Biosynthesis of porphyrins and related macrocycles. Part 49.[1] Exploration of synthetic routes to analogues of the spiro-intermediate for porphyrin biosynthesis

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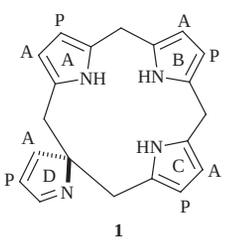
The proposed intermediacy of the spiro-pyrrolenine 1 for the biosynthesis of uroporphyrinogen III has focussed attention on its synthesis. Several different approaches to close analogues of this compound are explored, including (*a*) the synthesis of a dilactone bridged dipyrrolic pyrrolenine, (*b*) deactivation of two of the pyrrole rings of the macrocycle by attaching 3-methoxycarbonyl groups and (*c*) approaches to spiro-macrocyclic compounds *via* dipyrroketones. The chemistry of the different types of synthetic intermediates is described.

The proposed involvement of the spiro-system **1** in the reaction sequence by which the enzyme cosynthetase (uroporphyrinogen III synthase) converts hydroxymethylbilane into uroporphyrinogen III was described more fully with leading references in the introduction to the first paper in this set of four.[2] That paper described a way of making 2*H*-pyrrole (pyrrolenine) rings from the corresponding thiolactams, which promised well for our eventual goal of synthesising spiro-pyrrolenine **1**. However a number of difficulties became apparent which prevented us from achieving that goal. One was that 2-(pyrrolylmethyl)-pyrrolenines, especially 2,2-bis(pyrrolylmethyl)pyrrolenines, seem to be strongly resistant to the addition of nucleophiles to the imine carbon, C-5, possibly because of steric hindrance from the pyrrolic ring(s). The second difficulty was the lability under acidic conditions of both pyrrolylmethylpyrrolenines and their thiolactam precursors when the pyrrole ring(s) lacked deactivating electron-withdrawing groups.



1

A = CH_2CO_2H, P = $CH_2CH_2CO_2H$

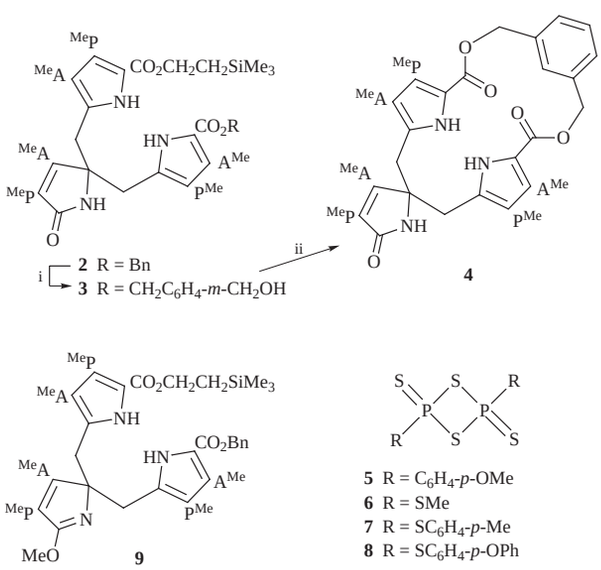
The present paper describes studies into the synthesis of analogues of spiro-system **1** in which the aim was to circumvent one or other of these difficulties by modification of the synthetic approach.

Results and discussion

Building a dilactonic bridge

The steric hindrance at C-5 of 2,2-disubstituted pyrrolenines was clear from all the experiments described in the previous paper,[2] especially so for those molecules carrying two pyrrolylmethyl groups. We therefore envisaged tying back the pyrrolylmethyl groups of a compound such as lactam **2** by replacing the two separate α-pyrrolic ester groups by a single diester bridge. For this we planned to use one of the three benzenedimethanols. These were chosen so as to allow subsequent removal of the bridge by hydrogenolysis after the lactam ring had been appropriately modified. The *meta*-isomer was selected as the best diol to use by molecular modelling using Macromodel version 5.5.[3] The macrocycle built from this *meta*-isomer was favoured by *ca.* 10 kJ mol^{-1} over that based on the *ortho*-isomer and by *ca.* 15 kJ mol^{-1} over the one built from the *para*-diol. It was also encouraging to find that the ring strain energy of the preferred macrocycle was calculated to be only *ca.* 10 kJ mol^{-1}, which is less than the ring strain of other macrocycles which have been successfully synthesised by macrolactonisation procedures.[4]

Preliminary experiments showed that the dilactone should be built in a stepwise fashion so the benzyl group was cleaved from lactam diester **2**[5] by hydrogenolysis and the resultant acid was directly coupled with benzene-1,3-dimethanol to yield the ester **3**, 71%, Scheme 1. Cleavage of the trimethylsilylethyl group from **3** using fluoride ion afforded the acid ready for macrocyclisation. In this case, the best yield of bis-lactone **4**, 46%, came from using the Mukaiyama conditions[6] (2-chloro-1-methylpyridinium iodide and triethylamine). Disappointingly, none of the thionating reagents **5**–**8**[2,7] converted **4** into the corresponding thiolactam; starting material was recovered



2 R = Bn
3 R = $CH_2C_6H_4$-*m*-CH_2OH
4
5 R = C_6H_4-*p*-OMe
6 R = SMe
7 R = SC_6H_4-*p*-Me
8 R = SC_6H_4-*p*-OPh
9

A^{Me} = CH_2CO_2Me, P^{Me} = $CH_2CH_2CO_2Me$

Scheme 1 *Reagents:* i, Pd/C, H_2 then 1,3-$C_6H_4(CH_2OH)_2$, DCC, DMAP; ii, TBAF then 2-chloro-1-methylpyridinium iodide, Et_3N

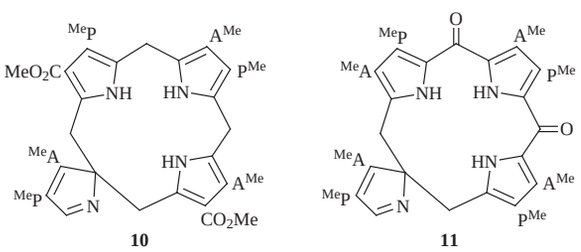
under mild conditions and more forcing ones caused total decomposition. It appeared that forming the bis-lactone, whilst possibly helping with steric hindrance, had now decreased the stability of the whole system and was not, therefore, helpful.

Before leaving this section, the methoxypyrrolenine **9** was prepared from lactam **2** during the foregoing work and is reported in the Experimental. However, in common with earlier work,[2] attempts at reduction of this imino ether were unsuccessful and so this approach was not pursued.

Approaches to deactivated analogues of the spiro-intermediate

The experience gained from the foregoing work and from the research in the preceding papers[1,2] pointed to the need for a reassessment of our general strategies so as to deal with the facile fragmentation reactions that we had frequently encountered. One possible way forward was to aim for a relative of the spiro-intermediate **1** in which the correctly substituted pyrrolenine ring would be in place but the pyrrole rings A and C of **1** would now be deactivated by electron-withdrawing groups.

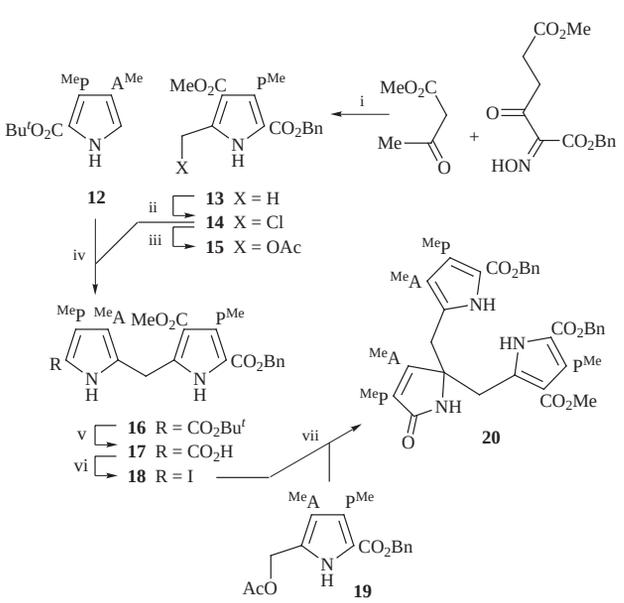
The sequence lactam→thiolactam→pyrrolenine described in the first paper[2] worked well for both mono- and di-pyrrolic systems provided the pyrrole ring(s) carried an electron-withdrawing group at C-5. To have such a group at C-3 should have a similar effect, so our synthetic target for the first foray was the spiro-macrocycle **10** having directly bonded methoxy-



10 **11**

carbonyl groups on rings A and C. An alternative approach was to deactivate rings A and C by means of interpyrrolic ketone groups which leads to **11** as the second target.

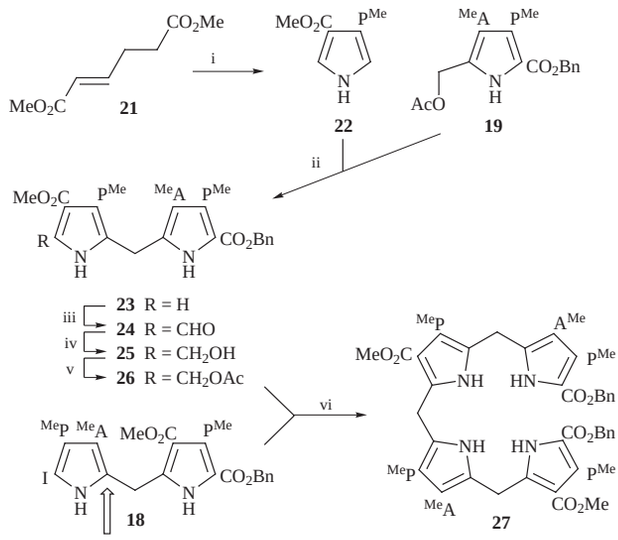
The chemistry for the former 'nuclear ester' approach was first explored by aiming for the lactam **20**. The required iododipyrromethane **18** was prepared by standard steps **13**→**14** (+ **12**)[8]→**16**→**17**→**18**, Scheme 2. The only change from normal



Scheme 2 *Reagents*: i, Zn, AcOH; ii, SO_2Cl_2; iii, NaOAc, AcOH; iv, PhMe, reflux; v, $SnCl_4$; vi, KI_3, $NaHCO_3$; vii, $SnCl_4$ then AgOAc, H_3O^+

was that the acetoxy compound **15** would not couple with the pyrrole **12** whereas the chloromethyl analogue **14** did so.[9] The usual conditions[2,10] were used to combine iododipyrromethane **18** with acetoxymethylpyrrole **19**[10] to give the lactam **20**.

With that success, the next step was to plan for methoxycarbonyl groups on both pyrrole rings flanking the lactam residue. Accordingly, the pyrrole **22** was synthesised by reacting tosylmethyl isocyanide[11] with dimethyl hex-2-enedioate **21**, Scheme 3. The coupling reaction of acetoxymethylpyrrole **19** with this

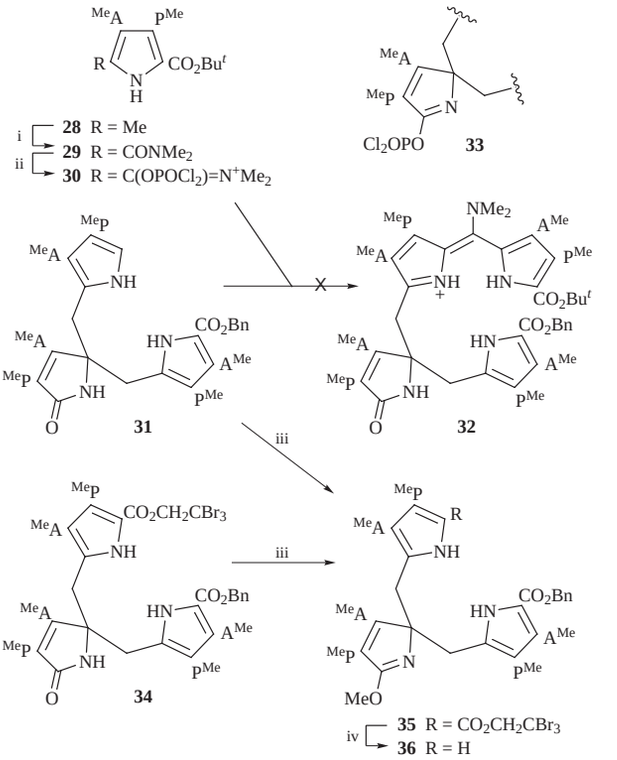


Scheme 3 *Reagents*: i, $TsCH_2NC$, NaH; ii, TsOH; iii, DMF, $POCl_3$; iv, $NaBH_4$; v, MsCl, Et_3N then NaOAc, AcOH; vi, $SnCl_4$

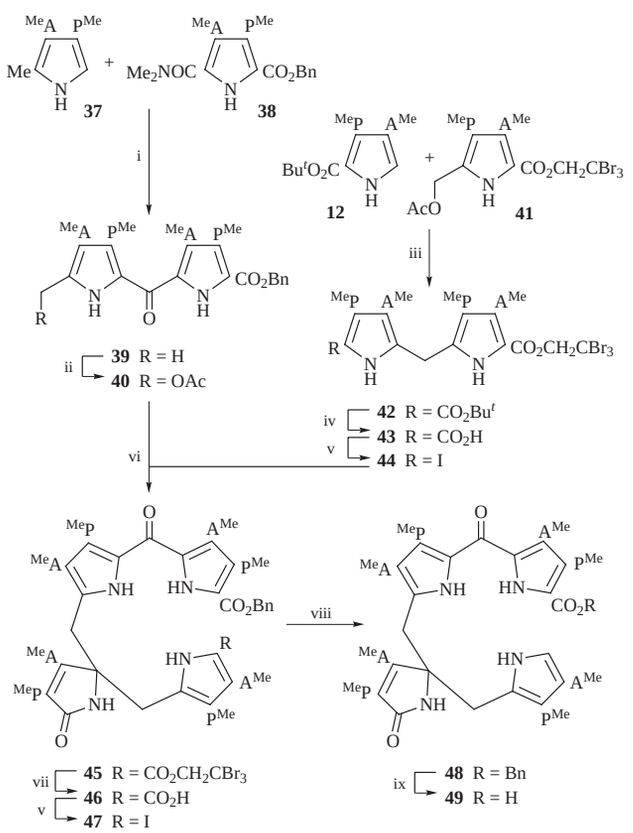
pyrrole **22** occurred at the expected site to afford the dipyrromethane **23**, whose structure was confirmed by NOE experiments. This was then formylated under Vilsmeier conditions and the steps forward from the resultant aldehyde **24** were standard ones, *via* **25** through to **26**. When the acetoxymethyl compound **26** and the iododipyrromethane **18** were treated with stannic chloride as usual,[2] the only product, 60%, was the bilane **27**, the result of bond formation between the iodine-bearing carbon of **18** and the acetoxymethyl carbon of **26** with loss of the iodine. There was no detectable amount of the desired halopyrrolenine arising from attack at the arrowed site of **18**. Evidently the delicate balance of reactivity that gave success earlier with this coupling process[2,10] had been too far disturbed in this case.

