Biosynthesis of porphyrins and related macrocycles. Part 47.[1,2] Synthesis and chemistry of 2*H*-pyrroles (pyrrolenines) related to the proposed spiro-intermediate for porphyrin biosynthesis

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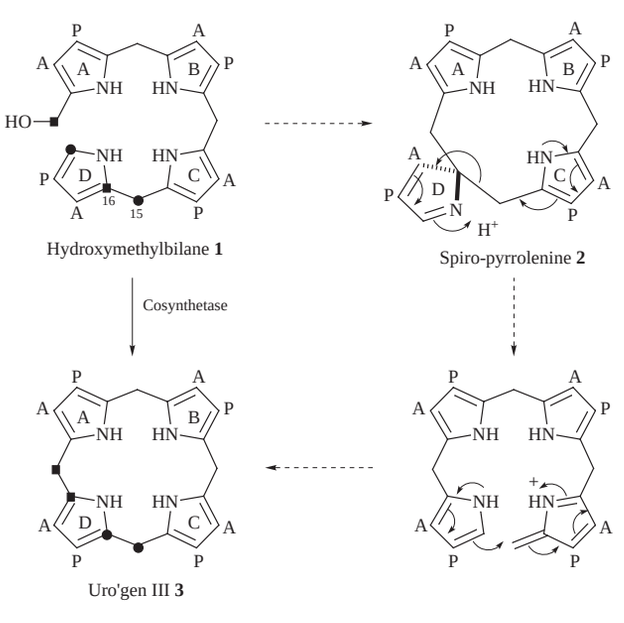
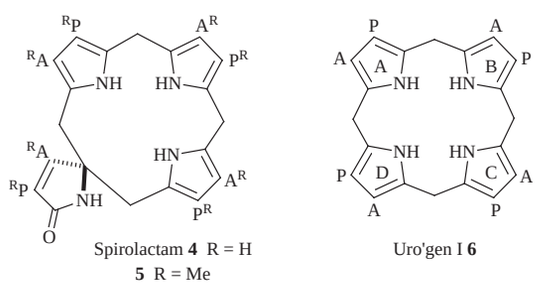
It is proposed that the biosynthesis of uroporphyrinogen III 3, the parent precursor of the natural porphyrins, chlorins and corrins, involves a pyrrolenine 2 as a key intermediate, yet methods for the synthesis of such systems are not available. Novel routes for the synthesis of pyrrolenines by desulfurisation of unsaturated thiolactams have now been devised and the chemistry of such compounds has been explored. Enzymic experiments are carried out using a model pyrrolenine indicating that deletion of one of the pyrrole rings of the putative intermediate 2 leads to loss of tight binding.

Uroporphyrinogen III synthase (E.C. 4.2.1.75), usually called cosynthetase, catalyses the conversion of hydroxymethylbilane **1** into uroporphyrinogen III **3**, shortened to uro'gen III. This macrocycle is the parent from which haem, chlorophyll and vitamin B_{12} are all biosynthesised and much interest has centred on the mechanism of its formation. Intriguingly, the cyclisation of hydroxymethylbilane **1** to produce uro'gen III **3** is accompanied by a rearrangement which leads to inversion of ring D in the product **3**. Extensive earlier studies have been made both of the biosynthesis of hydroxymethylbilane **1** and of its ring-closure by cosynthetase; this work has been reviewed.[3] Of central importance for the present paper was the discovery[4,5] that the inversion of ring D occurs by an intramolecular mechanism that only involves ring D of the bilane **1**. An attractive sequence for this inversion involves the spiro-pyrrolenine **2** as a key intermediate, Scheme 1. Such pyrrolylmethylpyrrolenines are known[6] to undergo the indicated fragmentation and this step could be followed by formation of a new carbon–carbon bond as illustrated. This proposed mechanism is based on a suggestion by Mathewson and Corwin,[7] as shown in Scheme 1 in a simplified form.



Scheme 1 Mechanism proposed for the production of uro'gen III by cosynthetase; some ^{13}C-labelling experiments which established the intramolecular rearrangement[4] are illustrated by the black spots and squares

The intermediacy of the spiro-pyrrolenine **2** for the biosynthesis of uro'gen III **3** was given strong support by synthesis[8] of the racemic spirolactam **4** and the finding that it



inhibits strongly the action of cosynthetase in cyclising hydroxymethylbilane **1** to uro'gen III **3**. This support was further strengthened by preparing both enantiomers of the spirolactam **4** and demonstrating that one enantiomer competitively inhibits cosynthetase over twenty times more strongly than the other.[9] Finally, the strongly inhibiting enantiomer of **4** has been shown[10] to have the *R*-configuration and therefore, if the spiro-intermediate **2** is in fact formed in the enzymic process, the evidence points to its absolute configuration also being *R*, as illustrated in Scheme 1.

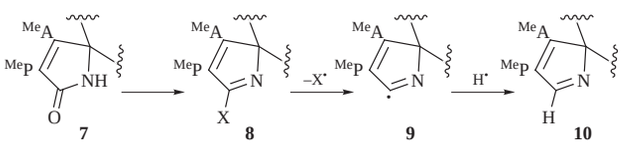
A synthesis of the spiro-pyrrolenine **2** itself, even as a racemate, would allow a decisive test of the mechanism in Scheme 1, since cosynthetase should convert one enantiomer of the synthetic product into uro'gen III **3** without formation of any significant amount of uro'gen I **6**. In contrast, non-enzymic rearrangement of **2** would be expected to yield a mixture of the type III **3** and type I **6** isomers (see the second in this series of four papers[11]). An earlier paper[6] described our first experiments aimed at developing chemistry necessary for the synthesis of **2**. The central problem was to devise routes to what were expected to be rather labile pyrrolylmethylpyrrolenines and bis(pyrrolylmethyl)pyrrolenines exemplified by the ring A–ring D–ring C system of **2**. In that earlier paper[6] the pyrrolenine ring of a model pyrrolenine was built up by conjugate addition of a nitro alkane to an acetylenic ester, followed

by reduction of the ester and nitro groups and cyclisation. This route does not permit substituents at C-4 of the pyrrolenine. Although a methyl group at C-4 was introduced in a round-about fashion by alkylation of an enolate, such chemistry would clearly be incompatible with the ester side-chains required for the synthesis of **2**. Furthermore, we were keen to exploit the coupling of iodopyrroles with acetoxymethyl-pyrroles to give 2-(pyrrolylmethyl)-5-halopyrrolenines (*e.g.* **11** + **12**→**13**, Scheme 3), which has been so successful in the formation of mono- and bis-(pyrrolylmethyl)lactams, culminating in the synthesis of spirolactam **4**.[8] The present paper describes how these 2,2,3,4-tetra-substituted pyrrolenines can be constructed and also some studies of their chemistry.

Results and discussion

Exploration of radical and other methods to reduce 5-substituted pyrrolenines

Our first approach to 5-unsubstituted mono- and bis-(pyrrolylmethyl)pyrrolenines **10**, Scheme 2, was by reduction of

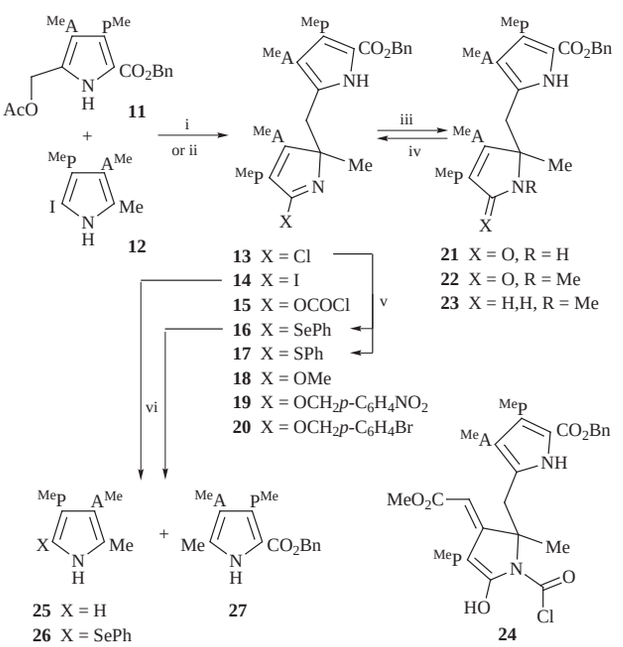


A^{Me} = CH_2CO_2Me, P^{Me} = $CH_2CH_2CO_2Me$,

Scheme 2

5-substituted pyrrolenines **8** (X = I or PhSe), derived from lactams **7**. It was hoped that generation of radicals **9** with quenching by hydrogen abstraction might afford the desired pyrrolenines.

