_4^{4+}).

G_1-$OCPy_3$ Dendrimer 25

Sodium tripyridylmethoxide (1.060 g, 3.72 mmol) and bromo dendrimer **18** (1.84 g, 3.72 mmol) in anhydrous dimethylformamide (7 cm^3) were stirred at room temperature for 18 hours before the solvent was removed under reduced pressure. Flash chromatography on silica gel (2 × 20 cm) using 2% methanol in dichloromethane as eluant gave dendrimer **25** (1.56 g, 62%) as a colourless oil (Found: C, 64.0; H, 6.9; N, 6.1. $C_{37}H_{47}N_3O_9{\cdot}H_2O$ requires C, 63.9; H, 7.0; N, 6.0%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3049w, 2881vs, 1594vs, 1465s, 1432s, 1295w, 1173s, 1107vs and 1070s; δ_H(300 MHz; $CDCl_3$) 3.35 (6H, s, OMe), 3.53 (4H, m, $–CH_2–$), 3.60–3.75 (12H, m, 3 × $–CH_2–$), 3.81 (4H, t, *J* 4.7, $–CH_2–$), 4.06 (4H, t, *J* 4.7, $–CH_2–$), 4.41 (2H, s, $–CH_2OCPy_3$), 6.35 (1H, t, *J* 2.4, 4-Ar), 6.51 (2H, d, *J* 2.4, 2-Ar), 7.13 (3H, ddd, *J* 7.4, 4.8, 1.2, 5-PyH), 7.64 (3H, ddd, *J* 8.2, 7.4, 1.8, 4-pyH), 7.71 (3H, d, *J* 8.2, 3-PyH), 8.56 (3H, d, *J* 4.8, 6-PyH); δ_C(75.5 MHz; $CDCl_3$) 59.4 (OMe), 67.3 (CH_2Ar), 67.8, 70.1, 70.9, 71.0, 71.2, 72.3 (CH_2), 88.8 (CPy_3), 100.8 (C4), 106.4 (C2), 122.5 (5-Py), 124.1 (3-Py), 136.5 (4-Py), 141.7 (C1), 148.9 (6-Py), 160.1 and 161.9 (2-Py and C3); *m*/*z* (CI^+) 678 (100%, MH^+).

G_2-$OCPy_3$ Dendrimer 26

Sodium tripyridylmethoxide (0.567 g, 2.00 mmol) and bromo dendrimer **20** (2.06 g, 2.00 mmol) in anhydrous dimethylformamide (4 cm^3) were stirred at room temperature for 18 hours before the solvent was removed under reduced pressure. Flash chromatography on silica gel (2 × 20 cm) using 2% methanol in dichloromethane as eluant gave dendrimer **26** (1.45 g, 60%) as a pale oil. ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3049w, 2881vs, 1596vs, 1450vs, 1351w, 1274w, 1174s, 1106vs and 1070s; δ_H(300 MHz; $CDCl_3$) 3.34 (12H, s, OMe), 3.52 (8H, m, $–CH_2–$), 3.60–3.75 (24H, m, 3 × $–CH_2–$), 3.80 (8H, t, *J* 4.6, $–CH_2–$), 4.06 (8H, t, *J* 4.6, $–CH_2–$), 4.42 (2H, s, $–CH_2OCPy_3$), 4.93 (4H, s, CH_2'), 6.42 (2H, t, *J* 2.4, 4′-Ar), 6.48 (1H, t, *J* 2.4, 4-Ar), 6.57 (6H, m, 2-Ar and 2′-Ar), 7.13 (3H, ddd, *J* 7.4, 4.8, 1.2, 5-PyH), 7.63 (3H, ddd, *J* 8.2, 7.4, 1.8, 4-PyH), 7.70 (3H, d, *J* 8.2, 3-PyH), 8.57 (3H, d, *J* 4.8, 6-PyH); δ_C(75.5 MHz; $CDCl_3$) 59.4 (OMe), 67.3, 67.8, 70.0, 70.3, 70.9, 71.0, 71.2 and 72.3 (CH_2), 88.8 (CPy_3), 101.3 and 101.4 (C4 and C4′), 106.4 and 106.6 (C2 and C2′), 122.5 (5-Py), 124.2 and 136.5 (3,4-Py), 139.5 (C1′), 141.9 (C1), 148.9 (6-Py), 160.1, 160.4 and 161.9 (C3, C3′ and 2-Py); *m*/*z* (ES^+ with added Na^+) 1236.5853 (20%, MNa^+. $C_{65}H_{87}N_3O_{19}Na^+$ requires 1236.5831), 630 (100%, MNa_2^{2+}), 619 (25%, $MNaH^{2+}$).

