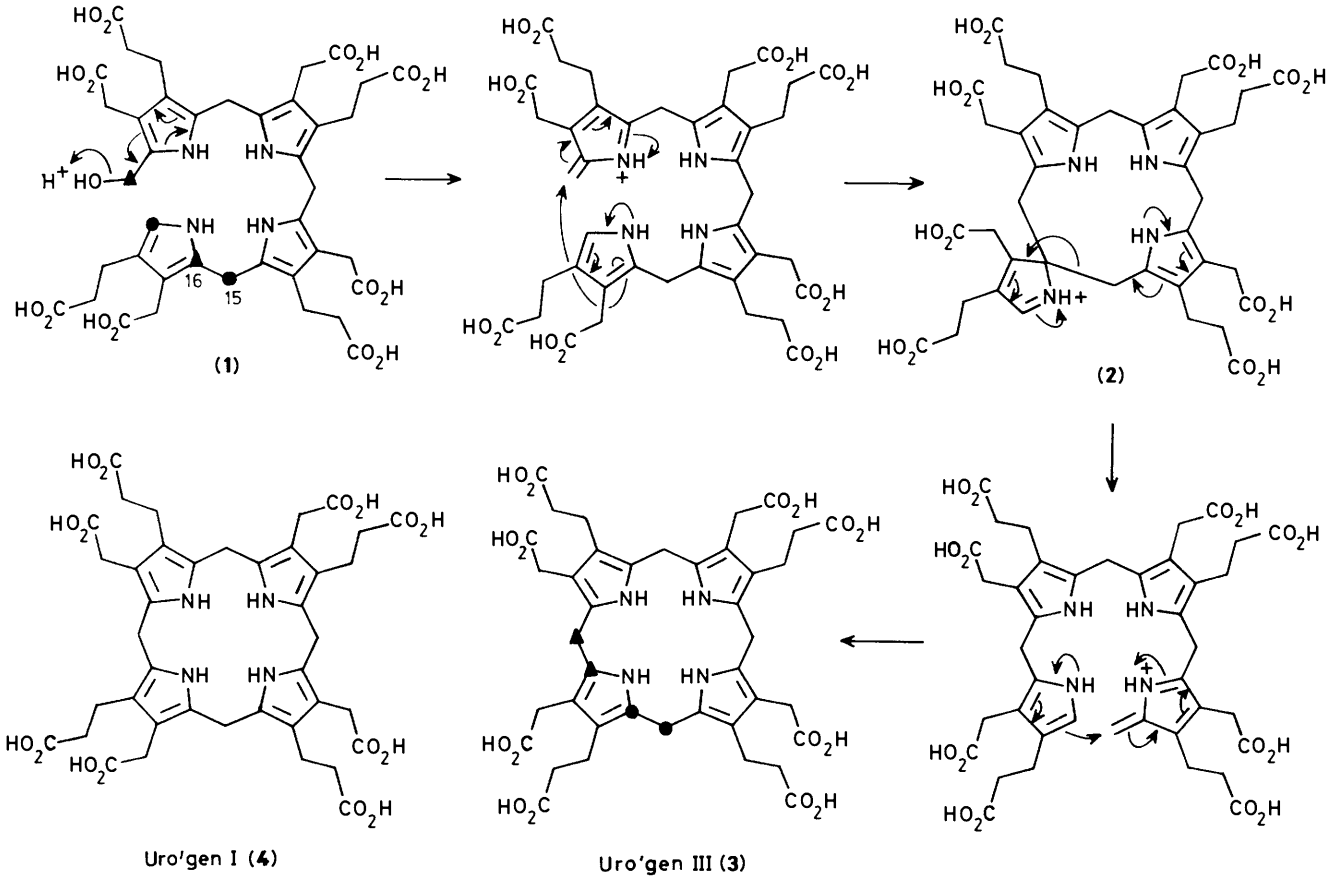
Biosynthesis of Porphyrins and Related Macrocycles. Part 30.[1,2] Synthesis of the Macrocycle of the Spiro System Proposed as an Intermediate Generated by Cosynthetase

W. Marshall Stark, Mark G. Baker, Finian J. Leeper, Paul R. Raithby, and Alan R. Battersby*
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

Syntheses are described of two compounds having the 1,14-(propane-1,3-diyl)tripyrrin macrocycle (**5**), which is the basis of the spiro compound (**2**) proposed as an intermediate during the cyclization of hydroxymethylbilane (**1**) to uro'gen III (**3**), catalysed by the enzyme cosynthetase. The first synthesis, of the dinitrile (**41**), starts with the alkylation of malononitrile with two different chloromethylpyrroles, whereas the second synthesis, of the spiro lactam (**59**) uses the condensation of nitroalkanes with pyrrole aldehydes. In both cases the macrocycle is completed by addition of a third pyrrole ring followed by acid-catalysed cyclization from an α-free pyrrole onto a hydroxymethyl substituent. The crystal structure of the dinitrile (**41**) shows a rigid, highly puckered macrocycle and the same conformation in the spiro lactam (**59**) is used to explain the existence of two non-interconvertible isomers, (**61**) and (**62**).

All the tetrapyrrolic pigments of life (*e.g.* haem, chlorophyll, and vitamin B_{12}) are derived in Nature from one macrocycle, uroporphyrinogen III (**3**), shortened to uro'gen III, which is in turn derived from the linear hydroxymethylbilane (**1**). Extensive studies have been made of the biosynthesis of these compounds and of the cyclization process itself and the results have been reviewed.[3] The hydroxymethylbilane (**1**) is unstable at physiological pH and it rapidly cyclizes non-enzymically (half-life *ca.* 4 min at pH 8) to give the unrearranged uro'gen I (**4**). However, (1) is normally intercepted by the enzyme cosynthetase (uro'gen III synthase) which ring-closes it with an intramolecular rearrangement of ring D to afford uro'gen III (**3**). The symbols ● and ▲ on structures (**1**) and (**3**) show the results of two ^{13}C-labelling experiments, one with ^{13}C at ● and the other with ^{13}C at ▲, which reveal the changes in bonding which occur as (**1**) is converted into (**3**).[4]

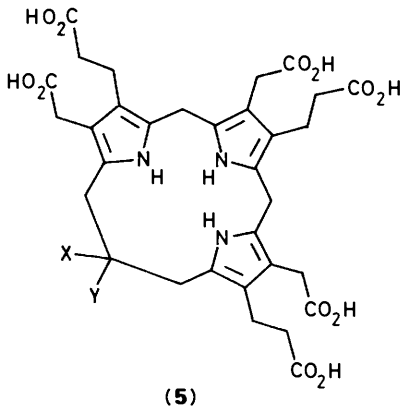
Two fundamentally different mechanisms have been put forward which would account for these labelling results.[5] In one mechanism, ring D of the hydroxymethylbilane (**1**) is detached by cleavage of the bond between C-15 and C-16; it is then turned



Scheme 1.

over and the new bonds to C-15 and the hydroxymethyl carbon are made. In the other mechanism, with which we will be concerned in this paper, the bond between C-16 and the hydroxymethyl carbon is made *first* to give the spiro pyrrolenine (**2**) and only after this is the bond from C-15 to C-16 broken and uro'gen III produced probably by the fragmentation–recombination mechanism shown in Scheme 1. It has been demonstrated that this fragmentation–recombination process is both feasible and facile by the synthesis of suitable 2-pyrrolylmethylpyrrolenines which readily underwent this type of rearrangement.[1-6]

Although the latter type of mechanism for cosynthetase was first suggested in 1961,[7] no example of this macrocyclic ring has ever been synthesized. Indeed doubts have been raised about whether structure (**2**) is sterically possible: the original proposers of a spiro mechanism did not use structure (**2**) but a modified protonated form of it in which the three pyrrole rings existed as pyrrolenines (2*H*-pyrroles) because, they argued, the increased flexibility due to the sp^3 carbons was important for macrocycle formation.[7] We therefore undertook the synthesis of model compounds of structure (**5**) in order to demonstrate

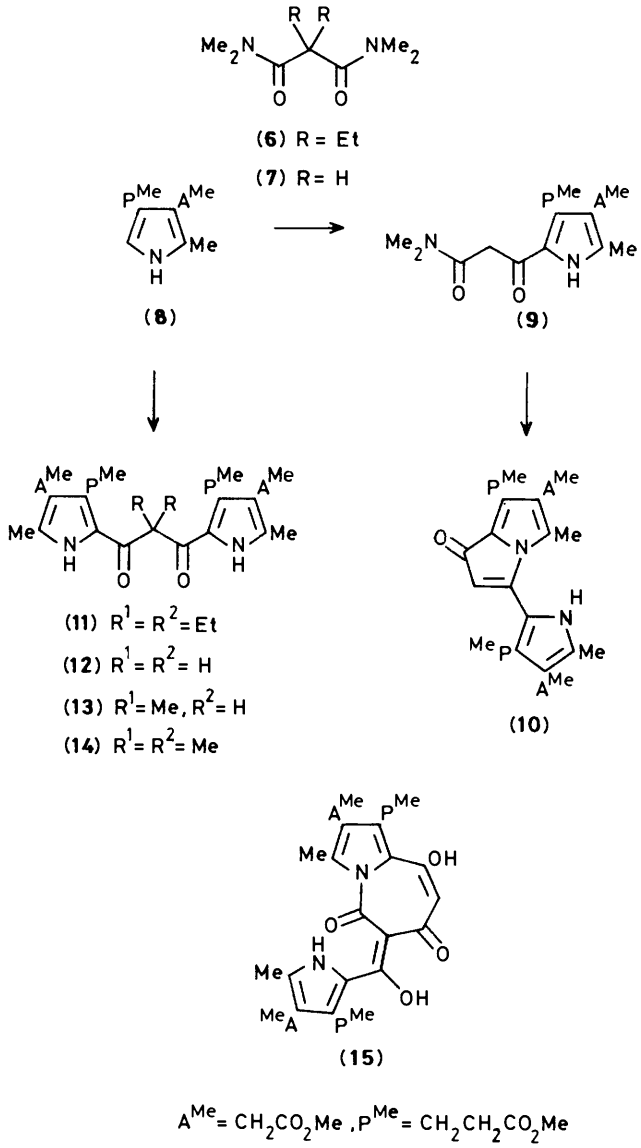


(**5**)

whether or not the spiro compound (**2**) is a viable intermediate in the enzyme-catalysed process.

Synthesis of the Dicyano Macrocycle (**41**).—In our first approach we planned to attach pyrroles to both ends of a three carbon unit using a double acylation reaction, which would yield a dipyrrolyl diketone such as (**11**) (Scheme 2). When 2,2-diethyl-*N*,*N*,*N*′,*N*′-tetramethylmalonamide (**6**) was used in an attempted Vilsmeier acylation of the α-free pyrrole (**8**), no mono- or di-acylation reaction products were observed. It was found by ^{1}H n.m.r. spectroscopy that on refluxing the malonamide (**6**) with phosphoryl chloride, the Vilsmeier reagent was formed only very slowly and from only one of the two amide groups. Even after it was prepared in this way no reaction with the pyrrole (**8**) was observed. Similarly Friedel–Crafts acylation with 2,2-diethylmalonyl dichloride was totally unsuccessful.

On the assumption that acylation with the diethylmalonamide derivative (**6**) was being prevented by steric hindrance, *N*,*N*,*N*′,*N*′-tetramethylmalonamide (**7**) was treated with phosphoryl chloride. Rapid formation at room temperature of the Vilsmeier reagent from one amide group was observed by n.m.r. spectroscopy and this reacted readily with the α-free pyrrole (**8**) to give the acyl derivative (**9**). However, when the latter compound was treated with further α-free pyrrole (**8**) and phosphoryl chloride, the product was not the desired dipyrrole (**12**) but a deep red cyclized form of this, pyrrolizine (**10**). A Friedel–Crafts reaction of the α-free pyrrole (**8**) with malonyl dichloride in dichloromethane with no added catalyst was more successful, however, and yielded the desired dipyrrole (**12**) in

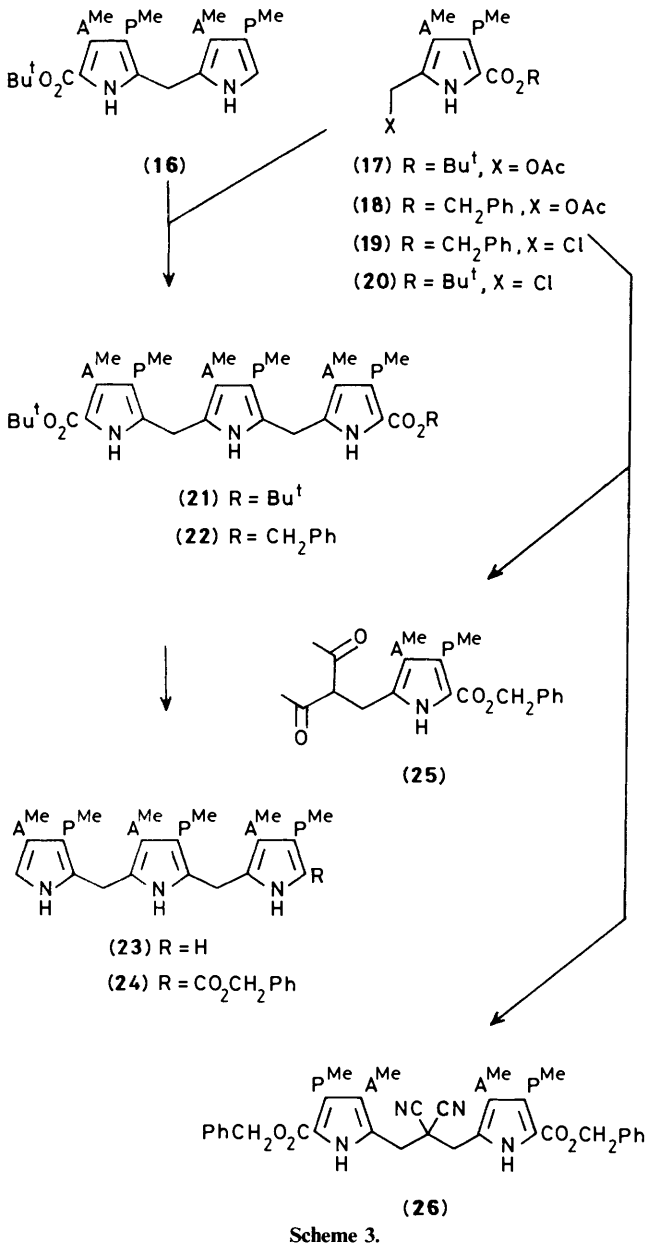


Scheme 2.

59% yield. If an excess of malonyl dichloride was used in this reaction, a bright yellow compound was formed which was assigned the structure (**15**) (or a tautomer of this).

The aim was now to introduce the alkyl groups which would be the X and Y groups of the target (**5**) by alkylation of the diketone (**12**). Treatment of (**12**) with base and methyl iodide gave the monomethyl derivative (**13**) but all attempts to alkylate a second time to give the dimethyl derivative (**14**) were unsuccessful as were attempted alkylations with 1,4-dibromobutane.

It was thought that the most straightforward route to the macrocyclic ring system of (**5**) using the successful Friedel–Crafts reaction would be by diacylation of the di-α-free tripyrrole (**23**) (Scheme 3) with malonyl dichloride. This tripyrrole was synthesized by acid-catalysed condensation of α-free dipyrrole (**16**) with acetoxymethylpyrrole (**17**),[8] followed by removal of the t-butyl groups and decarboxylation in trifluoroacetic acid (TFA). However, reaction of this di-α-free tripyrrole with malonyl dichloride or with *N*,*N*,*N*′,*N*′-tetramethylmalonamide under Vilsmeier conditions failed to give any macrocyclic products. Similarly the mono-α-free monobenzyl ester (**24**) [synthesized from the benzyl ester (**18**) by an



Scheme 3.

analogous route (Scheme 3)] could not be acylated successfully by either of these methods.