When the reaction of acetoxymethylpyrrole **11** with iodo-pyrrole **12** is catalysed by stannic chloride,[8] the product is mainly the chloropyrrolenine **13** with lesser amounts of the iodide **14**, Scheme 3. The iodo analogue **14** was the preferred



Scheme 3 *Reagents:* i, $SnCl_4$; ii, BF_3; iii, AgOAc, H_3O^+ or SmI_2, THF, H_2O; iv, $COCl_2$ or triphosgene; v, PhSeH (or PhSH); vi, Ph_3SnH, AIBN (or *hν*)

material for radical generation yet under none of the wide variety of conditions tested was it possible to displace chloride from **13** by iodide. The rather unstable iodopyrrolenine **14** was obtained, albeit in 19% yield, by changing the Lewis acid catalyst for the reaction of **11** with **12** to boron trifluoride. Sufficient iodo derivative **14** was obtained to allow it to be photolysed in the presence of triphenyltin hydride but the major product, 59%, was the pyrrole **27**[12] together with a small amount of the α-free pyrrole[13] **25**. These arise either by the cationic fragmentation pathway (*e.g.* see Scheme 8; also fully exemplified in the following paper[11]), with reduction of the intermediate azafulvene by triphenyltin hydride, or by an analogous process involving radicals. Essentially the same result was obtained when the iodo derivative **14** was heated with triphenyltin hydride and a catalytic amount of 2,2′-azobis-isobutyronitrile (AIBN).

The phenylseleno group has been widely used for the generation of radicals[14] and so attention now focused on the selenopyrrolenine **16**, Scheme 3. Despite the lack of reactivity of chloropyrrolenine **13** towards iodide ion, we expected that displacement of chloride by selenophenol or its anion might be successful. It was also important to develop a way to prepare chloropyrrolenines *e.g.* **13**, from lactams, *e.g.* **21**, since the final application of any reductive method would be to the spiro-lactam ester **5**.

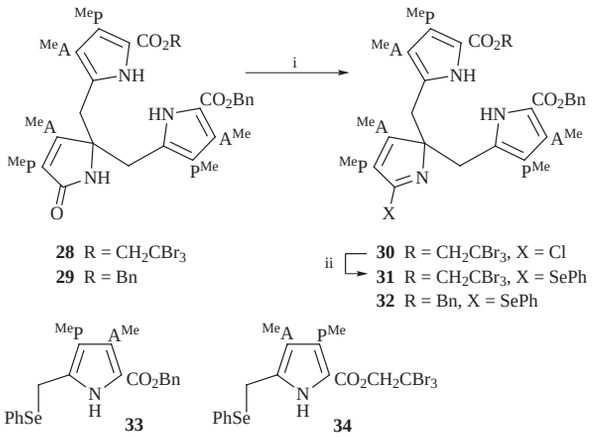
Lactam **21** had been synthesised earlier[8] from pyrroles **11** and **12**, as in Scheme 3. An improved procedure described for a close relative[10] has now doubled the yield of **21** from the earlier *ca.* 30% to 62%. The best conversion of lactam **21** into the chloropyrrolenine **13** was by treatment with phosgene[15] but importantly with 4-dimethylaminopyridine (DMAP) in place of the originally used pyridine; use of triphosgene rather than phosgene gave identical results and was experimentally preferable. The reaction was not straightforward in that three compounds were formed in differing amounts depending on the conditions. All three materials were unstable but could be separated under argon for spectroscopic characterisation. The rapidly formed kinetic product appeared to be the enolised *N*-chloroformyl lactam **24**, the second product was thought to be the *O*-chloroformyl derivative **15**, and the chloropyrrolenine **13** only predominated after heating at reflux in CH_2Cl_2. The presence of an *N*-chloroformyl species was supported by the results of attempted reductions of the crude reaction mixture with $ZnBH_4$; reaction for 3 h followed by aqueous work-up gave the *N*-methyl lactam **22**, 44%, whereas reaction for 12 h followed by treatment with acetic acid gave the *N*-methyl dihydro-pyrrole **23**, 25%.

Treatment of chloropyrrolenine **13** (prepared from lactam **21** using phosgene) with selenophenol (prepared by reduction of diphenyl diselenide)[16] or with thiophenol gave the phenyl-selenopyrrolenine **16**, 92%, and the sulfur analogue **17**, 81%, respectively. Interestingly, these reactions occurred more rapidly and were higher yielding if no base (triethylamine) was added, presumably because the initial addition step is catalysed by protonation of the pyrrolenine nitrogen by the two phenols under the non-basic conditions.

Irradiation of the phenylseleno compound **16** in benzene with triphenyltin hydride or heating it at reflux in benzene with AIBN and either triphenyltin hydride or tributyltin hydride gave the same two products, pyrroles **26** and **27**, in good yield. Again these had been formed by fragmentation followed by reduction.

Strictly analogous steps to those just described were also carried out in the dipyrrolic series on lactam **28**[8] (Scheme 4). The chloropyrrolenine **30** was derived from it using phosgene and reacted with selenophenol to give the phenyl selenide **31** in low yield (34%) because the now familiar fragmentation also occurred. One of the products of this competing process was the phenylselenomethylpyrrole[17] **33** but the analogue **34** that would arise by the alternative fragmentation was not formed, no doubt due to the significant electron-withdrawing effect of the tribromoethyl group.

The same chemistry was also performed on lactam **29** which



Scheme 4 *Reagents:* i, $COCl_2$; ii, PhSeH

only differs from isomer **35** synthesised earlier[8] (Scheme 5) in the arrangement of the side-chains on one pyrrole ring. This change made the synthesis, described in the following paper,[11] easier and more reproducible than the earlier one. The phenylselenopyrrolenine **32** was prepared from lactam **29** in the usual way but without isolation of the chloro intermediate. Similar studies using tin hydrides to those described above for the monopyrrolic series were also carried out briefly with the dipyrrolic system **32** but here too, appreciable fragmentation occurred under all conditions tested, so this work is not further described.

The conclusion from these experiments was that either the desired radical is formed but the molecule then undergoes rapid homolytic fragmentation or that heterolytic fragmentation dominates the chemistry under the conditions used.

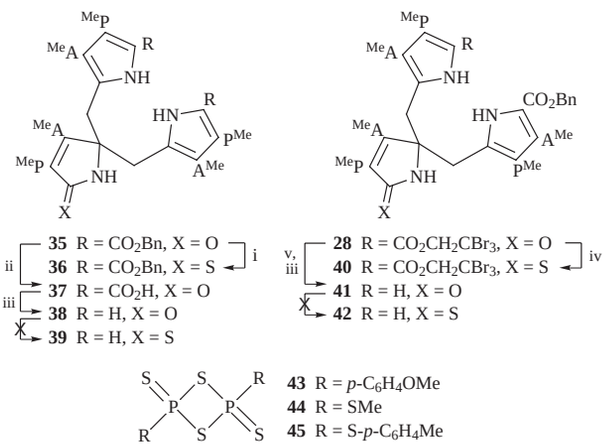
Reduction of the monopyrrolic chloropyrrolenine **13** under many conditions with a wide variety of hydride and other reducing agents was also attempted. These experiments usually led either to recovery of starting material or only to reduction of the side-chain ester(s). A few reactions did occur, however. Thus treatment of the halopyrrolenine mixture **13/14** with samarium(II) iodide and water gave the lactam **21**, Scheme 3, whereas treatment with lithium triethylborohydride resulted in the formation of a boronic acid complex of **21**.

We then aimed to replace the chlorine atom of **13** by another group for further reductive experiments. It proved impossible to displace the chlorine using methoxide or cyanide ions but the methoxy derivative **18** was available by methylation of lactam **21** with either trimethyloxonium tetrafluoroborate (Meerwein's reagent), in 83% yield, or methyl iodide and silver carbonate, 75% yield. Similarly, *p*-nitrobenzyl bromide or *p*-bromobenzyl bromide together with silver carbonate and 18-crown-6 afforded the imino ethers **19** and **20**, respectively, in yields of 71 and 62%. Earlier work[6] had shown that a close analogue of **18** lacking the acetate and propionate side chains could be smoothly reduced with DIBAL but the use of this reducing agent is precluded in the case of **18** by the presence of the ester groups. Many other reducing agents were tested but again they either left **18** unchanged or just reduced one or more of the side-chain esters. The only exception was the high-yielding conversion of **18** into the original lactam **21** by samarium(II) iodide, with or without tributyltin hydride.

Exploration of the thionation route

The obvious and apparently simple way to prepare the spiropyrrolenine **2** would be to reduce the spiro-lactam ester **5**, followed by a final hydrolysis step. Clearly the reduction of the lactam would have to be effected in the presence of the eight more reactive ester groups and therefore some means of activation of the lactam would be required. We thought that conversion of a lactam into the corresponding thiolactam might allow selective reduction using Raney nickel[18] or some similar reagent. Alternatively alkylation of the sulfur atom might be used to increase the reactivity of the thiolactam towards different reducing agents. The pyrrole rings of spiro-lactam **5**, however, lack any electron-withdrawing ester groups to deactivate them and it was necessary to test out the required chemistry on simpler model pyrrolylmethyllactams having similarly electron-rich pyrrole rings.

