Biosynthesis of porphyrins and related macrocycles. Part 48.[1,2] The rearrangement of 2*H*-pyrroles (pyrrolenines) related to the proposed spiro-intermediate for porphyrin biosynthesis

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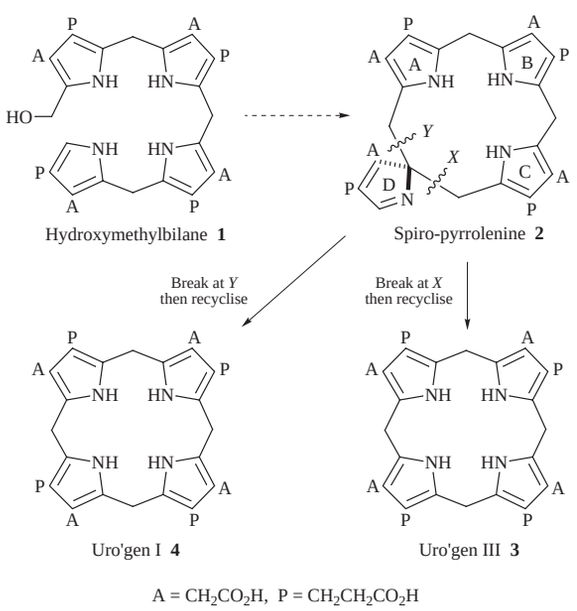
It is proposed that the biosynthesis of uroporphyrinogen III 3, the parent precursor of the natural porphyrins, chlorins and corrins, involves a 2*H*-pyrrole (pyrrolenine) 2 as a key intermediate. Model pyrrolenines have now been used to show that (*a*) pyrrolylmethylpyrrolenines, *e.g.* 32, readily undergo rearrangement in a way which matches that suggested in the biosynthetic proposal; (*b*) there is regioselectivity in the rearrangement which also parallels that required for the biosynthesis of uroporphyrinogen III. This work adds further support to the biosynthetic proposal by showing that all the required chemistry is both feasible and facile.

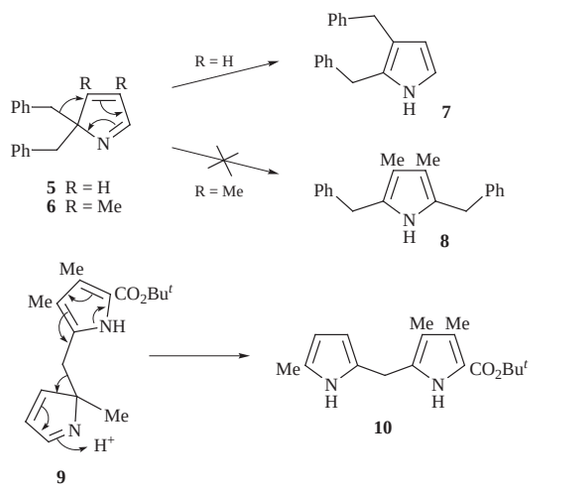
Uroporphyrinogen III synthase (E.C. 4.2.1.75), usually called cosynthetase, catalyses the conversion of hydroxymethylbilane **1** into uroporphyrinogen III **3**, shortened to uro'gen III, the parent macrocycle from which haem, chlorophyll and vitamin B_{12} are all biosynthesised. This cyclisation is accompanied by a rearrangement which leads to inversion of ring D in the product **3**. Mechanistic studies on this reaction were briefly reviewed in the preceding paper.[1] An attractive mechanism consistent with all the available evidence involves 2*H*-pyrrole (pyrrolenine) **2** as a key intermediate, Scheme 1. Fragmentation of this spiro-



Scheme 1 Alternative modes of fragmentation of the spiro-pyrrolenine **2**

pyrrolenine **2** at the bond marked *X* followed by recyclisation would then give uro'gen III. In contrast to the enzymic reaction, non-enzymic rearrangement of spiro-pyrrolenine **2** would be expected to proceed to yield a mixture of the type III **3** and type I **4** isomers, because fragmentation at the bond *Y* is almost equivalent to that at *X* (Scheme 1).

In our earlier paper[3] we described the synthesis and rearrangement reactions of some simple 2,2-disubstituted pyrrolenines. It was shown that the 3,4-unsubstituted pyrrolenine **5** rearranged thermally, or less efficiently under acidic catalysis, to yield **7**, illustrated in Scheme 2 as occurring by a [1,5]sigma-



Scheme 2 Previous studies on the rearrangement of pyrrolenines

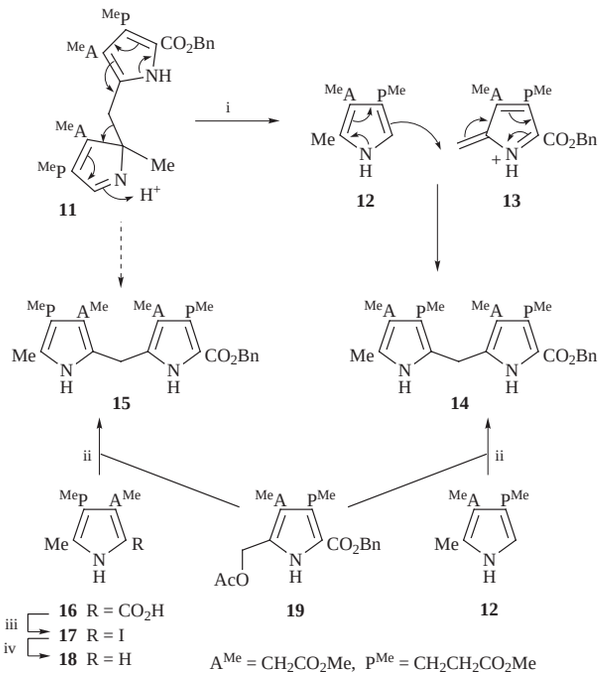
tropic shift. Rearrangement of the 3,4-disubstituted analogue **6** would require a series of three such shifts to reach the stable pyrrole **8**. In fact, no detectable amount of the pyrrole **8** was formed from **6** even under rather vigorous thermal or acid-catalysed conditions. When a pyrrolylmethyl group was one of the 2,2-substituents on the pyrrolenine ring as in **9**, the major product from both acid-catalysed and thermal rearrangement was the dipyrromethane **10** in sharp contrast to that from **5**. This product **10** was interpreted as being formed by fragmentation as illustrated followed by recombination of the pieces.

In this paper we present studies on the rearrangement reactions of some of the pyrrolylmethylpyrrolenines synthesised in the preceding paper.[1] These compounds have the natural acetate and propionate side-chains (as esters) both on the pyrrole ring(s) and on C-3 and -4 of the pyrrolenine ring. In particular we aimed (a) to provide definitive proof that such compounds follow the fragmentation–recombination mechanism proposed for the enzymic reaction and for the rearrangement of **9** to **10** and (b) to investigate whether there is any regioselectively (*viz.* cleavage at *X vs. Y*) when there are two pyrrolylmethyl groups present.

Results and discussion

Rearrangement of mono(pyrrolylmethyl)pyrrolenines

The synthetic work described in the preceding paper[1] provided pyrrolenine **11**, which was the starting material for the studies described in this section. The effect of treatment of a solution of the pyrrolenine **11** in $CDCl_3$ at room temperature with an excess of TFA was examined by ^1H NMR spectroscopy. Under these conditions the reaction was slow and after 3 h, the spectrum corresponded essentially just to protonation of **11**. This had changed after 24 h to one showing signals expected for the rearrangement product **14** or possibly **15**, Scheme 3. The



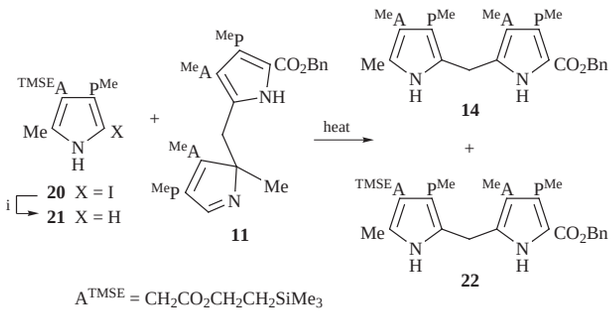
Scheme 3 Mechanism of the rearrangement of pyrrolenine **11**. *Reagents:* i, TsOH or heat; ii, pyridine, reflux; iii, KI_3, $NaHCO_3$; iv, PtO_2, H_2.

former could arise by fragmentation to yield the pyrrole **12** and azafulvene **13**, which could then recombine now with bonding to the free α-position of **12**; a far less likely possibility was that **14** could be formed by three [1,5]sigmatropic shifts of the pyrrolylmethyl group of **11**. Although the dipyrromethane **15** could only arise improbably by three [1,5] shifts of the quaternary methyl group of **11**, it had to be considered in the analysis.

The best conditions for the rearrangement were treatment of pyrrolenine **11** in degassed dichloromethane with one equivalent of toluene-*p*-sulfonic acid; a single product was isolated in 69% yield. This was rigorously identified as the dipyrromethane **14** by unambiguous synthesis of both **14** and **15** as shown in Scheme 3. Coupling of α-free pyrrole **12**[4] with acetoxymethylpyrrole[5] **19** was low-yielding under the normal mildly acidic conditions but worked well in hot pyridine[6] to afford dipyrromethane **14**, 52%, whilst the second dipyrromethane **15** was similarly prepared, 50%, by the reaction of **19** with α-free pyrrole **18**, prepared by the sequence **16**[5]→**17**→**18**.

