New large cage receptors. An example of selective phloroglucinol binding

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An efficient and convergent procedure has been developed for the synthesis of a range of related, large-ring monocyclic and bicyclic (cage) receptor molecules. The interaction of one such cage 8b, incorporating three central pyridyl groups, with a number of mono-, di- and tri-phenol derivatives has been investigated. In accordance with the inference from molecular modelling, this cage exhibits preferential inclusive binding of the symmetrical guest phloroglucinol.

Compared to monocyclic ligands, cryptands show enhanced potential for obtaining more preorganised coordination cavities for the binding of small molecules.[1,2] In a previous study, Vögtle and co-workers[3,4] have described a novel series of macrobicyclic 'cages' which were shown to bind a number of polyphenols in non-polar solvents such as dichloromethane. These molecules incorporate three bipyridyl moieties, bridging two 1,3,5-trisubstituted benzene caps, and function as effective receptors for complementary phenol guests such as phloroglucinol (1,3,5-trihydroxybenzene). Robbins *et al.*[5] have also demonstrated the uptake of polyphenol substrates by a 'large cavity' hemicarcerand.

In a recent communication we have demonstrated that the moderately rigid cryptands **8a** and **8b** contain cavities that are large enough to encapsulate a guest molecule of up to approximately 8–9 Å in diameter.[6] In that study the X-ray structure of **8b**, crystallised from benzene, showed that a single benzene molecule occupies the cavity. The cage adopts an arrangement in which a pseudo three-fold axis passes through the bridgehead nitrogens. The planes of the pyridyl rings lie approximately parallel to this axis with the benzene guest orientated such that its plane is perpendicular to the pseudo-C_3 axis.

Full details of the synthesis and characterisation of the extended series **8a–d** are now described together with a discussion of the interaction of **8b** with a range of mono-, di- and tri-phenols.

Results and discussion

Synthesis

The strategy employed to synthesise **8a–d** (Scheme 1) is broadly similar to that reported previously for the synthesis of a smaller, N_2O_6-cryptand.[7]

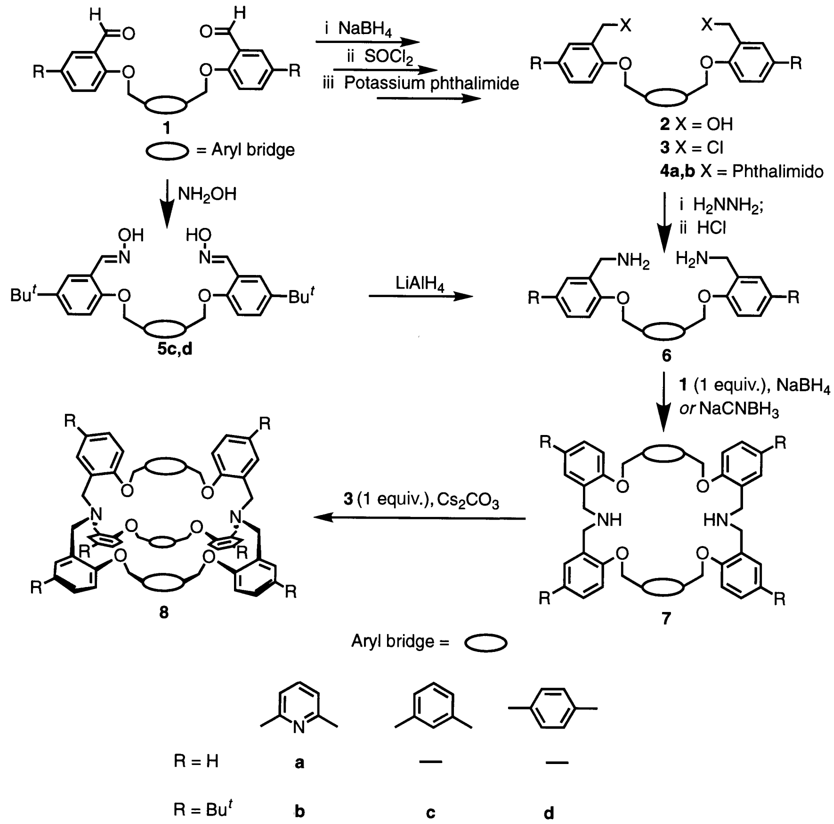
The single ring macrocycles **7a–c** were prepared by Schiff base condensation of the appropriate dialdehyde, chosen from **1a–d**, and diamine, chosen from **6a–d**, to yield the corresponding diimine intermediates which were reduced *in situ* (under moderate dilution conditions) using the imine-selective reducing reagent, sodium cyanoborohydride.[8] Molecular sieves (4 Å) were added to the reaction mixture to facilitate the formation of the Schiff base intermediate in each case. This procedure led to reasonable yields of the resulting precursor macrocycles **7a** (30%), **7b** (81%), **7c** (47%) and **7d** (58%).

The 2,6-dimethylpyridyl bridged dialdehyde **1a** was synthesised as described previously.[9] Dialdehydes **1b** (90%), **1c** (90%) and **1d** (86%) were prepared in high yields from 5-*tert*-butylsalicylaldehyde and 2,6-bis(chloromethyl)pyridine, 1,3-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene, respectively, using a related procedure to that used for **1a**; however, for these alkylations phase transfer conditions (Bu_4NBr, NaOH, toluene) were employed. Functional group manipulations were then performed on the respective dialdehydes to yield the required corresponding dichloro and diamine derivatives. The dialdehydes were reduced to diols **2a–d** almost quantitatively (>97%) using sodium borohydride in ethanol; for the reduction of **1d** to **2d**, toluene was added to the reaction mixture to aid solubility. In turn, the diols **2a–d** were converted to the dichloro analogues **3a–d** in high yield using thionyl chloride in dichloromethane. The synthesis of the diamines **6a–d** was performed by two different methods. The xylyl bridged dialdehydes **1c** and **1d** were converted to dioximes **5c** (97%) and **5d** (98%) using hydroxylamine in ethanol. These dioximes were subsequently reduced to diamines **6c** (84%) and **6d** (92%) with lithium aluminium hydride in THF. An analogous procedure was attempted for the pyridyl-containing dialdehydes **1a** and **1b**; however, reduction of the dioxime derivatives to diamines **6a** and **6b** was in each case unsuccessful. Subsequently, the required diamines **6a** and **6b** were successfully prepared from the dichlorides **3a** and **3b** using Gabriel methodology. Namely, dichlorides **3a** and **3b** were converted to the corresponding diphthalimides **4a** (99%) and **4b** (93%) by reaction with potassium phthalimide in *N*,*N*-dimethylformamide. The diphthalimides were then cleaved using hydrazine to yield diamines **6a** (86%) and **6b** (93%) as viscous oils (upon acid work-up).

