Synthesis of polyester dendrimers

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Phloroglucinol 4, hydroquinone 5 and naphthalene-2,6-diol 6 react with the monomer 2, activated either by 1,3-dicyclohexylcarbodiimide (DCC) or as its acid chloride 3. Hydrogenolysis of the benzyl protecting groups, followed by repetition of these procedures leads, divergently, to three series of analytically pure aryl polyester dendrimers in high yields. The de Gennes limit appears to lie between generations three and four with the three-branched initiator core 4 and between generations four and five with the two-branched cores 5 and 6.

Introduction

Dendrimers are monodisperse high molecular weight macro-molecules.[1] A perfect dendrimer will have a geometrically increasing number of monomer units in each 'generation' (the core molecule is assigned generation 0, G_0) and all the terminal functional groups will be equidistant (through bond) from the core.

There are a number of strategies for dendrimer synthesis. The syntheses described here use the divergent method[1] (i.e. they start from the core as in Scheme 2) as opposed to the more recently developed convergent method in which syntheses start from the terminal groups.[1] The exponential double growth method, introduced in 1994,[2] is currently attracting much interest.

Dendrimers have, in the last 10 years, captured the imagination of a growing number of chemists.[1] The reasons given for this interest are diverse. Potential uses are, for example, in the area of carriers and controlled release of bioactive molecules for both agrochemical and pharmaceutical applications,[3] in catalysis[4] and as materials with novel photochemical and photophysical properties.[5] Dendrimers may also have applications in the fields where conventional synthetic polymers are prominent. For example, dendrimers have lower viscosities than their linear polymer counterparts of the same molecular weight, which should lead to significant improvements in handling properties of, in particular, surface coatings.[6]

The aim of the synthetic work described here was the preparation of three geometric series of aromatic polyester dendrimers,[7] in order to carry out a rigorous assessment of their physical properties. In particular, we wished to investigate the following features.

(1) The nature of the terminal groups is critically important to the properties of a given dendrimer. We wished to probe this phenomenon by preparing series of dendrimers which differed only in bearing hydrophilic or hydrophobic terminal groups. We selected hydroxy substituted compounds for the hydrophilic series and their benzyl protected analogues as hydrophobic counterparts, since these were ideal for our synthetic strategy and because Fréchet's group have shown that such compounds are accessible using the monomer 2.[8]

(2) The effect of the degree of branching of the initiator core both on dendrimer properties and on synthetic access to higher generations was also of interest. Hydroquinone 5 and phloroglucinol 4 are both readily available and provide a comparison between a two- and a three-branched initiator core.

(3) It should be possible to probe many of the interesting properties of dendrimers using luminescence studies. To this

end we chose to prepare analogues of the hydroquinone series with a fluorescent initiator core, viz. naphthalene-2,6-diol 6. Fréchet's group have previously prepared a number of aromatic polyester dendrimers.[8] Although the convergent methodology they adopted is apparently attractive for preparation of a range of dendrimers differing only at the initiator core, we were concerned that, with the smaller core molecules which we had selected, problems would arise in the sterically congested final step of a convergent synthesis due to the proximity of the reaction centres. The divergent approach, in addition to eliminating this problem, is uniquely effective in providing the series described in (1) above, every compound in the synthetic scheme being a target dendrimer.

Having made our choice of monomer 2 and initiator cores 4, 5 and 6, we proceeded to select suitable reaction conditions. The esterification requires activation of monomer 2, an obvious method for which is its transformation to the acid chloride 3, which is expected to undergo base-catalysed reaction with hydroxy groups. However, Fréchet's group prefer another literature method, viz. in situ activation of the acid with dicyclohexylcarbodiimide (DCC) in the presence of the acidic dimethylaminopyridinium tosylate catalyst proposed by Moore and Stupp.[9] We decided to investigate both these methods. Cleavage of the benzyl protecting groups with the usual palladium-on-carbon catalysed hydrogenolysis was chosen for deprotection.[10]
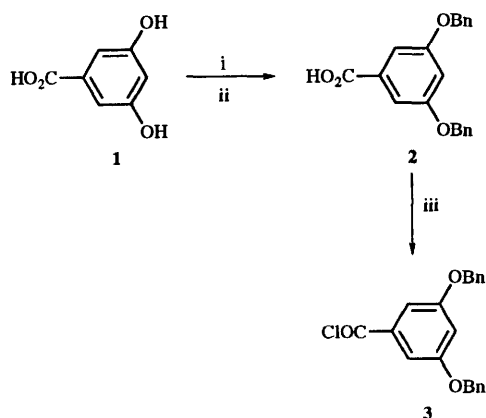
Results and discussion

Both monomer 2 and its acid chloride 3 were prepared using adaptations of literature methods (Scheme 1).[8,11]

Our divergent synthesis of phloroglucinol initiator core-derived polyester dendrimers is shown in Scheme 2. The analogous syntheses with hydroquinone and naphthalene-2,6-diol initiator cores are shown in abbreviated form in Scheme 3. Our nomenclature gives the dendrimer generation (G_1, G_2, etc.) followed by a letter denoting the nature of the core (P = phloroglucinol 4; H = hydroquinone 5; N = naphthalene-2,6-diol 6), a number in square brackets giving the number of surface functional groups and finally the nature of the surface functionality, viz. -OBn (Bn = benzyl) or -OH.

The two-branched initiator cores both led to fourth generation (G_4) dendrimers, but it was not possible to extend the syntheses to G_5 compounds which are presumably beyond the de Gennes limit.[12] With the three-branched initiator core, which leads to greater steric congestion, this limit appears to be reached before G_4. No G_4 dendrimers could be produced from G_3P-[24]-OH despite repeated attempts under a variety of conditions. In total, 22 different dendrimers were prepared,

Table 1

Initiator core	Method	% Yield G_1-OBn	% Yield G_2-OBn	% Yield G_3-OBn	% Yield G_4-OBn
Phloroglucinol 4	A	25	74	94	—
	B	100	0	0	—
Hydroquinone 5	A	8	85	88	86
	B	100	86	0	0
Naphthalene-2,6-diol 6	A	30	92	96	95
	B	100	80	0	0

Scheme 1 *Reagents and conditions:* i, BnBr, K_2CO_3, dimethylform-amide (DMF), 60 °C, 14 h; ii, KOH, EtOH, H_2O, reflux, 14 h; iii, $SOCl_2$, 80 °C, 2 h

all of which were isolated analytically pure. However, gel-permeation chromatography (GPC) results for all G_4 dendrimers indicated the presence of around 5% of an unidentified higher molecular weight species, even after repeated purification.

The yields for each esterification step are shown in Table 1. Deprotection of the benzyl-protected dendrimers was always high-yielding (89–97%). All the esterification steps were carried out with (a) acid chloride activation and (b) DCC activation as described above. It is clear that, despite previous experience,[7] the acid chloride method can be a useful one for polyester dendrimer synthesis. However, the most important observation is that the two methods of activation are entirely complementary. That is, the acid chloride method (a) is much higher yielding in preparation of low generation dendrimers, whereas the DCC method (b) is clearly superior for higher generations. We currently have no explanation for this phenomenon.

In all the reactions described, the starting materials and products have markedly different solubilities, *viz.* polar to non-polar in esterification steps and non-polar to polar on deprotection. Therefore, as the intermediates in a particular step become more 'product-like', the intermediates are prone to precipitation, thus preventing completion of the step. In the case of the deprotection, we have solved this problem by simply using mixed solvent systems (of a polar and a non-polar solvent) and increasing the polarity of the solvent during the reaction.