At this stage we considered an alternative route for the synthesis of the macrocyclic ring of (**5**) which involved alkylation of an active methylene compound with chloromethylpyrroles. It was found that acetylacetone could be alkylated with the chloromethylpyrrole (**19**) using sodium carbonate as the base to give the monopyrrolyl derivative (**25**) but we were unable to alkylate this a second time. When the less hindered malononitrile was used, however, dialkylation was possible to give the dipyrrole (**26**).

If this alkylation reaction was to be applied to the synthesis of a macrocyclic compound such as (**5**) it would be necessary to alkylate with two different pyrroles. Accordingly malononitrile was alkylated with a deficiency of the chloromethylpyrrole (**27**) which ensured monoalkylation to give the monopyrrole dinitrile (**28**) (Scheme 4). This in turn reacted with a second chloromethylpyrrole (**20**) to give the dipyrrole dinitrile (**29**).

The differential protection of the two α-carboxyl groups of (**29**) now allowed the regiospecific addition of the third pyrrole. Treatment with TFA caused cleavage of the t-butyl ester but, unusually, it did not cause decarboxylation as well. This was effected by the standard two-step procedure of iodinative decarboxylation of the acid (**30**), followed by catalytic reduction of the resulting iodopyrrole (**31**).

The third pyrrole was to be added using the acetoxymethylpyrrole (**35**), which is a known compound.[9] However, an improved synthesis had to be developed to provide the quantity of material required. The t-butyl ester (**33**)[10] was converted into the aldehyde (**34**) in one pot using TFA and trimethyl orthoformate. Acetoxylation of the methyl group to give (**35**) could be effected with lead tetra-acetate but a cleaner reaction was monochlorination using t-butyl hypochlorite followed by displacement of the chloride with sodium acetate in acetic acid.

The best conditions for the coupling of (**35**) with the α-free dipyrrole (**32**) were to use stannic chloride as a Lewis acid catalyst, which gave the tripyrrole aldehyde (**36**) in 82% yield. After hydrogenolysis of the benzyl ester, the acid (**37**) was decarboxylated *via* the iodopyrrole (**38**). Reduction of the α-free aldehyde (**39**) then gave the hydroxymethyl tripyrrole (**40**) ready for the all-important cyclization.

The hydroxymethyl compound was not characterized due to its instability but was treated directly with a catalytic amount of toluene-*p*-sulphonic acid in dichloromethane which gave the desired macrocycle (**41**) in 25% yield over the last two steps. This macrocycle was stable at room temperature provided that light and air were rigorously excluded. It was fully characterized by physical methods and the signals in the 400 MHz ^{1}H n.m.r. spectrum were completely assigned using the n.O.e. difference technique. The macrocycle crystallized from benzene–hexane and an *X*-ray crystal structure determination* on a crystal suspended in its mother liquor (as the crystals powdered when the solvent of crystallization was removed) revealed the structure shown in the Figure. This confirms the structure of the macrocycle and demonstrates that, in accord with predictions based on molecular models, a high degree of puckering is required to allow closure of the ring. The molecular models show that there is not enough space in the centre of the macrocycle for the pyrrole N–H's and this forces the two

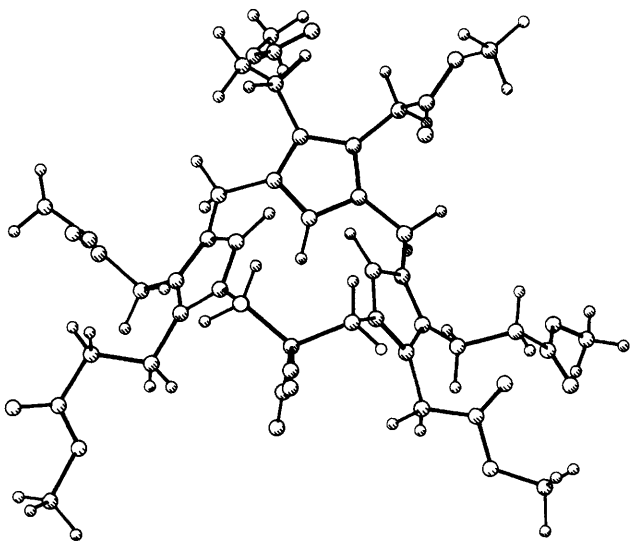
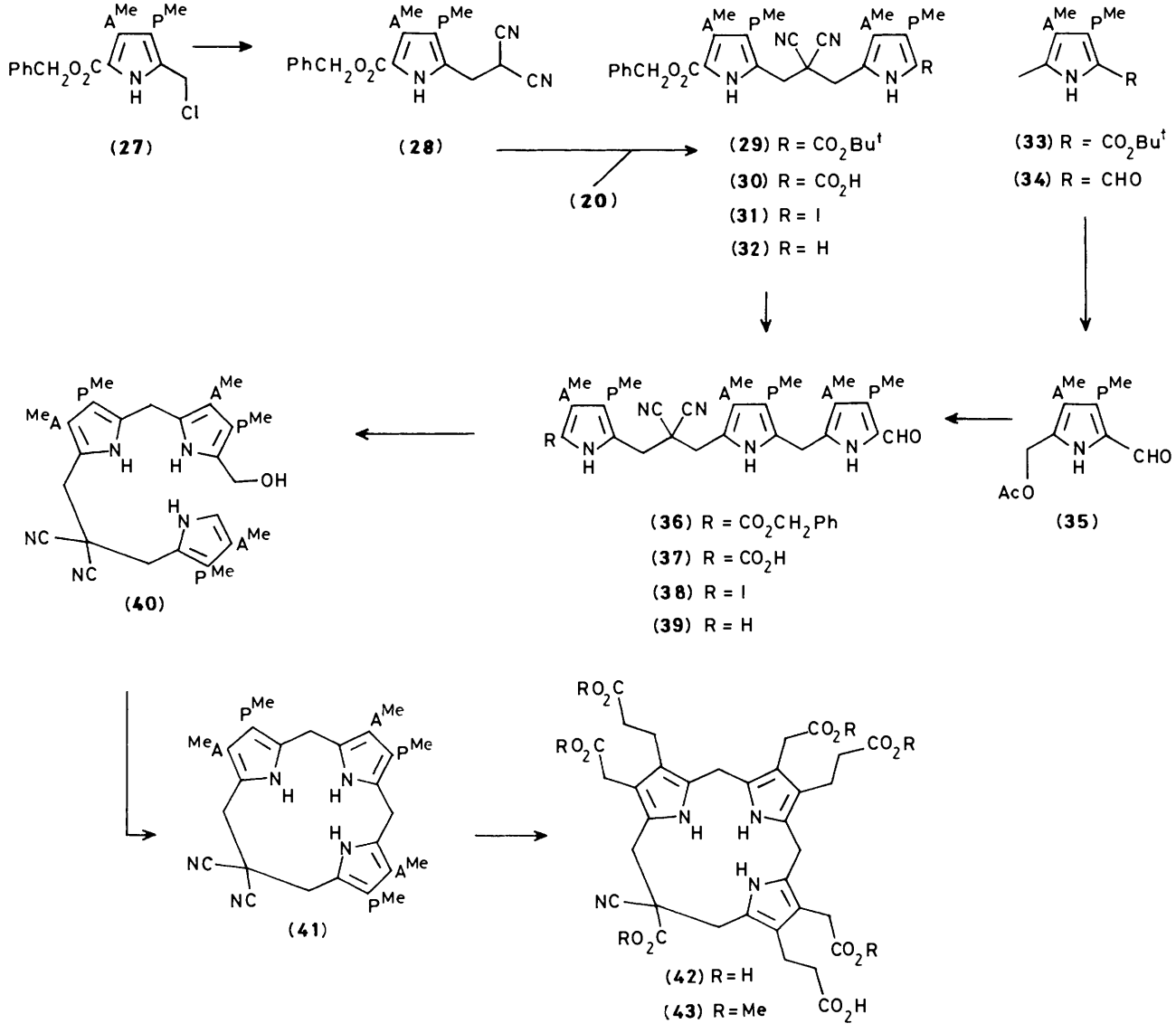


Figure. *X*-Ray crystal structure of the macrocycle (**43**)

* The full *X*-ray data have been deposited with the Cambridge Crystallographic Data Centre.



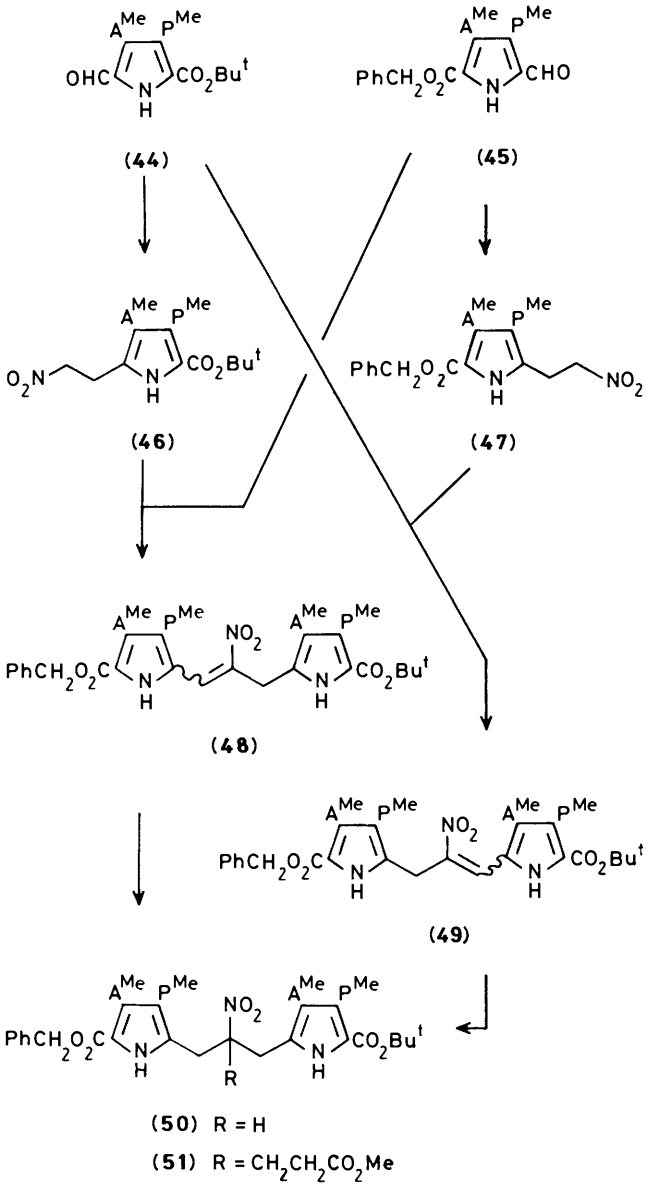
Scheme 4.

opposing N–H's to point up above the plane of the ring while the third, central N–H points down.

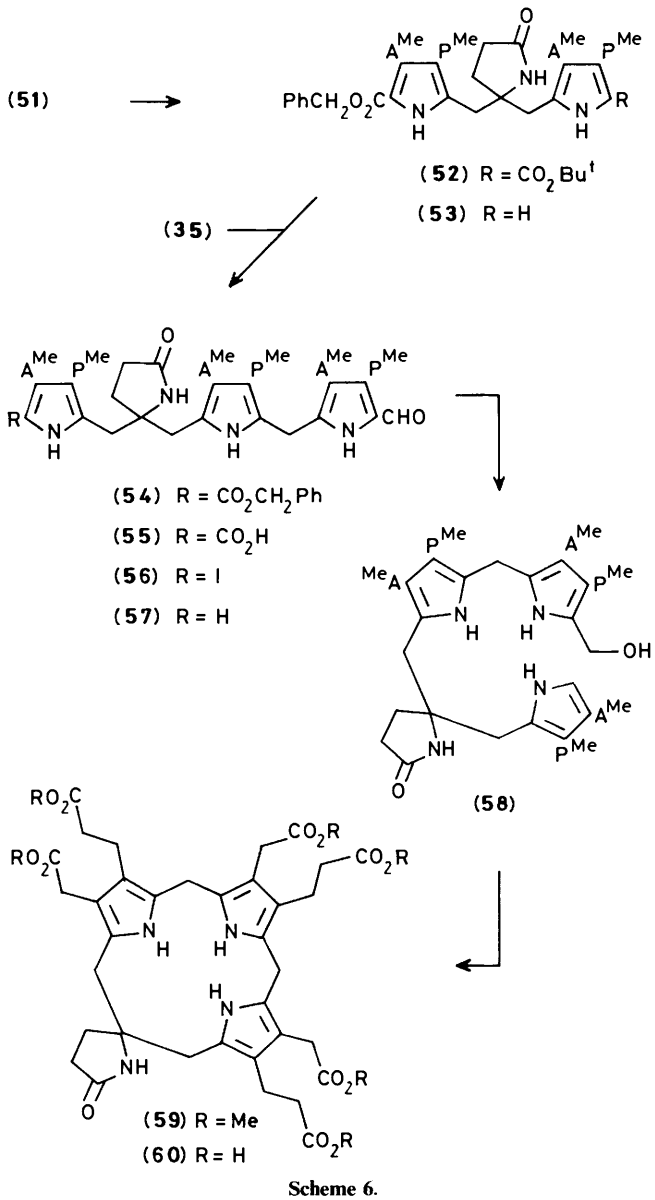
The tripyrrole portion of the macrocycle (**41**) is identical to that of the postulated spiro intermediate (**2**) and therefore our future plans included studies of whether the acid corresponding to ester (**41**) would bind to and inhibit the enzyme cosynthetase. Hydrolysis of the ester groups was carried out using the standard conditions[5] of potassium hydroxide in tetrahydrofuran–water. In order to check whether any reaction other than hydrolysis of the esters had occurred, the product from the hydrolysis was re-esterified using diazomethane. None of the original macrocyclic dinitrile was recovered but the major product was identified as the heptaester (**43**) so the major product of the hydrolysis was the hepta-acid mononitrile (**42**) and the macrocycle is therefore stable in the alkaline conditions used. All the enzymic experiments on this hepta-acid and on several related tripyrrolic macrocycles will be fully reported shortly.

Synthesis of the Macrocyclic Spiro Lactam (**59**).—In our second synthesis we aimed to make a closer model of the proposed spiro intermediate (**2**) which incorporated the five-membered nitrogen-containing ring. In place of the pyrrolenine ring, however, we planned to have a more stable lactam ring, as in (**59**). For the synthesis of the bis(pyrrolylmethyl)lactam (**52**), the precursor of (**59**), we hoped to use nitroalkane chemistry similar to that previously used in the synthesis of pyrrolylmethylpyrrolenines.[1]

Two routes to the dipyrrolylnitropropane (**50**) starting with nitromethane and the two pyrrole aldehydes (**44**) and (**45**) are possible as shown in Scheme 5. Initially we chose the condensation of aldehyde (**45**)[9] with nitroethylpyrrole (**46**)[11] as both were known compounds; the nitroethylpyrrole (**46**) is made by condensation of the aldehyde (**44**) with nitromethane, followed by reduction of the resulting nitrovinylpyrrole with sodium borohydride. The condensation of the nitro compound (**46**) with aldehyde (**45**) using the usual catalyst of methylammonium acetate in dry methanol gave at most 10% of the desired bright yellow nitropropene (**48**). More forcing conditions only caused extensive decomposition. A number of different catalysts and solvents were used but all of them gave an even lower yield. Furthermore, the product (**48**) was very difficult to separate from the unchanged starting materials. After partial purification by flash chromatography, h.p.l.c. was



Scheme 5.



Scheme 6.

required for the final purification. This also allowed separation of the *E*- and *Z*-isomers of the product (**48**), which were present in a ratio of 3:2.

