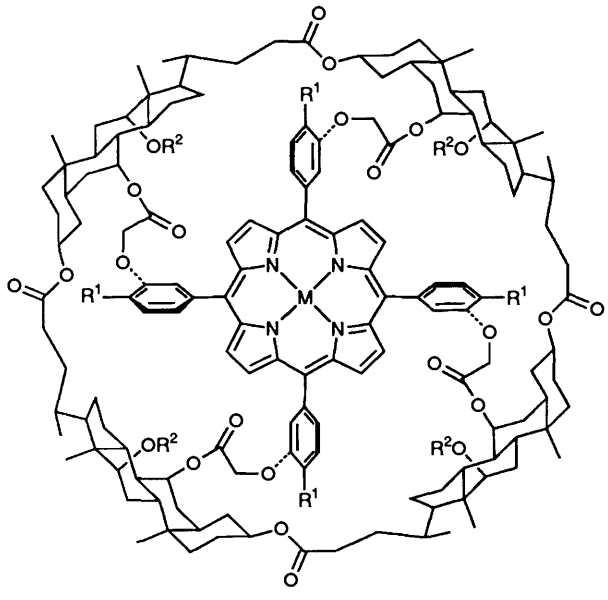
Concise Synthesis of a Porphyrin–Cyclocholate Molecular Bowl

Lindsey G. Mackay, Richard P. Bonar-Law and Jeremy K. M. Sanders*
Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK

An efficient sequence is described from cholic acid to a porphyrin–cyclocholate molecular bowl.

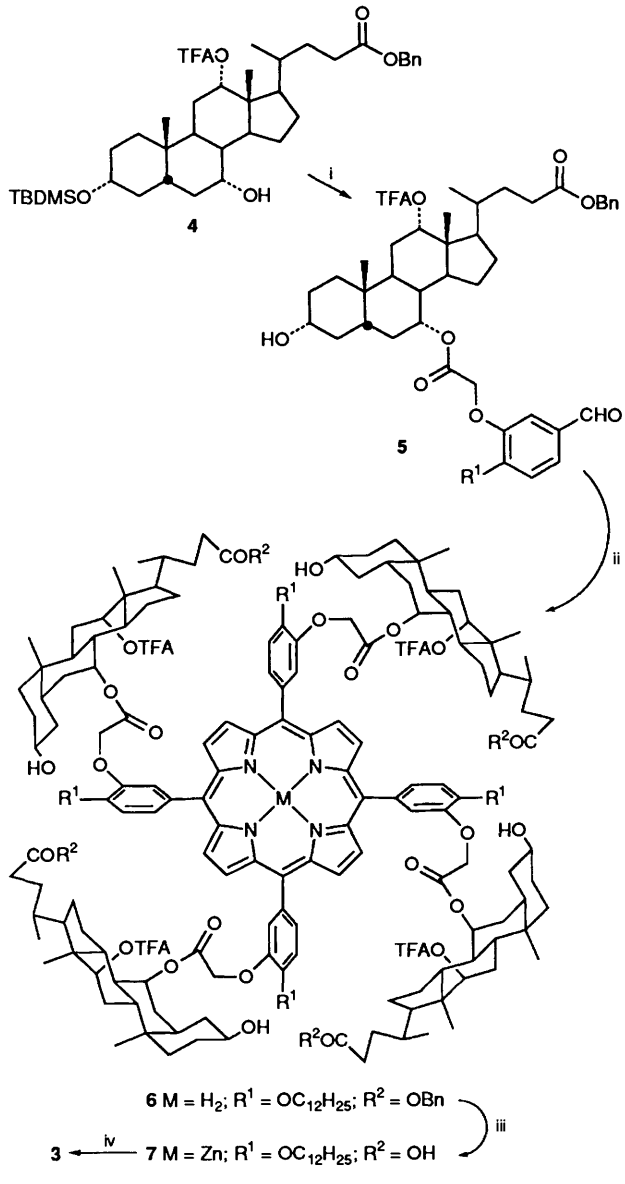
We have previously reported a synthesis of the porphyrin–cyclocholate molecular bowl **1**;[1] the final step involved formation of the porphyrin within the preformed tetracholate macrocycle in a very low yield. We describe here a more efficient synthesis of the related bowl **2**, involving initial formation of a porphyrin substituted with four peripheral cholate groups, followed by intramolecular linking together of the cholates (Scheme 1). These bowls are of interest for their selective ligand-binding properties[1] and their catalytic potential.