The pyrrolenine **11** also underwent rearrangement thermally, though with greater general decomposition than in the foregoing experiments. The best conditions in solution involved heating **11** in degassed benzene at reflux for 24 h with one equivalent of proton sponge [1,8-bis(dimethylamino)naphthalene] to give the same rearrangement product **14** in 39% yield. Better still was to heat **11** neat as a thin film at 100 °C for 5 min under argon when the same single product **14** was formed in 59% isolated yield. The ^1H NMR spectrum of the entire material after the latter heating conditions showed that the product **14** made up at least 85% of the total.

The latter conditions were then used in an experiment to demonstrate formation of the azafulvene **13** in the rearrangement process by trapping it with an added different pyrrole; α-free pyrrole **21**, prepared as shown from the iodopyrrole[7] **20** (Scheme 4), was chosen because the change of esterifying group



Scheme 4 Crossover experiment to prove fragmentation of **11**. *Reagents:* i, PtO_2, H_2.

from methyl to trimethylsilylethyl should not affect the reactivity of the pyrrole but would make the respective products easily separable. Accordingly, equimolar quantities of the pyrrolenine **11** and the pyrrole **21** were dissolved together in toluene and the solvent evaporated. Heating the resultant film as above gave two products which were isolated and identified, one being the same dipyrromethane **14** as before, 28%, the other being dipyrromethane **22**, 39%, in which the azafulvene **13** had combined with the added pyrrole **21**. This result together with those above establish that fragmentation–recombination is by far the major pathway, and probably the sole pathway, for thermal rearrangement of the pyrrolenine **11**. The finding that the trapped product **22** is formed in greater yield is understandable since during the initial period of the reaction, the added pyrrole **21** will be present in greater amount than the pyrrole **12** produced by fragmentation.

Regioselectivity of the rearrangement of bis(pyrrolylmethyl)-pyrrolenines

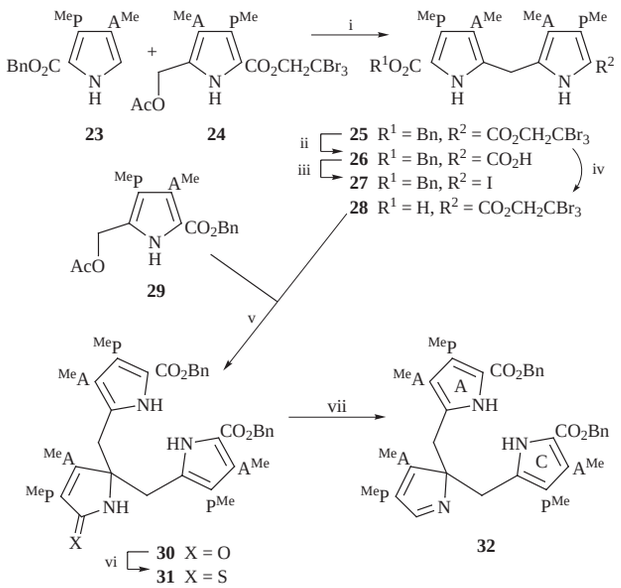
Looking back at Scheme 1, the most fascinating aspect of the idea that the spiro-system **2** is the key intermediate for the rearrangement process is the requirement for specific enzymic cleavage at *X* of **2** to produce uro'gen III **3** rather than at *Y*, which is mechanistically equivalent, to give uro'gen I **4**. The synthetic work described in the preceding paper[1] had provided a route to bis(pyrrolylmethyl)pyrrolenines, which closely match the structure and substitution pattern of the pyrrolenine system and rings A and C of the putative intermediate **2**. We therefore decided to test whether the arrangement of the acetate and propionate side-chains results in an intrinsic preference in the non-enzymic rearrangement process for cleavage of one pyrrolylmethyl group rather than the other, *e.g.* at *X* rather than at *Y* in Scheme 1. The pyrrolenine chosen for this study was **32**, which has the required unsymmetrical arrangement of acetate and propionate side-chains on the pyrrole rings and identical benzyloxycarbonyl deactivating groups (as we did not want any difference in these groups to influence the outcome).

Lactam **30**, required for the synthesis of pyrrolenine **32**, had not been made before, but corresponding lactams having a benzyl ester on one pyrrole and a tribromoethyl ester on the other pyrrole have been prepared.[1,5] The synthesis of lactam **30** followed an analogous route, **23** + **24**→**25**→**26**→**27** + **29**→**30**, as shown in Scheme 5. Having **25** available, the opportunity was taken to investigate whether the benzyl group could be removed in the presence of the tribromoethyl ester. Hydrogenolysis caused loss of bromine from the tribromoethyl group as well as cleavage of the benzyl ester. Trimethylsilyl iodide, however, was found to cleave the benzyl ester selectively to give acid **28**, which could be used in a synthesis of differentially protected dipyrrolic lactams related to **30**. The final steps in the synthesis

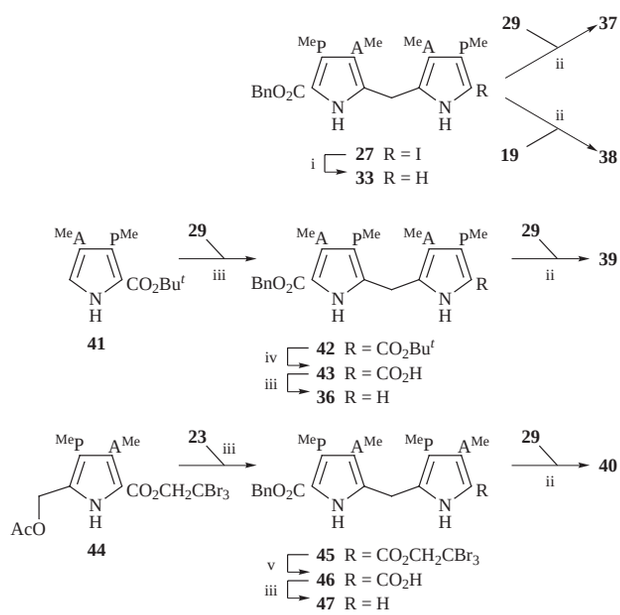
of pyrrolenine dibenzyl ester **32** were, as described in the preceding paper,[1] thionation of lactam **30** with Lawesson's reagent to yield **31** followed by reduction with nickel boride.

When **32** was treated with acid under the best conditions found for the rearrangement of monopyrrolic pyrrolenine **11**, a mixture of four tripyrroles was formed in a total yield of 67%. Bearing in mind the results from rearrangements of **11**, Schemes 3 and 4, these four tripyrroles were expected to be **37** from cleavage at *X* and recombination of the products, **40** from the analogous process at *Y* together with **38** and **39** arising from crossover recombinations, Scheme 6.

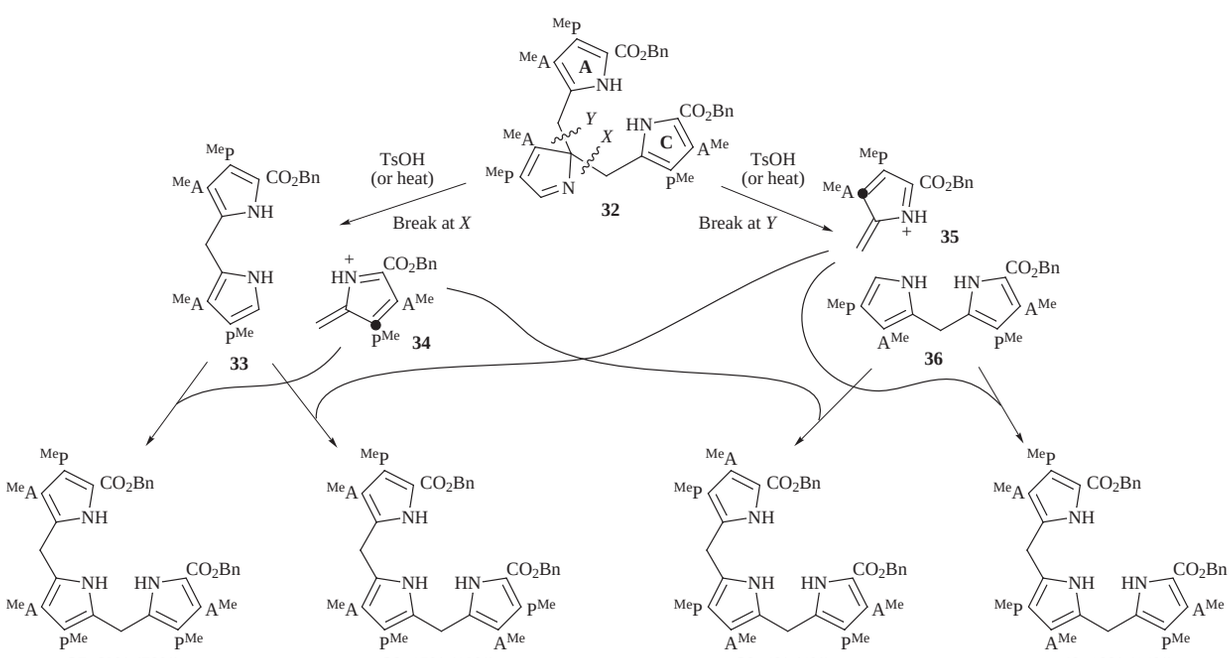
All four tripyrroles **37**–**40** were synthesised unambiguously by standard methods, as shown in Scheme 7. The final coupling of a dipyrromethane having an unsubstituted 2-position with an acetoxymethylpyrrole was carried out in boiling pyridine in each case.[6] All the tripyrroles were obtained pure in good to high yields (60–88%) and were distinguishable by ^{1}H NMR spectroscopy and separable by HPLC. This allowed three of the tripyrroles from the rearrangement of pyrrolenine **32** to be isolated in a pure state and rigorously identified by comparison with the synthetic samples. The percentages of these three in the total amount of tripyrroles produced was **37** 62%, **40** 19% and the crossover product **38** 15%. Only a small amount, 4%, of the other tripyrrole **39** from crossover recombination was formed; it was detected and its amount determined by ^{1}H NMR spectroscopy. All these percentages are shown by the figures not in brackets under the structures in Scheme 6. Finally, it was established that treatment of the four synthetic tripyrroles **37**–**40** separately under the acidic conditions used for the rearrangement experiments left all four unchanged. Thus, the foregoing percentages of the tripyrroles represent true proportions of products. It then follows that the product **37** (62%) from cleavage of **32** at *X* had been clearly favoured over **40** (19%) from breaking at *Y*. When the amounts of the crossover



