Synthesis of cyclocholate-capped porphyrins

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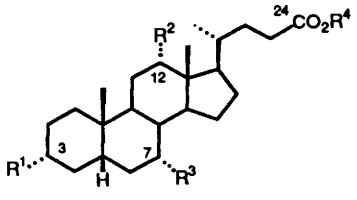
The syntheses of two types of semisynthetic receptor composed of porphyrins capped on one or both faces by a cyclic dilactone of cholic acid (a 7,24-cyclo[2]cholate) are presented. The singly capped diarylporphyrin was made by macrolactonisation over a preformed porphyrin and also by porphyrin synthesis beneath a preformed cyclocholate cap. The doubly capped tetraarylporphyrin has been prepared by condensation of an aldehyde-functionalised cyclocholate with pyrrole under equilibrium conditions. A preparatively useful synthesis of 7,24-cyclo[2]cholates has been developed, and different conformations of protected and unprotected cyclocholates invoked to explain product distributions in porphyrin-cyclocholate synthesis. The ability of zinc porphyrins to bind basic species such as pyridine, hydrazine and DABCO has been used to support structural assignments and also to catalyse synthetically useful self-acylations and deacylations.

The readily available natural product cholic acid **1a** is increasingly being used as a building block for the construction of semisynthetic receptors.[1-3] We have focused on cyclic polyesters of cholic acid, christened 'cyclocholates', as readily available frameworks for host-guest type chemistry.[3] Cholic acid has three secondary hydroxy groups at positions 3, 7 and 12 and an acid group at C-24, so three 'natural' series of cyclic polyesters are possible, 3,24-cyclo[*n*]cholates, 7,24-cyclo[*n*]-cholates and 12,24-cyclo[*n*]cholates, where [*n*] is the number of steroid units in the ring. Cyclo[2]cholates are the smallest and most conformationally well defined cyclooligomers in each series. This paper describes the synthesis of two porphyrin-based receptors **4** (Scheme 1) and **6** (Scheme 4) which employ the 7,24-cyclo[2]cholate as a structural and recognition element. Part of this work has been communicated.[3g]

Model building suggested that a 7,24-cyclo[2]cholate could span across a *meso* arylporphyrin without significant strain if attached to the *meta* positions of the aryl rings *via* ester links. Porphyrins **4** and **6** represent first generation receptors, with no modification of the basic natural product skeleton, and it was hoped that the all-ester construction would make for straightforward syntheses, extendable to more functionalised analogues. As previously reported, zinc derivatives **Zn4** and **Zn6** are capable of including a variety of medium sized molecules by a combination of Lewis acid co-ordination to zinc, hydrogen bonding to the pair of inwardly projecting hydroxy groups, dispersive interactions with the steroidal superstructure and solvophobic forces.[3a,g]



	R^1	R^2	R^3	R^4
1a	OH	OH	OH	H
1b	OH	$OCOCF_3$	OH	Bu^t
1c	OAr*	$OCOCF_3$	OH	Bu^t
1d	OAr	$OCOCF_3$	OH	H
1e	OAr	$OCOCF_3$	OH	Bn
1f	OAc	$OCOCF_3$	OH	H
1g	OH	H	OH	H

*Ar = 3-formylbenzoyl

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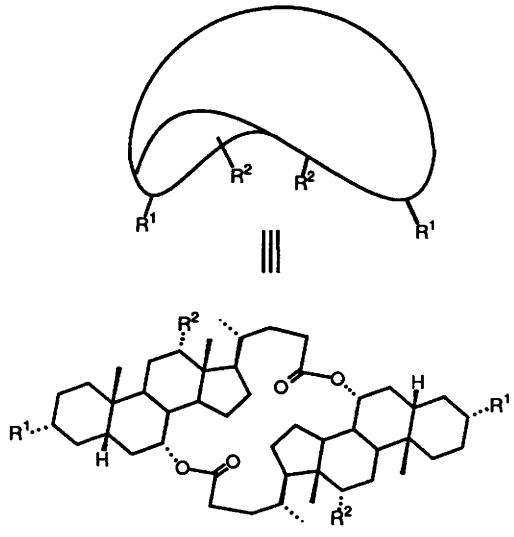
Results and discussion

Synthesis

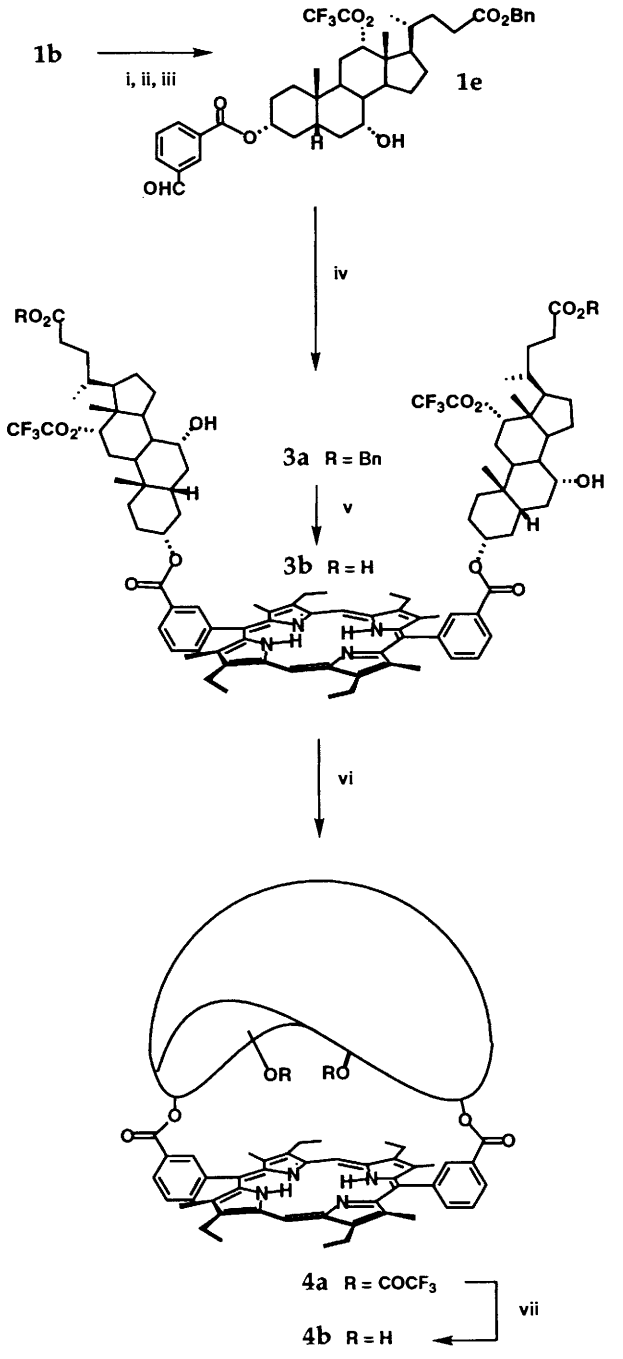
There are three obvious disconnections for **4**: (1) coupling a porphyrin diacid to a preformed dilactone diol, (2) synthesis of the dilactone over the top of the porphyrin using the porphyrin as a covalent template and (3) synthesis of the porphyrin under the dilactone using the dilactone as a template. Only approaches (2) and (3) have been explored to date.

Starting with the porphyrin-first dilactone-last route, Scheme 1, the equatorial 3-hydroxy group of the 3,7-diol **1b**, available in one step from cholic acid (65%)[4] was selectively acylated with 3-formylbenzoic acid and the ester protecting group changed from *tert*-butyl to benzyl to give the aldehyde **1e**. Acid-catalysed condensation with 3,3'-diethyl-4,4'-dimethyl-5,10-dihydrodi-pyrrin[5] followed by oxidation gave the crystalline steroidal porphyrin **3a** in good yield. Hydrogenolysis of **Zn3a** and removal of zinc, which served to protect the porphyrin during



	R^1	R^2
2a	OAr*	$OCOCF_3$
2b	OAr	OH
2c	OAc	$OCOCF_3$
2d	OH	$OCOCF_3$
2e	OH	OH
2f	OSO_2Ph	H

*Ar = 3-formylbenzoyl

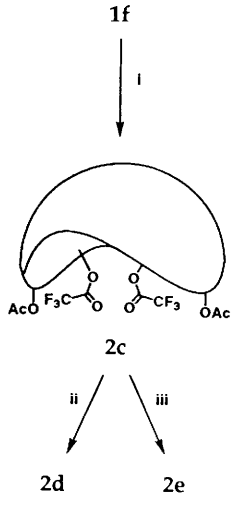


Scheme 1 *Reagents:* i, DCC, DMAP, 3-formylbenzoic acid (74%); ii, TFA (80%); iii, DCC, DMAP, benzyl alcohol (75%); iv, 3,3′-diethyl-4,4′-dimethyl-5,10-dihydrodipyrrin, *p*-TsOH in MeOH, then DDQ (73%); v, $Zn(OAc)_2$, H_2/Pd, aq. HCl (95%); vi, 2,6-dichlorobenzoyl chloride, triethylamine, then slow addition to DMAP in toluene at 100 °C (18%); vii, $Zn(OAc)_2$, $N_2H_4 \cdot H_2O$, (90%), aq. HCl

benzyl ester cleavage, produced the diacid **3b**. Slow addition of the mixed anhydride formed from **3b** and 2,6-dichlorobenzoyl chloride[6] to a solution of DMAP in hot toluene provided, after metallation, crystalline **Zn4a** in low and rather variable yields (2–27% on a small scale, 18% on a larger scale) along with traces of dimeric porphyrin **$Zn_2$5a**. The main by-product was usually half-cyclised material in which only one of the ester bridges had formed. Several other macrolactonisation methods[7] gave similar results. The trifluoroacetate protecting groups were finally removed with hydrazine to give capped porphyrin diol **Zn4b**.

The zinc derivative **Zn4a** was found to react faster than the free base porphyrin **4a** with hydrazine, implying that either the trifluoroacetate groups in the zinc derivative are inherently more reactive (due for example to a small difference in trifluoroacetate conformation in **Zn4a** and **4a**) or that zinc is increasing the concentration of nucleophilic species inside the cavity. To examine this point the reaction of an equimolar mixture of **Zn4a** and **4a** was followed by ^1H and ^{19}F NMR spectroscopy in $CDCl_3$–methanol (10:1) containing a large excess of hydrazine hydrate. Under these conditions **Zn4a** hydrolysed 8 times faster than **4a**, producing *N*-trifluoroacetylhydrazine as the main fluorine-containing reaction product.† If the same reaction was run omitting the methanol co-solvent so that the hydrazine hydrate remained as an undissolved upper phase, **Zn4a** hydrolysed >20 times faster than **4a**. This difference in relative rates between homogeneous and heterogeneous reactions supports an intramolecular mechanism for trifluoroacetate hydrolysis, with the zinc porphyrin concentrating nucleophile from a dilute solution in the organic phase under heterogeneous conditions. Measurement of equilibrium constants (see below) showed that hydrazine is capable of binding inside the cavity of **Zn4a**.

The dilactone-first porphyrin-last approach proved to be a more efficient route to **4b**. It was first necessary to find an efficient synthesis of 7,24-dilactones. In what appears to be the only previous report of a bile acid 7,24-dilactone, Illi *et al.* found that treatment of 12-deoxycholic acid **1g** with benzenesulfonyl chloride in pyridine gave the dilactone diphenylsulfonate **2f** (no yield reported).[8] Attempted cyclisation of **1d** or **1f** under similar conditions gave only low yields ($\leq$15%) of the corresponding dilactones. The most practical large-scale synthesis found to date is a modification of the Yamaguchi method,[6] involving addition of an excess of DMAP in one portion to a pre-heated toluene solution of the mixed anhydride prepared from a cholic acid derivative protected in the 3 and 12 positions and 2,6-dichlorobenzoyl chloride, at substrate concentrations of 5–10 mmol dm^{-3}. In this way the crystalline dilactone **2c** was obtained in 56% yield from hydroxy acid **1f** (Scheme 2) and the dilactone **2a** was prepared from **1d** in 49% yield (Scheme 3). In some exploratory studies the dilactone **2a** was also prepared in a stepwise fashion. Condensation of **1c** with the 7-trimethylsilyloxy derivative of **1d**, followed by removal of protecting groups and macrolactonisation of the resulting dimeric hydroxy acid gave **2a** in 65% yield from **1c**. While



Scheme 2 *Reagents:* i, 2,6-dichlorobenzoyl chloride, triethylamine, DMAP, toluene, 100 °C (56%); ii, aq. HCl (76%); iii, aq. KOH (85%)

† Other bases such as 1,1,3,3-tetramethylguanidine and tetrabutylammonium fluoride also hydrolysed **Zn4a** faster than **4** under these conditions, although the selectivities were lower and the reactions much slower.

