Biosynthesis of porphyrins and related macrocycles. Part 50.[1] Synthesis of the *N*-formyl-dihydro analogue of the spiro-intermediate and its interaction with uroporphyrinogen III synthase

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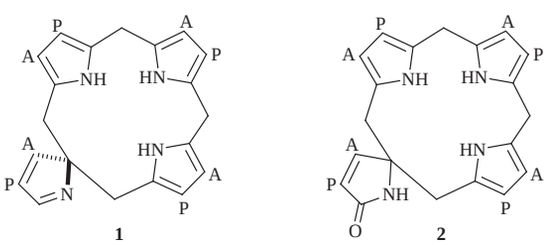
The proposed intermediacy of the spiro-system 1 for the biosynthesis of uroporphyrinogen III has focused attention on its synthesis. In this paper the approach that is explored is to carry a dihydropyrrole through the entire synthesis with the intention of converting it into a 2*H*-pyrrole (pyrrolenine) in one of the final steps. The chemistry of the different types of synthetic intermediates is described and also it is demonstrated that the *N*-formyl dihydropyrrole 37 is a strong inhibitor of cosynthetase. The conclusion is reached that of all the possible routes to the spiro-pyrrolenine 1, that *via* the protected dihydropyrrole 30 shows the greatest promise.

The proposed involvement of the spiro-pyrrolenine **1** in the reaction sequence by which the enzyme cosynthetase (systematically uroporphyrinogen III synthase, E.C.4.2.1.75) 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] Support for the intermediacy of the spiro-system **1** came from the synthesis of the spirolactam **2**, first as the racemate[3] but later as the separate enantiomers.[4] The racemate and the (*R*)-enantiomer[5] strongly inhibited cosynthetase and they acted competitively against the substrate. The spirolactam **2** resembles neither the substrate nor the product but is closely similar to the proposed intermediate **1**. Thus, the most plausible explanation of its inhibition of cosynthetase is that the spirolactam locks into the enzyme's active site to occupy the space that normally binds the spiro-intermediate **1** and further, that the latter has the illustrated (*R*)-configuration.



1 **2**

A = CH_2CO_2H, P = $CH_2CH_2CO_2H$

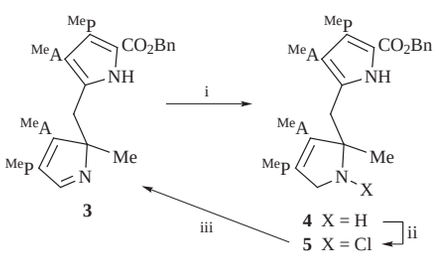
We wished to build on the progress made in the preceding papers[1,2] to develop a synthetic route to the spiro-pyrrolenine **1**. The present paper describes these studies which have led to the closest relative of **1** yet built. The spiro-pyrrolenine itself, however, has remained elusive. Indeed, the reasons why **1** remains as a formidable synthetic challenge will become clear from the chemistry now described.

Results and discussion

Synthesis of the *N*-formyl-dihydro derivative of the spiro-intermediate

The plan for this work involved preparation of dihydropyrrole **11**, Scheme 2, ready for attachment of a further pyrrole ring to allow construction of the macrocycle of the dihydro spiro-system **31**, Scheme 4. Generation of the spiro-intermediate itself **1** would then involve removal of two hydrogen atoms followed by ester hydrolysis. Trial experiments were carried out first on the dehydrogenation step.

The model dihydropyrrole **4** had been prepared earlier[2] and it could readily be obtained by reduction of the pyrrolenine **3**[2] with sodium cyanoborohydride, Scheme 1. This product **4** reacted with *tert*-butyl hypochlorite to afford the chloramine **5** which on treatment with 1,8-diazabicyclo[5.4.0]undecane (DBU) smoothly regenerated the pyrrolenine **3**. This encouraged us that the final step in the proposed synthesis at least had precedent on a related system.



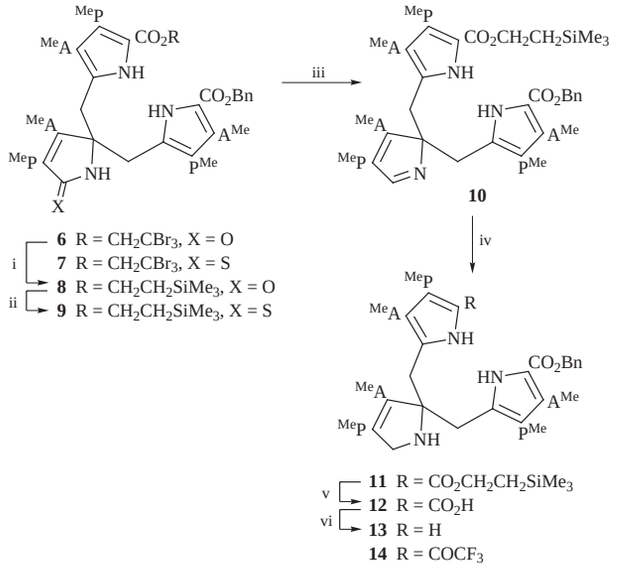
3 **4** X = H **5** X = Cl

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

Scheme 1 *Reagents:* i, $NaBH_3CN$; ii, Bu^{t}OCl; iii, DBU

For the synthesis of the dihydro spiro-system **31** it was necessary to have different α-ester groups on the two pyrrole rings, so that they could be removed one at a time. Initial experiments aimed at reduction of the previously synthesised[2] thiolactam **7** to the corresponding pyrrolenine showed that the tribromoethyl ester was not compatible with the reaction conditions involving nickel boride. Therefore the tribromoethyl group was removed from lactam octaester **6**[3] and replaced by a trimethylsilylethyl group using trimethylsilylethanol, DMAP and dicyclohexylcarbodiimide (DCC). Thionation of the resulting lactam **8** with *p*-tolyl Davy's reagent gave the corresponding thiolactam **9** (71%), Scheme 2. Desulfurisation with nickel boride[2] then yielded the pyrrolenine **10** in good yield (78%). Treatment of this pyrrolenine with sodium borohydride apparently left it unchanged as judged by TLC, including 'co-spotting'. However, NMR and mass spectrometry showed that reduction had in fact occurred to give dihydropyrrole **11** in good yield (80%). The identical chromatographic behaviour of the imine **10** and the amine **11** was very surprising and our efforts were misled for a while.

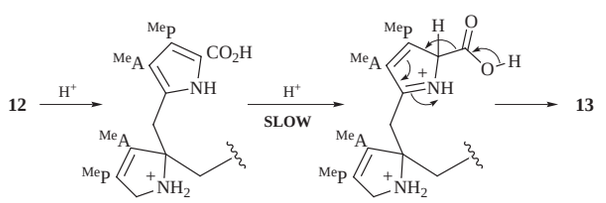
Fluoride ion smoothly removed the trimethylsilylethyl group



Scheme 2 *Reagents:* i, Zn, AcOH then $Me_3SiCH_2CH_2OH$, DCC, DMAP; ii, *p*-tolyl Davy's reagent; iii, nickel boride; iv, $NaBH_4$; v, TBAF; vi, TFA

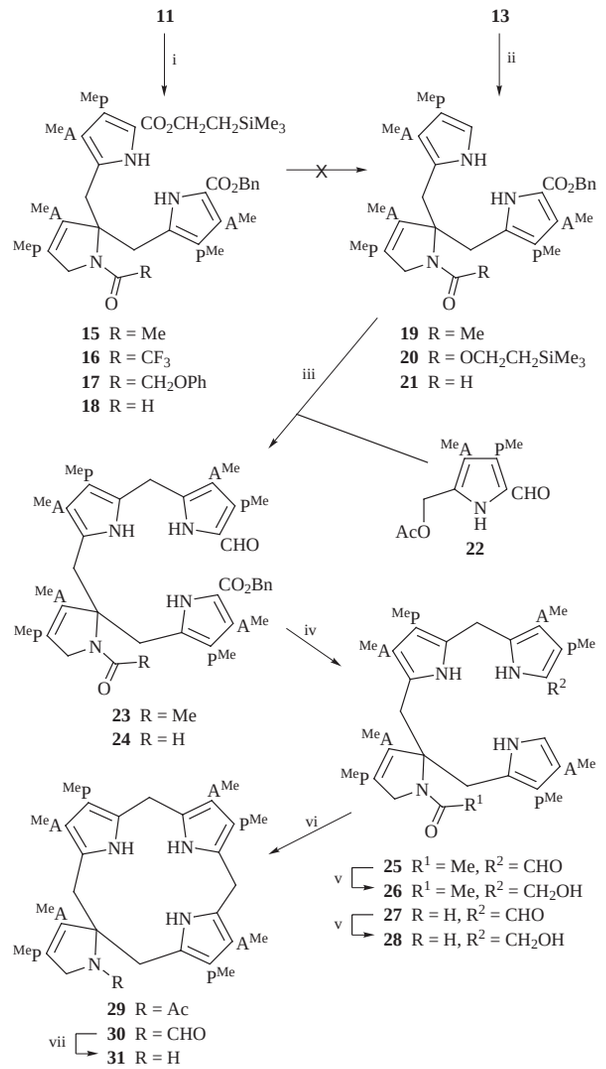
from **11** but problems arose when decarboxylation of the resultant acid **12** was attempted with TFA under conditions routinely used for this step with analogues having a lactam ring in place of the dihydropyrrole. The α-free pyrrole **13** was formed very slowly and a useless by-product **14** appeared in substantial amounts; the latter became the sole product when longer treatments with TFA were used. However, by limiting the time to 3 h, 47% of **13** was isolated, very little **14** was formed and the recovered acid, 36%, could be recycled.

The slow decarboxylation of **12** is probably due to protonation of the basic nitrogen which will discourage attachment of the second proton onto the pyrrole ring needed for the decarboxylation step, Scheme 3. The α-free product **13** is then exposed for a long period to TFA, so leading to the trifluoroacetyl derivative **14** (possibly due to small amounts of anhydride being present in the TFA even after careful purification).