Bis-*N*-alkylation of macrocycles **7a–d** with dichlorides **3a–d**, respectively, using sodium hydrogen carbonate or caesium carbonate as the base, gave the target cages **8a** (41%), **8b** (52%), **8c** (48%) and **8d** (42%).

The stepwise approach exemplified in Scheme 1 should allow the ready synthesis of a variety of closely related cage systems in which different bridges link the terminal nitrogen bridgeheads. For example, starting from the four precursor dialdehydes **1a–d**, different combinations of the derived diamine and dichloro moieties could, in principle, result in the extension of the present series to encompass a total of 20 different cages.†

† The successful preparation (not reported here) of 'mixed' cages containing 2,6-dimethylpyridyl and *p*-xylyl bridges illustrates this potential.



Scheme 1 Synthesis of cages **8a–d**

Selective phloroglucinol binding

Molecular modelling at the semi-empirical AM1 level indicates that **8b** should exhibit complementary binding of phloroglucinol by means of hydrogen bonds between the pyridyl nitrogens of the cryptand and the phenolic hydrogens of the guest. The AM1 minimised structure of the resulting complex is illustrated in Fig. 1. The orientation of the phloroglucinol in this structure is approximately perpendicular to the bridgehead N · · · N axis, with mean pyridine N · · · H and pyridine N · · · O phloroglucinol distances being 1.8 and 2.5 Å respectively.

Cage **8b** was found to solubilise phloroglucinol in dichloromethane and chloroform. The ^{1}H NMR spectrum of a mixture containing phloroglucinol and excess **8b** in CD_2Cl_2 shows a single set of resonances indicating that the complex is in fast exchange at 303 K. Integration of particular host and guest resonances confirmed that a 1 : 1 complex is formed upon the addition of excess phloroglucinol.‡ A signal for the guest aryl protons is present at 4.82 ppm. The identity of this signal was confirmed by a HMQC experiment which showed that this proton was attached to the aromatic carbon whose ^{13}C resonance (96.4 ppm) also appears upon addition of phloroglucinol. It is noted that the aryl proton signal of phloroglucinol occurs at a higher field in the complex (4.82 ppm) than when this substrate is 'free' in solution (5.91 ppm). Complementary downfield shifts of the pyridyl proton signals were also observed. These shifts are consistent with proton transfer occurring from the guest to the host. Undoubtedly, anisotropic effects due to the pyridine rings of the host and the aryl ring of the guest also play a significant role in determining the observed shifts. Such effects can also explain the upfield shift ($\Delta\delta = 0.24$ ppm) of the benzylamine methylene signal which occurs upon complexation. The above NMR observations are in accord with the hydrogen bonded structure predicted by the molecular modelling studies (Fig. 1). The broad signal at 7.7 ppm is assigned to the hydrogen bonded protons in the complex. A small NOE difference (+0.5%) was observed between the aryl protons of the guest and the benzylamine protons of **8b**. Also, NOESY crosspeaks (mixing time 500 ms) were observed between these protons indicating their close spatial proximity.§

In a further NMR experiment, cage **8c**, incorporating three *m*-xylyl groups, was substituted for **8b** in order to investigate whether this species might also include phloroglucinol. However, no indication of complex formation was obtained in this case. This result is in keeping with the inability of **8c** to bind phloroglucinol by means of stereo-complementary hydrogen bonds. As such, it indirectly supports the presence of the H-bonding network proposed to occur in the complex of **8b**.

A series of comparative experiments has been undertaken (in $CDCl_3$) in order to examine the relative affinity of **8b** for the range of related mono-, di- and tri-phenol derivatives shown in Fig. 2. In these experiments a similar procedure to that described above was employed. Unfortunately, quantitative determination of the corresponding stability constants proved impractical for this series owing to limitations associated with

‡ ^{1}H NMR of free **8b**: δ_H(CD_2Cl_2; 600 MHz; 303 K) 1.32 [54 H, s, $(CH_3)_3$], 3.63 (12 H, s, CH_2N), 4.94 (12 H, s, CH_2O), 6.90 (6 H, d, *J* 8, H-6′), 7.24 (6 H, dd, *J* 2, 8, H-5′), 7.25 [6 H, d, *J* 7, H-3(5)], 7.31 (3 H, t, *J* 7, H-4) and 7.96 (6 H, d, *J* 2, H-3′). ^{1}H NMR of 1 : 1 complex between **8b** and phloroglucinol: δ_H(CD_2Cl_2; 600 MHz; 303 K) 1.32 [54 H, s, $(CH_3)_3$], 3.39 (12 H, br, CH_2N), 4.82 (3 H, br, phloroglucinol CH), 4.99 (12 H, s, CH_2O), 6.94 (6 H, d, *J* 8, H-6′), 7.20 (6 H, dd, *J* 3, 8, H-5′), 7.53 [6 H, d, *J* 8, H-3(5)], 7.7 (3 H, br s, O*H* · · · N), 7.79 (3 H, t, *J* 8, H-4) and 8.01 (6 H, d, *J* 3, H-3′).

§ Intermolecular NOESY crosspeak volumes were converted to interproton distances using the two spin approximation [$r_{ij} = r_{ref}(R_{ref}/R_{ij})^{1/6}$].[10] An $H^{5''}$–$H^{6'}$ (intramolecular) distance of 2.49 Å was used for calibration (r_{ref}). The distance between the benzylamine protons of **8a** and the aryl protons of the complexed phloroglucinol was calculated from the NOESY data to be 4.5 Å; this compares favourably with the mean distance of 4.86 Å in the AM1 calculated structure. It needs to be noted that in a system exchanging rapidly between its bound and unbound form, the calculated distance may represent the weighted mean of several structures present in dynamic equilibrium.

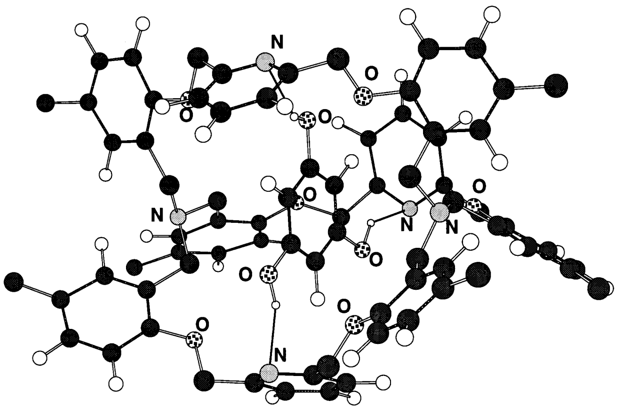


Fig. 1 AM1 minimised structure of the 1:1 complex formed between **8b** and phloroglucinol; all non-aromatic protons, except the phenolic protons, are omitted for clarity as are the Bu^t substituents on the aryl rings