Scheme 5 *Reagents:* i, TsOH; ii, Zn, AcOH; iii, KI_3, $NaHCO_3$; iv, Me_3SiI; v, $SnCl_4$ then AgOAc, H_3O^+; vi, Lawesson's reagent; vii, nickel boride



Scheme 7 *Reagents:* i, PtO_2, H_2; ii, pyridine, reflux; iii, TsOH; iv, $SnCl_4$; v, Zn, AcOH



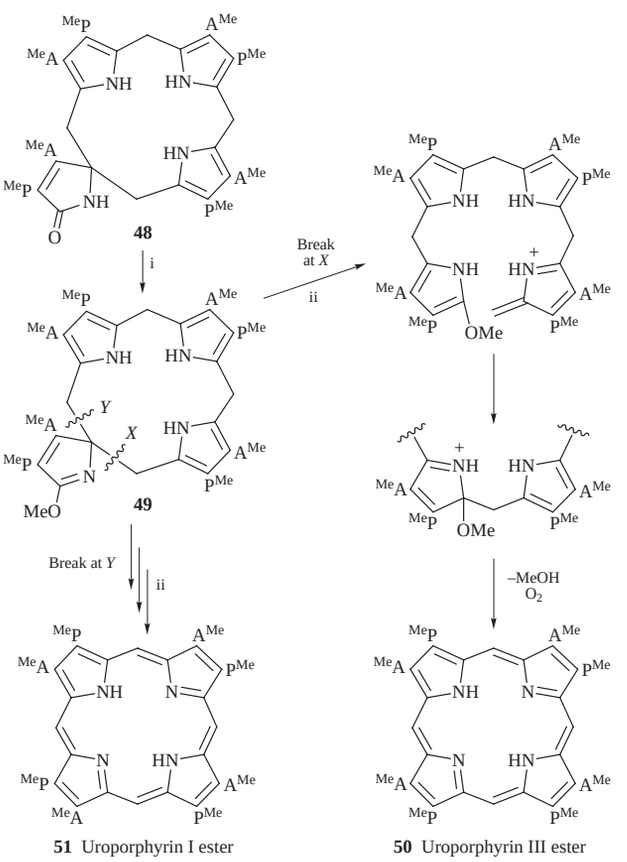
Scheme 6 Products from the rearrangement of pyrrolenine **32**. The percentage yields not in brackets are for the acid-catalysed rearrangement whereas the yields in brackets are for the thermal reaction.

products **38** and **39** are taken into account, it can be calculated that cleavage at *X*, Scheme 6, makes up *ca.* 70% of the total with the remaining *ca.* 30% occurring at *Y*. These values remained essentially unchanged when the acid-catalysed reaction was carried out in a variety of solvents ranging from toluene to methanol.

When the rearrangement of **32** was carried out thermally in boiling benzene, the same four tripyrroles were formed in a total yield of 60%; they were identified and their quantities were determined as before. Again, by far the major product, 70% of the total, was the tripyrrole **37** arising from cleavage at *X* and the proportions of the other tripyrroles are given in brackets under the relevant structures in Scheme 6. Allowing as before for the crossover products, there had been preferential cleavage at *X*, *ca.* 75%, rather than *Y*, *ca.* 25%.

The intriguing feature of these results is that the preferred fragmentation of the pyrrolenine **32**, which is intrinsic to the chemistry of the molecule, corresponds to the requirement for specific enzymic cleavage at *X* of the spiro-system **2**, Scheme 1, in order to form uro'gen III **3**. A reasonable explanation of the results from our non-enzymic experiments is that formation of the azafulvene **35** is disfavoured relative to the isomer **34** because the former carries an electron-withdrawing acetate group on an electron-deficient carbon (marked ●) rather than a propionate group in the latter.

Although it has not yet been possible to synthesise the spiro-pyrrolenine **2** as its octamethyl ester, we hoped that preparation of its methoxy derivative **49** (an imino ether) would allow the selectivity in the rearrangement of a very close analogue to be studied, Scheme 8. This material proved to be available in 60%



Scheme 8 Mechanism of the rearrangement of imino ether **49** to give uroporphyrins I and III, after oxidation. *Reagents:* i, Me_3OBF_4; ii, TsOH.

yield from spirolactam octamethyl ester **48**[5] by *O*-methylation with trimethyloxonium tetrafluoroborate and proton sponge. Treatment of this imino ether with one equivalent of toluene-*p*-sulfonic acid in CH_2Cl_2 for 16 h followed by aerial oxidation gave 71% of a mixture of products showing a UV/visible spectrum corresponding to the chromophore of uroporphyrin. The ^{1}H NMR spectrum, Fig. 1(a), proved that only the esters of uroporphyrin III **50**, 65% of the total, and uroporphyrin I **51**, 35% of the total, were present, formed as illustrated in Scheme 8. This striking result again demonstrates the intrinsic preference for cleavage at site *X* of **49** in a molecule very closely related structurally to the putative spiro-pyrrolenine **2**.

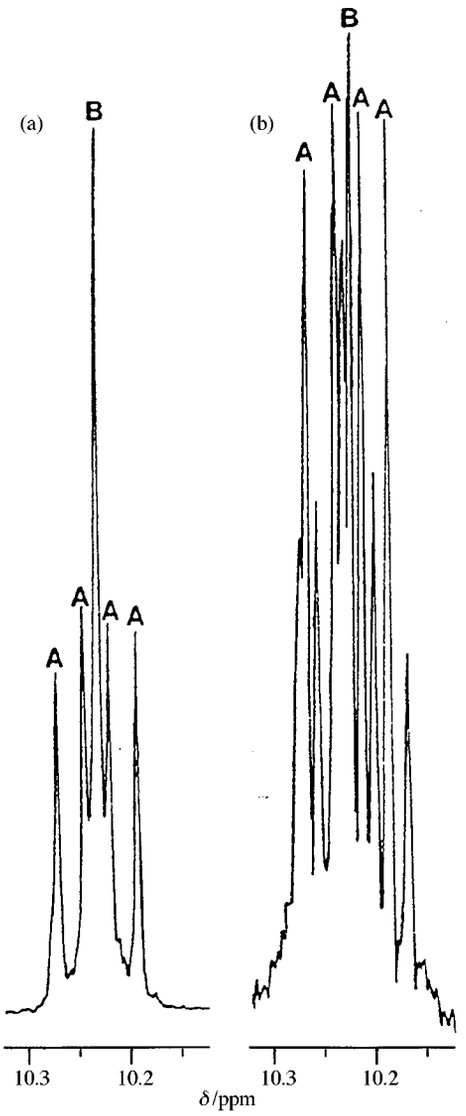


Fig. 1 The *meso*-proton regions of the 400 MHz NMR spectra ($CDCl_3$) of the octamethyl esters of (a) uroporphyrin I (marked B) and uroporphyrin III (marked A) produced by rearrangement of the imino ether **49** followed by aerial oxidation and (b) a statistical mixture of uroporphyrins I–IV (I, 12.5%; II, 12.5%; III, 50%; IV, 25%); the unmarked signals in (b) arise from the type II and IV isomers.

Conclusions

The probable involvement of a 2,2-disubstituted pyrrolenine (2*H*-pyrrole) in the biosynthesis of uro'gen III **3**, the parent of all the natural porphyrins, chlorins and corrins, has focused attention on the chemistry of such systems. In this paper we have investigated the rearrangements of model pyrrolenines carrying one or two pyrrolylmethyl groups at the disubstituted 2-position of the 3,4-disubstituted pyrrolenine ring. The results show that rearrangement of pyrrolylmethylpyrrolenines *e.g.* **32**, exactly as proposed for the biosynthetic step, occurs readily under both acid-catalysed and thermal conditions. By far the major route for the rearrangement is by a mechanism involving fragmentation–recombination; indeed, it is highly probable that

this is the sole route. No evidence was found implicating possible 1,5-sigmatropic shifts. In two cases where there was a choice between cleavage at one or other of two pyrrolylmethyl groups attached to the pyrrolenine, the preferred cleavage has been shown to correspond to the specific cleavage of pyrrolenine **2** that must occur if it is an intermediate in the biosynthesis of uro'gen III **3**, Scheme 1.