Scheme 3 Mechanism for the decarboxylation of **12**

Unfortunately the usual conditions for Lewis acid-catalysed condensation of the α-free pyrrolic amine **13** with the acetoxymethyl pyrrole **22** (Scheme 4) failed, as did variations on these conditions. Presumably coordination of the amine to the Lewis acid (analogous to the protonation by TFA, Scheme 3) was responsible for the lack of reaction. Accordingly, protection of the basic nitrogen by acylation was explored. Acetylation of the amine octaester **11** was effected using acetic anhydride and DMAP to afford **15**, Scheme 4. Removal of the trimethylsilylethyl group from **15** using tetra-*n*-butylammonium fluoride (TBAF) was successful but attempted decarboxylation of the resulting acid using TFA only caused decomposition and none of the desired α-free pyrrole **19** was obtained. Alternative protecting groups which would have been easier to remove later in the synthesis were also tried. Thus the trifluoroacetamide **16** and the phenoxyacetamide **17** were made but again only decomposition was observed upon attempted decarboxylation following removal of the trimethylsilylethyl group.

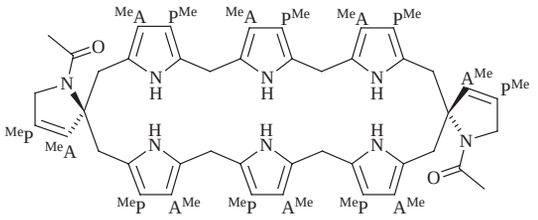


Scheme 4 *Reagents:* i, RCOCl, DMAP; ii, AcCl, DMAP or *N*-(TeocO)succinimide or HCO_2Me, 2-pyridone; iii, BF_3 or $SnCl_4$; iv, Pd/C, H_2 then KI_3, $NaHCO_3$ then PtO_2, H_2; v, $NaBH_4$; vi, TsOH; vii, Me_3OBF_4, DMAP then H_2O

In the view of the failure to convert **15** into **19**, the alternative approach of acetylating the α-free pyrrolic amine **13** was explored. An excellent yield (92%) of **19** was obtained using acetyl chloride and DMAP. At this stage we also investigated the introduction of a protecting group that would be stable under the various conditions required for the remainder of the synthesis and then readily removed at or near the end. The trimethylsilylethoxycarbonyl (Teoc) group was selected as a suitable candidate and it could be introduced by heating the Teoc derivative of *N*-hydroxysuccinimide and DMAP with amine **13** to give carbamate **20** in 51% yield.

With the basic nitrogen atom now protected, the coupling of acetamide **19** with acetoxymethylpyrrole **22**[3] gave the required tripyrrolic product **23**, although the stannic chloride normally used had to be replaced by boron trifluoride and the yield was modest, 38%. The standard steps of hydrogenolysis, iodinative decarboxylation and reduction were applied to **23** to afford the α-free pyrrole **25**, ready for borohydride reduction to the alcohol **26**. This was cyclised under the best acidic conditions developed[3] for synthesis of the ester of spirolactam **2**, which gave a yield of *ca*. 60% in that case. However, in the present case, the combined yield of a mixture of products was only 38%. Chromatography afforded one band which could not be further resolved, shown by NMR and mass spectrometry to contain the desired monomer **29** together with one of the two possible diastereoisomeric dimers, **32** and **33** (only one

enantiomer of each is illustrated). A second band contained the other dimer. The yield of the monomer **29** could be calculated to be at most 10%.



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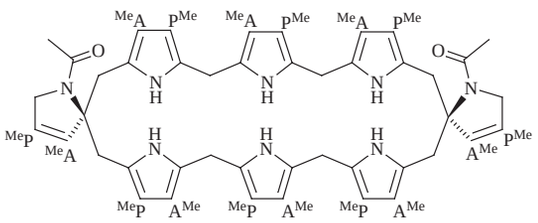

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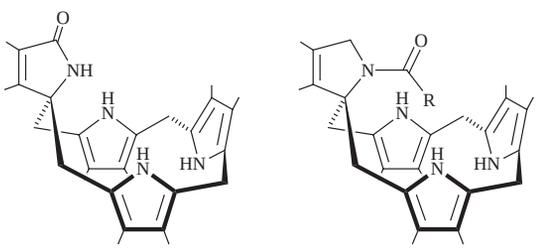


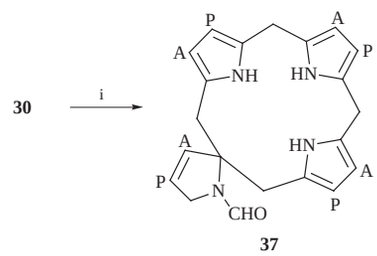
34 ≡ **2**

35 R = Me ≡ **29**
36 R = H ≡ **30**

Bearing in mind the preferred conformation **34** of the spirolactam ring system,[3] it appears that the *N*-acetyl group is disfavouring formation of the monomer by increasing the steric pressures around the top of the macrocycle as is shown in structure **35**. Accordingly, *N*-formylation was explored since then only a hydrogen atom would be placed in the somewhat restricted region close to the pyrrole rings; molecular modelling confirmed that there was fully sufficient space to accommodate it.

The formylation step was studied first using the amine **11**; treatment with formic acetic anhydride failed but the *N*-formyl derivative **18** was obtained in 63% yield by long heating of **11** with methyl formate and 2-pyridone.[6] The product was a 4:1 mixture of two rotamers about the amide bond. Unexpectedly, these could be separated as two bands by PLC on silica gel, each of which re-equilibrated during elution from the silica to give the original 4:1 mixture. Experience with the *N*-acetyl analogue **15** above showed that though the trimethylsilylethyl group could be removed, there were difficulties with the subsequent decarboxylation. Thus the way forward was not *via* **18** and so the α-free pyrrolic formamide **21** was instead prepared from the amine **13** using the foregoing conditions in 75% yield as a 1:1 mixture of rotamers. This formamide was smoothly coupled with the acetoxymethylpyrrole **22** to afford the aldehyde **24**, also as a 1:1 rotameric mixture, in 75% yield. The precursor **27** of the macrocycle **30** was then generated, as a 2:1 mixture of rotamers, by removal of the benzyloxycarbonyl group using standard steps as earlier (see Scheme 4). Satisfyingly, borohydride reduction of **27** followed by acid-catalysed ring-closure of the resultant alcohol **28** gave the macrocycle **30** as a single rotamer in 55% yield over the two steps without significant formation of dimeric products. The high yield of a single monomeric product in this cyclisation seems to point to assistance for the cyclisation from the formyl group but we refrain from speculation about the nature of this assistance.

There remained the apparently trivial step of removing the *N*-formyl group from **30**. Hydrolysis of **30** using aqueous methanolic potassium hydroxide removed the eight ester groups and the product was shown to be the salt of the octaacid **37** (Scheme 5) by ^{1}H and ^{13}C NMR spectroscopy; the formyl group remained intact. This product was used for enzymic experiments to be described later. Increasing the vigour of this hydrolysis simply caused decomposition. Although hydrazine normally cleaves *N*-formyl groups efficiently,[7] in this case competing attack at the ester groups of **30** afforded a family of mono- to hepta-acylhydrazides all shown by mass spectrometry still to carry the *N*-formyl group.

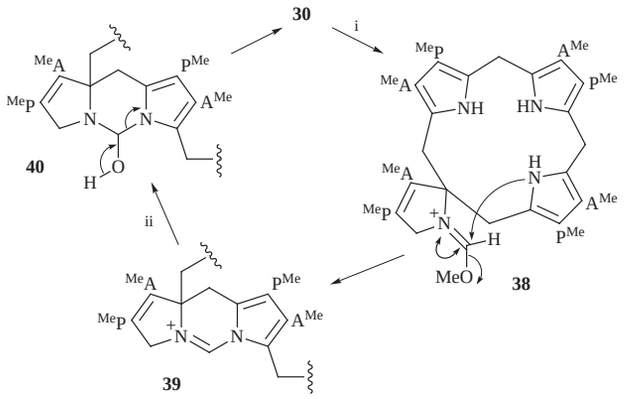


Scheme 5 *Reagent:* i, KOH

The final experiments made use of Hanessian's approach[8] in which an amide is converted by Meerwein's reagent into the corresponding imino ether followed by hydrolysis at controlled pH to achieve cleavage. When this method was applied to the formamide **30** there were complications. Work-up after the hydrolysis step gave mainly the starting formamide with only a minute amount of material (*ca.* 2%) having the correct accurate mass corresponding to the desired amine **31**. Examination of the crude reaction mixture by electrospray mass spectrometry before chromatography showed a major peak at *m*/*z* 961, none at 979 corresponding to the protonated formamide **30** and a small one at 951 which matches the protonated amine **31**. The interpretation of these observations is shown in Scheme 6. We envisage initial formation of the imino ether **38** but that this is trapped by one of the pyrrolic NH groups ideally situated (see the conformational drawing **36**) to form the amidinium ion **39** of molecular weight *m*/*z* 961. Molecular mechanics calculations confirmed that the macrocyclic ring does not prevent formation of the planar amidinium ion; in fact formation of the amidinium ion from the formamide was predicted to be *ca.* 40 kJ mol^{-1} *more* favourable in the macrocyclic case than for a corresponding non-macrocyclic structure. Under hydrolytic conditions including chromatography on moist silica gel, amidinium ion **39** would give the tetrahedral intermediate **40** which mainly collapses to the starting formamide **30**, though with formation also of a minute amount of the amine **31** by the alternative breakdown. It was not possible by varying the hydrolytic conditions to improve the amount of amine **31** formed, which meant that the enzymic studies (next section) focused on the *N*-formyl system **37**. These problems emphasise the difficulties involved in manipulating these molecules when faced with the combined effects of severe steric crowding and facile neighbouring group interactions. Nevertheless, we feel that the route to the spiropyrrolenine **1** *via* the *N*-formyl system **30** is a very promising one, well worthy of substantial further effort.