We therefore explored thionation of bis(pyrrolylmethyl)-lactams having non-deactivated α-free pyrrole group(s). Hydrogenolysis of the previously synthesised[8] lactam dibenzyl ester **35** gave the diacid **37** which was decarboxylated using trifluoroacetic acid (TFA), Scheme 5. The product **38** was then treated



Scheme 5 *Reagents:* i, **43**; ii, Pd/C, H_2; iii, TFA; iv, **44**; v, Zn, AcOH

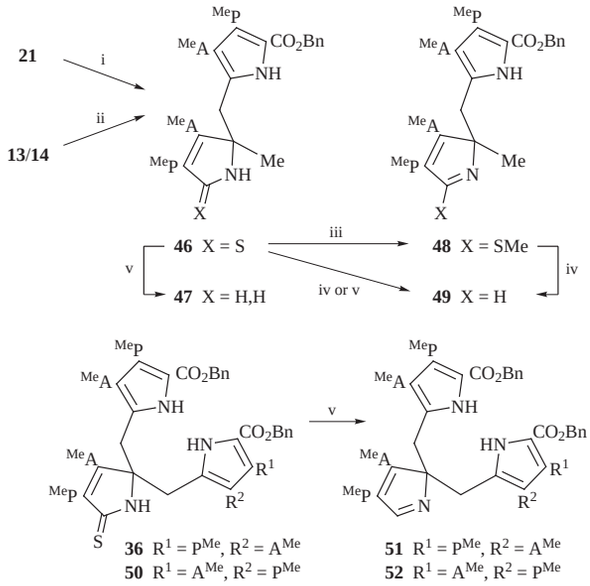
with Lawesson's reagent[19] **43** in tetrahydrofuran, conditions that had been found to allow relatively mild conversion of **35** into the thiolactam **36**. However, the bis-α-free system **38** did not react and even more forcing conditions left it largely unaffected; the thiolactam **39** was not produced. This may be due to association of the two electron-rich pyrrole rings with the lactam residue by π–π interaction and hydrogen bonding, a phenomenon previously observed.[6]

One final hope for this approach was to use Davy's reagent **44** for thionation[20] since it is milder than Lawesson's reagent **43**. Indeed, this reagent converted the closely related bis(pyrrolylmethyl)lactam **28** into thiolactam **40** at room temperature in 94% yield. Because of the foregoing results with **38**, just one α-free pyrrolylmethyl group was generated by removal of the tribromoethyl group from **28** using zinc and acetic acid and then decarboxylation of the resultant acid using TFA. The product **41** was treated directly with **44** under the same conditions as before; **42** was not formed and there was essentially complete decomposition of the material. Thus, on the one hand, there was insufficient reactivity for the system **38** with two α-free pyrroles whereas, on the other hand, there was destructive lability for the analogue **41** with one α-free pyrrole.

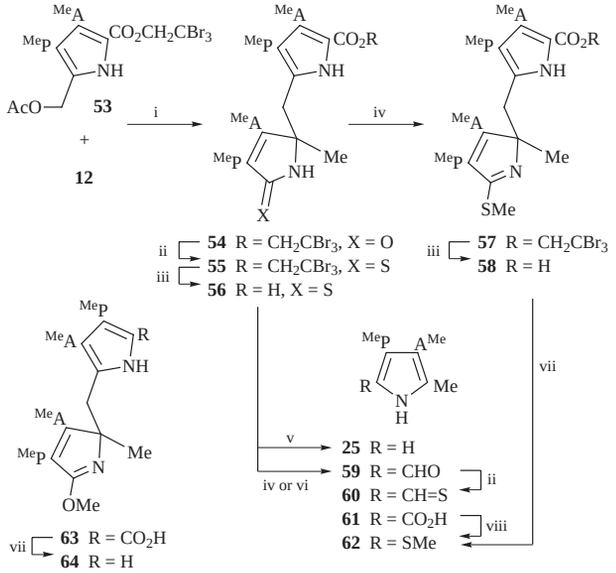
Synthesis of pyrrolenines

Because of the failure to thionate pyrrolylmethyl lactams having a non-deactivated pyrrole ring, we changed to studying thionation of systems having deactivated pyrroles, with the thought that it might be possible to remove or use the deactivating groups at a later stage and further steps would then allow formation of the macrocycle. Our initial studies were performed on the more readily available monopyrrolic lactams before we progressed to dipyrrolic systems.

Lactam **21** was smoothly converted into the thiolactam **46** using Lawesson's reagent (Scheme 6), which clearly demonstrates the difference that the deactivating ester groups can make. An alternative procedure for the preparation of this thiolactam was found to be treatment of halopyrrolenine mixture **13/14** with H_2S. Desulfurisation of thiolactam **46** with Raney



Scheme 6 *Reagents:* i, **43**; ii, H_2S; iii, TMOF, TFA; iv, Raney nickel; v, nickel boride



Scheme 7 *Reagents:* i, $SnCl_4$ then AgOAc, H_3O^+; ii, **43**; iii, Zn, AcOH; iv, TFA, TMOF; v, TFA; vi, DMF, $POCl_3$; vii, TsOH; viii, KI_3, $(NH_2)_2C{=}S$ then KOH, MeI

nickel, or more reproducibly with nickel boride,[21] then yielded the desired pyrrolenine **49**, 45%. Alternatively, methylation of the thiolactam with trimethyl orthoformate (TMOF) and trifluoroacetic acid (TFA) afforded the thioimino ether **48**, 95%, which was desulfurised using Raney nickel yielding the pyrrolenine **49**, 41%. When nickel boride replaced Raney nickel in the foregoing experiment, the yield of **49** was only 10–16% and a second product proved to be the amine **47**. The latter became the sole product when either **46** or **48** was treated with nickel boride for 15–24 h, yields 51 and 37%, respectively.

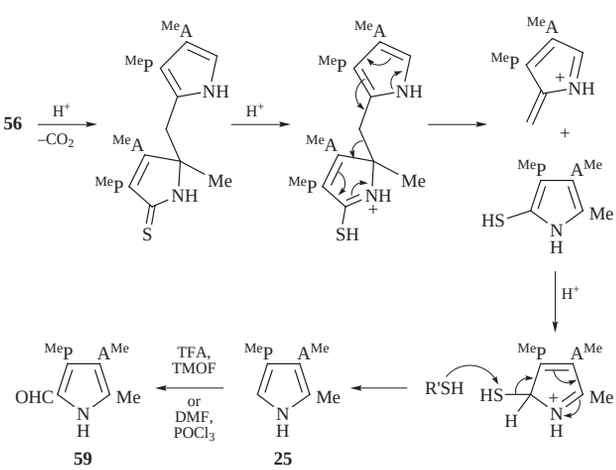
The pyrrolenine **49** was reasonably stable if handled carefully but it decomposed completely after storage for one month at 0 °C under argon. It was thought that an adduct of the pyrrolenine with a nucleophile might produce a more stable compound, amenable to further synthetic steps. However, neither thiols, selenophenol nor cyanide could be added to the imine residue of pyrrolenine **49** by any of the many methods tested, including *e.g.* trimethylsilyl cyanide–zinc iodide.[22] Clearly the 5-position of these 2,2,3,4-substituted pyrrolenines is strongly hindered.

In the dipyrrolic series, the synthesis of pyrrolenines was just as successful as in the monopyrrolic series. Reduction of thiolactam **36** with nickel boride gave pyrrolenine **51** (46%). Similar reduction of the isomeric thiolactam **50** to give the corresponding pyrrolenine **52** (52%) is reported in the following paper.[11]

Chemistry of thiolactams

Having established an effective route to pyrrolenines such as **49** and **51** from the corresponding thiolactams, we wished to explore some of the chemistry that would be necessary if a thiolactam similar to **51** were to be converted into the thiolactam corresponding to spirolactam **5**. For this to be possible it would be necessary to make a bis(pyrrolylmethyl)thiolactam with a pyrrolic α-formyl group to allow attachment of the third pyrrole ring. The chemistry was first explored in the mono-(pyrrolylmethyl) series.