In view of these difficulties we investigated the alternative route to the nitropropane (**50**) *via* nitroethylpyrrole (**47**). The latter was made in the standard way by condensation of aldehyde (**45**) with nitromethane to give the nitrovinylpyrrole (68%), which was reduced with sodium borohydride (87%). Condensation of this nitroethylpyrrole (**47**) with aldehyde (**44**) gave a somewhat better yield [21%; 41% based on unrecovered (**47**)] of the nitropropene (**49**) and it turned out that this could be adequately purified using two flash chromatography columns. H.p.l.c. was only required to separate the *E*- and *Z*-isomers for characterization. Reduction of the nitropropene (**49**) then gave the nitropropane (**50**) in virtually quantitative yield.

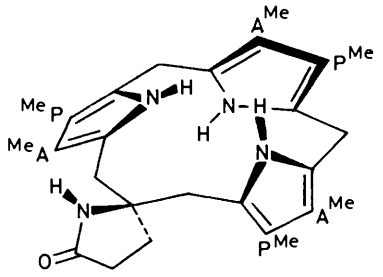
Five-membered lactams (pyrrolidones) have previously been made by the Michael addition of the anions of nitropropanes to α,β-unsaturated esters, followed by reduction of the nitro group (see ref. 1). Our experience has been that this reaction is very sensitive to steric constraints[1] and therefore, having an already rather hindered nitropropane (**50**), we chose a Michael addition to the unsubstituted α,β-unsaturated ester, methyl acrylate. This gave the adduct (**51**) in 54% yield. Reduction of the nitro group with zinc in acetic acid proceeded with concomitant cyclization to give the lactam (**52**).

For the elaboration of the bis(pyrrolylmethyl)lactam (**52**) to the macrocycle (**59**) the same strategy (shown in Scheme 6) was used as had been developed for the dinitrile (Scheme 4). First the t-butyl ester was cleaved and decarboxylated and then the third pyrrole was added by condensation with the acetoxymethylpyrrole (**35**). The benzyl ester of the tripyrrole (**54**) was hydrogenolysed and the decarboxylation was achieved using the milder iodinative method. Finally reduction of the formyl group with sodium borohydride gave the hydroxymethyl compound (**58**) ready for the cyclization.

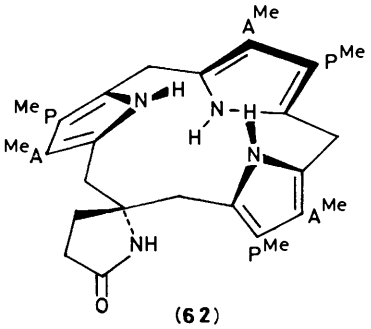
Preliminary attempts to cyclize the hydroxymethyl compound (**58**) using acid catalysis did yield a new compound with a high R_F value on t.l.c. but this decomposed during purification. Therefore the whole procedure was repeated in the nitrogen atmosphere of a glove box, which permitted the isolation of two distinct products both having the macrocyclic spiro lactam

structure (**59**) (yields 23 and 13%). The two isomers had all their ^1H and ^{13}C n.m.r. signals in very similar but not identical positions. However, the major isomer showed broad ^1H signals at room temperature which became sharper on warming to 50 °C. Also for both isomers the ^{13}C signals for the methylene carbons between the lactam and pyrrole rings were broad. Similar broadening of the ^{13}C n.m.r. signals was also observed for the dipyrrole lactam (**52**) and broadening of both ^1H and ^{13}C signals has been described for dipyrrole lactam (**63**).[1] One possible explanation is aggregation due to intermolecular hydrogen-bonding as observed in the crystal structure of (**63**).

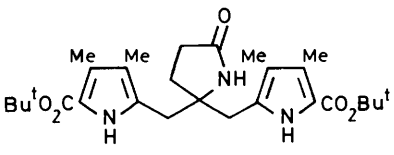
The existence of two isomers of the spiro lactam (**59**) was at first surprising. However, the *X*-ray crystal structure of the dinitrile (**41**) showed that the top and bottom faces of the macrocycle are different (two pyrrole N–H's point up and the third one down) and therefore two diastereoisomers (**61**) and (**62**) of the spiro lactam, in which the nitrogen atom of the



(**61**)



(**62**)



(**63**)

lactam is either up or down, can exist. Furthermore, space-filling models show that it is not possible to interconvert isomers (**61**) and (**62**) as the space in the centre of the macrocycle is too constricted for the pyrrole N–H's to pass through. Attempted equilibration of the two isomers (**61**) and (**62**), using an excess of toluene-*p*-sulphonic acid (*i.e.* more vigorous conditions than used for their formation), did not change either isomer. Thus they are formed under kinetic rather than thermodynamic control.

Here again, the acid (**60**) corresponding to the ester (**59**) was required for future enzymic experiments but we were unsure whether the alkaline conditions would also hydrolyse the lactam. However, it was found that the lactam ring of (**63**) was totally unaffected by treatment with 2M potassium hydroxide for 17 h. Therefore each of the isomers of the spiro lactam (**59**) was separately hydrolysed under these conditions. Proton n.m.r. spectra of the products in D_2O showed that the ester groups had been lost and that they were still different compounds; no significant interconversion had occurred.

Conclusion

The crystal structure of the dinitrile (**41**) and the existence of two isomers of the spiro lactam (**59**) both indicate the tight, conformationally restricted nature of the macrocycle. This is reflected in the rather low yields for the cyclizations (25 and 36%). It should be said, however, that the conditions for these cyclizations are not extremely forceful; indeed elimination–addition at a hydroxymethylpyrrole seems exactly the type of reaction used by Nature. The synthesis of macrocycles (**41**) and (**59**) proves that such structures can exist and it is therefore reasonable to consider the spiropyrrolenine (**2**) as an intermediate in the formation of uro'gen III by cosynthetase.

Our studies of the effect on cosynthetase of the hepta- and hexa-acids (**42**) and (**60**) [derived, respectively, from the esters (**41**) and (**59**)] will be reported soon in full; a brief preliminary account has been published.[12]

Experimental

General Directions.—Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Electronic spectra were recorded on a Pye Unicam SP8-100 spectrophotometer in 1-cm cells using either ethanol (for the synthesis of the dicyano macrocycle) or methanol (for the synthesis of the spirolactam) as the solvent. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer as solutions in 0.5-mm sodium chloride cells, using chloroform which had been filtered through UG1 alumina as the solvent. ^1H N.m.r. spectra were recorded on solutions in $CDCl_3$ using Varian EM390 (90 MHz) and Bruker WP80 (80 MHz), WM250 (250 MHz), and WH400 (400 MHz) spectrometers. For spectra run on the Varian EM390, tetramethylsilane was used as an internal standard, whilst for spectra run in the Fourier transform mode (Bruker WP80, WM250, and WH400) the solvent proton signal was used as the standard. ^{13}C N.m.r. spectra were recorded at 100 MHz on the Bruker WH400 spectrometer using proton decoupling. Deuteriochloroform was used as the solvent and the solvent carbon signal was used as an internal standard. Mass spectra were obtained on A.E.I. MS30, MS902, and MS50 machines; field desorption (f.d.) spectra were run on the latter instrument.

The glove box was operated at 1—3 inH_2O* above atmospheric pressure using nitrogen as the inert gas. The oxygen concentration was maintained below 25 p.p.m. throughout the experiments.

Analytical t.l.c. was performed on commercial Merck plates coated with silica gel GF_{254} (0.25 mm thick). Preparative thin layer chromatography (p.l.c.) was carried out on 20 × 20 cm plates coated with the same silica (1 mm thick). Silica for column chromatography was Merck Kieselgel 60 (70—230 mesh) and for flash chromatography was Merck Kieselgel 60 (230—400 mesh). Packed column dimensions are quoted (diameter × height). Analytical high pressure liquid chromatography (h.p.l.c.) was carried out on a Kontron S5W silica column using a Waters 6000 A pump connected to a Cecil CE 272 u.v. spectrophotometer. Preparative h.p.l.c. was carried out on a Du Pont Zorbax column packed with 7-μm silica (column

* 1 inH_2O = 2.490 89 × 10^2 Pa

dimensions 25 cm × 21.2 mm) using a Gilson 303 pump connected to a Cecil CE 272 u.v. spectrophotometer. Solvents for h.p.l.c. were redistilled and then filtered through a 0.5 μm millipore sieve.

Organic solutions which had been in contact with water were dried over anhydrous magnesium sulphate. Evaporation of solvents was performed on a Buchi rotary film evaporator at reduced pressure (*ca.* 30 Torr).

All solvents were redistilled. Degassing was performed by bubbling nitrogen from a fine sinter through the solvent for 1 h. Ether refers to diethyl ether; Hunig's base is *N*-ethyldiisopropylamine. Zinc powder was activated by washing successively with 3M hydrochloric acid, water, ethanol, and ether followed by drying in an oven.

N,N,N′,N′-*Tetramethyl*-2,2-*diethylmalonamide* (**6**).—2,2-Diethylmalonyl dichloride (5 ml, 27.7 mmol) in ether (5 ml) was added over 10 min with stirring to a solution of dimethylamine (8.8 g) in ether (55 ml) at 0 °C. After 20 min at 0 °C, the mixture was allowed to warm to room temperature and was stirred for a further 1 h. The white salt was filtered off, and the filtrate was evaporated to an oil, which solidified on standing. This was distilled in a bulb-to-bulb apparatus, then crystallised from ether–hexane to give the *diamide* as needles (4.9 g, 83%), m.p. 71—72 °C (Found: C, 61.9; H, 10.6; N, 13.2. $C_{11}H_{22}N_2O_2$ requires C, 61.65; H, 10.35; N, 13.1%); $\nu_{max.}$ 2 970, 1 615, 1 495, 1 380, and 1 125 cm^{-1}; δ_H(90 MHz) 0.74 (6 H, t, *J* 7 Hz, CH_2Me), 1.93 (4 H, q, *J* 7 Hz, CH_2Me), 2.93 (6 H, s, NMe), and 2.98 (6 H, s, NMe); *m/z* 214 (M^+, 75%), 199, 170 (100), and 132.

3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrole* (**8**).—3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylic acid[10] (0.84 g, 2.97 mmol) was dissolved in trifluoroacetic acid (5 ml) and the solution was stirred for 1.5 h. The solvent was evaporated and the residue was dissolved in dichloromethane (15 ml) and washed with 2% aqueous sodium carbonate (2 × 10 ml), then dried and evaporated to give the α-free pyrrole (**8**) as an oil (0.71 g, *ca.* 100%), which was used directly in the next step; δ_H(90 MHz) 2.13 (3 H, s, CMe), 2.40—2.84 (4 H, m, $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.68 (6 H, s, 2 × OMe), 6.38 (1 H, d, *J* 2 Hz, α-H), and 8.10 (1 H, br s, NH).

2-(N,N-*Dimethylcarbamoylacetyl*)-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrole* (**9**).—*N,N,N′,N′*-Tetramethylmalonamide (**7**)[13] (1.42 g, 9 mmol) and phosphoryl chloride (1.38 g, 9 mmol) were mixed at room temperature, then cooled in ice for 20 min. A solution of the α-free pyrrole (**8**) (0.71 g, 2.97 mmol) in dry acetonitrile (4 ml) was added to the Vilsmeier reagent and the mixture was stirred for 1.5 h, then poured into 5% aqueous sodium carbonate (40 ml). After the mixture had been stirred for 10 min, it was extracted with dichloromethane (5 × 10 ml) and the extract washed with water (30 ml), and then evaporated. The oil thus obtained was purified on a column of silica gel PF254 [6 cm × 2.5 cm; eluant: ether–methanol (1:0) then (9:1)] to give an oil (890 mg), which was crystallised from ether, to give the *acylated pyrrole* (**9**) as needles (726 mg, 69%), m.p. 88—89 °C (Found: C, 57.8; H, 6.9; N, 7.85. $C_{17}H_{24}N_2O_6$ requires C, 57.9; H, 6.9; N, 7.95%); $\lambda_{max.}$ 304 nm; $\nu_{max.}$(KBr disc) 3 280br, 3 000, 2 960, 1 735s, 1 645s, 1 630, 1 495, 1 430, 1 190, and 1 170 cm^{-1}; δ_H(80 MHz) 2.25 (3 H, s, CMe), 2.56 and 2.98 (each 2 H, m, $CH_2CH_2CO_2$), 2.97 (3 H, s, NMe), 3.17 (3 H, s, NMe), 3.43 (2 H, s, CH_2CO_2), 3.64 and 3.66 (each 3 H, s, OMe), 3.81 (2 H, s, $COCH_2CO$), and 10.67 (1 H, br s, NH); *m/z* 352 (M^+, 100%), 321, 293, 206, 178, and 146.

7-(2-*Methoxycarbonylethyl*)-3-[3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrol*-2-*yl*]-6-*methoxycarbonylmethyl*-5-*methylpyrrolizin*-1-*one* (**10**).—The dimethylamide (**9**) (106 mg, 0.3 mmol) was dissolved in dichloromethane (1 ml), and phosphoryl chloride (48 mg, 0.315 mmol) was added. The solution was stirred for 1 h, then evaporated to dryness at room temperature. A solution of the α-free pyrrole (**8**), made as described above from the carboxylic acid (168 mg, 0.59 mmol), in acetonitrile (1 ml) was added, and the mixture was stirred for 48 h, then poured into 5% aqueous sodium carbonate (25 ml). Methanol (5 ml) was added and the mixture was allowed to stand for 5 min and then extracted with dichloromethane (3 × 5 ml), dried, and evaporated. The residue was purified on a column of silica gel PF254 [2.5 cm × 6 cm; eluant: ether–hexane (7:3), then ether] to give the *pyrrolizine* (**10**) which was crystallised from methanol–water as orange prisms, (66 mg, 41%), m.p. 113–115 °C (Found: C, 61.6; H, 6.1; N, 5.3. $C_{27}H_{32}N_2O_9$ requires C, 61.4; H, 6.1; N, 5.3%); $\lambda_{max.}$ 408 and 310 nm; $\nu_{max.}$(KBr disc) 3 220, 2 950, 1 735s, 1 700s, 1 530, 1 435, 1 165, and 1 155 cm^{-1}; δ_H(400 MHz) 2.27 and 2.33 (each 3 H, s, CMe), 2.53 (8 H, m, 2 × $CH_2CH_2CO_2$), 3.31 and 3.46 (each 2 H, s, CH_2CO_2), 3.67 and 3.69 (each 3 H, s, OMe), 3.70 (6 H, s, 2 × OMe), 5.45 (1 H, s, C=CH), and 9.52 (1 H, br s, NH); *m/z* 528 (M^+, 30%), 441 (100), 381, 86, and 84.

9-*Hydroxy*-1-(2-*methoxycarbonylethyl*)-6-[3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrol*-2-*ylhydroxymethylene*]-2-*methoxycarbonylmethyl*-3-*methyl*-6H-*pyrrolo*[1,2-a]*azepine*-5,7-*dione* (**15**) *or Tautomers*.—The α-free pyrrole (**8**) [prepared from the corresponding α-free carboxylic acid (84 mg, 0.3 mmol)] was dissolved in dichloromethane (1 ml) and cooled in ice. A solution of malonyl dichloride (140 mg, 1 mmol) in dichloromethane (1 ml) was added with stirring over 0.5 min. The mixture was stirred at 0 °C for 15 min, then methanol (2 ml) was added and the mixture was stirred for 1 h at room temperature, then poured into 5% aqueous sodium carbonate (25 ml) and shaken for 2 min. This mixture was then extracted with dichloromethane (3 × 5 ml), dried, and evaporated, and the residue crystallised from methanol to give the *pyrroloazepine* (**15**) as fine yellow needles (26 mg, 29%), m.p. 225—227 °C (Found: M^+, 614.2127. $C_{30}H_{34}N_2O_{12}$ requires *M*, 614.2112); $\lambda_{max.}$ 433 and 358—200br nm; $\nu_{max.}$ 3 500—2 800, 3 430, 2 950, 1 720, 1 665, 1 615, 1 470, 1 375, and 1 070 cm^{-1}; δ_H(250 MHz) 2.27 and 2.31 (each 3 H, s, CMe), 2.54—2.66 (4 H, m, 2 × $CH_2CH_2CO_2$), 3.00 and 3.13 (each 2 H, m, $CH_2CH_2CO_2$), 3.48 and 3.52 (each 2 H, s, CH_2CO_2), 3.66 and 3.68 (each 3 H, s, OMe), 3.69 (6 H, s, 2 × OMe), 6.14 (1 H, s, C=CH), 8.93 (1 H, br s, NH), 11.22 (1 H, s, OH), and 13.32 (1 H, br s, OH); *m/z* 614 (M^+, 100%), 375, 349, 239, 180, 120, and 108.

