New Syntheses of Biliverdins, Corroles and Azaporphyrins from 1,19-Dibromo-*ac*-biladiene Salts[1]

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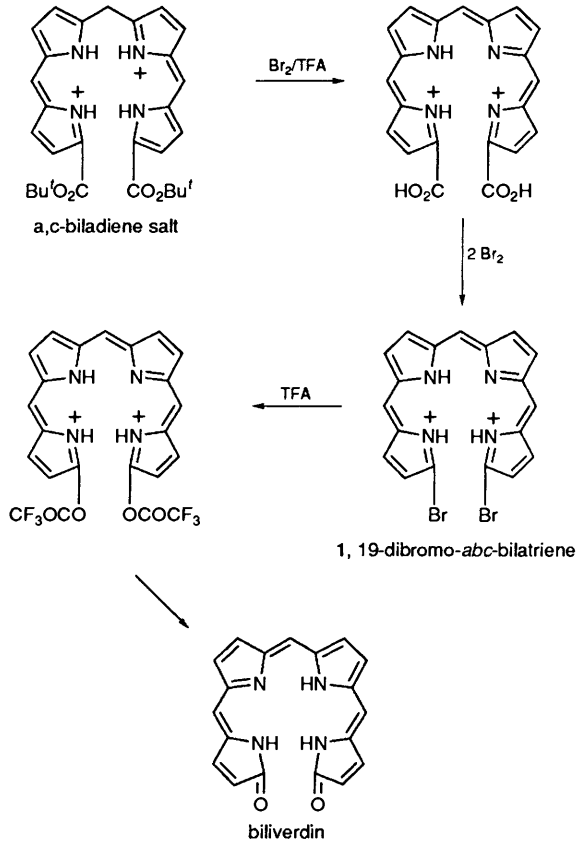
Treatment of the readily available, 1,19 dibromo-*ac*-biladiene dihydrobromide salts **3** with dimethyl sulfoxide (DMSO) in presence of a catalytic amount of toluene-*p*-sulfonic acid affords symmetrical and unsymmetrical biliverdins **4** in excellent yield; unsymmetrically substituted 1,19 dibromo-*ac*-biladiene dihydrobromide **3c** was prepared in a stepwise fashion *via* a tripyrrin salt. Under appropriate reaction conditions, the *ac*-biladiene dihydrobromides were also converted in modest yields into the corroles **5** and the azaporphyrins **6**.

So-called bile pigments, such as biliverdins, bilirubins, phycobilins and phytochrome, are widely distributed in animals or plants.[2-8] For example, biliverdin **1** occurs in all vertebrates, in many invertebrates as well as in bile of most of the birds, amphibians and reptiles.[9] The eggs of some birds contain biliverdin IXα in the free acid form and as its zinc complex.[10] Biliverdin IXα also occurs in the hemolymph and integument of the grasshopper, spiders and flies.[11] Another isomer, biliverdin IXγ occurs in the wings of Lepidoptera.[11] On the other hand bilirubin **2**, a reduced form of biliverdin, seems to have no physiological function. So far as is known, it is merely a waste product of heme catabolism.[12] Although biliverdin does not occur in plants, except in the root nodules of legumes, closely related bilatrienes occur covalently bound to apoproteins.[13] Phytochrome,[13a,b] the photoperiodic regulator that exists in very low concentrations in higher plants and algae, and phycocyanins, the photosynthetically active biliproteins that occur in blue green algae, contain bilatrienes as their functional groups.[13a,c] A related open-chain tetrapyrrole, phycoerythrobilin, also covalently attached to protein, acts as the important photosynthetic chromophore in phycoerythrin.[13a,d]

The identification of bile pigments in natural materials has frequently been far from rigorous. This has been due to lack of material and, until recently, a lack of suitable synthetic methods for structure confirmation. In recent years, there have been a number of reports regarding the synthesis of these classes of compounds.[14-19] However, these synthetic methods, particularly for unsymmetrical bilins, are laborious. We have reported a fairly efficient method for the synthesis of biliverdin compounds from readily available *b*-bilenes and *ac*-biladienes.[17-19] There, we postulated (Scheme 1) that 1,19-dibromobilitriene species were possible intermediate species in biliverdin formation, which upon further reaction with trifluoroacetic acid followed by base hydrolysis produced the desired biliverdins.

The most important open-chain tetrapyrroles used in modern rational porphyrin syntheses are the *ac*-biladienes, usually prepared as the crystalline dihydrobromide salts. The substituents at the terminal 1,19-positions can be varied.[20-23] Depending on the 1,19-substituents, the *ac*-biladiene can be converted into unconjugated macrocycles,[20-23] porphyrins, biliverdins, corroles, azaporphyrins and tetrahydrocorrins. Some years ago, Harris *et al.*[24] reported the preparation of 1,19-dibromo-*ac*-biladienes from bromodihydrodipyrrins, which were then used as precursors for the synthesis of azaporphyrins and corroles. Azaporphyrins, in general, do not have much biological significance, but have recently generated some interest in photodynamic therapy (PDT) of cancer due to their strong absorption in the red region of the absorption spectrum.[25]

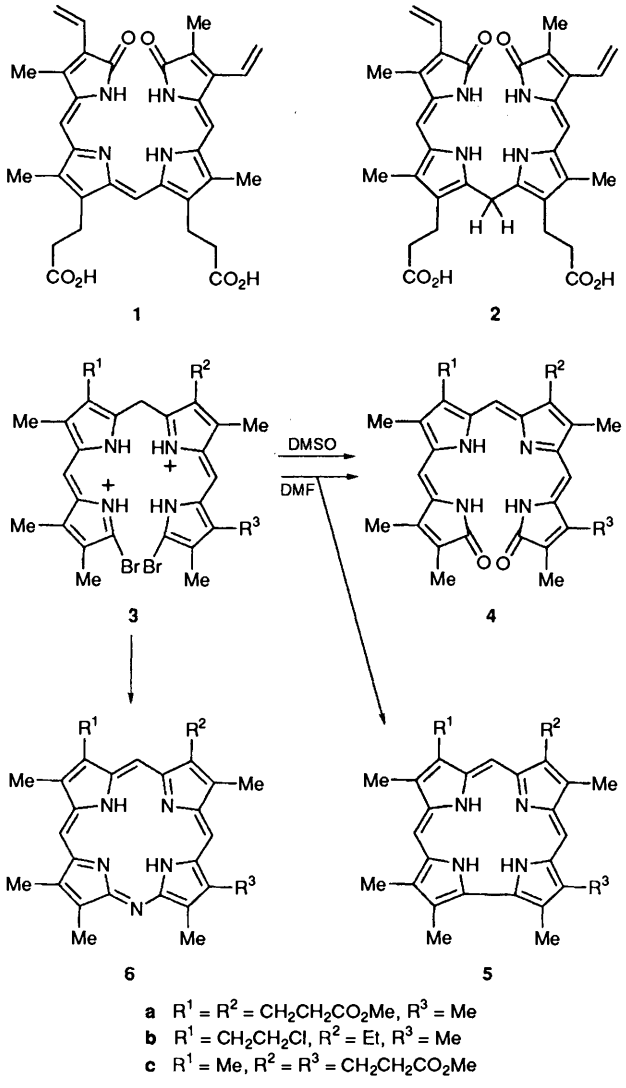


Scheme 1 Proposed mechanism[18] for formation of biliverdin from di-*tert*-butyl *ac*-biladiene-1,19-dicarboxylate, using bromine in trifluoroacetic acid. Peripheral substituents have been omitted for clarity.