Taken together, the present research adds further strong support to the mechanism proposed for the biosynthesis of uro'gen III **3** by showing that all the chemistry involved is both feasible and facile.

Experimental

General directions

General directions are as in the preceding paper.[1]

1-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyldipyrromethane 14

A solution of α-free pyrrole **12**[4] (130 mg, 0.54 mmol) and acetoxymethylpyrrole **19**[5] (235 mg, 0.54 mmol) in pyridine was heated at reflux under argon for 24 h and then evaporated under reduced pressure. A solution of the residue in chloroform (20 cm^3) was washed with water (2 × 20 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography (20 × 2 cm column), eluting with hexane–diethyl ether (1:9), gave *dipyrromethane* **14** (170 mg, 52%) as a light-sensitive oil (Found: C, 62.6; H, 6.4; N, 4.8. $C_{32}H_{38}N_2O_{10}$ requires C, 62.9; H, 6.3; N, 4.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2960, 1730s, 1690, 1440 and 1070; $\delta_H(CDCl_3$, 250 MHz) 2.10 (3 H, s, 9-Me), 2.47 and 3.00 (each 2 H, t, *J* 7, CH_2CH_2), 2.59 and 2.75 (each 2 H, *J* 6, CH_2CH_2), 3.36 and 3.56 (each 2 H, s, CH_2CO_2), 3.51, 3.61, 3.64 and 3.74 (each 3 H, s, OMe), 3.86 (2 H, s, 5-H_2), 5.24 (2 H, s, CH_2Ph), 7.28–7.38 (5 H, m, Ph) and 9.12 and 9.84 (each 1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 62.5 MHz) 11.04 (9-Me), 18.96, 20.66, 22.07, 29.39, 30.55, 34.59 and 34.79 (CH_2), 51.33, 51.66 and 52.33 (OMe), 65.65 (CH_2), 109.45, 113.91, 116.12, 117.75, 123.00, 125.00, 130.04 and 133.78 (pyrrole-C), 128.00, 128.22 and 128.44 (phenyl-CH), 136.21 (phenyl-C) and 160.57, 172.83, 173.54, 174.30 and 174.87 (C=O); *m*/*z* (FD) 610 (M^+, 100%).

5-Iodo-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-2-methylpyrrole 17

A solution of pyrrole carboxylic acid **16**[5] (950 mg, 3.36 mmol) in dichloromethane (25 cm^3) was stirred vigorously with water (25 cm^3) containing sodium hydrogen carbonate (670 mg) while a solution of iodine (0.1 mol dm^{-3}) in aqueous potassium iodide (0.2 mol dm^{-3}; 40 cm^3) was added over 3 min. After a further 15 min, sodium metabisulfite was added to destroy excess iodine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by flash chromatography (20 × 2 cm), eluting with diethyl ether, gave *iodide* **17** (1.05 g, 86%) as an oil which was light-sensitive and unstable (Found: M^+, 365.0106. $C_{12}H_{16}INO_4$ requires *M*, 365.0083); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1725s, 1430 and 1050; $\delta_H(CDCl_3$, 400 MHz) 2.20 (3 H, s, 2-Me), 2.35–2.86 (4 H, m, CH_2CH_2), 3.40 (2 H, s, CH_2CO_2), 3.70 and 3.75 (each 3 H, s, OMe) and 8.06 (1 H, br s, NH); *m*/*z* 365 (M^+, 100%), 239, 238, 234, 166, 128 (100) and 108.

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-2-methylpyrrole 18

The iodopyrrole **17** (1.00 g, 2.74 mmol) was dissolved in methanol (30 cm^3) containing sodium acetate (800 mg) and Adams' catalyst (100 mg). The mixture was stirred under hydrogen until uptake ceased and the catalyst was then filtered off. Sodium hydrogen carbonate (200 mg) was added and the methanol was evaporated under reduced pressure. Water (100 cm^3) was added and the mixture was extracted with dichloromethane (5 × 25 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by flash chromatography (20 × 2 cm), eluting with diethyl ether, gave the α-*free pyrrole* **18** (479 mg, 73%) as a light-sensitive, unstable oil (Found: M^+, 239.1147. $C_{12}H_{17}NO_4$ requires *M*, 239.1157); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2970, 1750s, 1710, 1440, 1200 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.20 (3 H, s, 2-Me), 2.30–2.80 (4 H, m, CH_2CH_2), 3.45 (2 H, s, CH_2CO_2), 3.68 and 3.70 (each 3 H, s, OMe), 6.53 (1 H, d, *J* 3, 5-H) and 8.05 (1 H, br s, NH); *m*/*z* 239 (M^+, 30%), 195, 166, 122 (100) and 108 (40).

1-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-methyldipyrromethane 15

The α-free pyrrole **18** was reacted with acetoxymethylpyrrole **19**[5] using exactly the same procedure as employed in the synthesis of **14** to give the *dipyrromethane* **15** (50%) as a light-sensitive oil (Found: C, 62.5; H, 6.4; N, 4.8. $C_{32}H_{38}N_2O_{10}$ requires C, 62.9; H, 6.3; N, 4.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2960, 1720s, 1430 and 1070; $\delta_H(CDCl_3$, 250 MHz) 2.09 (3 H, s, 9-Me), 2.37 and 2.67 (each 2 H, t, *J* 7, CH_2CH_2), 2.50 and 3.02 (each 2 H, t, *J* 8, CH_2CH_2), 3.46 and 3.57 (each 2 H, s, CH_2CO_2), 3.58, 3.61, 3.64 and 3.74 (each 3 H, s, OMe), 3.76 (2 H, s, 5-H_2), 5.23 (2 H, s, C*H*Ph), 7.29–7.42 (5 H, m, Ph) and 9.08 and 10.19 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 11.04 (9-Me), 19.81, 20.52, 22.40, 29.42, 30.03, 34.86 and 35.59 (CH_2), 51.34, 52.17 and 52.28 (OMe), 65.63 (OCH_2), 110.38, 113.23, 115.80, 117.90, 123.60, 124.25, 130.03 and 133.87 (pyrrole-C), 127.95, 128.36 and 128.39 (phenyl-CH), 136.36 (phenyl-C), 160.43, 173.61, 173.68, 174.11 and 174.36 (C=O); *m*/*z* (FD) 610 (M^+, 100%).

Rearrangement of pyrrolenine 11

(a) Acid-catalysed. A solution of pyrrolenine **11** (29 mg, 48 μmol) in dry degassed acid-free dichloromethane (15 cm^3) was stirred with toluene-*p*-sulfonic acid monohydrate (9.1 mg, 48 μmol) at room temperature under argon in the dark for 18 h, then washed with 5% aqueous sodium hydrogen carbonate (2 × 10 cm^3) followed by water (10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the major product (20 mg, 69%) as a gum, having the same R_f value and infrared, mass and ^1H and ^{13}C NMR spectral properties as the pyrromethane **14** unambiguously synthesised above.

(b) Thermally in solution. A solution of pyrrolenine **11** (59 mg, 97 μmol) and 1,8-bis(dimethylamino)naphthalene (20 mg, 94 μmol) in dry degassed benzene (30 cm^3) was heated at reflux under argon in the dark for 12 h and then evaporated under reduced pressure. Purification by PLC gave the major product (23 mg, 39%), identical to an authentic sample of dipyrromethane **14**.

(c) Thermally as thin film. The pyrrolenine **11** (18 mg) was dissolved in dry degassed toluene and evaporated to form a thin film over the flask. This was heated under argon for 5 min at 100 °C and the product was purified by PLC using ethyl acetate–hexane (1:1) to give the dipyrromethane **14** (10.6 mg, 59%), again identified by direct comparison as earlier.

Crossover experiment using pyrrolenine 11 and α-free pyrrole 21

A solution of iodopyrrole **20**[7] in methanol (5 cm^3) was stirred with sodium acetate (64 mg) and Adams' catalyst (20 mg) under an atmosphere of hydrogen for 1 h at room temperature, then filtered and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–hexane (1:1), gave the α-*free pyrrole* **21** (60 mg, 77%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3475, 2955, 1727, 1252, 1173, 860 and 839; $\lambda_{max}(CH_2Cl_2)$/nm no absorption peak above 200; $\delta_H(CDCl_3$, 400 MHz) 0.01 (9 H, s, Me_3Si), 0.97 (2 H, t, *J* 9, CH_2Si), 2.18 (3 H, s, CMe), 2.56 and 2.75 (each 2 H, t, *J* 7, CH_2CH_2), 3.35 (2 H, s, CH_2CO_2), 3.68 (3 H, s, OMe), 4.14 (2 H, t, *J* 9, OCH_2), 6.39 (1 H, d, *J* 2, α-H) and 7.70 (1 H, br s,

NH); δ_C($CDCl_3$, 100 MHz) −1.6 ($SiMe_3$), 11.4 (C*Me*), 17.3 (CH_2Si), 20.8 ($CH_2CH_2CO_2$), 30.5 (CH_2CO_2), 34.9 ($CH_2CH_2CO_2$), 51.5 (OMe), 62.8 (OCH_2), 110.7, 112.6, 121.8 and 133.9 (pyrrole-C) and 172.5 (2 × CO_2); *m*/*z* (+FAB) 325 (M^+, 100%).