1,3-*Bis*[3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrol*-2-*yl*]*propane*-1,3-*dione* (**12**).—The α-free pyrrole (**8**) was prepared as before from the corresponding carboxylic acid (566 mg, 2 mmol), then dissolved in dichloromethane (3 ml) and cooled in ice. A solution of malonyl dichloride (141 mg, 1 mmol) in dichloromethane (2 ml) was added dropwise with stirring over 1 min, and stirring was continued for 2 h. The mixture was added to 5% aqueous sodium carbonate (15 ml), and shaken for 2 min. This mixture was extracted with dichloromethane (3 × 5 ml), dried, and evaporated. The residue was purified on a column of silica gel PF254 (5 cm × 2.5 cm), eluting with ether–methanol (9:1). The eluate was evaporated and the residue crystallised from ethyl acetate–hexane to give the *malonyl dipyrrole* (320 mg, 59%) as needles, m.p. 135—136 °C (Found: C, 59.3; H, 6.3; N, 5.2. $C_{27}H_{34}N_2O_{10}$ requires C, 59.3; H, 6.3; N, 5.1%); $\lambda_{max.}$ 410, 390sh, and 314 nm; $\nu_{max.}$(KBr disc) 3 350, 3 320, 2 950, 1 740s, 1 710, 1 435, 1 255, 1 175, and 1 165 cm^{-1}; δ_H(250 MHz) shows a 1:1 mixture of keto and enol tautomers, 2.27 and 2.29 (each 3 H, s, CMe), 2.54 and 2.58 (each 2 H, m, $CH_2CH_2CO_2$), 3.00—3.11

(4 H, m, 2 × $CH_2CH_2CO_2$), 3.43 (4 H, s, 2 × CH_2CO_2), 3.64, 3.66, 3.67, and 3.69 (each 3 H, s, OMe), 4.12 (*ca.* 1 H, s, $COCH_2CO$), 6.19 (*ca.* 0.5 H, s, C=CH of enol), 9.60 (1 H, br s, NH), and 9.72 (1 H, br s, NH); *m/z* 546 (M^+, 60%), 487, 307, 281, 239 (100), 180, and 120.

1,3-*Bis*[3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrol*-2-*yl*]-2-*methylpropane*-1,3-*dione* (**13**).—The malonyl dipyrrole (**12**) (55 mg, 0.1 mmol) was suspended in dry methanol (15 ml), and sodium methoxide (13 mg, 0.24 mmol) was added. The mixture was heated gently until everything had dissolved, then methyl iodide (200 μl) was added, and the mixture was heated at reflux for 4 h. The mixture was acidified with acetic acid, added to water, and extracted with dichloromethane (3 × 5 ml). The *methylmalonyl dipyrrole* (**13**) crystallised from methanol–water as needles (39 mg, 69%), m.p. 123—124 °C (Found: C, 59.7; H, 6.4; N, 5.1. $C_{28}H_{36}N_2O_{10}$ requires C, 60.0; H, 6.5; N, 5.0%); $\lambda_{max.}$ 314 nm; $\nu_{max.}$ 3 420, 3 340, 2 950, 1 725, 1 605, 1 435, and 1 200 cm^{-1}; δ_H(90 MHz) 1.60 (3 H, d, *J* 7 Hz, CH*Me*), 2.28 (6 H, s, 2 × CMe), 2.57 and 3.10 (each 4 H, m, $CH_2CH_2CO_2$), 3.47 (4 H, s, CH_2CO_2), 3.70 and 3.72 (each 6 H, s, 2 × OMe), 4.45 (1 H, q, *J* 7 Hz, C*H*Me), and 9.71 (2 H, br s, NH); *m/z* (f.d.) 560 (M^+, 100%).

Di-t-butyl 2,7,12-*Tris*(2-*methoxycarbonylethyl*)-3,8,13-*tris*-(*methoxycarbonylmethyl*)-10,15,16,17-*tetrahydro*-5H-*tripyrrin*-1,14-*dicarboxylate* (**21**).—To a solution of α-free pyrromethane (**16**) [prepared by decarboxylation of the corresponding α-carboxylic acid (606 mg, 1 mmol)[8]] and acetoxymethylpyrrole (**17**) (397 mg, 1 mmol) in dichloromethane (30 ml) was added toluene-*p*-sulphonic acid monohydrate (380 mg, 2 mmol). The mixture was stirred at room temperature under nitrogen for 2 h, washed with water (10 ml), dried, and evaporated, and the residue was purified on a column of silica gel PF254 (2.5 cm × 5 cm), eluting with ether. The product obtained on evaporation of the eluate was crystallised from ether–hexane, and the supernatants from the crystallisation were purified again as above, to give the *tripyrrole* (**21**) as needles (total 524 mg, 59%), m.p. 70—72 °C (Found: M^+, 899.4062. $C_{45}H_{61}N_3O_{16}$ requires *M*, 899.4052); $\lambda_{max.}$ 282 nm; $\nu_{max.}$(KBr disc) 3 330br, 2 980, 2 950, 1 735s, 1 685, 1 435, 1 365, 1 275, and 1 135 cm^{-1}; δ_H(250 MHz) 1.48 (9 H, s, Bu^t), 1.50 (9 H, s, Bu^t), 2.39—2.55 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.69—2.79 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.93 (2 H, m, $CH_2CH_2CO_2$), 3.39 and 3.49 (each 2 H, s, CH_2CO_2), 3.59, 3.64, 3.64, 3.66, 3.69, and 3.71 (each 3 H, s, OMe), 3.74, 3.75, and 3.79 (each 2 H, s, CH_2CO_2 and 2 × pyrr-CH_2-pyrr), 9.41, 9.53, and 9.59 (each 1 H, br s, NH); *m/z* (f.d.) 899 (M^+, 100%).

Benzyl 2,7,12-*Tris*(2-*methoxycarbonylethyl*)-3,8,13-*tris*(*methoxycarbonylmethyl*)-14-*t-butoxycarbonyl*-10,15,16,17-*tetrahydro*-5H-*tripyrrin*-1-*carboxylate* (**22**).—Toluene-*p*-sulphonic acid monohydrate (250 mg) was added to a solution of the α-free pyrromethane (**16**) [prepared by decarboxylation of the corresponding α-carboxylic acid[8] (404 mg, 0.67 mmol)] and the acetoxymethylpyrrole benzyl ester (**18**) (287 mg, 0.67 mmol) in dichloromethane (25 ml) and the mixture was stirred in the dark under nitrogen for 2 h. The mixture was washed with water (15 ml), dried, and passed down a column of silica gel PF254 (2.5 cm × 5 cm) eluting with ether. Crystallisation of the eluate from ether–hexane under nitrogen gave the *tripyrrole benzyl ester* (**22**) (240 mg, 39%) as needles, m.p. 116—117 °C (Found: M^+, 933.3917. $C_{48}H_{59}N_3O_{16}$ requires *M*, 933.3895); $\lambda_{max.}$ 282 nm; $l_{max.}$(KBr disc) 3 350, 3 320, 2 950, 1 750s, 1 725s, 1 685, 1 665, 1 445, 1 270, 1 245, and 1 170 cm^{-1} ± ^dH(400 MHz) 1.48 (9 H, s, Bu^t), 2.40, 2.47, 2.54, 2.71, 2.75, and 2.97 (each 2 H, m, 3 × $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.52 (5 H, s, OMe and CH_2CO_2), 3.59, 3.60, 3.65, 3.67, and 3.71 (each 3 H, s, OMe), 3.74, 3.75, and 3.82 (each 2 H, s, CH_2CO_2 and 2 × pyrr-CH_2-pyrr), 5.23 (2 H, s, CH_2Ph), 7.28—7.37 (5 H, m, Ph), 9.48, 9.54, and 9.80 (each 1 H, br s, NH); *m/z* (f.d.) 933 (M^+, 100%).

Benzyl 5-(2,2-*Diacetylethyl*)-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole*-2-*carboxylate* (**25**).—Sodium carbonate (50 mg) was added to a solution of chloromethylpyrrole[14] (**19**) (163 mg, 0.4 mmol) and acetylacetone (40 mg, 0.4 mmol) in acetone (2 ml) and the mixture was stirred for 20 h and then added to water (20 ml). The mixture was extracted with dichloromethane (3 × 5 ml), the solvent was evaporated, and the product was crystallised from ether–hexane to give the β-*diketone* (**25**) (90 mg, 48%), m.p. 74—75 °C (Found: C, 63.4; H, 6.0; N, 2.8. $C_{25}H_{29}NO_8$ requires C, 63.7; H, 6.2; N, 3.0%); $\lambda_{max.}$ 280 nm; $\nu_{max.}$(KBr disc) 3 310s, 2 950, 1 735s, 1 695, 1 655s, 1 435, 1 195, and 1 170 cm^{-1}; δ_H(90 MHz) 2.04 (*ca.* 1 H, s, CMe in enol form), 2.20 (*ca.* 6 H, s, CMe in keto form), 2.50 and 2.99 (each 2 H, m, $CH_2CH_2CO_2$), 3.04 (2 H, d, *J* 7 Hz, CH_2CH in keto form), 3.46 (*ca.* 2.3 H, s, CH_2CO_2 and CH_2C=C in enol form), 3.63 (3 H, s, OMe), 3.69 (3 H, s, OMe), 4.07 (1 H, t, *J* 7 Hz, CH_2CH in keto form), 5.30 (2 H, s, CH_2Ph), 7.41 (5 H, s, Ph), and 9.05 (1 H, br s, NH); *m/z* 471 (M^+, 38%), 413, 380, 320, 278, and 91 (100).

Benzyl 5-(2,2-*Dicyanoethyl*)-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrole*-2-*carboxylate* (**28**).—Benzyl 4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate[8] (8.80 g, 23.6 mmol) was dissolved in dry dichloromethane (100 ml), and cooled in ice. Freshly redistilled sulphuryl chloride (1.9 ml, 23.6 mmol) was added over 2 min with vigorous stirring, and the mixture was stirred for 10 min at 0 °C, then at room temperature for 1 h. The solvent was evaporated at room temperature, and the residual chloromethyl pyrrole (**27**) was used directly in the next reaction [δ_H(90 MHz) 2.52 and 2.80 (each 2 H, m, $CH_2CH_2CO_2$), 3.63 and 3.68 (each 3 H, s, OMe), 3.82 (2 H, s, CH_2CO_2), 4.64 (2 H, s, CH_2Cl), 5.32 (2 H, s, CH_2Ph), 7.44 (5 H, br s, Ph), and 9.66 (1 H, br s, NH)].

Malononitrile (9.35 g, 141.6 mmol) was dissolved in tetrahydrofuran (80 ml) and Hunig's base (6 ml, 35.4 mmol) was added with stirring, followed by a solution of the chloromethyl pyrrole (23.6 mmol) in tetrahydrofuran (20 ml) added over 5 min. After 1 h, the solution was added to water (300 ml), and extracted with dichloromethane (3 × 50 ml). The extract was washed with water (3 × 50 ml), dried, and evaporated, and the residual oil was purified on a short fat silica gel PF_{254} column (10 cm diam. × 3 cm long), eluting with ether. The residual oil from the evaporation of the eluates was crystallised from dichloromethane–ether to give the *dinitrile* (**28**) as needles (6.81 g). Chromatography of the supernatants as above, followed by crystallisation of appropriate fractions gave further product (total 7.62 g, 74%), m.p. 102—103 °C (Found: C, 63.2; H, 5.3; N, 9.7. $C_{23}H_{23}N_3O_6$ requires C, 63.15; H, 5.3; N, 9.6%); $\lambda_{max.}$ 276 nm; $\nu_{max.}$(KBr disc) 3 300, 2 950, 2 920, 1 740s, 1 730s 1 670s, 1 280, and 1 260 cm^{-1}; δ_H(90 MHz) 2.38—2.94 (4 H, m, $CH_2CH_2CO_2$), 3.38 [2 H, d, *J* 7 Hz, $CH_2CH(CN)_2$], 3.58 and 3.68 (each 3 H, s, OMe), 3.81 (2 H, s, CH_2CO_2), 4.26 [1 H, t, *J* 7 Hz, $CH(CN)_2$], 5.32 (2 H, s, CH_2Ph), 7.45 (5 H, s, Ph), and 10.10 (1 H, br s, NH); *m/z* 437 (M^+, 2%), 372, 346, 314, 286, and 91 (100).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t-butoxycarbonylpyrrol*-2-*yl*]-*propane*-2,2-*dicarbonitrile* (**29**).—Sulphuryl chloride (1.56 ml, 19.34 mmol) was added with vigorous stirring over 1 min to an ice-cooled solution of t-butyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate[10] (6.56 g, 19.34 mmol) in dry dichloromethane (80 ml) containing

a suspension of precipitated calcium carbonate (5.5 g). After 20 min at 0 °C, the mixture was evaporated at below room temperature under reduced pressure. The residue was redissolved in dichloromethane (100 ml) and filtered through Celite. This solution of the chloromethylpyrrole (**20**) was used directly in the next step. An evaporated sample had δ_H(90 MHz) 1.57 (9 H, s, Bu^t), 2.58 and 3.04 (each 2 H, m, $CH_2CH_2CO_2$), 3.57 (2 H, s, CH_2CO_2), 3.69 and 3.71 (each 3 H, s, OMe), 4.68 (2 H, s, CH_2Cl), and 9.76 (1 H, br s, NH).