Reactions were monitored by GPC and judged to be complete when the dispersity of the product peak approached monodisperse. As noted by ourselves and others, GPC does not generally give a good measure of molecular weight of dendrimers.[13] Hence, after work-up, the dendrimers were analysed by MALDI-TOF mass spectrometry, to measure both molecular weight and homogeneity.[13] MALDI-TOF is particularly useful in monitoring the deprotection step, when incomplete reaction is evident from mass-ions at higher than expected mass. ^1H and ^{13}C NMR are used to confirm the

proposed structure, but may not be sensitive enough to detect low levels of defects in higher generation dendrimers.

MALDI-TOF mass spectra were obtained for all dendrimers, with the exception of the G_1-[4]-OH dendrimers derived from two-branched initiator cores (whose low mass coincided with peaks due to the matrix) and all the G_4 dendrimers. We, at present, have no explanation for the latter observation. 2,5-Dihydroxybenzoic acid was the matrix of choice for all these samples, though sinapinic acid [3-(4-hydroxy-3,5-dimethoxy-phenyl)prop-2-enoic acid] and α-cyano-4-hydroxycinnamic acid [2-cyano-2-(4-hydroxyphenyl)prop-2-enoic acid] were also successful in some cases.

GPC traces and mass and NMR spectra for the largest dendrimer for which MALDI-TOF mass spectra could be obtained (G_3P-[24]-OBn) are shown in Fig. 1. The GPC showed that an essentially monodisperse product (PDi = 1.000) had been produced and the MALDI-TOF mass spectrum showed only one major peak (M + Na^+) at 5168. The NMR spectra confirmed the structure to be the expected highly symmetrical dendrimer. The most useful ^1H signals are the singlet due to 2-H (7.3 ppm, 3 H), the doublets due to 2'-, 2''- and 2'''-H (8.1, 8.05 and 7.5 ppm, 6, 12 and 24 H) and the triplets due to 4'-, 4''- and 4'''-H (7.6, 7.55 and 6.9 ppm, 3, 6 and 12 H). In the ^{13}C spectrum the three different carbonyl peaks (C-5', -5'' and -5''', 162–164 ppm) are particularly clear with the expected relative integrals of 1:2:4 and the presence of only one type of benzyl site was confirmed by a single CH_2 signal at 70 ppm, three CH signals around 128 ppm and the quaternary signal at 136 ppm.
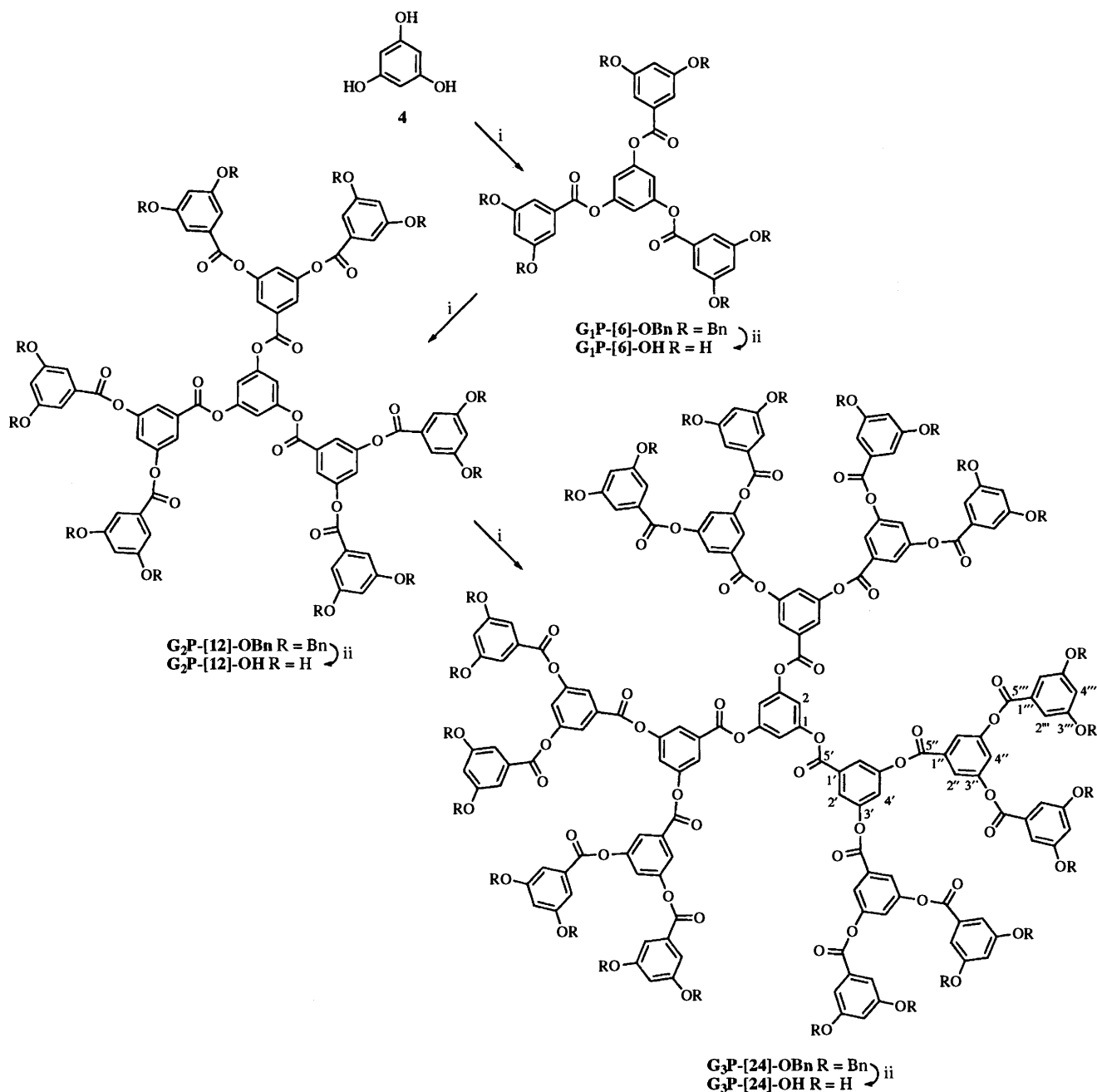
Conclusion

High-yielding divergent syntheses of hydroxy- and benzyloxy-terminated aromatic polyester dendrimers are possible if the appropriate method of acid activation (*i.e.* acid chloride or DCC) is selected for each step and if solvent polarity is controlled during the reactions. The de Gennes limit appears to lie between generations three and four with the three-branched initiator core 4 and between generations four and five with the two branched cores 5 and 6. MALDI-TOF mass spectrometry and NMR allow complete characterisation of the product dendrimers and thus allow the synthesis to proceed with confidence to each successive generation.