Attention therefore turned to the second plan based on dipyrroketones and having **11** as the target. This had the further attraction that dipyrroketones can be reduced under mild conditions to give dipyrromethanes[12] thus offering the possibility of a final reductive step to reach the spiro-intermediate **1** as its octamethyl ester.

The best synthesis of dipyrroketones is that of Kenner and co-workers[12] which uses Vilsmeier chemistry. Accordingly, the amide **29** was prepared by standard steps[12] from the pyrrole **28**[8] and its conversion by phosphorus oxychloride into the reactive species **30** was demonstrated spectroscopically, Scheme 4. However, on mixing **30** with the α-free pyrrolic lactam **31**[2] under a variety of conditions, the new chromophore **32** was not generated; work-up gave starting amide **29**, 50%, and none of the desired dipyrroketone. Use of the more stable benzyl ester **38** (Scheme 5) gave the same result. It was possible that the reagent **30** was reacting preferentially with the lactam functionality of **31** to form an *O*-phosphorylated species, *e.g.* **33**. Therefore, methoxypyrrolenine **36** was prepared, either from the lactam **34** using Meerwein's reagent to give methoxypyrrolenine **35** followed by removal of the tribromoethyl ester functionality or by direct methylation of lactam **31**. However, compound **36** also failed to react with the reagent **30**.



Scheme 4 *Reagents*: i, Bu^{t}OCl then Me_2NH then H_2O; ii, $POCl_3$; iii, Me_3OBF_4, proton sponge; iv, Zn, AcOH then KI_3, $NaHCO_3$ then PtO_2, H_2



Scheme 5 *Reagents*: i, $POCl_3$; ii, Bu^{t}OCl then NaOAc, AcOH; iii, TsOH; iv, $SnCl_4$; v, KI_3, $NaHCO_3$; vi, $SnCl_4$ then AgOAc, H_3O^+; vii, Zn, AcOH; viii, PtO_2, H_2; ix, Pd/C, H_2

These results led to a change in the order of the coupling steps illustrated in Scheme 5; now the aim was to construct the tripyrrolic lactam **46** in one step from the acetoxymethyl dipyrroketone **40** and the iododipyrromethane **44**. Vilsmeier coupling of **37**[13] and **38** gave the ketone **39** in 93% yield and this was converted into the acetoxy derivative **40** by standard chlorination followed by displacement with acetate ion. Synthesis of the iododipyrromethane **44** from **12**[8] and **41**[10] ran smoothly through the steps **42**→**43**→**44**. The usual conditions[2,10] for the reaction of an acetoxypyrrole with an iodopyrrole had to be modified for the coupling of **40** and **44**; then the complete dipyrroketone **45** was obtained in 29% yield. Deprotection of ring C of **45** was by the familiar steps **45**→**46**→**47**→**48** and hydrogenolysis then removed the benzyl group to afford the acid **49** ready for experiments on closing the macrocycle.

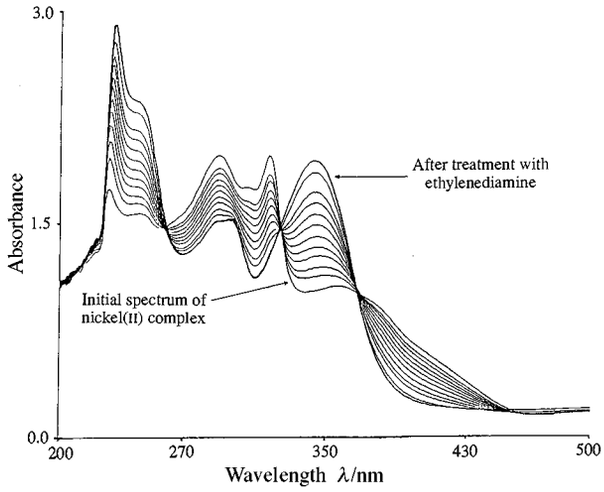
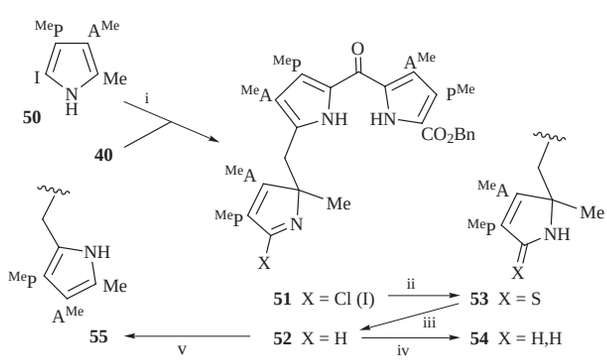


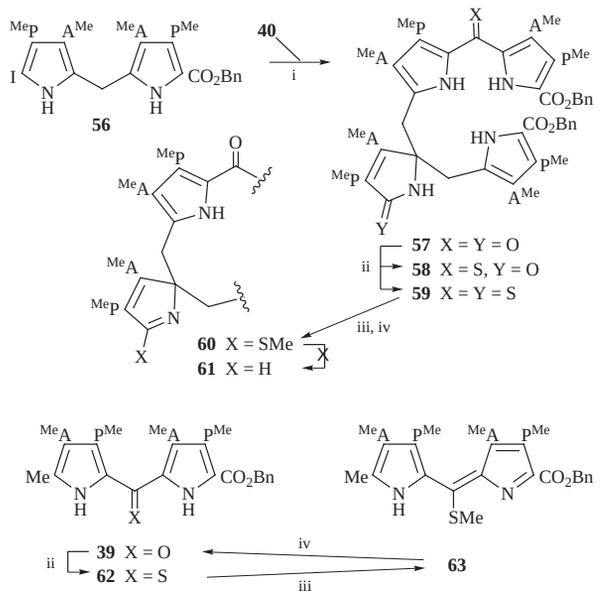
Fig. 1 Change in the UV–VIS spectrum as the nickel(II) complex of pyrrolenine **52** is treated with ethylene diamine to give uncomplexed **52**

In parallel with the foregoing work, we were also exploring other facets of the required chemistry. It was especially important to learn whether a pyrrolenine attached to a dipyrroketone would be sufficiently stable to handle. The simpler system **51** was therefore built by alkylating iodopyrrole **50**[10] with acetoxymethylpyrrole **40** as above and the product was treated with hydrogen sulfide in the presence of silver acetate to afford the thiolactam **53**, Scheme 6. Desulfurisation using nickel boride[2] led to the desired pyrrolenine **52** but as a nickel complex, indicated to be a 1 : 1 complex by mass spectrometry. The pyrrolenine **52** was smoothly decomplexed by treatment with ethylenediamine as shown by the striking changes in the UV–VIS spectrum, Fig. 1; the pyrrolenine **52** was satisfyingly stable. Reduction of the nickel complex with borohydride also released the organic component but as the dihydropyrrolenine **54**, identical to material prepared by borohydride reduction of the pyrrolenine **52** itself. Treatment of the uncomplexed pyrrolenine **52** or its nickel complex with toluene-*p*-sulfonic acid caused fragmentation–rearrangement to afford the tripyrroketone **55** in 76 and 30% yield, respectively, together with 50% recovered starting material in the latter case.



Scheme 6 *Reagents*: i, $SnCl_4$; ii, H_2S, AgOAc; iii, nickel boride then $H_2NCH_2CH_2NH_2$; iv, $NaBH_4$; v, TsOH

The stability of the foregoing pyrrolenine **52** encouraged efforts to run the sequence lactam→thiolactam→pyrrolenine and for these experiments a still closer model dipyrroketone was used. The system **57** was constructed by alkylating the iodide **56**[1] with **40** as usual (Scheme 7), and this product with Davy's



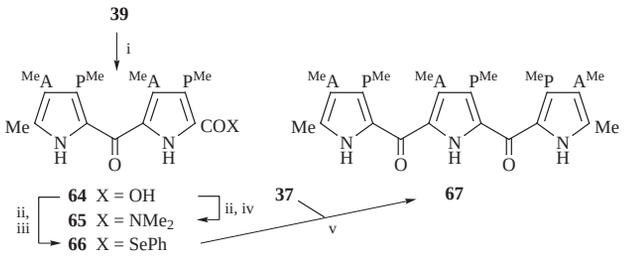
Scheme 7 *Reagents*: i, $SnCl_4$ then AgOAc, H_3O^+; ii, Davy's reagent **6**; iii, TFA, TMOF; iv, H_3O^+

reagent **6** yielded a mixture of the dipyrrothioketone lactam **58**, 50%, and the dipyrrothioketone thiolactam **59**, 30%. Increasing the amount of **6** used led to 52% of the thiolactam **59** being isolated. Attempted hydrolysis of the thioketone group of **59** with alkaline hydrogen peroxide[14] destroyed the material, so other conditions were sought.

Trials were carried out on the dipyrrothioketone **62**, prepared in 69% yield by reacting the ketone **39** with Davy's reagent. Trimethyl orthoformate and TFA converted **62** into the *S*-methyl derivative **63**, which was hydrolysed back to the starting ketone **39**, 82%, by aqueous toluene-*p*-sulfonic acid. When this procedure was applied to the thiolactam **59**, both sulfur atoms were methylated and just one *S*-methyl moiety was hydrolysed by the aqueous acid. Judging by the hydrolysis of **63** to **39** under these conditions, the product was expected to be methylthiopyrrolenine **60** and this was confirmed by the similarity of its UV spectrum to the spectra of dipyrroketones **39** and **57**; that of **62** was substantially different. Difficulties had been previously experienced in reducing such a methylthiopyrrolenine with nickel boride but in that case Raney nickel was successful.[2] Disappointingly, neither of these nickel reagents yielded any of the desired pyrrolenine **61** from **60**. Other ways for selective hydrolysis of the thioketone can be envisaged but have not so far been studied.

Another key step for the synthesis of the macrocyclic system **11** is the generation of a tripyrrodiketone unit; there is no precedent in the literature for this synthesis. Clearly the best tripyrrodiketone to build is the macrocycle **11** and many attempts were made to cyclise the acid **49**. These ranged from a variety of acidic and Lewis acidic conditions and use of dehydrating agents through to many standard reagents for activation of carboxy groups. All of these led to one or a combination of three results: recovery of starting material, decomposition or decarboxylation of the pyrrolic carboxy group.

Further studies were made with simpler molecules. The dimethylamide **65** was prepared from **39** *via* **64** by standard steps but the Vilsmeier reagent prepared from it did not react with the α-free pyrrole **37**, Scheme 8. However, seleno esters



Scheme 8 *Reagents*: i, Pd/C, H_2; ii, $(imidazolyl)_2C{=}O$; iii, PhSeNa; iv, Me_2NH; v, CuOTf–PhH, $CaCO_3$

have been used as acylating agents[15] in reactions catalysed by the copper(I) complex $[Cu(OSO_2CF_3)]C_6H_6$ and this approach was shown to be very effective in the pyrrole series.[16] The seleno ester **66** was prepared from **64** and in the presence of the Cu^I catalyst, did react with **37** to give the tripyrrodiketone **67** but in a very low yield (*ca*. 5%) that we were unable to improve. From these results, the lack of examples of such tripyrrodiketones in the literature is understandable.

Despite these difficulties, the approach *via* **49** to **11** does offer some promise for the future though not as much, we believe, as that to be described in the next paper.[5]

Experimental

General directions are as in the preceding paper.[2]

Molecular modelling

Molecular modelling was performed using the program MacroModel ver. 5.5.[3] To simplify the energy minimisation process all acetate and propionate side-chains were replaced by methyl groups. The search for the global minimum used the Monte Carlo method. In each case, the torsion angles of eight of the C–C bonds of the macrocycle were varied and one was used as the ring-closure bond. The ester C–O bond was set in the s-*trans* conformation and was not varied. 1000 Starting conformations were minimised using the MM2* force-field. The global minimum energies were as follows: diester **4** with benzene-1,3-dimethanol, $E = 461.12$ kJ mol^{-1} (found 23 times); diester with benzene-1,2-dimethanol, $E = 472.72$ kJ mol^{-1} (found 5 times); diester with benzene-1,4-dimethanol, $E = 476.45$ kJ mol^{-1} (found 30 times).