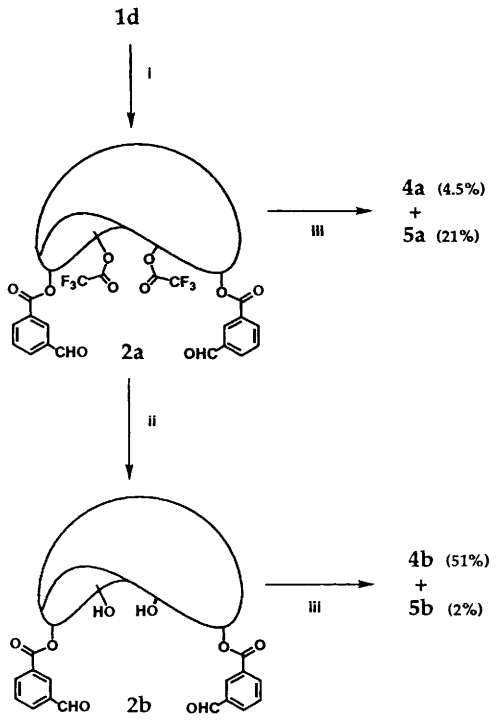
this stepwise route has little advantage for preparation of symmetrical 7,24-dilactones because of the extra steps involved, it is potentially useful for the preparation of unsymmetrically substituted cyclocholates.

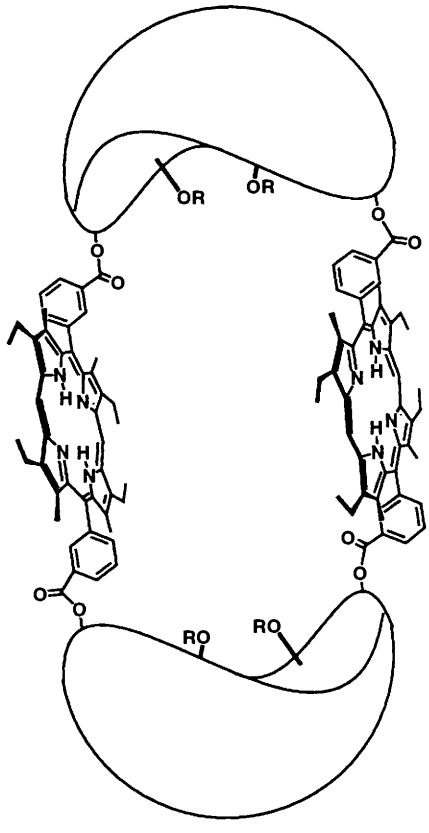
Protection of hydroxy groups in both the 3 and 12 positions was necessary for 7,24-dilactone synthesis. Cyclisation of 3-protected derivatives with a free 12-OH produced mainly internal 12,24-lactones,[8] and cyclisation of 12-protected derivatives with a free 3-OH generated mixtures of 3,24-cyclo-[*n*]-cholates.[3f] It is worth noting that trifluoroacetate has proved to be a particularly useful and orthogonal protecting group for bile acid chemistry,[4] and for cyclocholate synthesis in particular. It survives both macrolactonisation conditions (excess of DMAP in hot toluene) and ester hydrolysis under acidic conditions, as demonstrated by the conversion of the bistrifluoroacetate diacetate **2c** into bistrifluoroacetate diol **2d** in Scheme 2, yet can be selectively removed in the presence of other esters under mildly basic conditions as illustrated by hydrolysis of the bistrifluoroacetate diester **2a** to the diol diester **2b** in Scheme 3. The parent 7,12-cyclo-[2]-cholate tetraol **2e** was readily obtained by basic hydrolysis of **2c** without cleavage of the more hindered dilactone linkages.

Condensation of the trifluoroacetate-protected dilactone bisaldehyde **2a** with 3,3'-diethyl-4,4'-dimethyl-5,10-dihydrodipyrrin at high dilution[9] followed by oxidation gave the dimeric species **5a** as the main product (21%) along with a small amount of **4a** (4.5%) (Scheme 3). However, if the trifluoroacetates were removed before condensation, the monomeric porphyrin **4b** became the major product (51%) and **5b** the minor one (2%). This constitutes a relatively short and efficient synthesis of **4b** (4 steps from **1b**, 20% overall yield from cholic acid). The reversal of product distribution merely by removing protecting groups is interesting and implies that the porphyrinogen precursor of **4a** is thermodynamically disfavoured, being only a minor component of the (presumed) equilibrium mixture of porphyrinogens present in the reaction mixture before oxidative quench. Molecular mechanics calculations[11] suggest that 7,12-dilactones can flex around their ester 'hinges' at little energetic cost, and are able to adopt more or less curved conformations. A more curled-up cup-like conformation for the diol **2b** compared to the bistrifluoroacetate **2a** might explain why **2b** prefers to bridge a single porphyrin rather than form dimers. The difficult cyclisation of **3b** may also be caused by the bulk of the trifluoroacetate protecting groups on the underside of the cap.

Since the dilactone **2b** appeared to have the right geometry to span a *trans*-diaryl porphyrinogen it seemed possible that two molecules could strap across opposite faces of a tetraaryl porphyrinogen. Condensation of **2b** with pyrrole under Lindsey's conditions for *meso*-tetraarylporphyrin synthesis[10] gave the crystalline doubly *trans*-capped porphyrin **6** in 7% yield (Scheme 4), along with a trace of the doubly *cis*-strapped equatorial isomer **7**.[12] For comparison, simple tetraarylporphyrin **10** was prepared in 24% yield under similar conditions.

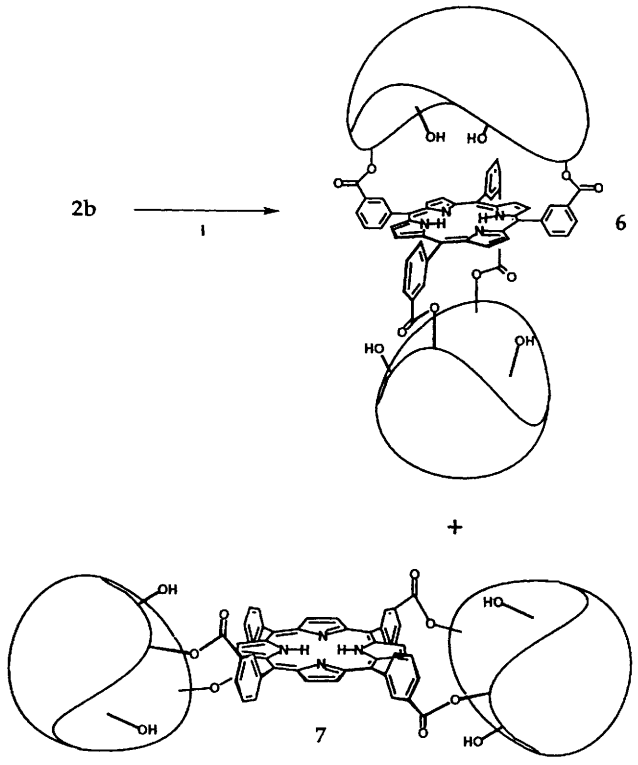
Metalloporphyrins with covalently attached axial ligands are of interest both as catalysts for oxygen transfer reactions,[13] and as models for haem proteins, particularly if the axial ligand can be fixed in one particular rotational orientation.[14] The base-tailed derivative **Zn8** was prepared by again taking advantage of metal amine co-ordination chemistry to position a reactive species within the cavity. Addition of DMAP to a mixture of **Zn6**, **6** and an excess of the mixed anhydride formed from pyridine-3-carboxylic acid and 2,6-dichlorobenzoyl chloride resulted in rapid and quantitative monoacylation of **Zn6**, leaving **6** unchanged. No reaction occurred on extended heating of mixtures of **Zn6** and mixed anhydride without DMAP, or **6** and mixed anhydride with DMAP. However acylation of the free base porphyrin was possible under different conditions. Treatment of **6** with the acid chloride of pyridine-3-carboxylic





5a R= $COCF_3$
5b R= H

Scheme 3 *Reagents:* i, 2,6-dichlorobenzoyl chloride, triethylamine, DMAP, toluene 100 °C (49%); ii, aq. NH_3 (88%); iii, 3,3'-diethyl-4,4'-dimethyl-5,10-dihydrodipyrrin, TFA in CH_2Cl_2, then DDQ



Scheme 4 *Reagents:* i, pyrrole, $BF_3{\cdot}Et_2O$, CH_2Cl_2, then DDQ

acid and DMAP gave a mixture of species from which **Zn8** was isolated in 22% yield after metallation.

Structural assignments and spectroscopic properties of cyclocholate-porphyrins

Capped porphyrins **4a** and **4b** are chiral but rotationally symmetrical, with one set of ^1H and ^{13}C resonances for the steroids and two sets of resonances for the non-equivalent pyrrole rings. As expected, the steroid resonances are shifted upfield by the porphyrin ring current. For example, the 18-methyl groups on the top of bistrifluoroacetate **4a** are shifted upfield by 0.36 ppm (^1H) relative to the dilactone **2a**, the C-12 carbons on the edge of the dilactone are shifted by 1.2 ppm (^{13}C), and the ^{19}F resonance for the trifluoroacetates on the underside of the cap is shifted by 3.5 ppm. The diol **4b** shows similar, although not identical, upfield shifts, with the 12-OH protons (δ 0.35, J 4 Hz) shifted by 1.53 ppm relative to **2b**. The shifts of **4a** and **4b** are in good qualitative agreement with shifts calculated from a porphyrin ring current model[15] using averaged distances generated by molecular mechanics calculations.

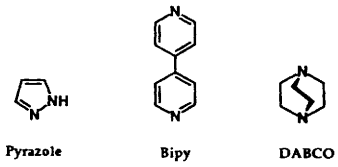
The Soret band of the bistrifluoroacetate **4a** in CH_2Cl_2 is red shifted by 1.5 nm compared to reference porphyrin **9** (Table 1) whereas the diol **4b** is red shifted by 4.5 nm. Red shifts can be produced by distorting or bending a porphyrin.[16] In conjunction with the small differences in NMR spectra, this implies that **4a** and **4b** have slightly different conformations. The diol **4b** gave a large positive CD response around the Soret λ_{max}, consistent with a chirally twisted chromophore. The zinc derivatives **Zn4a** and **Zn4b** have very similar NMR spectra and similar trends in Soret λ_{max} compared to **Zn9** (Table 1). Since there are only minor spectroscopic differences between zinc and free-base cyclocholate-porphyrins, only the free-base versions are discussed further in this section.

The ^1H NMR spectra of trifluoroacetate-protected dimer **5a** is broadened compared to **4a** and is similar to a superposition of its precursor dilactone **2a** and reference porphyrin **9**, with one

Table 1 Spectroscopic and ligand binding properties of cyclocholate porphyrins

	Soret		Pyrazole		Bipy		DABCO	
	λ_{max}	$(W_{\frac{1}{2}})^a$	K^b	K/K_{Zn9}	K	K/K_{Zn9}	K	K/K_{Zn9}
9	408	(29)						
Zn9	410.5	(12)	800	1	5.4×10^3	1	1.6×10^4	1
4a	409.5	(28)						
Zn4a	411	(13)	180	0.2	970	0.2	—	—
4b	412.5	(29)						
Zn4b	414.5	(15)	590	0.7	2.6×10^3	0.5	—	—
5a	408	(32)						
$Zn_2$5a	410.5	(15.5)	660	0.8	1.7×10^4 800^c	3.1	2.0×10^5 $< 10^{3c}$	12.5
5b	409	(32)						
$Zn_2$5b	411.5	(16.5)	690	0.9	2.5×10^6 $< 10^{3c}$	460	8.0×10^7 $< 10^{5c}$	5000
				K/K_{Zn10}		K/K_{Zn10}		
10	418.5	(11.5)						
Zn10	420	(10)	2.6×10^3	1	2.5×10^4	1	—	—
6	424.5	(12.5)						
Zn6	426	(12)	1.3×10^3	0.5	80	0.003	—	—
7	420.5	(11.5)						
Zn7	422	(10)	2.3×10^3	0.9	2.0×10^4	0.8	—	—

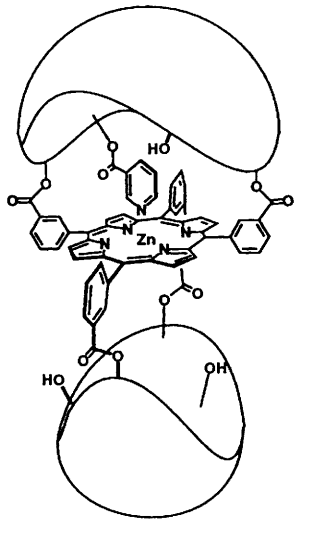
[a] Width at half height (nm). [b] Equilibrium constants K ($dm^3\ mol^{-1}$) measured by UV titration in CH_2Cl_2 at 295 K. Reproducibility ± 10% $K < 10^5$, ± 30% $K > 10^6$. [c] K for addition of second ligand to 1 : 1 sandwich complex.