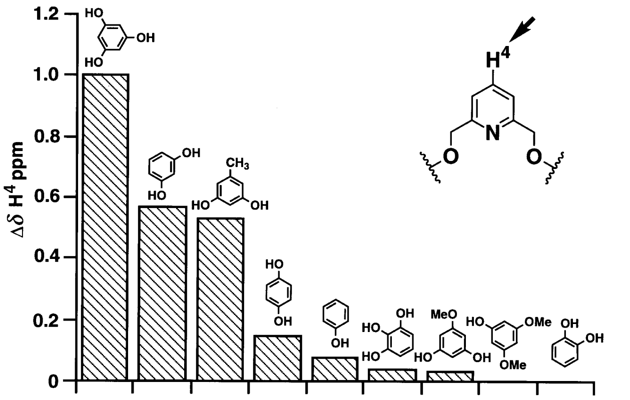
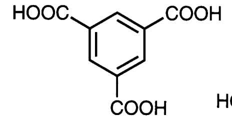


Fig. 2 The change in ^{1}H NMR shift $\Delta\delta$(CDCl$_3$; 300 MHz; 298 K) of proton H^4 upon addition of the phenol derivatives shown to a solution of **8b**



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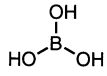

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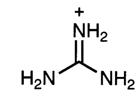

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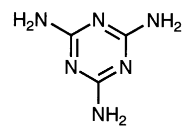

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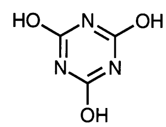

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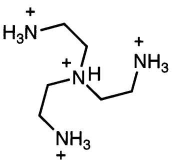

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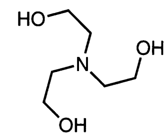

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the low solubilities of the respective unbound phenolic guests in CDCl$_3$. However, inspection of the spectra revealed that the shift ($\Delta\delta$) of the pyridyl H^4 proton appeared to be a useful indicator of the degree of host–guest interaction along this series. While such a procedure must be considered, at best, only semi-quantitative, the results (Fig. 2) are in good agreement with expectations based on host–guest complementarity, as judged from inspection of CPK molecular models.

Finally, it is noted that a series of similar (solid–liquid extraction) NMR experiments were attempted in which a range of other potential guests, given by **9–15,** were substituted for phloroglucinol in the procedure described above. Despite their potential complementarity with **8b**, none of these guests induced a change in the ^{1}H NMR spectrum of this cage: no significant complexation of these guests appears to occur under the conditions employed for these experiments.

Experimental

General

^{1}H and ^{13}C NMR Spectra were determined on a Bruker AM300 spectrometer at 300 and 75 MHz, respectively in CDCl$_3$ solution unless specified otherwise. *J* Values are given in Hz. High resolution mass spectra were obtained on the following instruments: Bruker BioApex 47e, electrospray (ES); Kraytos M25RFA, electron impact (EI) and liquid secondary ion (LSI). Microanalyses were determined at James Cook University. All melting points are uncorrected. Chromatography was carried out using Kieselgel 60H or neutral Al$_2$O$_3$. Toluene was AR grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl before use. Dialdehyde **1a**,[9] 2,6-bis-(chloromethyl)pyridine[9] and 5-*tert*-butylsalicylaldehyde[11] were prepared by the literature procedures. Light petroleum (petrol) refers to that fraction with bp 60–80 °C.

Molecular modelling

The AM1 minimised structure of the 1:1 complex formed between **8b** and phloroglucinol was generated using the Spartan 4.0 program[12] running on an IBM RS/6000 workstation. Initial coordinates were taken from the X-ray structure of **8b**.[6] Other conformations of the cage were also investigated, however, the X-ray structure was found to be the most stable. Several different orientations of the phloroglucinol within the cage were considered, including those where the phloroglucinol was parallel, as well as perpendicular to the N · · · N bridgehead axis. The reported complex (Fig. 1) formed between **8b** and phloroglucinol was the lowest energy structure computed from each of these starting geometries. The enthalpy of complexation was estimated to be ~20 kJ mol^{-1}. To achieve SCF convergence a damping factor of 1.0 was employed in the SCF minimisation, while full geometry optimisation required >400 steps.

2,6-Bis[(2′-formyl-4′-*tert*-butylphenoxy)methyl]pyridine 1b

A solution of sodium hydroxide (2.8 g, 70.0 mmol) and tetrabutylammonium bromide (22.5 g, 70.0 mmol) dissolved in water (80 cm^3) was added to a solution of 5-*tert*-butylsalicylaldehyde[11] (12.5 g, 70.0 mmol) dissolved in toluene (30 cm^3). The bright yellow mixture was stirred at reflux for 30 min and a solution of 2,6-bis(chloromethyl)pyridine[9] (5.6 g, 31.8 mmol) dissolved in toluene (60 cm^3) added. This mixture was heated at reflux overnight and then cooled to room temperature. The organic phase was extracted with hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3) then aqueous sodium hydroxide (1 mol dm^{-3}, until washes remained colourless) and finally water. Routine work-up yielded a yellow solid which was slurried in cold methanol (25 cm^3), cooled (2 °C) and collected as a white solid which was recrystallised from ethanol to yield colourless needles of *dialdehyde* **1b** (13.1 g, 90%), mp 144–145 °C [Found: C, 75.5; H, 7.2; N, 2.9. $C_{29}H_{33}NO_4$ requires C, 75.8; H, 7.2; N, 3.1%. Found: M$^+$, 459.2411 (EI). $C_{29}H_{33}NO_4$ requires *M*, 459.2409]; δ_H 1.31 [18 H, s, (CH$_3$)$_3$], 5.31 (4 H, s, CH$_2$O), 6.98 (2 H, d, *J* 9, H-6′), 7.51 [2 H, d, *J* 8, H-3(5)], 7.58 (2 H, dd, *J* 3, 9, H-5′), 7.82 (1 H, t, *J* 8, H-4), 7.89 (2 H, d, *J* 3, H-3′) and 10.62 (2 H, s, CHO); δ_C 31.2, 34.3, 70.9, 112.6, 120.4, 124.4, 125.3, 133.2, 138.0, 144.2, 156.2, 158.5 and 189.8.