1 $R^1 = R^2 = H$; M = Zn
2 $R^1 = OC_{12}H_{25}$; $R^2 = H$; M = Zn
3 $R^1 = OC_{12}H_{25}$; R^2 = TFA; M = H_2

Cholic acid was readily converted in three steps into the partially protected compound **4**.[1,2] The unprotected 7-hydroxy group was then esterified with 2-dodecyloxy-5-formylphenoxyacetic acid, and the 3-TBDMS group was removed to give **5** in 78% yield.† This was converted in 46% yield under Lindsey conditions[3] into the benzyl-protected tetrasteroidal porphyrin **6**. Metallation, followed by hydrogenation of the benzyl esters afforded the tetrahydroxy tetraacid **7** (97%).‡

Macrolactonisation to give the molecular bowl **3** in 18% yield was achieved using Yamaguchi conditions:[4] the mixed anhydride formed with 2,6-dichlorobenzoyl chloride and triethylamine was added under high dilution conditions to a solution of 4-dimethylaminopyridine in toluene at 100 °C. The apparent low efficiency of this final reaction corresponds to a yield of *ca.* 65% for each of the four ester linkages created. This new approach yields bowl **3** in 6.3% overall yield from the



6 M = H_2; $R^1 = OC_{12}H_{25}$; R^2 = OBn
7 M = Zn; $R^1 = OC_{12}H_{25}$; R^2 = OH

Scheme 1 *Reagents and conditions:* i, (a) 2-dodecyloxy-5-formylphenoxyacetic acid, dicyclohexylcarbodimide, dimethylaminopyridine (DMAP); (b) HF (aq); ii, pyrrole, BF_3·Et_2O in CH_2Cl_2 then tetrachloroquinone; iii, (a) $Zn(OAc)_2$; (b) H_2, 10% Pd/C; iv, (a) acetic acid; (b) 2,6-dichlorobenzoyl chloride, triethylamine, 4 Å sieves; (c) add slowly to DMAP in toluene at 100 °C (1.0 mmol dm^{-3} final concentration)

† The C_{12}-side chain plays a solubilising role in the final macrolactonisation step of the synthesis; the tetrahydroxy tetraacid leading to the original unsubstituted bowl **1** was rather insoluble, leading to a greatly reduced yield.

‡ (Found: C, 67.2; H, 7.9; N, 1.7. Calc. for $C_{204}H_{280}F_{12}N_4O_{36}Zn$: C, 66.98; H, 7.72; N, 1.53%); *m/z* (FAB MS) 3658 (M^+).

monomeric cholate **4**, and further improvements are still possible; removal of the TFA protecting group and metallation gave **2** in 83% yield. By comparison, the overall yield from **4** to **1** *via* our original route was only 1.5%. The greater availability of bowl from this improved route opens up the prospect of more detailed ligand binding studies; these will be reported elsewhere.

