Ring Syntheses of the Four *N*-Methylprotoporphyrin Isomers and of Related *N*-Methyl and *N,N'*-Dimethylporphyrins

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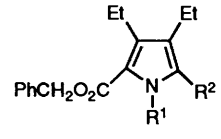
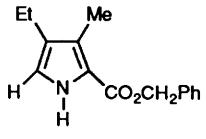
Total syntheses of the four isomeric *N*-methylprotoporphyrin IX dimethyl esters have been achieved by the MacDonald and tripyrrene/*a,c*-biladiene routes using appropriate *N*-methylpyrroles and *N*-methyldipyrromethanes as intermediates. The syntheses of related *N*-methyl and *N,N'*-dimethylporphyrins have also been achieved by the MacDonald route.

A variety of *N*-substituted porphyrins have recently been isolated from mammalian liver where they arise by suicide inactivation of cytochrome P450.[1–3] These are formed either by direct *N*-alkylation of the heme of the enzyme, or by an oxidative alkylation process involving olefinic or acetylenic drugs and other materials. The *N*-alkyl derivatives of protoporphyin-IX have attracted considerable biochemical and pharmacological interest because they are inhibitors of the enzyme ferrochelatase which inserts iron into protoporphyrin IX during heme biosynthesis. The *N*-methylated pigments appear to be the most effective inhibitors, the effects diminishing with larger alkyl groups, and they have also been used in studies of the biosynthetic pathways to hemes, chlorophylls, and algal bile pigments.[4]

Prior to the present work, *N*-methylated porphyrins have been synthesised from the parent porphyrins by direct alkylation with methyl iodide, or better with methyl fluorosulphonate,[5] but this leads not only to mixtures of mono-, di- and tri-*N*-methylporphyrins, but also to mixtures of isomers with unsymmetrical porphyrins. Polyalkylation can be minimised by carrying out the reactions in the presence of acetic acid,[6] which protonates the highly basic *N*-methylporphyrins and hence prevents further alkylation, but mixtures of isomers are still formed, as in the case of protoporphyin IX. These isomers have been separated by high performance liquid chromatography (HPLC),[7] but the production of even a few milligrams of each isomer is a tedious and time-consuming process. For this reason, and to facilitate pharmacological studies with individual isomers, we sought an alternative approach to isomerically pure *N*-alkylporphyrins by a total synthesis from *N*-substituted pyrroles.



1a; R^1 = H, R^2 = Me
1b; R^1 = R^2 = Me
1c; R^1 = Me, R^2 = CH_2OAc



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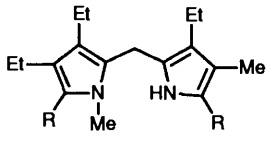
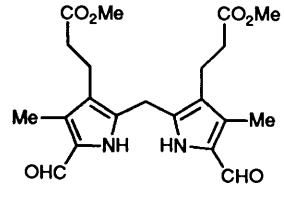


3a; R = CO_2CH_2Ph
3b; R = CO_2H



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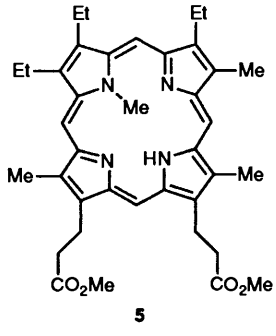

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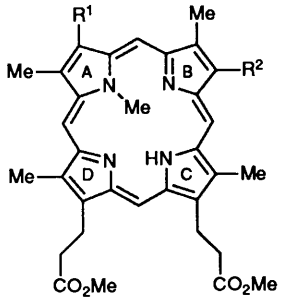
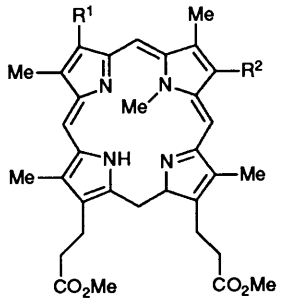
Syntheses using the MacDonald Approach.—Preliminary experiments had shown that copolymerisation of an acetoxymethylpyrrole and its *N*-methyl analogue led to formation of *N*-methylporphyrin in moderate yield, together with the parent *N*-unsubstituted porphyrin.[8] While this method was clearly unsuitable for synthesis of specific unsymmetrical *N*-substitued porphyrins, it nevertheless augured well for the success of more rational syntheses through open chain di-, tri- and tetra-pyrrolic intermediates.

Initially, we turned to the MacDonald route because of the mild conditions which are used throughout, especially in the cyclisation step.[9] We synthesised the model *N*-methylporphyrin **5**[10] because the appropriate pyrroles were to hand, to assess the feasibility of the synthesis. Thus, *N*-methylation of the pyrrole **1a** with methyl iodide–dimethyl sulphoxide (DMSO) in presence of base and subsequent treatment with lead tetraacetate afforded the acetoxymethylpyrrole **1c** in very good yield. Condensation of the latter with the α-free pyrrole **2** in the presence of toluene-*p*-sulphonic acid[9b] or clay[11a] then gave the desired mono-*N*-methyldipyrromethane **3a** which was hydrogenated over palladised charcoal to give the corresponding dicarboxylic acid **3b**. The latter was coupled with the 5,5'-diformyldipyrromethane **4**[12,13] in dichloromethane containing toluene-*p*-sulphonic acid as catalyst, and the product was aerated in the presence of zinc(II) acetate. Isolation, reesterification (5% H_2SO_4 in methanol) and chromatographic purification afforded the target *N*-methylporphyrin **5** in 20% overall yield from the dipyrromethanes. The structure of this porphyrin was readily confirmed by its NMR, mass and visible spectra, and by its behaviour upon treatment with acid (*i.e.* the successive formation of the mono- and di-cationic species).

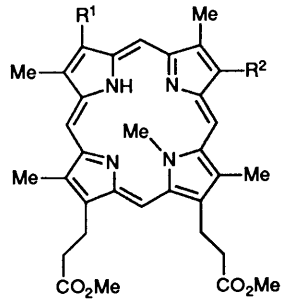
† Deceased, 12th September 1990.



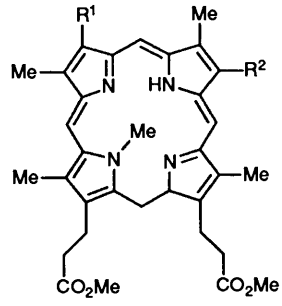
6a; $R^1 = R^2 = CH{=}CH_2$
6b; $R^1 = R^2 = CH_2CH_2Cl$



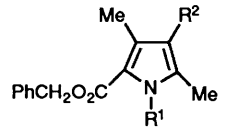
7a; $R^1 = R^2 = CH{=}CH_2$
7b; $R^1 = R^2 = CH_2CH_2Cl$



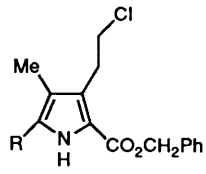
8a; $R^1 = R^2 = CH{=}CH_2$
8b; $R^1 = R^2 = CH_2CH_2Cl$
8c; $R^1 = R^2 = CH_2CH_2OH$



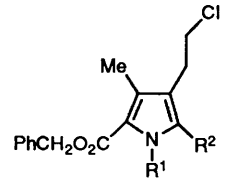
9a; $R^1 = R^2 = CH{=}CH_2$
9b; $R^1 = R^2 = CH_2CH_2Cl$
9c; $R^1 = R^2 = CH_2CH_2OH$



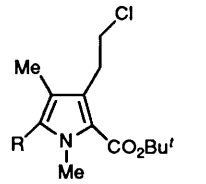
10a; $R^1 = H$, $R^2 = CH_2CO_2Me$
10b; $R^1 = Me$, $R^2 = CH_2CO_2Me$
10c; $R^1 = Me$, $R^2 = CH_2CH_2OH$
10d; $R^1 = Me$, $R^2 = CH_2CH_2Cl$



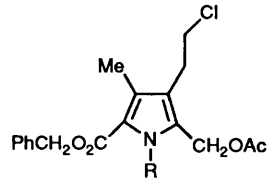
11a; R = Me
11b; R = CO_2H
11c; R = I
11d; R = H



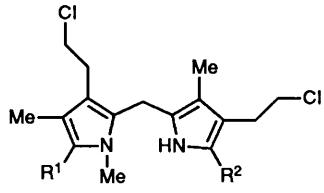
12a; $R^1 = H$, $R^2 = Me$
12b; $R^1 = H$, $R^2 = CO_2Bu^t$
12c; $R^1 = Me$, $R^2 = CO_2Bu^t$



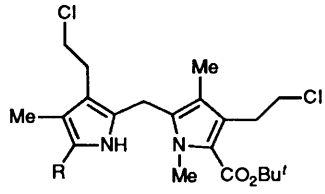
13a; R = CO_2H
13b; R = I
13c; R = H



14a; R = Me
14b; R = H



15a; $R^1 = R^2 = CO_2CH_2Ph$
15b; $R^1 = R^2 = CO_2H$



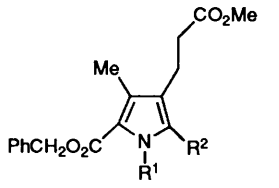
16a; R = CO_2CH_2Ph
16b; R = CO_2H
16c; R = H

With these encouraging results to hand, we then embarked on the somewhat lengthier syntheses of the four *N*-methylprotoporphyrin isomers **6a**–**9a**.