1,3-Bis[(2′-formyl-4′-*tert*-butylphenoxy)methyl]benzene 1c

In a similar manner to that described above, 5-*tert*-butylsalicylaldehyde[11] (9.4 g, 52.0 mmol) and 1,3-bis(bromomethyl)benzene (6.7 g, 25.4 mmol) yielded a yellow solid which was recrystallised from diethyl-ether–petrol to yield *dialdehyde* **1c** (10.5 g, 90%) as colourless crystals, mp 77–79 °C [Found: M^+, 458.2443 (EI). $C_{30}H_{34}O_4$ requires *M*, 458.2457]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 5.20 (4 H, s, CH_2O), 6.99 (2 H, d, *J* 9, H-6′), 7.44 [3 H, br, H-4(6) and H-5], 7.52 (1 H, br, H-2), 7.58 (2 H, dd, *J* 3, 9, H-5′), 7.88 (2 H, d, *J* 3, H-3′) and 10.55 (2 H, s, CHO); δ_C 31.2, 34.2, 70.2, 112.6, 124.4, 124.9, 125.9, 127.0, 129.1, 133.1, 136.9, 143.9, 158.9 and 189.9.

1,4-Bis[(2′-formyl-4′-*tert*-butylphenoxy)methyl]benzene 1d

In a similar manner to that described above, 5-*tert*-butylsalicylaldehyde[11] (9.2 g, 51.7 mmol) and 1,4-bis(bromomethyl)benzene (6.2 g, 23.5 mmol) yielded a yellow solid which was recrystallised from ethanol to yield *dialdehyde* **1d** (9.3 g, 86%) as colourless crystals, mp 139–141 °C [Found: M^+, 458.2451 (EI). $C_{30}H_{34}O_4$ requires *M*, 458.2457]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 5.19 (4 H, s, CH_2O), 6.99 (2 H, d, *J* 9, H-6′), 7.48 (4 H, s, *p*-xylyl-H), 7.57 (2 H, dd, *J* 3, 9, H-5′), 7.88 (2 H, d, *J* 3, H-3′) and 10.62 (2 H, s, CHO); δ_C 31.2, 34.2, 70.1, 112.7, 124.5, 125.0, 127.6, 133.1, 144.0, 159.0 and 189.9.

2,6-Bis[2′-(hydroxymethyl)phenoxymethyl]pyridine 2a

Sodium borohydride (1.26 g, 33.3 mmol) was added slowly to a solution of dialdehyde **1a** (1.16 g, 3.33 mmol) in refluxing ethanol (50 cm^3). The reaction mixture was refluxed for 2 h then the solvent evaporated. The resulting solid was transferred to a separating funnel with water and dichloromethane then extracted with dichloromethane. Drying (Na_2SO_4) and evaporation of the combined organic layers yielded *diol* **2a** (1.13 g, 97%) as a white powder, mp 128–130 °C (from acetone) [Found: M^+, 351.1469 (EI). $C_{21}H_{21}NO_4$ requires *M*, 351.1470]; δ_H 3.87 (2 H, t, *J* 6, OH), 4.74 (4 H, d, *J* 6, CH_2OH), 5.27 (4 H, s, CH_2O), 6.92–7.32 (8 H, m, ArH), 7.38 [2 H, d, *J* 8, H-3(5)] and 7.76 (1 H, t, *J* 8, H-4); δ_C 62.0, 70.3, 112.4, 120.6, 121.5, 129.1, 129.4, 130.1, 138.0 and 156.6.

2,6-Bis[(2′-hydroxymethyl-4′-*tert*-butylphenoxy)methyl]pyridine 2b

In a similar procedure to that described above sodium borohydride (1.3 g, 34.4 mmol) and dialdehyde **1b** (4.0 g, 8.7 mmol) yielded *diol* **2b** (3.9 g, 97%) as a colourless powder, mp 89 °C [Found: $(M + H)^+$, 464.2795 (ES). $C_{29}H_{38}NO_4$ requires *M* + H, 464.2801]; δ_H 1.29 [18 H, s, $(CH_3)_3$], 3.79 (2 H, t, *J* 7, OH), 4.75 (4 H, d, *J* 7, CH_2OH), 5.25 (4 H, s, CH_2O), 6.87 (2 H, d, *J* 9, H-6′), 7.26 (2 H, dd, *J* 3, 9, H-5′), 7.32 (2 H, d, *J* 3, H-3′), 7.38 [2 H, d, *J* 8, H-3(5)] and 7.76 (1 H, t, *J* 8, H-4); δ_C 31.5, 34.2, 62.5, 70.6, 112.0, 120.5, 125.6, 126.6, 129.4, 138.0, 144.2, 154.5 and 156.9.

1,3-Bis[(2′-hydroxymethyl-4′-*tert*-butylphenoxy)methyl]benzene 2c

In a procedure similar to that described above, sodium borohydride (1.5 g, 40 mmol) and dialdehyde **1c** (1.8 g, 3.9 mmol) dissolved in a mixture of absolute ethanol (100 cm^3) and toluene (20 cm^3) yielded *diol* **2c** as a clear viscous oil (1.8 g, 98%) [Found: M^+, 462.2770 (EI). $C_{30}H_{38}O_4$ requires *M*, 462.2770]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 2.56 (2 H, t, *J* 7, OH), 4.73 (4 H, d, *J* 6, CH_2OH), 5.13 (4 H, s, CH_2O), 6.88 (2 H, d, *J* 9, H-6′), 7.27 (2 H, dd, *J* 3, 9, H-5′), 7.35 (2 H, d, *J* 3, H-3′), 7.3–7.4 (6 H, m, ArH) and 7.54 (2 H, s, H-2); δ_C 31.5, 34.1, 62.4, 69.8, 111.2, 125.5, 125.8, 126.3, 126.8, 128.6, 128.9, 137.6, 143.8 and 154.3.

1,4-Bis[(2′-hydroxymethyl-4′-*tert*-butylphenoxy)methyl]benzene 2d

Using a procedure similar to that described above, sodium borohydride (0.9 g, 23 mmol) and dialdehyde **1d** (1.0 g, 2.3 mmol) yielded *diol* **2d** (1.0 g, 97%) as a colourless powder, mp 141–142 °C [Found: M^+, 462.2763 (EI). $C_{30}H_{38}O_4$ requires *M*, 462.2770]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 2.32 (2 H, t, *J* 7, OH), 4.74 (4 H, d, *J* 7, CH_2OH), 5.12 (4 H, s, CH_2O), 6.88 (2 H, d, *J* 9, H-6′), 7.27 (2 H, dd, *J* 3, 9, H-5′), 7.33 (2 H, d, *J* 3, H-3′) and 7.45 (4 H, s, *p*-xylyl-H); δ_C 31.5, 34.1, 62.6, 69.8, 111.1, 125.4, 126.1, 127.6, 128.7, 136.8, 143.8 and 154.3.