G_3-$OCPy_3$ Dendrimer 27

Sodium tripyridylmethoxide (0.203 g, 0.713 mmol) and bromo dendrimer **22** (1.50 g, 0.713 mmol) in anhydrous dimethylformamide (2.0 cm^3) were stirred at room temperature for 18 hours before the solvent was removed under reduced pressure. Flash chromatography on silica gel (2 × 20 cm) using 2–3% methanol in dichloromethane as eluant gave dendrimer **27** (0.060 g, 55%) as a pale oil (Found: C, 62.5; H, 7.3; N, 1.6. $C_{121}H_{167}N_3O_{39}{\cdot}2H_2O$ requires C, 62.5; H, 7.4; N, 1.8%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3049w, 2881s, 1596vs, 1450vs, 1372s, 1274s, 1173vs, 1105vs and 1070s; δ_H(300 MHz; $CDCl_3$) 3.35 (24H, s, OMe), 3.53 (16H, m, $–CH_2–$), 3.60–3.75 (48H, m, 3 × $–CH_2–$), 3.81 (16H, t, *J* 4.7, $–CH_2–$), 4.09 (16H, t, *J* 4.7, $–CH_2–$), 4.44 (2H, s, $–CH_2OCPy_3$), 4.91 (8H, s, CH_2''), 4.93 (4H, s, CH_2'), 6.42 (4H, t, *J* 2.3, 4-Ar″), 6.52 (3H, m, 4-Ar and 4-Ar′), 6.56 (8H, d, *J* 2.1, 2-Ar″), 6.60 (2H, d, *J* 2.1, 2-Ar), 6.65 (4H, d, *J* 2.1, 2-Ar′), 7.17 (3H, m, 5-PyH), 7.66 (6H, m, 3-PyH and 4-PyH), 8.61 (3H, d, *J* 4.7, 6-PyH); δ_C(75.5 MHz; $CDCl_3$) 59.9 (OMe), 67.3, 67.8, 70.0, 70.3, 70.9, 71.0, 71.2 and 72.3 (CH_2), 88.8 (CPy_3), 101.3 (C4), 101.5 (C4″), 101.8 (C4′), 106.0, 106.5 and 106.7 (C2, C2′ and C2″), 122.5 (5-Py), 124.1 (3-Py), 136.5 (4-Py), 139.4 (C1″), 139.8 (C1′), 141.9 (C1), 148.9 (6-Py), 160.1 (C3), 160.4 (C3″) and 161.9 (C3′); *m*/*z* (ES^+ with added Na^+) 2310 (1%, MNa^+), 1167 (100%, MNa_2^{2+}), 785 (80%, MNa_3^{3+}), 595 (10%, MNa_4^{4+}).

G_4-$OCPy_3$ Dendrimer 28

Sodium tripyridylmethoxide (0.038 g, 0.133 mmol) and bromo dendrimer **24** (0.370 g, 0.087 mmol) in anhydrous dimethylformamide (0.75 cm^3) were stirred at room temperature for 18 hours before the solvent was removed under reduced pressure. Flash chromatography on silica gel (2 × 20 cm) using 2.5% methanol in dichloromethane as eluant gave dendrimer **28** (0.231 g, 60%) as a colourless oil (Found: C, 56.2; H, 6.9; N, 0.6. $C_{233}H_{327}N_3O_{79}{\cdot}9CH_2Cl_2$ requires C, 55.9; H, 6.7; N, 0.8%); ν_{max} (CH_2Cl_2 solution)/cm^{-1} 3060w, 2881s, 1596vs, 1450vs, 1372s, 1297s, 1245w, 1244vs, 1105vs and 1070s; δ_H(300 MHz; $CDCl_3$) 3.32 (48H, s, OMe), 3.51 (32H, m, $–CH_2–$), 3.55–3.75 (96H, m, 3 × $–CH_2–$), 3.83 (32H, t, *J* 4.6, $–CH_2–$), 4.05 (32H, t, *J* 4.6, $–CH_2–$), 4.43 (2H, s, $–CH_2OCPy_3$), 4.90–4.94 (28H, m, CH_2', CH_2'' and CH_3'''), 6.42 (8H, t, *J* 2.1, 4-Ar‴), 6.51 (6H, m, 4-Ar′ and 4-Ar″), 6.55 (18H, m, 2-Ar‴ and 4-Ar), 6.61 (2H, d, *J* 2.1, 2-Ar), 6.64 (8H, d, *J* 2.1, 2-Ar″), 6.68 (4H, d, *J* 2.1, 2-Ar′), 7.09 (3H, br, 5-PyH), 7.57–7.69 (6H, br, 3-PyH and 4-PyH), 8.54 (3H, br, 6-PyH); δ_C(75.5 MHz; $CDCl_3$) 59.4 (OMe), 67.3, 67.9, 70.0, 70.4, 70.9, 71.0, 71.2 and 72.3 (CH_2), 88.8 (CPy_3), 101.5, 101.7 and 101.9 (C4, C4′, C4″, C4‴), 106.5 and 106.9 (C2, C2′, C2″, C2‴), 122.5 (5-Py), 124.2 (3-Py), 136.5 (4-Py), 139.4 (C1′, C1″ and C1‴), 139.9 (C1), 148.9 (6-Py), 160.1 (C3), 160.4 (C3′, C3″ and C3‴) and 161.9 (2-Py); *m*/*z* (ES^+ with added Na^+) 2240 (3%, MNa_2^{2+}), 1501 (50%, MNa_3^{3+}), 1131 (80%, MNa_4^{4+}), 909 (20%, MNa_5^{5+}).

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