Here we report an efficient route for the conversion of symmetrical as well as unsymmetrical 1,19-dibromo-*ac*-biladienes into the corresponding biliverdins, corroles and azaporphyrins.

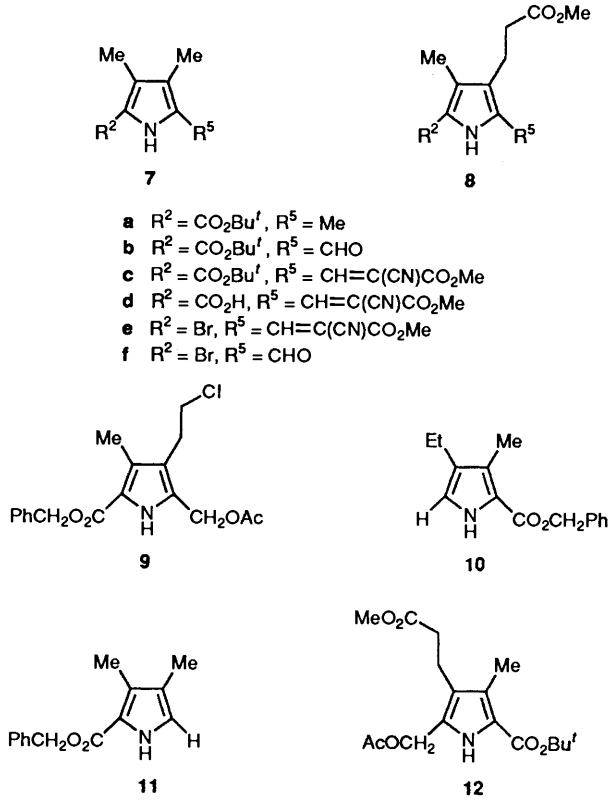
Results and Discussion

Syntheses of ac-*Biladiene Dihydrobromides.*—In order to synthesize symmetrical and unsymmetrical biliverdins **4**, corroles **5** and azaporphyrins **6**, *ac*-biladienes **3** were used as starting



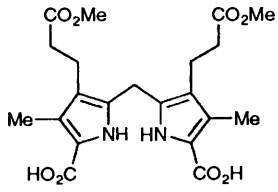
materials. For the preparation of the *ac*-biladiene **3a**, dihydrodipyrrin-1,9-dicarboxylic acid **13**[26] was condensed with 2 equiv. of bromoformylpyrrole **7f** in the presence of toluene-*p*-sulfonic acid, and **3a** was isolated as its dihydrobromide salt in 70% yield. *ac*-Biladiene dihydrobromide **3b** was likewise prepared by allowing the bromoformylpyrrole **7f** to react with dihydrodipyrrin-1,9-dicarboxylic acid **15**, obtained after hydrogenation of the corresponding dibenzyl ester derivative **14**; this, in turn, was prepared in > 85% yield by condensation of the acetoxymethylpyrrole **9** with pyrrole **10** in the presence of montomorillonite K-10 clay.[27]

The bromoformylpyrrole **7f** had earlier been synthesized by Fisher *et al.* in a very low yield by treating 5-formyl-3,4-dimethylpyrrole with bromine.[28] This method was modified by Woodward *et al.* and was later used by Paine *et al.*[29] in the preparation of related bromoformylpyrroles. We further modified this method and prepared a series of bromoformylpyrroles in excellent yield. In a typical procedure (*e.g.* in the preparation of 2-bromo-3,4-dimethyl-5-formylpyrrole **7f**), *tert*-butyl 3,4,5-trimethylpyrrole-2-carboxylate **7a** was used as the starting material. Attempts to convert the pyrrole **7a** into the formylpyrrole **7b** by treating it with 2 equiv. of sulfuryl chloride, followed by hydrolysis of the dichloromethyl intermediate using aqueous alkali was not satisfactory. The low yield of the desired product was possibly due to cleavage of the *tert*-butyl ester group, followed by decarboxylation and polymerization by the HCl that was produced in the reaction. There was no significant improvement in the yield even when anhydrous potassium carbonate was used to trap the HCl produced. However, the desired formylpyrrole **7b** was obtained in almost quantitative yield upon reaction of the pyrrole **7a** with 2 equiv. of lead(IV) tetraacetate under an inert atmosphere. The next step in the reaction sequence was to protect the formyl group, and this was achieved by following the methodology of Woodward[28] and Paine *et al.*[29] Thus, the formylpyrrole was protected as its cyanovinyl derivative **7c** by reaction with methyl cyanoacetate;



treatment with trifluoroacetic acid gave the corresponding pyrrolecarboxylic acid **7d**. Bromination of **7d** afforded the corresponding bromopyrrole **7e** in modest yield. Deprotection of the formyl group was accomplished in aqueous sodium hydroxide, and the bromoformylpyrrole **7f** was isolated in 70% yield. 2-Bromo-5-formyl-4-(2-methoxycarbonylethyl)pyrrole **8f** was obtained under similar reaction conditions, except that after deprotection of the formyl group the reaction mixture was treated with diazomethane in order to reesterify the propionate group.