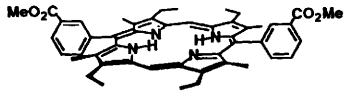
set of resonances for dilactone and porphyrin components (although the porphyrin pyrrole rings are still non-equivalent) and no pronounced porphyrin-induced upfield shifts. However the spectrum of the tetraol **5b** in $CDCl_3$ is complicated, with at least two unsymmetrical species exchanging slowly on the NMR timescale.‡ A simpler spectrum, comparable to **5a**, was obtained on addition ~25% (v/v) of methanol or heating to ~ 140 °C in $C_2D_2Cl_4$. The complexity of **5b** may be due to slow rotation of the *meta* linked aryl rings on the NMR timescale. Models suggest that dimers are very flexible, with easy rotation around the porphyrin-phenyl and ester bonds. Other *meta*-phenyl substituted porphyrins such as **3a** display distinct atropisomers at room temperature. The UV–VIS spectra of both types of dimer are broadened relative to **9**, but otherwise unremarkable.

Doubly capped porphyrin **6** is spectroscopically similar to the mono capped porphyrin **4b**. Compared to **4b** the upfield shifts are slightly smaller for some resonances due to deshielding by the extra pair of *meso* phenyl rings, with the 12-OH doublet (δ 0.68, J 4 Hz), for example, appearing 0.33 ppm downfield of the same resonance in **4b**. The Soret band is red shifted by 6 nm and broadened relative to **10**, and like **4b**, **6** gives a large CD response. In contrast to **6**, the ^1H NMR spectrum of its equatorial isomer **7** shows only slight shifts of the dilactone resonances relative to **2b**, and the Soret band is less red shifted (2 nm) relative to **10**. The porphyrin **7** appears to be an interconverting mixture of atropisomers since the aromatic resonances, which are slightly broadened at room temperature, sharpened on heating and broadened further and eventually split up on cooling.

Acylation of **Zn6** to give **Zn8** makes all four steroids and pyrrole rings non-equivalent, with four sets of signals for the *meso* phenyl rings and steroidal methyl groups, and eight doublets ($J_{\beta\beta'}$ 4.9 Hz) for the pyrrole protons. The internally co-ordinated ligand shows the characteristic red-shifted Soret λ_{max} and upfield shifts of a pyridine-zinc porphyrin adduct (Fig. 1). The free base **8** has a similar spectrum to **Zn8** except that the pyridine ring has rotated and now hydrogen bonds to the neighbouring 12-hydroxy group with a corresponding inversion in the shifts of the pyridine ring protons. The 12-OH proton involved in the intramolecular hydrogen bond (δ 3.86, J 9.9 Hz) has a *trans*-like vicinal coupling constant and is shifted downfield compared to the hydroxy groups in the other half of the molecule (δ 0.64 and 0.70, J 4.6 Hz).



Zn8



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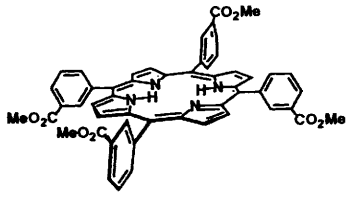

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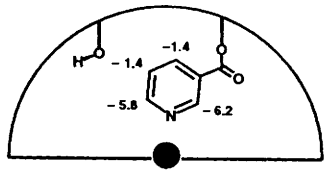
‡ The spectra were independent of concentration over the range 0.5–5 mmol dm^{-1}, and similar in acetone, $C_2D_2Cl_4$ and CD_2Cl_2.

Binding properties of cyclocholate porphyrins

The co-ordination chemistry of zinc derivatives **Zn4** to **Zn10** illustrates nicely the differences in structural types, providing support for the NMR assignments. Binding constants were measured by UV–VIS titration using the ~ 10 nm red shift of the Soret band on co-ordination of amine ligands to zinc.[17] Models predict that a large ligand such as bipy (4,4'-bipyridine) should be repelled by the dilactone caps of **Zn6** or **Zn4b** when co-ordinated to zinc in the normal perpendicular orientation, whereas a smaller ligand like pyrazole should bind without hindrance.

Pyrazole and bipy bind with near-normal equilibrium constants to **Zn7**, consistent with an equatorial arrangement of cyclocholates. Here a 'normal' binding constant is taken to be the binding constant to uncapped reference **Zn10**; see K/K_{Zn10} values in Table 1. As expected, bipy binds very weakly to doubly capped **Zn6** and co-ordinates to the monocapped porphyrin **Zn4b** half as strongly as to reference **Zn9** since it is excluded from one side of the porphyrin. Pyrazole binds to capped porphyrins **Zn6** and **Zn4b** less strongly than to the reference monomers. This is attributed to cavity solvation effects rather than steric interactions. In fact large solvent effects are characteristic of ligand inclusion by these capped porphyrins; K_{Zn6}/K_{Zn10} ratios for pyrazole vary by more than two orders of magnitude in different non-polar organic solvents.§ In CH_2Cl_2 cavity solvation makes a relatively minor contribution to overall binding energies, reducing binding to **Zn6** slightly. If solvation of the cavities in **Zn6** and **Zn4b** were identical, then a ratio $K/K_{Zn9} = 0.75$ for pyrazole would be expected for **Zn4b**, close to the experimental value of 0.73.

It is noticeable that pyrazole and bipy bind more weakly than expected to the trifluoroacetate-protected porphyrin **Zn4a**. Pyrazole is evidently excluded from the cavity by the



Zn8

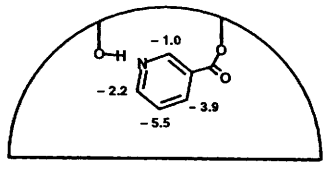


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Fig. 1 Orientations of internal ligand in **Zn8** and **8** based on the chemical shifts of the ring protons relative to the methyl ester of pyridine-3-carboxylic acid, with negative $\Delta\delta$ values corresponding to upfield shifts

§ Unpublished results, R. P. Bonar-Law and J. K. M. Sanders.

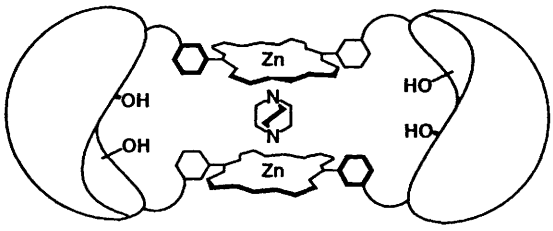

Fig. 2 Schematic illustration of the Zn_2**5a**–**DABCO** complex

trifluoroacetates since $K/K_{Zn9} = 0.2$ for both ligands. The weak binding by **Zn4a** is not significantly solvent or ligand dependent, so must derive from structural differences between **Zn4a** and **Zn4b**. While the origin of this effect is not clear, it is presumably related to different degrees of porphyrin bending making the outer uncapped face of **Zn4a** behave as a weaker Lewis acid than one face of **Zn9**. Hydrazine is small enough to bind inside **Zn4a**, since it binds equally well to both **Zn9** and **Zn4a** in the solvent mixture used for trifluoroacetate hydrolysis (10% v/v methanol in $CHCl_3$, $K = 150$ dm^3 mol^{-1}). For comparison pyridine binds with $K/K_{Zn9} = 0.3$ under the same conditions.

The dimers Zn_2**5a** and Zn_2**5b** bind pyrazole with near-normal monomer binding constants. Binding isotherms were well fitted assuming two independent binding sites per dimer, implying that both faces of the porphyrins in Zn_2**5a** and Zn_2**5b** are equally accessible to ligand and hence the dimers have open conformations.[18] Bidentate ligands bipy and DABCO (4,4'-diazabicyclo[2.2.2]octane) formed stable and spectroscopically distinct 1:1 complexes, and binding of a second ligand was weak. ^{1}H NMR titration of Zn_2**5b** with DABCO gave a mixture of unbound Zn_2**5b** and a symmetrical 1:1 complex in slow exchange, with only the 1:1 adduct present when 1.05 equivalents of DABCO had been added. The porphyrin meso protons of the complex are shifted upfield by 0.7 ppm relative to Zn_2**5a**, DABCO appears at −5.1 ppm, and the dilactone resonances are shifted downfield. These porphyrin and ligand shifts are characteristic of porphyrin–DABCO–porphyrin sandwich complexes[18] (Fig. 2), and support the assignments of **5a** and **5b** as cyclic dimers. Zn_2**5b** bound bipy and DABCO more strongly than Zn_2**5a** implying that Zn_2**5b** is more complementary to these bidentate ligands due to conformational differences between trifluoroacetate-protected and free diol cyclocholate linkers.

^{1}H NMR titration of **Zn8** with pyridine in $CDCl_3$ gave an equilibrium constant for displacement of the covalently linked pyridine ligand of $K = 3$ dm^3 mol^{-1}. Pyridine binds to **Zn6** in $CHCl_3$ with an equilibrium constant of 3×10^3 dm^3 mol^{-1}, so the ligand in **Zn8** is estimated to reside on zinc ~99.9% of the time, with an effective molarity for intramolecular co-ordination of $\sim 1/K = 0.3$ mol dm^{-3}. This appears to be sufficient, in conjunction with weak binding of the mixed anhydride reagent ($K \leqslant 50$ dm^3 mol^{-1} from ^{1}H NMR titration) to ensure that only one hydroxyl in **Zn6** is acylated.

Summary

Cyclocholate-capped porphyrins **4** and **6** were prepared in short sequences from cholic acid by condensation of the bisaldehyde **2b** with a 5,10-dihydrodipyrrin or with pyrrole under equilibrium conditions. A useful synthesis of symmetrical 7,24-cyclo[2]cholates was developed, with differential protection of the 3 and 12 hydroxyls. The different product distributions from protected and unprotected dilactones **2a** and **2b**, the different binding selectivities of dimers Zn_2**5a** and Zn_2**5a**, and the difficult cyclisation **3a** were rationalised in terms of a flatter conformation of the bistrifluoroacetate **2b** compared to **2a**, with a greater distance between the aromatic aldehydes. Zinc porphyrin binding was used both to confirm structural and spectroscopic assignments and to catalyse two synthetically useful acyl-transfer reactions, hydrolysis of hindered bistrifluoroacetate **Zn4a** and acylation of **Zn6**.

Experimental

NMR spectra were recorded on Bruker WM-250, AM-400 or DRX-500 spectrometers. Chemical shifts in $CDCl_3$ are given relative to $CHCl_3$ (7.25 ppm for ^{1}H, 77 ppm for ^{13}C) or relative to $FCCl_3$ (0 ppm for ^{19}F) and coupling constants are in Hz. Porphyrin substituents are distinguished when necessary with a p- prefix. UV-VIS spectra: Perkin-Elmer Lambda 2. IR spectra: Perkin-Elmer 1600 series FTIR. Mass spectra: Kratos MS-890 (FAB) or Kratos MS-50 (FIB, Cs^+). The matrix was *m*-nitrobenzyl alcohol unless stated otherwise. Masses are quoted for the most intense isotopomer peak in the molecular ion envelope in the form $M^+ + n$, where the M^+ mass is calculated using the most abundant isotopes. Low resolution FAB/FIB masses are accurate to ±0.5 amu or better. Melting points were determined on a Reichert-Kofler block and are uncorrected. Kieselgel 60 (Merck) 230–400 mesh silica was used for flash chromatography.[19] Macrolactonisations and other water-sensitive reactions were conducted in dry solvents under argon. Solutions of aqueous acid, base or buffer used during work-up were of 1 mol dm^{-3} strength and organic extracts were dried with Na_2SO_4 unless stated otherwise. UV-VIS and ^{1}H NMR titrations were performed and analysed as previously described.[3a,18]

tert-Butyl 3α-(3-formylbenzoyloxy)-7α-hydroxy-12α-trifluoroacetoxy-5β-cholan-24-oate 1c

A solution of DCC (dicyclohexylcarbodiimide; 3.53 g, 17.1 mmol) in CH_2Cl_2 (20 cm^3) was added to a stirred suspension of the diol **1b**[4] (8.0 g, 14.3 mmol), 3-formylbenzoic acid[20] (2.16 g, 14.4 mmol) and DMAP (175 mg, 1.4 mmol) in a mixture of CH_2Cl_2 (200 cm^3) and DMF (30 cm^3) at ice-bath temperature. The mixture was stirred at RT (room temp.) overnight, after which a further portion of DCC (220 mg, 1.1 mmol) was added, and stirring continued for a further 5 h. The suspension was filtered, and the filtrate evaporated. The resulting crude product was suspended in 50% ether–hexane (100 cm^3), and then filtered. The filtrate was washed with aqueous H_3PO_4, dried, and evaporated. Chromatography (30% EtOAc in hexane) of the residue followed by crystallisation from benzene–hexane afforded **1c** (7.3 g, 74%), mp 155–160 °C (Found: C, 66.1; H, 7.45. $C_{38}H_{51}F_3O_8$ requires C, 65.88; H, 7.42); ν_{max}(Nujol)/cm^{-1} 3550, 1780, 1720 and 1705; δ_H(250 MHz, $CDCl_3$) 0.81 (3 H, s, 18-Me), 0.83 (3 H, d, *J* 6.6, 21-Me), 0.95 (3 H, s, 19-Me), 1.44 (9 H, s, *tert*-butyl), 2.46 (1 H, q, *J* 15.5, 4α-H), 3.92 (1 H, q, *J* 3, 7-H), 4.85 (1 H, tt, *J* 11.5, 4, 3-H), 5.35 (1 H, t, *J* 3, 12-H), 7.62 (1 H, t, *J* 7.7, Ar), 8.08 (1 H, dt, *J* 7.7, 1.5, Ar), 8.28 (1 H, dt, *J* 7.7, 1.5, Ar), 8.50 (1 H, t, *J* 1.5, Ar) and 10.07 (1 H, s, ArCHO); *m*/*z* (FABMS) 637.4 ($M^+ - Bu^t$), 619, 523.4, 505, 469.2, 373 and 355.