The strain energy of the macrocycle was calculated by comparing the energy change between the diester ($E_{diester}$) and the corresponding diacid plus diol ($E_{diacid} + E_{diol}$) with twice the energy change between a simple non-macrocyclic monoester (benzyl 3,4,4-trimethylpyrrole-2-carboxylate; $E_{monoester}$) and the corresponding monoacid plus alcohol ($E_{monoacid} + E_{BnOH}$). Thus:

$$\text{Strain Energy} = (E_{diester} - E_{diacid} - E_{diol}) - 2(E_{monoester} - E_{monoacid} - E_{BnOH}).$$

Various different conformations of the diacid were minimised to find the global minimum but a full conformational search was not considered necessary for this or the simpler molecules. The strain energies so calculated were: diester **4** with benzene-1,3-dimethanol, 9.52 kJ mol^{-1}; diester with benzene-1,2-dimethanol, 15.61 kJ mol^{-1}; diester with benzene-1,4-dimethanol, 23.62 kJ mol^{-1}.

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

A solution of benzyl ester **2**[5] (110 mg, 0.11 mmol) in methanol (8 cm^3) was stirred with sodium carbonate (70 mg) and 10%

palladium-on-charcoal (30 mg) under an atmosphere of hydrogen for 30 min, then filtered through Celite, diluted with water (50 cm^3), acidified with glacial acetic acid and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the resultant crude carboxylic acid and benzene-1,3-dimethanol (170 mg, 1.1 mmol) in dry tetrahydrofuran (10 cm^3) under argon was treated with a solution of *N*,*N*′-dicyclohexylcarbodiimide (25 mg, 0.12 mmol) and 4-dimethylaminopyridine (1.3 mg, 11 μmol) in tetrahydrofuran (1 cm^3) and heated at reflux for 1 h, then filtered through Celite, diluted with dichloromethane (100 cm^3), washed with dilute hydrochloric acid (2 mol dm^{-3}; 2 × 20 cm^3) then water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (4:1), gave the 3-*hydroxymethylbenzyl ester* **3** (80 mg, 71%) as an oil (Found: MH_2^+, 1025.4232. $C_{50}H_{65}N_3O_{18}Si$ requires MH_2, 1025.4189); $\delta_H(CDCl_3)$ 0.02 (9 H, s, $SiMe_3$), 1.04 (2 H, t, *J* 9, CH_2Si), 2.32–2.49 (8 H, m), 2.69 (2 H, t, *J* 8) and 2.90 (2 H, t, *J* 8, 3 × CH_2CH_2), 2.75 and 2.99 (each 1 H, d, *J* 15, 4-CH_2), 2.81 and 3.06 (each 1 H, d, *J* 15, 4-CH_2), 3.13 and 3.33 (each 1 H, d, *J* 17, CH_2CO_2), 3.44 and 3.63 (each 1 H, d, *J* 15, CH_2CO_2), 3.50, 3.50, 3.55, 3.58, 3.59, 3.81 (each 3 H, s, OMe), 3.74 and 3.89 (each 1 H, d, *J* 17, CH_2CO_2), 4.18–4.28 (2 H, m, C*H*$_2$$CH_2Si$), 4.62 (2 H, s, ArC*H*$_2$OH), 5.16 and 5.21 (each 1 H, d, *J* 12.6, CO_2CH_2Ar), 7.17–7.32 (4 H, m, Ar), 7.55, 7.74, 9.32 and 10.14 (each 1 H, br s, 3 × NH and OH); $\delta_C(CDCl_3)$ −1.75 ($SiMe_3$), 17.32 (CH_2Si), 19.10, 19.43, 20.29, 29.10, 29.48, 30.31, 30.68, 31.95, 33.61, 34.61 and 34.66 (11 × CH_2), 51.26, 51.41, 51.57, 51.77, 52.14 and 52.95 (OMe), 62.11, 64.19, 65.36 and 66.28 (3 × CH_2O and C-4), 115.22, 118.57, 118.88, 121.84, 122.70, 127.66, 127.90, 128.94, 135.98, 137.53, 141.15, 142.00 and 149.46 (C=C), 125.28, 126.10, 126.44 and 128.10 (C=*C*H) and 159.88, 160.83, 171.42, 171.89, 172.08, 173.26, 173.40, 173.47 and 173.69 (C=O); *m*/*z* (FD) 1023 (M^+, 100%).

Macrocyclic diester 4

A solution of lactam trimethylsilylethyl ester **3** (163 mg, 159 μmol) and tetrabutylammonium fluoride (125 mg, 478 μmol) in tetrahydrofuran (10 cm^3) was stirred at room temperature under argon for 24 h, then diluted with dichloromethane (20 cm^3), washed with dilute sulfuric acid (2 × 10 cm^3) then water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with dichloromethane–methanol (9:1), gave the hydroxy acid (93 mg, 63%) as an oil; *m*/*z* (FD) 923 (M^+, 100%).

A solution of 2-chloro-1-methylpyridinium iodide (66 mg, 260 μmol) in toluene (35 cm^3) was heated at reflux under argon and a solution of the hydroxy acid (60 mg, 65 μmol) and triethylamine in toluene (25 cm^3) and acetonitrile (1 cm^3) was added continuously over 1 h. The solution was heated at reflux for a further 1 h, then diluted with ethyl acetate (50 cm^3), washed with dilute hydrochloric acid (2 × 5 cm^3) then water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with dichloromethane–methanol (9:1), gave the *dilactone* **4** (27 mg, 46%) as an oil (Found: M^+, 905.3187. $C_{45}H_{51}N_3O_{17}$ requires *M*, 905.3217); the ^1H NMR spectrum at room temperature showed a number of broad or poorly resolved peaks; $\delta_H(C_7D_8$, 70 °C) 2.06–2.08, 2.36–2.45 and 2.49–2.69 (each 4 H, m, 3 × CH_2CH_2), 3.14 (1 H, d, *J* 15.5), 3.19 (1 H, d, *J* 13.4), 3.21 (1 H, d, *J* 14.6) and 3.34–3.54 (7 H, obscured, 3 × CH_2CO_2 and CH_2CCH_2), 3.34, 3.35, 3.36, 3.39, 3.43, 3.48 (each 3 H, s, OMe), 4.74, 5.04, 5.18 and 5.40 (each 1 H, br d, *J* 11, 2 × CO_2CH_2Ar), 6.69–7.27 (4 H, m, Ar) and 8.63, 9.86 and 9.91 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 25 °C) 19.30, 19.34, 20.76, 29.50, 29.67, 30.94, 31.27, 31.49, 34.50 and 34.59 (CH_2), 51.47, 51.54, 51.86, 52.46 and 52.63 (OMe), 64.40 (br, 2 × OCH_2), 77.20 (C-4), 116.07, 117.09, 119.54, 122.56, 123.50, 125.08, 125.21, 127.70, 128.08, 128.81, 130.39, 133.77, 137.61, 137.75 and 153.64 (C=C) and 160.50, 160.82, 169.56, 172.33, 173.24, 173.40 and 173.76 (C=C); *m*/*z* (FD) 905 (M^+, 100%).

Heating a solution of the hydroxy acid (10 mg, 11 μmol), *N*,*N*′-dicyclohexylcarbodiimide (2.5 mg, 12 μmol) and 4-dimethylaminopyridine (0.1 mg, 1 μmol) in toluene (3 cm^3) at reflux under argon for 22 h gave the same macrocyclic diester **4** (3.6 mg, 37%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-1-methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2-trimethylsilylethoxycarbonyl)-4,5-dihydrodipyrrin 9

A mixture of lactam **2**[5] (15 mg, 15 μmol), trimethyloxonium tetrafluoroborate (4.5 mg, 30 μmol) and 1,8-bis(dimethylamino)naphthalene (3.6 mg, 17 μmol) was stirred in dry dichloromethane (2 cm^3) at room temperature under argon for 3 h and then evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave the *methoxypyrrolenine* **9** (11.8 mg, 78%) as an oil (Found: M^+, 1007.4087. $C_{50}H_{65}N_3O_{17}Si$ requires *M*, 1007.4083); $\delta_H(CDCl_3)$ 0.04 (9 H, s, $SiMe_3$), 1.04 (2 H, t, *J* 9, CH_2Si), 2.27–2.41 and 2.90–2.95 (11 H, m), 2.45 (1 H, d, *J* 15), 2.50 (2 H, t, *J* 8) and 2.64 (2 H, t, *J* 7.6, 3 × CH_2CH_2 and CH_2CCH_2), 2.98 and 3.05 (each 1 H, d, *J* 15, CH_2CO_2), 3.30 and 3.39 (each 1 H, d, *J* 16, CH_2CO_2), 3.46, 3.58, 3.59, 3.59, 3.59, 3.64, 3.76 (each 3 H, s, OMe), 3.74 and 3.86 (each 1 H, d, *J* 17, CH_2CO_2), 4.20–4.32 (2 H, m, C*H*$_2$$CH_2Si$), 5.18 and 5.25 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.30–7.40 (5 H, m, Ph) and 9.98 and 10.31 (each 1 H, br s, NH); $\delta_C(CDCl_3)$ −1.57 ($SiMe_3$), 17.57 (CH_2Si), 19.24, 19.55, 20.46, 29.46, 30.47, 30.47, 31.12, 31.37, 34.84 and 35.00 (CH_2), 51.35, 51.52, 51.59, 51.75, 51.81, 52.84 and 55.11 (OMe), 61.98 (*C*H_2CH_2Si), 65.75 (*C*H_2Ph), 77.19 (C-4), 115.26, 117.45, 117.71, 121.82, 122.53, 129.05, 129.60, 129.78, 134.25 and 136.22 (C=C), 128.14, 128.44 and 128.59 (C=*C*H), 155.99 (N=C−C=*C*) and 160.27, 160.89, 171.15, 171.37, 172.01, 172.23, 172.98, 173.34 and 173.77 (C=O and C=N); *m*/*z* (FD) 1007 (M^+, 100%).

2-Benzyloxycarbonyl-4-methoxycarbonyl-3-(2-methoxycarbonylethyl)-5-methylpyrrole 13

A solution of sodium nitrite (1.3 g) in water (2.5 cm^3) was added dropwise to a mixture of acetic acid (10 cm^3) and benzyl 5-methoxycarbonyl-3-oxopentanoate (5 g, 18 mmol) at such a rate that the temperature did not exceed 25 °C. The solution was stirred at room temperature overnight and then added dropwise to a mixture of methyl acetoacetate (2.5 g, 2.3 cm^3, 20 mmol), acetic acid (8 cm^3), zinc dust (3.5 g) and ammonium acetate (3.5 g) at such a rate that the temperature was maintained at between 50 and 70 °C. The mixture was vigorously stirred at room temperature for 30 min, then diluted with ice–water (50 cm^3), stirred for a further 30 min and then filtered. The filtrate was extracted with dichloromethane (4 × 50 cm^3) and the combined extracts were washed with aqueous sodium carbonate, dried and evaporated under reduced pressure. Recrystallisation from diethyl ether gave the *pyrrole* **13**, mp 120–121 °C (Found: C, 63.8; H, 6.1; N, 3.65. $C_{19}H_{21}NO_6$ requires C, 63.5; H, 5.9; N, 3.9%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 3020, 1710, 1430, 1260 and 910; $\delta_H(CDCl_3$, 400 MHz) 2.48 (3 H, s, 5-Me), 2.53 and 3.37 (each 2 H, t, *J* 7, CH_2CH_2), 3.61 and 3.80 (each 3 H, s, OMe), 5.29 (2 H, s, OCH_2), 7.30–7.41 (5 H, m, Ph) and 9.15 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 14.29 (5-Me), 21.28 (*C*$H_2CH_2CO_2$), 34.93 ($CH_2CH_2CO_2$), 50.89 and 51.44 (OMe), 66.31 (OCH_2), 112.94, 117.64, 128.34, 128.60, 133.59, 135.67 and 139.40 (C=C) and 160.78, 165.30 and 173.49 (C=O); *m*/*z* (FD) 359 (M^+, 100%).

5-Acetoxymethyl-2-benzyloxycarbonyl-4-methoxycarbonyl-3-(2-methoxycarbonylethyl)pyrrole 15

A solution of pyrrole **13** (1.5 g, 4.2 mmol) in dry dichloromethane (20 cm^3) at 0 °C was stirred with freshly distilled sulfuryl

chloride (0.35 cm^3, 4.4 mmol) under argon for 1 h and then evaporated under reduced pressure. A mixture of the residue, glacial acetic acid (20 cm^3) and sodium acetate (1.00 g) was heated at 70 °C for 1 h, then cooled, poured into water (500 cm^3) and extracted with dichloromethane (4 × 50 cm^3). The combined extracts were washed with water (100 cm^3), dried and evaporated under reduced pressure. Recrystallization from dichloromethane–diethyl ether–hexane gave *acetoxymethylpyrrole* **15** (1.58 g, 91%) as fine needles, mp 90–91 °C (Found: C, 60.2; H, 5.55; N, 3.4. $C_{21}H_{23}NO_8$ requires C, 60.4; H, 5.55; N, 3.35%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3450, 1730, 1230 and 1100; $\delta_H(CDCl_3$, 400 MHz) 2.10 (3 H, s, Ac), 2.52 and 3.37 (each 2 H, t, *J* 7, CH_2CH_2), 3.60 and 3.81 (each 3 H, s, OMe), 5.30 (2 H, s, CH_2Ph), 5.37 (2 H, s, CH_2OAc), 7.31–7.40 (5 H, m, Ph) and 9.64 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.74 and 20.96 (*Me*CO and $CH_2CH_2CO_2$), 34.76 ($CH_2CH_2CO_2$), 51.19 and 51.37 (OMe), 58.40 (CH_2OAc), 66.45 (CH_2Ph), 113.51, 119.40, 128.29, 128.53, 132.86 and 135.47 (C=C) and 160.47, 164.38, 170.94 and 173.21 (C=O); *m*/*z* (FD) 417 (M^+, 100%).