Enzymic experiments

Earlier studies with the racemic spirolactam[3] **2** and also with the two separate enantiomers[4] had established the procedures for determining their inhibition of the enzyme cosynthetase (measured as K_i) as it catalyses the conversion of hydroxymethylbilane into uroporphyrinogen III. Different determinations[3,4] of K_i for racemic **2** gave K_i in the range 1.3–2.5 μmol dm^{-3}. In the same set of experiments where K_i for the racemate was 2.5 μmol dm^{-3}, K_i for the strongly inhibiting enantiomer of **2** was 1.8 μmol dm^{-1} and that for the other enantiomer was



Scheme 6 *Reagents:* i, Me_3OBF_4, DMAP; ii, H_2O

38 μmol dm^{-1}. As reported above, the *N*-formyl system **30** was hydrolysed to yield the salt of the octaacid **37**. This was then used exactly as before[3,4] for inhibition studies using cosynthetase and synthetic hydroxymethylbilane and gave a K_i value of 0.5 μmol dm^{-3}. We do not believe too much significance should be given to the slightly lower value found for **37** relative to those above because, as is evident, the values obtained in K_i determinations can vary somewhat. However, it is clear that the *N*-formyl system **37** does strongly inhibit the action of cosynthetase.

Conclusions

The wide ranging exploration of possible routes for synthesis of the spiro-pyrrolenine **1**, described in this paper and the others in this set of four, point the way to make progress between the Scylla of decomposition by fragmentation and the Charybdis of unreactivity due to steric hindrance. The approach *via* the *N*-formyl amine **30** is particularly promising. Also, the derived octaacid **37** acts as a strong inhibitor of cosynthetase, a result that adds further evidence to that already accumulated[2–4] in support of the spiro-mechanism for the biosynthesis of uroporphyrinogen III.

Experimental

General directions are as given in ref. 2.

Dehydrogenation of dihydropyrrole 4

A solution of dihydropyrrole **4**[2] (129 mg, 0.21 mmol) in dry dichloromethane (3 cm^3) was stirred with *tert*-butyl hypochlorite (26 μl, 0.26 mmol) at −23 °C under argon for 2 h and then evaporated under reduced pressure below room temperature. Purification by PLC, eluting with diethyl ether (R_f 0.9), gave the *N*-chloro derivative **5**; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3380, 2950, 1720s, 1695, 1430, 1250, 1170 and 940; $\delta_H(CDCl_3$, 400 MHz) 1.21 (3 H, s, 4-Me), 2.28–2.31 and 2.80–3.00 (10 H total, m, 2 × CH_2CH_2 and 5-H_2), 2.71 and 2.97 (each 1 H, d, *J* 17, NCH_2), 3.43 and 3.49 (each 1 H, d, *J* 16, CH_2CO_2), 3.57, 3.59, 3.60 and 3.65 (each 3 H, s, OMe), 3.72 (2 H, s, CH_2CO_2), 5.21 and 5.29 (each 1 H, d, *J* 12, CH_2Ph), 7.32–7.48 (5 H, m, Ph) and 10.20 (1 H, br s, NH); *m*/*z* (FD) 646 and 648 (3 : 1, M^+, 100%).

A solution of *N*-chloro derivative **5** in dry dichloromethane (3 cm^3) at −23 °C was stirred with DBU (50 μl, 0.30 mmol) under argon for 10 min, warmed to room temperature over 1 h and then evaporated under reduced pressure. Purification by PLC, eluting with 10% methanol in diethyl ether, gave pyrrolenine **3** (66 mg, 51%) identical to the material reported in a preceding paper.[2]

4-[5-Benzyloxycarbonyl-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 8

A mixture of tribromoethyl ester **6**[3] (200 mg, 173 μmol), zinc dust (400 mg) and glacial acetic acid (5 cm^3) were stirred at room temperature for 30 min, then filtered through Celite, diluted with water (20 cm^3) and extracted with dichloromethane (4 × 20 cm^3). The combined extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the resulting crude carboxylic acid and 2-trimethylsilylethanol (0.50 cm^3, 3.43 mmol) in dichloromethane (7 cm^3) was stirred at room temperature under argon with *N*,*N*′-dicyclohexylcarbodiimide (DCC) (41 mg, 190 μmol) and 4-dimethylaminopyridine (1.9 mg, 17 μmol) for 3 h, then filtered through Celite, washed with dilute hydrochloric acid (2 mol dm^{-3}; 10 cm^3) then water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by column chromatography, eluting with ethyl acetate–light petroleum (4 : 1), gave *trimethylsilylethyl ester* **8** (166 mg, 97%) as an oil (Found: M^+, 993.3954. $C_{49}H_{63}N_3O_{17}Si$ requires *M*, 993.3927); $\delta_H(CDCl_3)$ 0.02 (9 H, s, $SiMe_3$), 1.04 (2 H, t, *J* 8.7, CH_2Si), 2.39–2.52, 2.65–2.70 and 2.88–2.91 (13 H, m, 3 × CH_2CH_2 and 4-CH_AH_B), 2.72 and 2.80 (2 H, d, *J* 15, 4-CH_2), 3.00 (1 H, d, *J* 15, 4-CH_AH_B), 3.11 and 3.15 (2 H, m, CH_2CO_2), 3.41 and 3.48 (2 H, d, *J* 17, CH_2CO_2), 3.54–3.83 (2 H, obscured, CH_2CO_2), 3.55, 3.58, 3.61, 3.66, 3.66, 3.81 (each 3 H, s, OMe), 4.18–4.32 (2 H, m, CH_2CH_2Si), 5.16 and 5.27 (each 1 H, d, *J* 12, CH_2Ph), 7.28–7.38 (5 H, m, Ph) and 7.49, 9.32 and 9.99 (each 1 H, br s, NH); $\delta_C(CDCl_3)$ −1.63 ($SiMe_3$), 17.48 (CH_2Si), 19.20, 19.77, 20.39, 29.16, 30.29, 30.56, 30.80, 32.48, 33.66, 34.66 and 34.77 (11 × CH_2), 51.36, 51.50, 51.71, 51.79, 52.22 and 53.13 (6 × OMe), 62.17 (C-4), 65.70 and 65.90 (2 × OCH_2), 115.29, 118.75, 119.29, 122.08, 122.42, 127.74, 127.90, 129.00, 136.00, 138.20 and 149.01 (C=C), 128.08, 128.33 and 128.41 (C=*C*H), 160.20, 160.82, 171.73, 171.95, 173.31, 173.40, 173.58 and 173.74 (C=O); *m*/*z* (FD) 993 (M^+, 100%).

4-[5-Benzyloxycarbonyl-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*)-thione 9

A solution of trimethylsilylethyl ester lactam **8** (120 mg, 167 μmol) and *p*-tolyl Davy's reagent (80 mg, 0.184 mmol) in 1,2-dimethoxyethane was heated at reflux under argon for 10 min and then evaporated. Purification by PLC, eluting with ethyl acetate–light petroleum (2 : 1), gave the *thiolactam* **9** (120 mg, 71%) as an oil (Found: M^+, 1009.3624. $C_{49}H_{63}N_3O_{16}SSi$ requires *M*, 1009.3698); $\delta_H(CDCl_3)$ 0.02 (9 H, s, $SiMe_3$), 1.04 (2 H, t, *J* 9, CH_2Si), 2.43–2.69 and 2.91–2.97 (13 H, m, 3 × CH_2CH_2 and 4-CH_AH_B), 2.85 and 2.88 (each 1 H, d, *J* 15, 4-CH_2), 3.09 (1 H, d, *J* 15, 4-CH_AH_B), 3.17 and 3.21 (each 1 H, d, CH_2CO_2), 3.39 (1 H, d, *J* 18), 3.52 (1 H, d, *J* 16) and 3.57–3.87 (2 H, obscured, 2 × CH_2CO_2), 3.57, 3.59, 3.61, 3.61, 3.65, 3.81 (each 3 H, s, OMe), 4.20–4.33 (2 H, m, CH_2CH_2Si), 5.18 and 5.24 (each 1 H, d, *J* 12, CH_2Ph), 7.28–7.39 (5 H, m, Ph) and 9.28, 9.39 and 9.96 (each 1 H, br s, NH); $\delta_C(CDCl_3)$ −1.65 ($SiMe_3$), 17.44 (CH_2Si), 19.19, 20.44, 20.77, 29.43, 30.58, 30.72, 31.45, 33.83, 34.63 and 34.77 (CH_2), 51.40, 51.47, 51.81, 52.41 and 53.09 (OMe), 62.33 (*C*H_2CH_2Si), 65.80 (*C*H_2Ph), 73.73 (C-4), 115.06, 116.60, 119.36, 122.09, 122.48, 127.18, 129.30, 135.68, 143.72 and 147.39 (C=C), 128.03, 128.33 and 128.37 (C=*C*H), 160.20, 161.0, 171.70, 173.52 and 173.71 (C=O) and 197.74 (C=S); *m*/*z* (FD) 1009 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2-trimethylsilylethoxycarbonyl)-4,5-dihydrodipyrrin 10