3α-(3-Formylbenzoyloxy)-7α-hydroxy-12α-trifluoroacetoxy-5β-cholan-24-oic acid 1d

Trifluoroacetic acid (8.0 cm^3) was added to a stirred solution of the *tert*-butyl ester **1c** (1.46 g, 2.11 mmol) in CH_2Cl_2 (20 cm^3) at ice-bath temperature. After 1.5 h the acid was neutralised by careful addition of sat. aqueous sodium hydrogen carbonate and the organic layer was separated, washed with pH 3 buffer, dried and evaporated. Slow crystallisation of the residue from CH_2Cl_2–hexane afforded the acid **1d** as fine needles (1.07 g, 80%), mp 207–209 °C (Found: C, 63.6; H, 6.7. $C_{34}H_{43}F_3O_8$ requires C, 64.14; H, 6.81); ν_{max}(Nujol)/cm^{-1} 3520, 1780, 1730 and 1700; δ_H(250 MHz, $CDCl_3$) 0.79 (3 H, s, 18-Me), 0.82 (3 H, d, *J* 6.6, 21-Me), 0.93 (3 H, s, 19-Me), 3.92 (1 H, br s, 7-H), 4.84

(1 H, m, 3-H), 5.34 (1 H, br t, *J* 3, 12-H), 7.60 (1 H, t, *J* 7.7, Ar), 8.07 (1 H, dt, *J* 7.7, 1.5, Ar), 8.27 (1 H, dt, *J* 7.7, 1.5, Ar), 8.49 (1 H, t, *J* 1.5, Ar) and 10.09 (1 H, s, ArCHO); δ_F\{235 MHz, 10% (v/v) [$^2H_4$]-MeOH in $CDCl_3$\} −75.68 (s); δ_C\{100 MHz, 10% (v/v) [$^2H_4$]-MeOH in $CDCl_3$\} 191.73 (ArCHO), 176.81, 165.13, 157.0 (q, *J* 41, *C*OCF$_3$), 136.43, 135.21, 132.59, 131.87, 131.67, 129.19, 114.80 (q, *J* 286, CO*C*F$_3$), 80.86 (CHO), 75.32 (CHO), 67.58 (CHO), 47.45, 45.11, 43.37, 41.09, 39.09, 35.11, 34.64, 34.54, 34.49, 34.26, 30.56, 27.17, 26.52, 25.36, 22.72, 22.45 (Me), 17.44 (Me) and 12.19 (Me); *m/z* (FABMS) 659.3 (MNa^+), 637.3 (M^+ + 1), 619.3, 523.3, 505.3, 469.2 and 355.

Benzyl 3α-(3-formylbenzoyloxy)-7α-hydroxy-12α-trifluoroacetoxy-5β-cholan-24-oate 1e

DCC (970 mg, 4.7 mmol) was added to a stirred suspension of the acid **1d** (2.5 g, 3.93 mmol), benzyl alcohol (0.6 cm^3, 5.78 mmol) and DMAP (50 mg, 0.4 mmol) in CH_2Cl_2 (20 cm^3) at ice-bath temperature. After 3 h the mixture was diluted with diethyl ether (25 cm^3), filtered, washed consecutively with aqueous H_2SO_4, sat. aqueous sodium hydrogen carbonate and brine, dried and evaporated. Chromatography (30% EtOAc in hexane) followed by crystallisation from benzene–hexane afforded the benzyl ester **1e** (2.14 g, 75%), mp 112–114 °C (Found: C, 68.05; H, 6.8. $C_{41}H_{49}F_3O_8$ requires C, 67.75; H, 6.79); ν_{max}(Nujol)/cm^{-1} 3550, 1780, 1735 and 1695; δ_H(250 MHz, $CDCl_3$) 0.78 (3 H, s, 18-Me), 0.82 (3 H, d, *J* 6.6, 21-Me), 0.95 (3 H, s. 19-Me), 3.92 (1 H, br s, 7-H), 4.70 (1 H, br s, D_2O exchangeable), 4.86 (1 H, m, 3-H), 5.05, 5.15 (2 H, ABq, *J* 16, OCH_2Ph), 5.33 (1 H, t, *J* 3, 12-H), 7.35 (5 H, m, OCH$_2$*Ph*), 7.61 (1 H, t, *J* 7.7, Ar), 8.08 (1 H, dt, *J* 7.7, 1.5, Ar), 8.28 (1 H, dt, *J* 7.7, 1.5, Ar), 8.45 (1 H, t, *J* 1.5, Ar) and 10.08 (1 H, s, CHO); δ_F(235 MHz, $CDCl_3$) −75.59 (s); *m/z* (FABMS) 749.2 (MNa^+), 727.3 (M^+ + 1), 709, 635, 613.2, 595.2, 577, 559.2, 505.2, 485.2, 469, 463.2, 445.2 and 355.

Porphyrin diester 3a

p-TsOH (toluene-*p*-sulfonic acid monohydrate; 75 mg, 0.4 mmol) was added to a solution of the aldehyde **1e** (2.10 g, 2.91 mmol) and 4,4′-diethyl-3,3′-dimethyl-5,10-dihydrodipyrrin[5] (675 mg, 2.93 mmol) in dry degassed MeOH (15 cm^3) at RT. After storage overnight at 0 °C, the supernatant was decanted from the purple precipitate and the precipitate was washed with MeOH (2 cm^3), and then dried for 1 h at 0.1 mmHg. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 2.0 g, 8.8 mmol) was added to a stirred solution of the crude porphyrinogen in dry THF (30 cm^3) at ice-bath temperature. After 2 h, the mixture was evaporated and a solution of the residue in CH_2Cl_2 washed with aqueous NaOH and brine, dried and evaporated. Chromatography of the residue (30% EtOAc in cyclohexane) followed by crystallisation from CH_2Cl_2–MeOH afforded the porphyrin **3a** as small purple needles (1.98 g, 73%), mp 182–183 °C (Found: C, 72.15; H, 7.2; N, 2.8. $C_{112}H_{132}F_6N_4O_{14}$ requires C, 71.86; H, 7.11; N, 2.99); ν_{max}(CH_2Cl_2)/cm^{-1} 3500, 1775, 1725 and 1710; λ_{max}(CH_2Cl_2)/nm 408 (log ε 5.35), 506 (4.25), 540 (3.77), 574 (3.87) and 626 (3.23); δ_H(250 MHz, $CDCl_3$) −2.41 (2 H, br s, NH), 0.72 (6 H, s, 18-Me), 0.78 (6 H, d, *J* 6.6, 21-Me), 0.92 (6 H, s. 19-Me), 1.77 (12 H, t, *J* 7.5, p-CH$_2$CH_3), 2.44 (12 H, s, p-CH$_3$), 3.84 (2 H, br s. 7-H), 4.01 (8 H, q, *J* 7.5, p-CH_2CH$_3$), 4.93 (2 H, m, 3-H), 5.09 (4 H, s, OCH_2Ph), 5.25 (2 H, br s, 12-H), 7.34 (10 H, br s, OCH$_2$*Ph*), 7.82 (2 H, t, *J* 7.7, Ar), 8.22 (1 H, d, *J* 7.7, Ar), 8.24 (1 H, d, *J* 7.7, Ar), 8.46 (2 H, d, *J* 7.7, Ar), 8.77 (1 H, s, Ar), 8.80 (1 H. s, Ar) and 10.24 (2 H, s, p-*meso*); δ_F(235 MHz, $CDCl_3$) −75.59 (s); δ_C(100 MHz, $CDCl_3$) 173.74 (CO), 166.46 (CO), 156.84 (q, *J* 41, *C*OCF$_3$), 145.07, 145.0, 144.93, 144.89, 144.86, 142.52, 141.15, 136.93 (CH, Ar), 135.98, 135.56, 135.54, 133.51 (CH, Ar), 130.14, 129.44 (CH, Ar), 128.51 (CH, OBn), 128.23 (CH, OBn), 128.18 (CH, OBn), 116.73, 114.60 and 114.65 (q, *J* 286, COCF$_3$), 96.69 (CH, p-*meso*), 80.69 (CHO), 74.98 (CHO), 67.59 (CHO), 66.13 (CH_2OBn), 47.32, 44.98, 43.25, 41.06, 38.98, 35.18, 34.68, 34.42, 34.37, 34.23, 30.92, 30.55, 27.60, 27.00, 26.60, 25.30, 22.56, 22.39 (CH$_3$), 19.90 (p-CH$_2$), 17.58 (p-CH$_3$), 17.55 (p-CH$_3$), 17.37 (CH$_3$), 14.90 (p-CH$_3$), 14.87 (p-CH$_3$) and 12.04 (CH$_3$); *m/z* (FABMS) 1872.1 (M^+ + 1.1), 1295.7, 719.3 and 355.2. For zinc derivative **Zn3a** *m/z* (FABMS) 1934.8 (M^+ + 1.9).

Porphyrin diacid 3b

A solution of porphyrin dibenzyl ester **3a** (650 mg, 0.348 mmol) in $CHCl_3$ (25 cm^3) was refluxed briefly with Zn(OAc)$_2$·2H$_2$O (500 mg, 2.3 mmol) and stirred at RT for 1 h. The mixture was diluted with CH_2Cl_2, washed with water, dried and evaporated to give **Zn3a**. This was stirred with Pd-black (400 mg) in dry THF (50 cm^3) under an atmosphere of H_2 until TLC (6% MeOH in $CHCl_3$) showed hydrogenolysis to be complete (9 h). The reaction mixture was filtered, evaporated and partitioned between $CHCl_3$ and aqueous HCl. The emerald-green organic layer was washed with water, pH 7 buffer, and the by now dark-red solution was dried and evaporated. Crystallisation of the residue from refluxing toluene (50 cm^3) afforded the diacid **3b** (560 mg, 95%) as a granular purple solid after drying at 50 °C, 0.1 mmHg: mp (sinter) 260–265 °C (Found: C, 69.5; H, 7.1; N, 3.2. $C_{98}H_{120}F_6N_4O_{14}$ requires C, 69.57; H, 7.15; N, 3.31); δ_H(250 MHz, $C_2D_2Cl_4$, 400 K) −2.3 (2 H, br s, NH), 1.85 (12 H, br t, *J* 7.5, p-CH$_2$CH_3), 2.45 (12 H, s, p-CH$_3$), 3.80 (2 H, br s, 7-H), 4.00 (8 H, br q, *J* 7.5, p-CH_2CH$_3$), 4.90 (2 H, m, 3-H), 5.25 (2 H, br s, 12-H), 7.85 (2 H, t, *J* 7.7, Ar), 8.25 (2 H, br d, *J* 7.7, Ar), 8.48 (2 H, d, *J* 7.7, Ar), 8.80 (2 H, s, Ar) and 10.20 (2 H, s, p-*meso*); *m/z* (HRFABMS) 1691.76 (MH^+ requires 1691.87). For zinc derivative **Zn3b** *m/z* (FABMS) 1754.9 (M^+ + 2.1).