1-Benzyloxycarbonyl-9-*tert*-butoxycarbonyl-3-methoxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyldipyrromethane 16

A solution of pyrrole **13** (100 mg, 0.28 mmol) in dry dichloromethane (2 cm^3) was stirred at room temperature under argon with freshly distilled sulfuryl chloride (24 μl, 0.28 mmol) for 30 min and then evaporated under reduced pressure. A solution of the residue and α-free pyrrole **12**[8] (91 mg, 0.28 mmol) in dry toluene (5 cm^3) was heated under reflux for 16 h, then cooled and evaporated under reduced pressure. Purification by PLC, eluting with 15% hexane in diethyl ether, gave *dipyrromethane* **16** as a gum (Found: M^+, 682.2731. $C_{35}H_{42}N_2O_{12}$ requires *M*, 682.2738); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 1725, 1700, 1170 and 1070; $\delta_H(CDCl_3$, 400 MHz) 1.51 (9 H, s, Bu′), 2.49–2.54 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.96 and 3.33 (each 2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.51 (2 H, s, CH_2CO_2), 3.50, 3.63, 3.63 and 3.90 (each 3 H, s, OMe), 4.15 (2 H, s, 5-H_2), 5.26 (2 H, s, CH_2Ph), 7.29–7.41 (5 H, m, Ph) and 9.93 and 10.39 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.33, 21.28, 23.66, 29.73 and 34.97 (CH_2), 28.31 (CMe_3), 51.42, 51.45, 51.50 and 52.40 (OMe), 66.10 (CH_2Ph), 80.68 (CMe_3), 113.11, 118.57, 119.59, 128.17, 128.38, 128.45, 130.58, 135.77 and 139.37 (C=C) and 160.16, 166.52, 173.48, 173.66 and 174.11 (C=O); *m*/*z* (FD) 682 (M^+, 100%).

1-Benzyloxycarbonyl-9-iodo-3-methoxycarbonyl-2,8-bis-(2-methoxycarbonylethyl)-7-methoxycarbonylmethyldipyrromethane 18

A solution of *tert*-butyl ester **16** (500 mg, 0.73 mmol) in dry dichloromethane (20 cm^3) was stirred at 0 °C under argon while stannic chloride (96 μl, 0.80 mmol) was added dropwise. After 75 min aqueous sodium acetate (10%; 18 cm^3) was added and, after a further 5 min, the organic layer was separated and the aqueous layer was extracted with dichloromethane (5 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the residue in dichloromethane (10 cm^3) was stirred vigorously with sodium hydrogen carbonate (500 mg) and water (10 cm^3) while an aqueous solution (8 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added dropwise over 3 min. After a further 20 min excess iodine was destroyed by the addition of sodium metabisulfite. The organic layer was separated and the aqueous layer was then extracted with dichloromethane (3 × 10 cm^3). The combined organic phases were dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with hexane–diethyl ether (1:4), gave *iododipyrromethane* **18** (341 mg, 66%) as a gum (Found: M^+, 708.1150. $C_{30}H_{33}IN_2O_{10}$ requires *M*, 708.1139); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2970, 1740, 1710, 1440 and 1070; $\delta_H(CDCl_3$, 400 MHz) 2.41, 2.53, 2.65 and 3.33 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.50 (2 H, s, CH_2CO_2), 3.50, 3.63, 3.66 and 3.90 (each 3 H, s, OMe), 4.10 (2 H, s, 5-H_2), 5.27 (2 H, s, CH_2Ph), 7.30–7.35 and 7.40–7.42 (5 H, m, Ph) and 9.26 and 10.41 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 21.29, 22.02, 23.84, 30.47, 34.73 and 35.03 (CH_2), 51.47, 51.56, 51.59 and 52.38 (OMe), 66.10 (CH_2Ph), 111.58, 112.90, 118.49, 125.53, 128.16, 128.39, 128.46, 131.43, 132.31, 135.80 and 140.23 (C=C) and 160.18, 166.93, 173.35, 173.47 and 174.06 (C=O); *m*/*z* (FD) 708 (M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-3-methoxycarbonyl-4-(2-methoxycarbonylethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 20

Acetoxymethylpyrrole **19**[10] and iododipyrromethane **18** were coupled using stannic chloride and the resulting halopyrrolenine was hydrolysed under the standard conditions (see for example the synthesis of lactam **30** in the preceding paper[1]). The product was purified by flash chromatography, eluting with diethyl ether then 5% methanol in diethyl ether, to give the *lactam* **20** (29%) as a gum (Found: M^+, 969.3518. $C_{50}H_{55}N_3O_{17}$ requires *M*, 969.3531); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1740, 1685, 1450 and 1065; $\delta_H(CDCl_3$, 400 MHz) 2.27–2.33 (8 H, m), 2.48 (2 H, t, *J* 7), 2.92 (2 H, t, *J* 7), 3.02 (1 H, d, *J* 15) and 3.20–3.30 (5 H, m, 3 × CH_2CH_2, CH_2CCH_2 and CH_2CO_2), 3.42 and 3.50 (each 1 H, d, *J* 17, CH_2CO_2), 3.52, 3.58, 3.60, 3.61, 3.70 and 3.79 (each 3 H, s, OMe), 5.17 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 5.21 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 7.27–7.39 (11 H, m, Ph and lactam-NH) and 9.89 and 10.09 (each 1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 100 MHz) 19.52, 20.38, 21.35, 29.42, 30.20, 30.80, 31.46, 33.08, 34.65 and 35.03 (CH_2), 51.32, 51.42, 51.44, 51.53, 52.30 and 53.14 (OMe), 65.74 and 66.24 (CH_2Ph), 114.24, 115.36, 118.23, 119.21, 128.04, 128.26, 128.30, 128.41, 128.54, 129.91, 132.14, 135.68, 136.11, 138.35, 149.09 (C=C) and 160.08, 165.98, 172.15, 172.25, 173.13, 173.34 and 173.67 (C=O); *m*/*z* (FD) 969 (M^+, 100%).

3-Methoxycarbonyl-4-(2-methoxycarbonylethyl)pyrrole 22

A solution of dimethyl hex-2-enedioate **21** (700 mg, 4.07 mmol) and tosylmethyl isocyanide (794 mg, 4.07 mmol) in dry diethyl ether (13 cm^3) and dry dimethyl sulfoxide (6 cm^3) was added dropwise under argon to a stirred mixture of sodium hydride (60% dispersion in oil; 200 mg, 5.0 mmol) in dry diethyl ether (7 cm^3). The mixture was stirred for 25 min and then water (20 cm^3) was added followed by glacial acetic acid (1.5 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with hexane–diethyl ether (2:3), gave the *pyrrole* **22** (395 mg, 44%) as a gum (Found: M^+, 211.0832. $C_{10}H_{13}NO_4$ requires *M*, 211.0845); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500, 1725, 1160 and 1090; $\delta_H(CDCl_3$, 400 MHz) 2.64 and 3.04 (each 2 H, t, *J* 7, CH_2CH_2), 3.64 and 3.78 (each 3 H, s, OMe), 6.56 (1 H, br s, CH), 7.33 (1 H, t, *J* 3, CH) and 9.13 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 21.57 ($CH_2CH_2CO_2$), 34.84 ($CH_2CH_2CO_2$), 50.66 and 51.36 (OMe), 113.60, 117.21, 123.74 and 124.84 (C=C) and 165.78 and 174.18 (C=O); *m*/*z* (FD) 211 (M^+, 100%).

1-Benzyloxycarbonyl-8-methoxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3-methoxycarbonylmethyldipyrromethane 23

A solution of pyrrole **22** (150 mg, 0.71 mmol) and toluene-*p*-sulfonic acid (14 mg, 0.07 mmol) in dry dichloromethane (3 cm^3) under argon at room temperature was treated dropwise over 30 min with a solution of acetoxymethylpyrrole **19** (306 mg, 0.71 mmol) in dichloromethane (10 cm^3), stirred for 90 min and then added to water (100 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 25 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–diethyl ether (1:2), gave

dipyrromethane **23** (292 mg, 71%) as an oil (Found: M^+, 582.2221. $C_{30}H_{34}N_2O_{10}$ requires *M*, 582.2214); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 1720, 1150 and 1050; $\delta_H(CDCl_3$, 400 MHz) 2.47 (2 H, t, *J* 7), 2.81 (2 H, t, *J* 7) and 2.94–3.00 (4 H, m, 2 × CH_2CH_2), 3.46, 3.60, 3.74 and 3.76 (each 3 H, s, OMe), 3.59 (2 H, s, CH_2CO_2), 3.90 (2 H, s, 5-H_2), 5.22 (2 H, s, CH_2Ph), 7.26–7.34 (6 H, m, Ph and 9-H) and 10.12 and 10.14 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.39, 20.53, 21.60, 29.27, 34.05 and 34.72 (CH_2), 50.53, 51.39, 51.58 and 52.64 (OMe), 65.61 (*C*H_2Ph), 112.72, 113.98, 117.97, 118.47, 124.44, 127.81, 128.04, 128.13, 128.42, 133.03 and 136.06 (C=C) and 160.30, 165.52, 173.56, 175.15 and 175.76 (C=O); *m*/*z* (FD) 582 (M^+, 100%).

1-Benzyloxycarbonyl-9-formyl-8-methoxycarbonyl-2,7-bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyldipyrromethane 24

A solution of α-free dipyrromethane **23** (210 mg, 0.36 mmol) in dry dimethylformamide (1 cm^3) was added dropwise under argon to a stirred solution of phosphorus oxychloride (50 μl, 0.45 mmol) in dry dimethylformamide (250 μl). The solution was heated at 60 °C for 10 min, stirred at room temperature for 1 h and then poured into methanol–water (2:1; 25 cm^3). The mixture was stirred for 10 min at 40 °C, then added to saturated aqueous sodium carbonate (50 cm^3) and extracted with dichloromethane (4 × 15 cm^3). The combined organic extracts were washed with water (2 × 15 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether–hexane (1:3), gave *formyldipyrromethane* **24** (156 mg, 71%), which was recrystallised from diethyl ether–hexane, mp 143–144 °C (Found: C, 60.5; H, 5.7; N, 4.45. $C_{31}H_{34}N_2O_{11}$ requires C, 60.9; H, 5.7; N, 4.6%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2930, 1700, 1650 and 1070; $\delta_H(CDCl_3$, 400 MHz) 2.49 (2 H, t, *J* 7), 2.81 (2 H, t, *J* 7) and 2.97–3.01 (4 H, m, 2 × CH_2CH_2), 3.48, 3.61, 3.84 and 3.87 (each 3 H, s, OMe), 3.60 (2 H, s, CH_2CO_2), 4.06 (2 H, s, 5-H_2), 5.23 (2 H, s, CH_2Ph), 7.29–7.33 (5 H, m, Ph), 10.07 (1 H, s, CHO) and 10.16 and 10.91 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.52, 20.53, 21.78, 29.43, 33.88 and 34.75 (CH_2), 51.52, 51.89 and 52.97 (OMe), 65.76 (*C*H_2Ph), 114.86, 118.42, 118.86, 123.50, 128.15, 128.52, 129.93, 131.24, 133.06, 134.62 and 136.04 (C=C), 160.52, 164.50, 173.63, 174.36 and 175.46 (CO_2) and 181.35 (CHO); *m*/*z* (FD) 610 (M^+, 100%).

9-Acetoxymethyl-1-benzyloxycarbonyl-8-methoxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-dipyrromethane 26

A solution of aldehyde **24** (95 mg, 0.156 mmol) in dry dichloromethane (1 cm^3) and methanol (2 cm^3) was stirred with sodium borohydride (7 mg, 0.2 mmol) at room temperature for 10 min, then poured into water (10 cm^3) and extracted with dichloromethane (5 × 5 cm^3). The combined extracts were dried and evaporated under reduced pressure. A solution of the residue in dry dichloromethane (3 cm^3) was stirred at 0 °C while triethylamine (45 μl, 0.3 mmol) followed by mesyl chloride (25 μl, 0.3 mmol) were added and after 30 min the mixture was evaporated under reduced pressure. A solution of the residue and sodium acetate (90 mg) in glacial acetic acid (3 cm^3) was heated at 70 °C for 1 h, then poured into water (25 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The combined extracts were washed with water (2 × 10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave *acetoxymethyldipyrromethane* **26** (52 mg, 52%) as a gum (Found: M^+, 654.2411. $C_{33}H_{38}N_2O_{12}$ requires *M*, 654.2425); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 1720, 1700, 1350 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.10 (3 H, s, Ac), 2.48 and 2.78 (each 2 H, t, *J* 7) and 2.94–3.01 (4 H, m, 2 × CH_2CH_2), 3.60 (2 H, s, CH_2CO_2), 3.49, 3.61, 3.76 and 3.77 (each 3 H, s, OMe), 3.90 (2 H, s, 5-H_2), 5.23 and 5.29 (each 2 H, s, CH_2O), 7.28–7.36 (5 H, m, Ph) and 10.13 and 10.22 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.68, 20.56, 20.82, 21.54, 29.28, 34.11 and 34.77 (6 × CH_2 and CO*Me*), 50.69, 51.42, 51.69 and 52.63 (OMe), 59.44 (*C*H_2OAc), 65.69 (*C*H_2Ph), 109.97, 114.15, 118.08, 119.77, 126.88, 128.10, 128.21, 128.47, 129.79, 132.42, 132.78 and 136.11 (C=C) and 160.54, 165.41, 170.67, 173.58, 175.05 and 175.75 (C=O); *m*/*z* (FD) 654 (M^+, 100%).