Pyrrolenine **11** (32 mg, 50 μmol) and α-free pyrrole **21** (18 mg, 50 μmol) were dissolved in dry, degassed toluene (5 cm^3) and then evaporated at 0 °C. The process was repeated three times and then the residue, which formed a clear film in the flask, was placed under argon and heated at 100 °C for 5 min. Purification by PLC, eluting with ethyl acetate–hexane (1 : 1), gave dipyrromethane **14** (9.0 mg, 28%) and, at higher R_f, *dipyrromethane* **22** (14.4 mg, 39%) as an amorphous solid (Found: M^+, 696.3140. $C_{36}H_{48}N_2O_{10}Si$ requires *M*, 696.3078); ν_{max}($CHCl_3$)/cm^{-1} 3343, 2954, 1729, 1438, 1252, 1172, 860 and 839; λ_{max}(CH_2Cl_2)/nm 283; δ_H($CDCl_3$, 400 MHz) 0.01 (9 H, s, Me_3Si), 0.97 (2 H, t, *J* 9, CH_2Si), 2.10 (3 H, s, CMe), 2.47, 2.61, 2.72 and 2.99 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.29 and 3.56 (each 2 H, s, CH_2CO_2), 3.51, 3.62 and 3.74 (each 3 H, s, OMe), 4.12 (2 H, t, *J* 9, C$H_2$$CH_2Si$), 5.23 (2 H, s, C$H_2$Ph), 7.25–7.37 (5 H, m, Ph) and 9.04 and 9.79 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) −1.5 ($SiMe_3$), 11.2 (C*Me*), 17.3 (CH_2Si), 18.9, 20.7 and 22.1 (2 × *C*$H_2CH_2CO_2$ and C-5), 29.5 and 31.0 (CH_2CO_2), 34.6 and 34.8 ($CH_2CH_2CO_2$), 51.2, 51.7 and 52.4 (OMe), 62.8 (*C*H_2CH_2Si), 65.7 (*C*H_2Ph), 109.6, 113.9, 116.2, 117.8, 123.0, 125.1, 130.1 and 133.9 (pyrrole-C), 128.1, 128.3, 128.5 and 136.2 (Ph), 160.8, 172.6, 173.6, 174.4 and 175.0 (C=O); *m*/*z* (+FAB) 696 (M^+, 95%), 605 (60) and 372 (100).

1-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-dipyrromethane 25

A solution of α-free pyrrole **23**[8] (412 mg, 1.15 mmol) and acetoxymethylpyrrole **24**[5] (696 mg, 1.15 mmol) in dichloromethane (15 cm^3) was stirred with toluene-*p*-sulfonic acid (40 mg, 0.20 mmol) at room temperature under argon for 3 h, then washed with saturated aqueous sodium carbonate (2 × 20 cm^3), dried and evaporated under reduced pressure. The residue was purified by flash chromatography (25 × 2 cm), eluting with diethyl ether–hexane (1 : 3), to give *dipyrromethane* **25** (1.04 g, 87%), which crystallised from diethyl ether–hexane, mp 136.5–137.5 °C (Found: C, 45.4; H, 4.2; N, 3.9. $C_{34}H_{37}Br_3N_2O_{12}$ requires C, 45.1; H, 4.1; N, 3.1%); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2970, 1720s, 1690, 1420, 1160, 1125 and 1050; δ_H($CDCl_3$, 400 MHz) 2.50, 2.58, 3.00 and 3.09 (each 2 H, t, *J* 8, 2 × CH_2CH_2), 3.58 and 3.59 (each 2 H, s, CH_2CO_2), 3.60, 3.60, 3.61 and 3.79 (each 3 H, s, OMe), 3.84 (2 H, s, 5-H_2), 5.06 and 5.23 (each 2 H, s, OCH_2), 7.27–7.39 (5 H, m, Ph) and 10.32 and 10.43 (each 1 H, br s, NH); *m*/*z* (FD) 902, 904, 906 and 908 (1 : 3 : 3 : 1, M^+, 100%).

1-Benzyloxycarbonyl-9-carboxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)dipyrromethane 26

A solution of tribromethyl ester **25** (8.94 g, 9.88 mmol) in glacial acetic acid (60 cm^3) was stirred with zinc dust (3.0 g) for 20 min, then filtered, mixed with water (200 cm^3) and extracted with dichloromethane (5 × 60 cm^3). The combined extracts were washed with water (100 cm^3), dried and evaporated under reduced pressure to give the acid **26** (5.75 g, 91%), mp 177–179 °C (from dichloromethane–diethyl ether) (lit.,[5] 178–180 °C); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 3500–2450, 1720s, 1680, 1445 and 1180; δ_H($CDCl_3$, 250 MHz) 2.48 and 2.55 (each 2 H, t, *J* 8) and 2.99 (4 H, m, 2 × CH_2CH_2), 3.54 and 3.57 (each 2 H, s, CH_2CO_2), 3.59, 3.61, 3.61 and 3.74 (each 3 H, s, OMe), 3.85 (2 H, s, 5-H_2), 5.24 (2 H, s, OCH_2), 7.25–7.40 (5 H, m, Ph) and 10.34 and 10.56 (each 1 H, br s, NH); *m*/*z* (FD) 640 (100%).

1-Benzyloxycarbonyl-9-iodo-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)dipyrromethane 27

Acid **26** (3.80 g, 6 mmol) was stirred vigorously with dichloromethane (60 cm^3) and water (60 cm^3) containing sodium hydrogen carbonate (3.0 g). A solution of iodine (0.1 mol dm^{-3}) in aqueous potassium iodide (0.2 mol dm^{-3}; 66 cm^3) was added over 3 min. After a further 20 min, sodium metabisulfite was added until the colour of the excess iodine was discharged. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 40 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification on a flash column (45 × 4 cm), eluting with hexane–diethyl ether (1 : 4), gave *iododipyrromethane* **27** (3.98 g, 92%) as needles, mp 129.5–130 °C (from diethyl ether–hexane) (Found: C, 51.7; H, 4.8; N, 3.9. $C_{31}H_{35}IN_2O_{10}$ requires C, 51.5; H, 4.9; N, 3.9%); ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1745s, 1710, 1590, 1440, 1175 and 1065; δ_H($CDCl_3$, 250 MHz) 2.40, 2.50, 2.65 and 3.02 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.53 (2 H, s, CH_2CO_2), 3.57 (5 H, s, CH_2CO_2 and OMe), 3.61 and 3.65 (each 3 H, s, OMe), 3.78 (5 H, s, OMe and 5-H_2), 5.24 (2 H, s, OCH_2), 7.25–7.42 (5 H, m, Ph) and 9.64 and 10.20 (each 1 H, br s, NH); δ_C($CDCl_3$, 62.5 MHz) 20.42, 22.01, 22.63, 29.36, 30.07 and 34.77 (7 × CH_2), 51.33, 51.42, 52.29 and 52.23 (OMe), 63.78 and 65.67 (OCH_2 and C=*C*–I), 127.94, 128.35 and 131.65 (phenyl-CH), 111.69, 113.36, 118.06, 125.26, 129.93, 132.93 and 136.20 (C=C), 160.32, 173.28, 173.55, 173.93 and 174.20 (C=O); *m*/*z* (FD) 722 (M^+, 100%).

1-Carboxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-dipyrromethane 28

A solution of diester **25** (100 mg, 0.11 mmol) in dry chloroform (2.5 cm^3) was stirred with trimethylsilyl iodide (1.5 cm^3) under argon in the dark for 6 h and then evaporated under reduced pressure. The residue was partitioned between chloroform (15 cm^3) and water (15 cm^3) and the water layer was extracted with chloroform (2 × 10 cm^3). The combined organic layers were washed with water (2 × 10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with ethanol–diethyl ether (1 : 9), gave *monoacid* **28** (45 mg, 50%) as crystals, mp 116–118 °C (from dichloromethane–diethyl ether–hexane) (Found: C, 39.7; H, 3.9; N, 3.4. $C_{27}H_{31}Br_3N_2O_{12}$ requires C, 39.8; H, 3.8; N, 3.4%); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 3400–2400, 1725s, 1680, 1450, 1250 and 1180; δ_H($CDCl_3$, 250 MHz) 2.56, 2.60, 3.01 and 3.10 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.57 and 3.60 (each 2 H, s, CH_2CO_2), 3.62, 3.62, 3.76 and 3.76 (each 3 H, s, OMe), 3.88 (2 H, s, 5-H_2), 5.07 (2 H, s, OCH_2) and 10.34 and 10.60 (1 H, br s, NH); *m*/*z* (FD) 812, 814, 816 and 818 (1 : 3 : 3 : 1, M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 30

A solution of iododipyrromethane **27** (750 mg, 1.04 mmol) and acetoxymethylpyrrole **29**[5] (448 mg, 1.04 mmol) in dry dichloromethane (10 cm^3) was stirred at 0 °C under argon with stannic chloride (290 mg, 130 μl, 1.1 mmol) for 20 min. Saturated aqueous sodium hydrogen carbonate (20 cm^3) was added and after 10 min the organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the residual oil in tetrahydrofuran (14 cm^3) and water (1.4 cm^3) was stirred with toluene-*p*-sulfonic acid monohydrate (277 mg, 1.45 mmol) and silver acetate (93 mg, 0.56 mmol) under argon for 7 h, then mixed with water (70 cm^3) and extracted with dichloromethane (4 × 20 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3) and then water (20 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography (25 × 2.5 cm), eluting with 0–1% ethanol in diethyl ether, gave *lactam* **30** (430 mg, 42%), which crystallized from methanol, mp 117.5–119 °C (Found: C, 62.0; H, 5.7; N, 4.2.