The pyrrole dinitrile (**28**) (7.61 g, 17.41 mmol) was added to the dichloromethane solution of (**20**); the mixture was cooled in ice, and Hunig's base (3.64 ml, 20.9 mmol) was added with stirring over 2 min. The ice-bath was removed, and the mixture was stirred for a further 1 h. The solvent was evaporated off, and the residue was purified on a short column of silica PF254 (2.5 cm × 5 cm), eluting with ether (200 ml). Evaporation of the eluate gave the dipyrrole dinitrile (**29**) as a foam (14 g), which was used directly for the next step (Found: M^+, 774.3127. $C_{40}H_{46}N_4O_{12}$ requires M, 774.3112); $\lambda_{max.}$ 279 nm; $\nu_{max.}$ 3 450br, 2 960, 1 740s, 1 705s, 1 460, 1 440, 1 170, and 1 085 cm^{-1}; δ_H(400 MHz) 1.51 (9 H, s, Bu^t), 2.48, 2.55, 2.78, and 2.96 (each 2 H, t, J 7 Hz, 2 × $CH_2CH_2CO_2$), 3.36 and 3.38 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.57 (5 H, s, OMe and CH_2CO), 3.61, 3.64, and 3.65 (each 3 H, s, OMe), 3.77 (2 H, s, CH_2CO_2), 5.23 (2 H, s, CH_2Ph), 7.17—7.42 (5 H, m, Ph), 9.39 (1 H, br s, NH), and 9.52 (1 H, br s, NH); m/z (f.d.) 774 (M^+, 100%).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[5-*carboxy*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*yl*]*propane*-2,2-*dicarbonitrile* (**30**).—The dinitrile diester (**29**) (14 g, 18.1 mmol) was dissolved in trifluoroacetic acid (50 ml) and stirred for 15 min. The mixture was added to water (400 ml), and the products were extracted with dichloromethane (3 × 60 ml). The extract was washed with water (2 × 100 ml) and evaporated, and the residue was redissolved in dichloromethane (50 ml) and ether (250 ml). The solution was extracted with 10% aqueous sodium carbonate (4 × 80 ml) (the dark oil which came out of solution was combined with the aqueous phase). The aqueous extract was acidified with hydrochloric acid and re-extracted with dichloromethane (3 × 60 ml). The extract was dried and evaporated, and the residual oil was crystallised from dichloromethane–ether, to give the *carboxylic acid* (**30**) (5.36 g, 41%) as powdery crystals. The supernatants from crystallisation were passed down a column of silica PF254 (2.5 cm × 6 cm), eluting with ether–methanol (9:1). This gave further acid (3.1 g), which was virtually pure by t.l.c., although it could not be induced to crystallise (total yield 8.47 g, 65%), m.p. 135—137 °C (Found: M^+, 718.2463. $C_{36}H_{38}N_4O_{12}$ requires M, 718.2486); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 3 310, 2 950, 1 735s, 1 705s, 1 435, 1 265, and 1 175 cm^{-1}; δ_H(400 MHz) 2.51, 2.62, 2.81, and 3.03 (each 2 H, t, J 7 Hz, 2 × $CH_2CH_2CO_2$), 3.45 and 3.48 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.54, 3.62, and 3.66 (each 3 H, s, OMe), 3.64 (5 H, s, OMe and CH_2CO_2), 3.77 (2 H, s, CH_2CO_2), 5.26 (2 H, s, CH_2Ph), 7.30—7.35 (5 H, m, Ph), and 9.86 and 10.00 (each 1 H, br s, NH); m/z (f.d.) 718 (M^+, 100%), and 674 ($M^+ - CO_2$, 20).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[5-*iodo*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*yl*]-2,2-*dicyanopropane*-2,2-*dicarbonitrile* (**31**).—The carboxylic acid (**30**) (5.36 g, 7.46 mmol) was suspended in dichloromethane (100 ml), and stirred vigorously with 5% aqueous sodium hydrogen carbonate (100 ml) while an aqueous solution (80 ml) of iodine (0.1M) and potassium iodide (0.2M) was added over 5 min. The mixture was stirred for a further 20 min, then sodium metabisulphite was added until the excess iodine was destroyed, and the organic layer was decanted. The aqueous phase was extracted with dichloromethane (2 × 50 ml), and the combined organic phase was dried, then passed down a short column of silica gel PF254 (4 cm × 4 cm) eluting with ether (250 ml). Evaporation of the eluate gave the *iodopyrrole* (**31**) as a gum, (5.02 g, 84·%), which was used immediately in the next step. In a separate experiment, the iodopyrrole (**31**) was crystallised from methanol as prisms, m.p. 169—171 °C (Found: M^+, 800.1560. $C_{35}H_{37}IN_4O_{10}$ requires M, 800.1553); $\lambda_{max.}$ 278 nm; $\nu_{max.}$ 3 420, 2 950, 1 725s, 1 435, 1 175, and 1 090 cm^{-1}; δ_H(400 MHz) 2.47 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.58 and 2.77 (each 2 H, t, J 7 Hz, $CH_2CH_2CO_2$), 3.32 and 3.36 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.56 (5 H, s, OMe and CH_2CO_2), 3.62 (3 H, s, OMe), 3.66 (6 H, s, 2 × OMe), 3.77 (2 H, s, CH_2CO_2), 5.25 (2 H, s, CH_2Ph), 7.20—7.40 (5 H, m, Ph), and 8.71 and 9.48 (each 1 H, br s, NH); m/z (f.d.) 800 (M^+, 100%).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*yl*]*propane*-2,2-*dicarbonitrile* (**32**).—The iododipyrrole (**31**) (930 mg, 1.16 mmol) was dissolved in methanol (40 ml), along with sodium acetate (500 mg). 10% Palladium-on-charcoal (100 mg) was added and the mixture was hydrogenated at room temperature until a total of 35 ml of hydrogen had been taken up (40 min). The catalyst was filtered off through Celite, and the solvent was evaporated. The residue was partitioned between dichloromethane (30 ml) and water (20 ml). The organic layer was decanted and washed with water (25 ml), then evaporated, and the residue was crystallised from methanol to give the α-*free benzyl ester* (**32**) as needles (729 mg, 93%), m.p. 147—149 °C (Found: C, 62.2; H, 5.5; N, 8.3. $C_{35}H_{38}N_4O_{10}$ requires C, 62.3; H, 5.7; N, 8.3%); $\lambda_{max.}$ 277 nm; $\nu_{max.}$(KBr disc) 3 390, 3 310, 2 950, 1 730s, 1 690, 1 435, 1 200, and 1 175 cm^{-1}; δ_H(400 MHz) 2.48, 2.56, 2.74, and 2.76 (each 2 H, t, J 7 Hz, 2 × $CH_2CH_2CO_2$), 3.37 and 3.39 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.50 (2 H, s, CH_2CO_2), 3.57, 3.62, 3.65, and 3.66 (each 3 H, s, OMe), 3.78 (2 H, s, CH_2CO_2), 5.25 (2 H, s, CH_2Ph), 6.56 (1 H, d, J 2.4 Hz, α-H), 7.25—7.40 (5 H, m, Ph), and 8.22 and 9.15 (each 1 H, br s, NH); m/z (f.d.) 674 (M^+, 100%).

2-*Formyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-*methylpyrrole* (**34**).—t-Butyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate (**33**)[11] (6.79 g, 20 mmol) was dissolved in trifluoroacetic acid (24 ml) at room temperature and the solution was stirred for 2.3 h. The reaction mixture was cooled to 0 °C and stirred during the addition of distilled trimethyl orthoformate (32 ml). After 30 min the mixture was allowed to warm to room temperature, and was kept at this temperature for a further 1 h. The mixture was cooled again to 0 °C, poured into ice-cold 10% aqueous sodium carbonate (400 ml) with stirring and the resulting emulsion was extracted with dichloromethane (3 × 70 ml). The combined organic extracts were washed with water (250 ml), dried, and evaporated. The residue was purified by flash chromatography [3 cm × 16 cm; eluant: dichloromethane–ether (1:0) then (5:2)] and then crystallised from dichloromethane–ether to yield the pyrrole aldehyde (**34**) (5.02 g, 94%) as rhombs, m.p. 114—115.5 °C (lit.,[10] 112—114 °C) (Found: C, 58.1; H, 6.45; N, 5.3. Calc. for $C_{13}H_{17}NO_5$: C, 58.4; H, 6.4; N, 5.2%); $\lambda_{max.}$ 267sh and 308 nm; $\nu_{max.}$ 3 420, 3 240, 1 730, 1 630, 1 580, 1 500, 1 440, and 1 375 cm^{-1}; δ_H(90 MHz) 2.28 (3 H, s, CMe), 2.50—2.74 (2 H, m, $CH_2CH_2CO_2$), 2.96—3.19 (2 H, m, $CH_2CH_2CO_2$), 3.44 (2 H, s, CH_2CO_2), 3.69 and 3.72 (each 3 H, s, 2 × OMe), 9.48 (1 H, s, CHO), and 10.35 (1 H, br s, NH); m/z 267 (M^+), 239, 235, 208, 207, 206, 180, 166, and 148.

5-*Acetoxymethyl*-2-*formyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole* (**35**).—The methylpyrrole (**34**)

(3.34 g, 12.5 mmol) was dissolved in a mixture of dry tetrahydrofuran (125 ml) and dry ether (125 ml) under argon and cooled to 0 °C. The solution was stirred during the dropwise addition of a solution of t-butyl hypochlorite[15] (2.03 g, 18.7 mmol) in dry ether (20 ml) over 40 min. On completion of the addition, the reaction mixture was allowed to warm to room temperature over 30 min and was then evaporated. An n.m.r. spectrum of the intermediate *chloromethylpyrrole* showed δ_H(90 MHz) 2.49—2.76 (2 H, m, $CH_2CH_2CO_2$), 2.99—3.22 (2 H, m, $CH_2CH_2CO_2$), 3.55 (2 H, s, CH_2CO_2), 3.69 and 3.73 (each 3 H, s, 2 × OMe), 4.68 (2 H, s, CH_2Cl), 9.65 (1 H, s, CHO), and 9.85 (1 H, br s, NH). The residue was taken up in a solution of sodium acetate (5.0 g, 60.9 mmol) in acetic acid (100 ml) and the resulting mixture was stirred at 50 °C for 2 h. After having been cooled, the mixture was poured into water (800 ml) and the resulting emulsion was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with dilute brine (2 × 500 ml), dried, and evaporated. The residue was purified by flash chromatography [3 cm × 17 cm; eluant: dichloromethane–ether (1:0) then (7:3)] and then crystallised from ethyl acetate–ether to yield the acetoxymethylpyrrole (**35**) (2.375 g, 58.5%) as rhombs, m.p. 77.5—78.5 °C [lit.,[9] 70—71 °C from benzene–light petroleum (b.p. 60—80 °C)] (Found: C, 55.2; H, 5.9; N, 4.3. Calc. for $C_{15}H_{19}NO_7$: C, 55.4; H, 5.9; N, 4.3%); $\lambda_{max.}$ 299 nm; $\nu_{max.}$ 3 410, 3 240, 1 730, 1 645, and 1 440 cm^{-1}; δ_H(90 MHz) 2.08 (3 H, s, COMe), 2.48—2.75 (2 H, m, $CH_2CH_2CO_2$), 2.98—3.22 (2 H, m, $CH_2CH_2CO_2$), 3.56 (2 H, s, CH_2CO_2), 3.68 and 3.72 (each 3 H, s, 2 × OMe), 5.13 (2 H, s, OCH_2–pyrr), 9.60 (1 H, s, CHO), and 9.80 (1 H, br s, NH); *m/z* 325 (M^+), 294, 283, 266, 265, 222, 206, and 146.

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*yl*}*propane*-2,2-*dicarbonitrile* (**36**).—The α-free compound (**32**) (1.23 g, 1.82 mmol) and the acetoxymethyl aldehyde (**35**) (593 mg, 1.82 mmol) were dissolved in dichloromethane (50 ml) and tetrahydrofuran (1.2 ml). Stannic chloride (0.22 ml, 1.83 mmol) was added, and the mixture was stirred under argon in the dark at room temperature for 24 h. Methanol (4 ml) was added, then chloroform (150 ml), and the mixture was washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and water (200 ml), then dried and evaporated. The residue was purified on a column of silica gel PF254 (2.5 cm × 8 cm), eluting with ether then ether–methanol (9:1). The fractions containing the product were evaporated and crystallised from dichloromethane–ether to give the *tripyrrole* (**36**) (1.41 g, 82%) as needles, m.p. 89—97 °C (decomp.) (Found: C, 61.55; H, 5.7; N, 7.5%; M^+, 939.3505. $C_{48}H_{53}N_5O_{15}$ requires C, 61.3; H, 5.7; N, 7.45%; *M*, 939.3538); $\lambda_{max.}$ 308 and 278 nm; $\nu_{max.}$ 3 420, 3 300, 2 950, 1 725s, 1 635, 1 435, and 1 175 cm^{-1}; δ_H(400 MHz) 2.44 and 2.50 (each 2 H, t, *J* 7 Hz), 2.69 (6 H, m), and 3.00 (2 H, t, *J* 7 Hz), (3 × $CH_2CH_2CO_2$), 3.32 and 3.37 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.50 (2 H, s, CH_2CO_2), 3.57 (3 H, s, OMe), 3.58 (2 H, s, CH_2CO_2), 3.61, 3.64, 3.65, 3.72, and 3.76 (each 3 H, s, OMe), 3.76 and 3.92 (each 2 H, s, CH_2CO_2 and pyrr–CH_2–pyrr), 5.25 (2 H, s, CH_2Ph), 7.25—7.45 (5 H, m, Ph), 9.07 (1 H, br s, NH), 9.55 (1 H, s, CHO), and 9.76 and 10.25 (each 1 H, br s, NH); *m/z* (f.d.) 939 (M^+, 100%).

1-[3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*yl*}*propane*-2,2-*dicarbonitrile* (**39**).—The benzyl ester (**36**) (1.41 g, 1.5 mmol) was dissolved in methanol (50 ml), 10% palladium-on-charcoal (100 mg) was added, and the mixture was hydrogenated at room temperature and pressure until 41 ml of hydrogen had been absorbed (30 min). The catalyst was filtered off through Celite, and the filtrate was evaporated to give the carboxylic acid (**37**) as a gum (1.27 g, 100%). The acid was normally used directly, but a sample was crystallised from dichloromethane–ether to give powdery crystals, m.p. 111—113 °C; $\lambda_{max.}$ 310 and 270 nm; $\nu_{max.}$(KBr disc) 3 360, 3 225, 2 955, 1 735s, 1 710s, 1 625s, 1 440, 1 210, and 1 175 cm^{-1}; δ_H(400 MHz) 2.44—2.52 (4 H), 2.60, 2.73, and 2.79 (each 2 H, m), and 2.99 (2 H, t, *J* 7 Hz) (3 × $CH_2CH_2CO_2$), 3.38 [4 H, br s, $CH_2C(CN)_2CH_2$], 3.51 and 3.55 (each 2 H, s, CH_2CO_2), 3.62 and 3.64 (each 3 H, s, OMe), 3.66 (6 H, s, 2 × OMe), 3.70 and 3.73 (each 3 H, s, OMe), 3.80 and 3.91 (each 2 H, s, CH_2CO_2 and pyrr–CH_2–pyrr), 9.49 (1 H, s, CHO), and 9.66, 9.70, and 10.46 (each 1 H, br s, NH); *m/z* (f.d.) 849 (M^+, 100%).

The crude carboxylic acid (**37**) (1.27 g, 1.5 mmol) was dissolved in dichloromethane (40 ml), and stirred vigorously with water (40 ml) containing sodium hydrogen carbonate (1.2 g) while a solution of iodine (420 mg, 1.65 mmol) and potassium iodide (550 mg) in water (20 ml) was added over 2 min. After a further 15 min of stirring, aqueous sodium hydrogen sulphite was added to destroy the excess of iodine, and the organic phase was decanted. The aqueous phase was extracted with dichloromethane (2 × 30 ml), and the combined organic phases were dried and evaporated. The residue was purified on a column of silica gel PF254 (2.5 cm × 5 cm), eluting with ether–methanol (9:1), to give the iodotripyrrole (**38**) as a rather unstable gum (1.085 g, 78%); δ_H(400 MHz) 2.46, 2.51, 2.73, and 3.00 (each 2 H, t, *J* 7 Hz) and 2.66 and 2.81 (each 2 H, m) (3 × $CH_2CH_2CO_2$), 3.27 and 3.34 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.38, 3.50, and 3.58 (each 2 H, s, CH_2CO_2), 3.62, 3.64, 3.75, and 3.76 (each 3 H, s, OMe), 3.68 (6 H, s, 2 × OMe), 3.92 (2 H, s, pyrr–CH_2–pyrr), 8.27 (1 H, br s, NH), 9.56 (1 H, s, CHO), 9.66 (1 H, br s, NH), and 10.21 (1 H, br s, NH); *m/z* (f.d.) 931 (M^+, 100%).