1,19-Bis(benzyloxycarbonyl)-3,12-bis(methoxycarbonyl)-2,8,13,18-tetrakis(2-methoxycarbonylethyl)-7,17-bis(methoxycarbonylmethyl)bilane 27

The coupling of acetoxymethyldipyrromethane **26** and iododipyrromethane **18** was carried out using the standard stannic chloride-catalysed conditions (see for example the synthesis of **30** in the preceding paper[1]). Purification by PLC, eluting with diethyl ether, gave the bilane **27** (60%) as a gum (Found: M^+, 1176.4374. $C_{61}H_{68}N_4O_{20}$ requires *M*, 1176.4426); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 1740, 1720, 1160 and 1080; $\delta_H(CDCl_3$, 400 MHz) 2.26, 2.45, 2.51, 2.72, 2.76, 2.95, 2.97 and 3.34 (each 2 H, t, *J* 8, 4 × CH_2CH_2), 3.38 and 3.47 (each 2 H, s, CH_2CO_2), 3.50, 3.59, 3.61, 3.61, 3.63, 3.73, 3.77 and 3.84 (each 3 H, s, OMe), 3.83, 3.92 and 4.08 (each 2 H, s, 5-, 10 and 15-H_2), 5.22 and 5.25 (each 2 H, s, CH_2Ph), 7.26–7.40 (10 H, m, 2 × Ph) and 9.24, 10.10, 10.21 and 10.26 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.16, 19.98, 20.62, 21.26, 21.54, 23.89, 24.17, 29.48, 30.14, 34.39, 34.73, 34.91 and 35.76 (CH_2), 50.60, 51.14, 51.72, 52.24 and 52.51 (OMe), 65.69 and 66.04 (*C*H_2Ph), 109.01, 109.95, 112.31, 114.08, 116.06, 117.98, 118.40, 118.80, 124.41, 125.43, 128.13, 128.22, 128.38, 128.48, 129.88, 129.98, 132.85, 132.90, 135.88, 136.15 and 137.31 (C=C) and 160.40, 160.53, 165.71, 166.35, 173.55, 173.61, 173.83, 174.42, 175.33 and 175.74 (C=O); *m*/*z* (FD) 1176 (M^+, 100%).

5-*tert*-Butoxycarbonyl-2-dimethylaminocarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole 29

A solution of pyrrole **28**[8] (2.0 g, 5.9 mmol) in dry tetrahydrofuran (25 cm^3) under argon at 0 °C was treated dropwise with *tert*-butyl hypochlorite (2.15 cm^3), stirred at room temperature for 3 h, then evaporated under reduced pressure. A solution of the residue in dry tetrahydrofuran (20 cm^3) was stirred with 40% methanolic dimethylamine (20 cm^3) for 15 min and then evaporated under reduced pressure. The residue was dissolved in benzene (10 cm^3) and stirred overnight with water (10 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with 5% methanol in diethyl ether, gave *dimethylamide* **29** (0.95 g, 81%), mp 111–112 °C (from diethyl ether–hexane) (Found: C, 57.3; H, 7.1; N, 7.1. $C_{15}H_{28}N_2O_7$ requires C, 57.55; H, 7.1; N, 7.1%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3420, 3000, 1750, 1710, 1640, 1430, 1260 and 1180; $\delta_H(CDCl_3$, 400 MHz) 1.52 (9 H, s, Bu^t), 2.54 and 2.91 (each 2 H, t, *J* 8, CH_2CH_2), 3.00 (6 H, s, NMe_2), 3.58 (2 H, s, CH_2CO_2), 3.62 and 3.65 (each 3 H, s, OMe) and 9.35 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.34 (*C*$H_2CH_2CO_2$), 28.18 (C*Me*$_3$), 29.82 (*C*H_2CO_2), 34.62 ($CH_2CH_2CO_2$), 36.87 (NMe_2), 51.32 and 51.86 (OMe), 81.54 (*C*Me$_3$), 117.52, 121.28, 126.58 and 128.42 (C=C) and 160.13, 163.99, 171.70 and 173.40 (C=O); *m*/*z* (FD) 396 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-1-methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin 35

An equimolar mixture of lactam **34**,[10] trimethyloxonium tetrafluoroborate and 1,8-bis(dimethylamino)naphthalene was stirred in dichloromethane at room temperature under argon for 28 h and then evaporated under reduced pressure. Purification by flash chromatography, eluting with diethyl ether, gave *methoxypyrrolenine* **35** (82%) as a foam (Found: M^+, 1169.0091. $C_{47}H_{54}{}^{79}Br_3N_3O_{17}$ requires *M*, 1169.1001); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2950, 1730s, 1450 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.31–

2.47 (10 H, m), 2.55 and 2.63 (each 2 H, t, *J* 7) and 3.00–3.05 (2 H, m, 3 × CH_2CH_2 and CH_2CCH_2), 3.32 and 3.42 (each 1 H, d, *J* 17, CH_2CO_2), 3.49 (2 H, s, CH_2CO_2), 3.58, 3.59, 3.61 and 3.76 (21 H total, 4 × s, 7 × OMe), 3.73 and 3.85 (each 1 H, d, *J* 17, CH_2CO_2), 5.02 and 5.11 (each 1 H, d, *J* 17, CH_2CBr_3), 5.17 and 5.25 (each 1 H, d, *J* 12, CH_2Ph), 7.30–7.39 (5 H, m, Ph) and 10.31 (2 H, br s, 2 × NH); δ_C($CDCl_3$, 100 MHz) 19.27, 19.70, 20.54, 29.51, 30.45, 30.58, 30.73, 31.21, 31.54, 35.10 and 36.38 (CH_2 and CBr_3), 51.56, 51.71, 51.78, 51.93, 52.02, 53.12 and 55.49 (OMe), 65.93 (*C*H_2Ph), 76.86 and 77.49 (*C*H_2CBr_3 and C-4), 115.72, 116.31, 117.84, 121.98, 122.64, 128.32, 128.59, 128.78, 129.60, 132.23, 134.55 and 136.29 (C=C) and 156.03, 158.73, 160.37, 171.37, 171.48, 172.13, 172.21, 173.06, 173.49 and 173.70 (C=O and N=*C*–C=C); *m*/*z* (FD) 1169, 1171, 1173 and 1175 (1 : 3 : 3 : 1, M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-1-methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin 36

Lactam **31**[2] was methylated with trimethyloxonium tetrafluoroborate using the above procedure. Purification by flash chromatography, eluting with diethyl ether, gave methoxypyrrolenine **36** (69%) as a gum (Found: M^+, 863.3431. $C_{44}H_{53}N_3O_{15}$ requires *M*, 863.3477); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2950, 1735s, 1445 and 1180; δ_H($CDCl_3$, 400 MHz) 2.31–2.62 (12 H, m), 2.68 (2 H, t, *J* 7) and 2.96–3.03 (2 H, m, 3 × CH_2CH_2 and CH_2CCH_2), 3.28 and 3.37 (each 1 H, d, *J* 16, CH_2CO_2), 3.43 and 3.49 (each 1 H, d, *J* 16, CH_2CO_2), 3.57, 3.58, 3.59, 3.61, 3.64 and 3.72 (21 H total, 6 × s, 7 × OMe), 3.73 and 3.82 (each 1 H, d, *J* 17, CH_2CO_2), 5.16 and 5.24 (each 1 H, d, *J* 12, CH_2Ph), 6.32 (1 H, d, *J* 2, 9-H), 7.28–7.38 (5 H, m, Ph) and 9.01 and 10.24 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.16, 19.62, 20.82, 29.83, 30.06, 30.53, 31.09, 31.18, 31.42 and 35.06 (CH_2), 51.54, 51.65, 51.76, 52.82 and 55.10 (OMe), 65.67 (*C*H_2Ph), 77.65 (C-4), 112.06, 113.48, 117.49, 120.90, 121.63, 122.47, 125.23, 128.12, 128.44, 128.64, 130.00, 133.82 and 136.34 (C=C) and 156.28, 160.37, 171.08, 171.44, 172.14, 172.76, 173.15, 173.47 and 173.93 (C=O and N=*C*–C=C); *m*/*z* (FD) 863 (M^+, 100%).

1-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyldipyrromethan-5-one 39

A solution of dimethylamide **38** (3.20 g, 7.44 mmol), prepared as for **29** above, in phosphorus oxychloride (3 cm^3) was heated at 60 °C for 30 min and then evaporated under reduced pressure. Dry 1,2-dichloroethane (1 cm^3) was added and the solution was re-evaporated. A solution of the residue and α-free pyrrole **37**[13] (1.75 g, 7.40 mmol) in dry 1,2-dichloroethane (25 cm^3) was heated at 70 °C with a stream of argon bubbling through for 4 h. Aqueous sodium carbonate (25 cm^3) was added and the mixture heated under reflux for 1 h and then cooled. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 25 cm^3). The combined organic layers were washed with water (50 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with diethyl ether, gave the *dipyrroketone* **39** (3.76 g, 81%) as a foam (Found: M^+, 624.2348. $C_{32}H_{36}N_2O_{11}$ requires *M*, 624.2319); λ_{max}(CH_2Cl_2)/nm 343 ($\log_{10}\varepsilon$ 4.32),† 294 (4.08) and 240 (4.18); ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 1730, 1590 and 1160; δ_H($CDCl_3$, 400 MHz) 2.17 (3 H, s, 9-Me), 2.50, 2.60, 2.95 and 3.01 (each 2 H, t, *J* 8, 2 × CH_2CH_2), 3.45 (2 H, s, CH_2CO_2), 3.61, 3.62, 3.67 and 3.76 (14 H total, 4 × s, 4 × OMe and CH_2CO_2), 5.29 (2 H, s, CH_2Ph), 7.30–7.37 (5 H, m, Ph) and 9.65 and 9.80 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 11.47 (9-Me), 20.32, 20.86, 29.50, 30.30 and 34.23 (CH_2), 51.46, 51.98 and 52.65 (OMe), 66.60 (*C*H_2Ph), 116.29, 118.52, 121.34, 126.13, 128.55, 128.65, 130.66, 132.13, 133.66 and 134.33 (C=C) and 159.94, 171.93, 173.29, 173.75, 173.88 and 174.36 (C=O); *m*/*z* (FD) 624 (M^+, 100%).

9-Acetoxymethyl-1-benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)dipyrromethan-5-one 40

A solution of dipyrroketone **39** (1.77 g, 3 mmol) in dry tetrahydrofuran (25 cm^3) and dry diethyl ether (30 cm^3) was stirred at 0 °C under argon while a solution of *tert*-butyl hypochlorite (400 μl) in dry diethyl ether (10 cm^3) was added dropwise and then after a further 20 min evaporated under reduced pressure. A solution of the residue and sodium acetate (1.5 g) in glacial acetic acid (25 cm^3) was heated at 60 °C for 1 h, cooled, poured into water (300 cm^3) and extracted with dichloromethane (5 × 50 cm^3). The combined extracts were washed with water (50 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with diethyl ether, gave *acetoxymethyl dipyrroketone* **40** (1.93 g, 94%) as a gum (Found: M^+, 682.2333. $C_{34}H_{38}N_2O_{13}$ requires *M*, 682.2374); ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 1710, 1350, 1160 and 1050; δ_H($CDCl_3$, 400 MHz) 1.96 (3 H, s, Ac), 2.47 and 2.57 (each 2 H, t) and 2.91–2.98 (4 H, m, 2 × CH_2CH_2), 3.54 and 3.67 (each 2 H, s, CH_2CO_2), 3.57, 3.59, 3.65 and 3.70 (each 3 H, s, OMe), 4.99 (2 H, s, CH_2OAc), 5.24 (2 H, s, CH_2Ph), 7.30–7.41 (5 H, m, Ph) and 9.90 and 10.20 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 20.00, 20.3, 20.3, 28.97, 29.83, 34.01 and 34.06 (6 × CH_2 and *Me*CO), 51.25, 51.32, 51.87 and 52.29 (OMe), 56.62 (*C*H_2OAc), 66.51 (*C*H_2Ph), 117.85, 120.04, 121.41, 127.29, 128.23, 128.38, 130.39, 131.36, 131.94 and 135.05 (C=C) and 159.93, 170.80, 171.52, 172.98, 173.34, 173.38 and 174.92 (C=O); *m*/*z* (FD) 682 (M^+, 100%).