Experimental

General
Melting points of 3,5-dibenzyloxybenzoic acid and 3,5-dibenzyloxybenzoyl chloride were determined on a Stuart Scientific SMP1 instrument. Other melting points and glass transition points were determined on a Netzsch High Temperature DSC 404. IR spectra were recorded on a Perkin–Elmer infra-red spectrophotometer as thin films of KBr disks. ^1H NMR spectra were recorded in $CDCl_3$, CD_3OD or $[^2H_6]$acetone solution on a Bruker AC400 spectrometer (400 MHz) using solvent deuterium signal as internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or

OH

HO   OH

4

RO   OR

O   O

O   O

RO   OR

RO   OR

G_1P-[6]-OBn R = Bn
G_1P-[6]-OH R = H   } ii

RO   RO

OR   OR

O   O

RO   O   O   OR

O   O   OR

RO   O   O

O   OR

O   O   OR

RO   OR

RO

G_2P-[12]-OBn R = Bn
G_2P-[12]-OH R = H   } ii

G_3P-[24]-OBn R = Bn
G_3P-[24]-OH R = H   } ii

Scheme 2 *Reagents and conditions:* i, (method A), 2, DCC, 4-(dimethylamino)pyridinium toluene-*p*-sulfonate (DPTS), acetone, 20 °C, 48–168 h; (method B), 3, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, 20 °C, 120 h; ii, H_2, 10% Pd/C, CH_2Cl_2, MeOH, 20 °C, 50 lb in^{-2}, 24 h

[$^2H_6$]acetone solution at 101 MHz on a Bruker AC400 spectrometer using solvent deuterium signal as internal standard: UV spectra were recorded on a Philips PU8700 Series UV–VIS spectrophotometer in a Quartz cell. Analytical TLC was performed on commercial plates coated with silica gel 60 F_{254} (0.2 mm thick). Merck Kieselgel 60 (230–400 mesh) was used for flash chromatography. GPC analysis was carried out on a Polymer Laboratories™ modular system using a 3 µm, 15 cm Mixed-E column with PL Caliber™ GPC software (version 5.1) with tetrahydrofuran (THF) eluent at 1 cm³ min^{-1} and DRI detection. Calibration was with Polymer Labs polystyrene narrow molecular weight standards. All mass spectra of dendrimers were measured by Matrix Assisted Laser Desorption Ionisation Mass Spectrometry (MALDI-MS) carried out on a KRATOS KOMPACT. Irradiation was at 337 nm from a nitrogen laser source. 2,5-Dihydroxybenzoic acid was used as a matrix laid down in solution with the sample. Deprotected dendrimers were deposited from a water–acetone mixture whilst protected dendrimers were cast from chloroform.

The following abbreviations are used for dendrimers: Ar refers to the core aromatic ring, Ar′ refers to first generation aromatic rings, Ar″ refers to second generation aromatic rings, *etc.*, PhCH$_2$ refers to benzyl groups. Other abbreviations are DCC (1,4-dicyclohexylcarbodiimide) and DPTS (4-dimethylamino)-pyridinium toluene-*p*-sulfonate).

3,5-Dibenzyloxybenzoic acid 2[9]

This compound was prepared by an adaption of two literature methods.[8,14] A suspension of anhydrous potassium carbonate (17 g) in a solution of 3,5-dihydroxybenzoic acid (10 g, 65 mmol) and benzyl bromide (24 cm³, 200 mmol) in DMF (35 cm³), was stirred, using an overhead stirrer, at 60 °C for 14 h. The mixture was allowed to cool and then evaporated under reduced pressure. Water (200 cm³) was added to the resulting oil and the slurry was extracted with dichloromethane (4 × 100 cm³). The combined extracts were evaporated under reduced pressure and the resulting oil was dissolved in ethanol (50 cm³) and refluxed with 40% aqueous potassium hydroxide (100 cm³)
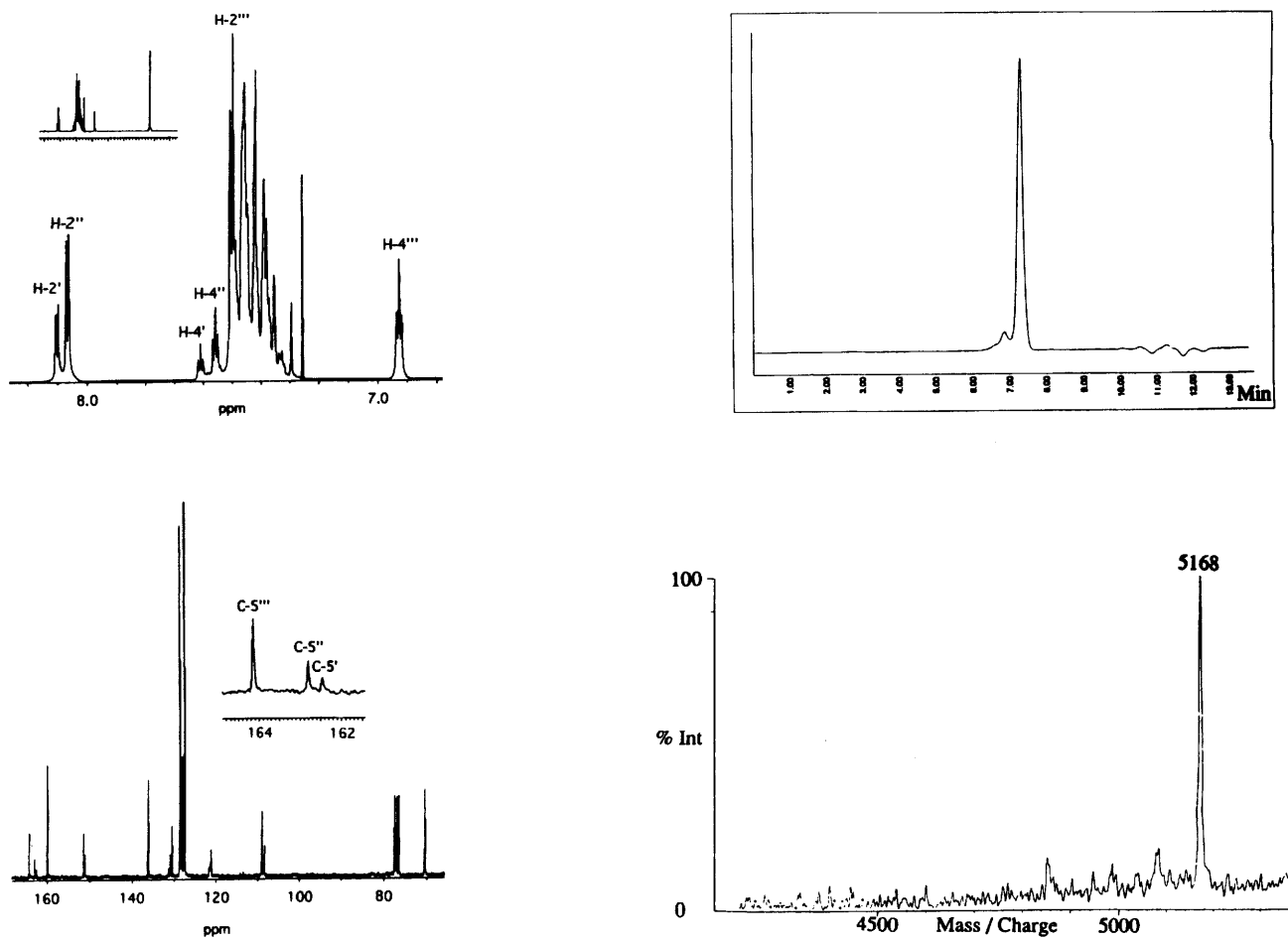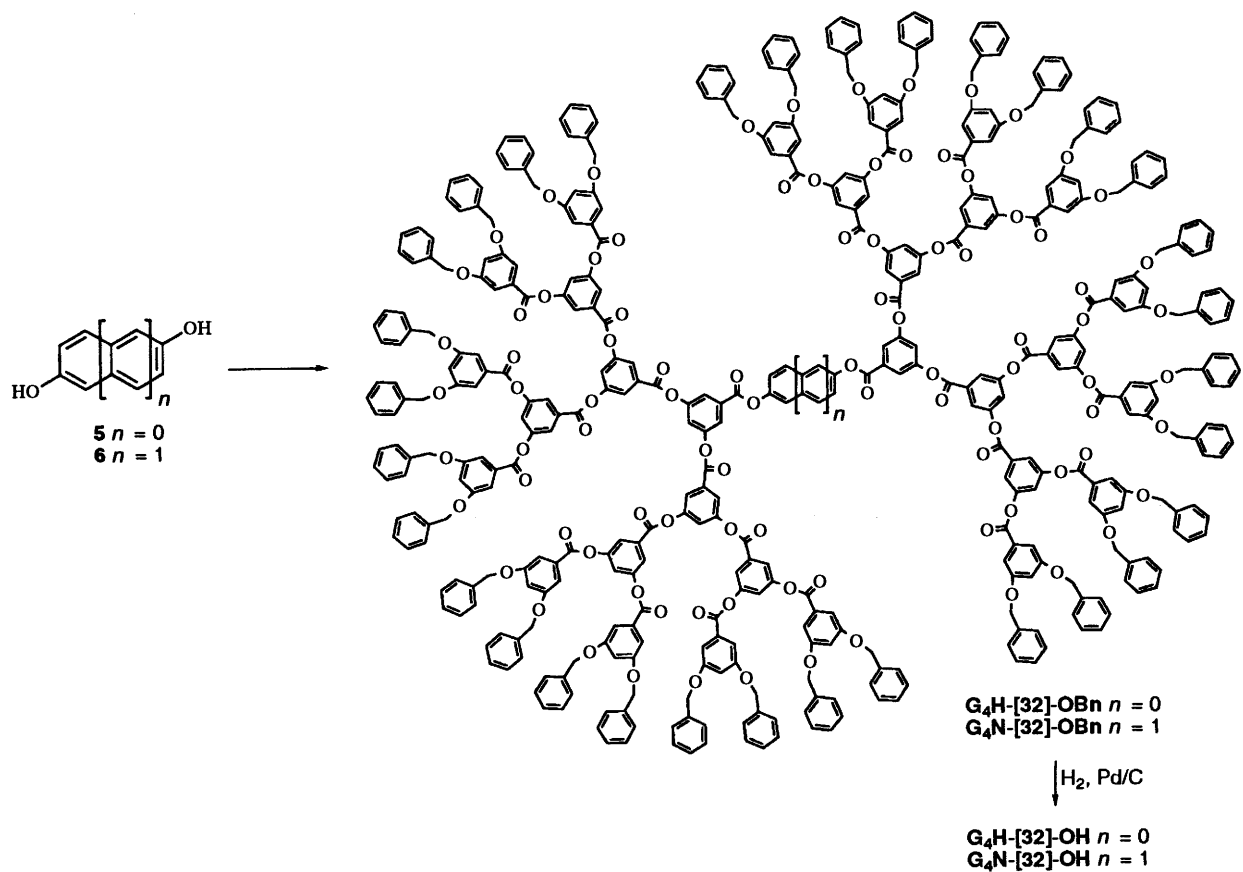
Fig. 1 Analytical data for **G₃P-[24]-OBn**: above left ¹H NMR; below left ¹³C NMR; above right GPC; below right MALDI mass spectrum