The iodotripyrrole (**38**) (1.08 g, 1.16 mmol) was dissolved in methanol (50 ml) with sodium acetate (350 mg), 10% palladium-on-charcoal (100 mg) was added, and the mixture was hydrogenated at room temperature until 28 ml of hydrogen had been absorbed (35 min). The catalyst was filtered off through Celite, and the filtrate was evaporated. The residue was partitioned between dichloromethane (40 ml) and water (40 ml); the organic phase was decanted, and the aqueous layer was extracted with dichloromethane (2 × 20 ml). The combined dichloromethane solutions were washed with water (20 ml), dried, and evaporated. The residue was purified on a column of silica gel PF254 (2.5 cm × 5 cm), eluting with ether–methanol (9:1). Crystallisation of appropriate fractions from methanol gave the *α-free tripyrrole* (**39**) as air-sensitive needles (758 mg, 71%), m.p. 85—87 °C (Found: M^+, 805.3146. $C_{40}H_{47}N_5O_{13}$ requires *M*, 805.3170); $\lambda_{max.}$ 309 nm; $\nu_{max.}$(KBr disc) 3 350, 3 310, 3 250, 2 950, 1 735s, 1 620, 1 435, 1 270, 1 200, and 1 170 cm^{-1}; δ_H(400 MHz) 2.50 (4 H, m), 2.64 and 2.79 (each 2 H, m), and 2.70 and 3.00 (each 2 H, t, *J* 7 Hz) (3 × $CH_2CH_2CO_2$), 3.27 and 3.33 [each 2 H, s, $CH_2C(CN)_2CH_2$], 3.43, 3.50, and 3.57 (each 2 H, s, CH_2CO_2), 3.63, 3.65, 3.67, 3.74, and 3.74 (each 3 H, s, OMe), 3.92 (2 H, s, pyrr–CH_2–pyrr), 6.68 (1 H, d, *J* 2.7 Hz, α-H), 8.27 (1 H, br s, NH), 9.55 (1 H, s, CHO), 9.63 (1 H, br s, NH), and 10.20 (1 H, br s, NH); *m/z* (f.d.) 805 (M^+, 100%).

1,14-(2,2-*Dicyanopropane*-1,3-*diyl*)-2,7,12-*tris*(2-*methoxycarbonylethyl*)-3,8,13-*tris*(*methoxycarbonylmethyl*)-10,15,16,17-*tetrahydro*-5H-*tripyrrin* (**41**).—The α-free formyl tripyrrole (**39**) (290 mg, 0.36 mmol) was dissolved in dichloromethane (10 ml) and methanol (10 ml), and triethylamine (0.2 ml) was added. The solution was stirred while sodium borohydride (200 mg) was added in portions over 1 min. After a further 10 min of

stirring, dichloromethane (20 ml) was added. The solution was washed with brine (15 ml), and 25% aqueous glucose (15 ml), then dried, and evaporated at room temperature. The residual crude hydroxymethyl compound (**40**), which showed one spot on t.l.c., was used immediately. The gum was dissolved in dry dichloromethane (400 ml), and stirred under nitrogen while a solution of toluene-*p*-sulphonic acid monohydrate in methanol (100 mg in 10 ml) was added dropwise until the solution's colour changed from yellow to red. The mixture was stirred for 10 min, then triethylamine (50 μl) was added, and the solvents were evaporated off below room temperature. The residual brown oil was separated on a column of silica gel PF254 (2.5 cm × 5 cm), eluting with ether–methanol (97:3). The highest R_F product was further purified on another similar column eluting with ether, to give the *dicyano macrocycle* (**41**) as a gum (70 mg, 25%) which crystallised from benzene–hexane as prisms, m.p. 123—124 °C (Found: M^+. 789.3211. $C_{40}H_{47}N_5O_{12}$ requires *M*, 789.3221); $\lambda_{max.}$ no significant absorption greater than 220 nm; $\nu_{max.}$ 3 390, 3 320, 2 950, 1 720, 1 435, and 1 170 cm^{-1}; $\delta_H(CD_2Cl_2$; 400 MHz) 2.40, 2.43, 2.50, and 2.77 (each 2 H, t, *J* 7 Hz) and 2.65 (4 H, m) (3 × $CH_2CH_2CO_2$), 3.29 [4 H, s, $CH_2C(CN)_2CH_2$],3.34, 3.39, and 3.53 (each 2 H, s, CH_2CO_2), 3.54, 3.55, 3.62, 3.62, 3.65, and 3.71 (each 3 H, s, OMe), 3.72 and 3.78 (each 2 H, s, pyrr–CH_2–pyrr), and 7.80, 7.94, and 9.07 (each 1 H, br s, NH); δ_C(multiplicities assigned using the DEPT pulse sequence) 19.30, 19.63, 19.79 (3 × $CH_2CH_2CO_2$), 22.40 (2 C, 2 × pyrr–CH_2–pyrr), 29.77, 30.18, and 30.39 (3 × CH_2CO_2), 33.80, 34.07, 34.71, 35.24, and 35.44 [3 × $CH_2CH_2CO_2$ and $CH_2C(CN)_2CH_2$], 36.52 [$C(CN)_2$], 51.53, 51.59, 51.64, 52.07, 52.13, and 52.34 (6 × OMe), 110.56, 111.19, 114.77, 116.08 (2 C), 116.47, 117.58, 118.46, 119.71, 121.14, 126.06, 127.46, 129.54, and 131.45 (12 × pyrr-C and 2 × CN), and 172.08, 173.18, 173.43, 174.00, 174.13, and 174.80 (6 × CO_2); *m/z* 789 (M^+, 25%), 758, 731, 550 (100), and 538. The *X*-ray crystal structure of (**41**) is described in the Discussion.

Alkaline Hydrolysis of the Dinitrile Macrocycle (**41**).—The macrocycle (**41**) (22 mg, 0.028 mmol) was dissolved in tetrahydrofuran (1 ml), and aqueous KOH (2M; 1 ml) was added. The mixture was stirred under argon in the dark for 17 h. The solution was washed with ether (2 × 2 ml), and evaporated nearly to dryness. The residue was dissolved in acetic acid (200 μl) and methanol (2 ml); ether (10 ml) was added, and the mixture was treated with diazomethane at room temperature until the yellow colour persisted. It was then stirred for a further 1 h. The mixture was evaporated, and the residue was partitioned between aqueous sodium hydrogen carbonate (5%; 10 ml) and dichloromethane (3 ml). The organic phase was decanted, and the aqueous phase was extracted with dichloromethane (2 × 3 ml). The combined organic extracts were evaporated. T.l.c. of the residue indicated that there were three non-baseline products, but that none of these was the starting material. The main product (*ca.* 2 mg) at highest R_F was assigned as the heptacarboxylic ester (**43**); δ_H(400 MHz) 2.41 and 2.52 (each 2 H, m), 2.61 (4 H, m), and 2.77 (4 H, m) (3 × $CH_2CH_2CO_2$), 2.96 and 3.31 [2 H, AB system, *J* 16 Hz, $CH_2C(CN)CO_2Me$], 2.99 and 3.16 [2 H, AB system, *J* 16 Hz, $CH_2C(CN)CO_2Me$], 3.35 (4 H, m, probably 2 × CH_2CO_2, both AB systems), 3.47 (2 H, m, probably CH_2CO_2, AB system), 3.52, 3.61, 3.62, 3.63, 3.64, 3.68, and 3.77 (each 3 H, s, 7 × OMe), 3.80 and 3.86 (each 1 H, half of AB system, *J* 17 Hz, other halves obscured by OMe signals, 2 × pyrr–CH_2–pyrr), 7.75, 7.85, and 9.00 (each 1 H, br s, NH); *m/z* (f.d.) 822 (M^+, 100%) and 820 (due to aerial oxidation).

(E)- *and* (Z)-1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*]-2-*nitropropene* (**48**).—Anhydrous potassium acetate (74 mg, 0.75 mmol) and methylamine hydrochloride (44 mg, 0.65 mmol) were added to a stirred solution of t-butyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2-nitroethyl)pyrrole-2-carboxylate (**46**)[11] (199 mg, 0.50 mmol) and benzyl 5-formyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylate (**45**)[9] (484 mg, 1.25 mmol) in dry methanol (5 ml) at 50 °C under argon. The mixture was stirred at 50 °C for 7 h, then cooled to room temperature and poured into hydrochloric acid (1M; 50 ml). The resulting emulsion was extracted with dichloromethane (3 × 20 ml), and the combined organic extracts were dried and evaporated. The residue was partially separated by flash chromatography [3 cm × 18 cm; eluant: hexane–ethyl acetate (2:1)]. Fractions containing the nitroethylpyrrole (**46**) were evaporated and crystallised from ethyl acetate–hexane yielding recovered starting material (103 mg). Product-containing fractions were combined and evaporated, to yield a yellow oil. The two isomers were separated by preparative h.p.l.c. [eluant hexane–ethyl acetate (4:1)] affording the less polar (E)-*nitropropene* (26 mg, 7%) and the more polar (Z)-*nitropropene* (16 mg, 4%) as yellow gums which could not be crystallized [total yield of nitropropenes (**48**) 42 mg, 11%, or 23% based on unrecovered nitroethylpyrrole (**46**)]. For the (*E*)-nitropropene (Found: M^+, 767.2889. $C_{38}H_{45}N_3O_{14}$ requires *M*, 767.2902); $\lambda_{max.}$ 272 and 386 nm; $\nu_{max.}$ 3 440, 3 330, 1 740, 1 710sh, 1 640, 1 500, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.51 (9 H, s, CMe_3), 2.47—2.55 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.85—2.89 and 2.95—2.99 (each 2 H, m, 2 × $CH_2CH_2CO_2$), 3.51 (2 H, s, CH_2CO_2), 3.53, 3.62, 3.63, and 3.66 (each 3 H, s, 4 × OMe), 3.75 (2 H, s, CH_2CO_2), 4.24 (2 H, s, CH_2CNO_2), 5.25 (2 H, s, $PhCH_2$), 7.33—7.38 (5 H, m, Ph), 8.16 (1 H, s, C=CH), and 8.90 and 9.40 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 767 (M^+, 100%). For the (*Z*)-nitropropene (Found: M^+, 767.2897); $\lambda_{max.}$ 272 and 387 nm; $\nu_{max.}$ 3 440, 3 410, 1 740, 1 705sh, 1 635, 1 500, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.52 (9 H, s, CMe_3), 2.44—2.49 and 2.52—2.56 (each 2 H, m, 2 × $CH_2CH_2CO_2$), 2.84—2.87 and 2.95—2.99 (each 2 H, m, 2 × $CH_2CH_2CO_2$), 3.53 (2 H, s, CH_2CO_2), 3.59, 3.61, 3.63, and 3.64 (each 3 H, s, 4 × OMe), 3.82 (2 H, s, CH_2CO_2), 3.99 (2 H, s, CH_2CNO_2), 5.32 (2 H, s, $PhCH_2$), 7.09 (1 H, s, C=CH), 7.32—7.42 (5 H, m, Ph), and 9.22 and 10.63 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 767 (M^+, 100%).

(E)-*Benzyl* 4-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-(2-*nitroethenyl*)*pyrrole*-2-*carboxylate*.—Anhydrous potassium acetate (2.73 g, 27.8 mmol) and methylamine hydrochloride (1.71 g, 25.3 mmol) were added to a stirred solution of benzyl 5-formyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylate (**45**)[9] (9.67 g, 25 mmol) and nitromethane (3.06 g, 50 mmol) in dry methanol (55 ml) at 50 °C. The mixture was maintained at this temperature for 2 h during which time some of the product crystallised out of the reaction mixture. The whole mixture was cooled, taken up in dichloromethane (100 ml) and washed with water (600 ml). The aqueous washing was extracted with dichloromethane (3 × 50 ml), the combined organic phase was washed with brine (200 ml), and then dried and evaporated. The residue was purified by flash chromatography [4.5 cm × 16 cm; eluant: dichloromethane–ether (9:1)] and then crystallised from dichloromethane–methanol to yield the *nitrovinylpyrrole* (7.37 g, 69%) as yellow needles, m.p. 163—164.5 °C (Found: C, 58.9; H, 5.2; N, 6.4. $C_{21}H_{22}N_2O_8$ requires C, 58.6; H, 5.15; N, 6.5%); $\lambda_{max.}$ 264 and 381 nm; $\nu_{max.}$ 3 420, 3 300, 1 735, 1 700sh, 1 625, 1 560, 1 465, and 1 350 cm^{-1}; δ_H(400 MHz) 2.49 (2 H, t, *J* 7.4 Hz, $CH_2CH_2CO_2$), 2.87 (2 H, t, *J* 7.4 Hz, $CH_2CH_2CO_2$), 3.56 and 3.65 (each 3 H, s, 2 × OMe), 3.78 (2 H, s, CH_2CO_2), 5.31 (2 H, s, $PhCH_2$), 7.38 (5 H, s, Ph), 7.54 (1 H, d, *J* 13.6 Hz, CH=CHNO$_2$),

7.93 (1 H, d, *J* 13.6 Hz, C*H*=CHNO$_2$), and 9.76 (1 H, br s, NH); *m/z* 430 (M^+), 352, 339 ($M^+ - C_7H_7$), 307, 279, and 91 ($C_7H_7^+$).

Benzyl 4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-5-(2-nitroethyl)pyrrole-2-carboxylate (**47**).—A solution of the nitrovinylpyrrole (7.37 g, 17.1 mmol) in dry dichloromethane (100 ml) was stirred vigorously during the rapid addition of dry methanol (150 ml) and then solid sodium borohydride (1.3 g, 34.3 mmol). After 2 min the mixture was poured into ice-cold hydrochloric acid (1M; 400 ml) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 ml) and the combined organic extracts were dried and evaporated. The residue was crystallised from dichloromethane–ether–methanol to give the *nitroethylpyrrole* (**47**) (6.46 g, 87%) as needles, m.p. 120.5—121.5 °C (from ethyl acetate–hexane) (Found: C, 58.6; H, 5.8; N, 6.45. $C_{21}H_{24}N_2O_6$ requires C, 58.3; H, 5.6; N, 6.5%); $\lambda_{max.}$ 278 nm; $\nu_{max.}$ 3 450, 1 740, 1 705, and 1 560 cm^{-1}; δ_H(400 MHz) 2.44 (2 H, t, *J* 7.4 Hz, CH$_2$C*H*$_2$CO$_2$), 2.70 (2 H, t, *J* 7.4 Hz, C*H*$_2$CH$_2$CO$_2$), 3.30 (2 H, t, *J* 7.0 Hz, C*H*$_2$CH$_2$NO$_2$), 3.55 and 3.63 (each 3 H, s, 2 × OMe), 3.76 (2 H, s, CH$_2$CO$_2$), 4.56 (2 H, t, *J* 7.0 Hz, CH$_2$C*H*$_2$NO$_2$), 5.26 (2 H, s, PhC*H*$_2$), 7.32—7.38 (5 H, m, Ph), and 9.54 (1 H, br s, NH); *m/z* 432 (M^+), 385 ($M^+ - HNO_2$), 341 ($M^+ - C_7H_7$), 167, and 91 ($C_7H_7^+$).