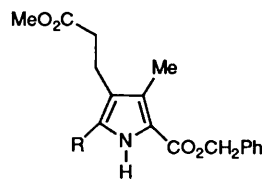
Our next targets were the N_a- and N_b-methylprotoporphyrins[11b] **6a** and **7a** for which the key intermediates were the two dipyrromethanes **15a** and **16a**, which could be coupled with the diformylpyrromethane **4** as in the synthesis of the model porphyrin **5**. The *N*-methylpyrrole **14a** as first prepared by *N*-methylation of the pyrrole acetate **10a** followed by a standard series of manipulations,[9b] *i.e.* diborane reduction to the hydroxyethyl derivative **10c**, conversion into the chloroethyl analogue **10d**, and finally acetoxylation of the α-methyl group with lead tetraacetate. The chloroethylpyrrole **10d** was also prepared by direct *N*-methylation of the known chloroethylpyrrole **12a**. The α-free pyrrole **11d** required for the synthesis of the *N*-methyldipyrromethane **15a** was prepared from the benzyl chloroethylpyrrolecarboxylate **11a** by degradation of the α-methyl group in the usual way, *i.e.* by chlorination and hydrolysis to the carboxylic acid **11b** followed by iodinative decarboxylation and hydrogenolysis of the resulting iodopyrrole **11c**. Coupling the acetoxymethyl-*N*-methylpyrrole **14a** with the α-free pyrrole **11d** then afforded the dipyrromethane **15a** in 68% yield. The latter was hydrogenolysed over palladised charcoal, and the dicarboxylic acid **15b** formed was decarboxylated by treatment with cold trifluoroacetic acid; the resulting di-α-free dipyrromethane was condensed with the diformyldipyrromethane **4**[14] in dichloromethane with toluene-*p*-sulphonic acid as catalyst, followed by addition of zinc(II) acetate, aeration and re-esterification as before. The desired bis(chloroethyl)-porphyrin **6b** was formed in 22% yield and was then dehydrochlorinated with aqueous potassium hydroxide and pyridine[15] to give the *N*-methylprotoporphyrin IX dimethyl ester **6a**.

For the synthesis of the N_b-methylprotoporphyrin isomer, we prepared the *N*-methyl-α-free pyrrole **13c** from the chloroethylpyrrole **12a** by conversion into the *tert*-butyl ester **12b**, followed by *N*-methylation to produce the *N*-methylpyrrole **12c**, hydrogenolysis of the benzyl ester to give the acid **13a** iodinative decarboxylation and hydrogenolysis of the intermediate iodopyrrole **13c**; an alternative route involving direct *N*-methylation of the α-free pyrrole *tert*-butyl ester was less efficient, some 60% of the starting material being recovered. The *N*-methylpyrrole **13c** was then coupled with the α-acetoxymethylpyrrole **14b** in the usual way to afford the dipyrromethane diester **16a** in 66% yield. The latter, upon hydrogenolysis (to give **16b**) followed by treatment with cold trifloroacetic acid then gave the required α-free dipyrromethane **16c** which was condensed with the diformylpyrromethane **4** in the usual manner to afford the N_b-methylbis(chloroethyl)-porphyrin **7b** in 21% yield. Dehydrochlorination, as before, gave the desired N_b-methylprotoporphyrin IX dimethyl ester **7a** in good yield.

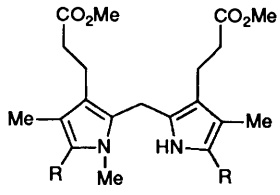
The MacDonald synthesis of porphyrins from dipyrromethanes is effectively limited by symmetry restrictions to those porphyrins in which two adjacent pyrrole rings have a symmetrical arrangement of substituents,[14] and thus it was not possible to synthesise the individual N_c- and N_d-methylprotoporphyrin isomers **8a** and **9a** in this way.[11b] However, it



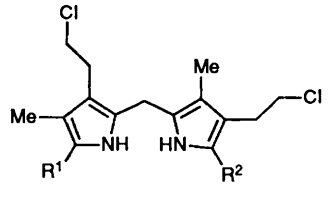
17a; $R^1 = H$, $R^2 = Me$
17b; $R^1 = R^2 = Me$
17c; $R^1 = Me$, $R^2 = CH_2OAc$



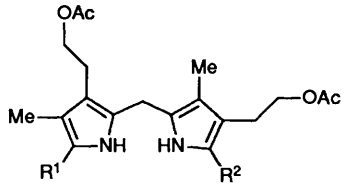
18a; R = Me
18b; R = CO_2H
18c; R = H



19a; R = CO_2CH_2Ph
19b; R = CO_2H
19c; R = H
19d; R = CHO



20a; $R^1 = CO_2CH_2Ph$, $R^2 = CO_2Bu^t$
20b; $R^1 = CO_2H$, $R^2 = CO_2Bu^t$
20c; $R^1 = R^2 = H$
20d; $R^1 = R^2 = CHO$



21a; $R^1 = CO_2CH_2Ph$, $R^2 = CO_2Bu^t$
21b; $R^1 = CO_2H$, $R^2 = CO_2Bu^t$
21c; $R^1 = R^2 = H$
21d; $R^1 = R^2 = CHO$

was decided to prepare a mixture of these two isomers from the mono-*N*-methyl analogue **19d** of the diformyldipyrromethane **4** and to separate them chromatographically—a somewhat less formidable task than separation of all four isomers.

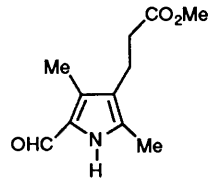
N-Methylation of the pyrrole **17a**, followed by treatment with lead tetraacetate, afforded the α-acetoxymethylpyrrole **17c**. This was coupled with the α-free pyrrole **18c** to afford the dibenzyl dipyrromethane-5,5′-dicarboxylate **19a**; hydrogenolysis of the latter, followed by thermal decarboxylation in hot dimethylformamide (DMF) afforded the α-free dipyrromethane **19c**. Treatment with phosphoryl chloride–DMF and hydrolysis of the intermediate imine salt then gave the *N*-methyldiformyldipyrromethane **19d** in 65% yield. However, attempts to condense this material with the di-α-free dipyrromethane **20c** (prepared from the benzyl *tert*-butyl dipyrromethanedicarboxylate **20a** by hydrogenolysis to the acid **20b** followed by treatment with trifluoroacetic acid) were unsuccessful, giving negligible yields of the desired porphyrin. An alternative approach involving condensation of the diformyldipyrromethane **20d** (prepared in low yield by direct formylation of the di-α-free dipyrromethane **20c** using phosphoryl chloride–DMF, or trimethyl orthoformate–trifluoroacetic acid) with the dipyrromethanedicarboxylic acid **19b** gave a very low overall yield of the N_c- and N_d-methyl-bis-chloroethylporphyrins **8b** and **9b**. A much more successful method was to condense the diformylbis(acetoxyethyl)dipyrromethane **21d** (prepared from the mixed benzyl *tert*-butyl ester **21a**) with the dipyrromethanedicarboxylic acid **19b**. The mixture of bis(hydroxyethyl)*N*-methylporphyrins **8c** and **9c** (formed by hydrolysis of the acetoxyethyl groups during work-up) was converted into the corresponding bis(chloroethyl)-porpyrins **8b** and **9b** by treatment with thionyl chloride in chloroform in presence of potassium carbonate. Dehydrohalogenation with potassium hydroxide in pyridine then afforded a mixture of the desired N_c- and N_d-methyl-protoporphyrin IX dimethyl esters **8a** and **9a**. The latter were separated from each other by semi-preparative HPLC on silica gel using a mixture of hexane, tetrahydrofuran (THF) and methanol as eluent. The relative amounts of the two isomers **8a** and **9a** were in the ratio 3:2.

Syntheses Using the Tripyrrene–a,c-Biladiene Approach.—The standard method for cyclisation of 1′,8′-dimethyl-*a,c*-biladiene salts [copper(II) chloride or acetate in boiling DMF][15] yielded only *N*-unsubstituted porphyrin when mono-*N*-methylated-*a,c*-biladiene was used. Even using the recently developed method of room temperature copper(II) promoted cyclisation[16] resulted in the loss of the *N*-methyl group in the final porphyrin product, indicating that the unavoidable copper(II) chelation in this reaction was probably the cause of methyl extrusion from the nitrogen atom, rather than simple thermal phenomena. As a result of these observations, we chose to further investigate the Russian cyclisation procedure,[17] in which an *a,c*-biladiene is cyclised in hot *o*-dichlorobenzene in presence of iodine and/or bromine, but in the absence of metallic oxidants. We had already experienced some success with this approach[18] and felt that it warranted wider application. It transpires that this approach was perfectly adaptable[11b] to synthesis of the N_c- and N_d-methylprotoporphyrins, and that the symmetry restrictions inherent in the MacDonald dipyrromethane synthesis were circumvented. Along with the required *N*-methylporphyrins, the cyclisation also afforded a small amount of *N*-unsubstituted porphyrin, and it was also discovered that use of iodine alone as the oxidant (in place of iodine–bromination mixtures) gave the same yields of porphyrin.