$C_{51}H_{57}N_3O_{17}$ requires C, 62.25; H, 5.8; N, 4.3%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2960, 1740s, 1695, 1435, 1250 and 1080; $\delta_H(CDCl_3$, 250 MHz) 2.32–2.54, 2.65–2.75 and 2.88–2.94 (12 H, m, 3 × CH_2CH_2), 2.38 and 3.13 (each 1 H, d, *J* 15, CH_2CCH$_2$), 2.79 and 3.00 (each 1 H, d, *J* 15, CH$_2$CCH_2), 3.38 (1 H, d, *J* 18, CH_AH$_B$CO$_2$), 3.48 (1 H, d, *J* 16, CH_AH$_B$CO$_2$), 3.54, 3.56, 3.57, 3.58, 3.62 and 3.73 (each 3 H, s, OMe), 3.54–3.73 (2 H, obscured, 2 × CH$_A$$H_BCO_2$), 3.72 and 3.82 (each 1 H, d, *J* 17, CH$_2$CO$_2$), 5.17 and 5.27 (each 2 H, d, *J* 12, 2 × CH_2Ph), 7.26–7.40 (10 H, m, Ph), and 7.49, 9.26 and 10.12 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 19.27, 19.69, 20.43, 29.22, 30.34, 30.58, 30.85, 32.54 and 34.69 (CH_2), 51.28, 51.41, 51.64, 51.70, 52.17 and 53.02 (OMe), 65.97 (C-4), 65.70 (*C*H$_2$Ph), 115.53, 118.24, 119.36, 122.16, 122.43, 127.75, 129.77, 136.05, 136.18, 138.17 and 149.01 (C=C), 128.04, 128.18, 128.27, 128.32, 128.39, 128.47 (phenyl-CH) and 160.24, 171.58, 171.67, 171.92, 173.15, 173.27 and 173.52 (C=O); *m*/*z* (FD) 983 (M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methyoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 31

The lactam **30** (400 mg, 0.44 mmol) was reacted with Lawesson's reagent (95 mg, 0.23 mmol) following the general procedure described in the preceding paper.[1] Purification by flash chromatography (20 × 2 cm), eluting with dichloromethane then 1% ethanol in diethyl ether, gave *thiolactam* **31** (270 mg, 70%) as a gum (Found: M^+, 999.3449. $C_{51}H_{57}N_3O_{16}S$ requires *M*, 999.3459); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3415, 3300, 2960, 1725, 1695, 1440, 1175 and 1090; $\delta_H(CDCl_3$, 250 MHz) 2.40–2.54 and 2.88–2.99 (10 H, m) and 2.69 (2 H, t, *J* 7, 3 × CH_2CH_2), 2.48 and 3.19 (each 1 H, d, *J* 16) and 2.88 and 3.09 (each 1 H, d, *J* 14, CH_2CCH_2), 3.36 (1 H, d, *J* 18, CH_AH$_B$-CO$_2$), 3.53 (1 H, d, *J* 17, CH_AH$_B$CO$_2$), 3.56, 3.59, 3.62, 3.63 and 3.72 (18 H, each s, 6 × OMe), 3.56–3.72 (2 H, obscured, 2 × CH$_A$$H_BCO_2$), 3.73 and 3.83 (each 1 H, d, *J* 17, CH$_2$CO$_2$), 5.16 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 5.18 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 7.28–7.38 (10 H, m, 2 × Ph) and 9.26, 9.39 and 10.09 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 19.23, 20.43, 20.73, 29.40, 30.59, 30.71, 31.45, 31.65, 34.64 and 34.70 (CH_2), 51.38, 51.45, 51.80, 52.45 and 53.07 (OMe), 65.81 (*C*H$_2$Ph), 73.64 (C-4), 115.23, 118.26, 119.41, 122.12, 122.51, 127.16, 130.01, 135.90, 136.09 and 147.32 (C=C), 127.92, 128.05, 128.14, 128.33 and 128.39 (phenyl-CH), 160.15, 171.66, 173.46, 173.55 and 173.68 (C=O) and 197.84 (C=S); *m*/*z* (FD) 999 (M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin 32

Thiolactam **31** (200 mg, 0.2 mmol) was reduced with nickel boride following the general procedure described in the preceding paper.[1] Purification by PLC, eluting with 1% ethanol in diethyl ether, gave *pyrrolenine* **32** (100 mg, 52%) as an oil (Found: M^+, 967.3719. $C_{51}H_{57}N_3O_{16}$ requires *M*, 967.3739); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2950, 1725s, 1685, 1440, 1250 and 1070; $\delta_H(CDCl_3$, 400 MHz) 2.31–2.50 and 2.91–2.95 (10 H, m) and 2.60 (2 H, t, *J* 8, 3 × CH_2CH_2), 2.33 and 3.17 (each 1 H, d, *J* 15, 4-CH$_2$), 2.37 and 3.12 (each 1 H, d, *J* 15, 4-CH$_2$), 3.31 and 3.39 (each 1 H, d, *J* 16, CH$_2$CO$_2$), 3.48 (2 H, s, CH$_2$CO$_2$), 3.55, 3.57, 3.58, 3.59 and 3.72 (18 H, each s, 6 × OMe), 3.66 and 3.83 (each 1 H, d, *J* 17, CH$_2$CO$_2$), 5.21 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 5.21 and 5.30 (each 1 H, d, *J* 12, CH_2Ph), 7.27–7.41 (10 H, m, Ph), 7.80 (1 H, s, 2-H) and 9.98 and 10.07 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.01, 20.43, 29.34, 29.79, 29.99, 30.50, 30.90, 32.20, 34.69, 34.84 and 35.24 (CH_2), 51.26, 51.43, 51.66, 51.78 and 52.83 (OMe), 65.44 (2 × OCH_2), 85.85 (C-4), 115.48, 117.09, 118.05, 121.79, 122.15, 128.97, 129.66, 129.78, 136.33, 140.39 and 155.94 (C=C), 127.90, 128.12 and 128.35 (phenyl-CH), 166.07 (C-2) and 160.28, 160.37, 171.16, 171.92, 172.22, 172.58, 173.34, 173.44 and 173.59 (C=O); *m*/*z* (FD) 967 (M^+, 100%).

1-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)dipyrromethane 33

A solution of iodide **27** (112 mg, 155 μmol) in methanol (10 cm^3) was stirred with Adams' catalyst (10 mg) and sodium acetate (100 mg) under an atmosphere of hydrogen until uptake of gas ceased (*ca.* 2 h), then filtered and evaporated under reduced pressure. The residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3) and the aqueous layer was further extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the α-*free pyrromethane* **33** (62 mg, 67%) as a light-sensitive gum (Found: M^+, 596.2351. $C_{31}H_{36}N_2O_{10}$ requires *M*, 596.2370); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2950, 1730, 1690, 1430, 1250 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.47–2.53 (4 H, m), 2.72 (2 H, t, *J* 8) and 3.00 (2 H, t, *J* 8, 2 × CH_2CH_2), 3.49 and 3.64 (each 2 H, s, CH_2CO_2), 3.57, 3.57, 3.60 and 3.74 (each 3 H, s, OMe), 3.79 (2 H, s, 5-H$_2$), 5.23 (2 H, s, CH_2Ph), 6.42 (1 H, d, *J* 2, 9-H), 7.26–7.40 (5 H, m, Ph) and 9.35 and 10.20 (each 1 H, br s, NH); *m*/*z* (FD) 596 (M^+, 100%).

1,14-Bis(benzyloxycarbonyl)-2,8,12-tris(2-methoxycarbonylethyl)-3,7,13-tris(methoxycarbonylmethyl)-5,10,15,17-tetrahydrotripyrrin 37

A solution of α-free dipyrromethane **33** (29 mg, 49 μmol) and acetoxymethylpyrrole **29**[5] (21 mg, 49 μmol) in pyridine (3 cm^3) was heated at reflux under argon in the dark for 16 h and then evaporated under reduced pressure. A solution of the residue in chloroform (10 cm^3) was washed with water (2 × 10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–hexane (3:2), gave the *tripyrrole* **37** (28.5 mg, 61%) which crystallised from ether–hexane, mp 114–116 °C (Found: C, 63.6; H, 6.1; N, 4.6. $C_{51}H_{57}N_3O_{16}$ requires C, 63.3; H, 5.9; N, 4.3%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 3040, 2950, 1730s, 1690, 1435, 1250 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.32–2.42 (4 H, m), 2.48 (2 H, t, *J* 8), 2.65–2.75 (4 H, m) and 2.99 (2 H, t, *J* 7, 3 × CH_2CH_2), 3.43, 3.51, 3.72, 3.75 and 3.79 (each 2 H, s, 5-H$_2$, 10-H$_2$ and 3 × CH_2CO_2), 3.54, 3.55, 3.58, 3.59, 3.60 and 3.62 (each 3 H, s, OMe), 5.19 and 5.22 (each 2 H, s, CH_2Ph), 7.27–7.41 (10 H, m, 2 × Ph) and 9.17, 9.37 and 10.14 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 19.29, 19.49, 20.8, 22.7, 23.0, 29.38, 30.03, 30.70, 34.80, 34.89 and 35.24 (CH_2), 51.28, 51.42, 51.47, 51.71, 52.18 and 52.38 (OMe), 65.63 (2 × OCH_2), 110.8, 113.7, 117.1, 118.2, 118.6, 121.0, 123.0, 124.1, 126.4, 130.02, 131.99 and 133.9 (pyrrole-C), 127.9, 128.04, 128.16, 128.20, 128.29 and 128.40 (phenyl-CH), 136.3 (2 × phenyl-C) and 160.9, 161.1, 171.86, 173.39, 173.54, 173.75, 174.03 and 174.16 (C=O); *m*/*z* (FD) 967 (M^+, 100%).