The initial approach was to make the thiolactam first and then cleave the pyrrolic α-ester group, decarboxylate and formylate. This demanded a different ester, as it would probably not be possible to hydrogenolyse a benzyl group in a sulfur-containing molecule. Because tribromoethyl ester **53** was available,[8] lactam tribromoethyl ester **54**, with a reversed substitution pattern on the pyrrolic ring, was synthesised as before, Scheme 7. It was converted into the thiolactam **55** and the ester was cleaved with zinc and acetic acid to yield the thiolactam acid **56**. Unexpectedly, this underwent fragmentation under standard decarboxylation–formylation conditions, TMOF and TFA, to afford the monopyrrole **59** in 75% yield and the same product was also formed under Vilsmeier conditions (Me_2NCHO, $POCl_3$). Thiolactam **56** was also broken down by TFA alone, the major product being pyrrole **25**. The two pyrroles **25** and **59** were identified by comparison with authentic samples prepared by published methods.[13,23] A rationalisation of the outcome of these reactions is shown in Scheme 8; acid-



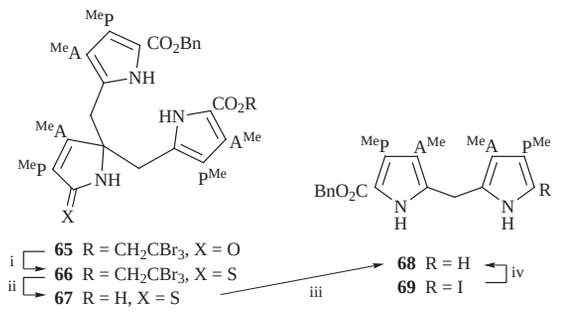
Scheme 8 Proposed mechanism for the formation of pyrroles **25** and **59** from thiolactam **56**

catalysed decarboxylation of **56** is probably the first step, generating an undeactivated pyrrole, which upon protonation of the sulfur atom would fragment as shown. A similar fragmentation by a related mechanism occurred when the thioimino ether **58**, prepared from thiolactam **55** by methylation followed by reductive ester cleavage, was treated with toluene-*p*-sulfonic acid. The sole product, apart from polymeric material, was the methylthiopyrrole **62**, 49%, identified by comparison with authentic material synthesised[24] from the acid **61**,[25] Scheme 7.

Surprisingly, treatment of acid **63**, prepared by hydrogenolysis of imino ether **18**, with either TFA or toluene-*p*-sulfonic acid gave the α-free pyrrole **64** in up to 87% yield whereas only fragmentation was observed with the sulfur analogue **58**. This result is somewhat puzzling but does fit in

with the greater stability of pyrrolylmethyl lactams compared with the corresponding thiolactams.

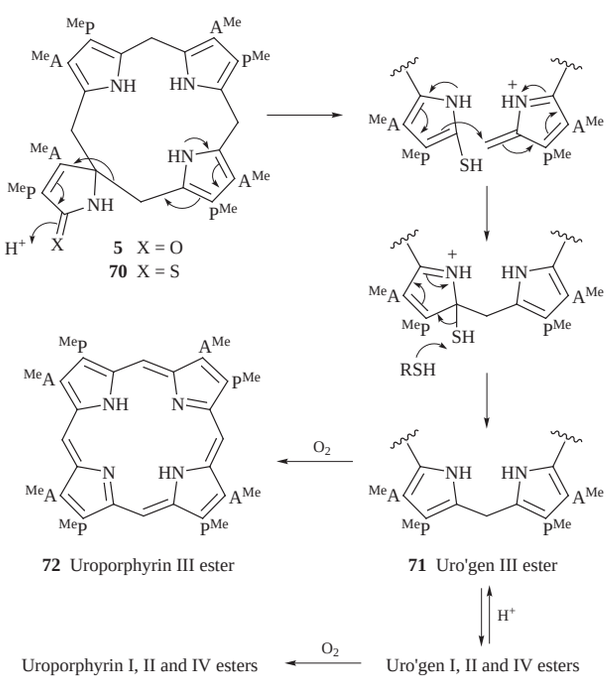
Concurrently with the above studies in the monopyrrolic series, analogous experiments were also tried in the dipyrrolic series. Thus treatment of lactam **65**, synthesised earlier,[8] with Lawesson's reagent afforded the thiolactam **66**, from which the tribromoethyl group was reductively removed, Scheme 9. The



Scheme 9 *Reagents:* i, **43**; ii, Zn, AcOH; iii, TsOH; iv, PtO_2, H_2

resultant acid **67**, on treatment with acid, underwent fragmentation as in the simpler mono-pyrrolyl case, to yield the dipyrromethane **68**. The mechanism of its formation is clearly analogous to that shown in Scheme 8; **68** was identified by comparison with a standard sample prepared from iodide **69**[11] by hydrogenolysis.

It was clear from the foregoing experiments that, due to the lability under acidic conditions of pyrrolylmethyl thiolactams having an undeactivated pyrrole ring, it would not be possible to set up the thiolactam system early in the synthesis and carry it forward through the remaining steps necessary[8] to generate the spirothiolactam ester **70**, Scheme 10.



Scheme 10 Proposed mechanism for the formation of uroporphyrin octamethyl esters upon thionation of spirolactam ester **5**

The alternative to early formation of the thiolactam system was to attempt the transformation of the spirolactam ester **5** into the thiolactam **70** at the end of the synthesis; all the experiments were carried out with racemic material. Naturally this conversion was tried as soon as the thiolactam route to pyrrolenines was developed, indeed before some of the studies described above, but without success. All the experience gained from the subsequent work led us to return to this desired conversion. For example, if the explanation offered for the lack of reactivity of the bis-α-free pyrrole system **38** is correct (*i.e.* steric hindrance from the pyrrole rings), then the spirolactam **5** should not be similarly affected because the pyrrole rings are tied back away from the lactam. The foregoing results with the mono-α-free pyrrole model **41** and the acid **56** forewarned of possible problems but even the smallest chance for the preparation of the spirothiolactam **70** could not be ignored. Accordingly, the spirolactam ester **5** was heated with Lawesson's reagent or with phosphorus pentasulfide. However the only products, in each case after aerial oxidation, were uroporphyrin octamethyl esters, 48% yield, shown by HPLC and ^{1}H NMR spectroscopy to contain the statistical mixture of the four possible isomers, *i.e.* type III **72**, 50%, type I, 12.5%, type II, 12.5% and type IV, 25%. Presumably these arise, Scheme 10, by fragmentation analogous to that shown in Scheme 8 followed by recyclisation and loss of sulfur (also similar to that in Scheme 8) to give uro'gen esters of both type I and type III (only the type III one **71** is shown). Then scrambling of the pyrrole rings at the uro'gen stage under the acidic conditions leads to the statistical mixture of isomers.[26] Davy's reagent **44** at room temperature only caused slow decomposition of **5**, and raising the temperature simply increased the rate of decomposition. The *p*-tolyl analogue[27] **45** left the lactam **5** unchanged up to 50 °C and decomposition set in at 60 °C. At roughly the half-way point of the last experiment, it was shown by ^{1}H NMR spectroscopy that the undecomposed substance was unchanged starting material.

Thus we were reluctantly forced to conclude that the route to pyrrolylmethylpyrrolenines from lactams by thionation followed by reduction, so successful when the pyrrole rings are deactivated, cannot be used for synthesis of the spiropyrrolenine **2** itself.

Synthesis of α-formyl- and α-cyano-pyrrolic pyrrolenines

Finally, in view of the fact that the the spiro-pyrrolenine **2** itself was not yet synthetically accessible, we wanted to make alternative pyrrolenines in which the necessary electron-withdrawing groups on the pyrrolic ring(s) are smaller than the benzyloxycarbonyl residue of **49** and **51**. This was because, in addition to studying the chemistry of pyrrolenines, a further aim was to explore how they interacted with the enzyme, cosynthetase. Formyl and cyano groups were chosen as being suitable for the envisaged enzymic experiments.

As in previous cases, we initially investigated the required chemistry in the monopyrrolic series. In view of the fragmentation that occurred upon attempted decarboxylation–formylation of thiolactam acid **56**, we investigated the alternative sequence of reactions, *i.e.* formylation first then thionation. Hydrogenolysis of lactam benzyl ester **21** gave the acid **73** which was treated with TMOF and TFA to afford the aldehyde **74** (Scheme 11). However, thionation using Lawesson's reagent converted this into a mixture of the lactam thioaldehyde **75** and the corresponding thiolactam thioaldehyde **79**. It was clear that the monothio product was thioaldehyde **75** and not the desired thiolactam **80** from the ^{1}H NMR chemical shift of the aldehyde proton, which had moved to δ 10.57 from 9.51 in the starting aldehyde **74**.

Since thioketones can be hydrolysed to give ketones,[28] we hoped to hydrolyse the bis-thio system **79** to the thiolactam aldehyde **80**. Trial experiments were carried out by converting the aldehyde **59** into the thioaldehyde **60** using Lawesson's reagent, Scheme 7. This thioaldehyde **60** crystallised as red rhombohedra and its structure, shown in Fig. 1, was determined by X-ray analysis.† It is monomeric in contrast to the case

† The experimental details and coordinates for the crystal structure determinations of **60** and **77** have been deposited with the Cambridge Crystallographic Data Centre (CCDC). Deposition numbers: **60**, 100546; **77**, 100545.