The dipyrromethane *tert*-butyl diester **20a** was prepared from the acetoxymethylpyrrole **14b** and the *tert*-butyl pyrrolecarboxylate **13c** and hydrogenolysed to the corresponding dipyrromethanecarboxylic acid **20b**. The latter was condensed with the α-formylpyrrole propionic ester **22** in presence of hydrobromic acid to afford the tripyrrene salt **23** in good yield. The *N*-methyl-α-formylpyrrole **24g** required for the N_c- and N_d-methylprotoporphyrin synthesis was prepared from the pyrrole propionic ester **24a** by a standard series of transformations **24a**–**24g**.[9b] Cleavage of the tripyrrene *tert*-butyl ester **23** with trifluoroacetic acid, followed by condensation with the *N*-methyl-α-formylpyrrole **24g** then led to the desired *a,c*-biladiene **25** (contaminated with a little unchanged tripyrrene salt, λ_{max} 485 nm), and treatment of the latter with iodine (or with iodine and bromine) in refluxing *o*-dichlorobenzene for 20 min gave the N_c-methylporphyin **8b** in 20% yield. Dehydrohalogenation with potassium hydroxide in pyridine then afforded the required N_c-methylprotoporphyrin IX dimethyl ester **8a** in 56% yield.

The *tert*-butyl benzyl dipyrromethane-5,5′-dicarboxylate **20a** on treatment with trifluoroacetic acid underwent deesterification and decarboxylation of the *tert*-butyl ester and then condensation with the α-formylpyrrole **22** afforded the tripyrrene **26**. The benzyl ester in the latter was cleaved by more vigorous acid treatment[15] and then condensation with the *N*-methyl α-formylpyrrole **24g** gave the *a,c*-biladiene **27** (slightly contaminated with unchanged tripyrrene), which underwent oxidative cyclisation (iodine–*o*-dichlorobenzene) to the bis-(chloroethyl)porphyrin **9b** (22%). Dehydrohalogenation with potassium hydroxide in pyridine then gave the N_d-methyl-protoporphyrin IX dimethyl ester **9a** in 60% yield. All four *N*-methylprotoporphyrin dimethyl esters **6a**–**9a** had spectroscopic properties compatible with the proposed structures.[4]

During the course of our work we also took the opportunity



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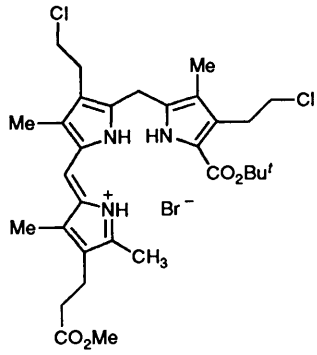

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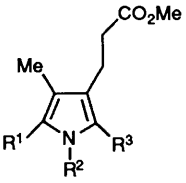
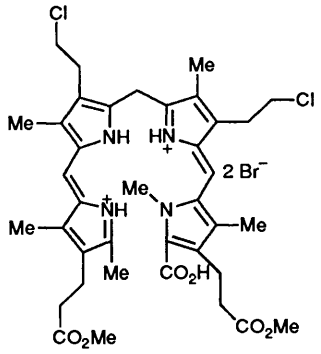
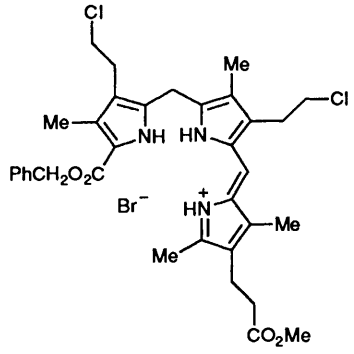


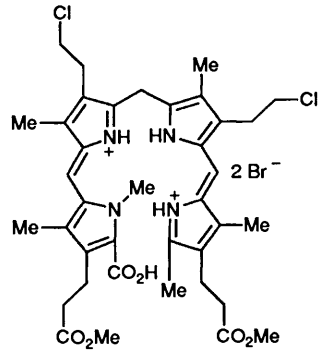
24a; $R^1 = CO_2CH_2Ph$, $R^2 = H$, $R^3 = Me$
24b; $R^1 = CO_2CH_2Ph$, $R^2 = H$, $R^3 = CO_2Bu^t$
24c; $R^1 = CO_2CH_2Ph$, $R^2 = Me$, $R^3 = CO_2Bu^t$
24d; $R^1 = CO_2H$, $R^2 = Me$, $R^3 = CO_2Bu^t$
24e; $R^1 = I$, $R^2 = Me$, $R^3 = CO_2Bu^t$
24f; $R^1 = H$, $R^2 = Me$, $R^3 = CO_2Bu^t$
24g; $R^1 = CHO$, $R^2 = Me$, $R^3 = CO_2Bu^t$



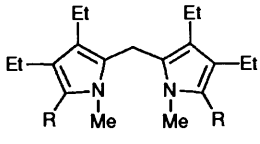
25



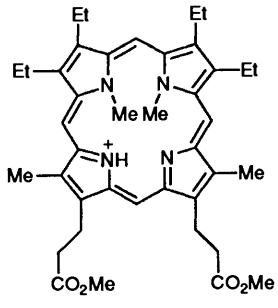
26



27



28a; $R = CO_2CH_2Ph$
28b; $R = CO_2H$



29

to assess the MacDonald route as a method for synthesis of *N,N'*-dimethylporphyrins. The *N*-methyl acetoxymethylpyrrole **1c** was converted in virtually quantitative yield into the viscous oily *N,N'*-dimethyldipyrromethane **28a** by stirring the dichloromethane solution with Montmorillonite clay[12] for 30 min at room temperature. Hydrogenolysis of the benzyl ester groups over palladised charcoal afforded the crystalline dipyrromethanedicarboxylic acid **28b**, which was condensed with the diformylpyrromethane **4**[12,13] in dichloromethane containing toluene-*p*-sulphonic acid as catalyst, followed by treatment with zinc(II) acetate and aeration. Reesterification with 5% sulphuric acid in methanol and chromatographic purification then afforded the N_a,N_b-dimethylporphyrin **29** as its monocationic salt, in 25% yield. This preparation clearly showed that the possible steric effects of *N*-methyl substituents on neighbouring pyrrole rings do not have a deleterious effect on the cyclisation step.

Experimental

Melting points, which are uncorrected, were measured on a microscopic hot-stage apparatus. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer in dichloromethane solutions, and mass spectra were measured on a Varian CH5D, or Finnigan 3200 spectrometer (direct insertion probe, 70 eV, 50 μA, source temperature from 200 to 300 °C or field desorption at wire currents 10–20 μA, and source temperatures increasing from 50–200 °C). Proton NMR spectra were obrained at 360 MHz on Bruker or Nicolet spectrometers, or at 90 MHz on Perkin-Elmer or Varian EM390 spectrometers, in $CDCl_3$ solution; chemical shifts are reported in ppm from Me_4Si, *J* values are given in Hz. Reactions were monitored by thin-layer chromatography (TLC) using cut strips (*ca.* 2 by 6 cm) of Merck silica gel 60 F254 precoated (0.25 mm thickness) plastic or aluminium-backed sheets. Preparative TLC was performed on freshly prepared 20 by 20 cm TLC plates of *ca.* 1 mm thick Merck silica gel GF 254 and 60 G. Plates were activated prior to use by heating at 150 °C for at least 8 h. Two types of packing material were employed in column chromatography; Merck neutral alumina (70–230 mesh) and Merck silica gel 60. The alumina was deactivated with either 6% H_2O (Brockman Grade III) or 15% H_2O (Brockman Grade V) before use. A 250 cm^{-1} J. T. Baker column was used for flash chromatography. Analytical high performance liquid chromatography (HPLC) was performed on a Waters Associates instrument equipped with a Model 6000A solvent delivery

system, A Valco model C6U injector and a Perkin-Elmer LC55B or Cecil variable wavelength detector. A Waters Associates Z-Module system equipped with a 10 μm silica gel normal phase cartridge was used. The solvent systems used as specified where appropriate. All solvents were reagent grade and were filtered through a 0.45 μm Millipore filter before use. Light petroleum refers to the fraction boiling 40–60 °C. The house deionised water was distilled before use. The samples, but not the solvents, were filtered through 0.45 μm filters before injection. Owing to the *N*-methyl groups, many synthetic intermediates were oils which could not be induced to crystallise; however, all were fully characterised by NMR spectroscopy and their purities were established by chromatographic methods before proceeding to the following stages.

Benzyl 3,4-*Diethyl*-5-*methylpyrrole*-2-*carboxylate* **1a** (*with Dr. E. Roberts*).—Ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate[19] (10 g) in dry benzyl alcohol (50 cm^3) containing sodium (400 mg) was heated on a water-bath at 85–90 °C for 8 h under reduced pressure (11 mmHg). The benzyl alcohol was then distilled off at 56 °C/0.1 mmHg, and the residue was taken up in ether, washed with water, dried (Ng_2SO_4) and evaporated to dryness. The *pyrrole* (9.7 g, 76%) crystallised from light petroleum as colourless needles, m.p. 66 °C (Found: C, 75.4; H, 7.8; N, 5.8. $C_{17}H_{21}NO_2$ requires C, 75.2; H, 7.8; N, 5.2%); δ_H 9.52 (br s, 1 H, NH), 7.41 (s, 5 H, Ph), 5.32 (s, 2 H, PhCH_2), 2.18 (s, 3 H, Me), 2.75 and 2.40 (each 2 H, CH_2Me) and 1.12 and 1.05 (each t, 3 H, CH_2CH_3).