Monocapped porphyrin Zn4a

2,6-Dichlorobenzoyl chloride (74 mg, 0.354 mmol) was added to a solution of the diacid **3b** (198 mg, 0.117 mmol) and triethylamine (80 mm^3, 0.574 mmol) in THF (1.5 cm^3). After being stirred for 10 h at RT, the solution was diluted with CH_2Cl_2 (1.5 cm^3) and added over the course of 4 h by syringe pump to a solution of DMAP (150 mg) in toluene (100 cm^3) maintained at 100 °C. After being heated for a further 10 h, the mixture was evaporated, and a solution of the residue in CH_2Cl_2 was washed with aqueous HCl, water and sat. aqueous sodium hydrogen carbonate, dried and evaporated. A solution of the residue in $CHCl_3$ (25 cm^3) was refluxed briefly with Zn(OAc)$_2$·2H$_2$O (200 mg), stored at RT for 1 h and then washed with water, dried and evaporated. Chromatography (0–2.5% EtOAc in CH_2Cl_2) followed by slow crystallisation of the main red band from hot toluene (5 cm^3) provided the capped porphyrin **Zn4a** as pink prisms (36 mg, 18%): mp > 300 °C (Found: C, 68.8; H, 6.7; N, 3.1. $C_{98}H_{114}F_6N_4O_{12}Zn$ requires C, 68.46; H, 6.68; N, 3.26); λ_{max}(CH_2Cl_2)/nm 411 (log ε 5.60), 539 (4.29) and 575 (4.06); δ_H(250 MHz, $CDCl_3$) 0.32 (6 H, d, *J* 6.6, 21-Me), 0.45 (6 H, s, 18-Me), 0.77 (6 H, s, 19-Me), 1.70 (6 H, t, *J* 7.5, p-CH$_2$CH_3), 1.74 (6 H, t, *J* 7.5, p-CH$_2$CH_3), 2.21 (6 H, s, p-Me), 2.54 (6 H, s, p-Me), 3.8–4.2 (8 H, m, p-CH_2CH$_3$), 4.52 (2 H, br s, 7-H), 4.70 (2 H, br s, 12-H), 4.99 (2 H, m, 3-H), 7.92 (2 H, t, *J* 7.7, Ar), 8.1 (2 H, s, Ar), 8.45 (2 H, d, *J* 7.7, Ar), 8.75 (2 H, d, *J* 7.7, Ar) and 10.14 (2 H, s, p-*meso*); δ_F(235 MHz, $CDCl_3$) −80.04 (s); δ_C(100 MHz, $CDCl_3$) 174.40 (CO), 166.69 (CO), 155.50 (q, *J* 41, *C*OCF$_3$), 148.10, 147.19, 146.28, 146.23, 145.30, 145.12, 144.02, 137.04 (CH, Ar), 136.54, 136.10, 135.57 (CH, Ar), 130.42, 129.32 (CH, Ar), 127.12 (CH, Ar), 117.38, 111.85 (q, *J* 287, CO*C*F$_3$), 97.58 (p-*meso*), 79.20 (CHO), 73.80 (CHO), 70.54 (CHO), 44.88, 43.96, 42.84, 40.04, 37.50, 33.50, 31.31, 30.54, 28.79, 27.89, 26.86, 25.62, 25.51, 24.01, 22.42, 21.57 (CH$_3$), 19.88 (p-CH$_2$), 17.95 (CH$_3$), 17.18 and 17.08 (p-CH$_3$), 16.66 (p-CH$_3$), 14.65 (p-CH$_3$) and 12.01 (CH$_3$); *m/z* (FIBMS) 1718 (M^+ + 1.2), 1603 and 1489.

Monocapped porphyrin 4a

A sample of **Zn4a** in CH_2Cl_2 was treated with trifluoroacetic acid [1% (v/v) 1 min]. Aqueous work-up followed by trituration with methanol gave the free-base porphyrin **4a** as a purple powder: mp >300 °C; $\lambda_{max}(CH_2Cl_2)$/nm 409.5 (log ε 5.31), 508 (4.21), 541 (3.73), 577 (3.79) and 629.5 (3.24); δ_H(250 MHz, $CDCl_3$) −2.33 (2 H, br s, NH), 0.34 (6 H, d, *J* 6.5, 21-Me), 0.47 (6 H, s, 18-Me), 0.78 (6 H, s, 19-Me), 1.75 (12 H, m, *p*-CH_2CH_3), 2.30 (6 H, s, p-Me), 2.55 (6 H, s, p-Me), 3.8–4.2 (8 H, m, p-CH_2CH_3), 4.57 (2 H, br s, 7-H), 4.73 (2 H, br s, 12-H), 5.02 (2 H, m, 3-H), 7.93 (2 H, t, *J* 7.7, Ar), 8.13 (2 H, s, Ar), 8.45 (2 H, d, *J* 7.7, Ar), 8.79 (2 H, d, *J* 7.7, Ar) and 10.19 (2 H, s, p-*meso*); δ_F(235 MHz, $CDCl_3$) −80.09 (s); *m*/*z* (HRFABMS) 1656.86 [MH^+ ($^{12}C_{97}{}^{13}C_1$) requires 1656.86].

Monocapped porphyrin Zn4b

Hydrazine hydrate (20 mm^3, 0.41 mmol) was added to a solution of **Zn4a** (10 mg, 5.8 μmol) in a mixture of chloroform (1.0 cm^3) and MeOH (0.2 cm^3). After 6 h at RT further hydrazine hydrate (10 mm^3) was added to the mixture which after 12 h was diluted with CH_2Cl_2, washed with pH 7 buffer, dried and evaporated. Chromatography (10–30% $CHCl_3$ in CH_2Cl_2) gave **Zn4b** (8 mg, 90%) as a microcrystalline purple powder, mp >300 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3602 (OH); $\lambda_{max}(CH_2Cl_2)$/nm 414.5 (log ε 5.48), 541.5 (4.19) and 578 (3.95); δ_H(250 MHz, $CDCl_3$) 0.35 (2 H, d, *J* 4, 12-OH), 0.40 (6 H, s, 18-Me), 0.56 (6 H, d, *J* 6.5, 21-Me), 0.79 (6 H, s, 19-Me), 1.73 (6 H, t, *J* 7.7, p-CH_2CH_3), 1.75 (6 H, t, *J* 7.7, p-CH_2CH_3), 2.28 (6 H, s, p-Me), 2.49 (6 H, s, p-Me), 3.52 (2 H, br s, 12-H), 4.0 (8 H, m, p-CH_2CH_3), 4.53 (2 H, br s, 7-H), 5.0 (2 H, m, 3-H), 7.94 (2 H, t, *J* 7.7, Ar), 8.27 (2 H, s, Ar), 8.47 (2 H, d, *J* 7.7, Ar), 8.79 (2 H, d, *J* 7.7, Ar) and 10.11 (2 H, s, p-*meso*); *m*/*z* (HRFABMS) 1525.808 (MH^+ requires 1528.806).

Reaction of Zn4b and 4b with hydrazine

Hydrazine hydrate (10 mm^3, 0.32 mmol) was added to a solution of **Zn4a** (0.5 mg) and **4a** (0.5 mg) in a mixture of $CDCl_3$ (500 mm^3) and [$^2H_4$]-MeOH (50 mm^3) in a septum capped NMR tube and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy. In the ^{19}F spectra the singlets at −80.1 and −80.3 ppm due to **Zn4a** and **4a** decreased in intensity with appearance of an initial reaction product at −75.9 ppm. As the reaction progressed, a minor peak at −76.4 ppm grew in intensity. In separate experiments, addition of trifluoroacetic acid to hydrazine in the reaction solvent produced a singlet at −75.9 ppm, and addition of trifluoroacetic anhydride gave singlets at −76.4 and −75.9 ppm, confirming the production of hydrazinium trifluoroacetate (−75.9 ppm) and *N*-trifluoroacetylhydrazine (−76.4 ppm). Analysis of peak intensities gave pseudo first-order rate constants of 1.03 (±0.01) × 10^{-5} s^{-1} and 1.27 (±0.1) × 10^{-6} s^{-1} for the reactions of **Zn4a** and **4a**, respectively. Separate peaks for intermediates with only one trifluoroacetate were not detected. If methanol was not included as co-solvent, hydrazine hydrate remained as an upper phase. Pseudo first-order rate constants for reaction of **Zn4a** and **4a** under these conditions were 1.3 × 10^{-5} s^{-1} and < 6.5 × 10^{-7} s^{-1}, respectively.

Monocapped porphyrin 4b

A sample of **Zn4b** in CH_2Cl_2 was treated with trifluoroacetic acid [1% (v/v) 1 min]. Crystallisation from CH_2Cl_2–MeOH gave **4b** as small red plates: mp >300 °C (Found: C, 75.25; H, 8.13; N, 3.60. $C_{94}H_{118}N_4O_{10}\cdot 2H_2O$ requires C, 75.27; H, 8.20; N, 3.74); $\lambda_{max}(CH_2Cl_2)$/nm 412.5 (log ε 5.31), 510 (4.19), 544 (3.73), 578.5 (3.82) and 629.5 (3.19); δ_H(250 MHz, $CDCl_3$) −2.33 (2 H, s, NH), 0.40 (2 H, d, *J* 4, 12-OH), 0.41 (6 H, s, 18-Me), 0.57 (6 H, d, *J* 6.5, 21-Me), 0.79 (6 H, s, 19-Me), 1.75 (12 H, m, p-CH_2CH_3), 2.33 (6 H, s, p-Me), 2.51 (6 H, s, p-Me), 3.53 (2 H, br s, 12-H), 3.95 (8 H, m, p-CH_2CH_3), 4.54 (2 H, br s, 7-H), 5.03 (2 H, m, 3-H), 7.95 (2 H, t, *J* 7.7, Ar), 8.3 (2 H, s, Ar), 8.46 (2 H, d, *J* 7.7, Ar), 8.79 (2 H, d, *J* 7.7, Ar), 10.15 (2 H, s, p-*meso*); δ_C(100 MHz, $CDCl_3$) 175.06 (CO), 166.77 (CO), 145.59, 145.30, 144.82, 144.69, 141.94, 141.88, 140.69, 136.49 (CH, Ar), 136.09 (CH, Ar), 135.43, 135.32, 130.88, 129.61 (CH, Ar), 127.43 (CH, Ar), 116.63, 96.69 (p-*meso*), 74.75 (CHO), 72.20 (CHO), 70.94 (CHO), 45.60, 44.39, 41.94, 40.28, 37.94, 34.66, 33.77 (×2), 33.59, 31.48, 31.31, 29.05, 27.94, 27.70, 26.36, 25.93, 22.80, 21.82 (CH_3), 19.86, 17.63 (CH_3), 17.46 (p-CH_3), 17.37 (p-CH_3), 15.71 (p-CH_3), 14.30 (p-CH_3) and 12.37 (CH_3); *m*/*z* (HRFABMS) 1464.91 [MH^+ ($^{12}C_{93}{}^{13}C_1$) requires 1464.89].

3-Acetoxy-12-trifluoroacetoxycholanoic acid 7,24-dilactone 2c

2,6-Dichlorobenzoyl chloride (400 mm^3, 2.67 mmol) was added to a stirred solution of the hydroxy acid **1f**[4] (1.0 g, 1.83 mmol) and triethylamine (380 mm^3, 2.72 mmol) in THF (5 cm^3) at RT. After 7 h the solution was filtered through a glass frit, rinsing with THF (1 cm^3). The filtrate was diluted with dry toluene (375 cm^3), stirred and heated to 80 °C and then treated with a solution of DMAP (0.9 g, 7.4 mmol) in toluene (10 cm^3), added in one portion to produce immediate turbidity. After being heated for a further 12 h the mixture was cooled, filtered and evaporated. The crude product in $CHCl_3$ was washed successively with aqueous H_2SO_4, water, sat. aqueous sodium hydrogen carbonate and brine, dried and evaporated. Chromatography (30% EtOAc in hexane) of the residue followed by crystallisation of the main band from hexane–diethyl ether gave the dilactone **2c** (548 mg, 56%) as large colourless prisms (Found: C, 63.5; H, 7.8. $C_{56}H_{78}F_6O_{12}$ requires C, 63.62; H, 7.44); δ_H(250 MHz, $CDCl_3$) 0.79 (6 H, s, 18-Me), 0.81 (6 H, d, *J* 6.5, 21-Me), 0.89 (6 H, s, 19-Me), 2.0 (6 H, s, OAc), 4.54 (2 H, m, 3-H), 4.84 (2 H, br q, 7-H) and 5.24 (2 H, br t, 12-H); δ_F(235 MHz, $CDCl_3$) −76.47 (s); δ_C(100 MHz, $CDCl_3$) 173.90 (CO), 170.99 (CO), 156.94 (q, *J* 41, *C*OCF_3), 114.75 (q, *J* 287, CO*C*F_3), 80.37 (CHO), 73.40 (CHO), 70.08 (CHO), 45.21, 44.63, 43.99, 40.55, 37.43, 34.05, 33.69, 32.54, 31.05, 29.61, 28.68, 27.20, 26.93, 26.28, 26.01, 25.83, 22.64, 22.35, 21.30 (Me), 17.26 (Me) and 12.09 (Me); *m*/*z* [FABMS (thioglycerol)] 1057 (M^+ + 0.5), 998, 944, 684, 824, 469, 415 and 355.

3α-Hydroxy-12α-trifluoroacetoxy-5β-cholan-24-oic acid 7,24-dilactone 2d

Aqueous HCl (*d* 1.18; 4 cm^3) was added to a solution of **2c** (400 mg, 0.379 mmol) in acetonitrile (25 cm^3) followed after 4 days at RT by a further portion of aqueous HCl (1 cm^3). After a further 24 h the mixture was partitioned between $CHCl_3$ and water. The organic phase was separated, washed with pH 7 buffer, dried and evaporated. Chromatography (15% EtOAc in $CHCl_3$) of the residue followed by crystallisation from CH_2Cl_2–hexane gave the bistrifluoroacetate **2d** (280 mg, 76%), mp 269–272 °C (Found: C, 64.25; H, 7.6. $C_{52}H_{74}F_6O_{10}$ requires C, 64.18; H, 7.66); ν_{max}(5 mmol dm^{-3} in CH_2Cl_2)/cm^{-1} 3604 (OH); δ_H(250 MHz, $CDCl_3$) 0.77 (6 H, s, 18-Me), 0.81 (6 H, d, *J* 6.5, 21-Me), 0.88 (6 H, s, 19-Me), 3.45 (2 H, m, 3-H), 4.85 (2 H, br q, 7-H) and 5.22 (2 H, br t, 12-H); δ_F(235 MHz, $CDCl_3$) −76.40 (s); *m*/*z* (FABMS) 995.6 (MNa^+), 955.6, 937.5, 859.6, 841.5, 469.3 and 355.3.