A solution of thiolactam **9** (78 mg, 77 μmol) in methanol (10 cm^3) and acetic acid (0.23 cm^3) was stirred with nickel boride, freshly prepared from nickel(II) chloride hexahydrate (0.5 g),[2] under an atmosphere of hydrogen for 2 h, then filtered, mixed with saturated aqueous sodium hydrogen carbonate (10 cm^3)

and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave the *pyrrolenine* **10** (59 mg, 78%) as a gum (Found: M^+, 977.3981. $C_{49}H_{63}N_3O_{16}Si$ requires *M*, 977.3978); $\delta_H(CDCl_3)$ 0.03 (9 H, s, $SiMe_3$), 1.04 and 1.07 (each 1 H, d, *J* 8, CH_2Si), 2.27–2.53 and 2.90–3.00 (10 H total, 2 × m) and 2.60 (2 H, t, *J* 7.7, 3 × CH_2CH_2), 3.12 and 3.16 (each 1 H, d, *J* 13, 4-CH_2), 3.33 and 3.40 (each 1 H, d, *J* 16, 4-CH_2), 3.47–3.62 (4 H, obscured, 2 × CH_2CO_2), 3.54, 3.58, 3.58, 3.59, 3.62 and 3.75 (each 3 H, s, OMe), 3.66 and 3.82 (each 1 H, d, *J* 17, CH_2CO_2), 4.23–4.31 (2 H, m, C$H_2$$CH_2Si$), 5.20 and 5.27 (each 1 H, d, *J* 12, CH_2Ph), 7.28–7.39 (5 H, m, Ph), 7.83 (1 H, s, 1-H) and 9.87 and 10.02 (each 1 H, br s, NH); $\delta_C(CDCl_3)$ −1.54 ($SiMe_3$), 17.51 (CH_2Si), 19.08, 20.48, 29.45, 29.66, 30.24, 30.55, 30.99, 32.25, 33.86, 34.77 and 34.86 (CH_2), 51.31, 51.47, 51.68, 51.81, 52.84 (OMe), 61.98 (*C*H_2CH_2Si), 65.46 (*C*H_2Ph), 85.96 (C-4), 115.32, 117.72, 118.02, 121.77, 122.16, 128.99, 129.21, 129.26, 136.36, 140.36 and 155.90 (C=C), 127.96, 128.17 and 128.35 (C=CH), 166.16 (CH=N) and 160.34, 160.75, 171.17, 171.96, 172.29, 172.63, 173.33, 173.78 (C=O); *m*/*z* (FD) 977 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 11

A solution of pyrrolenine **10** (49 mg, 110 μmol) in methanol (5 cm^3) was stirred at room temperature under argon while a solution of sodium borohydride (1.9 mg, 50 μmol) in methanol (1 cm^3) was added over 5 min and then stirred for a further 5 min. The solvent was evaporated under reduced pressure and the residue redissolved in methanol (10 cm^3) and re-evaporated three times. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave *amine* **11** (40 mg, 80%) as an oil (Found: M^+, 979.4110. $C_{49}H_{65}N_3O_{16}Si$ requires *M*, 979.4134); $\delta_H(CDCl_3)$ 0.03 (9 H, s, $SiMe_3$), 1.04 and 1.06 (each 1 H, d, *J* 8, CH_2Si), 2.14 (2 H, m), 2.22 (2 H, m), 2.39, 2.53 and 2.54 (each 2 H, t, *J* 8) and 2.62–2.76 and 2.91–2.99 (5 H total, 2 × m, 3 × CH_2CH_2 and CH_2NH), 3.01 and 3.08 (each 1 H, d, *J* 15) and 3.30 and 3.49 (each 1 H, d, *J* 16, CH_2CCH_2), 3.56, 3.59, 3.62, 3.63, 3.64, 3.74 (each 3 H, s, OMe), 3.56–3.64 (4 H, obscured, 2 × CH_2CO_2), 3.74 and 3.87 (each 1 H, d, *J* 17, CH_2CO_2), 4.21–4.35 (2 H, m, C$H_2$$CH_2Si$), 5.14 and 5.29 (each 1 H, d, CH_2Ph, *J* 12.4), 7.17–7.38 (5 H, m, Ph) and 10.61 and 10.71 (each 1 H, br s, pyrrole-NH); $\delta_C(CDCl_3)$ −1.56 ($SiMe_3$), 17.53 (CH_2Si), 19.24, 20.51, 22.76, 29.47, 29.68, 30.55, 31.11, 34.35, 34.87 and 35.27 (CH_2), 51.42, 51.59, 51.65, 51.81, 52.13 and 52.79 (OMe), 53.56 (CH_2N), 62.05 (*C*H_2CH_2Si), 65.44 (*C*H_2Ph), 73.97 (C-4), 114.99, 116.20, 120.93, 122.13, 124.1, 128.07, 129.17, 130.01, 130.62, 136.34 and 142.12 (C=C), 128.00, 128.24 and 128.33 (C=*C*H), 160.41, 160.97, 172.13, 172.93, 173.03, 173.4, 173.72 and 173.83 (C=O); *m*/*z* (FD) 979 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1,4,5,10-tetrahydrodipyrrin 13

A solution of trimethylsilylethyl ester **11** (140 mg, 143 μmol) and tetrabutylammonium fluoride (112 mg, 429 μmol) in tetrahydrofuran (10 cm^3) was stirred at room temperature under argon for 3 h, then diluted with dichloromethane (40 cm^3) and washed with dilute sulfuric acid (10 cm^3) followed by water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the resultant acid **12** in redistilled trifluoroacetic acid (10 cm^3) was stirred at room temperature under argon for exactly 3 h and then evaporated under reduced pressure. A solution of the residue in dichloromethane (40 cm^3) was washed with water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave three compounds: (i) at high R_f value, 9-trifluoroacetyl pyrrole **14** (17 mg, 13%) (see next section for spectral data), (ii) at low R_f value, recovered acid **12** (45 mg, 36%) and (iii) at intermediate R_f value, α-*free pyrrole* **13** (56 mg, 47%) (Found: MH^+, 836.3589. $C_{43}H_{53}N_3O_{14}$ requires *M*H, 836.3606); $\delta_H(CDCl_3)$ 2.14–2.16, 2.36–2.41 and 2.63–2.75 (13 H total, 3 × m) and 2.52 (2 H, t, *J* 8, 3 × CH_2CH_2 and CH_2NH), 2.90 and 3.08 (each 1 H, d, *J* 18, 4-CH_2), 2.94 (1 H, d, *J* 17, 4-C$H_A$$H_B$), 3.17 (1 H, d, *J* 14, C$H_A$$H_B$$CO_2$), 3.30 and 3.40 (each 1 H, d, *J* 16, CH_2CO_2), 3.58, 3.59, 3.64, 3.65, 3.65, 3.72 (each 3 H, s, OMe), 3.58–3.72 (2 H, obscured, 4-$CH_A$$H_B$ and $CH_A$$H_B$$CO_2$), 3.74 and 3.85 (each 1 H, d, *J* 17, CH_2CO_2), 5.14 and 5.29 (each 1 H, d, *J* 12.4, CH_2Ph), 6.41 (1 H, s, 9-H), 7.26–7.37 (5 H, m, Ph) and 9.65 and 10.78 (each 1 H, br s, pyrrole-NH); $\delta_C(CDCl_3)$ 19.16, 20.71, 22.66, 29.45, 29.86, 30.48, 30.97, 34.20, 34.91 and 35.22 (CH_2), 51.38, 51.53, 51.68, 51.87 and 52.61 (OMe), 53.48 (CH_2N), 62.30 (*C*H_2Ph), 74.11 (C-4), 113.94 (C-9), 111.92, 117.87, 120.59, 120.71, 121.99, 125.26, 128.55, 131.31, 136.36 and 141.30 (C=C), 127.90, 128.13, 128.31 and 128.41 (C=*C*H), 160.36 (*C*O_2Bn) and 172.06, 172.99, 173.18, 173.35 and 173.81 (*C*O_2Me); *m*/*z* (FD) 835 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-trifluoroacetyl-1,4,5,10-tetrahydrodipyrrin 14

A stirred solution of the amine **13** (34 mg, 41 μmol) and 4-dimethylaminopyridine (5.5 mg, 45 μmol) in dichloromethane (2 cm^3) was treated with trifluoroacetic anhydride (1 cm^3) dropwise over 5 min, then stirred at room temperature under argon for 30 min, diluted with dichloromethane (10 cm^3), washed with dilute hydrochloric acid (5 cm^3) followed by water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave 9-*trifluoroacetyl derivative* **14** (23 mg, 60%) as an oil (Found: M^+, 931.3364. $C_{45}H_{52}F_3N_3O_{15}$ requires *M*, 931.3351); $\delta_H(CDCl_3)$ 2.08–2.15 and 2.68–2.72 (5 H total, 2 × m) and 2.41, 2.42, 2.56 and 2.57 (each 2 H, t, *J* 7.5, 3 × CH_2CH_2 and CH_2N*H*), 2.75 and 2.86 (each 1 H, d, *J* 16, 4-CH_2), 2.80 (1 H, d, *J* 15, 4-C$H_A$$CH_B$), 2.92 and 3.16 (each 1 H, d, *J* 14, CH_2CO_2), 3.03 and 3.06 (each 1 H, d, *J* 7, CH_2N), 3.44 and 3.56 (each 1 H, d, *J* 16, CH_2CO_2), 3.50, 3.60, 3.62, 3.63, 3.70 and 3.71 (each 3 H, s, OMe), 3.50–3.71 (1 H, obscured, 4-CH_ACH_B), 3.78 and 3.86 (each 1 H, d, *J* 16, CH_2CO_2), 5.18 and 5.30 (each 1 H, d, CH_2Ph, *J* 12.4), 7.29–7.39 (5 H, m, Ph) and 10.73 and 10.97 (each 1 H, br s, pyrrole-NH); $\delta_C(CDCl_3)$ 19.24, 20.98, 22.35, 29.10, 29.22, 30.50, 30.93, 33.21, 34.15, 34.76 and 35.15 (CH_2), 51.53, 51.68, 51.83, 52.24 and 52.85 (OMe), 53.03 (CH_2N), 65.58 (*C*H_2Ph), 73.76 (C-4), 117.40, 118.62, 121.36, 121.54, 122.40, 127.64, 129.17, 136.20, 137.61, 137.81 and 142.70 (C=C), 128.01, 128.28 and 128.35 (C=*C*H), 160.38 (*C*O_2Bn) and 171.69, 172.03, 172.76, 173.29, 173.60 and 173.76 (*C*O_2Me); *m*/*z* (FD) 931 (M^+, 100%).