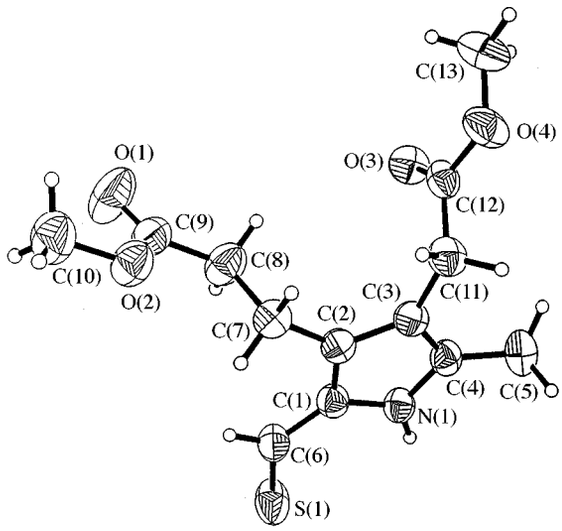
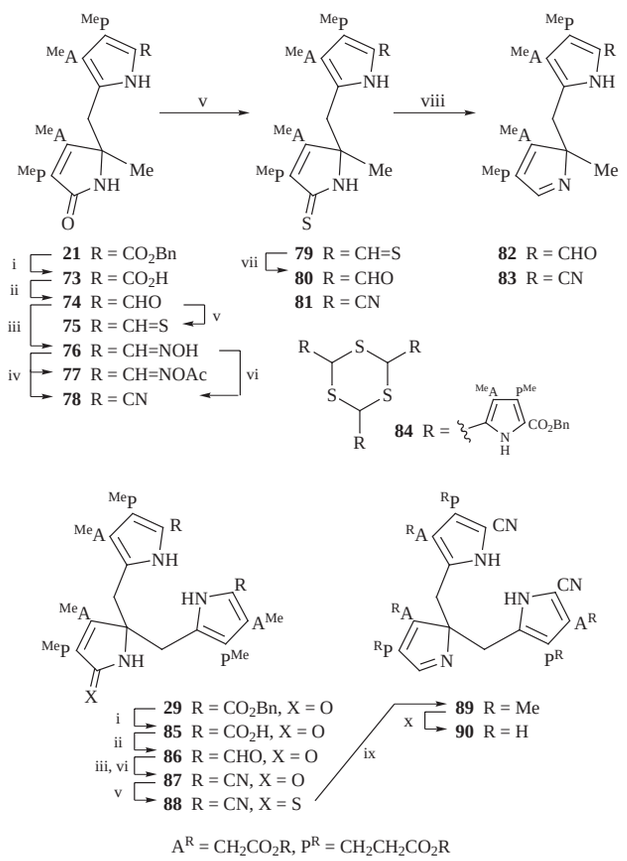


Fig. 1 X-Ray crystal structure of thioaldehyde **60**



Scheme 11 *Reagents:* i, Pd/C, H_2; ii, TFA, TMOF; iii, NH_2OH; iv, Ac_2O; v, **43**; vi, DMF, $POCl_3$; vii, morpholine, H_2O; viii, Raney nickel; ix, nickel boride; x, KOH

studied by Baker[29] which existed as the trimer **84**. Presumably the greater electron release from the pyrrole ring to the thioaldehyde residue in the case of **60** accounts for its greater stability.

Thioaldehyde **60** could be hydrolysed in aqueous morpholine to yield the starting aldehyde **59**. These conditions were then applied to the thiolactam thioaldehyde **79** and gave the thiolactam aldehyde **80**. Desulfurisation by Raney nickel then gave the desired formylpyrrolenine **82**.

The second target in the monopyrrolic series was the nitrile **83**, Scheme 11. Treatment of aldehyde **74** with hydroxylamine yielded a mixture of *syn*- and *anti*-oximes **76** and subsequent reaction with hot acetic anhydride then gave a mixture of

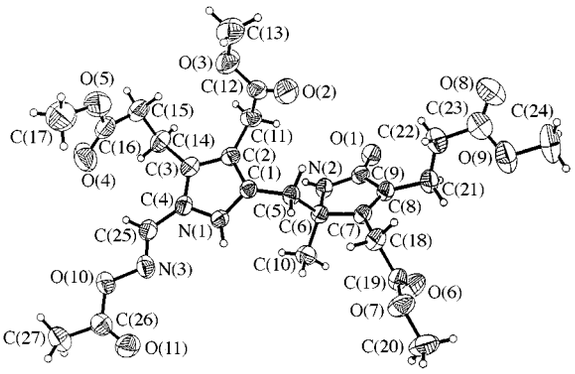


Fig. 2 X-Ray crystal structure of *anti-O*-acetyloxime **77**

products, some of them inseparable. However, mass spectrometry showed that the mixture contained the nitrile **78** and the acetylated oxime **77**. The latter was obtained pure by fractional crystallisation and an X-ray structure determination was carried out.† Fig. 2 shows that this product is the *anti*-isomer, which is understandable since the *syn*-isomer presumably undergoes rapid elimination of acetic acid to give the nitrile. This structure fully confirms all the features of this molecule and indeed of the entire monopyrrolic series, previously dependent on spectroscopic evidence. An alternative method for dehydration of oximes[30] (Me_2NCHO and $POCl_3$) smoothly converted the mixture of isomeric oximes **76** into the nitrile **78** in good yield. Preparation of the corresponding thiolactam **81**, as earlier, and desulfurisation with nickel boride then readily afforded the cyanopyrrolenine **83**.

Turning to the dipyrrolic series, hydrogenolysis of the benzyl groups of lactam **29** gave the diacid **85**, which with TMOF and TFA was converted into the required dialdehyde **86**. However, it was not possible to prepare the corresponding thiolactam dithioaldehyde cleanly using Lawesson's reagent and attempted hydrolysis (as in the monopyrrolic series) of the product mixture aiming to produce some of the thiolactam dialdehyde was unsuccessful. Attention therefore turned to the dinitrile **87** which was synthesised smoothly from dialdehyde **86** by forming the mixture of oximes followed by dehydration as earlier. Further, the lactam dinitrile **87** was converted into the thiolactam **88** by Lawesson's reagent ready for desulfurisation with nickel boride. Unlike the monopyrrolic case **81**→**83**, desulfurisation generated a mixture and caused serious loss of material. In order to obtain pure pyrrolenine **89** for the enzymic experiments, purification by HPLC was needed and we had to accept a yield of 14%.

Enzymic studies

The plan was to hydrolyse the six ester groups of the dicyanopyrrolenine **89** under conditions that left the cyano and pyrrolenine systems unaffected. These conditions were developed using the simpler monopyrrolic analogue **83**, Scheme 11, which on treatment with aqueous methanolic potassium hydroxide gave a homogeneous solution. Part of this solution was repeatedly evaporated and redissolved in deuterium oxide; the final solution gave a 400 MHz ^{1}H NMR spectrum fully consistent with the tetrapotassium salt derived from **83**. The remainder of the hydrolysate was re-esterified using diazomethane to give almost pure starting material **83**, together with trace amounts of higher R_f fragmentation products. Thus, the hydrolytic conditions met the requirements and were used to prepare the hexapotassium salt of the acid **90** from the ester **89**.

Hart studied the effect of the hexaacid **90** in buffered solution on the rate of conversion of synthetic hydroxymethylbilane[12] **1** into uro'gen III **3** by purified cosynthetase[31] using kinetic experiments exactly as had been used[8] to demonstrate strong inhibition of the enzyme by the spirolactam **4**. The outcome was that, even at high concentrations (500 μmol dm^{-3}), the acid

90 had no effect on the enzymic rate and is thus not an inhibitor of cosynthetase. This interlocks with earlier results[8] which showed that molecules lacking some part or all of the lactam ring present in the inhibitory spirolactam **4** did not inhibit the enzyme. The present results suggest either that the entire macrocyclic system is also necessary for strong binding to occur or that **90** cannot readily adopt the same conformation as that of rings A, D and C of **4**.

Conclusions

The probable involvement of a 2,2-disubstituted pyrrolenine (2*H*-pyrrole) in the biosynthesis of uro'gen III **3**, the parent of all the natural porphyrins, chlorins and corrins, has focused attention on the chemistry of such systems. However, methods for synthesis of close analogues of the proposed natural system were not available. The novel methods described in this paper have provided a variety of the required pyrrolenines carrying one or two pyrrolylmethyl groups at the disubstituted 2-position of the 3,4-substituted pyrrolenine ring. This has allowed extensive study of the chemistry of these systems and also of how one example interacted with the enzyme cosynthetase. It was found that whereas the spirolactam **4** strongly inhibited cosynthetase, the open-chain pyrrolenine **90**, lacking ring B of **4**, did not.