The unsymmetrical *ac*-biladiene **3c** was synthesized in a stepwise fashion *via* the corresponding tripyrrin salt.[30] Thus, the dihydrodipyrrin **16** (obtained by allowing the acetoxymethylpyrrole **12** to react with the 2-unsubstituted pyrrole **11** in the presence of K-10 clay) was hydrogenated to afford the dihydrodipyrrinmonocarboxylic acid **17** in quantitative yield. Condensation of the dihydrodipyrrin **17** with the bromoformylpyrrole **7f** in the presence of toluene-*p*-sulfonic acid produced the tripyrrin, isolated as its hydrobromide salt **18**, by bubbling HBr gas through a solution of the corresponding tripyrrin free base. During this process, the *tert*-butyl ester group was cleaved to the corresponding carboxylic acid, and this product was isolated in 80% yield. Further condensation of the tripyrrin hydrobromide **18** with bromoformylpyrrole **8f** in the presence of toluene-*p*-sulfonic acid gave the 1,19-dibromo-*ac*-biladiene **3c** in 72% yield. The reaction was monitored by spectrophotometry



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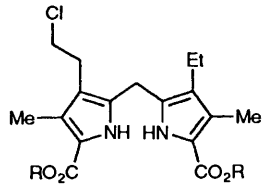
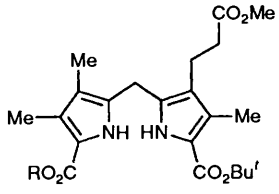
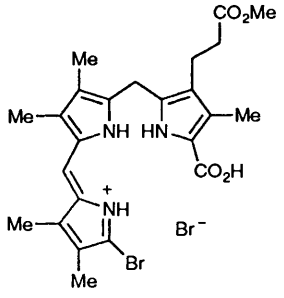


14 R = CH_2Ph
15 R = H



16 R = CH_2Ph
17 R = H



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(disappearance of the tripyrrin salt peak, λ_{max} 500; appearance of the *ac*-biladiene peaks, λ_{max} 458 and 532 nm).

Syntheses of Biliverdins and Corroles.—Some years ago, Gossauer *et al.* described the preparation of corroles by heating 1,19-dibromo-*ac*-biladiene salts with *N,N*-dimethylformamide.[31] To our surprise, when we carried out the reaction under similar conditions with the *ac*-biladiene **3a**, besides the corroles **5a** we obtained a significant amount of the biliverdin **4a**. This prompted us to investigate this reaction further by treating the *ac*-biladiene salts with a variety of solvents under various conditions. For the synthesis of corroles, our best results were obtained when the *ac*-biladiene salts were refluxed in methanol for 4 h. The corroles were isolated in 26–28% yield, along with corresponding biliverdins in 12–15% yield. A further increase in reaction time did not improve the yield.

When 1,19-dibromo-*ac*-biladiene dihydrobromide salts **3** were stirred with dimethyl sulfoxide (DMSO) in the presence of a catalytic amount of toluene-*p*-sulfonic acid at room temperature for 30 min the corresponding biliverdins were isolated as the sole product in 70–75% yield. The DMSO procedure appears to be unique for efficient biliverdin formation. A possible mechanism for the formation of biliverdin might involve the attack of DMSO at the 1- and 19-positions with subsequent elimination of bromide and dimethyl sulfide, leaving the original DMSO oxygen atoms to provide the lactam oxygens.

Synthesis of Azaporphyrins.—Since the use of hematoporphyrin derivative (Photofrin) as photosensitizer in PDT was reported,[32] a variety of porphyrins and related tetrapyrroles (*e.g.* chlorins, bacteriochlorins, pheophorbides) have been designed, synthesized and evaluated as potential photosensitizers.[33] Among such compounds, some phthalocyanines (in which the four meso-carbons of the porphyrin skeleton have been replaced by nitrogens), are currently in phase II and phase III clinical trials.[34] For the last several years, one of the objectives of our laboratories has been to understand the generic structural requirement(s) for an effective photosensitizer.[35] In order to understand the structure/activity effects of nitrogen bridging atoms (in phthalocyanines) compared with similar substitutions at the meso position(s) of the porphyrins we are currently interested in preparing mono-, di-, tri- and tetra-azaporphyrins for comparison of the biological activity with related phthalocyanines. Thus, by following the methodology of Harris *et al.*,[24] the 1,19-dibromo-*ac*-biladienes **3** were successfully converted into the monoazaporphyrins **6** in 50–52% yield by refluxing them with sodium azide in methanol under anaerobic conditions.

Experimental

M.p.s were measured on a Thomas/Bristoline microscopic hot-stage apparatus and were uncorrected. Silica gel 60 (70–230 and 230–400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, i.e. deactivated with 6% water) were used for column chromatography. Preparative thin layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck G 254 silica gel (1 mm thick). Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. ^1H NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.258 ppm). Elemental analyses were performed at the Midwest Microlab Ltd., Indiana, USA. Unless stated otherwise, electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained at the Mass Spectrometry Facility, University of California, San Francisco, CA.

tert-*Butyl* 5-[(E)-2-*Cyano*-2-(*methoxycarbonyl*)*vinyl*]-3,4-*dimethylpyrrole*-2-*carboxylate* **7c**.—A mixture of *tert*-butyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate **7b**[36] (18.0 g), methyl cyanoacetate (11.0 cm^3), triethylamine (2.0 cm^3) and toluene (65.0 cm^3) was stirred at room temperature for about 5 min. The precipitated product was washed with light petroleum to give yellow fluffy crystals (18.4 g, 75%), m.p. 207–208 °C (Found: C, 63.0; H, 6.5, N, 9.3. $C_{16}H_{20}N_2O_4$ requires C, 63.13; H, 6.63; N, 9.21); δ_H 1.59 (9 H, s, Bu^t), 2.17, 2.26 (each 3 H, s, Me), 3.89 (3 H, s, OMe), 8.04 (1 H, s, HC=C) and 10.12 (1 H, br s, NH) [Found (HRMS): *m/z* 304.1413. Calc. for $C_{16}H_{20}N_2O_4$: 304.1423].

2-*Bromo*-5-[(E)-2-*cyano*-2-(*methoxycarbonyl*)*vinyl*]-3,4-*dimethylpyrrole* **7e**.—The foregoing pyrrole **7c** (17.5 g) was stirred in trifluoroacetic acid (78.0 cm^3) at room temperature for 1 h after which the mixture was poured into ice–water (300 cm^3). The precipitate was filtered off, washed with cold water, and air dried to give 5-[(*E*)-2-cyano-2-(methoxycarbonyl)ethenyl]-3,4-dimethylpyrrole-2-carboxylic acid, **7d** as a light yellow solid which was crystallized from CH_2Cl_2–hexane (13.8 g, 97%); m.p. > 200 °C (decomp.). This material was used immediately without further purification. The pyrrole **7d** (13.1 g) was dissolved in acetic acid (130 cm^3) at 60–70 °C and a solution of bromine (3.3 cm^3) in acetic acid (130 cm^3) was added to the mixture dropwise at 70 °C over a period of 40 min. The mixture was stirred at the same temperature for a further 40 min. After a standard work-up the crude product was purified by column chromatography on silica gel G. The appropriate fractions were combined and the title compound was obtained as yellow fluffy

crystals (9.8 g, 66%) from light petroleum, m.p. 146–148 °C (Found: C, 64.5; H, 4.0; N, 10.0. $C_{11}H_{11}BrN_2O_2$ requires C, 64.81; H, 3.93; N, 9.93); δ_H 2.00 and 2.18 (each 3 H, s, Me), 3.87 (3 H, s, OMe), 7.94 (1 H, s, H–C=C) and 9.67 (1 H, br s, NH) [Found (HRMS): 283.9977. Calc. for $C_{11}H_{11}BrN_2O_2$: 283.9983].