10-Acetyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 15

A solution of amine **11** (9.9 mg, 10 μmol) and acetic anhydride (0.1 cm^3, 1.1 mmol) in dichloromethane (2 cm^3) was stirred at room temperature under argon with 4-dimethylaminopyridine (0.1 mg) for 23 h, then diluted with dichloromethane (10 cm^3), washed with dilute hydrochloric acid (5 cm^3) followed by water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate– light petroleum (2:1), gave *acetamide* **15** (9.2 mg, 89%) as an oil (Found: M^+, 1021.4253. $C_{51}H_{67}N_3O_{17}Si$ requires *M*, 1021.4240); $\delta_H(CDCl_3)$ 0.03 (9 H, s, $SiMe_3$), 1.05 (2 H, t, *J* 9, CH_2Si), 1.65 (3 H, s, Ac), 2.24–2.38, 2.52–2.57 and 2.69–2.78 (10 H total, 3 × m) and 2.94

(2 H, t, J 7.8, 3 × CH_2CH_2), 3.28 (2 H, s, CH_2N), 3.36 (1 H, d, J 17, 4-CH_AH_B), 3.45 and 3.51 (each 1 H, d, J 14, 4-CH_2), 3.58, 3.59, 3.63, 3.63, 3.66 and 3.77 (each 3 H, s, OMe), 3.56–3.67 (3 H, obscured, CH_2CO_2 and 4-CH_AH_B), 3.70 and 3.76 (each 1 H, d, J 17, CH_2CO_2), 3.79 and 3.85 (each 1 H, d, J 17, CH_2CO_2), 4.19–4.34 (2 H, m, CH_2CH$_2$Si), 5.14 and 5.28 (each 1 H, d, J 12, CH_2Ph), 7.27–7.39 (5 H, m, Ph) and 9.63 and 9.70 (each 1 H, br s, NH); δ_C($CDCl_3$) −1.6 ($SiMe_3$), 17.59 (CH_2Si), 23.21 (CO*Me*), 18.99, 20.58, 22.35, 29.27, 29.56, 30.39, 30.73, 31.61, 33.9, 34.77 and 35.41 (CH_2), 51.4, 51.6, 51.8, 51.9 and 53.1 (OMe), 56.66 (CH_2N), 62.12 (*C*H$_2$CH$_2$Si), 65.67 (*C*H$_2$Ph), 76.41 (C-4), 115.8, 118.36, 118.4, 122.39, 122.6, 129.39, 129.74, 136.09, 138.27 (C=C), 128.2 and 128.5 (C=*C*H), 160.2, 160.95, 170.4, 172.5, 172.63, 172.7, 173.37 and 173.8 (C=O); *m*/*z* (FD) 1021 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-10-trifluoroacetyl-9-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 16

A stirred solution of amine **11** (11.5 mg, 12 μmol) and 4-dimethylaminopyridine (1.6 mg, 13 μmol) in dichloromethane (1 cm^3) was treated dropwise with a solution of trifluoroacetic anhydride (100 μl) in dichloromethane (1 cm^3), stirred at room temperature under argon for 20 h and then evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave at lower R_f the starting amine (3.5 mg, 30%) and at higher R_f the *trifluoroacetamide* **16** (7.7 mg, 61%, 88% based on unrecovered starting material) (Found: MH^+, 1076.4029. $C_{51}H_{64}F_3N_3O_{17}Si$ requires *M*H, 1076.4035); δ_H($CDCl_3$) 0.03 (9 H, s, $SiMe_3$), 1.04 (2 H, t, J 9, CH_2Si), 2.23–2.75 and 2.90–3.00 (12 H total, 2 × m) and 2.50 (2 H, t, J 8, 3 × CH_2CH_2 and 4−CH_2), 2.82 and 2.86 (each 1 H, d, J 13.4, 4-CH_2), 3.36 and 3.49 (each 1 H, d, J 16.5, CH_2CO_2), 3.56, 3.60, 3.63, 3.63, 3.66 and 3.79 (each 3 H, s, OMe), 3.56–3.79 (6 H, obscured, 2 × CH_2CO_2 and CH_2N), 4.23–4.31 (2 H, m, CH_2CH$_2$Si), 5.18 and 5.24 (each 1 H, d, J 12.2, CH_2Ph), 7.28–7.37 (5 H, m, Ph) and 9.44 and 9.60 (each 1 H, br s, NH); δ_C($CDCl_3$) −1.60 ($SiMe_3$), 17.50 (CH_2Si), 18.87, 20.41, 22.26, 29.22, 29.48, 30.49, 30.52, 31.06, 31.30, 34.66 and 35.11 (CH_2), 51.39, 51.63, 51.81, 51.84, 51.95 and 53.30 (OMe), 55.06 (CH_2N), 62.26 (*C*H$_2$CH$_2$Si), 65.78 (*C*H$_2$Ph), 78.79 (C-4), 116.38, 118.91, 119.07, 122.79, 127.48, 127.97, 129.60, 135.97 and 138.22 (C=C), 128.15, 128.31 and 128.40 (C=*C*H) and 160.14, 160.88, 171.76, 172.26, 172.38, 172.65, 173.32 and 173.67 (C=O); *m*/*z* (FD) 1075 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-10-phenoxyacetyl-9-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 17

A solution of amine **11** (10.5 mg, 11 μmol) and 4-dimethylaminopyridine (1.4 mg, 12 μmol) in dichloromethane (1 cm^3) was stirred at room temperature under argon with phenoxyacetyl chloride (1.6 μl, 12 μmol) for 2 h, then diluted with dichloromethane (20 cm^3), washed with dilute hydrochloric acid (5 cm^3) followed by water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave *phenoxyacetamide* **17** (9.1 mg, 76%) as an oil (Found: M^+, 1113.4509. $C_{57}H_{71}N_3O_{18}Si$ requires *M*, 1113.4502); δ_H($CDCl_3$) 0.04 (9 H, s, $SiMe_3$), 1.07 (2 H, m, CH_2Si), 2.31–2.49, 2.65–2.69 and 2.82–2.92 (12 H total, 3 × m) and 2.46 (2 H, t, J 7, 3 × CH_2CH_2 and 4-CH_2), 2.50 and 3.11 (each 1 H, d, J 18, 4-CH_2), 3.02 and 3.45 (each 1 H, d, J 18, CH_2CO_2), 3.18 (1 H, d, J 19, C$H_AH_BCO_2$), 3.27 (2 H, s, CH_2N), 3.55, 3.60 and 3.85 (each 3 H, s, OMe), 3.61 (9 H, s, 3 × OMe), 3.55–3.63 (3 H, obscured, $CH_AH_BCO_2$ and CH_2CO_2), 4.07 and 4.12 (each 1 H, d, J 17, CH_2OPh), 4.25–4.38 (2 H, m, CH_2CH$_2$Si), 5.19 and 5.23 (each 1 H, d, J 12.4, CH_2Ph), 6.84–6.93, 7.19–7.29 and 7.39–7.41 (10 H total, 3 × m, 2 × Ph) and 10.96 and 11.4 (each 1 H, br s, NH); δ_C($CDCl_3$) −1.59 ($SiMe_3$), 17.46 (CH_2Si), 19.51, 20.27, 22.41, 28.37, 29.13, 29.48, 29.67, 30.36, 31.31, 34.88 and 34.91 (CH_2), 51.02, 51.54, 51.82 and 52.59 (OMe), 53.27 (CH_2N), 62.59 (*C*H$_2$CH$_2$Si), 65.42 (*C*H$_2$Ph), 75.62 (C-4), 77.2 (*C*H$_2$OPh), 114.64, 121.05, 128.36, 128.40 and 129.33 (C=*C*H), 115.74, 119.52, 119.89, 122.76, 122.80, 126.05, 126.51, 127.60, 128.00, 129.24, 136.21, 140.39 and 158.06 (C=C) and 160.30, 160.77, 171.94, 172.77, 173.37, 173.5, 173.55 and 175.38 (C=O).

10-Acetyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1,4,5,10-tetrahydrodipyrrin 19

A stirred solution of amine **13** (66 mg, 79 μmol) and acetic anhydride (3 cm^3) in dichloromethane (6 cm^3) was treated with 4-dimethylaminopyridine (11 mg, 87 μmol) in portions over 1 min, stirred for 15 h at room temperature under argon, then diluted with dichloromethane (20 cm^3), washed with water (5 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave the *acetamide* **19** (64 mg, 92%) as an oil (Found: MH^+, 878.3745. $C_{45}H_{55}N_3O_{15}$ requires *M*H, 878.3712); δ_H($CDCl_3$) 1.64 (3 H, s, Ac), 2.11–2.81 (14 H, m, 3 × CH_2CH_2 and 4-CH_2), 2.64 and 2.73 (each 1 H, d, J 15, 4-CH_2), 3.30 and 3.48 (each 1 H, d, J 16, CH_2CO_2), 3.37 and 3.50 (each 1 H, d, J 14, CH_2CO_2), 3.57, 3.61, 3.62, 3.63, 3.64, 3.76 (each 3 H, s, OMe), 3.57–3.76 (1 H, obscured) and 3.75 (1 H, d, J 15, CH_2N), 3.69 and 3.86 (each 1 H, d, J 17, CH_2CO_2), 5.16 and 5.26 (each 1 H, d, J 12.2, CH_2Ph), 6.33 (1 H, d, J 2.3, 9-H), 7.29–7.38 (5 H, m, Ph) and 8.77 and 9.91 (each 1 H, br s, NH); δ_C($CDCl_3$) 23.15 (CO*Me*), 16.89, 20.80, 22.30, 29.60, 29.77, 30.38, 30.45, 31.16, 31.79, 34.89 and 35.50 (CH_2), 51.42, 51.54, 51.72, 51.83 and 53.04 (OMe), 56.42 (CH_2N), 65.58 (*C*H$_2$Ph), 76.52 (C-4), 113.97 (C-9), 112.44, 116.32, 121.05, 122.51, 122.68, 124.80, 128.85, 129.79, 136.15 and 137.75 (C=C), 128.08, 128.37 and 128.44 (C=*C*H), 160.32 (*C*O$_2$Bn), 170.06 (*C*OMe) and 172.11, 172.89, 173.04, 173.38 and 173.90 (*C*O$_2$Me); *m*/*z* (FD) 877 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-10-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 20