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

A solution of α-free pyrrole **12**[8] (1.25 g, 3.85 mmol) and acetoxymethylpyrrole **41**[10] (2.35 g, 3.85 mmol) in dry dichloromethane (50 cm^3) was stirred with toluene-*p*-sulfonic acid (73 mg, 0.39 mmol) at room temperature under argon for 2.5 h, then washed with 10% aqueous sodium hydrogen carbonate (15 cm^3) followed by water (15 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with diethyl ether–hexane (3 : 2), gave the *dipyrromethane* **42** (2.85 g, 85%) as a foam (Found: M^+, 868.0054. $C_{31}H_{39}{}^{79}Br_3N_2O_{12}$ requires *M*, 868.0053); ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 1730s, 1430, 1170 and 1040; δ_H($CDCl_3$, 400 MHz) 1.51 (9 H, s, Bu^t), 2.49, 2.57, 2.78 and 2.95 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.54, 3.93 and 3.94 (each 2 H, s, 2 × CH_2CO_2 and 5-H_2), 3.65, 3.66, 3.72 and 3.77 (each 3 H, s, OMe), 5.04 (2 H, s, OCH_2) and 9.63 and 10.13 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.76, 20.70, 22.41, 29.50, 30.99, 34.28 and 35.18 (7 × CH_2 and CBr_3), 28.36 (C*Me*$_3$), 51.45, 51.98, 52.17 and 52.69 (OMe), 76.69 (OCH_2), 80.80 (*C*Me_3), 114.27, 118.06, 120.24, 120.39, 123.48, 127.91, 130.44, 132.94 (C=C) and 158.90, 160.65, 171.69, 173.58, 173.75 and 174.24 (C=O); *m*/*z* (FD) 868, 870, 872 and 874 (1 : 3 : 3 : 1, M^+, 100%).

1-Iodo-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)dipyrromethane 44

The *tert*-butyl group of dipyrromethane **42** was cleaved using stannic chloride following the standard procedure (see the preparation of acid **43** in the preceding paper[1]). The resulting acid was subjected to the standard iodination–decarboxylation procedure (as for the preparation of iododipyrromethane **27** in the preceding paper[1]). Purification by flash chromatography, eluting with diethyl ether, gave the iododipyrromethane **44** (90%) as an unstable light-sensitive gum; ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1740s, 1440 and 1170; δ_H($CDCl_3$, 400 MHz) 2.40,

† ε Values are measured in units of $dm^3\ mol^{-1}\ cm^{-1}$.

2.59, 2.65 and 2.77 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.53, 3.87 and 3.91 (each 2 H, s, 2 × CH_2CO_2 and 5-H_2), 3.64, 3.65, 3.68 and 3.75 (each 3 H, s, OMe), 5.02 (2 H, s, OCH_2) and 9.36 and 10.28 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.64, 21.97, 22.34, 30.07, 31.03, 34.24 and 34.62 (CH_2), 36.08 (CBr_3), 51.50, 51.90, 52.00 and 52.62 (OMe), 63.77 (C–I), 76.62 (OCH_2), 112.52, 114.43, 117.91, 119.75, 123.31, 125.44, 131.08 and 133.80 (C=C) and 158.50, 171.62, 173.24, 173.76 and 174.65 (C=O); *m*/*z* (FD) 894, 896, 898 and 900 (1 : 3 : 3 : 1, M^+, 100%).

14-Benzyloxycarbonyl-2,8,13-tris(2-methoxycarbonylethyl)-4-[3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2,2,2-tribromoethoxycarbonyl)pyrrol-2-ylmethyl]-3,7,12-tris(methoxycarbonylmethyl)-4,5-dihydrotripyrrin-1,10(15*H*,17*H*)-dione 45

A solution of acetoxymethyldipyrroketone **40** (1.03 g, 1.51 mmol) and iododipyrromethane **44** (1.35 g, 1.51 mmol) in dry benzene (100 cm^3) under argon at room temperature was treated dropwise with stannic chloride (190 μl, 1.55 mmol) and stirred for 45 min. Saturated aqueous sodium hydrogen carbonate (30 cm^3) was added and after 10 min the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the residue in glacial acetic acid (10 cm^3) was stirred at room temperature under argon for 1 h, then poured into saturated aqueous sodium carbonate (150 cm^3) and extracted with dichloromethane (5 × 20 cm^3). The combined extracts were washed with water (50 cm^3), dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with 0% then 5% methanol in diethyl ether, gave *lactam* **45** (605 mg, 29%) as a foam (Found: M^+, 1406.1598. $C_{58}H_{65}{}^{79}Br_3N_4O_{22}$ requires *M*, 1406.1638); λ_{max}(CH_2Cl_2)/nm 341, 287 and 246; ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 2950, 1730, 1700, 1580, 1430 and 1080; δ_H($CDCl_3$, 400 MHz) 2.37–2.61 and 2.77–3.00 (18 H total, 2 × m, 4 × CH_2CH_2 and $CH_AH_BCCH_AH_B$), 3.07 and 3.17 (each 1 H, *J* 15, $CH_AH_BCCH_AH_B$), 3.38 and 3.48 (each 1 H, d, *J* 17, CH_2CO_2), 3.78 and 3.97 (each 1 H, d, *J* 17, CH_2CO_2), 3.53–3.80 (4 H, obscured, 2 × CH_2CO_2), 3.53, 3.58, 3.61, 3.64, 3.67, 3.68, 3.76 and 3.80 (each 3 H, s, OMe), 5.00 and 5.05 (each 1 H, d, *J* 17, CH_2CBr_3), 5.25 and 5.33 (each 1 H, d, *J* 12, CH_2Ph), 7.16 (1 H, br s, lactam-NH), 7.30–7.36 (5 H, m, Ph) and 9.78, 10.00 and 10.24 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.01, 19.70, 20.28, 20.64, 29.58, 29.68, 29.75, 30.64, 30.73, 31.28, 32.84, 34.10, 34.31 and 34.43 (CH_2), 35.92 (CBr_3), 51.51, 51.65, 51.87, 52.00, 52.33, 52.50 and 53.26 (OMe), 65.91 and 66.54 (*C*H_2Ph and C-4), 76.69 (*C*H_2CBr_3), 107.87, 117.58, 117.98, 120.23, 121.15, 122.69, 123.56, 127.79, 128.46, 128.63, 129.11, 130.49, 130.70, 131.89, 135.49, 138.05 and 148.70 (C=C) and 158.56, 160.25, 171.48, 171.67, 172.94, 173.26, 173.35, 173.44, 173.55, 174.07 and 175.53 (C=O); *m*/*z* (FD) 1406, 1408, 1410 and 1412 (1 : 3 : 3 : 1, M^+, 100%).

14-Benzyloxycarbonyl-2,8,13-tris(2-methoxycarbonylethyl)-4-[3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-3,7,12-tris(methoxycarbonylmethyl)-4,5-dihydrotripyrrin-1,10(15*H*,17*H*)-dione 48

A solution of tribromoethyl ester **45** (400 mg, 0.28 mmol) in glacial acetic acid (5 cm^3) was stirred with zinc dust (600 mg) under argon at room temperature for 30 min, then filtered, diluted with water (100 cm^3) and extracted with dichloromethane (5 × 30 cm^3). The combined extracts were dried and evaporated under reduced pressure. A solution of the residual acid **46** in dichloromethane (20 cm^3) was stirred vigorously with 5% aqueous sodium hydrogen carbonate (20 cm^3) and an aqueous solution (2.9 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added dropwise. After 25 min at room temperature sodium metabisulfite was added to destroy excess iodine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the residual iodopyrrole **47** in methanol (10 cm^3) was stirred with sodium acetate (100 mg) and Adams' catalyst (30 mg) under an atmosphere of hydrogen for 35 min, then filtered, diluted with water (100 cm^3) and extracted with dichloromethane (4 × 30 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by flash chromatography, eluting with 0% then 5% methanol in diethyl ether, gave the α-*free pyrrolic lactam* **48** (193 mg, 69%) as a gum (Found: M^+, 1100.4119. $C_{55}H_{64}N_4O_{20}$ requires *M*, 1100.4114); λ_{max}(CH_2Cl_2)/nm 340, 298 and 245; ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1720, 1700, 1595 and 1180; δ_H($CDCl_3$, 400 MHz) 2.34–2.52, 2.61–2.67 and 2.77–2.84 (15 H total, 3 × m), 2.97 (2 H, t, *J* 8) and 3.02 (1 H, d, *J* 15, 4 × CH_2CH_2 and 4-CH_2), 2.73 and 3.05 (each 1 H, d, *J* 15, 4-CH_2), 3.27 and 3.49 (each 1 H, d, *J* 17, CH_2CO_2), 3.37 (2 H, s, CH_2CO_2), 3.56, 3.57, 3.60, 3.61, 3.64, 3.65, 3.68 and 3.71 (each 3 H, s, OMe), 3.56–3.71 (4 H, obscured, 2 × CH_2CO_2), 5.24 and 5.32 (each 1 H, d, *J* 12, CH_2Ph), 6.46 (1 H, d, *J* 2, α-H), 7.30–7.36 (6 H, m, Ph and lactam-NH) and 8.51, 10.06 and 10.20 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.43, 19.59, 20.26, 20.55, 29.41, 29.67, 30.46, 30.59, 31.32, 31.72, 32.05, 34.15, 34.40 and 34.84 (CH_2), 51.49, 51.64, 51.70, 51.84, 52.16, 52.44 and 53.01 (OMe), 66.49 (*C*H_2Ph), 113.84, 116.61, 117.11, 118.50, 120.54, 122.20, 127.59, 128.46, 128.60, 130.66, 130.95, 131.40, 131.73, 135.46, 137.28 and 149.65 (C=C) and 160.28, 171.53, 172.03, 172.72, 173.07, 173.32, 173.55, 174.28 and 175.53 (C=O); *m*/*z* (FD) 1100 (M^+, 100%).

14-Benzyloxycarbonyl-1-chloro-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4-methyl-4,5-dihydrotripyrrin-10(17*H*)-one 51

Acetoxymethyldipyrroketone **40** and iodopyrrole **50**[10] were coupled following the procedure for the synthesis of **45**. Purification by PLC, eluting with diethyl ether, gave the chloropyrrolenine **51** (20%) as a moisture sensitive gum; λ_{max}(CH_2Cl_2)/nm 342, 296 and 245; δ_H($CDCl_3$, 400 MHz) 1.11 (3 H, s, 4-Me), 2.36 and 3.12 (each 1 H, d, *J* 15, 5-H_2), 2.41–2.45, 2.53–2.58 and 2.94–3.03 (12 H total, 3 × m, 3 × CH_2CH_2), 3.46 and 3.55 (each 1 H, d, *J* 16, CH_2CO_2), 3.48 (2 H, s, CH_2CO_2), 3.59, 3.60, 3.62, 3.64, 3.66 and 3.67 (each 3 H, s, OMe), 3.69 and 3.77 (each 1 H, d, *J* 17, CH_2CO_2), 5.25 and 5.32 (each 1 H, d, *J* 12, CH_2Ph), 7.32–7.38 (5 H, m, Ph) and 9.74 and 10.07 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.66, 19.96, 20.23, 20.59, 29.50, 29.94, 31.69, 31.83, 32.46, 34.31, 34.41 (10 × CH_2 and 4-Me), 51.41, 51.49, 51.78, 51.95, 52.08 and 52.49 (OMe), 66.53 (*C*H_2Ph), 80.99 (C-4), 117.50, 120.80, 126.63, 128.39, 128.47, 128.58, 130.95, 131.52, 132.02, 132.19, 135.44 and 136.02 (C=C) and 160.05, 160.70, 169.54, 171.99, 172.36, 172.66, 173.29, 173.62 and 174.70 (C=O and C=N); *m*/*z* (FD) 895 and 897 (3 : 1, M^+, 100%).

14-Benzyloxycarbonyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4-methyl-10-oxo-4,5,10,17-tetrahydrotripyrrin-1(15*H*)-thione 53

A solution of chloropyrrolenine **51** (200 mg, 0.22 mmol) in dry dichloromethane (1 cm^3) was added dropwise to a saturated solution of hydrogen sulfide in dichloromethane (20 cm^3). Silver acetate (200 mg) was then added and the black mixture was stirred at room temperature for 10 min and then evaporated under a stream of argon. A solution of the residue in dichloromethane was filtered and evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave *thiolactam* **53** (120 mg, 60%) as a gum (Found: M^+, 893.3081. $C_{44}H_{51}N_3O_{15}S$ requires *M*, 893.3041); λ_{max}(CH_2Cl_2)/nm 340, 299 and 243; ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1720, 1695, 1580 and 1080; δ_H(CD_3CN, 400 MHz) 1.29 (3 H, s, 4-Me), 2.38–2.51, 2.75–2.79 and 2.93–2.98 (14 H total, 3 × m, 3 × CH_2CH_2 and 5-H_2), 3.44–3.50 (4 H, m, 2 × CH_2CO_2), 3.54, 3.56, 3.58, 3.59, 3.65 and 3.71 (each 3 H, s, OMe), 3.54–3.71

(2 H, obscured, CH_2CO_2), 5.24 and 5.33 (each 1 H, d, *J* 12, CH_2Ph), 7.32–7.42 (5 H, m, Ph) and 9.02, 9.81 and 10.27 (each 1 H, br s, NH); δ_C(CD_3COCD_3, 100 MHz) 19.05, 19.52, 19.97, 29.72, 30.58, 31.06, 31.99, 33.09 and 33.14 (CH_2 and 4-Me), 49.86, 49.93, 50.33, 50.56, 50.78 and 51.00 (OMe), 64.86 (*C*H_2Ph), 70.61 (C-4), 116.19, 119.50, 120.03, 126.83, 127.25, 127.45, 127.94, 129.82, 120.03, 130.57, 130.97, 135.17, 139.23, 150.09 (C=C), 159.06, 168.97, 170.84, 171.72, 171.85, 172.01 and 174.75 (C=O) and 195.38 (C=S); *m*/*z* (FD) 893 (M^+, 100%).