3α,12α-Dihydroxy-5β-cholan-24-oic acid 7,24-dilactone 2e

Aqueous KOH (1 mol dm^{-3}; 1 cm^3) was added to a solution of **2c** (190 mg, 0.18 mmol) in MeOH (1.2 cm^3) and THF (4 cm^3). After 4 h the mixture was partitioned between $CHCl_3$ and aqueous H_2SO_4, and the organic layer separated, dried and evaporated. After chromatography (5% MeOH in $CHCl_3$) of the residue, the main fraction was dissolved in the minimum volume of hot toluene. On cooling a gel formed which was slowly transformed into large colourless prisms of the tetraol **2e** (119 mg, 85%), mp >290 °C (decomp.) (Found: C, 72.05; H, 9.8. $C_{48}H_{76}O_8\cdot H_2O$ requires C, 72.14; H, 9.84); ν_{max}(1 mmol

dm^{-3} in CH_2Cl_2)/cm^{-1} 3601 (OH); δ_H(400 MHz, $CDCl_3$) 0.67 (6 H, s, 18-Me), 0.89 (6 H, s, 19-Me), 0.98 (6 H, d, *J* 6.5, 21-Me), 3.50 (2 H, m, 3-H), 3.93 (2 H, br t, 12-H) and 4.83 (2 H, br q, 7-H); *m/z* (FABMS) 1563.5 (M_2^+ + 3), 781.5 (M^+ + 0.9), 763.5, 745.5, 727.4, 373 and 355.

3α-(3-Formylbenzoyloxy)-12α-trifluoroacetoxy-5β-cholan-24-oic acid 7,24-dilactone 2a

2,6-Dichlorobenzoyl chloride (1.4 g, 6.68 mmol) was added to a stirred solution of the hydroxy acid **1d** (3.0 g, 4.71 mmol) and triethylamine (1.3 cm^3, 9.3 mmol) in THF (15 cm^3) at RT. After 4 h the solution was filtered and diluted with dry toluene (450 cm^3). The mixture was stirred and heated at 80 °C and then a solution of DMAP (2.5 g, 20.5 mmol) in toluene (50 cm^3) was added in one portion to produce immediate turbidity. After being heated for a further 12 h the mixture was cooled, filtered and evaporated. Chromatography (7% EtOAc in CH_2Cl_2) of the residue followed by trituration of the main band in hot cyclohexane afforded the dilactone **2a** (1.44 g, 49%) as an amorphous powder, mp 175–180 °C sufficiently pure for use in the next reaction. An analytical sample was obtained by reprecipitation from hot cyclohexane, mp 180–185 °C (Found: C, 66.2; H, 6.8. $C_{68}H_{82}F_6O_{14}$ requires C, 66.00; H, 6.68); ν_{max}(CH_2Cl_2)/cm^{-1} 1780, 1720 and 1705; δ_H(250 MHz, $CDCl_3$) 0.80 (6 H, d, *J* 6, 21-Me), 0.81 (6 H, s, 18-Me), 0.95 (6 H, s, 19-Me), 4.89 (4 H, m, 3-H and 7-H), 5.27 (2 H, br s, 12-H), 7.61 (2 H, t, *J* 7.6, Ar), 8.08 (2 H, d, *J* 7.6, Ar), 8.22 (2 H, d, *J* 7.6, Ar), 8.49 (2 H, s, Ar) and 10.06 (2 H, s, ArCHO); δ_F(235 MHz, $CDCl_3$) −76.52; δ_C(100 MHz, $CDCl_3$) 191.37 (ArCHO), 173.79 (CO), 164.95 (CO), 156.6 (q, *J* 41, $COCF_3$), 136.60 (Ar), 134.79 (CH, Ar), 132.56 (CH, Ar), 131.78, 131.65 (CH, Ar), 129.16 (CH, Ar), 114.75 (q, *J* 287, $COCF_3$), 80.40 (CHO), 74.60 (CHO), 70.15 (CHO), 45.13, 44.64, 44.10, 40.63, 37.52, 34.52, 34.16, 33.75, 32.43, 31.10, 29.58, 28.72, 27.12, 26.92, 26.43, 25.92, 25.78, 22.63, 22.31 (Me), 17.28 (Me) and 12.08 (Me); *m/z* (FABMS) 1237.9 (M^+ + 1.3), 1123.7, 1105.7, 1087.7, 1063.7, 1001.7, 973.6 and 355.2.

3α-(3-Formylbenzoyloxy)-12α-hydroxy-5β-cholan-24-oic acid 7,24-dilactone 2b

A solution of the dilactone trifluoroacetate **2a** (500 mg, 0.405 mmol) in THF (40 cm^3), MeOH (15 cm^3) and conc. aqueous ammonia (*d* 0.88, 15 cm^3) was left at RT for 24 h after which it was diluted with $CHCl_3$ (150 cm^3), washed with aqueous H_2SO_4, sat. aqueous sodium hydrogen carbonate and pH 7 buffer, dried and evaporated. Chromatography (10% EtOAc in CH_2Cl_2) of the residue afforded the diol **2b** (366 mg, 88%) as an amorphous glass, pure enough for use in the next reaction. Crystallisation from toluene–hexane provided an analytical sample, mp 175–185 °C (Found: C, 73.7; H, 8.2. $C_{64}H_{84}O_{12}$ requires C, 73.54; H, 8.10); ν_{max}(5 mmol dm^{-3} in CH_2Cl_2)/cm^{-1} 3605 (OH); δ_H(250 MHz, $CDCl_3$) 0.69 (6 H, s, 18-Me), 0.94 (6 H, s, 19-Me), 0.97 (6 H, d, *J* 6.6, 21-Me), 1.88 (2 H, d, *J* 5, 12-OH), 3.97 (2 H, br s, 12-H), 4.86 (2 H, br s, 7-H), 4.90 (2 H, m, 3-H), 7.61 (2 H, t, *J* 7.7, Ar), 8.04 (2 H, d, *J* 7.7, Ar), 8.32 (2 H, d, *J* 7.7, Ar), 8.54 (2 H, s, Ar) and 10.07 (2 H, s, ArCHO); δ_C(100 MHz, $CDCl_3$) 191.69 (ArCHO), 174.27 (CO), 164.95 (CO), 136.42, 135.35 (CH, Ar), 133.18 (CH, Ar), 132.02 (Ar), 131.12 (CH, Ar), 129.17 (CH, Ar), 75.25 and 72.79 and 70.75 (CHO), 46.12, 44.30, 43.74, 40.88, 38.17, 34.75, 34.33, 33.97, 31.36, 29.09, 28.95, 28.77, 27.03, 26.80, 26.70, 22.98, 22.46 (Me), 17.45 (Me) and 12.55 (Me); *m/z* (FABMS) 1046.9 (M^+ + 2.3), 875.9, 505.6 and 355.3.

Monocapped porphyrin 4a and dimer 5a from the bisaldehyde 2a

Trifluoroacetic acid (10 mm^3, 0.13 mmol) was added to a degassed solution of the bisaldehyde **2a** (175 mg, 0.142 mmol) and 3,3′-diethyl-4,4′-dimethyl-5,10-dihydrodipyrrin (66 mg, 0.287 mmol) in dry CH_2Cl_2 (150 cm^3). The mixture was stored in the dark at RT for 48 h after which it was treated with DDQ (100 mg, 0.44 mmol). After a further 2 h the mixture was washed with sat. aqueous sodium hydrogen carbonate and pH 7 buffer, dried and evaporated. The main red band collected by initial chromatography (10–40% $CHCl_3$ in CH_2Cl_2) was re-chromatographed (2–10% EtOAc in CH_2Cl_2) to give dimeric porphyrin **5a** (51 mg, 21%) followed by **4a** (10.5 mg, 4.5%).

Compound **5a**: λ_{max}(CH_2Cl_2)/nm 408, 507, 541 and 574; δ_H values for **5a** are similar to **$Zn_2$5a** given below except for the NH peak at −2.2; δ_F(235 MHz, $CDCl_3$) −76.42 (s); *m/z* (FABMS) 3312.3 (M^+ + 2.6).

Compound **$Zn_2$5a**: λ_{max}(CH_2Cl_2)/nm 410.5, 538.5 and 574.5; δ_H(250 MHz, $CDCl_3$) 0.86 (12 H, s, 18-Me), 0.87 (12 H, br d, *J* 6, 21-Me), 0.97 (12 H, s, 19-Me), 1.80 (24 H, m, p-CH_2CH_3), 2.38 (12 H, s, p-Me), 2.46 (12 H, s, p-Me), 4.0 and 4.3 (16 H, 2 × m, p-CH_2CH_3), 4.32 (4 H, m, 3-H), 4.93 (4 H, br s, 7-H), 5.3 (4 H, br s, 12-H), 7.78 (4 H, t, *J* 7.7, Ar), 8.25 (4 H, d, *J* 7.7, Ar), 8.37 (4 H, d, *J* 7.7, Ar), 8.78 (4 H, s, Ar) and 10.2 (4 H, s, p-*meso*); δ_F(235 MHz, $CDCl_3$) −76.46 (s); *m/z* (FABMS) 3436.7 (M^+ + 3.2) and 1794.

Monocapped porphyrin 4b and dimer 5b from bisaldehyde 2b

Trifluoroacetic acid (5 mm^3, 0.065 mmol) was added to a degassed solution of the bisaldehyde **2b** (91 mg, 0.087 mmol) and 3,3′-diethyl-4,4′-dimethyl-5,10-dihydrodipyrrin (43 mg, 0.187 mmol) in dry CH_2Cl_2 (80 cm^3). The mixture was stored in the dark at RT for 15 h after which it was treated with DDQ (60 mg, 0.264 mmol). After a further 4 h at RT the mixture was washed with sat. aqueous sodium hydrogen carbonate and pH 7 buffer, dried and evaporated. The main red band collected by initial chromatography (5–50% $CHCl_3$ in CH_2Cl_2) of the residue was re-chromatographed (1–5% EtOAc in CH_2Cl_2). Crystallisation of the faster running component from MeOH–CH_2Cl_2 gave **4b** as red plates (65 mg, 51%). The slower running component was dimeric porphyrin **5b** (3 mg, 2%). A mixture of free base porphyrin **4b** (23 mg, 16 μmol) and $Zn(OAc)_2{\cdot}2H_2O$ (25 mg) was warmed briefly in $CHCl_3$ (1 cm^3). After 1 h at RT the mixture was diluted with CH_2Cl_2, washed with pH 7 buffer, dried (K_2CO_3), and evaporated. Chromatography (10–30% $CHCl_3$ in CH_2Cl_2) of the residue gave the zinc derivative **Zn4b** (20 mg, 82%) which was identical with the material prepared as described above.

Compound **5b**: λ_{max}(CH_2Cl_2)/nm 408, 507, 541 and 574; δ_H\{250 MHz, 25% (v/v) [$^2H_4$]-MeOH in $CDCl_3$\} 0.57 (12 H, br s, 18-Me), 0.75 (12 H, br d, *J* 6, 21-Me), 0.83 (12 H, br s, 19-Me), 2.25 (12 H, s, p-Me), 2.34 (12 H, s, p-Me), 3.4 (4 H, br s), 3.7 and 4.0 (16 H, 2 × br m, p-CH_2CH_3), 4.75 (4 H, br s), 4.80 (4 H, m), 7.6 (4 H, t, *J* 7.7, Ar), 8.15 (4 H, d, *J* 7.7, Ar), 8.25 (4 H, d, *J* 7.7, Ar), 8.6 (4 H, s, Ar) and 10.12 (4 H, s, p-*meso*); *m/z* (FABMS) 2929 (M^+ + 3.2).

Compound **$Zn_2$5b**: λ_{max}(CH_2Cl_2)/nm 411.5, 538.5 and 574; δ_H(400 MHz, $CDCl_3$) for 1 : 1 the **Zn5b**–DABCO complex −5.1 (12 H, s, DABCO), 0.66 (12 H, br s, 18-Me), 1.15 (12 H, br d, *J* 6, 21-Me), 1.24 (12 H, br s, 19-Me), 1.33 (24 H, m, p-CH_2CH_3), 2.04 (12 H, s, p-Me), 2.10 (12 H, s, p-Me), 3.6 and 3.9 (16 H, 2 × br m, p-CH_2CH_3), 4.27 (4 H, br s, 7-H), 5.27 (8 H, br s, 3-H and 12-H), 7.48 (4 H, d, *J* 7.7, Ar), 7.55 (4 H, t, *J* 7.7, Ar), 8.43 (4 H, d, *J* 7.7, Ar), 8.51 (4 H, s, Ar) and 9.51 (4 H, s, p-*meso*); *m/z* (FABMS) 3053 (M^+ + 3.4) and 1528.

Interconversion of the dimers 5a and 5b

A solution of the dimer **5a** (10 mg, 2.9 μmol) in THF (2 cm^3), MeOH (1 cm^3) and conc. aqueous ammonia (*d* 0.88; 0.5 cm^3) was left in the dark at RT for 1 week and then evaporated. A chloroform solution of the residue was washed with pH 7 buffer, dried and evaporated. Chromatography (0–5% EtOAc in CH_2Cl_2) of the residue afforded the dimer **5b** (7 mg, 80%). A sample of the dimer **5b** prepared in this fashion was cleanly converted back into the dimer **5a** by treatment with an excess of trifluoroacetic anhydride in THF (0 °C for 2 min).