2,6-Bis[2′-(chloromethyl)phenoxymethyl]pyridine 3a

Thionyl chloride (6.77 g, 57.0 mmol) was added to a solution of diol **2a** (2.0 g, 5.7 mmol) dissolved in dichloromethane (60 cm^3). The reaction mixture was refluxed for 4 h then water (10 cm^3) was added and stirring continued for a further 30 min. The reaction mixture was transferred to a separating funnel and washed with aqueous sodium hydroxide (2 mol dm^{-3}, 2 × 50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated yielding *dichloride* **3a** (1.96 g, 88%) as a colourless solid, mp 143–145 °C (from acetone) [Found: M^+, 387.0794 (EI). $C_{21}H_{19}NO_2Cl_2$ requires *M*, 387.0793]; δ_H 4.77 (4 H, s, CH_2Cl), 5.29 (4 H, s, CH_2O), 6.93 (2 H, d, *J* 8, H-6′), 6.98 (2 H, t, *J* 8, H-4′), 7.26–7.41 (4 H, m, H-3′ and H-5′), 7.57 [2 H, d, *J* 8, H-3(5)] and 7.80 (1 H, t, *J* 8, H-4); δ_C 41.9, 70.4 , 112.0, 120.0, 121.2, 126.0, 130.2, 130.7, 138.0, 156.0 and 156.5.

2,6-Bis[(2′-chloromethyl-4′-*tert*-butylphenoxy)methyl]pyridine 3b

In a similar manner to that described above, thionyl chloride (6.8 g, 57.0 mmol) and diol **2b** (2.9 g, 6.3 mmol) yielded a waxy solid which was triturated with petrol yielding *dichloride* **3b** (3.0 g, 97%) as colourless needles, mp 108–109 °C [Found: C, 69.4; H, 7.0; N, 2.6. $C_{29}H_{35}NO_2Cl_2$ requires C, 69.6; H, 7.0; N, 2.8%. Found: $(M + H)^+$, 500.2124 (ES). $C_{29}H_{36}NO_2Cl_2$ requires *M* + H, 500.2123]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 4.78 (4 H, s, CH_2Cl), 5.27 (4 H, s, CH_2O), 6.87 (2 H, d, *J* 9, H-6′), 7.31 (2 H, dd, *J* 3, 9, H-5′), 7.40 (2 H, d, *J* 3, H-3′), 7.57 [2 H, d, *J* 8, H-3(5)] and 7.80 (1 H, t, *J* 8, H-4); δ_C 31.4, 34.1, 42.3, 70.5, 111.5, 119.9, 125.2, 126.9, 127.8, 137.9, 143.8, 153.8 and 156.6.

1,3-Bis[(2′-chloromethyl-4′-*tert*-butylphenoxy)methyl]benzene 3c

In a similar manner to that described above, thionyl chloride (4.8 g, 40.3 mmol) and diol **2c** (1.8 g, 4.0 mmol) yielded *dichloride* **3c** (1.9 g, 95%) as colourless needles, mp 89–91 °C [Found: M^+, 498.2090 (EI). $C_{30}H_{36}O_2Cl_2$ requires *M*, 498.2092]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 4.73 (4 H, s, CH_2Cl), 5.15 (4 H, s, CH_2O), 6.88 (2 H, d, *J* 9, H-6′), 7.31 (2 H, dd, *J* 3, 9, H-5′), 7.39 (2 H, d, *J* 3, H-3′), 7.44 [3 H, br, H-4(6) and H-5] and 7.58 (1 H, s, H-2); δ_C 31.4, 34.1, 42.3, 70.0, 111.8, 125.4, 125.8, 126.6, 126.8, 127.7, 128,8, 137.5, 143.7 and 154.3.

1,4-Bis[(2′-chloromethyl-4′-*tert*-butylphenoxy)methyl]benzene 3d

In a similar manner to that described above, thionyl chloride (0.9 g, 7.6 mmol) and diol **2d** (0.35 g, 0.76 mmol) yielded *dichloride* **3d** (0.36 g, 95%) as a colourless powder, mp 157–158 °C [Found: M^+, 498.2096 (EI). $C_{30}H_{36}O_2Cl_2$ requires *M*, 498.2092]; δ_H 1.32 [18 H, s, $(CH_3)_3$], 4.74 (4 H, s, CH_2Cl), 5.15 (4 H, s, CH_2O), 6.88 (2 H, d, *J* 9, H-6′), 7.31 (2 H, dd, *J* 3, 9, H-5′), 7.40 (2 H, d, *J* 3, H-3′) and 7.51 (4 H, s, *p*-xylyl-H); δ_C 31.5, 34.1, 42.2, 70.0, 111.8, 125.5, 126.8, 127.3, 127.7, 136.8, 143.8 and 154.3.

2,6-Bis[2′-(phthalimidomethyl)phenoxymethyl]pyridine 4a

Potassium phthalimide (1.05 g, 5.67 mmol) was added to a solution of dichloride **3a** (1.0 g, 2.5 mmol) in dimethylformamide (25 cm^3). The temperature was raised to 120 °C and the reaction heated for 5 h. The reaction mixture was then cooled to room temperature and poured into ice–water (200 cm^3). After stirring this mixture for 1 h the precipitate was collected by filtration, washed with water and dried to afford *diphthalimide* **4a** (1.52 g, 99%) as a colourless powder, mp 201–203 °C [Found: $(M + H)^+$, 610.1970 (ES). $C_{37}H_{28}N_3O_6$ requires *M* + H, 610.1978]; δ_H 5.06 (4 H, s, CH_2N), 5.26 (4 H, s, CH_2O) and 6.9–7.87 (19 H, m, ArH); δ_C 36.8, 70.7, 111.8, 120.2, 121.0, 123.3, 128.7, 128.9, 132.2, 134.0, 137.8, 155.7 and 168.2.

2,6-Bis[(2′-phthalimidomethyl-4′-*tert*-butylphenoxy)methyl]-pyridine 4b

In a similar manner to that described above, potassium phthalimide (3.2 g, 17.3 mmol) and dichloride **3b** (3.0 g, 4.2 mmol) in dimethylformamide (25 cm^3) yielded a cream coloured solid which was dried *in vacuo*. This crude product was purified by dissolving it in hot dichloromethane (40 cm^3) and adding diethyl ether (80 cm^3). After cooling overnight (2 °C) the colourless product was collected and washed with acetone yielding *diphthalimide* **4b** (2.8 g, 93%) as a colourless powder, mp 207–210 °C (from toluene) [Found: C, 75.4; H, 5.9; N, 5.1. $C_{45}H_{43}N_3O_6\cdot 0.5C_7H_8$ requires C, 75.9; H, 6.2; N, 5.5%. Found: M^+, 721.3152 (EI). $C_{45}H_{43}N_3O_6$ requires *M*, 721.3152]; δ_H 1.25 [18 H, s, $(CH_3)_3$], 5.04 (4 H, s, CH_2N), 5.22 (4 H, s, CH_2O), 6.84 (2 H, d, *J* 9, H-6′), 7.23 (2 H, dd, *J* 3, 9, H-5′), 7.37 (2 H, d, *J* 3, H-3′), 7.54 [2 H, d, *J* 8, H-3(5)], 7.70 (4 H, dd, *J* 3, 6, phthalimide-H), 7.76 (1 H, t, *J* 8, H-4) and 7.84 (4 H, dd, *J* 3, 6, phthalimide-H); δ_C 31.4, 34.0, 37.1, 70.7, 111.3, 120.1, 123.2, 125.6, 126.9, 132.1, 133.9, 137.7, 143.5, 153.6, 156.7 and 168.1.