A solution of amine **13** (19 mg, 22 μmol), 1-(2-trimethylsilylethoxycarbonyloxy)pyrrolidine-2,5-dione (23 mg, 90 μmol) and 4-dimethylaminopyridine (5.5 mg, 45 μmol) in toluene (5 cm^3) was heated at reflux under argon for 46 h, then diluted with ethyl acetate (10 cm^3), washed with dilute hydrochloric acid (5 cm^3) followed by water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave the *carbamate* **20** (11.2 mg, 51%) as an oil (Found: MH^+, 981.4335. $C_{48}{}^{13}CH_{65}N_3O_{16}Si$ requires *M*H, 981.4245); δ_H($CDCl_3$) 0.02 (9 H, s, $SiMe_3$), 0.82 (2 H, m. CH_2Si), 2.15–2.80 (14 H, m, 3 × CH_2CH_2 and 4-CH_2), 3.19 and 3.28 (each 1 H, d, J 18, 4-CH_2), 3.26 and 3.70 (each 1 H, d, J 16, CH_2CO_2), 3.40 and 3.47 (each 1 H, d, J 15.6, CH_2CO_2), 3.56, 3.60, 3.62, 3.63, 3.64 and 3.73 (each 3 H, s, OMe), 3.56–3.73 (4 H, obscured, CH_2CO_2 and CH_2N), 3.99 and 4.14 (each 1 H, m, CH_2CH$_2$Si), 5.18 and 5.22 (each 1 H, d, J 12.4, CH_2Ph), 6.33 (1 H, d, J 2.3, 9-H), 7.26–7.37 (5 H, m, Ph) and 8.73 and 9.74 (each 1 H, br s, NH); δ_C($CDCl_3$) −1.51 ($SiMe_3$), 16.64, 17.46, 17.65, 18.98, 20.79, 22.33, 29.65, 29.80, 31.38, 31.74, 34.90 and 35.41 (CH_2), 51.40, 51.54, 51.71, 51.77 and 52.95 (OMe), 54.94 (CH_2N), 63.08 (*C*H$_2$CH$_2$Si), 65.53 (*C*H$_2$Ph), 74.90 (C-4), 114.04 (C-9), 112.49, 118.41, 120.95, 122.41, 124.76, 129.71, 132.49, 136.22, 138.25 (C=C), 128.05 and 128.36 (C=*C*H), 153.90 (NCO_2), 160.33 (*C*O$_2$Bn) and 171.51, 171.96, 172.78, 172.89, 173.05, 173.37 (*C*O$_2$Me); *m*/*z* (FD) 979 (M^+, 100%).

15-Acetyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-14-formyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-1,4,5,10,15,17-hexahydrodipyrrin 23

A solution of α-free pyrrole **19** (64 mg, 73 μmol) and acetoxymethylpyrrole **22**[3] (24 mg, 73 μmol) in dry dichloromethane (12 cm^3) containing dry tetrahydrofuran (25 μl) at room temperature under argon was treated dropwise over 5 min with a solution of boron trifluoride–diethyl ether (10 μl) in dichloromethane (3 cm^3) and then stirred in the dark for 25 h. Methanol (3 cm^3) was added followed by saturated aqueous sodium hydrogen carbonate (10 cm^3) and the mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was diluted with water (10 cm^3) and extracted with dichloromethane (2 × 10 cm^3). The combined organic layers were washed with water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave **22** (10 mg, 43%), **19** (17 mg, 27%) and *tripyrrole* **23** (32 mg, 38%, 52% based on unrecovered **19**) as a gum (Found: MH^+, 1143.4553. $C_{58}H_{70}N_4O_{20}$ requires *M*H, 1143.4661); $\delta_H(CDCl_3)$ 1.54 (3 H, s, Ac), 1.7–1.8, 2.0–2.7 and 2.8–3.1 (10 H total, 3 × m) and 2.83, 2.95 and 3.01 (each 2H, t, *J* 7.5, 4 × CH_2CH_2), 3.09 and 3.22 (each 1 H, d, *J* 18, 4-CH_2), 3.27 (2 H, s, CH_2N), 3.28 and 3.51 (each 1 H, d, *J* 16, 4-CH_2), 3.49 and 3.84 (each 1 H, d, *J* 17), 3.54 and 3.85 (each 1 H, d, *J* 15), 3.76 and 3.83 (each 1 H, d, *J* 16) and 3.55–3.73 (4 H, obscured, 4 × CH_2CO_2 and 10-H_2), 3.55, 3.59, 3.60, 3.64, 3.65, 3.69, 3.71, 3.73 (each 3 H, s, OMe), 5.11 and 5.31 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.29–7.38 (5 H, m, Ph), 9.52 (1 H, s, CHO) and 8.63, 9.81 and 10.09 (each 1 H, br s, NH); $\delta_C(CDCl_3)$ 18.78, 18.93, 19.37, 22.20, 22.39, 28.93, 29.44, 29.67, 30.08, 30.42, 30.68, 31.09, 31.38, 34.68 and 35.57 (CH_2), 22.98 (CO*Me*), 51.50, 51.70, 51.75, 51.81, 51.95, 52.45 and 53.00 (OMe), 56.41 (CH_2N), 65.45 (*C*H$_2$Ph), 76.7 (C-4), 112.28, 114.49, 116.82, 118.37, 122.69, 122.83, 123.14, 124.92, 128.44, 129.88, 136.27, 137.63 and 137.79 (C=C), 127.99, 128.33 and 128.36 (C=*C*H), 160.36 (*C*O$_2$Bn), 169.65 (N*C*OMe), 172.12, 172.79, 172.99, 173.03, 173.06, 173.44 and 174.59 (*C*O$_2$Me) and 176.93 (CHO); *m*/*z* (FD) 1142 (M^+, 100%).

15-Acetyl-4-[3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-14-formyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-1,4,5,10,15,17-hexahydrodipyrrin 25

A solution of benzyl ester **23** (32 mg, 28 μmol) in methanol (6 cm^3) was stirred with sodium carbonate (18 mg) and 10% palladium-on-charcoal (6 mg) under an atmosphere of hydrogen for 1 h, then filtered through Celite, diluted with water (20 cm^3), acidified with glacial acetic acid and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the residual carboxylic acid in dichloromethane (3 cm^3) was stirred vigorously with 5% aqueous sodium hydrogen carbonate (3 cm^3) at room temperature while an aqueous solution (310 μl) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added over 1 min. After a further 15 min, sodium metabisulfite was added to destroy excess iodine and the organic layer was separated. The aqueous layer was diluted with water (17 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the iodopyrrole as a gum and a single non-baseline spot on TLC with dichloromethane–methanol (9:1); *m*/*z* (FD) 1134 (M^+, 100%).

The iodopyrrole was immediately dissolved in methanol (3 cm^3). The solution was stirred with sodium acetate (12 mg) and Adams' catalyst (6 mg) under an atmosphere of hydrogen at room temperature for 1 h, then filtered through Celite, diluted with water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (4:1), gave the α-*free pyrrolic acetamide* **25** (11 mg, 39%) as an oil (Found: MH^+, 1010.4418. $C_{49}{}^{13}CH_{64}N_4O_{18}$ requires *M*H, 1010.4326); $\delta_H(CDCl_3)$ 1.60 (3 H, s, Ac), 2.05–2.15, 2.25–2.75 and 2.90–3.10 (18 H total, 3 × m, 4 × CH_2CH_2 and 4-CH_2), 2.51 and 2.59 (each 1 H, d, *J* 15.2, 4-CH_2), 3.19 and 3.28 (each 1 H, d, *J* 17, CH_2CO_2), 3.21–3.38 (2 H, m, CH_2CO_2), 3.38 (2 H, s, CH_2N), 3.48 and 3.55 (each 1 H, d, *J* 17, CH_2CO_2), 3.56 (1 H, d, *J* 16.5) and 3.62–3.75 (1 H, obscured, CH_2CO_2), 3.62, 3.63, 3.64, 3.65, 3.65, 3.68, 3.72, 3.75 (each 3 H, s, OMe), 3.79 and 3.84 (each 1 H, d, *J* 14.7, 10-H_2), 6.44 (1 H, d, α-H, *J* 2.3), 8.88, 8.91 and 9.7 (each 1 H, br s, NH) and 9.52 (1 H, s, CHO); $\delta_C(CDCl_3)$ 18.96, 19.31, 19.46, 22.27, 22.49, 29.05, 29.60, 29.66, 30.02, 30.09, 30.45, 31.29, 31.40, 34.83 and 35.79 (CH_2), 23.11 (CO*Me*), 51.44, 51.72, 51.85, 52.34 and 52.98 (OMe), 56.31 (CH_2N), 76.89 (C-4), 115.51 (C=*C*H), 112.37, 113.74, 114.54, 116.89, 118.62, 122.65, 124.11, 125.23, 128.14, 128.85, 136.79 and 138.00 (C=C), 169.59 (*C*OMe), 172.46, 172.63, 172.77, 173.05, 173.15, 173.21, 173.84 and 174.48 (*C*O$_2$Me) and 176.77 (CHO); *m*/*z* (FD) 1008 (M^+, 100%).