2-*Bromo*-5-*formyl*-3,4-*dimethylpyrrole* **7f**.—The foregoing pyrrole **7e** (9.2 g) was refluxed in a solution of sodium hydroxide (10.0 g) in water (200 cm^3) under an inert atmosphere for 2.5 h. The solution was then cooled and the pH was adjusted to 7. The precipitated product was filtered off, washed with water and purified by column chromatography (silica gel, eluting with 3% MeOH in CH_2Cl_2). The appropriate eluates were collected, and the solvent was evaporated to give a residue which was crystallized from CH_2Cl_2–light petroleum to give light purplish white needles (4.84 g, 73.7%), m.p. > 175 °C (decomp.) (Found: C, 41.5; H, 3.9; N, 6.9. C_7H_8BrNO requires C, 41.79; H, 4.02; N, 6.97); δ_H 1.98, 2.32 (each 3 H, s, Me), 9.31 (1 H, br s, NH) and 9.50 (1 H, s, CHO) [Found (HRMS): 202.9766. Calc. for C_7H_8BrNO: 202.9769.].

tert-*Butyl* 5-*Formyl*-4-(2-*methoxycarbonylethyl*)-3-*methylpyrrole*-2-*carboxylate* **8b**.—The pyrrole **8a**[37] (27.0 g), lead(IV) tetraacetate (89.5 g) and acetic acid (750 cm^3) were stirred under N_2 at 65 °C for 2 h after which ethylene glycol (1.0 cm^3) was added to the solution to destroy residual lead(IV) tetraacetate. The mixture was then poured into water (2.5 dm^3) and extracted with dichloromethane (2 × 500 cm^3). The combined extracts were washed with water (2 × 500 cm^3), saturated aqueous sodium hydrogen carbonate (3 × 500 cm^3) and water (2 × 500 cm^3) dried (Na_2SO_4) and evaporated to give the title compound **8b** as yellowish white crystals (26.7 g, 94.3%), m.p. 89–90 °C (Found: C, 59.9; H, 7.0; N, 4.6. $C_{15}H_{21}NO{\cdot}0.5H_2O$ requires: C, 59.20; H, 7.29; N, 4.50); δ_H 1.57 (9 H, s, Bu^t), 2.29 (3 H, s, Me), 2.57 (2 H, t, CH_2CH_2CO), 3.06 (2 H, t, CH_2CH_2CO), 3.63 (3 H, s, OMe), 9.34 (1 H, br s, NH) and 9.77 (1 H, s, CHO) [Found (HRMS): *m/z* 295.1418. Calc. for $C_{15}H_{21}NO_5$: 295.1420.].

tert-*Butyl* 5-[(E)-2-*Cyano*-2-(*methoxycarbonyl*)*vinyl*]-4-(2-*methoxycarbonylethyl*)-3-*methylpyrrole*-2-*carboxylate* **8c**.—A mixture of the foregoing formylpyrrole **8b** (12.0 g), methyl cyanoacetate (6.5 cm^3), triethylamine (1.0 cm^3) and toluene (100 cm^3) was stirred at room temperature for 30 min after which it was diluted with light petroleum (400 cm^3) to give the title product as light yellow crystals (11.5 g, 75%), m.p. 140–141 °C (Found: C, 60.6; H, 6.2; N, 7.5. $C_{19}H_{24}N_2O_6$ requires C, 60.61; H, 6.43; N, 7.44); δ_H 1.58 (9 H, s, Bu^t), 2.30 (3 H, s, Me), 2.52 (3 H, t, CH_2CH_2CO), 2.91 (3 H, t, CH_2CH_2CO), 3.67 (3 H, s, $CH_2CH_2CO_2Me$), 3.91 (3 H, s, $CH{=}CCO_2Me$), 8.12 (1 H, s, H–C=C) and 10.27 (1 H, br s, NH) [Found (HRMS): *m/z* 376.1629. Calc. for $C_{19}H_{24}N_2O_6$: 376.1634].

2-*Bromo*-5-[(E)-2-*cyano*-2-(*methoxycarbonyl*)*vinyl*]-4-(2-*methoxycarbonylethyl*)-3-*methylpyrrole* **8e**.—The foregoing pyrrole **8c** (11.5 g) was stirred in trifluoroacetic acid (75 cm^3) at room temperature for 1 h after which the mixture was poured into ice–water (250 cm^3). The precipitated product was filtered off, washed with cold water and air dried to give 5-[(E)-2-cyano-2-(methoxycarbonyl)vinyl]-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic acid **8d** as a light yellow solid in quantitative yield (9.8 g), m.p. 168–170 °C. This material was used immediately without further purification: **8d** (9.8 g) was dissolved in acetic acid (90 cm^3) at 60–70 °C and a solution of bromine (1.8 cm^3) in acetic acid (90 cm^3) was added to the mixture, dropwise, at 60–70 °C over a 30 min period. The mixture was stirred at the same temperature for a further 40 min after which it was worked up and purified as described for the preparation of pyrrole **7e**. The solvent was evaporated and the pyrrole was crystallized from $CHCl_3$–light petroleum to give the title pyrrole (6.1 g, 68%), m.p. 127–129 °C (Found: C, 47.4; H, 4.2; N, 7.8. $C_{14}H_{15}BrN_2O_4$ requires C, 47.46; H, 4.27; N, 7.91); δ_H 2.05 (3 H, s, Me), 2.53 (3 H, t, CH_2CH_2CO), 2.95 (3 H, t, CH_2CH_2CO), 3.70 (3 H, s, $CH_2CH_2CO_2Me$), 3.91 (3 H, s, $CH{=}CCO_2Me$), 7.97 (1 H, s, H–C=C) and 9.67 (1 H, br s, NH) [Found (HRMS): 356.01322. Calc. for $C_{14}H_{15}BrN_2O_4$: 356.0109].