1,3-Bis[(2′-hydroxyiminomethyl-4′-*tert*-butylphenoxy)methyl]-benzene 5c

A suspension of dialdehyde **1c** (1.58 g, 3.4 mmol) in absolute ethanol (100 cm^3) was stirred at room temperature. A solution of hydroxylamine hydrochloride (2.4 g, 35 mmol) and sodium hydroxide (1.7 g, 43 mmol) dissolved in water (50 cm^3) was added and the mixture stirred overnight. The mixture was poured into hydrochloric acid (2 mol dm^{-3}, 100 cm^3) and stirred. The suspension was collected and washed with water (3 × 50 cm^3). Drying *in vacuo* yielded *dioxime* **5c** (1.61 g, 97%) as a colourless powder, mp 87–90 °C [Found: $(M + H)^+$, 489.2734 (ES). $C_{30}H_{37}N_2O_4$ requires *M* + H, 489.2753]; δ_H([$^2H_6$]acetone) 1.28 [18 H, s, $(CH_3)_3$], 5.19 (4 H, s, CH_2O), 7.07 (2 H, d, *J* 9, H-6′), 7.39 (2 H, dd, *J* 3, 9, H-5′), 7.48 [3 H, br, H-4(6) and H-5], 7.64 (1 H, br, H-2), 7.81 (2 H, d, *J* 3, H-3′), 8.50 (2 H, s, CHN) and 10.25 (2 H, br, OH); δ_C([$^2H_6$]acetone) 31.6, 34.6, 70.8, 113.4, 121.8, 123.2, 127.6, 127.9, 128.5, 129.6, 138.6, 144.1, 145.1 and 155.2.

1,4-Bis[(2′-hydroxyiminomethyl-4′-*tert*-butylphenoxy)methyl]-benzene 5d

In a similar manner to that described above, dialdehyde **1d** (1.88 g, 4.1 mmol), hydroxylamine hydrochloride (2.9 g, 42 mmol) and sodium hydroxide (1.7 g, 43 mmol) yielded *dioxime* **5d** (1.96 g, 98%) as a colourless solid, mp 226–228 °C [Found: $(M + H)^+$, 489.2746 (ES). $C_{30}H_{37}N_2O_4$ requires *M* + H, 489.2753]; δ_H([$^2H_6$]-acetone) 1.28 [18 H, s, $(CH_3)_3$], 5.19 (4 H, s, CH_2O), 7.07 (2 H, d, *J* 9, H-6′), 7.39 (2 H, dd, *J* 3, 9, H-5′), 7.54 (4 H, s, *p*-xylyl-H), 7.81 (2 H, d, *J* 3, H-3′), 8.49 (2 H, s, CHN) and 10.22 (2 H, s, OH); δ_C([$^2H_6$]acetone) 31.6, 34.7, 70.6, 113.4, 121.9, 123.2, 128.5, 137.9, 144.1, 145.2 and 155.2.

2,6-Bis[2′-(aminomethyl)phenoxymethyl]pyridine 6a

Diphthalimide **4a** (1.5 g, 2.46 mmol) was dissolved in refluxing absolute ethanol (60 cm^3). Hydrazine (0.79 g, 24.6 mmol) was added dropwise and the reaction was refluxed for 2 h. The solvent was removed and hydrochloric acid (2 mol dm^{-3}, 50 cm^3) added. The reaction mixture was heated to 60 °C and stirred for 1 h. The phthalohydrazide salt was removed by filtration and the filtrate basified with sodium hydroxide (pH > 12). This aqueous solution was extracted with dichloromethane. The combined organic phases were re-extracted with water, dried (Na_2SO_4) and evaporated yielding the crude diamine as a light brown powder. This was purified by chromatography (silica; MeOH–$CHCl_3$, 3:97 as eluent) to yield *diamine* **6a** (0.74 g, 86%) as a colourless solid, mp 107–110 °C (Found: C, 71.2; H, 6.4; N, 11.5. $C_{21}H_{23}N_3O_2\cdot 0.3H_2O$ requires C, 71.1; H, 6.7; N, 11.8%); δ_H 1.70 (4 H, br, NH_2), 3.95 (4 H, s, CH_2N), 5.25 (4 H, s, CH_2O), 6.92 (2 H, d, *J* 8, H-6′), 6.96 (2 H, t, *J* 7, H-4′), 7.22 (4 H, m, H-3′ and H-5′), 7.47 [2 H, d, *J* 8, H-3(5)] and 7.78 (1 H, t, *J* 8, H-4); δ_C 42.7, 70.3, 111.5, 119.9, 121.2, 128.2, 128.6, 132.1, 137.9, 156.0 and 156.8.

2,6-Bis[(2′-aminomethyl-4′-*tert*-butylphenoxy)methyl]pyridine 6b

In a similar manner to that described above, diphthalimide **4b** (2.0 g, 2.8 mmol) and hydrazine (1.8 g, 56 mmol) yielded *diamine* **6b** (1.2 g, 93%) as a viscous, brown oil [Found: M^+, 462.3124 (EI). $C_{29}H_{40}N_3O_2$ requires *M*, 462.3121]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 1.75 (4 H, br, NH_2), 3.94 (4 H, br, CH_2N), 5.23 (4 H, s, CH_2O), 6.85 (2 H, d, *J* 9, H-6′), 7.23 (2 H, dd, *J* 3, 9, H-5′), 7.29 (2 H, d, *J* 3, H-3′), 7.47 [2 H, d, *J* 8, H-3(5)] and 7.77 (1 H, t, *J* 8, H-4); δ_C 31.5, 34.1, 43.2, 70.3, 111.1, 119.8, 124.7, 125.9, 137.8, 143.8, 153.9 and 157.0.