14-Benzyloxycarbonyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4-methyl-4,5-dihydrotripyrrin-10(17*H*)-one 52

Thiolactam **53** was treated with nickel boride using the standard procedure (as for the synthesis of pyrrolenine **32** in the preceding paper[1]). Purification by PLC, eluting with 5% methanol in diethyl ether, gave a nickel complex of pyrrolenine **52** (45%) as a gum; λ_{max}(CH_2Cl_2)/nm 359br, 319, 290 and 245; ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 1720 and 1580; δ_H(CD_3COCD_3, 400 MHz) 1.43 (3 H, s, 4-Me), 2.44–2.49 (3 H, m), 2.69–2.81 and 2.98–3.02 (10 H total, 2 × m) and 3.10 (1 H, d, *J* 15, 3 × CH_2CH_2 and 5-H_2), 3.31 and 3.37 (each 1 H, d, *J* 17, CH_2CO_2), 3.56, 3.57, 3.58, 3.60, 3.61 and 3.72 (each 3 H, s, OMe), 3.56–3.72 (2 H, obscured, CH_2CO_2), 3.96 and 4.03 (each 1 H, d, *J* 17, CH_2CO_2), 5.39 and 5.48 (each 1 H, d, *J* 12, CH_2Ph) and 8.27 (1 H, s, 2-H); δ_C(CD_3COCD_3, 100 MHz) 19.43, 20.37, 21.03, 22.74, 31.67, 33.22, 33.68, 34.36 and 35.42 (CH_2 and 4-Me), 51.23, 51.56, 51.62, 51.73, 52.63 and 54.93 (OMe), 70.61 (*C*H_2Ph), 80.12 (C-4), 110.04, 113.52, 117.14, 118.56, 122.31, 129.04, 129.27, 129.49, 132.75, 135.94, 136.08, 137.49 and 138.07 (C=C) and 164.99, 169.82, 170.44, 171.75, 173.31, 173.40, 173.46, 173.78 and 174.52 (C=O and C=N); *m*/*z* (FD) 917, 918, 919, 920, 921 and 922 (M^+, 100%).

A solution of the nickel complex (23 mg, 25 μmol) in dry dichloromethane (1 cm^3) was stirred with ethylenediamine (18 mg, 0.3 mmol) at room temperature under argon for 5 min and then evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave *pyrrolenine* **52** (17 mg, 80%) as a gum (Found: M^+, 861.3351. $C_{44}H_{51}N_3O_{15}$ requires *M*, 861.3320); λ_{max}(CH_2Cl_2)/nm 342, 289 and 245; ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 2950, 1720, 1695, 1580 and 1180; δ_H(CD_3COCD_3, 400 MHz) 1.09 (3 H, s, 4-Me), 2.05 (6 H, obscured by solvent) and 2.48–2.61 (6 H, m, 3 × CH_2CH_2), 2.28 and 3.33 (each 1 H, d, *J* 15, 5-H_2), 3.37 and 3.47 (each 1 H, d, *J* 17, CH_2CO_2), 3.56 and 3.77 (each 2 H, s, 2 × CH_2CO_2), 3.57, 3.58, 3.59, 3.60, 3.63 and 3.66 (each 3 H, s, OMe), 5.32 and 5.38 (each 1 H, d, *J* 12, CH_2Ph), 7.33–7.49 (5 H, m, Ph), 7.97 (1 H, s, 2-H), 10.60 (1 H, br s, NH) and 11.10 (1 H, v br s, NH); δ_C(CD_3COCD_3 and Et_3N, 100 MHz, some peaks obscured by background noise) 19.36, 20.64, 20.95, 22.98, 32.98, 33.75, 34.39, 34.71 and 35.37 (CH_2 and 4-Me), 50.97, 51.30, 51.47, 51.61, 52.36 and 54.69 (OMe), 70.60 (*C*H_2Ph), 81.44 (C-4), 119.07, 126.67, 128.78, 129.05, 129.23, 135.69, 142.24 (C=C), 159.90, 172.07, 172.74, 172.88, 173.17, 173.36, 174.29 and 175.32 (C=O and C=N); *m*/*z* (FD) 861 (M^+, 100%).

14-Benzyloxycarbonyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4-methyl-1,4,5,15-tetrahydrotripyrrin-10(17*H*)-one 54

A solution of pyrrolenine **52** (10 mg, 11 μmol) in dry methanol was stirred with sodium borohydride (10 mg) at room temperature for 30 min under argon, then diluted with water (10 cm^3) and extracted with dichloromethane (4 × 5 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave *amine* **54** (8 mg, 80%) as a gum (Found: M^+, 863.3490. $C_{44}H_{53}N_3O_{15}$ requires *M*, 863.3477); λ_{max}(CH_2Cl_2)/nm 345, 295 and 245; ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 3250, 2950, 1720, 1580 and 1075; δ_H(CD_3COCD_3, 400 MHz) 1.12 (3 H, s, 4-Me), 2.30–2.33 and 2.51–2.61 (9 H total, 2 × m), 2.68 (1 H, d, *J* 15) and 2.92 and 3.03 (each 2 H, t, *J* 7, 3 × CH_2CH_2 and 5-H_2), 3.12 and 3.54 (each 1 H, d, *J* 17, CH_2CO_2), 3.15 and 3.30 (each 1 H, d, *J* 15, NCH_2), 3.57, 3.57, 3.58, 3.60, 3.61 and 3.63 (each 3 H, s, OMe), 3.57–3.63 (2 H, obscured, CH_2CO_2), 3.75 and 3.79 (each 1 H, d, *J* 17, CH_2CO_2), 5.31 and 5.38 (each 1 H, d, *J* 12, CH_2Ph) and 7.35–7.51 (5 H, m, Ph); δ_C(CD_3COCD_3, 100 MHz) 20.75, 21.28, 22.99, 24.85, 29.04, 30.50, 32.27, 33.88, 34.77 and 34.82 (4-Me and 9 × CH_2), 51.24, 51.35, 51.51, 51.71, 51.77, 52.01 and 53.19 (CH_2N and 6 × OMe), 66.44 (*C*H_2Ph), 72.18 (C-4), 107.04, 117.04, 120.75, 121.44, 127.56, 128.85, 129.15, 129.19, 131.65, 131.80, 133.16, 134.11, 137.18 and 139.27 (C=C) and 160.87, 172.14, 172.68, 173.45, 173.71 and 175.70 (C=O); *m*/*z* (FD) 863 (M^+, 100%).

14-Benzyloxycarbonyl-3,8,13-tris(2-methoxycarbonylethyl)-2,7,12-tris(methoxycarbonylmethyl)-1-methyl-5,15-dihydrotripyrrin-10(17*H*)-one 55

A solution of pyrrolenine **52** (3.2 mmol dm^{-3}) in dry degassed acid-free dichloromethane was stirred with an equimolar amount of toluene-*p*-sulfonic acid monohydrate at room temperature under argon in the dark for 18 h, then washed with 5% aqueous sodium hydrogen carbonate followed by water, dried and evaporated under reduced pressure. Purification by PLC gave tripyrrole **55** (75%) as a gum (Found: M^+, 861.3297. $C_{44}H_{51}N_3O_{15}$ requires *M*, 861.3320); λ_{max}(CH_2Cl_2)/nm 340, 285 and 240; ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1720, 1575 and 1160; δ_H($CDCl_3$, 400 MHz) 2.09 (3 H, s, 1-Me), 2.46–2.55 (6 H, m, 3 × $CH_2CH_2CO_2$), 2.61, 2.71 and 2.94 (each 2 H, t, 3 × $CH_2CH_2CO_2$), 3.31, 3.60, 3.61, 3.63, 3.64 and 3.75 (each 3 H, s, OMe), 3.31, 3.58, 3.72 and 3.84 (each 2 H, s, 3 × CH_2CO_2 and 5-H_2), 5.30 (2 H, s, CH_2Ph), 7.30–7.38 (5 H, m, Ph), 9.03, 9.62 and 10.05 (each 1 H, br s, NH); δ_C($CDCl_3$, 100.57 MHz) 11.08 (1-Me), 19.08, 20.15, 20.69, 27.22, 29.34, 29.79, 30.50, 34.30, 34.47 and 34.60 (10 × CH_2), 51.32, 51.48, 51.52, 51.77, 52.21 and 52.48 (OMe), 66.60 (*C*H_2Ph), 109.63, 115.57, 116.43, 120.85, 121.02, 122.33, 125.17, 127.02, 128.46, 128.55, 128.66, 130.86, 131.49, 132.10 and 135.20 (C=C) and 160.00, 172.86, 173.23, 173.62, 173.97, 174.84 and 174.97 (C=O); *m*/*z* (FD) 861 (M^+, 100%).

14-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4,5-dihydrotripyrrin-1,10(15*H*,17*H*)-dione 57

Iododipyrromethane **56**[1] and acetoxymethyldipyrroketone **40** were coupled according to the procedure described above for the synthesis of lactam **45**. Purification by flash chromatography, eluting with 0% then 5% methanol in diethyl ether, gave lactam **57** (22%) as a gum (Found: M^+, 1234.4547. $C_{63}H_{70}N_4O_{22}$ requires *M*, 1234.4482); λ_{max}(CH_2Cl_2)/nm 342, 295 and 245; ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 2950, 1725, 1575, 1445 and 1075; δ_H($CDCl_3$, 400 MHz) 2.35–2.59 and 2.75–3.04 (18 H total, 2 × m, 4 × CH_2CH_2 and 4-CH_2), 2.70 and 3.01 (each 1 H, d, *J* 15, 4-CH_2), 3.21 (1 H, d, *J* 16, C$H_AH_BCO_2$), 3.38, 3.57, 3.57, 3.61, 3.62, 3.62, 3.64 and 3.73 (each 3 H, s, OMe), 3.38–3.73 (1 H, obscured, $CH_AH_BCO_2$), 3.48 (2 H, m, CH_2CO_2), 3.67 and 3.81 (each 1 H, d, *J* 17, CH_2CO_2), 5.05 and 5.50 (each 1 H, d, *J* 12, CH_2Ph), 5.17 and 5.31 (each 1 H, d, *J* 12, CH_2Ph), 7.26–7.39 (10 H, m, 2 × Ph) and 7.43, 9.59, 10.16 and 10.52 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.73, 20.08, 20.36, 20.62, 28.86, 29.47, 29.53, 29.74, 30.16, 30.78, 33.20, 33.96, 34.29 and 34.70 (14 × CH_2), 51.37, 51.46, 51.51, 51.60, 52.20, 52.28, 52.62 and 53.12 (OMe), 65.66 and 66.27 (*C*H_2Ph), 115.19, 117.94, 118.12, 121.10, 121.38, 127.79, 127.97, 128.25, 128.35, 128.43, 128.52, 128.60, 129.61, 130.59, 130.98, 131.31, 132.26, 135.98, 136.16, 138.24 and 149.00 (C=C) and 159.85, 160.07, 171.56, 171.96, 172.49, 172.97, 173.36, 173.53, 173.59, 174.23 and 175.45 (C=O); *m*/*z* (FD) 1234 (M^+, 100%).

14-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-4,5-dihydrotripyrrin-1,10(15*H*,17*H*)-dithione 59

A solution of lactam **57** in dry dimethoxyethane (1 cm^3) was stirred with an equimolar quantity of Davy's reagent **6** at room temperature under argon for 10 min and then evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave the *dipyrrothioketone thiolactam* **59** (52%) as a gum; $\lambda_{max}(CH_2Cl_2)$/nm 426, 285 and 250; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1730, 1700, 1440 and 1180; $\delta_H(CDCl_3$, 400 MHz) 2.35–2.56, 2.67–2.73 and 2.90–2.98 (18 H total, 3 × m, 4 × CH_2CH_2 and 4-CH_2), 2.83 and 3.09 (each 1 H, d, *J* 15, 4-CH_2), 3.34 and 3.42 (each 1 H, d, *J* 17, 2 × CH_A-H_BCO_2), 3.53, 3.55, 3.58, 3.61, 3.62, 3.63, 3.64 and 3.76 (each 3 H, s, OMe), 3.53–3.76 (6 H, obscured, 2 × $CH_AH_BCO_2$ and 2 × CH_2CO_2), 5.20 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 5.27 and 5.35 (each 1 H, d, *J* 12, CH_2Ph), 7.26–7.39 (10 H, m, 2 × Ph) and 9.27, 9.78, 9.85 and 9.94 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.35, 20.43, 20.73, 20.88, 29.49, 29.65, 29.92, 30.51, 30.66, 31.45, 31.85, 33.78, 34.31 and 34.62 (CH_2), 51.41, 51.48, 51.52, 51.60, 52.12, 52.48, 52.66 and 53.21 (OMe), 65.73 and 66.35 (*C*H_2Ph), 73.23 (C-4), 115.34, 118.37, 119.35, 119.67, 120.54, 127.70, 128.04, 128.25, 128.28, 128.37, 128.43, 128.54, 129.99, 131.61, 133.19, 135.69, 136.03, 138.03, 138.30, 138.56, 144.26 and 147.03 (C=C), 160.11, 160.23, 171.55, 172.70, 172.77, 173.08, 173.46 and 173.57 (C=O) and 197.81 and 198.52 (C=S); *m*/*z* (FD) 1266 (M^+, 100%).