(E)- *and* (Z)-3-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-1-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*]-2-*nitropropene* (**49**).—The nitroethylpyrrole (**47**) (6.48 g, 15 mmol) and anhydrous potassium acetate (2.2 g, 22.5 mmol) were dissolved in dry methanol (150 ml) at 50 °C. t-Butyl 5-formyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**44**)[11] (13.25 g, 37.5 mmol) and methylamine hydrochloride (1.320 g, 19.5 mmol) were added and the mixture was stirred at 50 °C for 7.3 h. The reaction mixture was cooled, poured into hydrochloric acid (0.3M; 600 ml), and the resulting emulsion extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried, and evaporated. The residue was purified by flash chromatography [6.5 cm × 15 cm; eluant: light petroleum (b.p. 30—40 °C)–hexane–ethyl acetate (5:0:2) then (0:2:1)] to give reasonable separation. The small mixed fractions were rechromatographed on a second flash chromatography column (3 cm × 15 cm; same eluants). The pure fractions from both columns were combined and evaporated to yield recovered nitroethylpyrrole (**47**) (3.18 g, after recrystallisation from ethyl acetate–hexane) and the (*E*)- and (*Z*)-nitropropenes (**49**) [2.42 g, 21% or 41% based on unrecovered nitroethylpyrrole (**47**)] as a yellow gum comprising a 2:1 mixture of the *E*- and *Z*-isomers. This mixture was carried straight through to the next step without further purification, but in a separate experiment the isomers (**49**) were separated by preparative h.p.l.c. [eluant hexane–ethyl acetate (4:1)] to give the less polar (E)-*nitropropene* and more polar (Z)-*nitropropene* as yellow gums for characterisation. For the (*E*)-nitropropene: (Found: M^+, 767.2889. $C_{38}H_{45}N_3O_{14}$ requires *M*, 767.2902); $\lambda_{max.}$ 277 and 390 nm; $\nu_{max.}$ 3 450, 3 330, 1 740, 1 705, 1 640, 1 460, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.51 (9 H, s, CMe$_3$), 2.48—2.54 (4 H, m, 2 × CH$_2$C*H*$_2$CO$_2$), 2.77—2.81 and 2.92—2.96 (each 2 H, m, 2 × C*H*$_2$CH$_2$CO$_2$), 3.56, 3.63, 3.65, and 3.68 (each 3 H, s, 4 × OMe), 3.64 and 3.78 (each 2 H, s, 2 × CH$_2$CO$_2$), 4.30 (2 H, s, CH$_2$CNO$_2$), 5.22 (2 H, s, PhC*H*$_2$), 7.29—7.38 (5 H, s, Ph), 8.10 (1 H, s, C=CH), and 8.96 and 9.28 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 767 (M^+, 100%). For the (*Z*)-nitropropene (Found: M^+, 767.2889. $C_{38}H_{45}N_3O_{14}$ requires *M*, 767.2902); $\lambda_{max.}$ 276 and 389 nm; $\nu_{max.}$ 3 430, 3 390, 1 735, 1 705, 1 635, 1 500, 1 455, 1 445, and 1 370 cm^{-1}; δ_H(400 MHz) 1.57 (9 H, s, CMe$_3$), 2.42—2.46 and 2.55—2.58 (each 2 H, m, 2 × CH$_2$C*H*$_2$CO$_2$), 2.72—2.76 and 2.99—3.03 (each 2 H, m, 2 × C*H*$_2$CH$_2$CO$_2$), 3.57, 3.59, 3.61, and 3.63 (each 3 H, s, 4 × OMe), 3.59 and 3.79 (each 2 H, s, 2 × CH$_2$CO$_2$), 4.01 (2 H, s, CH$_2$CNO$_2$), 5.24 (2 H, s, PhC*H*$_2$), 6.79 (1 H, s, C=CH), 7.30—7.38 (5 H, m, Ph), and 9.19 and 10.68 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 767 (M^+, 100%).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*]-2-*nitropropane* (**50**).—Sodium borohydride (400 mg, 10.6 mmol) was added to a vigorously stirred ice-cold solution of the mixture of isomeric nitropropenes (**49**) (2.42 g, 3.15 mmol) in dry methanol (250 ml) under argon. Strong effervescence was observed and the mixture was rapidly decolourised from deep orange to pale yellow. After 3 min the mixture was poured into ice-cold hydrochloric acid (0.5M; 500 ml). The resulting emulsion was extracted with dichloromethane (2 × 50 ml), and the combined organic extracts were dried and evaporated to give the *nitropropane* (**50**) (2.41 g, 99%) as an oil. This material was carried through to the next step without further purification, but in a separate experiment a sample of (**50**) was purified by flash chromatography [eluant: hexane–ethyl acetate (1:1)] (Found: M^+, 769.3038. $C_{38}H_{47}N_3O_{14}$ requires *M*, 769.3058); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 3 450, 3 360, 1 735, 1 700sh, 1 555, 1 450, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.52 (9 H, s, CMe$_3$), 2.46—2.52 (4 H, m, 2 × CH$_2$C*H*$_2$CO$_2$), 2.64—2.71 and 2.88—2.94 (each 2 H, m, 2 × C*H*$_2$CH$_2$CO$_2$), 3.05 (1 H, d, *J* 15.2 Hz, C*H*HCHNO$_2$), 3.06 [1 H, dd, *J* 15.3 and 1.9 Hz, CH(NO$_2$)-C*H*H], 3.33 [1 H, dd, *J* 15.3 and 8.4 Hz, CH(NO$_2$)CH*H*], 3.34 (1 H, dd, *J* 15.2 and 7.8 Hz, CH*H*CHNO$_2$), 3.40 and 3.44 (2 H, AB system, *J* 16.2 Hz, CH$_2$CO$_2$), 3.56, 3.63, 3.64, and 3.67 (each 3 H, s, 4 × OMe), 3.74 and 3.80 (2 H, AB system, *J* 16.9 Hz, CH$_2$CO$_2$), 5.22 and 5.24 (2 H, AB system, *J* 12.2 Hz, PhC*H*$_2$), 5.25 (1 H, m, CHNO$_2$), 7.26—7.36 (5 H, m, Ph), and 9.12 and 9.40 (each 1 H, br s, 2 × pyrr-NH); *m/z* (f.d.) 769 (M^+, 100%).

1-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*yl*]-3-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*]-2-(2-*methoxycarbonylethyl*)-2-*nitropropane* (**51**).—A solution of the nitropropane (**50**) (2.41 g, 3.13 mmol) and methyl acrylate (5.52 g, 64.1 mmol) in dry dimethylformamide (80 ml) was treated with benzyltrimethylammonium hydroxide 40 wt% solution in methanol; 4.46 g, 11.1 mmol). The mixture was stirred at room temperature for 40 min, then poured into hydrochloric acid (0.7M; 800 ml) and the resulting emulsion extracted with ether (4 × 100 ml). The combined organic extracts were washed with brine (200 ml), dried, and evaporated. The residue was purified by flash chromatography [6.5 cm × 11 cm eluant:dichloromethane–ether (1:0) then (4:1)] to yield the *nitro ester* (**51**) [1.44 g, 54% or 22% over 3 steps from the nitroethylpyrrole (**47**) based on unrecovered nitroethylpyrrole] (Found: M^+, 855.3431. $C_{42}H_{53}N_3O_{16}$ requires *M*, 855.3426); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 3 450, 3 320, 1 735, 1 700, 1 580, 1 545, 1 500, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.54 (9 H, s, CMe$_3$), 2.23—2.31 [4 H, m, C(NO$_2$)CH$_2$CH$_2$CO$_2$]), 2.39—2.43 and 2.50—2.54 (each 2 H, m, 2 × CH$_2$C*H*$_2$CO$_2$), 2.63—2.67 and 2.91—2.95 (each 2 H, m, 2 × C*H*$_2$CH$_2$CO$_2$), 3.17 and 3.34 (each 1 H, d, *J* 15.8 Hz, pyrr–CH$_2$CNO$_2$), 3.21 and 3.27 (2 H, AB system, *J* 15.9 Hz, pyrr–CH$_2$CNO$_2$), 3.39 (2 H, s, CH$_2$CO$_2$), 3.55 (3 H, s, OMe), 3.63 (9 H, s, 3 × OMe), 3.67 (3 H, s, OMe), 3.76 (2 H, s, CH$_2$CO$_2$), 5.23 and 5.26 (2 H, AB system *J* 12.3 Hz, PhC*H*$_2$), 7.30—7.39 (5 H, m, Ph), and 9.21 and 9.31 (each 1 H, br s, 2 × pyrr-NH); *m/z* (f.d.) 855 (M^+, 100%).

5-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-5-[4-(2-*methoxy*-

carbonylethyl)-3-methoxycarbonylmethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl]pyrrolidin-2-one (**52**).—Activated zinc powder (2.41 g, 36.9 mmol) was added to a vigorously stirred solution of the nitro ester (**51**) (1.05 g, 1.23 mmol) in acetic acid (25 ml) at room temperature. The mixture was stirred for 10 min without heating, then at 70 °C for 1.3 h. The mixture was cooled, filtered through Celite, and the filtrate was evaporated. The residue was taken up in dichloromethane (50 ml) and washed with water (50 ml). The aqueous washing was extracted with dichloromethane (2 × 25 ml) and the combined organic solutions were dried and evaporated. The residue was purified by flash chromatography [3 cm × 17 cm; eluant: hexane–ethyl acetate (1:2) then (0:1)] to give the *lactam* (**52**) (0.63 g, 65%) (Found: M^+, 793.3400. $C_{41}H_{51}N_3O_{13}$ requires M, 793.3422); $\lambda_{max.}$ 281 nm; $\nu_{max.}$ 3 470—3 100br, 1 740, 1 645sh, 1 580, 1 455, 1 440, and 1 370 cm^{-1}; δ_H(400 MHz) 1.36 (9 H, s, CMe_3), 1.72—2.23 (4 H, m, CH_2CH_2CONH), 2.41—2.55 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.70—2.87 (2 H, m, $CH_2CH_2CO_2$), 2.88—3.08 (6 H, m, 2 × pyrr–CH_2–lactam and $CH_2CH_2CO_2$), 3.47 and 3.50 (2 H, AB system, J 15.0 Hz, CH_2CO_2), 3.50 and 3.62 (each 3 H, s, 2 × OMe), 3.66 (6 H, s, 2 × OMe), 3.77 (2 H, s, CH_2CO_2), 5.02 and 5.16 (2 H, AB system, J 12.2 Hz, $PhCH_2$), 7.18 (5 H, br s, Ph), 7.76 (1 H, br s, lactam NH), and 10.43 (2 H, br s, 2 × pyrr-NH); δ_C 19.4 and 21.0 (each t, 2 × $CH_2CH_2CO_2$), 28.2 (3 C, q, CMe_3), 29.7, 30.0, 30.1, and 30.7 (each t, CH_2CH_2CONH and 2 × CH_2CO_2), 34.9 and 35.0 (each t, 2 × $CH_2CH_2CO_2$), 35.0 and 36.1 (each br t, 2 × pyrr–CH_2–lactam), 51.1, 51.3, 51.4, and 51.7 (each q, 4 × OMe), 63.0 (s, lactam quaternary), 65.8 (t, OCH_2Ph), 80.9 (s, $OCMe_3$), 115.3, 119.3, 120.0, 122.2, 122.5, and 128.8 (each s, 6 × pyrr-C), 127.7, 127.9 (2 C), and 128.1 (2 C) (each d, 5 × phenyl-CH) 129.7 and 130.3 (each br s, 2 × pyrr-C), 135.9 (s, phenyl-C), 161.1 and 161.4 (each br s, 2 × pyrr-CO_2), 171.6, 171.9, 173.1, and 173.5 (each s, 4 × CO_2Me), and 178.6 (s, CONH); m/z (f.d.) 793 (M^+, 100%).

5-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-5-[4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]*pyrrolidin*-2-*one* (**53**).—The t-butyl ester (**52**) (631 mg, 0.795 mmol) was dissolved in trifluoroacetic acid (15 ml) at room temperature under argon. After standing for 3 h the solution was poured into water (150 ml) and the resulting emulsion extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (100 ml), dried, and evaporated. The residue was purified by flash chromatography [3 cm × 12 cm; eluant: ethyl acetate–methanol (1:0) then (97:3)]to give the *α-free pyrrole* (**53**) (524 mg, 95%) (Found: M^+, 693.2896. $C_{36}H_{43}N_3O_{11}$ requires M, 693.2898); $\lambda_{max.}$ 283 nm; $\nu_{max.}$ 3 340br, 1 735, 1 690, 1 650sh, 1 495, 1 460. and 1 440 cm^{-1}; δ_H(400 MHz) 1.68—1.89 (4 H, m, CH_2CH_2CONH), 2.41—2.49 and 2.50—2.57 (each 2 H, m, 2 × $CH_2CH_2CO_2$), 2.69—2.80 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.85 and 2.88 (2 H, AB system, J 15.4 Hz, pyrr–CH_2–lactam), 2.88 and 2.95 (2 H, AB system, J 14.8 Hz, pyrr–CH_2–lactam), 3.44 (2 H, s. CH_2CO_2), 3.46, 3.62, 3.64, and 3.66 (each 3 H, s, 4 × OMe) 3.70 and 3.74 (2 H, AB system, J 17.0 Hz, CH_2CO_2), 5.10 and 5.14 (2 H, AB system, J 12.4 Hz, $PhCH_2$), 6.29 (1 H, br s, pyrr-H), 7.28 (5 H, m, Ph), 7.36 (1 H, br s, lactam NH), and 9.19 and 11.13 (each 1 H, br s, pyrr-NH); m/z (f.d.) 693 (M^+, 100%).

5-[5-*Benzyloxycarbonyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-5-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*}*pyrrolidin*-2-*one* (**54**).—A solution of the α-free pyrrole (**53**) (524 mg, 0.755 mmol) and the acetoxymethylpyrrole aldehyde (**35**) (369 mg, 1.134 mmol) in dry dichloromethane (15 ml) containing dry tetrahydrofuran (0.5 ml) under argon in the dark was stirred vigorously at room temperature during the addition of dry stannic chloride (0.25 ml, 2.14 mmol). The reaction was stirred for 15.5 h whereupon methanol (2 ml) was added and the reaction mixture was poured into a mixture of dichloromethane (50 ml) and saturated sodium hydrogen carbonate (100 ml). The resulting emulsion was filtered through Celite and then the layers in the filtrate were separated. The aqueous phase was extracted with dichloromethane (2 × 50 ml) and the combined organic solutions were dried and evaporated. The residue was purified by flash chromatography [3 cm × 18 cm; eluant: ethyl acetate–methanol (1:0) then (99:1) and (97:3)] to yield the *tripyrrole* (**54**) (559 mg, 77%) (Found: M^+, 958.3806. $C_{49}H_{58}N_4O_{16}$ requires M, 958.3848); $\lambda_{max.}$ 286 and 310sh nm; $\nu_{max.}$ 3 300br, 1 735, 1 685, 1 645, and 1 495 cm^{-1}; δ_H(400 MHz) 1.71—1.96 (4 H, m, CH_2CH_2CONH), 2.37—2.44 (2 H, m, $CH_2CH_2CO_2$), 2.44—2.53 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.65—2.73 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.77 (2 H, s, pyrr–CH_2–lactam), 2.78 and 2.83 (2 H, AB system, J 16.5 Hz, pyrr–CH_2– lactam), 2.91—2.97 (2 H, m, $CH_2CH_2CO_2$), 3.38 and 3.47 (each 2 H, s, 2 × CH_2CO_2), 3.50, 3.62, 3.63, 3.64, 3.68, and 3.69 (each 3 H, s, 6 × OMe), 3.73 and 3.76 (each 2 H, s, CH_2CO_2 and pyrr–CH_2–pyrr), 5.04 and 5.08 (2 H, AB system, J 12.3 Hz, $PhCH_2$), 7.11 (1 H, br s, lactam NH), 7.25 (5 H, br s, Ph), 9.42 (1 H, s, CHO), and 9.45, 10.00, and 10.35 (each 1 H, br s, 3 × pyrr-NH); m/z (f.d.) 958 (M^+, 100%).