Benzyl 3,4-*Diethyl*-1,5-*dimethylpyrrole*-2-*carboxylate* **1b** (*with Dr. E. Roberts*).—Dimethyl sulphoxide (DMSO) (100 cm^3) was added to crushed pellets of potassium hydroxide (4.5 g) and the mixture was stirred for 5 min. The foregoing pyrrole **1a** (5.4 g) was added and stirring was continued for 1 h. Methyl iodide (5.7 g) was then added and the mixture was stirred for a further 1 h. Analytical TLC then showed that reaction was complete, and water (200 cm^3) was added, the mixture was extracted with ether (3 × 50 cm^3) and the combined extracts were washed well with water (2 × 200 cm^3) and then dried (Na_2SO_4) and evaporated to dryness. The yellowish oily product (5.4 g, 95%) failed to crystallise; δ_H 7.40 (s, 5 H, Ph), 5.30 (s, 2 H, CH_2Ph), 3.75 (s, 3 H, NMe), 2.20 (s, 3 H, Me), 2.75 and 2.40 (each q, 2 H, C$H_2$$CH_3$) and 1.10 (t, 6 H, CH_2CH_3).

Benzyl 5-*Acetoxymethyl*-3,4-*diethyl*-1-*methylpyrrole*-2-*carboxylate* **1c**.—Lead tetraacetate (2.65 g) was added to the foregoing pyrrole **1b** (1.35 g) in glacial acetic acid (30 cm^3) and acetic anhydride (5 cm^3) during 20 min, and the mixture was stirred overnight. The mixture was poured into ice-cold water (50 cm^3) and extracted with dichloromethane. The organic phase was washed with aqueous sodium hydrogen carbonate (10%; 50 cm^3), water (2 × 50 cm^3), and then dried (Na_2SO_4). Evaporation afforded the pyrrole (1.31 g, 80%) as a viscous oil; δ_H 7.18 (s, 5 H, Ph), 5.20 (s, 2 H, CH_2Ph), 4.85 (s, 2 H, CH_2OAc), 3.75 (s, 3 H, NMe), 2.20–2.75 (m, 4 H, C$H_2$$CH_3$), 2.00 (s, 3 H, OCOMe) and 1.10 (t, 6 H, CH_2CH_3).

Benzyl 4-(2-*Chloroethyl*)-1,3,5-*trimethylpyrrole*-2-*carboxylate* **10d**.—Benzyl 4-(2-chloroethyl)-3,5-dimethylpyrrole-2-carboxylate **12a**[20] (5.0 g) was added to dimethyl sulphoxide (DMSO) (50 cm^3) containing potassium hydroxide (4.5 g). Methyl iodide (5.7 g) was then added and the reaction mixture was stirred at 20 °C under nitrogen for another 2 h. It was then worked up as described for the *N*-methylpyrrole **1b**. After evaporation of the solvent the N-*methylpyrrole* was crystallised from dichloromethane–hexane (4.98 g, 95%); m.p. 45–46 °C (Found: C, 66.8; H, 6.55; N, 4.5. $C_{17}H_{20}ClNO_2$ requires C, 66.8; H, 6.5; N, 4.5%); δ_H 7.40 (s, 5 H, Ph), 5.30 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, NMe), 3.50 and 2.85 (each t, 2 H, CH_2CH_2Cl) and 2.18 and 2.22 (each s, 3 H, Me).

Benzyl 5-*Acetoxymethyl*-4-(2-*chloroethyl*)-1,3-*dimethylpyrrole*-2-*carboxylate* **14a**.—The foregoing pyrrole **10d** (2.90 g) in acetic acid (50 cm^3) and acetic anhydride (5 cm^3) was treated with lead tetraacetate (4.3 g) as described for analogue **1c**. The title pyrrole (2.76 g, 80%) was obtained as a viscous oil; δ_H 7.45 (s, 5 H, Ph), 5.35 (s, 2 H, CH_2Ph), 5.10 (s, 2 H, CH_2OAc), 3.75 (s 2, H, NMe), 3.50 and 3.92 (each t, 2 H, CH_2CH_2Cl) and 2.25 and 2.15 (each s, 3 H, Me).

Benzyl 5-tert-*Butoxycarbonyl*-4-(2-*chloroethyl*)-1,3-*dimethylpyrrole*-2-*carboxylate* **12c**.—Benzyl 5-*tert*-butoxycarbonyl-4-(2-chloroethyl)-3-methylpyrrole-2-carboxylate[20] (1.8 g) was stirred for 1.5 h in DMSO (25 cm^3) containing potassium hydroxide (1.5 g). Methyl iodide (2.2 g) was added and the mixture was stirred for a further 2 h before being worked up as described above for other *N*-methylpyrrole syntheses. The title pyrrole was purified by chromatography on a silica gel column (elution with dichloromethane), and evaporation of the appropriate eluates afforded a viscous oil which failed to crystallise (1.68 g, 90%); δ_H 7.20 (s, 5 H, Ph), 5.15 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, NMe), 3.32 and 2.85 (each t, 2 H, CH_2CH_2Cl), 2.05 (s, 3 H, Me) and 1.40 (s, 9 H, Bu^t).

tert-*Butyl* 3-(2-*Chloroethyl*)-1,4-*dimethyl*-5-*iodopyrrole*-2-*carboxylate* **13b**.—The foregoing pyrrole **12c** (1.5 g) in tetrahydrofuran (THF) (50 cm^3) containing triethylamine (0.1 cm^3) and 5% palladised charcoal (15 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite and the filtrate was evaporated to afford the carboxylic acid **13a**, which was dissolved in methanol (15 cm^3) and water (10 cm^3) containing sodium hydrogen carbonate (800 mg). The solution was stirred at 60 °C and treated dropwise with a solution of iodine (1.2 g) and potassium iodide (1.8 g) in methanol (10 cm^3) and water (5 cm^3). After complete addition, water (20 cm^3) was added and the mixture was stirred for a further 1 h at 60 °C. The mixture was then poured into ice cold water (100 cm^3), extracted with dichloromethane (2 × 100 cm^3), dried (Na_2SO_4), and evaporated to dryness to give a residue which was chromatographed on a short silica gel column (elution with dichloromethane). Evaporation of the appropriate eluates gave the title pyrrole as an oil (1.00 g, 70%); δ_H 3.85 (s, 3 H, NMe), 3.15 and 3.55 (each t, 2 H, CH_2CH_2Cl), 2.00 (s, 3 H, Me) and 1.55 (s, 9 H, Bu^t).

tert-*Butyl* 3-(2-*Chloroethyl*)-1,4-*dimethylpyrrole*-2-*carboxylate* **13c**.—The foregoing iodopyrrole **13b** (1.4 g) was dissolved in methanol (50 cm^3) containing sodium acetate (1.4 g) and hydrogenated at 20 °C and 760 mmHg pressure over Admans' platinum oxide catalyst (20 mg) until uptake of hydrogen ceased. The catalyst was filtered off through Celite and the solvent was evaporated to dryness. The residue was dissolved in dichloromethane (100 cm^3) and washed with water (2 × 100 cm^3), and the organic phase was dried (Na_2SO_4) and evaporated to give a residue which was chromatographed on a short silica gel column (elution with dichloromethane). Evaporation of the appropriate eluates gave the title pyrrole (900 mg, 98%) as a viscous oil; δ_H 6.50 (s, 1 H, 2-H), 3.80 (s, 3 H, NMe), 3.55 and 3.10 (each t, 2 H, CH_2CH_2Cl), 2.00 (s, 3 H, Me) and 1.55 (s, 9 H, Bu^t).

Benzyl 4-(2-*Methoxycarbonylethyl*)-1,3,5-*trimethylpyrrole*-2-*carboxylate* **17b**.—Benzyl 4-(2-methoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate[21] **17a** (3.0 g) in DMSO (50 cm^3) containing powdered potassium hydroxide (1.5 g) was stirred

for 1 h. Methyl iodide (10 cm^3) was then added and the mixture was stirred for a further 2 h under nitrogen at room temperature before being worked up as described above for other *N*-methylpyrroles. The title compound was obtained as a viscous oil (2.95 g, 94%); δ_H 7.30 (s, 5 H, Ph), 5.30 (s, 2, H, CH_2Ph), 3.75 and 3.65 (each s, 3 H, NMe and OMe), 2.25–2.75 (m, 4 H, CH_2CH_2CO) and 2.15 and 2.20 (each s, 3 H, Me).