2-*Bromo*-5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methylpyrrole* **8f**.—The foregoing pyrrole **8e** (6.1 g) was refluxed in a solution of sodium hydroxide (7.1 g) in water (150 cm^3) under N_2 at 105 °C for 2 h after which the solution was cooled to room temperature and its pH adjusted to 7–8. It was then extracted with dichloromethane (3 × 200 cm^3). The combined extracts were washed with water (200 cm^3), dried (Na_2SO_4) and then reduced to a volume of 50 cm^3 before treatment with an excess of ethereal diazomethane. The mixture was evaporated and the residue was purified by column chromatography (silica gel, eluting with 3% MeOH in CH_2Cl_2) to give after evaporation of the solvent and crystallization from CH_2Cl_2–light petroleum, the title compound as light purplish white fluffy crystals (1.74 g, 49%), m.p. 103–104 °C (Found: C, 43.9; H, 4.3; N, 5.0. $C_{10}H_{12}BrNO_3$ requires C, 43.96; H, 4.43; N, 5.13); δ_H 2.01 (3 H, s, Me), 2.58 (3 H, t, CH_2CH_2CO), 3.04 (2 H, t, CH_2CH_2CO), 3.69 (3 H, s, OMe), 9.39 (1 H, br s, NH) and 9.51 (1 H, s, CHO) [Found (HRMS): 274.9983. Calc. for $C_{10}H_{12}BrNO_3$: 274.9980].

Benzyl 9-tert-*Butoxycarbonyl*-7-(2-*methoxycarbonylethyl*)-2,3,8-*trimethyl*-5,10-*dihydrodipyrrin*-1-*carboxylate* **16**.[40]—Benzyl 3,4-dimethylpyrrole-2-carboxylate[38] **11** (0.884 g), *tert*-butyl 5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate[39] **12** (1.20 g) and Montmorillonite K-10 clay (5.0 g) were stirred overnight in dichloromethane (20 cm^3) at room temperature. The clay was then filtered off and evaporation of the filtrate afforded the title compound[40] as a viscous oil (1.53 g, 85%); δ_H 1.50 (9 H, s, Bu^t), 2.02 (3 H, s, Me), 2.32 (6 H, s, Me), 2.32 (2 H, t, CH_2CH_2CO), 2.75 (2 H, t, CH_2CH_2CO), 3.65 (3 H, s, OMe), 3.82 (2 H, s, 5-CH_2), 5.20 (2 H, s, CO_2CH_2Ph), 7.30 (5 H, m, CH_2Ph) and 9.80 and 10.00 (each 1 H, br s, NH).

Dibenzyl 3-(2-*Chloroethyl*)-7-*ethyl*-2,8-*dimethyl*-5,10-*dihydrodipyrrin*-1,9-*dicarboxylate* **14**.—Benzyl 5-acetoxymethyl-4-(2-chloroethyl)-3-methylpyrrole-2-carboxylate **9** (0.67 g) and benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (0.65 g, 1.92 mmol) were dissolved in dichloromethane (50 cm^3) under N_2. Montmorillorite K-10 clay (5.0 g) was added to the yellow-clear solution and the slurry was stirred overnight at room temperature. The clay was filtered off and washed several times with dichloromethane, and the combined clear-yellow filtrate and washings were concentrated to give an oil. Crystallization of the oil from dichloromethane–MeOH gave clear-yellow crystals of the title compound (0.80 g, 78%), m.p. 124–125 °C (Found: C, 69.8; H, 6.2; N, 5.3. $C_{31}H_{33}ClN_2O_4$ requires C, 69.85; H, 6.24; N, 5.26); δ_H 1.03 (3 H, t, CH_2CH_3), 2.27 and 2.28 (each 3 H, s, Me), 2.38 (2 H, q, CH_2CH_3), 2.86 and 3.47 (each 4 H, t, CH_2CH_2Cl), 3.84 (2 H, s, 5-H), 5.23 (4 H, s, CH_2Ph), 7.30 (5 H, m, Ph) and 9.10 and 9.17 (each 1 H, br s, 1 H, NH).

14-*Bromo*-3-(2-*methoxycarbonylethyl*)-2,7,8,12,13-*pentamethyltripyrrin*-1-*carboxylic Acid Hydrobromide* **18**.—The foregoing dihydrodipyrrin **16** (1.53 g), 10% palladized charcoal (0.34 g) and triethylamine (0.1 cm^3) were stirred overnight in

tetrahydrofuran (800 cm^3) under hydrogen at room temperature and atmospheric pressure. The solution was filtered through a bed of Celite and the filtrate evaporated to give a viscous residue, which was crystallized from THF–hexane, to give 9-*tert*-butoxycarbonyl-7-(2-methoxycarbonylethyl)-2,3,8-trimethyl-5,10-dihydrodipyrrin-1-carboxylic acid **17** as a white powder (1.25 g). This dihydrodipyrrincarboxylic acid (0.45 g), bromoformylpyrrole **7f** (0.23 g), a solution of toluene-*p*-sulfonic acid hydrate (0.40 g) in methanol (5.0 cm^3) and dichloromethane (15.0 cm^3) were stirred at room temperature under nitrogen for 45 min after which the reaction was poured into water (200 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (250 cm^3) until the pH was around 7, dried (Na_2SO_4) and reduced in volume to 15 cm^3. Hydrogen bromide gas was passed through the residual solution, after which it was diluted with ether (300 cm^3) to precipitate the product. The product was filtered off and washed with anhydrous ether to give the title tripyrrin salt, as brick red crystals (0.464 g, 70%), m.p. >195 °C (decomp.) (Found: C, 49.1; H, 5.2; N, 7.0. $C_{24}H_{29}Br_2N_3O_4$ requires: C, 49.42; H, 5.01; N, 7.20); λ_{max} nm 502 (ε dm^3 mol^{-1} cm^{-1} 63 500); δ_H 2.17 (6 H, s, 2 × Me), 2.24 (6 H, s, 2 × Me), 2.31 (3 H, s, Me), 2.42 (2 H, t, CH_2CH_2CO), 2.80 (2 H, t, CH_2CH_2CO), 3.67 (3 H, s, OMe), 4.37 (2 H, s, 5-CH_2), 7.07 (1 H, s, 10-CH) and 10.48, 13.49 and 13.69 (each 1 H, br s, NH).