Scheme 3

for 14 h. After being allowed to cool, the solution was poured into water (300 cm^3) and the resulting mixture adjusted to pH 5 with hydrochloric acid. The resulting precipitate was filtered off and dried *in vacuo*. The off-white solid was recrystallised from acetone to give white crystals (67% yield), mp 210–211 °C (Found: C, 75.4; H, 5.5. Calc. for C$_{21}$H$_{18}$O$_4$: C, 75.4; H, 5.4%); ν_{max}/cm^{-1} 3300–2400, 1695, 1600 and 1500; δ_H([^{2}H$_6$]acetone) 5.18 (4 H, s, CH$_2$), 6.92 (1 H, t, *J* 2, ArH), 7.28 (2 H, d, *J* 2, ArH) and 7.3–7.5 (10 H, m, PhH); δ_C([^{2}H$_6$]acetone) 70.7, 107.4, 109.2, 128.4, 128.7, 129.3, 133.5, 137.9, 160.8 and 167.2.

3,5-Dibenzyloxybenzoyl chloride 3[11]

3,5-Dibenzyloxybenzoic acid 2 (10 g, 30 mmol) was heated at 80 °C in freshly distilled thionyl chloride (30 cm^3) for 2 h. The excess of thionyl chloride was removed by distillation under reduced pressure and the resulting solid was recrystallised from diethyl ether–hexane (1:1); it was found that the crude solid could be used without purification with no effect on subsequent reactions; mp 81–83 °C (Found: M$^+$, 352.0869. *M*$^+$ requires 352.0866); ν_{max}/cm^{-1} 3100–2700 (CH), 1760 (C=O) and 1500 (C=C ring); δ_H(CDCl$_3$) 5.10 (4 H, s, CH$_2$), 6.99 (1 H, t, *J* 2, ArH), 7.37 (2 H, d, *J* 2, ArH) and 7.3–7.5 (10 H, m, PhH); δ_C(CDCl$_3$) 70.4, 109.6, 109.9, 127.6, 127.7, 128.3, 128.7, 135.9, 151.2 and 160.1.

General procedure for the synthesis of benzyl-terminated dendritic esters

Method A. Reactions were carried out on a 0.01–4 g scale. To a solution of phloroglucinol, hydroquinone, 2,6-dihydroxy-napththalene or dendritic ester (1.0 equiv.) in dry acetone (5–400 cm^3) was added 3,5-dibenzyloxybenzoic acid (1.2 equiv. per hydroxy group), DCC (1.2 equiv. per hydroxy group) and DPTS[5] (0.2 equiv. per hydroxy group). The mixture was stirred vigorously at room temperature under nitrogen for 2–7 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The crude product was filtered and purified as indicated below.

Method B. Reactions were carried out on a 0.5–20 g scale using an adaptation of a literature procedure.[15] To a solution of phloroglucinol, hydroquinone, napththalene-2,6-diol or dendritic ester (1.0 equiv.) in dry dichloromethane (5–400 cm^3), was added 3,5-dibenzyloxybenzoyl chloride (1.2 equiv. per hydroxy group) and 4-(dimethylamino)pyridine (1 equiv. per hydroxy group). The mixture was stirred at room temperature under nitrogen for 5 days during which time the reaction was monitored by GPC. The mixture was evaporated to dryness under reduced pressure and purified by flash chromatography.

General procedure for the deprotection of dendritic benzyl-terminated polyesters

Hydrogenolyses were carried out in batches of up to 3 g. The dendritic ester was dissolved in dichloromethane (chloroform for hydroquinone-based dendrimers) (150 cm^3) and methanol was added until a slight precipitation was seen. The precipitate was redissolved by addition of a small amount of dichloromethane (or chloroform). 10% Pd/C (100 mg g^{-1} of dendrimer) and a few drops of acetic acid were added to the solution which was then shaken under an atmosphere of hydrogen at 50 psi for 4–5 h.[6] An equivalent volume of methanol was added to the solution which was then shaken under hydrogen (50 psi) overnight.