Benzyl 5-Acetoxymethyl-4-(2-methoxycarbonylethyl)-1,3-dimethylpyrrole-2-carboxylate **17c**.—The foregoing pyrrole **17b** (2.84 g) was dissolved in acetic acid (75 cm^3) containing acetic anhydride (2.5 cm^3), and lead tetraacetate (3.83 g) was added. The procedure described above for pyrrole **1c** was followed and afforded 2.30 g (70%) of the title pyrrole as a viscous oil after purification by column chromatography on silica gel (elution with dichloromethane); δ_H 7.35 (s, 5 H, Ph), 5.25 (s, 2 H, CH_2Ph), 5.10 (s, 2 H, CH_2OAc), 3.80 and 3.60 (each s, 3 H, NMe and OMe), 2.78 and 2.40 (each t, 2 H, CH_2CH_2CO) and 2.22 and 2.00 (each s, 3 H, Me).

Benzyl 5-tert-*Butoxycarbonyl-4-(2-methoxycarbonylethyl)-1,3-dimethylpyrrole-2-carboxylate* **24c**.—Benzyl 5-*tert*-butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate[22] **24b** (4.5 g) was stirred under a nitrogen atmosphere at 20 °C in DMSO (70 cm^3) containing powdered potassium hydroxide (4.4 g). After work-up similar to that for other *N*-methylpyrroles the title pyrrole (4.5 g, 98%) was obtained as a viscous oil; δ_H 7.40 (m, 5 H, Ph), 5.30 (s, 2 H, CH_2Ph), 4.15 (s, 3 H, *N*-CH_3), 3.60 (s, 3 H, CO_2Me), 3.00 and 2.22 (t, 2 H, CH_2CH_2, CO_2Me), 2.20 (s, 3 H, CH_3) and 1.55 (s, 9 H, Bu^t).

tert-*Butyl 5-Iodo-3-(2-methoxycarbonylethyl)-1,4-dimethylpyrrole-2-carboxylate* **24e**.—The foregoing pyrrole **24c** (3 g) in THF (50 cm^3) containing triethylamine (0.1 cm^3) and 10% palladised charcoal (300 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite and the filtrate was evaporated to dryness. After addition of water (100 cm^3) and dichloromethane (100 cm^3) the organic phase was dried (Na_2SO_4) and evaporated to give a solid residue of the pyrrolecarboxylic acid **24d** (2.3 g, 95%); δ_H 4.10 (s, 3 H, N-CH_3), 3.70 (s, 3 H, CO_2Me), 3.00 and 2.50 (each t, CH_2CH_2), 2.30 (s, 3 H, CH_3) and 1.62 (s, 9 H, Bu^t). This was treated with iodine (1.7 g), potassium iodide (2.6 g) in water (5 cm^3) and methanol (20 cm^3), and sodium hydrogen carbonate (1.6 g) in water (15 cm^3) and methanol (20 cm^3) as described for pyrrole **13b**. The crude product was chromatographed on a silica gel column (elution with dichloromethane) and afforded the title pyrrole (2.3 g, 78.2%) as a sticky solid; δ_H 3.92 (s, 3 H, N-CH_3), 3.70 (s, 3 H, CO_2Me), 3.00 and 2.45 (each t, 2 H, CH_2CH_2), 2.05 (s, 3 H, CH_3) and 1.60 (s, 9 H, Bu^t).

tert-*Butyl 5-Formyl-3-(2-methoxycarbonylethyl)-1,4-dimethylpyrrole-2-carboxylate* **24g**.—The foregoing iodopyrrole **24e** (2.3 g) was dissolved in methanol (70 cm^3) containing sodium acetate (2.3 g) and Adams' catalyst (30 mg) and treated as described above for pyrrole **13c**. The resulting 5-unsubstituted pyrrole **24f** (1.3 g) was dissolved in dichloromethane (25 cm^3) and added to the Vilsmeier reagent prepared from dimethylformamide (DMF) (4 cm^3) and phosphoryl chloride (1 cm^3) at 0–5 °C. The mixture was stirred at this temperature for 3 h under anhydrous conditions and the mixture was then diluted with dichloromethane (200 cm^3) and washed with aqueous sodium hydrogen carbonate (pH 7–8). The mixture was stirred at room temperature overnight and was then washed with water, dried (Na_2SO_4), and evaporated to dryness to give a residue which was chromatographed on a short silica gel column (elution with dichloromethane). Evaporation of the appropriate eluates gave initially oily products which eventually crystallised from dichloromethane–hexane to give the title *compound* (1.12 g, 64.36%); m.p. 59–61 °C; δ_H 10.00 (s, 1 H, CHO), 4.12 (s, 3 H, N-Me), 3.70 (s, 3 H, CO_2Me), 2.95 and 2.45 (each t, 2 H, CH_2CH_2), 2.30 (s, 3, H, Me) and 1.60 (s, 9 H, Bu^t) (Found: C, 62.0; H, 7.5; N, 4.5. $C_{16}H_{23}NO_5$ requires C, 62.1; H, 7.5; N, 4.5%).

Dipyrromethanes.

Dibenzyl 3,4′-Bis(2-chloroethyl)-1,3′,4-trimethyldipyrromethane-5,5′-dicarboxylate **15a**.—Benzyl 5-acetoxymethyl-4-(2-chloroethyl)-1,3-dimethylpyrrole-2-carboxylate[20] **14a** (1.5 g) in glacial acetic acid (50 cm^3) was treated with benzyl 3-(2-chloroethyl)-4-methylpyrrole-2-carboxylate[23] **11d** (877 mg) together with toluene-*p*-sulphonic acid hydrate (35 mg) before being stirred under nitrogen at 45 °C for 4 h. The mixture was poured into water, extracted with chloroform (3 × 100 cm^3) and the extracts were washed with aqueous sodium hydrogencarbonate and water, and dried (Na_2SO_4). After evaporation to dryness, the residue was chromatographed on a silica gel column (elution with 20% ethyl acetate in cyclohexane) and the appropriate eluates were evaporated to give the oily dipyrromethane **15a** (1.62 g, 68%) which could not be induced to crystallise; δ_H 8.55 (br s, 1 H, NH), 7.40 (s, 10 H, Ph), 5.30 (s, 4 H, CH_2Ph), 3.90 (s, 2 H, $-CH_2-$), 3.70 (s, 3 H, NMe); 2.70–3.50 (m, 8 H, CH_2CH_2) and 2.05 and 2.30 (each s, 3 H, Me).

Benzyl 5′-tert-Butoxycarbonyl-3,4′-bis(2-chloroethyl)-1′,3′,4-trimethyldipyrromethane-5-carboxylate **16a**.—Benzyl 5-acetoxymethyl-4-(2-chloroethyl)-3-methylpyrrole-2-carboxylate[20] **14b** (1.14 g), *tert*-butyl 4-(2-chloroethyl)-1,3-dimethylpyrrole-5-carboxylate **13c** (808 mg) and toluene *p*-sulphonic acid hydrate (40 mg) in acetic acid (70 cm^3) were treated as described above for synthesis of dipyrromethane **15a**. The usual work-up afforded the title dipyrromethane as a viscous oil (1.14 g, 67%); δ_H 8.32 (br s, 1 H, NH); 7.30 (s, 5 H, Ph), 5.28 (s, 2 H, CH_2Ph), 3.85 (s, 2 H, $-CH_2-$), 3.65 (s, 3 H, NMe), 2.70–3.60 (m, 8 H, CH_2CH_2), 2.25 and 2.00 (each s, 3 H, Me) and 1.55 (s, 9 H, Bu^t).

Dibenzyl 3,3′-Bis(2-methoxycarbonylethyl)-1,4,4′-trimethyldipyrromethane-5,5′-dicarboxylate **19a**.—Benzyl 5-acetoxymethyl-4-(2-methoxycarbonylethyl)-1,3-dimethylpyrrole-2-carboxylate **17c** (3.0 g) and benzyl 4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate **18c** (2.33 g) in glacial acetic acid (150 cm^3) were heated with toluene *p*-sulphonic acid (100 mg) in the same manner as for the foregoing dipyrromethane. After the usual work-up and chromatography on a silica gel column, the title compound (70%) was obtained as a viscous oil; δ_H 8.52 (br s, 1 H, NH), 7.35 (s, 10 H, Ph), 5.20 and 5.22 (each s, 2 H, CH_2Ph), 3.92 (s, 2 H, CH_2), 3.68 (s, 3 H, NMe), 3.60 (s, 6 H, OMe) and 2.30–2.85 (m, 8 H, CH_2CH_2).