Experimental

Synthesis of Porphyrin **6**.—A solution of the aldehyde **5** (1.04 g, 1.11 mmol) in dry dichloromethane (120 cm^3) was degassed with argon for 15 min, pyrrole (77 mm^3,* 1.11 mmol) was then syringed in and degassing continued for a further 15 min. Boron trifluoride–diethyl ether (14.8 mm^3, 0.12 mmol) was added and the resulting orange solution stirred at room temperature for 2 h. Tetrachloroquinone (205 mg, 0.83 mmol) was then added to oxidise the porphyrinogen and the deep red solution refluxed for 2 h. After neutralisation with triethylamine (16.7 mm^3, 0.12 mmol) the solvent was removed under reduced pressure and the residue then purified by flash chromatography. Elution with dichloromethane–ethyl acetate (4:1, v/v) gave a crude band of the porphyrin which was then columned a second time. Initial elution with dichloromethane (to remove yellow tetrachloroquinone side products), followed by dichloromethane–ethyl acetate (97:3, v/v) afforded the pure tetrasteroidal porphyrin **6** (0.50 g, 46%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400 (OH), 1776 ($COCF_3$) and 1745 and 1736 (CO_2R); $\delta_H(CD_2Cl_4, 393\ K)$ −2.59 (2 H, br s, NH), 0.72 (12 H, s, 18-Me), 0.77 (12 H, d, *J* 7,† 21-Me), 0.83 (12 H, s, 19-Me), 0.9–2.3 (m, steroid and C-12 side chain), 2.55 (4 H, m, 3 βH), 4.39 [8 H, t, *J* 7, $OCH_2(CH_2)_{10}CH_3$], 4.81, 4.90 (8 H, ABq, *J* 16, OCH_2CO_2), 5.05 (4 H, br q, 7 βH), 5.06, 5.10 (8 H, ABq, *J* 13, CH_2Ph), 5.22 (4 H, br t, 12 βH), 7.29–7.35 (24 H, m, CH_2Ph and 3-ArH), 7.80 (4 H, dd, *J* 9, 2, 4-ArH), 7.82 (4 H, br s, 6-ArH) and 8.91 (8 H, s, β-pyrrole); *m/z* (FAB MS) 3955 (M^+); $\lambda_{max}(CH_2Cl_2)/nm$ 424, 518, 556, 586 and 644.

Molecular Bowl **3**.—The zinc porphyrin **7** was initially demetallated with acetic acid to give the free base. This tetrahydroxy tetraacid (79 mg, 22 μmol) was azeotropically dried from dry toluene (20 cm^3) and then stirred with powdered 4 Å molecular sieves (500 mg) in dry tetrahydrofuran (2.0 cm^3). After 2 h, 2,6-dichlorobenzoyl chloride (14.8 mm^3, 99 μmol) and triethylamine (freshly distilled ex. CaH_2, 18.4 mm^3, 0.13 mmol) were syringed in and stirring continued for 4 h. The solution of the mixed anhydride was then diluted with dry toluene (freshly distilled ex. CaH_2 then stirred over powdered 4 Å molecular sieves for 4 h, 8 cm^3) and then added over 5.5 h, *via* a syringe pump, to a solution of 4-dimethylaminopyridine (43 mg, 0.35 mmol) in dry toluene (14 cm^3) at 100 °C. The solution was heated at 100 °C for a further 10 h and the solvent then removed at reduced pressure. Chloroform (80 cm^3) was added to the residue and the red solution washed with 3 mol dm^{-3} aq. HCl (50 cm^3) and water (3 × 50 cm^3), dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by flash chromatography. Elution with dichloromethane–ethyl acetate (100:1, v/v) afforded the molecular bowl **2** (14 mg, 18%); $\delta_H(CDCl_3)$ −2.76 (2 H, br s, NH), 0.54 (12 H, br d, 21-Me), 0.68 (12 H, s, 18-Me), 0.87 [12 H, t, *J* 7, $(CH_2)_{11}CH_3$], 0.88 (12 H, s, 19-Me), 0.9–2.3 (m, steroid and C-12 side-chain), 4.30 [8 H, t, *J* 7, $OCH_2(CH_2)_{10}CH_3$], 4.49 (4 H, m, 3 βH), 4.70, 4.80 (8 H, ABq, *J* 15, OCH_2CO_2), 5.09 (4 H, br m, 7 βH or 12 βH), 5.13 (4 H, br m, 7 βH or 12 βH), 7.24 (4 H, d, *J* 8, 3-ArH), 7.64 (4 H, dd, *J* 9, 2, 4-ArH), 7.96 (4 H, br s, 6-ArH) and 8.88 (8 H, s, β-pyrrole); *m/z* (FAB MS) 3522 (M^+); $\lambda_{max}(CH_2Cl_2)/nm$ 423, 516, 554, 592 and 648.

Acknowledgements

We thank the Association of Commonwealth Universities, the New Zealand Vice-Chancellors' Committee, and the SERC for financial support and FAB mass spectra.

References

1 R. P. Bonar-Law, L. G. Mackay and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1993, 456.
2 R. P. Bonar-Law, A. P. Davis and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2245.
3 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.
4 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.

Paper 3/01926H
Received 5*th April* 1993
Accepted 19*th May* 1993

* 1 $mm^3 \equiv 1$ μl.
† *J* Values in Hz.