5-[5-*Carboxy*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-5-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*}*pyrrolidin*-2-*one* (**55**).—A solution of the benzyl ester (**54**) (295 mg, 0.308 mmol) in methanol (20 ml) was stirred vigorously with palladium-on-charcoal (10%; 30 mg) under hydrogen at room temperature and atmospheric pressure for 70 min, after which time the uptake of hydrogen was complete. The mixture was filtered through Celite and the filtrate was evaporated to give the *acid* (**55**) (250 mg, 93.5%) [Found: M^+ (f.d.), 868.3348. $C_{42}H_{52}N_4O_{16}$ requires M, 868.3378]; $\lambda_{max.}$ 269 and 310 nm; $\nu_{max.}$ 3 450—2 500br, 1 725, 1 650, and 1 440 cm^{-1}; δ_H(400 MHz) 1.50—2.08 (4 H, m, CH_2CH_2CONH), 2.22—3.09 (16 H, m, 3 × $CH_2CH_2CO_2$ and 2 × pyrr–CH_2–lactam), 3.37 and 3.46 (each 2 H, br s, 2 × CH_2CO_2), 3.61 and 3.62 (each 3 H, s, 2 × OMe), 3.64 (9 H, s, 3 × OMe), 3.70 (3 H, s, OMe), 3.83 (4 H, br s, CH_2CO_2 and pyrr-CH_2–pyrr), 8.12 (1 H, br s, lactam NH), 9.39 (1 H, br s, pyrr-NH), 9.42 (1 H, br s, CHO), and 10.35 (2 H, br s, 2 × pyrr-NH); m/z (f.d.) 937 (M^+ + 3 Na, 13%), 914 (M^+ + 2 Na, 40), 891 (M^+ + Na, 100), 868 (M^+, 41), 847 (M^+ − CO_2 + Na, 52), and 824 (M^+ − CO_2, 55).

5-[5-*Iodo*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-5-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*}*pyrrolidin*-2-*one* (**56**).—A solution of the acid (**55**) (116 mg, 0.134 mmol) in dichloromethane (4 ml) was stirred vigorously with a solution of sodium hydrogen carbonate (120 mg, 1.43 mmol) in water (4 ml) during the dropwise addition over 2 min of a solution of iodine (0.1M) and potassium iodide (0.2M) (2.01 ml, 0.201 mmol of iodine), at room temperature. The reaction was stirred for a further 15 min whereupon saturated aqueous sodium hydrogen sulphite (2 ml) was added to destroy the excess of iodine and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 × 10 ml) and the combined organic solutions were dried and evaporated. The residue was purified by flash chromatography [1 × 13 cm; eluant: ethyl acetate–methanol (1:0) then (19:1)] to yield the *iodopyrrole* (**56**) (120 mg, 94%) [Found: M^+ (f.d.), 950.2485. $C_{41}H_{51}IN_4O_{14}$ requires M,

950.2445]; $\lambda_{max.}$ 309 nm; $\nu_{max.}$ 3 450—3 150br, 1 725, 1 685, 1 640, and 1 440 cm^{-1}; δ_H(400 MHz) 1.88—2.07 (4 H, m, CH_2CH_2CONH), 2.36—2.44 (2 H, m, $CH_2CH_2CO_2$), 2.48—2.52 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.65—2.76 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.72 (2 H, s, pyrr–CH_2–lactam), 2.75 and 2.81 (2 H, AB system, *J* 15.3 Hz, pyrr–CH_2–lactam), 2.95—3.00 (2 H, m, $CH_2CH_2CO_2$), 3.33 and 3.42 (each 2 H, s, 2 × CH_2CO_2), 3.51 and 3.57 (2 H, AB system, *J* 16.6 Hz, CH_2CO_2), 3.63 (6 H, s, 2 × OMe), 3.66, 3.69, 3.71, and 3.72 (each 3 H, s, 4 × OMe), 3.76 (2 H, br s, pyrr–CH_2–pyrr), 7.30 (1 H, br s, lactam NH), 8.86 (1 H, br s, pyrr-NH), 9.44 (1 H, s, CHO), and 9.49 and 10.35 (each 1 H, br s, 2 × pyrr-NH); *m/z* (f.d.) 950 (M^+, 100%).

5-[3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-*pyrrol*-2-*ylmethyl*]-5-{5-[5-*formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*]-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethyl*}*pyrrolidin*-2-*one* (**57**).—A solution of the iodopyrrole (**56**) (120 mg, 0.126 mmol) in methanol (5 ml) containing sodium acetate (40 mg, 0.488 mmol) was stirred vigorously with 10% palladium-on-charcoal (15 mg) under hydrogen at room temperature and atmospheric pressure for 40 min, after which time the uptake of hydrogen had ceased. The mixture was filtered through Celite and then the filtrate was evaporated. The residue was partitioned between dichloromethane (10 ml) and water (10 ml), the organic phase was separated, and the aqueous phase was extracted with more dichloromethane (2 × 5 ml). The combined organic solutions were dried and evaporated. The residue was purified by flash chromatography [1 × 15 cm; eluant: ethyl acetate–methanol (1:0) then (24:1)] to yield the *α-free pyrrole* (**57**) (90 mg, 87%) (Found: M^+, 824.3475. $C_{41}H_{52}N_4O_{14}$ requires *M*, 824.3480); $\lambda_{max.}$ 309 nm; $\nu_{max.}$ 3 450—3 150br, 1 725, 1 685, 1 645, and 1 445 cm^{-1}; δ_H(400 MHz) 1.68—1.86 (4 H, m, CH_2CH_2CONH), 2.40—2.53 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.62—2.76 (8 H, m, 2 × $CH_2CH_2CO_2$ and 2 × pyrr–CH_2–lactam), 2.96—2.99 (2 H, m, $CH_2CH_2CO_2$), 3.38, 3.40, and 3.51 (each 2 H, s, 3 × CH_2CO_2), 3.62, 3.63, 3.64, 3.66, 3.69, and 3.70 (each 3 H, s, 6 × OMe), 3.80 and 3.86 (2 H, AB system, *J* 15.8 Hz, pyrr–CH_2–pyrr), 6.45 (1 H, s, pyrr-H), 7.07 (1 H, br s, lactam NH), 8.74 (1 H, br s, pyrr-NH), 9.42 (1 H, s, CHO), and 9.49 and 10.50 (each 1 H, br s, 2 × pyrr-NH); *m/z* (f.d.) 824 (M^+, 100%).

1,3-[2,7,12-*Tris*(2-*methoxycarbonylethyl*)-3,8,13-*tris*(*methoxycarbonylmethyl*)-10,15,16,17-*tetrahydro*-5H-*tripyrrin*-1,14-*diyl*]*propane*-2-*spiro*-5′-*pyrrolidin*-2′-*one* (**59**).—A solution of the α-free pyrrole aldehyde (**57**) (122 mg, 0.148 mmol) in dry methanol (4 ml) and dry dichloromethane (2 ml) under argon was treated with solid sodium borohydride (80 mg, 2.11 mmol) at room temperature. After 10 min the solution was poured into dilute brine (30 ml) and the resulting mixture was extracted with dichloromethane (3 × 15 ml). The combined organic extracts were dried and evaporated to give the highly unstable α-free hydroxymethylpyrrole (**58**) (122 mg, quantitative) which was immediately transferred into a glove box for all further operations. A solution of the gum in degassed acid-free dry dichloromethane (180 ml) was stirred vigorously while just enough of a solution of toluene-*p*-sulphonic acid (30 mg) in degassed dry methanol (2 ml) was added (30 drops) to produce a permanent deep orange reaction mixture. After 5 min triethylamine (6 drops) was added and the solution again became yellow. The solution was evaporated to give an orange gum which was purified by p.l.c. (two plates, eluant: degassed acid-free, dry ethyl acetate) to afford the higher R_F *spiro lactam* (**59**) (27 mg, 23%) and the lower R_F *spiro lactam* (**59**) (16 mg, 13%) as yellow gums. For the higher R_F spiro lactam: R_F(EtOAc) 0.39—0.46 (Found: M^+, 808.3510. $C_{41}H_{52}N_4O_{13}$ requires *M*, 808.3531); $\lambda_{max.}$ no peak above 240 nm; δ_H(400 MHz; 323 K) 1.50—1.74 and 1.90—1.99 (each 2 H, m, CH_2CH_2CONH), 2.25—2.42 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.48—2.90 (10 H, m, 3 × $CH_2CH_2CO_2$ and 2 × pyrr–CH_2–lactam), 3.40, 3.43, 3.54, 3.62, 3.64, and 3.65 (each 3 H, s, 6 × OMe), 3.48 and 3.56 (each 2 H, s, 2 × CH_2CO_2), 3.66—3.87 (4 H, m, 2 × pyrr–CH_2–pyrr), 7.79 (2 H, br s, lactam NH and pyrr-NH), and 8.59 (2 H, br s, 2 × pyrr-NH) (one of the CH_2CO_2 signals is either obscured or very broad); δ_C 19.8, 19.9, and 20.2 (3 × $CH_2CH_2CO_2$), 22.7 and 22.9 (2 × pyrr–CH_2–pyrr), 30.1, 30.2, 30.5, 30.6, and 33.9 (CH_2CH_2CONH and 3 × CH_2CO_2), 35.2, 35.5, and 35.7 (3 × $CH_2CH_2CO_2$), 36.6 and 36.9 (each br, 2 × pyrr–CH_2– lactam), 51.1, 51.2 (2 C), and 51.6 (3 C) (6 × OMe), 64.1 (spiro centre), 110.3, 111.4, 112.7, 116.7, 117.1, 119.3, 122.1, 123.0, 124.5, 125.9, 126.3, and 126.9 (12 × pyrr-C), 172.5, 173.1, 173.3, 173.5, 173.6, and 173.7 (6 × CO_2), and 179.8 (CONH); *m/z* (f.d.) 808 (M^+, 100%). For the lower R_F spiro lactam: R_F(EtOAc) 0.29—0.36 (Found: M^+, 808.3501); $\lambda_{max.}$ no peak above 240 nm; δ_H(400 MHz) 1.49—1.72 and 1.83—1.95 (each 2 H, m, CH_2CH_2CONH), 2.20—2.50 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.57—2.78 (8 H, m, 3 × $CH_2CH_2CO_2$ and pyrr–CH_2–lactam), 2.73 and 2.81 (each 1 H, d, *J* 15.7 Hz, pyrr–CH_2–lactam), 3.31 and 3.33 (2 H, AB system, *J* 16.4 Hz, CH_2CO_2), 3.36 and 3.38 (2 H, AB system, *J* 16 Hz, CH_2CO_2), 3.41 (2 H, s, CH_2CO_2), 3.58, 3.59, 3.62, 3.63, 3.64, and 3.65 (each 3 H, s, 6 × OMe), 3.60 and 3.83 (each 1 H, d, *J* 16.2 Hz, pyrr–CH_2–pyrr), 3.63 and 3.77 (each 1 H, d, *J* 16.7 Hz, pyrr–CH_2–pyrr), 7.57 (1 H, br s, lactam NH), and 8.18, 8.84, and 8.92 (each 1 H, br s, 3 × pyrr-NH); decoupling at δ 3.60 reduces the signal at δ 3.83 to a singlet and decoupling at δ 3.63 reduces the signal at δ 3.77 to a singlet; hence the presence of signals at δ 3.60 and 3.63 can be deduced even though they are obscured by the methoxy signals; δ_C 19.7 (2 C) and 19.8 (3 × $CH_2CH_2CO_2$), 22.2 and 22.3 (2 × pyrr–CH_2–pyrr). 30.0, 30.2 (2 C), 30.5, and 31.3 (CH_2CH_2CONH and 3 × CH_2CO_2), 35.3 and 35.5 (2 C) (3 × $CH_2CH_2CO_2$), 36.8 and 37.1 (each br, 2 × pyrr–CH_2–lactam), 51.4, 51.5 (2 C), 51.7, and 52.0 (2 C) (6 × OMe), 63.6 (spiro centre), 110.0, 110.5, 112.5, 116.0, 116.3, 119.2, 122.1, 123.2, 124.4, 125.7, 126.1, and 126.4 (12 × pyrr–C), 172.8, 173.3, and 173.8 (4 C) (6 × CO_2), and 179.8 (CONH); *m/z* (f.d.) 808 (M^+, 100%).

1,3-[2,7,12-*Tris*-(2-*carboxyethyl*)-3,8,13-*tris*(*carboxymethyl*)-10,15,16,17-*tetrahydro*-5H-*tripyrrin*-1,14-*diyl*]*propane*-2-*spiro*-5′-*pyrrolidin*-2′-*one* (**60**).—A solution of the appropriate spiro lactam hexamethyl ester (**59**) in dry degassed methanol (0.05 ml per mg of spiro compound) was treated with degassed potassium hydroxide (4M; 0.05 ml per mg of spiro compound). The resulting suspension was shaken under argon in the dark at room temperature for 15 h to give a homogeneous alkaline solution of the spiro lactam hexa-acid (**60**). For the n.m.r. samples, the hydrolysate solutions were repeatedly evaporated from 99.8% deuteriated water. For the hydrolysate from the higher R_F spiro lactam (**59**): δ_H(400 MHz; D_2O) 1.60—1.70 and 1.92—2.03 (each 2 H, br m, CH_2CH_2CONH), 2.17—2.36 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.53—2.74 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.79 and 2.87 (2 H, AB system, *J* 14 Hz, pyrr–CH_2–lactam), 2.81 and 2.86 (2 H, AB system, *J* 15 Hz, pyrr–CH_2–lactam), 3.27—3.44 (6 H, m, 3 × CH_2CO_2), 3.76 and 3.89 (each 1 H, d, *J* 18 Hz, pyrr–CH_2–pyrr), and 3.84 and 3.88 (2 H, AB system, *J* 19 Hz, pyrr–CH_2–pyrr). For the hydrolysate from the lower R_F spiro lactam (**59**): δ_H(400 MHz; D_2O) 1.55—1.70 and 1.88—1.95 (each 2 H, m, CH_2CH_2CONH), 2.21—2.37 (6 H, br m, 3 × $CH_2CH_2CO_2$), 2.57—2.73 (6 H, br m, 3 × $CH_2CH_2CO_2$), 2.82—2.93 (4 H, br m, 2 × pyrr–CH_2–lactam), 3.31—3.43 (6 H, m, 3 × CH_2CO_2), and 3.78—3.93 (4 H, br m, 2 × pyrr–CH_2–pyrr).

Acknowledgements

We are grateful to the S.E.R.C. and Roche Products Ltd. for financial support and to the former for a Studentship (to M. G. B.).

References

1 Part 29, A. R. Battersby, M. G. Baker, H. A. Broadbent, C. J. R. Fookes, and F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2027.
2 W. M. Stark, M. G. Baker, P. R. Raithby, F. J. Leeper, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1985, 1294.
3 F. J. Leeper, *Nat. Prod. Rep.*, 1985, **2**, 19 and 561; A. R. Battersby, C. J. R. Fookes, G. W. J. Matcham, and E. McDonald, *Nature (London)*, 1980, **285**, 17.
4 A. R. Battersby, C. J. R. Fookes, M. J. Meegan, E. McDonald, and H. K. W. Wurzinger, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2786.
5 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald. and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2427.
6 C. J. Hawker, W. M. Stark, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1987, 1313.
7 J. H. Mathewson and A. H. Corwin, *J. Am. Chem. Soc.*, 1961, **83**, 135.
8 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald, and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2413.
9 A. R. Battersby, M. Ihara, E. McDonald, J. Saunders, and R. J. Wells, *J. Chem. Soc., Perkin Trans. 1*, 1976, 283.
10 A. R. Battersby, S. Kishimoto, E. McDonald, F. Satoh, and H. K. W. Wurziger, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1927.
11 P. J. Harrison, Z.-C. Sheng, C. J. R. Fookes, and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1667.
12 W. M. Stark, G. J. Hart, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1986, 465.
13 J. K. Lawson, Jr., and J. A. T. Croom, *J. Org. Chem.*, 1963, **28**, 232.
14 A. R. Battersby, D. A. Evans, K. H. Gibson, E. McDonald, and L. Nixon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1546.
15 M. J. Mintz and C. Walling, *Org. Synth.*, Coll. Vol. V. 1973, 184.

Received 19*th June* 1987; *Paper* 7/1099