1,19-*Dibromo*-8,12-*bis*(2-*methoxycarbonylethyl*)-2,3,7,13,17,18-*hexamethyl*-ac-*biladiene Dihydrobromide* **3a**.—5,10-Dihydrodipyrrin-1,9-dicarboxylic acid **13** (0.292 g), a solution of bromoformylpyrrole **7f** (0.325 g) in methanol (40 cm^3) and dichloromethane (200 cm^3) were stirred at room temperature for *ca.* 20 min until most of the solid had dissolved. A solution of toluene-*p*-sulfonic acid (0.835 g) in methanol (40 cm^3) was added to the mixture, which was then stirred at room temperature for 12 h. The reaction was monitored by UV–VIS spectrometry. The mixture was then poured into water (400 cm^3) and the organic phase separated, washed with saturated aqueous sodium hydrogen carbonate (3 × 100 cm^3) and water (2 × 200 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure and at low temperature (30–35 °C) to a volume of *ca.* 10.0 cm^3. Hydrogen bromide gas was then passed through the residual solution for 5–6 s after which it was slowly diluted with ether (200 cm^3) to afford a precipitate. This was filtered off and washed with cold ether to give the title *ac*-biladiene salt as a dark brownish green solid (0.389 g, 66%), m.p. >200 °C (decomp.) (Found: C, 44.0; H, 4.8; N, 6.2. $C_{33}H_{40}Br_4N_4O_4 \cdot H_2O$ requires C, 44.49; H, 4.76; N, 6.29); λ_{max} nm 534 (ε dm^3 mol^{-1} cm^{-1} 120 000) and 458 (57 300); δ_H 2.08, 2.12 and 2.47 (each 6 H, s, Me), 2.52–2.89 (8 H, m, CH_2CH_2CO), 3.54 (6 H, s, OMe), 5.02 (2 H, s, 10-CH_2), 7.10 (2 H, s, 5- and 15-CH) and 13.60 and 13.75 (each 2 H, br s, NH).

1,19-*Dibromo*-8-(2-*chloroethyl*)-12-*ethyl*-2,3,7,13,17,18-*hexamethyl*-ac-*biladiene Dihydrobromide* **3b**.—Chloroethyl-7-ethyl-2,8-dimethylmethyl-5,10-dihydrodipyrrin-1,9-dicarboxylic acid **15** (90 mg, 0.257 mmol) and 2-bromo-5-formyl-3,4-dimethylpyrrole **7f** (124 mg, 0.614 mmol) were dissolved in dichloromethane (18 cm^3), and the suspension was stirred at room temperature under N_2 until the solid had dissolved. Toluene-*p*-sulfonic acid (443 mg) dissolved in methanol (9 cm^3) was added to the reaction flask all at once after which the reaction mixture was stirred at room temperature for 18 h since after this time the reaction was deemed complete by spectrophotometry (disappearance of the tripyrrin peak at λ 490 nm), the mixture was poured into water (50 cm^3) and dichloromethane (50 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (3 × 50 cm^3), water (100 cm^3), brine (100 cm^3), and water (100 cm^3), dried and concentrated to *ca.* 10 cm^3. A slow stream of hydrogen bromide gas was then bubbled into the residual liquid for 30 s after which it was diluted with ether to precipitate the product. The suspension was stored at −40 °C for several hours before collection of the green solid. This was recrystallized by dissolution in dichloromethane–methanol (1:1) followed by precipitation with a minimum of ether. The product was collected (111 mg, 54%) and had m.p. >300 °C (Found: C, 43.95; H, 4.7; N, 7.1. $C_{29}H_{35}Br_4ClN_4$ requires C, 43.83; H, 4.44; N, 7.05); λ_{max} nm 458 (ε dm^3 mol^{-1} cm^{-1} 57 500) and 534 (153 100); δ_H (in $CDCl_3$ with a drop of CF_3CO_2D) 2.35 (s, 6 H, Me), 2.07, 2.08, 2.33 and 2.37 (each 3 H, s, Me), 2.57 (2 H, q, CH_2CH_3), 3.01 (2 H, t, CH_2CH_2Cl), 3.53 (2 H, t, CH_2CH_2Cl), 4.62 (2 H, s, 10-CH_2), 7.26 and 7.30 (each 1 H, s, 5-, 15-H) and 12.56, 12.51, 12.40 and 12.36 (each 1 H, br s, NH).

1,19-*Dibromo*-3,8-*bis*(2-*methoxycarbonylethyl*)-2,7,12,13,-17,18-*hexamethyl*-ac-*biladiene Dihydrobromide* **3c**.—The tripyrrin hydrobromide **18** (0.200 g) was dissolved in dichloromethane (10 cm^3) and hydrogen bromide gas was passed through the solution for 20 s. A solution of bromoformylpyrrole **8f** (0.090 g) in methanol (10 cm^3) and toluene-*p*-sulfonic acid (200 mg) in methanol (5 cm^3) were added to the mixture which was then stirred at room temperature for *ca.* 40 min with UV–VIS monitoring. After this the reaction mixture was poured into water (200 cm^3) and the organic phase was separated, washed with aqueous sodium hydrogen carbonate (3 × 100 cm^3), and water (200 cm^3), dried (Na_2SO_4) and reduced in volume to 10.0 cm^3. Hydrogen bromide gas was bubbled through the residual liquid for 5–6 s after which it was diluted by slow addition of ether (200.0 cm^3). The title *ac*-biladiene salt precipitated, was filtered off and washed with cold ether to give a brownish green solid (0.210 g, 72%), m.p. >145 °C (decomp.) (Found: C, 44.0; H, 4.4; N, 6.3. $C_{33}H_{40}Br_4N_4O_4 \cdot H_2O$ requires: C, 44.32; H, 4.73; N, 6.26); λ_{max} nm 532 (ε dm^3 mol^{-1} cm^{-1} 146 600) and 458 (79 500); δ_H 1.96, 2.08, 2.10, 2.25, 2.33 and 2.38 (each 3 H, s, Me), 2.58 (4 H, m, CH_2CH_2CO), 2.75 and 3.05 (each 2 H, t, CH_2CH_2CO), 3.50 and 3.63 (each 3 H, s, OMe), 5.24 (2 H, s, 10-CH_2), 7.19 and 7.41 (each 1 H, s, 5-, 15-CH), 13.59, 13.78, 13.89 and 14.00 (each 1 H, s, NH).