1-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyldipyrromethane-5-thione 62

A solution of dipyrroketone **39** (50 mg, 80 μmol) in dry dimethoxyethane (1 cm^3) was stirred with Davy's reagent **6** (14 mg, 45 μmol) at room temperature under argon for 10 min and then evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave *dipyrrothioketone* **62** (35.5 mg, 69%) as a gum; $\lambda_{max}(CH_2Cl_2)$/nm 425, 261 and 226; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2950, 1725 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.17 (3 H, s, 9-Me), 2.50–2.56 (4 H, m, 2 × CH_2-CH_2CO_2), 2.91 and 2.97 (each 2 H, t, *J* 7, C$H_2CH_2CO_2$), 3.45 and 3.47 (each 2 H, s, CH_2CO_2), 3.59, 3.61, 3.67 and 3.69 (each 3 H, s, OMe), 5.29 (2 H, s, CH_2Ph), 7.33–7.40 (5 H, m, Ph) and 9.44 and 9.51 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 11.71 (9-Me), 20.47, 21.25, 29.67, 30.26, 33.63 and 34.11 (CH_2), 51.48, 52.06 and 52.34 (OMe), 66.50 (*C*H_2Ph), 116.80, 119.63, 121.49, 128.38, 128.47, 128.59, 131.23, 135.28, 135.46, 137.31, 137.67 and 138.24 (C=C), 160.08, 171.41, 173.30 and 173.34 (C=O) and 194.08 (C=S); *m*/*z* (FD) 640 (M^+, 100%).

The above product **62** was reconverted into the starting dipyrroketone **39**, 82%, without full purification of the intermediate **63**, by the standard method developed for hydrolysis of thioketones. This is described below for the conversion of **59** into **60**.

14-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-1-methylthio-4,5-dihydrotripyrrin-10(17*H*)-one 60

A solution of dipyrrothioketone thiolactam **59** (50 mg, 40 μmol) in distilled trifluoroacetic acid (2 cm^3) and trimethyl orthoformate (2 cm^3) was stirred at room temperature under argon for 1 h and then evaporated under reduced pressure. A solution of the residue in dichloromethane (5 cm^3) was washed with aqueous sodium hydrogen carbonate (10 cm^3), dried and evaporated under reduced pressure. A solution of the residue in tetrahydrofuran (3 cm^3) was stirred with water (20 drops) and toluene-*p*-sulfonic acid (10 mg, 50 μmol) at room temperature under argon for 16 h, then poured into water (20 cm^3) and extracted with dichloromethane (4 × 5 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with 2% methanol in diethyl ether, gave *methylthiopyrrolenine* **60** (28 mg, 56%) as a gum (Found: M^+, 1264.4421. $C_{64}H_{72}N_4O_{21}S$ requires *M*, 1264.4410); $\lambda_{max}(CH_2Cl_2)$/nm 343, 290 and 240; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1720, 1695, 1580 and 1175; $\delta_H(CDCl_3$, 400 MHz) 2.02 (3 H, s, SMe), 2.21–2.23, 2.32–2.54 and 2.85–3.05 (20 H total, 3 × m, 4 × CH_2CH_2 and CH_2CCH_2), 3.32 and 3.43 (each 1 H, d, *J* 16, CH_2CO_2), 3.36 and 3.44 (each 2 H, s, 2 × CH_2CO_2), 3.56, 3.58, 3.59, 3.59, 3.61, 3.62, 3.63 and 3.66 (each 3 H, s, OMe), 3.56–3.66 (2 H, obscured, CH_2CO_2), 5.19 and 5.26 (each 1 H, d, *J* 12, CH_2Ph), 5.26 and 5.32 (each 1 H, d, *J* 12, CH_2Ph), 7.27–7.39 (10 H, m, 2 × Ph) and 9.81, 10.04 and 10.24 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 12.42 (SMe), 19.65, 20.28, 20.36, 20.44, 29.36, 29.50, 29.61, 30.29, 30.60, 31.12, 31.74, 34.34 and 34.68 (CH_2), 51.41, 51.51, 51.76, 51.94, 52.04 and 52.71 (OMe), 65.84 and 66.46 (*C*H_2Ph), 84.07 (C-4), 115.25, 117.01, 117.22, 120.55, 126.75, 128.21, 128.42, 128.47, 128.51, 128.59, 128.68, 130.01, 130.27, 130.75, 131.54, 131.83, 132.68, 135.51, 136.06, 139.14 and 155.20 (C=C) and 160.13, 160.23, 170.93, 171.91, 172.17, 172.29, 172.61, 173.27, 173.35, 173.49 and 174.90 (C=O and C=N); *m*/*z* (FD) 1264 (M^+, 100%).

1-Carboxy-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyldipyrromethan-5-one 64

A solution of benzyl ester **39** (1.06 g, 1.70 mmol) in dry tetrahydrofuran (10 cm^3) was stirred with triethylamine (80 μl) and 10% palladium-on-charcoal (100 mg) under an atmosphere of hydrogen for 45 min, then filtered and evaporated under reduced pressure. Purification by flash chromatography, eluting with methanol–ethyl acetate (1:6), gave *acid* **64** (815 mg, 90%) as a gum (Found: M^+, 534.1865. $C_{25}H_{30}N_2O_{11}$ requires *M*, 534.1849); $\lambda_{max}(CH_2Cl_2)$/nm 344 ($\log_{10}\varepsilon$ 4.25), 289 (3.95) and 238 (4.04); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400, 3300–2500, 1720, 1590 and 1050; $\delta_H(CDCl_3$, 400 MHz) 2.18 (3 H, s, 9-Me), 2.57, 2.61, 2.77 and 3.02 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.56, 3.61, 3.63 and 3.65 (each 3 H, s, OMe), 3.46 and 3.75 (each 2 H, s, CH_2CO_2) and 9.88 and 10.00 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 11.25 (9-Me), 20.13, 20.50, 29.40, 30.00 and 34.20 (CH_2), 51.28, 51.80 and 52.22 (OMe), 115.78, 119.20, 126.27, 129.59, 131.16, 132.95 and 134.16 (C=C) and 164.08, 171.97, 173.69, 173.74 and 174.64 (C=O); *m*/*z* (FD) 534 (M^+, 100%).

1-Dimethylaminocarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyldipyrromethan-5-one 65

A solution of carboxylic acid **64** (486 mg, 0.91 mmol) and 1,1′-carbonyldiimidazole (162 mg, 1.0 mmol) in dry dichloromethane (5 cm^3) was stirred at room temperature under argon for 15 min, then treated with dimethylamine (40% in industrial methylated spirits; 5 cm^3) and after a further 1 h evaporated under reduced pressure. Purification by PLC, eluting with 10% methanol in diethyl ether, gave *dimethylamide* **65** (335 mg, 66%) as a gum (Found: M^+, 561.2326. $C_{27}H_{35}N_3O_{10}$ requires, *M*, 561.2322); $\lambda_{max}(CH_2Cl_2)$/nm 345, 295 and 229; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400, 2950, 1710, 1585 and 1150; $\delta_H(CDCl_3$, 400 MHz) 2.14 (3 H, s, 9-Me), 2.44, 2.56, 2.73 and 2.97 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 2.99 (6 H, s, NMe_2), 3.43 and 3.56 (each 2 H, s, CH_2CO_2), 3.59, 3.61, 3.65 and 3.71 (each 3 H, s, OMe) and 9.98 and 10.00 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 11.34 (9-Me), 19.89, 20.68, 29.49, 30.43, 34.30 and 34.41 (CH_2), 37.0 (NMe_2), 51.39, 51.54, 51.92 and 52.42 (OMe), 115.70, 118.37, 124.30, 126.04, 126.09, 129.97, 132.61, 133.69 (C=C) and 164.26, 172.05, 173.19, 173.82 and 174.42 (C=O); *m*/*z* (FD) 561 (M^+, 100%).

2,7-Bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-9-methyl-1-phenylselenocarbonyldipyrromethan-5-one 66

A solution of acid **64** (50 mg, 94 μmol) in dry dichloromethane (1 cm^3) was stirred with 1,1′-carbonyldiimidazole (18 mg, 120 μmol) at room temperature under argon for 15 min and then a

solution of sodium phenylselenide[17] (54 mg, 0.30 mmol) in diglyme (0.5 cm^3) was added. After a further 1 h the solution was poured into water (15 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The combined extracts were washed with water (10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the *seleno-ester* **66** (29 mg, 46%) as a gum (Found: C, 55.0; H, 4.9; N, 4.15. $C_{31}H_{34}N_2O_{10}Se$ requires C, 55.3; H, 5.1; N, 4.15%); $\lambda_{max}(CH_2Cl_2)$/nm 354 ($\log_{10}$ ε 4.42), 257 (4.19) and 220 (4.20); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3400, 1720, 1570, 1330 and 1030; $\delta_H(CDCl_3$, 400 MHz) 2.19 (3 H, s, 9-Me), 2.56, 2.64, 2.96 and 3.06 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 3.37, 3.64, 3.68 and 3.78 (each 3 H, s, OMe), 3.47 and 3.65 (each 2 H, s, CH_2CO_2), 7.39–7.43 and 7.55–7.57 (5 H total, 2 × m, Ph) and 9.70 and 9.89 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 11.54 (9-Me), 20.47, 20.94, 29.49, 30.29, 33.90 and 34.18 (CH_2), 51.51, 51.64, 52.04 and 52.79 (OMe), 116.59, 119.22, 124.70, 126.10, 129.33, 129.46, 133.25, 134.22, 134.95 and 136.38 (C=C) and 171.86, 173.16, 173.50, 173.75, 174.30 and 181.09 (C=O); *m*/*z* (FD) 674 (M^+, 100%).

3,7,12-Tris(2-methoxycarbonylethyl)-2,8,13-tris(methoxycarbonylmethyl)-1,14-dimethyltripyrrin-5,10(15*H*,17*H*)-dione 67

A solution of selenoester **66** (1 equiv.) and α-free pyrrole **37**[13] (1.1 equiv.) in dichloromethane was stirred with calcium carbonate (1.25 equiv.) and a solution of copper(I) triflate–benzene complex (0.5 equiv.) in benzene at room temperature for 30 min,[15,16] then poured into saturated aqueous sodium carbonate, shaken vigorously and extracted four times with dichloromethane. The combined extracts were washed with water, dried and evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol–diethyl ether, gave the *dioxotripyrrin* **67** (5%) as a gum (Found: M^+, 755.2853. $C_{37}H_{45}N_3O_{14}$ requires *M*, 755.2901); $\lambda_{max}(CH_2Cl_2)$/nm 343, 294 and 227; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3400, 1740, 1700, 1600 and 1180; $\delta_H(CDCl_3$, 400 MHz) 2.26 and 2.29 (each 3 H, s, C-Me), 2.57, 2.93, 2.97 and 3.03 (each 2 H, t, *J* 7) and 2.61–2.64 (4 H, m, 3 × CH_2CH_2), 3.47 (4 H, s, 2 × CH_2CO_2), 3.67 (2 H, s, CH_2CO_2), 3.61, 3.63, 3.63, 3.68, 3.68 and 3.77 (each 3 H, s, OMe) and 9.63 (2 H, br s, 2 × NH); $\delta_C(CDCl_3$, 100.57 MHz, some peaks obscured by background noise) 11.63 and 11.84 (C*Me*), 19.96, 20.60, 20.80, 29.56, 29.67, 30.16, 34.45 and 34.53 (CH_2), 51.53, 51.59, 52.03 and 52.44 (OMe), 107.90, 115.98, 120.12, 126.68, 131.80 and 139.47 (C=C); *m*/*z* (FD) 755 (M^+, 100%).

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References

1 Part 48. C. J. Hawker, A. C. Spivey, F. J. Leeper and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1509.
2 C. J. Hawker, W. M. Stark, A. C. Spivey, P. R. Raithby, F. J. Leeper and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1493.
3 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
4 F. J. Leeper, D. H. C. Smith, M. J. Doyle and P. R. Raithby, *J. Chem. Soc.*, *Perkin Trans. 2*, 1995, 777.
5 P. M. Petersen, C. J. Hawker, F. J. Leeper and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1531.
6 T. Mukaiyama, *Angew. Chem.*, *Int. Ed. Engl.*, 1979, **18**, 707.
7 G. Lajoie, F. Lepine, L. Maziak and B. Belleau, *Tetrahedron Lett.*, 1983, **24**, 3815.
8 A. R. Battersby, M. H. Block, C. J. R. Fookes, P. J. Harrison, G. B. Henderson and F. J. Leeper, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 2175.
9 B. Harrell and A. H. Corwin, *J. Am. Chem. Soc.*, 1956, **78**, 3135.
10 W. M. Stark, C. J. Hawker, G. J. Hart, A. Philippides, P. M. Petersen, J. D. Lewis, F. J. Leeper and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1993, 2875; W. M. Stark, G. J. Hart and A. R. Battersby, *J. Chem. Soc.*, *Chem. Commun.*, 1986, 465.
11 A. M. van Leusen, J. Wildeman and O. H. Oldenziel, *J. Org. Chem.*, 1977, **42**, 1153.
12 J. A. Ballentine, A. H. Jackson, G. W. Kenner and G. McGillivray, *Tetrahedron*, *Suppl. 7*, 1966, 241.
13 W. M. Stark, M. G. Baker, F. J. Leeper, P. R. Raithby and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 1187.
14 P. S. Clezy and G. A. Smythe, *Aust. J. Chem.*, 1969, **22**, 239.
15 A. P. Kozikowski and A. Ames, *J. Am. Chem. Soc.*, 1980, **102**, 860.
16 C. J. Hawker, A. Philippides and A. R. Battersby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 1833.
17 H. J. Reich and M. L. Cohen, *J. Org. Chem.*, 1979, **44**, 3148.

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