3,3′-Bis(2-methoxycarbonylethyl)-1,4,4′-trimethyldipyrromethane-5,5′-dicarbaldehyde **19d**.—The foregoing dypyrromethane **19a** (3.0 g) in THF (400 cm^3) containing triethylamine (0.1 cm^3) and 10% palladised charcoal (600 mg) was hydrogenated at 20 °C and 760 mmHg pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite and the filtrate was evaporated to give a residue which precipitated from THF upon addition of light petroleum to give the *dipyrromethane-5,5′-dicarboxylic acid* **19b** (2.09 g, 98%), m.p. 171–173 °C (Found: C, 59.0; H, 6.1; N, 6.1. $C_{22}H_{28}N_2O_8$ requires C, 58.9; H, 6.3; N, 6.25%); δ_H($CDCl_3$ + [$^2H_6$]-DMSO) 10.55 (br s, 2 H, CO_2H), 3.92 (s, 2 H, CH_2), 3.62 (s, 9 H, NMe and 2 × OMe), 1.85–2.70 (m, 8 H, CH_2CH_2) and 2.18 (s, 6 H, Me). A portion of the compound isolated (1.5 g) was

dissolved in DMF (10 cm^3) and refluxed under nitrogen for 1 h before being cooled to 0 °C and benzoyl chloride (5 cm^3) added during 40 min.[26] The mixture was stirred at 20 °C for 1 h and then benzene (30 cm^3) was added. The precipitated solid was filtered off, dissolved in 50% aqueous methanol (20 cm^3) containing sodium hydrogen carbonate (1.5 g) and stirred at 20 °C overnight to hydrolyse the intermediate bis-imine. The mixture was extracted with dichloromethane (3 × 50 cm^3), washed with water, and then the organic phase was dried (Na_2SO_4), and evaporated to dryness. The crude residue was chromatographed on a column of silica gel (elution with 50% ethyl acetate in cyclohexane) and the appropriate eluates were evaporated to give the title compound as a viscous oil (970 mg); δ_H 9.62 and 9.50 (each s, 1 H, CHO), 9.30 (br s, 1 H, NH), 3.95 (s, 2 H, CH_2), 3.68 (s, 6 H, OMe), 2.30–2.80 (m, 4 H, CH_2CH_2) and 2.20 (s, 6 H, Me).

3,4′-*Bis*(2-*acetoxyethyl*)-3′,4-*dimethyldipyrromethane*-5,5′-*dicarbaldehyde* **21d**.—Benzyl 5′-*tert*-butoxycarbonyl-3,4′-bis(2-acetoxyethyl)-3′,4-dimethyldipyrromethane-5-carboxylate[24] **21a** (2.48 g) was hydrogenated in the normal way over 11% palladised charcoal (250 mg) to give the dipyrromethane-carboxylic acid **21b** (2.0 g). This was treated with trifluoroacetic acid (10 cm^3) and stirred under nitrogen for 30 min before being cooled to 0 °C and treated with trimethyl orthoformate (10 cm^3). After being stirred at 0 °C for 30 min the mixture was poured into water and extracted with dichloromethane (2 × 20 cm^3) and the extract was washed with aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash chromatography (silica gel; elution with 70% ethyl acetate in cyclohexane). The title *compound* was obtained as a light yellow powder (1.0 g, 60%), m.p. 154 °C (Found: C, 62.65; H, 6.55; N, 6.9. $C_{21}H_{26}N_2O_6$ requires C, 62.7; H, 6.5; N, 7.0%); δ_H 9.50 (s, 2 H, CHO), 9.40 (s, 2 H, NH), 3.70–4.25 (m, 6 H, CH_2OAc and $-CH_2$), 2.50–3.10 (m, 4 H, CH_2CH_2OAc) and 2.00 (s, 6 H, COMe).

Dibenzyl 3,3′,4-*Triethyl*-1,4′-*dimethyldipyrromethane*-5,5′-*dicarboxylate* **3a**.—*Method A*. Acetoxymethylpyrrole **1c** (1.70 g) was treated with benzyl 4-ethyl-3-methylpyrrole-2-carboxylate[25] **2** (1.20 g) in acetic acid (50 cm^3) containing toluene-*p*-sulphonic acid (30 mg) and heated at 45 °C for 4 h under nitrogen. The mixture was then poured into water, extracted with chloroform (3 × 100 cm^3) and the extracts were washed with aqueous sodium hydrogen carbonate (2 × 100 cm^3) and water (3 × 100 cm^3) and dried (Na_2SO_4). After evaporation of the extracts to dryness, the oily residue was chromatographed on a silica gel column (elution with 20% ethyl acetate in cyclohexane). Evaporation of the appropriate eluates afforded the title dipyrromethane (1.82 g, 70%) as an oil; δ_H 9.35 (br s, 1 H, NH), 7.35 (s, 10 H, Ph), 5.30 (s, 4 H, CH_2Ph), 3.92 (s, 2 H, CH_2), 3.60 (s, 3 H, NMe), 2.25–2.60 (m, 6 H, CH_2CH_3), 2.20 (s, 3 H, Me) and 1.00 (m, 9 H, CH_2CH_3).

Method B (*with Dr. E. Roberts*). Acetoxymethylpyrrole **1c** (1.70 g) was added to a well-stirred solution of benzyl 4-ethyl-3-methylpyrrole-2-carboxylate **2** (1.20 g) in dichloromethane (100 cm^3) containing a suspension of Montmorillonite K10 clay (20 g). After being stirred for 30 min the mixture was filtered free from the clay and the latter was washed with dichloromethane (50 cm^3). Evaporation of the combined filtrates afforded the title dipyrromethane (2.34 g, 90%) as a viscous oil with an identical NMR spectrum to that described for the product using Method A.

Dibenzyl 3,3′,4,4′-*Tetraethyl*-1,1′-*dimethyldipyrromethane*-5,5′-*dicarboxylate* **28a** (*with Dr. E. Roberts*).—Acetoxymethylpyrrole **1c** (5.00 g) in dichloromethane (100 cm^3) containing Montmorillonite clays (20 g) was stirred at 20 °C for 30 min, after which time TLC analysis showed the reaction to be complete. The solution was filtered free from clay and the latter was washed with dichloromethane. The combined filtrates were evaporated to dryness to give the title compound as a viscous oil (3.62 g, 90%); δ_H 7.40 (s, 10 H, Ph), 5.30 (s, 4 H, CH_2Ph), 3.98 (s, 2 H, CH_2), 3.70 (s, 6 H, NMe), 2.30–2.75 (q, 8 H, CH_2CH_3) and 1.10 (m, 12 H, CH_2H_3).

3,3′,4,4′-*Tetraethyl*-1,1′-*dimethyldipyrromethane*-5,5′-*dicarboxylic Acid* **28b**.—The foregoing dipyrromethane **28a** (2.00 g) in THF (500 cm^3) and triethylamine (0.1 cm^3) containing 10% palladised charcoal (400 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite and the filtrate was evaporated to dryness. The residue was precipitated from THF–hexane to give a white solid (1.28 g, 95%) which because it slowly decomposed was not further characterised but used immediately; δ_H 3.90 (s, 2 H, $-CH_2-$), 3.65 (s, 6 H, NMe), 2.68 and 2.20 (each q, 4 H, CH_2CH_3) and 1.00 (m, 12 H, CH_2CH_3).

Porphyrins.

1,2,3-*Triethyl*-4,5,8-N_a-*tetramethyl*-6,7-*bis*(2-*methoxycarbonylethyl*)*porphyrin* **5**.—Dipyrromethanedicarboxylic acid **3b** (200 mg) was dissolved in dichloromethane (150 cm^3) and 3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarbaldehyde[24] (235 mg) was added, together with toluene-*p*-sulphonic acid hydrate (600 mg) in methanol (15 cm^3). The mixture was stirred under nitrogen at 20 °C for 24 h before a saturated solution of zinc(II) acetate in methanol (15 cm^3) was added; the mixture was then stirred at 20 °C in air for a further 24 h. The mixture was diluted with dichloromethane (100 cm^3), washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude product was taken up in 5% (w/v) sulphuric acid in methanol (50 cm^3) and kept overnight at 20 °C. It was then poured into saturated aqueous sodium acetate, extracted with chloroform and the extract washed with water, aqueous sodium hydrogen carbonate and then water again and finally dried (Na_2SO_4). The solvent was evaporated to give a residue which was chromatographed on a silica gel column (elution with dichloromethane and then 2% methanol in dichloromethane). The appropriate eluates were evaporated and the solid residue was crystallised from dichloromethane–hexane to give the title *porphyrin* (72 mg, 20%), m.p. 123–125 °C (Found: C, 72.05; H, 7.55; N, 9.4. $C_{36}H_{46}N_4O_4$ requires C, 72.2; H, 7.7; N, 9.4%); δ_H 9.95 and 9.85 (each s, 2 H, *meso*-H), 4.50 and 4.25 (each m, 6 H, CH_2CH_3), 3.90 (m, 4 H, CH_2CH_2CO), 3.70, 3.68, 3.77, 3.50 and 3.48 (each s, 3 H, OMe and Me), 3.25 (m, 4 H, CH_2CH_2CO), 1.48, 1.52 and 1.82 (each t, 3 H, CH_2CH_3) and −4.85 (s, 3 H, Me).

1,2,3,4-*Tetraethyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-5,8,N_a,N_b-*tetramethylporphyrin Hydrochloride* **29**.—Dipyrromethanedicarboxylic acid **28b** (400 mg) was dissolved in dichloromethane (200 cm^3) and treated with the diformyldipyrromethane **4** (420 mg) along with toluene-*p*-sulphonic acid hydrate (1.2 g) in methanol (20 cm^3) in the same way as described above for compound **5**. After the usual work-up, the product was purified by flash chromatography on silica gel (elution with 2% methanol in dichloromethane) and the *N*,*N*-dimethylporphyrin (175 mg, 25%) was obtained as its *hydrochloride salt*, m.p. 125–126 °C after crystallisation from dichloromethane–hexane (Found: M^+, 650.3804. $C_{40}H_{50}N_4O_4$ requires *M*, 650.3832); λ_{max}/nm 406, 576, 624 and 658; δ_H 10.34 (s, 3 H, *meso*-H), 10.3 (s, 1 H, *meso*-H), 4.38 and 3.82 (each m, 4 H, CH_2CH_3), 3.80 (m, 4 H, CH_2CH_2CO), 3.69 (s, 12 H, Me

and OMe), 3.30 (m, 4 H, CH_2CH_2CO), 1.70 and 1.45 (each t, 6 H, CH_2CH_3), −3.48 (s, 1 H, NH) and −5.38 (s, 6 H, NMe).