G$_1$P-[6]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane and precipitated from diethyl ether to yield a white solid. The solid was filtered off and washed with diethyl ether (25%).

Method B. The crude product was purified by flash chromatography eluting with dichloromethane and collected as

a white solid (100%), mp 200 °C (Found: C, 77.1; H, 5.1. C$_{69}$H$_{54}$O$_{12}$ requires C, 77.1; H, 5.1%); ν_{max}/cm^{-1} 3090–2930 (CH), 1740 (C=O) and 1500 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 229, 260, 311 and 323; δ_H(CDCl$_3$) 5.10 (12 H, s, CH$_2$), 6.88 (3 H, t, *J* 2, Ar'H), 7.13 (3 H, s, ArH), 7.3–7.4 (30 H, m, PhCH$_2$), 7.43 (6 H, d, *J* 2, Ar'H); δ_C(CDCl$_3$) 70.3, 108.1, 108.9, 113.2, 127.5, 128.1, 128.6, 130.7, 136.2, 151.4, 159.8 and 164.0; GPC: *M*$_n$ 1500, PDi 1.004; *m/z* 1097 (M + Na$^+$ requires 1098).

G$_1$P-[6]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (45:55) and collected as a white solid (93%), mp 250 °C (Found: C, 60.8; H, 3.4. C$_{27}$H$_{18}$O$_{12}$ requires C, 60.7; H, 3.4%); ν_{max}/cm^{-1} 3355 (OH, br) and 1720 (C=O); λ_{max}(MeOH)/nm 210, 260 and 317; δ_H([^{2}H$_6$]acetone) 6.68 (3 H, t, *J* 2, Ar'H), 7.18 (6 H, d, *J* 2, Ar'H), 7.26 (3 H, s, ArH) and 8.80 (6 H, br s, OH); δ_C([^{2}H$_6$] acetone) 108.9, 109.2, 114.6, 131.8, 152.7, 159.7 and 164.9 (carbonyl); GPC: *M*$_n$ 1200, PDi 1.005; *m/z* 556 (M + Na$^+$ requires 557).

G$_2$P-[12]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and purified by flash chromatography (pre-loading recommended) eluting with diethyl ether changing slowly to dichloromethane (74%), mp 55 °C (Found: C, 75.4; H, 4.7. C$_{153}$H$_{114}$O$_{30}$ requires C, 75.5; H, 4.7%); ν_{max}/cm^{-1} 3070–2930 (C–H), 1740 (C=O) and 1500 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 231, 257 and 313; δ_H(CDCl$_3$) 5.12 (24 H, s, CH$_2$), 6.91 (6 H, t, *J* 2, Ar''H), 7.24 (3 H, s, ArH), 7.3–7.45 (60 H, m, PhCH$_2$), 7.48 (12 H, d, *J* 2, Ar''H), 7.53 (3 H, t, *J* 2, Ar'H), 8.01 (6 H, d, *J* 2, Ar'H); δ_C(CDCl$_3$) 70.2, 108.2, 108.9, 113.2, 121.0, 121.4, 127.5, 128.0, 128.5, 130.4, 131.0, 136.1, 151.1, 151.3, 159.8, 162.5 (carbonyl) and 164.1 (carbonyl); GPC: *M*$_n$ 3200, PDi 1.003; *m/z* 2454 (M + Na$^+$ requires 2454).

G$_2$P-[12]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (30:70) and collected as a white solid (92%), mp 206 °C (Found: C, 61.1; H, 3.0. C$_{69}$H$_{54}$O$_{30}$ requires C, 61.3; H, 3.1%); ν_{max}/cm^{-1} 3370 (OH, br) and 1740 (C=O); λ_{max}(MeOH)/nm 208, 254 and 317; δ_H([^{2}H$_6$]acetone) 6.69 (6 H, t, *J* 2, Ar''H), 7.20 (12 H, d, *J* 2, Ar''H), 7.51 (3 H, s, ArH), 7.69 (3 H, t, *J* 2, Ar'H), 8.06 (6 H, d, *J* 2, Ar'H) and 8.78 (12 H, br s, OH); δ_C([^{2}H$_6$]acetone) 108.9, 109.3, 114.9, 121.9, 122.7, 131.6, 132.1, 152.5, 152.7, 159.6, 163.7 (carbonyl) and 165.1 (carbonyl); GPC: *M*$_n$ 2600, PDi 1.014; *m/z* 1374 (M + Na$^+$ requires 1373).

G$_3$P-[24]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and purified by flash chromatography (pre-loading recommended) eluting with diethyl ether changing slowly to dichloromethane (94%), mp 66 °C (Found: C, 74.7; H, 4.6. C$_{321}$H$_{234}$O$_{66}$ requires C, 74.9; H, 4.6%); ν_{max}/cm^{-1} 3090–2870 (CH), 1740 (C=O) and 1500 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 235, 254infl and 312; δ_H(CDCl$_3$) 5.12 (48 H, s, CH$_2$), 6.92 (12 H, t, *J* 2, Ar'''H), 7.29 (3 H, s, ArH), 7.3–7.5 (120 H, m, Ph), 7.49 (24 H, d, *J* 2, Ar''H), 7.55 (6 H, t, *J* 2, Ar''H), 7.60 (3 H, t, *J* 2, Ar'H), 8.06 (12 H, d, *J* 2, Ar''H) and 8.09 (6 H, d, *J* 2, Ar'H); δ_C(CDCl$_3$) 70.2, 108.2, 108.8, 113.3, 121.0, 121.1, 121.3, 121.4, 127.4, 128.0, 128.5, 130.4, 130.8, 131.2, 136.1, 151.05, 151.1, 151.3, 159.8, 162.3 (carbonyl), 162.7 (carbonyl) and 164.0 (carbonyl); GPC: *M*$_n$ 5800, PDi 1.000; *m/z* 5168 (M + Na$^+$ requires 5167).

G$_3$P-[24]-OH. The crude product was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The solid was purified by flash chromatography eluting with dichloromethane–acetone (30:70) and collected as a tan solid (92%); decomposed when heated (Found: C, 61.5; H, 3.0. Calc. for C$_{153}$H$_{90}$O$_{66}$: C, 61.6; H, 3.0%); λ_{max}(MeOH)/nm 207, 213infl, 250infl and 315; ν_{max}/cm^{-1} 3600–2900br (OH), 1740 (C=O) and 1500 (C=C ring); δ_H([^{2}H$_6$]acetone) 6.70 (12 H, t, *J* 2,

Ar‴H), 7.21 (24 H, d, J 2, Ar‴H), 7.40 (3 H, s, ArH), 7.70 (6 H, t, J 2, Ar″H), 7.90 (3 H, t, J 2, Ar′H), 8.09 (12 H, d, J 2, Ar″H), 8.21 (6 H, d, J 2, Ar′H) and 8.90 (24 H, br s, OH); δ_C([^{2}H$_6$]acetone) 109.0, 109.2, 121.9, 122.1, 122.5, 122.6, 131.5, 132.0, 132.2, 152.4 (2 C), 152.7, 159.6, 163.5 (carbonyl), 163.8 (carbonyl) and 165.1 (carbonyl); GPC: M_n 4000, PDi 1.016; m/z 3005 (M + Na$^+$ requires 3005).

G$_1$H-[4]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane as eluent; addition of diethyl ether to be filtrate yielded transparent needle-like crystals with time. The crystals were filtered off and washed with diethyl ether (8%).