Corroles and Biliverdins

8,12-*Bis*-(2-*methoxycarbonylethyl*)-2,3,7,13,17,18-*hexamethylcorrole* **5a** *and* 8,12-*Bis*(2-*methoxycarbonylethyl*)-2,3,7,13,17,18-*hexamethylbiliverdin* **4a** *by the DMF Method*.—A solution of *ac*-biladiene dihydrobromide **3a** (0.30 g) in DMF (9.0 cm^3) was stirred at 100 °C for 10 min after which it was diluted with saturated brine (300 cm^3) and extracted with ether (3 × 100 cm^3). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide a residue which was purified by column chromatography (silica gel, elution with 2% MeOH in CH_2Cl_2). The fast moving band was identified as the corrole **5a**, isolated as a dark purple solid (0.030 g, 16%), m.p. 193–195 °C (Found: C, 70.4; H, 6.6; N, 9.8. $C_{33}H_{38}N_4O_4$ requires C, 70.73; H, 6.83; N, 10.00); λ_{max} nm 397 (ε dm^3 mol^{-1} cm^{-1} 158 100), 408 (133 200), 536 (20 200), 548 (19 900), and 592 (23 000); δ_H −3.91 (3 H, br s, 3 × NH), 3.13–3.35 (18 H, m, 6 × Me), 3.70 (6 H, s, 2 × OMe), 4.13 (8 H, br s, 2 × CH_2CH_2CO), 9.00, 9.11 (overlapped, 3 H, br s, 5-, 10-, 15-CH) [Found (HRMS): 554.2894. Calc. for $C_{33}H_{38}N_4O_4$: 554.2893]. The second band was identified as biliverdin **4a**, isolated as a dark blue solid (0.048 g, 24%), m.p. 228–229 °C (Found: C, 65.6; H, 6.6; N, 8.7. $C_{33}H_{38}N_4O_6 \cdot H_2O$ requires C, 65.55; H, 6.72; N, 9.27); λ_{max} nm 369 (ε dm^3 mol^{-1} cm^{-1}

37 800), 371 (37 300) and 636 (11 400); δ_H 1.81 (6 H, s, 2-, 18-Me), 2.08 (12 H, s, 3-, 7-, 13-, 17-Me), 2.55 (4 H, t, 2 × CH_2CH_2CO), 2.91 (4 H, t, 2 × CH_2CH_2CO), 3.67 (6 H, s, 2 × OMe), 5.89 (2 H, s, 5-, 15-H), 6.73 (1 H, s, 10-H) and 8.16 (3 H, br s, 3 × NH); λ_{max} nm 371 (ε dm^3 mol^{-1} cm^{-1} 41 500) and 636 (13 600) [Found (HRMS): 586.2783. Calc. for $C_{33}H_{38}N_4O_6$: 586.2791].

8-(2-*Chloroethyl*)-12-*ethyl*-2,3,7,13,17,18-*hexamethylbilverdin* **4b** *and* 8-(2-*Chloroethyl*)-12-*ethyl*-2,3,7,13,17,18-*hexamethylcorrole* **5b** *by the DMF Method*.—A solution of *ac*-biladiene dihydrobromide **3b** (100 mg) was stirred in DMF at 100 °C for 10 min after which the reaction mixture was worked up by following the standard procedure described above for **4a** and **5a**. The residue was purified by preparative thick layer chromatography on silica gel and two main bands were separated. The fast moving band was the corrole **5b** (12 mg, 20%), m.p. 235–238 °C (decomp.); λ_{max} nm 397 (ε dm^3 mol^{-1} cm^{-1} 125 400), 406 (112 000), 536 (18 000), 548 (17 100) and 592 (20 500); δ_H −3.50 (3 H, br s, NH), 2.02 (t, 3 H, CH_2CH_3), 3.30, 3.50 (18 H, m, 18 H, 6 × Me), 3.85 and 3.65 (each t, 2 H, CH_2CH_2Cl), 4.42 (q, 2 H, CH_2CH_3), 8.90, 9.10, 9.20 (each 1 H, s, 5-, 10-, 15-H) [Found (HRMS): 472.2400. Calc. for $C_{29}H_{33}ClN_4$: 472.2389]. The second blue band to be eluted was identified as the biliverdin **4b** obtained as dark blue crystalline solid after crystallization from dichloromethane–hexane (17 mg, 31%), m.p. 225–228 °C; λ_{max} nm 370 (ε dm^3 mol^{-1} cm^{-1} 40 000) and 636 (14 000); δ_H 1.20 (3 H, t, CH_2CH_3), 1.80–2.30 (18 H, m, 6 × Me), 2.50–2.92 (m, 6 H, CH_2CH_2Cl and CH_2CH_3), 5.88, 5.94 and 6.80 (each 1 H, s, 5-, 10-, 15-H) and 8.20 (br s, NH) [Found (HRMS): 504.2280. Calc. for $C_{29}H_{33}ClN_4O_2$: 504.2287].

3,8-*Bis*(2-*methoxycarbonylethyl*)-2,7,12,13,17,18-*hexamethylcorrole* **5c** *and* 3,8-*Bis*(2-*methoxycarbonylethyl*)-2,7,12,13,17,18-*hexamethylbiliverdin* **4c** *by the DMF Method*.—A solution of the *ac*-biladiene dihydrobromide **3c** (0.050 g) in DMF (1.5 cm^3) was stirred at 100 °C for 10 min after which it was diluted with saturated brine (200 cm^3) and extracted with ether (3 × 50 cm^3). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to afford a residue which was then chromatographed (silica gel, elution with 2% MeOH in CH_2Cl_2). The fast moving band provided the corrole **5c** as a dark purple solid (0.006 g, 19%), m.p. 230–232 °C (decomp.) (Found: C, 70.0; H, 6.9; N, 9.9. $C_{33}H_{38}N_4O_4$ requires C, 70.45; H, 6.80; N, 9.96); λ_{max} nm 397 (ε dm^3 mol^{-1} cm^{-1} 128 400), 406 (112 400), 536 (17 800), 548 (17 100) and 592 (20 900); δ_H −3.53 (3 H, br s, 3 × NH), 3.35–3.51 (18 H, m, 6 × Me), 3.72 (6 H, s, 2 × OMe), 4.11 (8 H, br s, 2 × CH_2CH_2CO), 8.96, 9.11 and 9.18 (overlapped 3 H, br s, 5-, 10-, 15-H). The second band was biliverdin **4c**, isolated as a dark blue solid (0.010 g, 30.0%), m.p. 208–209 °C (Found; C, 65.1; H, 6.5; N, 9.1. $C_{33}H_{38}N_4O_6 \cdot H_2O$ requires C, 65.53; H, 6.67; N, 9.27); λ_{max} nm 366 (ε dm^3 mol^{-1} cm^{-1} 39 300), 371 (39 000) and 636 (11 500); δ_H 1.78, 1.82, 2.03, 2.04, 2.05 and 2.09 (each 3 H, s, 2-, 7-, 12-, 13-, 17-, 18-Me), 2.54 and 2.63 (each 2 H, t, CH_2CH_2CO), 2.82 and 2.91 (each 2 H, t, each CH_2CH_2CO), 3.68 and 3.71 (each 3 H, s, OMe), 5.89 and 5.95 (each 1 H, s, 5-, 15-H), 6.70 (1 H, s, 10-H) and 8.19 (3 H, br s, 3 × NH).