1,3-Bis[(2′-aminomethyl-4′-*tert*-butylphenoxy)methyl]benzene 6c

A solution of dioxime **5c** (1.15 g, 2.4 mmol) in dry THF (50 cm^3) was cooled (0 °C). Lithium aluminium hydride (0.5 g, 13.2 mmol) was added to the mixture which was refluxed for 3 h then cooled to room temperature. Water (0.5 cm^3), 20% aqueous sodium hydroxide (0.5 cm^3) and water (1.5 cm^3) were added sequentially and the mixture filtered through a bed of Celite. After thoroughly washing the lithium salts with dichloromethane (3 × 20 cm^3), the combined organic fractions were rotary evaporated and the residue transferred to a separating funnel using dichloromethane (100 cm^3). The organic layer was washed with aqueous sodium hydroxide (1 mol dm^{-3}, 50 cm^3) and the aqueous phase re-extracted with dichloromethane (2 × 50 cm^3). Routine work-up of the combined organic layers yielded *diamine* **6c** as a viscous, brown oil (0.93 g, 84%) [Found: M^+, 460.3088 (EI). $C_{30}H_{40}N_2O_2$ requires *M*, 460.3090]; δ_H 1.31 [18 H, s, $(CH_3)_3$], 1.73 (4 H, br, NH_2), 3.88 (4 H, br, CH_2N), 5.11 (4 H, s, CH_2O), 6.87 (2 H, d, *J* 9, H-6′), 7.23 (2 H, dd, *J* 3, 9, H-5′), 7.28 (2 H, d, *J* 3, H-3′), 7.40 [3 H, br, H-4(6) and H-5] and 7.50 (1 H, br, H-2); δ_C 31.5, 34.1, 43.1, 69.7, 111.1, 124.5, 125.7, 125.9, 126.6, 128.9, 131.4, 137.7, 143.6 and 154.3.

1,4-Bis[(2′-aminomethyl-4′-*tert*-butylphenoxy)methyl]benzene 6d

Using a procedure similar to that described above, dioxime **5d** (1.3 g, 2.8 mmol) and lithium aluminium hydride (0.6 g, 15.8 mmol) yielded *diamine* **6d** (1.1 g, 92%) as a viscous, colourless oil [Found: M^+, 460.3081 (EI). $C_{30}H_{40}N_2O_2$ requires *M*, 460.3090]; δ_H 1.32 [18 H, s, $(CH_3)_3$], 2.32 (4 H, br, NH_2), 3.89 (4 H, s, CH_2N), 5.11 (4 H, s, CH_2O), 6.88 (2 H, d, *J* 9, H-6′), 7.25 (2 H, dd, *J* 3, 9, H-5′), 7.45 (2 H, d, *J* 3, H-3′) and 7.46 (4 H, s, *p*-xylyl-H); δ_C 31.5, 34.1, 43.1, 69.6, 111.1, 124.5, 125.9, 127.4, 131.2, 136.9, 143.6 and 154.3.

Macrocycle 7a

Separate solutions of dialdehyde **1a** (1.99 g, 5.7 mmol) in absolute ethanol (400 cm^3) and diamine **6a** (2.0 g, 5.7 mmol) in absolute ethanol (400 cm^3) were added dropwise, over an 8 h period, into stirred, refluxing ethanol (400 cm^3). Sodium borohydride (2.58 g, 68.4 mmol) was then added in small portions and after a further 1 h reflux the solvent was evaporated to approximately 50 cm^3 and the mixture poured into ice–water (200 cm^3). The crude solid was filtered, washed with water and dried. Purification by column chromatography (silica; MeOH–$CHCl_3$–NH_4OH, 3:97:0.1 as eluent) afforded *macrocycle* **7a** (1.14 g, 30%) as a cream coloured solid, mp 208–210 °C [Found: M^+, 664.3046 (EI). $C_{42}H_{40}N_4O_4$ requires *M*, 664.3049]; δ_H 2.53 (2 H, br, NH), 3.99 (8 H, s, CH_2N), 4.98 (8 H, s, CH_2O), 6.80 (4 H, d, *J* 8, H-6′), 6.90 (4 H, t, *J* 7, H-4′) and 7.05–7.40 (14 H, m, ArH); δ_C 49.9, 69.9, 111.5, 119.4, 121.1, 127.2, 128.8, 130.9, 137.7, 156.0 and 156.3.

Macrocycle 7b

Method A. Separate solutions of dialdehyde **1b** (2.5 g, 5.4 mmol) dissolved in a 2:3 mixture of toluene and absolute ethanol (250 cm^3), and diamine **6b** (2.52 g, 5.5 mmol) dissolved in absolute ethanol (250 cm^3) were simultaneously added dropwise, over a 3 h period, into a stirred, refluxing suspension of 4 Å molecular sieves (14 g) in absolute ethanol (400 cm^3). Sodium cyanoborohydride (3.4 g, 54.4 mmol) was then added in small portions and the mixture refluxed for a further 24 h after which time the reaction mixture was filtered through a bed of Celite. The filter cake was washed thoroughly with dichloromethane and the combined filtrates rotary evaporated. The resulting solid was dissolved in dichloromethane (150 cm^3) and washed with aqueous sodium hydroxide (1 mol dm^{-3}, 2 × 50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated yielding a light brown powder which was washed with ethanol to yield *macrocycle* **7b** (3.9 g, 81%) as a colourless solid, mp 179–182 °C [Found: $(M + H)^+$, 889.5638 (ES). $C_{58}H_{73}N_4O_4$ requires *M* + H, 889.5623]; δ_H 1.30 [36 H, s, $(CH_3)_3$], 2.53 (2 H, br, NH), 3.95 (8 H, s, CH_2N), 5.03 (8 H, s, CH_2O), 6.75 (4 H, d, *J* 9, H-6′), 6.95 [4 H, d, *J* 8, H-3(5)], 7.09 (2 H, t, *J* 8, H-4), 7.20 (4 H, dd, *J* 3, 9, H-5′) and 7.35 (4 H, d, *J* 3, H-3′); δ_C 31.5, 34.1, 51.0, 70.2, 111.0, 119.0, 124.9, 127.9, 137.4, 137.7, 143.6, 154.2 and 156.5.

Method B. Separate solutions of dialdehyde **1b** (1.14 g, 2.47 mmol) in dry ethanol (400 cm^3) and diamine **6b** (1.14 g, 2.47 mmol) in dry ethanol (400 cm^3) were simultaneously added dropwise from separate dropping funnels into stirred, refluxing dry ethanol (400 cm^3) over an 8 h period. The resulting clear, yellow reaction mixture was refluxed for 11 h during which time excess sodium borohydride (0.49 g, 13 mmol) was added in small portions. Reflux was maintained for 4 h and then the mixture was cooled to room temperature. The solvent was reduced in volume (~100 cm^3) and the resulting white precipitate was collected and washed with water, then ice-cold ethanol and air-dried to afford a white solid which was purified by column chromatography (silica; MeOH–$CHCl_3$–NH_4OH 3:97:0.1 as eluent) yielding macrocycle **7b** (1.00 g, 45%) as a colourless solid.