Method B. The crude product was purified by flash chromatography eluting with chloroform to give the product as a white solid (100%), mp 113 °C (Found: C, 77.3; H, 5.2. C$_{48}$H$_{38}$O$_8$ requires C, 77.6; H, 5.2%); ν_{max}/cm^{-1} 3040–2870 (CH), 1740 (C=O) and 1505 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 229, 260, 311 and 323; δ_H(CDCl$_3$) 5.12 (8 H, s, CH$_2$), 6.89 (2 H, t, J 2, Ar′H), 7.27 (4 H, s, ArH), 7.3–7.4 (20 H, m, Ph) and 7.46 (4 H, d, J 2, Ar′H); δ_C(CDCl$_3$) 70.4, 108.0, 109.1, 122.5, 127.5, 128.0, 128.5, 131.3, 136.4, 148.4, 159.9 and 164.6 (carbonyl); GPC: M_n 1000, PDi 1.005; m/z 765 (M + Na$^+$ requires 765).

G$_1$H-[4]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (60:40) and collected as a white solid (95%), mp 278 °C (Found: C, 66.6; H, 3.7. C$_{48}$H$_{38}$O$_9$ requires C, 66.8; H, 3.7%); ν_{max}/cm^{-1} 3415br (OH), 1720 (C=O) and 1505 (C=C); λ_{max}(MeOH)/nm 208, 260 and 317; δ_H(CD$_3$OD) 6.60 (2 H, t, J 2, Ar′H), 7.13 (4 H, d, J 2, Ar′H) and 7.32 (4 H, s, ArH); δ_C(CD$_3$OD) 109.0, 109.2, 123.8, 132.2, 149.9, 160.0 and 166.6 (carbonyl); GPC: M_n 900, PDi 1.005.

G$_2$H-[8]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane as eluent; the product was precipitated from diethyl ether as a white solid. The solid was filtered off and washed with diethyl ether (85%).

Method B. The crude product was purified by eluting through a short pad of silica using dichloromethane as eluent; precipitation from diethyl ether yielded a white solid (86%), mp 181 °C (Found: C, 75.8; H, 4.8. C$_{104}$H$_{78}$O$_{20}$ requires C, 75.8; H, 4.8%); ν_{max}/cm^{-1} 3040–2870 (CH), 1745 (C=O) and 1500 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 230, 258 and 312; δ_H(CDCl$_3$) 5.12 (16 H, s, CH$_2$), 6.90 (4 H, t, J 2, Ar″H), 7.31 (4 H, s, ArH), 7.30–7.45 (40 H, m, PhCH$_2$), 7.46 (8 H, d, J 2, Ar″H), 7.49 (2 H, t, J 2, Ar′H) and 8.00 (4 H, d, J 2, Ar′H); δ_C(CDCl$_3$) 70.3, 108.2, 108.9, 121.0, 121.1, 122.5, 127.5, 128.1, 128.5, 130.5, 131.5, 136.2, 148.2, 151.3, 159.9, 163.2 (carbonyl) and 164.2 (carbonyl); GPC: M_n 1.008, PDi 2400; m/z 1670 (M + Na$^+$ requires 1670).

G$_2$H-[8]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (50:50) and collected as a white solid (89%), mp 210 °C (Found: C, 62.3; H, 3.4. C$_{48}$H$_{30}$O$_{20}$ requires C, 62.2; H, 3.3%); ν_{max}/cm^{-1} 3405br (OH), 1720 (C=O) and 1500 (C=C ring); λ_{max}(MeOH)/nm 205, 258 and 317; δ_H([^{2}H$_6$]acetone) 6.70 (4 H, t, J 2, Ar″H), 7.20 (8 H, d, J 2, Ar″H), 7.50 (4 H, s, ArH), 7.68 (2 H, t, J 2, Ar′H), 8.04 (4 H, d, J 2, Ar′H) and 8.88 (8 H, s, OH); δ_C([^{2}H$_6$]acetone) 109.0, 109.2, 121.8, 122.5, 123.7, 131.6, 132.5, 149.5, 152.7, 159.7, 164.1 (carbonyl) and 165.1 (carbonyl); GPC: M_n 2100, PDi 1.006; m/z 949 (M + Na$^+$ requires 949).

G$_3$H-[16]-OBn. *Method A.* The reaction mixture was

evaporated to dryness under reduced pressure and dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane as eluent and precipitated from diethyl ether to yield a white solid. The solid was filtered off and washed with diethyl ether (88%), T_g 71 °C (Found: C, 75.1; H, 4.6. Calc. for C$_{216}$H$_{158}$O$_{44}$: C, 75.0; H, 4.6%); ν_{max}/cm^{-1} 3030–2930 (CH), 1740 (C=O) and 1500 (C=C ring); λ_{max}(CH$_2$Cl$_2$)/nm 235, 254infl and 312; δ_H(CDCl$_3$) 5.12 (32 H, s, CH$_2$), 6.91 (8 H, t, J 2, Ar″H), 7.3–7.45 (84 H, m, Ph + ArH), 7.47 (16 H, d, J 2, Ar‴H), 7.53 (4 H, t, J 2, Ar′H), 7.56 (2 H, t, J 2, Ar′H), 8.03 (8 H, d, J 2, Ar″H) and 8.05 (4 H, d, J 2, Ar′H); δ_C(CDCl$_3$) 70.3, 108.2, 108.9, 121.1, 121.5, 122.5, 127.5, 128.1, 128.5, 130.8, 130.4, 131.7, 136.1, 148.1, 151.1, 151.4, 159.8, 162.8, 163.0 and 164.1; GPC: M_n 4700, PDi 1.000; m/z 3478 (M + Na$^+$ requires 3478).

G$_3$H-[16]-OH. The crude product was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The solid was purified by flash chromatography eluting with dichloromethane–acetone (30:70) and collected as a tan solid (89%); mp 206 °C (Found: C, 62.1; H, 3.1. Calc. for C$_{104}$H$_{62}$O$_{44}$: C, 62.0; H, 3.1%); λ_{max}(MeOH)/nm 206, 214infl, 254 and 316; ν_{max}/cm^{-1} 3700–2700br (OH), 1730 (C=O) and 1505 (C=C ring); δ_H([^{2}H$_6$]acetone) 6.70 (8 H, t, J 2, Ar‴H), 7.21 (16 H, d, J 2, Ar‴H), 7.49 (4 H, s, ArH), 7.70 (4 H, t, J 2, Ar″H), 7.89 (2 H, t, J 2, Ar′H), 8.09 (8 H, d, J 2, Ar″H), 8.19 (4 H, d, J 2, Ar′H) and 8.79 (16 H, br s, OH); δ_C([^{2}H$_6$]acetone) 109.0, 109.3, 121.9, 122.1, 122.4, 122.7, 123.7, 131.6, 132.0, 132.6, 149.5, 152.5, 152.7, 159.6, 163.8 (carbonyl), 164.0 (carbonyl) and 165.1 (carbonyl); GPC: M_n 3500, PDi 1.020; m/z 2037 (M + Na$^+$ requires 2037).