Attempted macrocyclisation of compound 25

A solution of aldehyde **25** (11 mg, 11 μmol) in dry acid-free dichloromethane (1 cm^3) and methanol (2.3 cm^3) was stirred with sodium borohydride (4.3 mg) for 40 min, then added to water (6 cm^3) and extracted with dichloromethane (3 × 15 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give alcohol **26**, one major spot by TLC using dichloromethane–methanol (9:1); *m*/*z* (FD) 1009 ($M^+ - H$, 100%). This was immediately dissolved in dry acid-free dichloromethane (36 cm^3) and a solution of toluene-*p*-sulfonic acid monohydrate (2.9 mg) in methanol (1.7 cm^3) was added dropwise to the stirred solution. After 30 min, triethylamine (1 drop) was added and the solution was evaporated. Purification by PLC, eluting with diethyl ether–methanol–triethylamine (95:10:0.1) and then with dichloromethane–methanol (95:5), gave two major bands. At higher R_f value was a mixture (1.9 mg, 18%) of the monomeric macrocycle **29** and one of the two diastereoisomeric dimers, **32** and **33**, as judged by ^1H NMR spectral analysis, which showed 15 methyl ester resonances, and mass spectrometry (Found: MH^+, 993.4439 and 1985.8596. $C_{50}H_{64}N_4O_{17}$ requires *M*H, 993.4343 and $C_{100}H_{128}N_8O_{34}$ requires *M*H, 1985.8608); *m*/*z* (FD) 992 (60%) and 1984 (40). At lower R_f value was the other diastereoisomeric dimer (1.6 mg, 15%) (Found: M^+, 1984.8482. $C_{100}H_{128}N_8O_{34}$ requires *M*, 1984.8532); $\delta_H(CDCl_3)$ all the peaks were very broad except 3.59, 3.60, 3.63, 3.65, 3.66, 3.67, 3.68 and 3.70 (8 × OMe); *m*/*z* (FD) 1984 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-10-formyl-2,8-bis-(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2-trimethylsilylethoxycarbonyl)-1,4,5,10-tetrahydrodipyrrin 18

A solution of the amine **11** (12 mg, 12.3 μmol) and 2-pyridone (0.9 mg, 9.2 μmol) in methyl formate (4 cm^3) containing *N*,*N*-dimethylformamide (2 drops) was heated at 100 °C in a sealed tube for 20 h and then evaporated under reduced pressure. A solution of the residue in dichloromethane (10 cm^3) was washed with water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1), gave two bands. Both bands gave the same *formamide* **18** (7.7 mg, 62%) as an oil, shown by ^1H NMR spectral analysis to be a 4:1 mixture of rotamers (Found: MH^+, 1009.4181. $C_{49}{}^{13}CH_{65}N_3O_{17}Si$ requires *M*H, 1009.4194); $\delta_H(CDCl_3$, distinguishable peaks for the minor rotamer are given in square brackets) 0.04 (9 H, s, $SiMe_3$), 1.06 [1.04] (2 H, t, *J* 7, CH_2Si), 2.23–3.5 (18 H, m, 3 × CH_2CH_2, 4-CH_2, CH_2CO_2 and CH_2N), 2.74 and 2.81 (each 1 H, d, *J* 15.5, 4-CH_2), 3.38 (1 H, d, *J* 18.9) and 3.57–3.78 (3 H, obscured, 2 × CH_2CO_2), 3.57,

3.59, 3.63, 3.63, 3.66 and 3.78 [3.59, 3.64, 3.68 and 3.74] (each 3 H, s, OMe), 4.21–4.33 (2 H, m, CH_2CH$_2$Si), 5.17 and 5.26 [5.19 and 5.26] (each 1 H, d, *J* 12.3, CH_2Ph), 7.28–7.38 (5 H, m, Ph), 7.93 [8.11] (1 H, s, CHO) and 9.55 and 9.81 [9.24 and 9.78] (each 1 H, br s, NH); *m*/*z* (FD) 1009 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-10-formyl-2,8-bis-(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1,4,5,10-tetrahydrodipyrrin 21

A solution of the α-free pyrrolic amine **13** (180 mg, 216 μmol) and 2-pyridone (15 mg, 160 μmol) in methyl formate (15 cm^3) containing *N*,*N*-dimethylformamide (10 drops) was heated to 100 °C in a sealed tube for 40 h and then evaporated under reduced pressure. A solution of the residue in dichloromethane (20 cm^3) was washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1) (two bands as before), gave the *formamide* **21** (140 mg, 75%) as an oil (Found: M^+, 863.3479. $C_{44}H_{53}N_3O_{15}$ requires *M*, 863.3477); δ_H($CDCl_3$, 1:1 mixture of rotamers) 2.1–3.9 [48 H, several multiplets including the following AB quartets and doublets: 2.61 and 2.63 (*J* 15), 2.69 and 2.71 (*J* 16), 2.78 and 2.86 (*J* 15.7), 3.10 (*J* 14), 3.14 and 3.39 (*J* 15.5), 3.24 (*J* 16), 3.25 and 3.33 (*J* 16.2), 3.37 and 3.47 (*J* 16.5), 3.84 (*J* 17.1), 6 × CH_2CH_2, 6 × CH_2CO_2, 4 × 4-CH_2 and 2 × CH_2N], 3.56, 3.57, 3.62, 3.63, 3.63, 3.64, 3.65, 3.66, 3.67, 3.75, 3.77 (each 3 H, s, OMe), 5.19 and 5.24 (each 1 H, d, *J* 12.2, CH_2Ph), 5.20 and 5.24 (each 1 H, d, *J* 12.4, CH_2Ph), 6.35 (2 H, s, 2 × 9-H), 7.29–7.38 (10 H, m, 2 × Ph), 7.89 and 7.99 (each 1 H, s, CHO) and 8.37, 8.77, 9.90 and 10.27 (each 1 H, br s, NH); δ_C($CDCl_3$) 18.98, 19.16, 20.55, 20.73, 22.24, 22.25, 29.33, 29.65, 29.82, 30.22, 30.36, 30.48, 30.68, 30.87, 31.36, 31.76, 34.09, 34.43, 34.72, 34.98 and 35.39 (CH_2), 51.49, 51.55, 51.63, 51.74, 51.87, 51.94 and 53.06 (OMe), 52.16 and 54.19 (CH_2N), 65.59 and 65.65 (*C*H_2Ph), 73.08 and 75.22 (C-4), 114.14 and 115.08 (C-9), 112.88, 118.57, 119.14, 121.27, 122.14, 122.32, 122.64, 122.78, 122.85, 124.31, 127.66, 128.86, 129.36, 136.10, 136.16, 138.23 and 138.98 (C=C), 128.06, 128.14, 128.35 and 128.36 (C=*C*H), 160.33 (*C*O_2Bn) and 171.92, 172.06, 172.35, 172.60, 172.74, 172.96, 173.07, 173.31, 173.45, 173.80 and 173.88 (*C*O_2Me); *m*/*z* (FD) 863 (M^+, 100%); (FIB) 864 (MH^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-14,15-formyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-1,4,5,10,15,17-hexahydrotripyrrin 24

The α-free pyrrole **21** (95 mg, 0.11 mmol) and the acetoxymethylpyrrole aldehyde **22** (72 mg, 0.22 mmol) were dissolved in dry dichloromethane (11 cm^3) containing dry tetrahydrofuran (50 μl). A solution of stannic chloride (50 μl) in dichloromethane (5 cm^3) was added slowly over 2 min and the mixture was stirred in the dark at room temperature under argon for 23 h. Methanol (7 cm^3) was added followed by saturated aqueous sodium hydrogen carbonate (15 cm^3) 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 washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (2:1) (two bands as before), gave the *tripyrrolic formamide* **24** (93 mg, 75%) as a gum (Found: MH^+, 1129.4455. $C_{57}H_{68}N_4O_{20}$ requires *M*H, 1129.4505); δ_H($CDCl_3$, 1:1 mixture of rotamers) 1.9–3.9 [60 H, several multiplets including the following AB quartets: 2.66 and 2.77 (*J* 15.5), 2.89 and 3.04 (*J* 15.8), 2.96 and 2.98 (*J* 15), 3.06 and 3.14 (*J* 18), 3.22 and 3.86 (*J* 15.7), 3.28 and 3.43 (*J* 16.7), 3.78 and 3.83 (*J* 17.6), 8 × CH_2CH_2, 8 × CH_2CO_2, 4 × 4-CH_2 and 2 × CH_2N], 3.50, 3.51, 3.52, 3.56, 3.56, 3.58, 3.58, 3.59, 3.60, 3.61, 3.62, 3.63, 3.65, 3.66, 3.67 and 3.70 (each 3 H, s, OMe), 5.10 (2 H, m, CH_2Ph), 5.25 and 5.28 (each 1 H, d, *J* 12.5, CH_2Ph), 7.23–7.34 (10 H, m, 2 × Ph), 7.65 and 7.79 (each 1 H, s, 2 × N–CHO), 9.49 and 9.51 (each 1 H, s, C–CHO) and 8.71, 9.11, 9.94, 10.18, 10.20 and 10.27 (each 1 H, br s, NH); δ_C($CDCl_3$) 18.75, 18.82, 18.98, 19.13, 19.21, 22.03, 22.17, 28.69, 28.90, 29.01, 29.22, 29.52, 30.22, 30.31, 30.42, 30.56, 30.68, 31.01, 31.14, 32.95, 34.33, 34.52, 34.89, 35.39, 35.72 and 36.02 (CH_2), 51.34, 51.47, 51.53, 51.61, 51.72, 51.85, 51.99, 52.33, 52.44, 52.50 and 52.86 (OMe), 52.13 and 54.45 (CH_2N), 65.26 and 65.36 (*C*H_2Ph), 73.31 and 75.40 (C-4), 111.99, 112.53, 114.29, 114.36, 116.44, 116.70, 118.50, 119.22, 122.32, 122.42, 122.50, 123.04, 123.60, 124.47, 124.67, 127.67, 127.96, 128.31, 129.31, 136.11, 136.20, 137.66 and 137.81 (C=C), 127.80, 128.17 and 128.28 (C=*C*H), 159.98 and 161.04 (N–CHO), 160.13 and 160.26 (*C*O_2Bn), 171.90, 171.99, 172.24, 172.47, 172.65, 172.75, 172.79, 173.28, 173.49, 173.94, 174.53 and 174.71 (*C*O_2Me) and 176.92 and 176.99 (C–*C*HO); *m*/*z* (FD) 1128 (M^+, 100%); (FIB) 1129 (MH^+, 100%).