Macrocycle 7c

Using a procedure similar to that described above (Method A), dialdehyde **1c** (1.1 g, 2.4 mmol) and diamine **6c** yielded a colourless solid which was washed with cold methanol yielding *macrocycle* **7c** (1.0 g, 47%) as a colourless powder, mp 188–189 °C (from benzene) [Found: $(M + H)^+$, 887.5755 (LSI). $C_{60}H_{75}N_2O_4$ requires *M* + H, 887.5726]; δ_H 1.30 [36 H, s, $(CH_3)_3$], 3.89 (8 H, s, CH_2N), 4.75 (8 H, s, CH_2O), 6.68 (4 H, d, *J* 9, H-6′), 7.15–7.23 (16 H, m, ArH) and 7.33 (4 H, br, H-3′); δ_C 31.5, 34.0, 50.8, 69.4, 110.0, 124.7, 125.6, 126.0, 127.5, 128.1, 137.6, 143.2 and 154.6.

Macrocycle 7d

In a similar procedure to that described above, dialdehyde **1d** (1.6 g, 3.5 mmol) and diamine **6d** (1.6 g, 3.5 mmol) yielded *macrocycle* **7d** (1.8 g, 58%) as a colourless powder, mp 246–248 °C (decomp.) (from chloroform–acetonitrile, 2:5) [Found: C, 75.9; H, 7.7; N, 2.7. $C_{60}H_{74}N_2O_4{\cdot}0.6CHCl_3$ requires C, 75.9; H, 7.8; N, 2.9%. Found: $(M + H)^+$, 887.5736 (ES). $C_{60}H_{75}N_2O_4$ requires *M* + H, 887.5726]; δ_H 1.30 [36 H, s, $(CH_3)_3$], 3.91 (8 H, s, CH_2N), 4.87 (8 H, s, CH_2O), 6.79 (4 H, d, *J* 9, H-6′), 7.20 (4 H, dd, *J* 3, 9, H-5′), 7.28 (8 H, s, *p*-xylyl-H) and 7.39 (4 H, d, *J* 3, H-3′); δ_C 31.5, 34.1, 50.3, 69.5, 111.1, 124.6, 126.9, 127.3, 128.4, 136.8, 143.4 and 154.7.

Cage 8a

Dichloride **3a** (0.15 g, 0.38 mmol) dissolved in toluene (90 cm^3) was added dropwise to a stirred refluxing suspension of sodium hydrogen carbonate (0.10 g, 1.2 mmol) and macrocycle **7a** (0.25 g, 0.38 mmol) in toluene (90 cm^3) under a nitrogen atmosphere. After 72 h the reaction mixture was cooled, transferred to a separating funnel and washed with water until the pH of the aqueous layer was approximately neutral. The organic layer was dried (Na_2SO_4) and evaporated yielding *cage* **8a** (0.152 g, 41%) as a colourless solid, mp >300 °C (from chloroform) (Found: C, 76.7; H, 6.0; N, 7.1. $C_{63}H_{57}N_5O_6{\cdot}0.25H_2O$ requires C, 76.9; H, 5.9; N, 7.1%); δ_H 3.64 (12 H, s, CH_2N), 4.93 (12 H, s, CH_2O) and 6.90–7.72 (33 H, m, ArH).

Cage 8b

Caesium carbonate (2.8 g, 8.6 mmol) was added to a solution of macrocycle **7b** (1.0 g, 1.1 mmol) and dichloride **3b** (0.55 g, 1.1 mmol) in toluene (100 cm^3). The reaction mixture was stirred at reflux for 9 days after which time the toluene was evaporated and the crude solid was partitioned between chloroform (100 cm^3) and water (50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated to yield a powder which was purified by column chromatography (neutral alumina, chloroform eluent) affording *cage* **8b** (0.72 g, 52%) as a colourless solid, mp >300 °C (from benzene) [Found: $(M + H)^+$, 1316.8185 (ES). $C_{87}H_{106}N_5O_6$ requires *M* + H, 1316.8143]; δ_H 1.33 [54 H, s, $(CH_3)_3$], 3.69 (12 H, s, CH_2N), 4.89 (12 H, s, CH_2O), 6.83 (6 H, d, *J* 9, H-6′), 6.95 (3 H, t, *J* 8, H-4), 7.07 [6 H, d, *J* 8, H-3(5)], 7.23 (6 H, dd, *J* 3, 9, H-5′) and 7.77 (6 H, d, *J* 3, H-3′); δ_C 31.6, 34.1, 52.5, 71.0, 111.0, 121.4, 124.0, 127.6, 127.9, 137.5, 143.6, 154.7 and 156.1.

Cage 8c

In a similar manner to that described above, macrocycle **7c** (173 mg, 195 µmol), dichloride **3c** (97 mg, 195 µmol) and caesium carbonate (630 mg, 19.5 mmol) yielded *cage* **8c** (124 mg, 48%) as a colourless powder, mp >300 °C [Found: $(M + 2H)^{2+}$, 657.4212 (ES). $C_{90}H_{110}N_2O_6$ requires $\frac{1}{2}$(*M* + 2H), 657.4182]; δ_H 1.32 [54 H, s, $(CH_3)_3$], 3.73 (12 H, s, CH_2N), 4.94 (12 H, s, CH_2O), 6.86 (6 H, d, *J* 9, H-6′), 7.07 (3 H, t, *J* 8, H-5), 7.18 (6 H, dd, *J* 3, 9, H-5′), 7.33 [6 H, dd, *J* 2, 8, H-4(6)], 7.48 (3 H, br, H-2) and 8.03 (6 H, d, *J* 3, H-3′); δ_C 31.7, 34.2, 51.9, 70.3, 110.6, 123.3, 125.6, 128.4, 128.6, 128.8, 137.3, 143.4 and 154.8.

Cage 8d

In a similar manner to that described above, macrocycle **7d** (209 mg, 240 µmol), dichloride **3d** (120 mg, 240 µmol) and caesium carbonate (780 mg, 2.4 mmol) yielded *cage* **8d** (132 mg, 42%) as a colourless powder, mp >300 °C [Found: $(M + 2H)^{2+}$, 657.4153 (ES). $C_{90}H_{110}N_2O_6$ requires $\frac{1}{2}$(*M* + 2H), 657.4182]; δ_H 1.31 [54 H, s, $(CH_3)_3$], 3.88 (12 H, s, CH_2N), 4.94 (12 H, s, CH_2O), 6.87 (6 H, d, *J* 9, H-6′), 7.22 (6 H, dd, *J* 3, 9, H-5′), 7.49 (12 H, s, *p*-xylyl-H) and 8.24 (6 H, d, *J* 3, H-3′); δ_C 31.7, 34.2, 52.6, 69.3, 109.7, 123.2, 124.4, 127.9, 128.2, 136.7, 143.4 and 154.3.

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