2,4-*Bis*(2-*chloroethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_a-*pentamethylporphyrin* **6b**.—Dipyrromethanedicarboxylic acid **15b** (400 mg) was coupled with the diformyldipyrromethane **4** (400 mg) in dichloromethane (200 cm^3) containing toluene-*p*-sulphonic acid hydrate (1.5 g) in methanol (20 cm^3) as described in the synthesis of the preceding porphyrins. The crude product, after the usual work-up, was first purified on a silica gel column (elution with 2% methanol in dichloromethane) and then by flash chromatography on silica gel (elution with 1% methanol in dichloromethane). The product was obtained by evaporation of the appropriate eluates, and was crystallised from dichloromethane–hexane to give the *porphyrin* (148 mg, 22%), m.p. 113–116 °C (Found: M^+, 676.2587. $C_{37}H_{42}N_2O_4$ requires *M*, 676.2583); $\lambda_{max}(\varepsilon_{max})$ (free base)/nm 414 (141 400), 506 (10 100), 536 (5100), 572 (3200), 616 (1900) and 644 (3000); λ_{max}(hydrochloride salt)/nm 398, 552 and 598; δ_H 9.95, 9.85, 9.80, 9.70 (each s, 1 H, *meso*-H), 4.00–4.50 (m, 8 H, CH_2CH_2Cl), 2.80 (m, 4 H, CH_2CH_2CO), 3.30 (m, 4 H, CH_2CH_2CO), 3.20, 3.48, 3.57 and 3.75 (each s, 3 H, Me), 3.70 (s, 6 H, OMe), −3.25 (br s, 1 H, NH) and −4.70 (s, 3 H, NMe).

2,4-*Bis*(2-*chloroethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_b-*pentamethylporphyrin* **7b**.—Benzyl 5′-t-butoxycarbonyl-1′,3′,4′-trimethyldipyrromethane-5-carboxylate **16a** was hydrogenated over 10% palladised charcoal and the resulting dipyrromethanecarboxylic acid **16b** (200 mg) was treated with trifluoroacetic acid (3 cm^3) for 5 min. The trifluoroacetic acid was then evaporated and the residue was taken up in dichloromethane (100 cm^3) and the solution washed with water, aqueous sodium hydrogen carbonate, then water again, and finally dried (Na_2SO_4). The mixture was made up to 150 cm^3 with dichloromethane and diformyldipyrromethane **4** (180 mg) and toluene-*p*-sulphonic acid (700 mg) in methanol (15 cm^3) were added. The mixture was treated in the same way as for the preceding porphyrin, and after work-up was flash chromatographed on silica gel (elution with dichloromethane). The appropriate eluates were evaporated and the title *porphyrin* (62 mg, 21%) was crystallised from dichloromethane–hexane, m.p. 110–113 °C (Found: M^+, 676.2573. $C_{37}H_{42}Cl_2N_4O_4$ requires *M*, 676.2583); $\lambda_{max}(\varepsilon_{max})$/nm 414 (139 000), 504 (10 600), 536 (5400), 592 (4000), 618 (2800) and 644 (2800); δ_H 9.89 and 9.85 (each s, 1 H, *meso*-H), 9.86 (s, 2 H, *meso*-H), 4.15–5.45 (m, 8 H, CH_2CH_2Cl), 3.78 (m, 4 H, CH_2CH_2CO), 3.67, 3.65, 3.64, 3.50, 3.49 and 3.20 (each s, 3 H, Me and OMe), 3.25 (m, 4 H, CH_2CH_2CO), −3.20 (br s, 1 H, NH) and −4.72 (s, 3 H, NMe).

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_a-*pentamethyl*-2,4-*divinylporphyrin* **6a**.—The bis-chloroethylporphyrin **6b** (56 mg) was heated under reflux in pyridine (40 cm^3) under nitrogen for 10 min before addition of aqueous sodium hydroxide (3%; 15 cm^3). The mixture was heated under reflux for a further 2 h and then cooled and treated with acetic acid (25%; 20 cm^3). The solvent was evaporated using toluene as a chaser, water was added, and the precipitate was filtered off, washed with water, and dried *in vacuo* at 40 °C. The residue was treated with 5% H_2SO_4 in methanol (50 cm^3) and stirred overnight under nitrogen. The mixture was poured into ice-cold aqueous sodium acetate, extracted with dichloromethane and the extract then washed with aqueous sodium hydrogencarbonate and water and dried (Na_2SO_4). The solvent was evaporated and the product was purified by silica gel column chromatography (elution with 1% methanol in dichloromethane). The solvent was then evaporated to dryness and the residue was dissolved in dichloromethane (100 cm^3) and the solution washed with dilute ammonium hydroxide and water and then dried ($MgSO_4$). The solvent was evaporated and the residue was recrystallised from dichloromethane–hexane to give the title *porphyrin* (30 mg, 60%), m.p. 148–153 °C (Found: M^+, 604.3042. $C_{37}H_{40}N_4O_4$ requires *M*, 604.3040); $\lambda_{max}(\varepsilon_{max})$/nm 428 (152 000), 512 (10 600), 546 (7300, 594 (5100), 624 (2000) and 652 (3100); ν_{max} (in dichloromethane containing 1% trifluroacetic acid, dication)/nm 412, 560 and 606; δ_H 9.80 and 10.05 (each s, 1 H, *meso*-H), 9.95 (s, 2 H, *meso*-H), 7.79–7.87 and 8.12–8.20 (each m, 1 H, $CH=CH_2$), 5.92–6.32 (m, 4 H, $CH_2=CH_2$), 4.42 and 4.23 (each 2 H, CH_2CH_2CO), 3.68, 3.66, 3.65, 3.63, 3.50 and 3.25 (each s, Me and OMe), 3.26 (m, 4 H, CH_2CH_2CO), −3.00 (br s, 1 H, NH) and −4.59 (s, 3 H, NMe).

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,3,5,8-N_b-*pentamethyl*-2,4-*divinylporphyrin* **7a**.—The bis(chloroethyl)porphyrin **7b** (65 mg) was heated with 3% aqueous sodium hydroxide (10 cm^3) in pyridine (40 cm^3) in the same manner as for the analogous porphyrin **6a** and, after work-up, the title *porphyrin* (36 mg, 26%) was obtained, m.p. 148–151 °C (Found: M^+, 604.3036. $C_{37}H_{40}N_4O_4$ requires *M*, 604.3040); $\lambda_{max}(\varepsilon_{max})$/nm 424 (153 000), 512 (11 500), 546 (6200), 596 (4800), 624 (2000) and 652 (3200); λ_{max} (in dichloromethane + 1% trifluoroacetic acid, dication)/nm, 414, 560 and 606; δ_H 10.04, 9.98, 9.88, 9.78 (each s, 1 H, *meso*-H), 7.70–7.85 and 8.10–8.19 (each m, 1 H, $CH=CH_2$) 5.92–6.29 (m, 4 H, $CH=CH_2$), 4.42 and 4.20 (each 2 H, CH_2CH_2CO), 3.68, 3.66, 3.65, 3.59, 3.46 and 3.21 (each s, Me and OMe), 3.30 (m, 4 H, CH_2CH_2CO), −3.00 (br s, 1 H, NH) and −4.58 (s, 3 H, NMe).

Mixture of N_c- *and* N_d-*Methyl*-2,4-*bis*(2-*hydroxyethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphyrins* **8c** *and* **9c**.—Diformyldipyrromethane **21d** (402 mg) and the *N*-methyldipyrromethanedicarboxylic acid **19b** (416 mg) were dissolved in dichloromethane and toluene-*p*-sulphonic acid (1.5 g) in in methanol (15 cm^3) was added. The reaction was carried out in the same manner as the preceding syntheses, and after work-up the porphyrin was found to be a mixture of the C and D ring *N*-methylporphyrins **8c** and **9c** (175 mg, 27%) in about a 60:40 ratio; λ_{max}/nm 414, 516, 536, 586, 616 and 644; λ_{max} (in dichloromethane + 1% trifluoroacetic acid, dication)/nm 414, 558 and 604; δ_H 9.85 and 9.90 (each m, 4 H, *meso*-H), 3.25 and 4.00–4.50 (m, 16 H, CH_2CH_2OH, CH_2CH_2CO), 3.70 (s, 18 H, Me and OMe), −3.60 (s, 2 H, NH) and −4.75 (s, 6 H, NMe).