1,14-Bis(benzyloxycarbonyl)-2,7,13-tris(2-methoxycarbonylethyl)-3,8,12-tris(methoxycarbonylmethyl)-5,10,15,17-tetrahydrotripyrrin 38

Acetoxymethylpyrrole **19**[5] and α-free dipyrromethane **33** were reacted exactly as in the synthesis of **37** to give the *tripyrrole* **38** (65%), which crystallised from diethyl ether–hexane, mp 83–85 °C (Found: C, 63.2; H, 6.2; N, 4.6. $C_{51}H_{57}N_3O_{16}$ requires C, 63.3; H, 5.9; N, 4.3%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 3040, 2950, 1730, 1695, 1440, 1250 and 1160; $\delta_H(CDCl_3$, 400 MHz) 2.44–2.50 (6 H, m), 2.69 (2 H, t, *J* 7) and 2.94–2.98 (4 H, m, 3 × CH_2CH_2), 3.39, 3.48 and 3.52 (each 2 H, s, CH_2CO_2), 3.53, 3.56, 3.57, 3.59, 3.60 and 3.61 (each 3 H, s, OMe), 3.73 and 3.80 (each 2 H, s, 5-H$_2$ and 10-H$_2$), 5.22 and 5.23 (each 2 H, s, CH_2Ph), 7.29–7.39 (10 H, m, 2 × Ph) and 9.44, 9.58 and 9.93 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.01, 20.44, 20.55, 22.26, 22.38, 29.24, 29.33, 30.03, 34.65 and 34.70 (CH_2), 51.25, 51.27, 51.57, 52.02, 52.09 and 52.11 (OMe), 65.52 and 65.60

(OCH_2), 110.24, 113.47, 113.98, 116.02, 117.53, 124.20, 125.49, 129.93, 130.00, 133.21 and 133.34 (pyrrole-C), 127.87, 127.97, 128.10, 128.17, 128.29 and 128.36 (phenyl-CH), 136.06 and 136.16 (phenyl-C) and 160.45, 160.56, 173.22, 173.43, 173.50, 173.54, 173.72 and 174.28 (C=O); *m*/*z* (FD) 967 (M^+, 100%).

1-Benzyloxycarbonyl-9-*tert*-butoxycarbonyl-3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)dipyrromethane 42

Acetoxymethylpyrrole **29**[5] was reacted with α-free pyrrole **41**[9] using the same procedure as described below for the synthesis of **45**. Purification by flash chromatography, eluting with hexane–diethyl ether (1:4), gave the *dipyrromethane* **42** (86.5%) as a foam (Found: M^+, 696.2906. $C_{36}H_{44}N_2O_{12}$ requires *M*, 696.2894); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 3000, 2960, 1725s, 1685s, 1430, 1200 and 1040; $\delta_H(CDCl_3$, 400 MHz) 1.51 (9 H, s, Bu^t), 2.48, 2.57, 2.77 and 2.94 (each 2 H, t, *J* 8, 2 × CH_2CH_2), 3.46, 3.79 and 3.91 (each 2 H, s, 2 × CH_2CO_2 and 5-H_2), 3.58, 3.61, 3.64 and 3.72 (each 3 H, s, OMe), 5.22 (2 H, s, CH_2Ph), 7.26–7.38 (5 H, m, Ph) and 9.66 and 10.10 (each 1 H, br s, NH); *m*/*z* (FD) 696 (M^+, 100%).

1-Benzyloxycarbonyl-9-carboxy-3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)dipyrromethane 43

A solution of dipyrromethane diester **42** (770 mg, 1.11 mmol) in dry dichloromethane (20 cm^3) was stirred at 0 °C under argon with stannic chloride (140 μl, 1.11 mmol) for 2 h and then 10% aqueous sodium acetate (20 cm^3) was added. After a further 10 min, the organic layer was separated and the aqueous layer was extracted with dichloromethane (6 × 15 cm^3). The combined organic layers were washed with brine (2 × 25 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with 0–5% methanol in diethyl ether, gave *acid* **43** (615 mg, 87%) as crystals, mp 176–178 °C (from dichloromethane–diethyl ether) (Found: C, 59.3; H, 5.6; N, 4.3. $C_{32}H_{36}N_2O_{12}$·0.5 H_2O requires C, 59.2; H, 5.7; N, 4.3%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3500–2450, 1725s, 1690, 1445 and 1180; $\delta_H(CDCl_3$, 400 MHz) 2.53–2.57 (4 H, m), 2.79 (2 H, t, *J* 8) and 3.00 (2 H, t, *J* 8, 2 × CH_2CH_2), 3.54, 3.63, 3.63 and 3.68 (each 3 H, s, OMe), 3.54, 3.76 and 3.94 (each 2 H, s, 2 × CH_2CO_2 and 5-H_2), 5.23 (2 H, s, CH_2Ph), 7.27–7.37 (5 H, m, Ph) and 10.34 and 10.67 (each 1 H, br s, NH); *m*/*z* (FD) 640 (M^+, 100%).

1-Benzyloxycarbonyl-3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)dipyrromethane 36

Acid **43** was decarboxylated using the procedure described below for its isomer **46**. Purification by PLC, eluting with hexane–diethyl ether (1:9), gave the α-*free dipyrromethane* **36** (82%) as a light-sensitive gum (Found: M^+, 596.2383. $C_{31}H_{36}N_2O_{10}$ requires *M*, 596.2370); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2960, 1720s, 1440 and 1070; $\delta_H(CDCl_3$, 400 MHz) 2.52, 2.58, 2.72 and 2.79 (each 2 H, t, *J* 8, 2 × CH_2CH_2), 3.48, 3.80 and 3.86 (each 2 H, s, 2 × CH_2CO_2 and 5-H_2), 3.58, 3.60, 3.62 and 3.66 (each 3 H, s, OMe), 5.22 (2 H, s, CH_2Ph), 6.43 (1 H, d, *J* 2, 9-H), 7.28–7.38 (5 H, m, Ph) and 8.84 and 10.06 (each 1 H, br s, NH); *m*/*z* (FD) 596 (M^+, 100%).

1,14-Bis(benzyloxycarbonyl)-3,7,12-tris(2-methoxycarbonylethyl)-2,8,13-tris(methoxycarbonylmethyl)-5,10,15,17-tetrahydrotripyrrin 39

Acetoxymethylpyrrole **29**[5] and α-free dipyrromethane **36** were reacted exactly as in the synthesis of **37** to give the *tripyrrole* **39** (65%) as a gum (Found: M^+, 967.3758. $C_{51}H_{57}N_3O_{16}$ requires *M*, 967.3739); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2950, 1730s, 1690, 1440, 1250 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.38–2.48 and 2.67–2.74 (12 H, m, 3 × CH_2CH_2), 3.42, 3.75, 3.77 and 3.79 (10 H, each s, 5-H_2, 10-H_2 and 3 × CH_2CO_2), 3.52, 3.54, 3.56, 3.57 and 3.60 (18 H, each s, 6 × OMe), 5.11 (4 H, br s, 2 × CH_2Ph), 7.26–7.31 (10 H, m, 2 × Ph), 8.99, 9.49 and 10.08 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 19.08, 19.30, 19.56, 22.41, 22.64, 30.12, 30.72, 30.80, 34.64, 34.76 and 35.17 (CH_2), 51.48, 51.53, 51.61, 52.06 and 53.31 (OMe), 65.54 and 65.62 (OCH_2), 111.28, 117.27, 118.43, 118.68, 119.73, 120.33, 122.77, 123.00, 123.62, 125.43, 132.12 and 132.31 (pyrrole-C), 127.87, 127.97, 128.04, 128.32 and 128.39 (phenyl-CH), 136.33 and 136.42 (phenyl-C) and 160.72, 171.80, 171.86, 173.52, 173.58 and 174.06 (C=O); *m*/*z* (FD) 967 (M^+, 100%).