Experimental

General directions

General directions are as in ref. 32. Coupling constants, *J*, are quoted in Hz. For ^{13}C NMR spectra in which the numbers of hydrogens attached to carbons were determined, this was achieved by heteronuclear *J*-resolved 2D spectra, off-resonance decoupling or DEPT experiments.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 21

A mixture of a solution of 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylic acid[25] (**25**, X = CO_2H) (200 mg, 0.7 mmol) in dichloromethane (10 cm^3) and a solution of sodium hydrogen carbonate (119 mg, 1.4 mmol) in water (8 cm^3) was stirred vigorously under argon and an aqueous solution (7.1 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added over 5 min. The resulting mixture was stirred for a further 2 min and then solid sodium metabisulfite was added to destroy the excess iodine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 15 cm^3). The combined organic layers were dried and evaporated under reduced pressure to give the crude iodopyrrole **12**. To this was added a solution of acetoxymethylpyrrole **11**[33] (305 mg, 0.7 mmol) in anhydrous dichloromethane (10 cm^3) and the resulting solution was cooled to −78 °C under argon. Stannic chloride (83 mm^3, 0.7 mmol) was added dropwise and the stirring continued for 3 h, during which time the solution was allowed to warm up to 0 °C. The solution was then re-cooled to −78 °C and a solution of samarium(II) iodide in THF (0.1 mol dm^{-3}; 14 cm^3, 1.4 mmol) was added, followed by water (100 mm^3). The solution was allowed to warm to room temperature over 1 h and then evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate–hexane (1 : 1) and then ethyl acetate, gave *lactam* **21** as an oil (238 mg, 54%), with physical characteristics identical to those reported.[8]

9-Benzyloxycarbonyl-1-chloro-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 13

A suspension of triphosgene (50 mg, 160 μmol), DMAP (920 mg, 160 μmol) and lactam **21** (50 mg, 80 μmol) in anhydrous dichloromethane (2 cm^3) was heated at reflux under argon for 1 h. The mixture was *rapidly* cooled in ice, filtered through a plug of Celite and evaporated under reduced pressure to give the crude 5-*chloropyrrolenine* **13** as an oil (52 mg), which was generally used without further purification.

TLC of this material (diethyl ether–methanol, 20 : 1) showed that it contained, in addition to **13**, two minor components. Their relative proportions were roughly equal after equilibration at room temperature for a few hours but strongly favoured **13** after heating at reflux. The three very air- and moisture-sensitive components were separated by PLC, eluting with diethyl ether–methanol (20 : 1) in the dark under argon, to give: (i) a compound thought to be *O*-chloroformylimidate **15** (R_f 0.6); δ_H($CDCl_3$, 400 MHz) 1.61 (3 H, s, 4-Me), 2.44–2.94 (8 H, 2 × CH_2CH_2), 2.79 and 3.41 (each 1 H, d, *J* 16, 5-H_2), 3.44 (2 H, s, CH_2CO_2), 3.53 and 3.84 (each 1 H, d, *J* 18, CH_2CO_2), 3.59, 3.62, 3.63 and 3.77 (each 3 H, s, OMe), 5.17 and 5.31 (each 1 H, d, *J* 12.5, CH_2Ph), 7.25–7.40 (5 H, m, Ph) and 10.02 (1 H, br s, NH); (ii) chloropyrrolenine **13** (R_f 0.8); ^1H NMR data identical to those previously[8] reported; (iii) a compound thought to be enolised *N*-chloroformyl lactam **24** (R_f 0.9); λ_{max}(CH_2Cl_2)/nm 277 and 332; ν_{max}($CHCl_3$)/cm^{-1} 3443, 3338, 3029, 2954, 1734, 1583, 1453 and 1175; δ_H($CDCl_3$, 400 MHz) 2.00 (3 H, s, 4-Me), 1.93–2.01 (1 H, m), 2.10–2.17 (1 H, m), 2.33–2.52 (5 H, m) and 2.86 (2 H, t, *J* 8, 2 × $CH_2CH_2CO_2$ and OH), 3.38 (2 H, s, CH_2CO_2), 3.58, 3.62, 3.64 and 3.73 (each 3 H, s, OMe), 3.73 and 4.12 (each 1 H, d, *J* 15.5, 5-H_2), 5.21 and 5.30 (each 1 H, d, *J* 12.5, CH_2Ph), 5.59 (1 H, s, C=$CHCO_2$), 7.33–7.36 (5 H, m, Ph) and 8.61 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.4 and 20.7 (2 × $CH_2CH_2CO_2$), 22.1 (4-Me), 29.3, 30.6, 31.6 and 34.6 (3 × CH_2CO_2 and C-5), 51.5, 51.9, 52.0 and 52.0 (OMe), 66.0 (CH_2Ph), 78.5 (C-4), 105.7 (C=$CHCO_2$), 116.6, 118.3, 125.0, 129.4, 130.5, 136.4, 136.5 and 142.5 (C=C), 128.3 and 128.7 (C=*C*H) and 158.7, 160.1, 166.4, 172.0, 172.4 and 173.5 (C=O); *m*/*z* (+FAB) 689 (MH^+, 4%) and 372 ($C_{20}H_{22}NO_6$, 100).

9-Benzyloxycarbonyl-1-iodo-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 14

A solution of acetoxymethylpyrrole **11**[33] (75 mg, 175 μmol) and iodopyrrole **12**[8] (64 mg, 175 μmol) in dry dichloromethane (3 cm^3) was stirred with boron trifluoride–diethyl ether (50 mg, 175 μmol) at 0 °C under argon for 1 h. Saturated aqueous sodium hydrogen carbonate (3 cm^3) was added and then, after 5 min, the organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 5 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave *iodopyrrolenine* **14** (19 mg, 13%) as a moisture-sensitive gum; physical data were as previously[8] described; *m*/*z* (FD) 736 (M^+, 100%).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)-4-methyl-1-phenylseleno-4,5-dihydrodipyrrin 16

A solution of chloropyrrolenine **13** (400 mg, 0.62 mmol) in dry degassed dichloromethane (10 cm^3) was added under argon to selenophenol[16] (471 mg, 3.0 mmol), stirred under argon for 30 min, poured into saturated aqueous sodium carbonate (50 cm^3) and extracted with dichloromethane (4 × 25 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by column chromatography, eluting with diethyl ether, gave *phenylselenopyrrolenine* **16** (452 mg, 95%) as a gum (Found: M^+, 766.2015. $C_{38}H_{42}N_2O_{10}{}^{80}Se$ requires *M*, 766.2005); ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 1720, 1700, 1160 and 1070; δ_H($CDCl_3$, 400 MHz) 1.10 (3 H, s, 4-Me), 2.33 and 3.09 (each 1 H, d, *J* 15, 5-H_2), 2.47–2.58 and 2.92–3.01 (8 H, m, 2 × CH_2CH_2), 3.30 and 3.38 (each 1 H, d, *J* 16, CH_2CO_2), 3.43 (2 H, s, CH_2CO_2), 3.59, 3.62, 3.65 and 3.69 (each 3 H, s, OMe), 5.27

(2 H, s, CH_2Ph), 7.28–7.37 and 7.53–7.57 (10 H, m, 2 × Ph) and 9.94 (1 H, m, NH); δ_C($CDCl_3$, 100 MHz) 20.30, 20.58, 20.65, 29.59, 31.37, 32.44 and 32.81 (7 × CH_2 and 4-Me), 51.40, 51.76, 51.89 and 52.52 (OMe), 65.38 (O*C*H_2Ph), 83.37 (C-4), 115.28, 117.19, 125.75, 127.92, 128.04, 128.44, 128.60, 129.50, 131.19, 134.86, 136.55 and 138.72 (C=C) and 157.05, 160.33, 167.99, 170.40, 172.32, 172.86 and 173.74 (C=O and N=*C*–C=*C*); *m*/*z* (FD) 766 (M^+ for ^{80}Se, 100%).

Attempted reduction of phenylselenopyrrolenine 16

A solution of phenylselenopyrrolenine **16** (31 mg, 42 μmol) in dry degassed toluene (5 cm^3) was added dropwise *via* a syringe pump to a solution of triphenyltin hydride (100 mg, 0.27 mmol) in dry degassed toluene (10 cm^3), which was being irradiated by UV light. After 4 h the solution was evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether–hexane (1 : 1), gave at lower R_f methylpyrrole **27** (13 mg, 84%), identical with authentic material,[12] and at higher R_f *phenylselenopyrrole* **26** (10.5 mg, 67%) (Found: M^+, 395.0639. $C_{18}H_{21}NO_4{}^{80}Se$ requires *M*, 395.0636); ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 2975, 1725, 1260 and 1170; δ_H($CDCl_3$, 400 MHz) 2.21 (3 H, s, C-Me), 2.45 and 2.83 (each 2 H, t, *J* 7, CH_2CH_2), 3.46 (2 H, s, CH_2CO_2), 3.61 and 3.68 (each 3 H, s, OMe), 7.07–7.25 (5 H, m, Ph) and 7.93 (1 H, br s, NH); *m*/*z* (FD) 395 (M^+ for ^{80}Se, 100%).