Doubly capped porphyrins 6 and 7

$BF_3{\cdot}Et_2O$ (18 mm^3, 0.15 mmol) was added to a degassed solution of the bisaldehyde **2b** (810 mg, 0.776 mmol) and pyrrole (105 mm^3, 1.585 mmol) in dry CH_2Cl_2 (155 cm^3). The mixture was stored in the dark at RT for 15 h after which it was treated with DDQ (265 mg, 1.17 mmol) and then stored for a further 1 h before being washed with sat. aqueous sodium hydrogen carbonate and pH 7 buffer, dried and evaporated. The main red band collected by initial chromatography (5–10% EtOAc in CH_2Cl_2) was re-chromatographed (5–7.5% EtOAc in CH_2Cl_2). Crystallisation of the faster running component from MeOH containing the minimum amount of $CHCl_3$ gave **6** as tufts of fine needles (60.2 mg, 6.8%). Further chromatography of the slower running component and overlap fractions (10% EtOAc in toluene) provided **7** (2.5 mg) along with some more **6** (4.8 mg). The free-base porphyrin **6** (25 mg, 11 μmol) in $CHCl_3$ (1 cm^3) was warmed briefly with $Zn(OAc)_2{\cdot}2H_2O$ (25 mg) and then left at RT for 4 h before being diluted with CH_2Cl_2, washed with pH 7 buffer, dried (K_2CO_3) and evaporated. Chromatography (50% $CHCl_3$ in CH_2Cl_2) of the residue followed by slow crystallisation from toluene provided **Zn6** (22 mg, 85%) as small purple–red plates.

Compound **6**: mp > 300 °C (Found: C, 75.7; H, 7.75; N, 2.35. $C_{144}H_{174}N_4O_{20}$ requires C, 75.83; H, 7.69; N, 2.46); $\lambda_{max}(CH_2Cl_2)$/nm 424.5, 522, 557 and 595; δ_H(400 MHz, $CDCl_3$) −1.98 (2 H, s, NH), 0.44 (12 H, s, 18-Me), 0.61 (12 H, d, *J* 6.6, 21-Me), 0.68 (4 H, d, *J* 4, 12-OH), 0.78 (12 H, s, 19-Me), 3.58 (4 H, br q, *J* 3.5, 12-H), 4.57 (4 H, br q, *J* 3, 7-H), 4.91 (4 H, tt, *J* 11, 5, 3-H), 8.06 (4 H, t, *J* 7.7, Ar), 8.19 (4 H, t, *J* 1.5, Ar), 8.44 (4 H, dt, *J* 7.7, 1.5, Ar), 8.59 (4 H, s, porphyrin β), 9.21 (4 H, dt, *J* 7.7, 1.5, Ar) and 9.33 (4 H, s, porphyrin β); *m/z* (FABMS) 2281.9 (M^+ + 2.6).

Compound **Zn6**: mp > 300 °C; $\lambda_{max}(CH_2Cl_2)$/nm 426, 553 and 592; δ_H(400 MHz, $CDCl_3$) 0.43 (12 H, s, 18-Me), 0.59 (4 H, d, *J* 4, 12-OH), 0.60 (12 H, d, *J* 6.6, 21-Me), 0.78 (12 H, s, 19-Me), 3.57 (4 H, br q, *J* 3.5, 12-H), 4.57 (4 H, br q, *J* 3, 7-H), 4.95 (4 H, tt, *J* 11, 5, 3-H), 8.05 (4 H, t, *J* 7.7, Ar), 8.29 (4 H, t, *J* 1.5, Ar), 8.44 (4 H, dt, *J* 7.7, 1.5, Ar), 8.75 (4 H, s, porphyrin β), 9.13 (4 H, dt, *J* 7.7, 1.5, Ar) and 9.33 (4 H, s, porphyrin β); δ_C(100 MHz, $CDCl_3$) 174.77 (CO), 166.44 (CO), 149.96, 148.82, 142.62, 138.08, 136.77, 132.44, 131.74, 129.80, 128.70, 127.24, 119.63, 74.50 (CHO), 72.40 (CHO), 70.91 (CHO), 45.59, 44.78, 42.33, 40.26, 37.81, 34.61, 33.66 (×2), 31.32, 31.31, 29.08, 27.92, 27.87, 27.25, 26.25, 25.98, 22.74, 21.86 (Me), 17.65 (Me) and 12.38 (Me); *m/z* (FIBMS) 2343 (M^+ + 1.8). Assignments were confirmed by ^1H COSY and NOESY and NOE difference experiments.

Compound **7**: $\lambda_{max}(CH_2Cl_2)$/nm 420.5, 517, 550 and 591; δ_H(250 MHz, $CDCl_3$) −2.61 (2 H, s, NH), 0.71 (12 H, s, 18-Me), 0.87 (12 H, s, 19-Me), 1.07 (12 H, br d, 21-Me), 3.95 (4 H, br q, 12-H), 4.69 (4 H, br m, 3-H), 4.90 (4 H, br t, 7-H), 7.75 (4 H, t, *J* 7.7, Ar), 7.96 (4 H, d, *J* 7.7, Ar), 8.32 (4 H, d, *J* 7.7, Ar), 8.69 (4 H, s, porphyrin β), 9.13 (4 H, s, Ar) and 9.38 (4 H, s, porphyrin β); *m/z* (FABMS) 2282.5 (M^+ + 3.2).

Compound **Zn7**: $\lambda_{max}(CH_2Cl_2)$/nm 422, 549 and 585; ^1H NMR signals similar to **7** but broader at RT; *m/z* (FABMS) 2344 (M^+ + 2.8).

Acylation of Zn6 to give base tailed porphyrin Zn8

2,6-Dichlorobenzoyl chloride (120 mm^3, 0.80 mmol) was added to a stirred solution of pyridine-3-carboxylic acid (100 mg, 0.81 mmol) and triethylamine (115 mm^3, 0.86 mol) in THF (2.5 cm^3). After 1 h at RT the mixture was evaporated and the residue dissolved in toluene (3 cm^3) and the solution filtered, washing with more toluene (3 cm^3). A portion of the filtrate was evaporated and made up in $[^2H_8]$-toluene to give a 0.18 mol dm^{-3} solution of the mixed anhydride (assay by integration with respect to added CH_2Cl_2 as an internal standard). A solution of **6** (1.0 mg, 0.43 μmol), **Zn6** (1.0 mg, 0.44 μmol) and 3,5-di-*tert*-butyl-4-methylpyridine (5 mg, 24 μmol) in $[^2H_8]$-toluene (500 mm^3) in a septum capped NMR tube containing one activated 4 Å sieve bead, was titrated with mixed anhydride (0.18 mmol dm^{-3}; 0 to 50 mm^3) to measure the equilibrium constant for binding to **Zn6** ($K \leqslant 50$ dm^3 mol^{-1}). After 50 mm^3 of mixed anhydride (9 μmol) had been added, reaction was initiated by injection of a solution of DMAP in $[^2H_8]$-toluene (0.1 mol dm^{-3}; 10 mm^3, 1 μmol). By the time the next spectrum had been acquired (~2 min), reaction was complete, producing a mixture of **Zn8** and unchanged **6**. The reaction mixture in CH_2Cl_2 was washed with pH 3.5 buffer, water and sat. aqueous sodium hydrogen carbonate and dried (K_2CO_3). Chromatography (10–50% $CHCl_3$ in CH_2Cl_2) gave greenish purple **Zn8** (~1 mg) and red **6** (~1 mg). In separate experiments **Zn6** was heated with an excess of mixed anhydride at 70 °C in the absence of DMAP for 4 d, with no change by ^1H NMR (except disproportionation of the mixed anhydride) or TLC. Under the same conditions, but in the presence of DMAP, **6** was similarly unchanged. **Zn8** was isolated in 92% yield from **Zn6** on a 10 mg scale using the same conditions as for the NMR competition experiment above, but omitting **6**. A sample of free base **8** was produced by treatment of **Zn8** in CH_2Cl_2 with trifluoroacetic acid [1% (v/v) 5 min] followed by aqueous work-up.

Acylation of 6 to give the base tailed porphyrin 8

DMAP (10 mg, 82 μmol) was added to a stirred solution of **6** (9 mg, 4 μmol), pyridine-3-carbonyl chloride hydrochloride (10 mg, 56 μmol) and 3,5-di-*tert*-butyl-4-methylpyridine (20 mg, 98 μmol) in dry ethanol-free $CHCl_3$ (1 cm^3). After 4 h at RT the reaction mixture was diluted with CH_2Cl_2, washed with pH 3.5 buffer, water and sat. aqueous sodium hydrogen carbonate and dried (K_2CO_3). Chromatography (1% EtOAc in CH_2Cl_2) gave **8** (2.1 mg, 22%). Metallation of **8** to give **Zn8** was unusually slow, requiring 10 h at 50 °C in $CHCl_3$ with a large excess of $Zn(OAc)_2{\cdot}2H_2O$.

Compound **8**: $\lambda_{max}(CH_2Cl_2)$/nm 424, 555, 595 and 651; δ_H(500 MHz, $CDCl_3$) 0.45, 0.46, 0.47, 0.63 (4 × 3 H, 4 × s, 18-Me), 0.49, 0.59, 0.61, 0.63 (4 × 3 H, 4 × d, *J* 6.6, 21-Me), 0.64, 0.70 (2 × 1 H, 2 × d, *J* 4.5, 12-OH, exchangeable), 0.78, 0.79, 0.80, 0.87 (4 × 3 H, 4 × s, 19-Me), 1.85 (1 H, dd, *J* 8, 5.1, ligand 5-H), 3.43 (1 H, dt, *J* 9.9, 3, 12-H), 3.57, 3.60 (2 × 1 H, 2 × dt, *J* 4.6, 3, 12-H), 3.87 (1 H, d, *J* 9.9, 12-OH, exchangeable), 4.36 (1 H, dt, *J* 8, 1.8, ligand 4-H), 4.54, 4.56, 4.57, 4.70 (4 × 1 H, 4 × br q, *J* 3, 7-H), 4.80 (1 H, br t, *J* 3, 12-H), 4.82, 4.95 (2 × 2 H, m, 3-H), 6.51 (1 H, dd, *J* 5.1, 1.8, ligand 6-H), 7.92, 8.08, 8.20, 8.29 (4 × 1 H, 4 × t, *J* 1.5, Ar), 8.04, 8.09, 8.11, 8.13 (4 × 1 H, 4 × t, *J* 7.8, Ar), 8.19 (1 H, d, *J* 1.8, ligand 2-H), 8.40, 8.41, 8.47, 8.49 (4 × 1 H, 4 × dt, *J* 7.8, 1.5, Ar), 8.57, 8.64, 8.65, 8.66 (4 × 1 H, 4 × d, *J* 4.9, porphyrin β), 9.18, 9.27, 9.28, 9.29 (4 × 1 H, 4 × dt, *J* 7.8, 1.5, Ar) and 9.26, 9.35, 9.37 and 9.41 (4 × 1 H, 4 × d, *J* 4.9, porphyrin β); *m/z* (FABMS) 2386 (M^+ + 1.7). Assignments were confirmed by ^1H COSY.

Compound **Zn8**: $\lambda_{max}(CH_2Cl_2)$/nm 433, 567 and 606; δ_H(400 MHz, $CDCl_3$) 0.42, 0.44, 0.46, 0.53 (4 × 3 H, 4 × s, 18-Me), 0.56, 0.61, 0.66, 0.79 (4 × 3 H, 4 × d, *J* 6.6, 21-Me), 0.77, 0.78, 0.79, 0.80 (4 × 3 H, 4 × s, 19-Me), 2.93 (1 H, dd, *J* 5.1, 1.8, ligand 6-H), 3.0 (1 H, d, *J* 1.8, ligand 2-H), 3.55, 3.60, 3.65 (3 × 1 H, 3 × br q, *J* 3.5, 12-H), 4.57 (1 H, br t, *J* 3, 12-H), 4.56 and 4.63 (1 H and 3 H, 2 × br t, 7-H), 4.95 (4 H, m, 3-H), 5.98 (1 H, dd, *J* 8, 5.1, ligand 5-H), 6.83 (1 H, dt, *J* 8, 1.8, ligand 4-H), 8.00, 8.02, 8.03, 8.08 (4 × 1 H, 4 × t, *J* 7.8, Ar), 7.79, 8.35, 8.39, 8.40 (4 × 1 H, 4 × t, *J* 1.5, Ar), 8.34, 8.36, 8.43, 8.45 (4 × 1 H, 4 × dt, *J* 7.8, 1.5, Ar), 8.59, 8.73, 8.79, 8.83 (4 × 1 H, 4 × d, *J* 4.9, porphyrin β), 9.05, 9.08, 9.11, 9.19 (4 × 1 H, 4 × dt, *J* 7.7, 1.5, Ar) and 9.21, 9.25, 9.30 and 9.32 (4 × 1 H, 4 × d, *J* 4.9, porphyrin β); *m/z* (FABMS) 2450 (M^+).