G$_4$H-[32]-OBn. *Method A.* The crude product was evaporated to dryness under reduced pressure and purified by flash chromatography (pre-loading recommended) eluting with diethyl ether changing slowly to dichloromethane (86%), mp 70 °C (Found: C, 74.7; H, 4.5. Calc. for C$_{440}$H$_{318}$O$_{92}$: C, 74.7; H, 4.5%); λ_{max}(CH$_2$Cl$_2$)/nm 231, 256infl and 312; ν_{max}/cm^{-1} 3200–2700 (CH), 1745 (C=O) and 1500 (C=C ring); δ_H(CDCl$_3$) 5.14 (64 H, s, CH$_2$), 6.95 (16 H, t, J 2, Ar⁗H), 7.3–7.5 (164 H, m, PhH + ArH), 7.52 (32 H, d, J 2, Ar‴H), 7.59 (8 H, t, J 2, Ar‴H), 7.64 (2 H, t, J 2, Ar′H), 7.66 (4 H, t, J 2, Ar″H), 8.09 (16 H, d, J 2, Ar‴H), 8.13 (4 H, d, J 2, Ar′H) and 8.15 (8 H, d, J 2, Ar″H); δ_C(CDCl$_3$) 70.1, 108.1, 108.8, 121.0 (3 C), 121.4 (3 C), 122.4, 127.4, 128.0, 128.4, 130.3, 130.7, 131.0, 131.6, 136.1, 148.1, 151.0, 151.1, 151.3, 159.8, 162.6 (carbonyl), 162.6 (carbonyl), 162.9 (carbonyl) and 164.0 (carbonyl); GPC: M_n 7800, PDi 1.000.

G$_4$H-[32]-OH. The crude product was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The solid was purified by flash chromatography eluting with dichloromethane–acetone (30:70) and collected as a tan solid (92%); T_g 168 °C (Found: C, 62.0; H, 2.9. Calc. for C$_{216}$H$_{26}$O$_{92}$: C, 61.9; H, 3.0%); λ_{max}(MeOH)/nm 209, 250infl and 314; ν_{max}/cm^{-1} 3700–2900br (OH), 1730 (C=O) and 1505 (C=C ring); δ_H([^{2}H$_6$]acetone) 6.70 (16 H, t, J 2, Ar⁗H), 7.21 (32 H, d, J 2, Ar⁗H), 7.47 (4 H, s, ArH), 7.70 (8 H, t, J 2, Ar″H), 7.89 (2 H, t, J 2, Ar′H), 7.90 (4 H, t, J 2, Ar″H), 8.09 (16 H, d, J 2, Ar‴H), 8.20 (4 H, d, J 2, Ar′H), 8.24 (8 H, d, J 2, Ar″H) and 8.86 (32 H, br s, OH); δ_C([^{2}H$_6$]acetone) 109.0, 109.2, 121.8 (2 C), 122.1, 122.6 (3 C), 123.6, 131.5, 131.9, 132.1, 132.5, 149.4, 152.4 (2 C), 152.6, 159.5, 163.7 (carbonyl), 163.7 (carbonyl), 163.9 (carbonyl) and 165.0 (carbonyl); GPC: M_n 2600, PDi 1.011.

G$_1$N-[4]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane. The residue was precipitated with diethyl ether to give a white solid which was filtered off and washed with diethyl ether (30%).

Method B. The crude product was purified by flash chromatography eluting with chloroform to give the product as a clear glass (100%), mp 168 °C (Found: C, 78.6; H, 5.2. $C_{52}H_{40}O_8$ requires C, 78.8; H, 5.1%); ν_{max}/cm^{-1} 3030–2920 (CH), 1730 (C=O) and 1500 (C=C ring); $\lambda_{max}(CH_2Cl_2)/nm$ 230, 259, 303, 324; $\delta_H(CDCl_3)$ 5.13 (8 H, s, CH_2), 6.90 (2 H, t, J 2, Ar'H), 7.3–7.5 (22 H, m, Ph + ArH), 7.51 (4 H, d, J 2, Ar'H), 7.72 (2 H, d, J 2, ArH) and 7.89 (2 H, d, J 9, ArH); $\delta_C(CDCl_3)$ 70.3, 107.8, 108.9, 118.6, 121.9, 127.5, 128.1, 128.5, 129.1, 131.2, 131.7, 136.2, 148.5, 159.8 and 164.9 (carbonyl); GPC: M_n 1200, PDi 1.006; m/z 816 (M + Na$^+$ requires 815).

G$_1$N-[4]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (60:40) and collected as a white solid (95%), mp 264 °C (Found: C, 66.6; H, 3.7. $C_{24}H_{16}O_8$ requires C, 66.65; H, 3.7%); ν_{max}/cm^{-1} 3365br (OH), 1720 (C=O) and 1500 (C=C ring); $\lambda_{max}(MeOH)/nm$ 223, 260 and 312; $\delta_H([^2H_6]acetone)$ 6.70 (2 H, t, J 2, Ar'H), 7.22 (4 H, d, J 2, Ar'H), 7.50 (2 H, dd, J 2 and 9, ArH), 7.85 (2 H, d, J 2, ArH), 8.04 (2 H, d, J 9, ArH) and 8.90 (4 H, br s, OH); $\delta_C([^2H_6]acetone)$ 108.7, 109.2, 119.6, 123.2, 129.8, 132.2, 132.7, 149.7, 159.7 and 165.6 (carbonyl); GPC: M_n 900, PDi 1.005.

G$_2$N-[8]-OBn. *Method A.* The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a small quantity of dichloromethane. The solution was eluted through a short pad of silica using dichloromethane as eluent and precipitated from diethyl ether to yield a white solid. The solid was filtered off and washed with diethyl ether (92%).

Method B. The crude product was purified by eluting through a short pad of silica using dichloromethane as eluent and was precipitated from diethyl ether to yield a white solid (80%), mp 128 °C (Found: C, 76.4; H, 4.8; $C_{108}H_{80}O_{20}$ requires C, 76.4; H, 4.8%); ν_{max}/cm^{-1} 3090–2870 (CH), 1740 (C=O) and 1500 (C=C ring); $\lambda_{max}(CH_2Cl_2)/nm$ 229, 259, 309 and 323; $\delta_H(CDCl_3)$ 5.13 (16 H, s, CH_2), 6.93 (4 H, t, J 2, Ar'H), 7.3–7.5 (42 H, m, Ph + ArH), 7.50 (8 H, d, J 2, Ar'H), 7.54 (2 H, t, J 2, Ar'H), 7.77 (2 H, d, J 2, ArH), 7.93 (2 H, d, J 9, ArH) and 8.08 (4 H, d, J 2, Ar'H); $\delta_C(CDCl_3)$ 70.2, 108.2, 108.9, 118.6, 121.0, 121.1, 121.8, 127.4, 128.0, 128.5, 129.2, 130.5, 131.6, 131.8, 136.1, 148.3, 151.3, 159.8, 163.5 (carbonyl) and 164.1 (carbonyl); GPC: M_n 2600, PDi 1.003; m/z 1720 (M + Na$^+$ requires 1720).