Reduction was also attempted by dropwise addition of **16** to a solution of triphenyltin hydride (4 equiv.) and AIBN in refluxing dry, degassed benzene. Again **27** (56%) and **26** (59%) were isolated.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-1-phenylthio-4,5-dihydrodipyrrin 17

A solution of chloropyrrolenine **13** (62 mg, 96 μmol) in dry dichloromethane (3 cm^3) was stirred with thiophenol (110 mg, 1 mmol) at room temperature for 90 min, then added to saturated aqueous sodium hydrogen carbonate (10 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the *phenylthiopyrrolenine* **17** (56 mg, 81%) as a gum (Found: M^+, 718.2562. $C_{38}H_{42}N_2O_{10}S$ requires *M*, 718.2560); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 1720, 1700 and 1170; δ_H($CDCl_3$, 400 MHz) 1.06 (3 H, s, 4-Me), 2.28 and 3.04 (each 1 H, d, *J* 15, 5-H_2), 2.45–2.64 and 2.90–2.99 (8 H, m, 2 × CH_2CH_2), 3.29 and 3.37 (each 1 H, d, *J* 16, CH_2CO_2), 3.36 and 3.43 (each 1 H, d, *J* 16, CH_2CO_2), 3.59, 3.61, 3.66 and 3.70 (each 3 H, s, OMe), 5.24 (2 H, s, CH_2Ph), 7.29–7.38 and 7.48–7.50 (10 H, m, 2 × Ph) and 9.91 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 20.02, 20.26, 20.55, 29.66, 31.41, 32.56, 32.67 and 34.86 (7 × CH_2 and 4-Me), 50.75, 51.28, 51.64 and 52.41 (OMe), 65.38 (O*C*H_2Ph), 81.71 (C-4), 115.20, 117.23, 127.90, 128.34, 128.61, 129.25, 129.56, 131.40, 133.77, 136.62 and 137.72 (C=C) and 157.49, 160.36, 169.57, 170.42, 172.35, 173.03 and 173.81 (C=O and N=*C*–C=*C*); *m*/*z* (FD) 718 (M^+, 100%).

9-Benzyloxycarbonyl-1-methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 18

A mixture of the lactam **21** (1.44 g, 2.3 mmol), trimethyloxonium tetrafluoroborate (340 mg, 2.3 mmol) and 1,8-bis(dimethylamino)naphthalene (492 mg, 2.3 mmol) was stirred in dry dichloromethane (20 cm^3) under argon for 28 h and then evaporated under reduced pressure. Purification on a flash chromatography column (25 × 2 cm), eluting with diethyl ether, gave *methoxypyrrolenine* **18** (1.22 g, 83%) as a gum (Found: M^+, 640.2634. $C_{33}H_{40}N_2O_{11}$ requires *M*, 640.2632); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2950, 1730s, 1690, 1450, 1380, 1250, 1170 and 1100; δ_H($CDCl_3$, 250 MHz) 1.03 (3 H, s, 4-Me), 2.15 and 2.96 (each 1 H, d, *J* 15, 5-H_2), 2.46–2.59 and 3.00–3.04 (8 H, m, 2 × CH_2-CH_2), 3.38 and 3.44 (each 2 H, s, CH_2CO_2), 3.61, 3.63, 3.64, 3.67 and 3.69 (each 3 H, s, OMe), 5.18 and 5.29 (each 1 H, d, *J* 12, CH_2Ph), 7.31–7.40 (5 H, m, Ph) and 10.61 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 20.5 (4-Me), 19.51, 20.5, 29.56, 31.26, 31.93, 32.85 and 34.68 (7 × CH_2), 51.23, 51.46, 51.73, 52.18 and 54.74 (OMe), 65.63 (O*C*H_2Ph), 74.51 (C-4), 128.00 and 128.36 (C=*C*H), 115.02, 116.74, 130.00, 131.12, 131.88 and 136.18 (C=C) and 158.30, 160.26, 169.86, 170.46, 172.08, 172.98 and 173.61 (C=O and N=*C*–C=*C*); *m*/*z* (FD) 640 (M^+, 100%).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-1-(4-nitrobenzyloxy)-4,5-dihydrodipyrrin 19‡

A solution of 18-crown-6 (42 mg, 0.16 mmol) in benzene (2 cm^3) was stirred with silver carbonate (400 mg, 1.5 mmol) at room temperature for 30 min and then lactam **21** (100 mg, 0.16 mmol) and *p*-nitrobenzyl bromide (340 mg, 1.6 mmol) were added. The mixture was stirred overnight and then evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave *imino ether* **19** (37 mg, 72%) (Found: M^+, 761.2799. $C_{39}H_{43}N_3O_{13}$ requires *M*, 761.2796); δ_H($CDCl_3$, 400 MHz) 1.03 (s, 4-Me), 2.16 (1 H, d, *J* 15, 5-H_A), 2.50–2.60 and 2.97–3.02 (9 H total, 2 × m, 2 × CH_2CH_2 and 5-H_B), 3.41 and 3.43 (each 2 H, s, CH_2CO_2), 3.60, 3.62, 3.63 and 3.71 (each 3 H, s, OMe), 5.24 and 5.31 (each 1 H, d, *J* 12, OCH_2Ar) and 5.28 (2 H, s, OCH_2Ar), 7.23–7.46 (5 H, m, Ph), 8.15 and 8.17 (each 2 H, d, Ar) and 10.41 (1 H, br s, NH); δ_C($CDCl_3$) 19.67 (4-Me), 20.57, 20.65, 29.73, 31.47, 32.18, 32.85 and 34.92 (7 × CH_2), 51.44, 51.72, 51.94 and 52.46 (OMe), 65.77 (O*C*H_2Ph), 68.16 (O*C*H_2Ar), 75.11 (C-4), 123.76, 128.18, 128.42 and 128.58 (C=*C*H), 115.36, 117.13, 122.75, 127.02, 127.71, 130.03, 131.10, 131.93, 136.38, 143.60, 147.69 (C=C) and 159.38, 160.69, 169.44, 169.96, 172.22, 173.01 and 173.74 (C=O and N=*C*–C=*C*); *m*/*z* (FD) 761 (M^+, 100%).

9-Benzyloxycarbonyl-1-(4-bromobenzyloxy)-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 20‡

A solution of the lactam **21** (238 mg, 0.38 mmol) in dry benzene (4 cm^3) was stirred with silver carbonate (315 mg, 1.14 mmol) and 18-crown-6 (99 mg, 0.38 mmol) at room temperature for 1.5 h and then *p*-bromobenzyl bromide (946 mg, 3.8 mmol) was added. The mixture was stirred for 3 h, then heated at reflux for 1.5 h and then evaporated under reduced pressure. Purification by PLC, eluting with 2% methanol in diethyl ether, gave the *imino ether* **20** (187 mg, 62%) as an oil (Found: M^+, 794.2039. $C_{39}H_{43}{}^{79}BrN_2O_{11}$ requires *M*, 794.2050); δ_H($CDCl_3$, 400 MHz) 1.07 (3 H, s, 4-Me), 2.22–2.25 (7 H, m), 2.68 (2 H, t, *J* 7) and 2.92 (1 H, d, *J* 15, 2 × CH_2CH_2 and 5-H_2), 3.37–3.45 (4 H, m, 2 × CH_2CO_2), 3.59, 3.60, 3.60 and 3.66 (each 3 H, s, OMe), 5.01 and 5.06 (each 1 H, d, *J* 12, OCH_2Ar), 5.22–5.26 (2 H, m, OCH_2Ar), 6.95 and 7.46 (each 2 H, d, *J* 8, Ar), 7.20–7.30 (5 H, m, Ph) and 10.50 (1 H, br s, NH); *m*/*z* (FD) 794 and 796 (1 : 1; M^+, 100%).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one *N*,*N*′-boronate