1-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-dipyrromethane 45

A solution of α-free pyrrole **23**[8] (315 mg, 877 μmol) and acetoxymethylpyrrole **44**[5] (530 mg, 875 μmol) in dry dichloromethane (15 cm^3) was stirred with toluene-*p*-sulfonic acid (17 mg, 88 μmol) at room temperature under argon for 3 h, then washed with 10% aqueous sodium hydrogen carbonate (15 cm^3) followed by water (15 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with diethyl ether–hexane (3:2), gave the *dipyrromethane* **45** (710 mg, 89.8%). An analytical sample was crystallised from methanol, mp 124.5–125.5 °C (Found: C, 44.9; H, 4.2; N, 2.85%; M^+, 901.9895. $C_{34}H_{37}Br_3N_2O_{12}$ requires C, 45.1; H, 4.1; N, 3.1%; *M*, 901.9897); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3430, 3350, 2950, 1725s, 1430, 1230, 1175, 1130, 1080 and 1040; $\delta_H(CDCl_3$, 250 MHz) 2.47 and 3.00 (each 2 H, t, *J* 8, CH_2CH_2), 2.58 and 2.78 (each 2 H, t, *J* 7, CH_2CH_2), 3.52, 3.61, 3.65 and 3.79 (each 3 H, s, OMe), 3.58 (2 H, s, CH_2CO_2), 3.94 and 3.97 (each 2 H, s, CH_2CO_2 and 5-H_2), 5.05 and 5.24 (each 2 H, s, CH_2CBr_3 and CH_2Ph), 7.28–7.37 (5 H, m, Ph) and 9.29 and 10.29 (each 1 H, br s, NH); *m*/*z* (FD) 902, 904, 906 and 908 (1:3:3:1, M^+, 100%).

1-Benzyloxycarbony-9-carboxy-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)dipyrromethane 46

A solution of diester **45** (500 mg, 0.55 mmol) in glacial acetic acid (10 cm^3) was stirred with zinc dust (200 mg) for 20 min under argon and then filtered. The filtrate was mixed with water (250 cm^3) and extracted with chloroform (5 × 50 cm^3). The combined extracts were washed with water (2 × 200 cm^3), dried and evaporated under reduced pressure to give the *carboxylic acid* **46** (330 mg, 93%), mp 155–156 °C (from methanol) (Found: C, 60.3; H, 5.7; N, 4.25. $C_{32}H_{36}N_2O_{12}$ requires C, 60.0; H, 5.7; N, 4.4%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3500–2600, 3010, 1720s, 1680, 1440, 1200s and 1040; $\delta_H(CDCl_3$, 250 MHz) 2.45 and 2.74 (each 4 H, t, *J* 7, 2 × CH_2CH_2), 3.59 (2 H, s, CH_2CO_2), 3.59, 3.59, 3.67 and 3.71 (each 3 H, s, OMe), 3.82 and 3.95 (each 2 H, s, CH_2CO_2 and 5-H_2), 5.27 (2 H, s, CH_2Ph), 7.29–7.38 (5 H, m, Ph) and 10.54 and 10.80 (each 1 H, br s, NH); *m*/*z* (FD) 640 (M^+, 100%).

1-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)dipyrromethane 47

A solution of carboxylic acid **46** (300 mg, 0.31 mmol) in dry chloroform (15 cm^3) was stirred with toluene-*p*-sulfonic acid (10 mg, 0.05 mmol) at room temperature under argon for 18 h and then evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the α-*free dipyrromethane* **47** (155 mg, 84%) as a gum (Found: M^+, 596.2372. $C_{31}H_{36}N_2O_{10}$ requires *M*, 596.2370); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2950, 1720s, 1680, 1430, 1250, 1170 and 1070; $\delta_H(CDCl_3$, 250 MHz) 2.47, 2.59, 2.78 and 2.99 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.41 and 3.56 (each 2 H, s, CH_2CO_2), 3.50, 3.61, 3.66 and 3.74 (each 3 H, s, OMe), 3.88 (2 H, s, 5-H_2), 5.23 (2 H, s, CH_2Ph), 6.56 (1 H, d, *J* 2, 9-H), 7.28–7.38 (5 H, m, Ph) and 9.36 and 9.85 (each 1 H, br s, NH); *m*/*z* (FD) 596 (M^+, 100%).

1,14-Bis(benzyloxycarbonyl)-2,7,12-tris(2-methoxycarbonylethyl)-3,8,13-tris(methoxycarbonylmethyl)-5,10,15,17-tetrahydrotripyrrin 40

Acetoxymethylpyrrole **29**[5] and α-free dipyrromethane **47** were reacted exactly as in the synthesis of **37** to give the *tripyrrole*

40 (88%), which crystallised from diethyl ether–hexane, mp 94–96 °C (Found: C, 63.1; H, 6.2; N, 4.3. $C_{51}H_{57}N_3O_{16}$ requires C, 63.3; H, 5.9; N, 4.3%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 3040, 2950, 1720s, 1690, 1430, 1250 and 1160; $\delta_H(CDCl_3$, 400 MHz) 2.40, 2.45, 2.54, 2.71, 2.75 and 2.96 (each 2 H, t, *J* 7, 3 × CH_2CH_2), 3.37, 3.50, 3.76, 3.76 and 3.81 (each 2 H, s, 5-H_2, 10-H_2 and 3 × CH_2CO_2), 3.51, 3.55, 3.58, 3.60, 3.61 and 3.64 (each 3 H, s, OMe), 5.20 and 5.22 (each 2 H, s, 2 × CH_2Ph), 7.27–7.36 (10 H, m, 2 × Ph) and 9.48, 9.73 and 9.80 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 18.97, 19.03, 20.57, 22.10, 22.40, 29.34, 30.20, 30.63, 34.57, 34.68 and 34.92 (CH_2), 51.32, 51.44, 51.65, 52.10 and 52.43 (OMe), 65.46 and 65.63 (OCH_2), 110.61, 113.93, 116.03, 117.65, 118.26, 119.97, 124.56, 125.09, 130.00, 132.19 and 133.36 (pyrrole-C), 127.88, 128.00, 128.13, 128.20, 128.28 and 128.40 (phenyl-CH), 136.10 and 136.26 (phenyl-C) and 160.61, 172.00, 173.46, 173.49, 173.57, 174.33 and 174.58 (C=O); *m*/*z* (FD) 967 (M^+, 100%).

Rearrangement of pyrrolenine 32

(a) Acid-catalysed. Pyrrolenine **32** was treated with toluene-*p*-sulfonic acid exactly as described above for **11**. Purification by PLC, eluting with ethyl acetate–hexane (3:2), gave a mixture of tripyrroles (67%). These were separated and identified by HPLC on a semi-preparative Kontron S5W silica gel column, eluting with ethyl acetate–hexane (7:3). By comparison with the authentic samples synthesised above they were shown to be **37** 62%, **40** 19%, **38** 15% and **39** 4%. Isomer ratios in the mixture were determined from both ^{1}H NMR and HPLC peak areas.

(b) Thermal. Pyrrolenine **32** was heated at reflux in benzene exactly as described above for **11**. Purification and analysis as above gave the tripyrrole mixture (60%) with isomer ratios: **37** 70%, **40** 14%, **38** 12% and **39** 4%.

1-Methoxy-2,8,13,18-tetrakis(2-methoxycarbonylethyl)-3,7,12,17-tetrakis(methoxycarbonylmethyl)-4,19-methylene-4,5,10,15,23,24-hexahydro-22*H*-bilin 49 and its acid-catalysed rearrangement

A mixture of the spirolactam octamethyl ester **48** (30 mg), dried trimethyloxonium tetrafluoroborate (15 mg) and 1,8-bis-(dimethylamino)naphthalene (40 mg) was stirred in dry dichloromethane (2 ml) under argon for 5 h and then evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave the *imino ether* **49** (60%) as a gum, which was stored at −23 °C under argon to reduce decomposition; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 1730, 1690 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.15–2.75 (16 H, m, 4 × CH_2CH_2), 2.10 and 2.91 (each 1 H, d, *J* 15, 4-CH_2), 2.10 and 2.97 (each 1 H, d, *J* 15, 4-CH_2), 3.31 (1 H, d, *J* 17, C$H_A$$H_B$$CO_2$), 3.33 (1 H, d, *J* 16, C$H_A$$H_B$$CO_2$), 3.39 and 3.49 (each 2 H, s, CH_2CO_2), 3.60, 3.63, 3.64, 3.65, 3.66, 3.70 and 3.71 (27 H, each s, 9 × OMe), 3.60–3.71 (6 H, obscured, 10-H_2, 15-H_2 and 2 × $CH_A$$H_B$$CO_2$), 7.49, 8.42 and 8.46 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.32, 19.57, 19.63, 22.22, 29.41, 29.67, 30.40, 31.15, 31.59, 31.95, 32.09, 35.52, 35.92 and 36.22 (CH_2), 51.37, 51.55, 51.66, 51.74, 51.90, 52.00, 52.37 and 54.81 (OMe), 77.63 (C-4), 107.77, 109.76, 110.32, 110.95, 115.70, 116.81, 117.33, 119.91, 124.52, 125.16, 126.15, 127.18, 127.44 and 129.96 (C=C), 161.61 (C-2) and 169.61, 171.79, 172.64, 172.90, 173.09, 173.43, 173.68 and 173.91 (C=O); *m*/*z* (FD) 978 (M^+, 100%).

A solution of **49** (2.5 mg) in dry degassed dichloromethane (1 cm^3) was stirred under argon at room temperature with toluene-*p*-sulfonic acid (0.5 mg) for 16 h. Air was then allowed to enter and the solution was exposed to light to allow complete oxidation to uroporphyrins. The solution was washed with aqueous sodium hydrogen carbonate and then water, then dried and evaporated under reduced pressure. ^{1}H NMR spectroscopy (Fig. 1) showed that the mixture was composed of uroporphyrin III and I esters, **50** and **51**, 65 and 35% respectively.

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