G$_2$N-[8]-OH. The reaction mixture was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The residue was purified by flash chromatography (pre-loading recommended) eluting with dichloromethane–acetone (30:70) and collected as a white solid (89%), mp 230 °C (Found: C, 63.8; H, 2.3. Calc. for $C_{52}H_{32}O_{20}$: C, 63.9; H, 3.3%); ν_{max}/cm^{-1} 3380br (OH) and 1720 (C=O); $\lambda_{max}(MeOH)/nm$ 220, 257 and 315; $\delta_H([^2H_6]acetone)$ 6.70 (4 H, t, J 2, Ar'H), 7.21 (8 H, s, Ar'H), 7.62 (2 H, dd, J 2 and 9, ArH), 7.70 (2 H, t, Ar'H), 7.97 (2 H, d, J 2, ArH), 8.09 (2 H, d, J 9, ArH), 8.09 (4 H, d, J 2, Ar'H) and 8.83 (8 H, br s, OH); $\delta_C([^2H_6]acetone)$ 109.0, 109.3, 119.3, 121.8, 122.5, 123.2, 130.0, 131.7, 132.6, 132.8, 149.6, 152.8, 159.7, 164.3 (carbonyl) and 165.1 (carbonyl); GPC: M_n 1900, PDi 1.003; m/z 999 (M + Na$^+$ requires 999).

G$_3$N-[16]-OBn. *Method A.* The crude product was evaporated to dryness under reduced pressure and purified by flash chromatography (pre-loading recommended) eluting with diethyl ether changing slowly to dichloromethane (96%) mp 122 °C (Found: C, 75.4; H, 4.6., Calc. for $C_{220}H_{160}O_{44}$: C, 75.3; H, 4.6%); $\lambda_{max}(CH_2Cl_2)/nm$ 235, 255infl and 310; ν_{max}/cm^{-1} 3090–2870 (CH), 1740 (C=O) and 1500 (C=C ring); $\delta_H(CDCl_3)$ 5.13 (32 H, s, CH_2), 6.93 (8 H, t, J 2, Ar'''H), 7.3–7.5 (82 H, m, PhH + ArH), 7.49 (16 H, d, J 2, Ar'''H), 7.55 (4 H, t, J 2, Ar''H), 7.60 (2 H, t, J 2, Ar'H), 7.79 (2 H, d, J 2, ArH), 7.93 (2

H, d, J 9, ArH), 8.06 (8 H, d, J 2, Ar''H) and 8.12 (4 H, d, J 2, Ar'H); $\delta_C(CDCl_3)$ 70.2, 108.2, 108.9, 118.6, 121.0 (2 C), 121.4 (2 C), 121.7, 127.4, 128.0, 128.5, 129.2 (2 C), 130.4, 130.8, 131.8, 136.1, 148.2, 151.1, 151.4, 159.8, 162.8 (carbonyl), 163.2 (carbonyl) and 164.1 (carbonyl); GPC: M_n 4300, PDi 1.003; m/z 3529 (M + Na$^+$ requires 3529).

G$_3$N-[16]-OH. The crude product was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The solid was purified by flash chromatography eluting with dichloromethane–acetone (30:70) and collected as a clear solid (96%), mp 184 °C (Found: C, 62.8; H, 3.2. Calc. for $C_{108}H_{64}O_{44}$: C, 62.8; H, 3.1%); $\lambda_{max}(MeOH)/nm$ 210, 217, 250infl and 310; ν_{max}/cm^{-1} 3000–3700br (OH), 1740 (C=O) and 1505 (C=C ring); $\delta_H([^2H_6]acetone)$ 6.70 (8 H, t, J 2, Ar'''H), 7.21 (16 H, d, J 2, Ar'''H), 7.61 (2 H, dd, J 2 and 9, ArH), 7.70 (4 H, t, J 2, Ar''H), 7.91 (2 H, t, J 2, Ar'H), 7.96 (2 H, d, J 2, ArH), 8.07 (2 H, d, J 9, ArH), 8.10 (8 H, d, J 2, Ar''H), 8.23 (4 H, d, J 2, Ar'H) and 8.81 (16 H, br s, OH); $\delta_C([^2H_6]acetone)$ 109.0, 109.2, 109.3, 119.6, 121.9, 122.1, 122.7, 123.1, 130.0, 132.0, 131.6, 132.7, 132.8, 149.6, 152.5, 152.7, 159.6, 163.8 (carbonyl), 164.1 (carbonyl) and 165.0 (carbonyl); GPC: M_n 3200, PDi 1.009; m/z 2086 (M + Na$^+$ requires 2087).

G$_4$N-[32]-OBn. *Method A.* The crude product was evaporated to dryness under reduced pressure and purified by flash chromatography (pre-loading recommended) eluting with diethyl ether changing slowly to dichloromethane (95%), mp 53 °C (Found: C, 74.9; H, 4.5. Calc. for $C_{444}H_{320}O_{92}$: C, 74.8; H. 4.5%); $\lambda_{max}(CH_2Cl_2)/nm$ 230, 256infl and 309; ν_{max}/cm^{-1} 3010–2880 (CH), 1740 (C=O) and 1500 (C=C ring); $\delta_H(CDCl_3)$ 5.13 (64 H, s, CH_2), 6.93 (16 H, t, J 2, Ar'''H), 7.3–7.5 (162 H, m, PhH + ArH), 7.51 (32 H, d, J 2, Ar'''H), 7.57 (8 H, t, J 2, Ar'''H), 7.64 (6 H, t, J 2, Ar'H + Ar''H), 7.79 (2 H, br m, ArH), 7.93 (2 H, d, J 9, ArH), 8.08 (16 H, d, J 2, Ar'''H), 8.14 (8 H, d, J 2, Ar''H) and 8.15 (4 H, d, J 2, Ar'H); $\delta_C(CDCl_3)$ 70.2, 108.2, 108.9, 118.5, 121.0 (2 C), 121.1 (2 C), 121.4 (2 C), 121.7, 127.4, 128.0, 128.5, 129.2, 130.4, 130.7, 131.0, 136.1, 131.7, 131.8, 148.2, 151.0, 151.1, 151.3, 159.8, 162.6 (carbonyl), 162.7 (carbonyl), 163.2 (carbonyl) and 164.0 (carbonyl); GPC: M_n 7800, PDi 1.000.

G$_4$N-[32]-OH. The crude product was evaporated to dryness under reduced pressure and freeze dried to remove traces of acetic acid. The solid was purified by flash chromatography eluting with dichloromethane–acetone (20:80) and collected as a clear solid (87%); decomposed when heated (Found: C, 62.2; H, 3.1. Calc. for $C_{220}H_{128}O_{92}$: C, 62.3; H, 3.0%); $\lambda_{max}(MeOH)/nm$ 206, 252infl and 313; ν_{max}/cm^{-1} 3700–2900br (OH), 1740 (C=O) and 1510 (C=C ring); $\delta_H([^2H_6]acetone)$ 6.69 (16 H, t, J 2, Ar'''H), 7.20 (32 H, d, J 2, Ar'''H), 7.60 (2 H, dd, J 2 and 9, ArH), 7.69 (8 H, t, J 2, Ar'''H), 7.91 (6 H, t, J 2, Ar'H and Ar''H), 7.95 (2 H, br m, ArH), 8.05 (2 H, d, J 9, ArH), 8.08 (16 H, d, J 2, Ar'''H), 8.22 (4 H, d, J 2, Ar'H), 8.24 (8 H, d, J 2, Ar''H) and 8.80 (32 H, br s, OH); $\delta_C([^2H_6]acetone)$ 109.0, 109.3, 119.6, 121.7, 121.9, 122.2 (2 C), 122.7, 123.1, 130.0, 131.6, 132.0, 132.2, 132.7, 132.8, 149.6, 152.5, 152.6, 152.7, 159.6, 163.7 (carbonyl), 163.8 (carbonyl) and 164.1 (carbonyl) and 165.0 (carbonyl); GPC: M_n 2600, PDi 1.088.

Acknowledgements

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