Mixture of N_c- *and* N_d-*Methyl*-2,4-*bis*(2-*chloroethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphyrins* **8b** *and* **9b**.—The foregoing mixture of (2-hydroxyethyl)porphyrins **8c** and **9c** (175 mg) in dry chloroform (60 cm^3) and DMF (30 cm^3) was treated with dry potassium carbonate (6 g). Thionyl chloride (4 cm^3) was then added and the mixture was stirred at 20 °C for 1 h, by which time the reaction was found to be complete (TLC analysis). The product was first purified by column chromatography on alumina (Brockmann Grade III, elution with dichloromethane) and then on silica gel (elution with 2% methanol in dichloromethane). The appropriate eluates were evaporated to dryness and the residue was dissolved in dichloromethane and washed with dilute ammonium hydroxide and then water. The organic phase was dried ($MgSO_4$) and evaporated to dryness and the title compounds were crystallised from dichloromethane–hexane to give the mixture of porphyrins **8b** and **9b** (95 mg, 51%); δ_H 9.80 and 9.95 (each s, 4 H, *meso*-H), 3.20, 3.25, 5.05, 5.15, 5.25 and 5.05 (each t, 16 H, CH_2CH_2Cl, CH_2CH_2CO), 5.25 (s, 18 H, Me and OMe) and −4.80 s, 6 H, NMe).

Mixture of N_c- *and* N_d-*Methyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-2,4-*divinylporphyrins* **8a** *and* **9a**.—The

foregoing mixture of *N*-methyl(2-chloroethyl)porphyrins **8b** and **9b** (80 mg) was treated with aqueous sodium hydroxide (3%, 20 cm^3) in pyridine (50 cm^3) in the same manner as for the synthesis of the isomerically pure N_a- and N_b-methylporphyrins, to give the products (41.3 mg, 58%). These were separated by normal phase HPLC using a Waters Associates Z-module equipped with a 10 micron silica gel cartridge, eluting with hexane–THF–methanol 97:97:6 (u/v). The leading or trailing edge of the two peaks, as appropriate, was clipped and collected, and then reinjected for a second separation. Each isomer was obtained free of the other to provide an approximately 60:40 ratio of the N_c and N_d porphyrins. Both compounds had spectroscopic and physical data identical with those described below for the compounds obtained isomerically pure.

2,4-*Bis*(2-*chloroethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_c-*pentamethylporphyrin* **8b**.—Tripyrrene hydrobromide **23** (460 mg) in trifluoroacetic acid (3 cm^3) was stirred for 10 min under a nitrogen atmosphere before addition of formylpyrrole **24g** (220 mg) in methanol (10 cm^3). A solution of 31% HBr in acetic (3 cm^3) was then added and the mixture was stirred for 30 min. Precipitation of the product was completed by addition of cold anhydrous ether, and filtration afforded 400 mg of deep red crystals (m.p. >300 °C). The resulting *a,c*-biladiene dihydrobromide **25** was contaminated with a small quantity of tripyrrene hydrobromide (λ_{max} 485 nm) and was therefore used directly by dissolving 200 mg in *o*-dichlorobenzene (40 cm^3) containing iodine (500 mg) and heating under reflux for 20 min. The mixture was cooled, triethylamine (0.5 cm^3) was added, and the solution was filtered through alumina (Brockman Grade III, elution first with hexane to remove the dichlorobenzene, and then with dichloromethane). Two fractions were collected and the solvent was evaporated separately. The fast moving porphyrin (10 mg) was the known 2,4-bis(2-chloroethyl)-6,7-bis(2-methoxycarbonylethyl)porphyrin, m.p. 217–218 °C (lit.,[27] m.p. 216–218 °C). The slower moving *porphyrin* (31 mg, 20%) crystallised from dichloromethane–hexane, m.p. 92–94 °C (Found: M^+, 676.2580. $C_{37}H_{42}Cl_2N_4O_4$ requires *M*, 676.2583); $\lambda_{max}(\varepsilon_{max})$/nm 420 (141 000), 506 (12 200), 538 (8100), 588 (5100), 620 (2400) and 646 (3100); δ_H 9.94, 9.89, 9.88 and 9.79 (each s, 1 H, *meso*-H), 4.10–4.50 (m, 8 H, CH_2CH_2Cl), 3.77 (m, 4 H, CH_2CH_2CO), 3.68, 3.67, 3.53, 3.50, 3.46 and 3.21 (each s, 3 H, Me and OMe), (CH_2CH_2CO), −3.2 (br s, 1 H, NH) and −4.70 (s, 3 H, NMe).

2,4-*Bis*(2-*chloroethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_d-*pentamethylporphyrin* **9b**.—Tripyrrene hydrobromide **26** (300 mg) in trifluoroacetic acid (7.5 cm^3) was stirred for 6 h under a nitrogen atmosphere before addition of formylpyrrole **24g** (130 mg) in methanol (7 cm^3). Reaction was monitored by spectrophotometry, and once no further significant decrease in the 485 nm absorption was detected (30 min), ether was added to precipitate the *a,c*-biladiene dihydrobromide **27**. This was filtered off as a sticky hygroscopic solid (400 mg), still contaminated with a little tripyrrene hydrobromide λ_{max} 485 nm. The product was dissolved in *o*-dichlorobenzene (50 cm^3) containing iodine (500 mg) and treated as described above to give, after chromatography, 2,4-bis(2-chloroethyl)-6,7-bis(2-methoxycarbonylethyl)porphyrin, m.p. 217–218 °C (lit.,[27] m.p. 216–218 °C) (12 mg) and the title *compound* (68 mg, 22%), m.p. 155–158 °C (Found: M^+, 676.2571. $C_{37}H_{42}Cl_2N_4O_4$ requires *M*, 676.2583); $\lambda_{max}(\varepsilon_{max})$/nm 420 (141 500), 506 (9700), 538 (5000), 588 (3400), 620 (2000) and 646 (3000); δ_H 9.89, 9.71, 9.46 and 9.38 (each s, 1 H *meso*-H), 4.28–4.73 (m, 8 H, CH_2CH_2Cl), 3.93 (m, 4 H, CH_2CH_2CO), 3.78, 3.68, 3.66, 3.62, 3.53 and 3.19 (each s, 3 H, Me and OMe), 4.25 (CH_2CH_2CO), −3.1 (br s, 1 H, NH) and −5.05 (s, 3 H, NMe).

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_c-*pentamethyl*-2,4-*divinylporphyrin* (N_c-*Methylprotoporphyrin* IX *Dimethyl Ester*) **8a**.—The bis(chloroethyl)porphyrin **8b** (30 mg) in pyridine (20 cm^3) under nitrogen was treated with 3% aqueous potassium hydroxide (5 cm^3) and refluxed for 3 h. The mixture was worked up as described for the preparation of **6a** and the crude product was column chromatographed on silica gel (elution with 1% methanol in dichloromethane). The appropriate eluates were evaporated and the residue was dissolved in dichloromethane, washed with aqueous ammonium hydroxide and then water, dried (Na_2SO_4), and evaporated to dryness. The title *compound* (15 mg, 56%) was obtained by crystallisation from dichloromethane–hexane, m.p. 75–77 °C (Found: M^+, 604.3036. $C_{37}H_{40}N_4O_4$ requires *M*, 604.3040); $\lambda_{max}(\varepsilon_{max})$/nm 424 (15 100), 512 (10 900), 544 (6100), 592 (4800) and 652 (3200); λ_{max} (in dichloromethane + 1% trifluoroacetic acid, dication)/nm 414, 558 and 604; δ_H 10.07, 9.99, 9.92 and 9.89 (each s, 1 H, *mexo*-H), 8.10–8.35 (each m, 1 H, $CH{=}CH_2$), 6.09–6.44 (m, 4 H, $CH{=}CH_2$), 4.25 and 4.03 (each m, 2 H, CH_2CH_2CO), 3.91, 3.69, 3.68, 3.57, 3.48 and 3.16 (each s, 3 H, Me and OMe), 2.74, 3.23, 4.05 and 4.25 (each t, 2 H, CH_2CH_2CO), −3.10 (br s, 1 H, NH) and −4.70 (s, 3 H, NMe).

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,3,5,8,N_d-*pentamethyl*-2,4-*divinylporphyrin* (N_d-*Methylprotoporphyrin* IX *Dimethyl Ester*) **9a**.—The bis(chloroethyl)porphyrin **8b** (60 mg) in pyridine (40 cm^3) under nitrogen was treated with 3% aqueous potassium hydroxide (10 cm^3) and refluxed for 3 h. The reaction was worked up and the product purified as described above for **8a**; the title *compound* (32 mg, 60%), m.p. 101–103 °C crystallised from dichloromethane–hexane (Found: M^+, 604.3037. $C_{37}H_{40}N_4O_4$ requires M, 604.3040); $\lambda_{max}(\varepsilon_{max})$/nm 424 (153 000), 512 (110 000), 544 (6100), 592 (4800) and 652 (3100); λ_{max} (in dichloromethane + 1% trifluoroacetic acid, dication)/nm 414, 558 and 604; δ_H 10.07, 10.00, 9.96 and 9.90 (each s, 1 H, *meso*-H), 8.10–8.30 (m, 2 H, $CH{=}CH_2$), 6.06–6.44 (m, 4 H, $CH{=}CH_2$), 4.28 and 4.04 (each m, 2 H, CH_2CH_2CO), 3.91, 3.69, 3.68, 3.57, 3.48 and 3.16 (each s, 3 H, Me and OMe); 2.74, 3.23, 4.108 and 4.25 (each t, CH_2CH_2CO), −3.10 (br s, 1 H, NH) and −4.70 (s, 3 H, NMe).

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