4-[3-(2-Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-pyrrol-2-ylmethyl]-14,15-diformyl-2,8,13-tris(2-methoxycarbonylethyl)-3,7,12-tris(methoxycarbonylmethyl)-1,4,5,10,15,17-hexahydrotripyrrin 27

A solution of benzyl ester **24** (148 mg, 0.13 mmol) in methanol (30 cm^3) was stirred with sodium carbonate (100 mg) and 10% palladium-on-charcoal (30 mg) under an atmosphere of hydrogen for 20 min, then filtered through Celite, diluted with water (20 cm^3), acidified with glacial acetic acid and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the residual carboxylic acid in dichloromethane (20 cm^3) was stirred vigorously with 5% aqueous sodium hydrogen carbonate (20 cm^3) at room temperature while an aqueous solution (1.6 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added over 1 min. After a further 5 min, sodium metabisulfite was added to destroy excess iodine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated, to give the iodopyrrole as a gum, showing two spots on TLC [ethyl acetate–light petroleum (4:1)]. The iodopyrrole was immediately dissolved in methanol (15 cm^3) and the solution was stirred with sodium acetate (60 mg) and Adams' catalyst (30 mg) under an atmosphere of hydrogen at room temperature for 1 h then filtered through Celite, added to water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–light petroleum (4:1) (two bands as before), gave the α-*free tripyrrolic formamide* **27** (79 mg, 61%) as an oil (Found: MH^+, 995.4141. $C_{49}H_{62}N_4O_{18}$ requires *M*H, 995.4137); δ_H($CDCl_3$, 2:1 mixture of rotamers, distinguishable peaks for the minor rotamer are given in square brackets) 1.85–2.75 (16 H, m, 4 × CH_2CH_2), 2.83 and 2.98 (each 1 H, d, *J* 15.9, 4-CH_2), 2.92 and 2.94 (each 1 H, d, *J* 13, 4-CH_2), 3.05 and 3.11 (each 1 H, d, *J* 15.8, CH_2CO_2), 3.28 and 3.32 (each 1 H, d, *J* 15.1, CH_2CO_2), 3.46 and 3.85 (each 1 H, d, *J* 16, CH_2CO_2), 3.58–3.69 (6 H, obscured, CH_2CO_2, 10-H_2 and CH_2N), 3.58, 3.59, 3.60, 3.61, 3.64, 3.67, 3.68, 3.69 (each 3 H, s, OMe), 6.43 [6.42] (1 H, d, α-H, *J* 2.6), 7.61 [7.81] (1 H, s, N–CHO), 9.01, 9.15 and 10.16 [8.95, 8.96 and 9.89] (each 1 H, br s, NH) and 9.50 [9.47] (1 H, s, C–CHO); δ_C($CDCl_3$) 18.84, 18.98, 19.05, 19.25, 19.34, 19.39, 19.51, 19.58, 22.06, 22.15, 22.30, 28.85, 28.93, 29.16, 29.35, 30.04, 30.31, 30.41, 31.11, 31.15, 33.10, 34.45, 34.77, 35.17, 35.59, 35.64 and 35.92 (CH_2), 51.24, 51.34, 51.49, 51.54, 51.59, 51.67, 51.76, 51.85, 52.23, 52.35, 52.68 and 52.79 (OMe), 52.07 and 54.25 (CH_2N), 73.58 and 75.61 (C-4), 115.56 and 116.53 (α-CH), 112.29, 112.53, 113.55, 114.45, 116.79, 118.66, 118.70, 122.09, 122.79, 122.92, 123.55, 124.19, 124.64, 128.06, 128.23, 128.46, 128.55, 136.85, 136.92, 137.38 and 137.82 (C=C), 160.22 and 161.11 (N–CHO), 172.32, 172.41, 172.71, 172.78, 172.81,

172.88, 172.95, 173.48, 173.64, 173.66, 174.33 and 174.56 (CO_2Me) and 176.85 and 176.90 (C–CHO); *m/z* (FIB) 995 (MH^+, 100%).

21-Formyl-2,8,13,18-tetrakis(2-methoxycarbonylethyl)-3,7,12,17-tetrakis(methoxycarbonylmethyl)-4,19-methylene-1,4-dihydrobilane 30

The crude aldehyde **27** (79 mg, 79 μmol) was dissolved in dry, acid-free dichloromethane (7.5 cm^3) and methanol (17 cm^3) and sodium borohydride (25 mg) was added in portions over 2 min. The mixture was stirred for 40 min, then added to water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give alcohol **28**, showing one major spot by TLC [ethyl acetate–light petroleum (4:1)]. This was immediately dissolved in dry acid-free dichloromethane (130 cm^3) and a solution of toluene-*p*-sulfonic acid monohydrate (21 mg) in methanol (6.2 cm^3) was added over 1 min. The solution was stirred for 20 min, then treated with triethylamine (3 drops) and evaporated. Purification by PLC, eluting with ethyl acetate–light petroleum–triethylamine (80:20:1), gave *spiroformamide* **30** (43 mg, 55%) as an oil (Found: M^+, 978.4109. $C_{49}H_{62}N_4O_{17}$ requires *M*, 978.4110); λ_{max}(MeOH) no peak above 220 nm; $\delta_H(CDCl_3)$ 2.2–2.75 (16 H, m, 4 × CH_2CH_2), 2.83 and 2.84 (each 1 H, d, *J* 15) and 2.93 and 2.97 (each 1 H, d, *J* 15, CH_2CCH_2), 3.09 (2 H, m), 3.20 (2 H, s), 3.33 and 3.37 (each 1 H, d, *J* 17) and 3.45 (2 H, s, 4 × CH_2CO_2), 3.59, 3.60, 3.60, 3.61, 3.66, 3.67, 3.70, 3.71 (each 3 H, s, OMe), 3.59–3.71 (2 H, obscured, CH_2N), 3.72 and 3.81 (each 1 H, d, *J* 16.6) and 4.10 (2 H, s, 10- and 15-H_2), 7.83 and 7.98 (each 1 H, br s, NH) and 9.00 (1 H, s, N–CHO); $\delta_C(CDCl_3)$ 19.39, 19.59, 19.72, 22.05, 22.16, 22.58, 29.47, 29.83, 30.26, 30.61, 31.54, 34.43, 34.71, 35.92, 37.49 and 37.72 (CH_2), 51.39, 51.52, 51.75, 51.76, 52.06 and 52.38 (OMe), 52.49 (CH_2N), 71.32 (C-4), 110.99, 111.33, 114.58, 117.45, 117.52, 120.58, 121.99, 125.71, 126.94, 127.66, 127.98, 130.65 and 134.94 (C=C), 161.29 (CHO) and 170.97, 172.44, 172.99, 173.44, 174.06 and 174.58 (CO_2Me); *m/z* (FD) 978 (M^+, 100%); (FIB) 979 (MH^+, 100%).

Hydrolysis of the ester groups of macrocycle 30

A solution of octamethyl ester **30** (2.8 mg, 2.9 μmol) in methanol (100 μl) was stirred vigorously with aqueous potassium hydroxide (4 mol dm^{-3}; 25 μl, 100 μmol) in the dark at room temperature under argon for 18 h and then evaporated at reduced pressure to give the octapotassium salt of acid **37**. For NMR spectroscopy the residue was dissolved three times in D_2O and re-evaporated at reduced pressure; λ_{max}(MeOH) no peak above 220 nm except weak bands at 406 and 310; $\delta_H(D_2O)$ 2.0–2.7 (14 H, m) and 2.65 (2 H, t, *J* 8, 4 × CH_2CH_2), 2.65 and 2.85 (each 1 H, d, *J* 16.5) and 2.97 and 3.08 (each 1 H, d, *J* 16.4, CH_2CCH_2), 3.29 and 3.41 (each 1 H, d, *J* 17), 3.22, 3.71 and 4.11 (each 2 H, s) and 2.9–3.3 (6 H, m, 4 × CH_2CO_2, 1-, 10- and 15-H_2) and 8.4 (1 H, s, N–CHO); $\delta_C(CDCl_3)$ 21.35, 21.59, 21.63, 21.86, 21.92, 21.97, 23.53, 33.10, 33.50, 35.96, 37.31, 38.70, 39.72 and 40.19 (CH_2), 53.03 (CH_2N), 72.41 (C-4), 114.59, 119.26, 119.35, 119.85, 120.54, 121.75, 122.02, 125.07, 126.17, 126.24, 128.00, 128.32, 137.80, 150.02 (C=C), 168.92 (CHO) and 181.79, 182.22, 182.28, 182.61, 182.82, 183.18, 183.63 and 183.69 (CO_2^-).

2,8,13,18-Tetrakis(2-methoxycarbonylethyl)-3,7,12,17-tetrakis(methoxycarbonylmethyl)-4,19-methylene-1,4-dihydrobilane 31

A solution of macrocyclic formamide **30** (6.9 mg, 7.1 μmol) and 4-dimethylaminopyridine (1.7 mg, 14.2 μmol) in dry dichloromethane (2 cm^3) was treated with trimethyloxonium tetrafluoroborate (2.1 mg, 14.2 μmol) over 1 min and stirred at room temperature under argon for 3 h. Water (2 cm^3) was added and the two-phase mixture was vigorously stirred for 1 h and then saturated aqueous sodium hydrogen carbonate (2 cm^3) was added. The mixture was vigorously stirred for a further 1 h and then the organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. Field desorption mass spectrometry revealed two peaks at *m/z* 951 (10%) and 961 (90). Purification by PLC, eluting with ethyl acetate–light petroleum–triethylamine (80:20:1), gave at lower R_f the starting formamide **30** (2.2 mg, 32%) and at higher R_f the amine **31** (*ca.* 2–3%) (Found: MH^+, 951.4325. $C_{48}H_{62}N_4O_{16}$ requires *M*H, 951.4239); *m/z* (FD) 950 (M^+, 100%).

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