8,12-*Bis*(2-*methoxycarbonylethyl*)-2,3,7,13,17,18-*hexamethylcorrole by the* MeOH *Method* **5a**.—The *ac*-biladiene dihydrobromide **3a** (0.086 g) was refluxed in methanol (80 cm^3) at room temperature for 3 h, the reaction being monitored by UV–VIS spectrometry until it was completed. After this the solvent methanol was removed and dichloromethane (60 cm^3) was added to dissolve the residue. The solution was then washed with water (2 × 100 cm^3), dried (Na_2SO_4) and evaporated. The product was purified by column chromatography (silica gel, elution with 2% MeOH in CH_2Cl_2) to afford the title corrole as dark purple crystals from dichloromethane–hexane (0.0153 g, 28%). It was identical in all respects with the sample described above.

3,8-*Bis*(2-*methoxycarbonylethyl*)-2,7,12,13,17,18-*hexamethylbiliverdin by the* Me_2SO *Method* **4c**.—The *ac*-biladiene dihydrobromide **3c** (0.040 g) was dissolved in dimethyl sulfoxide (20 cm^3) and the solution was stirred at room temperature; after 20–25 min the solution turned blue. The stirring was continued for a further 1 h before the reaction mixture was diluted with water (200 cm^3) and then extracted with ether (3 × 60 cm^3). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel, elution with 5% MeOH in CH_2Cl_2) to afford the product **4c** as a dark blue solid (0.019 g, 71%) after recrystallization from dichloromethane–hexane. This was identical in all respects with the biliverdin obtained from the DMF method. By following the same methodology, the biliverdins **4a** and **4b** were also prepared in high yield (> 70%) from corresponding *ac*-biladiene salts.

Azaporphyrins

3,7-*Bis*(2-*methoxycarbonylethyl*)-2,8,12,13,17,18-*hexamethyl*-15-*azaporphyrin* **6a**.—Solid sodium azide (557 mg) was added to the *ac*-biladiene salt **3a** (73.2 mg) suspended in dry methanol (25 cm^3) and the mixture was heated to 85 °C (reflux). The mixture was refluxed for 17 h before it was evaporated and the crude material, including salt, was chromatographed on a silica gel column, eluting with 1% methanol in dichloromethane. The only product obtained was the deep red title compound (24.8 mg, 52%), m.p. > 300 °C (Found: C, 69.0; H, 6.5; N, 12.2. $C_{33}H_{37}N_5O_4 \cdot 0.5\ H_2O$ requires C, 68.73; H, 6.64; N, 12.14%); λ_{max} nm 376 (ε dm^3 mol^{-1} cm^{-1} 104 000), 502 (8200), 534 (20 500), 560 (8300) and 610 (21 100); δ_H −2.69 (2 H, br s, NH), 3.48, 3.52 and 3.53 (each 6 H, s, Me), 3.64 (6 H, s, OMe), 3.22 and 4.32 (each 4 H, t, CH_2CH_2CO), 9.83 (2 H, s, 10-, 20-H) and 10.02 (1 H, s, 5-H) [Found (HRMS): 567.2842. Calc. for $C_{33}H_{37}N_5O_4$: 567.2845].

3-(2-*Chloroethyl*)-7-*ethyl*-2,8,12,13,17,18-*hexamethyl*-15-*azaporphyrin* **6b**.—Dry methanol (18 cm^3) was purged with a slow stream of nitrogen for 5 min before the *ac*-biladiene salt **3b** (42 mg) and solid sodium azide (350 mg) were added to it; the mixture was then heated (to *ca.* 85 °C) to reflux. The solution was refluxed for 15 h after which it was evaporated and the residue taken up in dichloromethane (100 cm^3). The solution was washed with water (75 cm^3), saturated aqueous sodium hydrogen carbonate (75 cm^3) and brine (75 cm^3), dried (Na_2SO_4) and evaporated. The residue was then column chromatographed on alumina (Brockmann Grade III), eluting with dichloromethane to provide a single product, the deep red title compound (8.1 mg, 32%), m.p. > 300 °C (Found: C, 70.1; H, 6.9; N, 13.7. $C_{29}H_{32}ClN_5 \cdot 0.5H_2O$ requires C, 70.36; H, 6.72; N, 14.15); λ_{max} nm 375 (ε dm^3 mol^{-1} cm^{-1} 98 800), 504 (7200), 536 (18 500), 558 (7600) and 610 (19 100), δ_H −2.69 (2 H, br s, NH), 1.80 (4 H, t, CH_2CH_3), 3.51 and 3.54 (each 6 H, s, Me), 3.47 and 3.55 (each 3 H, s, Me), 4.01 (2 H, q, CH_2CH_3), 4.24 (2 H, t, CH_2CH_2Cl), 4.42 (2 H, t, CH_2CH_2Cl), 9.847, 9.851 and 9.900 (each 1 H, s, 5-, 10-, 20-H) [Found (HRMS): 485.2364. Calc. for $C_{29}H_{32}ClN_5$: 485.2346].

2,7-*Bis*(2-*methoxycarbonylethyl*)-3,8,12,13,17,18-*hexamethyl*-10-*azaporphyrin* **6c**.—The *ac*-biladiene salt **3c** (52.7 mg) in dry methanol (17 cm^3) containing sodium azide (382 mg) was refluxed for 17 h. Work-up, followed by purification on a silica

gel column (eluting with 3% methanol in dichloromethane), afforded the deep red title compound (16.2 mg, 47%), m.p. 209–210 °C (Found: C, 69.5; H, 6.5; N, 12.0. $C_{33}H_{37}N_5O_4$ requires C, 69.82; H, 6.57; N, 12.34); λ_{max} nm 376 (ε dm^3 mol^{-1} cm^{-1} 108 000), 502 (4800), 534 (19 600), 560 (5400) and 610 (21 100); δ_H −3.41 (2 H, br s, NH), 3.15 (4 H, t, CH_2CH_2CO), 3.31, 3.34, 3.37, 3.45, 3.47 and 3.54 (each 3 H, s, Me), 3.66 and 3.69 (each 6 H, s, OMe), 4.22 (4 H, t, CH_2CH_2CO), 9.48, 9.64 and 9.68 (each 1 H, s, 5-, 10-, 20-H) [Found (HRMS): 567.2833. Calc. for $C_{33}H_{37}N_5O_4$: 567.2845].

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