2,8,12,18-Tetraethyl-5,15-bis(3-methoxycarbonylphenyl)-3,7,13,17-tetramethylporphyrin 9[21] and Zn9

p-TsOH·H_2O (145 mg, 0.76 mmol) was added to a solution of methyl 3-formylbenzoate[20] (0.50 g, 3.05 mmol) and 3,3′-

diethyl-4,4'-dimethyl-5,10-dihydrodipyrrin (0.71 g, 3.08 mmol) in dry degassed MeOH (30 cm^3) at RT. After storage overnight at 0 °C, the supernatant was decanted and the remaining pinkish precipitate dried *in vacuo*. DDQ (2.40 g, 10.6 mmol) was added to a stirred solution of the crude porphyrinogen in dry THF (40 cm^3) at ice-bath temperature. After 2 h the mixture was evaporated and the residue purified by chromatography (1% MeOH in CH_2Cl_2) the main red band being collected. The crude product was slurried with cyclohexane and the suspension filtered, washing with more cyclohexane to yield **9**[21] as a purple solid (0.85 g, 76%); $\lambda_{max}(CH_2Cl_2)$/nm 408 (log ε 5.32), 506 (4.22), 540 (3.75), 574 (3.80) and 626 (3.18); δ_H(250 MHz, $CDCl_3$) −2.20 (2 H, br s, NH), 1.80 (12 H, t, *J* 7.5, p-CH_2CH_3), 2.45 (12 H, s, p-CH_3), 4.00 (6 H, s, CO_2Me), 4.05 (8 H, q, *J* 7.5, p-CH_2CH_3), 7.84 (2 H, d, *J* 7.7, Ar), 8.28 (2 H, d, *J* 7.7, Ar), 8.52 (2 H, d, *J* 7.7, Ar), 8.80 (2 H, s, Ar) and 10.28 (2 H, s, p-*meso*); δ_C(100 MHz, 10% [$^2H_4$]-MeOH in $CDCl_3$) 167.52 (CO_2Me), 144.92, 142.46, 141.06, 137.08, 135.40, 129.53, 129.31, 127.79, 116.55, 96.70 (CH, p-*meso*), 52.29 (CO_2Me), 19.75 (p-CH_2), 17.40 (p-CH_3) and 14.72 (p-CH_3); *m/z* (FABMS) 747.4 (M^+). A solution of **9** (200 mg, 0.27 mmol) in $CHCl_3$ (10 cm^3) was refluxed briefly with $Zn(OAc)_2 \cdot 2H_2O$ (200 mg), stored at RT for 1 h and then washed with water, dried and evaporated. Two crystallisations from $CHCl_3$–MeOH provided **Zn9** (170 mg, 78%) (Found: C, 69.8; H, 5.8; N, 6.65. $C_{48}H_{48}N_4O_4Zn \cdot H_2O$ requires C, 69.60; H, 6.08; N, 6.76); ν_{max}(Nujol)/cm^{-1} 1720; $\lambda_{max}(CH_2Cl_2)$/nm 410 (log ε 5.65), 538 (4.30) and 574 (4.09); δ_H(250 MHz, $CDCl_3$) 1.76 (12 H, t, *J* 7.5, p-CH_2CH_3), 2.41 (12 H, s, p-CH_3), 3.97 (6 H, s, CO_2Me), 4.01 (8 H, q, *J* 7.5, p-CH_2CH_3), 7.84 (2 H, d, *J* 7.7, Ar), 8.30 (2 H, d, *J* 7.7, Ar), 8.51 (2 H, d, *J* 7.7, Ar), 8.78 (2 H, s, Ar) and 10.21 (2 H, s, p-*meso*).

Tetra-*meso*-(3-methoxycarbonylphenyl)porphyrin 10[22] and Zn10

p-TsOH·H_2O (30 mg) was added to a solution of 3-(bisacetoxymethyl)benzoic acid[20] (785 mg, 3.1 mmol) in methanol (10 cm^3) and trimethyl orthoformate (2 cm^3) and the mixture refluxed for 8 h. The mixture was evaporated and the residue dissolved in diethyl ether and the solution washed with sat. aqueous sodium hydrogen carbonate and water, dried and evaporated. $BF_3 \cdot Et_2O$ (40 mm^3, 0.33 mmol) was added to a solution of the crude product (largely methyl 3-formylbenzoate dimethyl acetal) and pyrrole (215 mm^3, 3.1 mmol) in CH_2Cl_2 (320 cm^3). After 5 h DDQ (530 mg, 2.33 mmol) was added to the mixture which after a further 1 h was evaporated. Chromatography (0–2% EtOAc in CH_2Cl_2) followed by crystallisation from methanol–CH_2Cl_2 gave the porphyrin **10**[22] (156 mg, 24%); $\lambda_{max}(CH_2Cl_2)$/nm 418.5, 515, 549 and 590; δ_H(250 MHz. $CDCl_3$) −2.81 (2 H, s, NH), 3.98 (12 H, s, CO_2Me), 7.85 (4 H, t, *J* 7.7, Ar), 8.40 (4 H, d, *J* 7.7, Ar), 8.48 (4 H, d, *J* 7.7, Ar), 8.79 (8 H, s, porphyrin β) and 8.89 (4 H, s, Ar); **Zn10**: $\lambda_{max}(CH_2Cl_2)$/nm 420, 547 and 586; δ_H(250 MHz, $CDCl_3$) 3.96 (12 H, s, CO_2Me), 7.84 (4 H, t, *J* 7.7, Ar), 8.42 (4 H, d, *J* 7.7, Ar), 8.49 (4 H, d, *J* 7.7, Ar) and 8.89 (12 H, br s, Ar and porphyrin β).

Molecular modelling and ring current calculations

Cyclocholate-porphyrin conformers were generated in the MULTIC submode of Macromodel (3.0)[11] and minimised using standard force fields (MM2, Amber). Solvent was not included and no special parameters were used for porphyrins. For ring-current calculations the low-energy structures were transferred to Chem3D Plus™ (2.0.1), and *x,y,z* coordinates obtained by setting the centre of the porphyrin as the origin with the porphyrin in the *x,y* plane. Porphyrin-induced shifts were calculated with the dipole model of Abraham *et al.*[15] Dipoles were spaced 2.1 Å apart on the sides of a rectangular grid, and the *meso* phenyl rings were assumed to be orientated perpendicular to the plane of the porphyrin with a distance of 6.32 Å between the centre of the porphyrin and the centre of a phenyl ring; other parameters were the same as in ref. 15. Minimised structures of **4b** and **6** were generally unsymmetrical with more or less tilted dilactone caps and tilted aryl rings, so the calculated shifts on both sides of the cap were averaged. For example the predicted upfield shifts for the 18-Me groups in one minimised structure of **4b** were 0.25 and 0.42 ppm compared to the experimental value of 0.29 ppm (relative to **2b**) and predicted upfield shifts for the 21-Me groups of **4b** were 0.52 and 0.30 ppm compared to the experimental value of 0.41 ppm (relative to **2b**).

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References

1 (*a*) R. Boyce, G. Li, P. Nestler, T. Suenaga and W. C. Still, *J. Am. Chem. Soc.*, 1994, **116**, 7955; (*b*) U. Maitra and B. G. Bag, *J. Org. Chem.*, 1994, **59**, 6114; (*c*) D. Albert and M. Feigel, *Tetrahedron Lett.*, 1994, **35**, 565; (*d*) J. Kikuchi, C. Matsushima, K. Suehiro, R. Oda, Y. Murakami, *Chem. Lett.*, 1991, 1807; (*e*) J. F. Kinneary, T. M. Roy, J. S. Albert, H. Yoon, T. R. Wagler, L. Shen and C. J. Burrows, *J. Inclusion Phenomena*, 1989, **7**, 155; (*f*) C. J. Burrows and R. A. Sauter, *J. Inclusion Phenomena*, 1987, **5**, 117; (*g*) J. McKenna, J. M. McKenna and D. W. Thornthwaite, *J. Chem. Soc., Chem. Commun.*, 1977, 809.

2 (*a*) A. P. Davis, *Chem. Soc. Rev.*, 1993, **22**, 243; (*b*) R. P. Bonar-Law and A. P. Davis, *Tetrahedron*, 1993, **49**, 9829 and 9845; (*c*) R. P. Bonar-Law, A. P. Davis and B. J. Dorgan, *Tetrahedron*, 1993, **49**, 9855; (*d*) K. M. Bhattarai, R. P. Bonar-Law, A. P. Davis and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1992, 752; (*e*) R. P. Bonar-Law, A. P. Davis and B. A. Murray. *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1407; (*f*) R. P. Bonar-Law and A. P. Davis, *J. Chem. Soc., Chem. Commun.*, 1989, 1050.

3 (*a*) R. P. Bonar-Law and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1995, **117**, 259; (*b*) R. P. Bonar-Law, L. G. Mackay, C. J. Walter, V. Marvaud and J. K. M. Sanders, *Pure Appl. Chem.*, 1994, **66**, 803; (*c*) R. P. Bonar-Law, L. G. Mackay and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1993, 456; (*d*) R. P. Bonar-Law, L. G. Mackay and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1377; (*e*) R. P. Bonar-Law and J. K. M. Sanders, *Tetrahedron Lett.*, 1993, **34**, 1677; (*f*) R. P. Bonar-Law and J. K. M. Sanders, *Tetrahedron Lett.*, 1992, **33**, 2071; (*g*) R. P. Bonar-Law and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1991, 574.

4 R. P. Bonar-Law, A. P. Davis and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2245.

5 (*a*) R. Young and C. K. Chang, *J. Am. Chem. Soc.*, 1985, **107**, 898; (*b*) M. J. Gunter and L. N. Mander, *J. Org. Chem.*, 1981, **46**, 4792.

6 (*a*) M. Hirota, Y. Sakurai, R. Horita and O. Yonemitsu, *Tetrahedron Lett.*, 1990, **31**, 6367; (*b*) P. P. Waanders, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.*, 1987, **28**, 2409; (*c*) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.

7 B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, 1993, pp. 112–143.

8 P. E. Schulze, A. Seeger and V. Illi, *Tetrahedron*, 1985, **39**, 2815.

9 For recent approaches to diaryl porphyrin synthesis see (*a*) T. Nagata, *Bull. Chem. Soc. Jpn.*, 1991, **52**, 3005; (*b*) T. Nagata, A. Osuka and K. Marayuma, *J. Am. Chem. Soc.*, 1990, **112**, 3054; (*c*) A. Osuka, F. Kobayashi, T. Nagata and K. Marayuma, *Chem. Lett.*, 1990, 287; (*d*) A. Osuka, F. Kobayashi and K. Marayuma, *Chem. Lett.*, 1990, 1521; (*e*) J. S. Manka and D. S. Lawrence, *Tetrahedron Lett.*, 1989, **30**, 6989.

10 J. S. Lindsey, I. C. Schrieman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.

11 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caulfield, G. Chang, T. Hendrickson and W. C. Still, *J. Computational Chem.*, 1990, **11**, 440.

12 For porphyrin strapping reactions see R. W. Wagner, P. A. Brown, T. E. Johnson and J. S. Lindsey, *J. Chem. Soc., Chem. Commun.*, 1991, 1464, and references therein.

13 (*a*) F. Montanari, M. Penso, S. Quici and P. Vigano, *J. Org. Chem.*, 1985, **50**, 4888; (*b*) B. Meunier, M.-E. de Carvalho, O. Bortolini and M. Momenteau, *Inorg. Chem.*, 1988, **27**, 161.

14 For leading references see F. A. Walker, U. Simonis, H. Zhang, J. M. Walker, T. M. Ruscutti, C. Kipp, M. A. Amputch, B. V. Castillo,

S. A. Cody, D. L. Wilson, R. E. Graul, G. J. Young, K. Tobin, J. T. West and B. A. Barichievich, *New J. Chem.*, 1992, **16**, 609.
15 R. J. Abraham, G. R. Bedford, D. McNeillie and B. Wright, *Org. Magn. Res.*, 1980, **14**, 418.
16 C. J. Medforth, T. D. Hobbs, M. R. Rodriguez, R. J. Abraham, K. M. Smith and J. A. Shelnutt, *Inorg. Chem.*, 1995, **34**, 1333 and references therein.
17 O. W. Kolling, *Inorg. Chem.*, 1979, **18**, 1175 and references therein.
18 (*a*) C. A. Hunter, M. N. Meah and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1990, **112**, 5773; (*b*) H. L. Anderson, C. A. Hunter, M. N. Meah and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1990, **112**, 5780.
19 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
20 F. Irreverre, H. Kny, S. Asen, J. F. Thompson and C. J. Morris, *J. Biol. Chem.*, 1961, **236**, 1093.
21 A. Asuhiro, T. Nagata, F. Kobayashi and M. Kazuhiro, *J. Heterocycl. Chem.*, 1990, **27**, 1657.
22 N. Datta-Gupta, E. Jones, L. K. Thomas and D. Malkar, *J. Indian Chem. Soc.*, 1981, 1171.

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