A solution of crude 5-chloropyrrolenine **13** (52 mg, 80 μmol; from reaction of lactam **21** with triphosgene) in dry THF (3 cm^3) was stirred with a solution of lithium triethylborohydride in THF (1.0 mol dm^{-3}; 160 mm^3, 160 μmol) initially at 0 °C and then at room temperature for 1 h. Saturated aqueous ammonium chloride (2 cm^3) and ethyl acetate (10 cm^3) were added and the organic phase was separated, dried and evaporated under reduced pressure. Purification by flash chromatography on silica, eluting with diethyl ether, gave the N,N′-*boronate* of lactam **21** (28 mg, 53%) as an oil (Found: MH^+, 653.2490. $C_{32}H_{37}BN_2O_{12}$ requires *MH*, 653.2518); λ_{max}(CH_2Cl_2)/

‡ With Dr A. Philippides.

nm 282; ν_{max}($CHCl_3$)/cm^{-1} 3691, 2954, 1778, 1736, 1438, 1345, 1173 and 1117; δ_H($CDCl_3$, 400 MHz) 1.23 (3 H, s, 4-Me), 2.42–2.56 (2 H, m), 2.63 (4 H, m) and 2.71–2.87 (2 H, m, 2 × CH_2CH_2), 2.63 and 3.11 (each 1 H, d, *J* 16, 5-H_2), 3.39 (2 H, s, CH_2CO_2), 3.52 and 3.57 (each 1 H, d, *J* 16, CH_2CO_2), 3.60, 3.63, 3.66 and 3.74 (each 3 H, s, OMe), 5.17 and 5.43 (each 1 H, d, *J* 12.5, OCH_2Ph) and 7.28–7.41 (5 H, m, Ph); δ_C($CDCl_3$, 100 MHz) 19.5 and 19.9 ($CH_2CH_2CO_2$), 21.8 (4-Me), 29.4, 30.9, 31.1, 31.1 and 34.5 (5 × CH_2), 51.6, 51.7, 52.3 and 52.8 (OMe), 65.0 (OCH_2Ph), 67.2 (C-4), 116.0, 121.6, 130.1, 134.4, 135.8, 141.3 and 153.7 (C=C), 128.2, 128.5 and 128.6 (C=*C*H), 160.8 (CO_2Bn), 162.2, 166.8, 170.8, 173.1 and 173.2 (C=O); *m*/*z* (+FAB) 653 (MH^+, 55%) and 545 (MH − BnOH, 100).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,10-dimethyl-4,5-dihydrodipyrrin-1(10*H*)-one 22

A solution of crude 5-chloropyrrolenine **13** (60 mg, 90 μmol; produced, as described above, by the action of triphosgene on lactam **21**) in dry THF (2 cm^3) was stirred with a solution of zinc borohydride[34] in diethyl ether (0.14 mol dm^{-3}; 1.32 cm^3, 180 μmol) at room temperature for 3 h. Saturated aqueous ammonium chloride (1 cm^3) was added and the phases were separated. The organic phase was dried and evaporated under reduced pressure. Purification by flash chromatography on silica, eluting with diethyl ether–methanol (20:1), gave N-*methyl lactam* **22** (27 mg, 44%) as an oil (Found: MH^+, 641.2715. $C_{33}H_{40}N_2O_{11}$ requires *MH*, 641.2710); λ_{max}(CH_2Cl_2)/nm 277; ν_{max}($CHCl_3$)/cm^{-1} 3319, 2954, 2930, 1731, 1689, 1438, 1252 and 1174; δ_H($CDCl_3$, 400 MHz) 1.30 (3 H, s, 4-Me), 2.33–3.01 (11 H, 2 × CH_2CH_2, 2 × C$H_A$$H_B$$CO_2$ and 5-$H_A$$H_B$), 2.68 (3 H, s, NMe), 3.30 (1 H, d, *J* 19.5, $CH_AH_BCO_2$), 3.37 (1 H, d, *J* 18, $CH_AH_BCO_2$), 3.50 (1 H, d, *J* 16, 5-H_AH_B), 3.59, 3.60, 3.64 and 3.69 (each 3 H, s, OMe), 5.17 and 5.33 (each 1 H, d, *J* 12.5, OCH_2Ph), 7.25–7.42 (5 H, m, Ph) and 9.70 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 20.1 and 20.4 (2 × $CH_2CH_2CO_2$), 22.4 (4-Me), 24.5, 29.7, 29.8, 30.4, 31.0 and 34.5 (5 × CH_2 and NMe), 51.4, 51.6, 52.1 and 52.9 (OMe), 65.7 (OCH_2Ph), 66.1 (C-4), 128.0 and 128.4 (C=*C*H), 115.2, 116.4, 128.2, 129.8, 136.2, 136.5 and 146.5 (C=C), 160.1 (CO_2Bn) and 169.3, 171.1, 172.1, 173.6 and 173.8 (C=O); *m*/*z* (+FAB) 641 (M^+, 40%) and 372 ($C_{20}H_{22}NO_6$, 100).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,10-dimethyl-1,4,5,10-tetrahydrodipyrrin 23

A solution of crude 5-chloropyrrolenine **13** (140 mg, 0.2 mmol; produced, as described above, by the action of triphosgene on lactam **21**) in dry THF (2.5 cm^3) was stirred with a solution of zinc borohydride[34] in diethyl ether (0.15 mol dm^{-3}; 1.45 cm^3, 0.2 mmol) at room temperature for 12 h, then cooled to 0 °C. Glacial acetic acid (0.5 cm^3) was dripped in over a period of 30 min, then saturated aqueous disodium EDTA (1 cm^3) was added and the phases were separated. The organic phase was dried and evaporated under reduced pressure. Purification by PLC, eluting with ethyl acetate, gave N-*methyl amine* **23** (37 mg, 25%) as an oil; λ_{max}(CH_2Cl_2)/nm 281; ν_{max}($CHCl_3$)/cm^{-1} 3030, 2953, 1732, 1696, 1437, 1248 and 1171; δ_H($CDCl_3$, 400 MHz) 0.96 (3 H, s, 4-Me), 2.18–2.34 and 2.49–2.62 (each 4 H, m, 2 × CH_2CH_2), 2.30 (3 H, s, NMe), 2.66 and 2.88 (each 1 H, d, *J* 16), 2.86–2.91 and 3.00–3.04 (each 1 H, m), 3.19, 3.37 and 3.43 (each 1 H, d, *J* 13) and 3.50–3.63 (1 H, obscured, 4 × CH_2), 3.50, 3.57, 3.60 and 3.63 (each 3 H, s, OMe), 5.18 and 5.24 (each 1 H, d, *J* 12.5, CH_2Ph), 7.30–7.39 (5 H, m, Ph) and 11.02 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.5 (4-Me), 20.4 and 22.4 ($CH_2CH_2CO_2$), 29.4, 29.9, 30.6, 31.7 and 38.7 (5 × CH_2), 34.8 (NMe), 51.4, 51.6, 52.0 and 52.0 (OMe), 59.9 (CH_2N), 65.4 (OCH_2Ph), 71.6 (C-4), 113.5, 116.4, 129.4, 132.6, 133.1, 136.2 and 136.4 (C=C), 128.0, 128.1 and 128.4 (C=*C*H), 160.3 (CO_2Bn) and 171.1, 172.3, 173.1 and 173.7 (C=O); *m*/*z* (+FAB) 627 (MH^+, 40%), 372 ($C_{20}H_{22}NO_6$, 10) and 254 (100).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-1-chloro-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin 30

A stirred solution of dipyrrolic lactam **28**[8] (250 mg, 215 μmol) and 4-(dimethylamino)pyridine (80 mg, 650 μmol) in dry dichloromethane (15 cm^3) was treated dropwise with a solution of phosgene (0.65 mmol) in toluene (0.5 cm^3) at room temperature under argon, then stirred for 2 h and the solvent evaporated under a stream of argon. Purification by PLC, eluting with diethyl ether, gave *chloropyrrolenine* **30** (200 mg, 86% based on unrecovered starting material) as a water-sensitive gum; ν_{max}(CH_2Cl_2)/cm^{-1} 3350, 2950, 1740, 1700, 1245 and 1150; δ_H($CDCl_3$, 400 MHz) 2.31–2.62 (12 H, m), 3.03 (2 H, t, *J* 8) and 3.16 and 3.19 (each 1 H, d, *J* 15, 3 × CH_2CH_2 and CH_2CCH_2), 3.34 and 3.45 (each 1 H, d, *J* 17, CH_2CO_2), 3.57 (2 H, s, CH_2CO_2), 3.58, 3.60, 3.60, 3.62, 3.63 and 3.79 (each 3 H, s, OMe), 3.71 and 3.80 (each 1 H, d, *J* 17, CH_2CO_2), 5.01 and 5.13 (each 1 H, d, *J* 12, OCH_2CBr_3), 5.21 and 5.29 (each 1 H, d, *J* 12, OCH_2Ph), 7.30–7.41 (5 H, m, Ph) and 9.80 and 10.10 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.01, 20.05, 20.27, 29.28, 29.66, 30.21, 30.42, 31.39, 31.52, 34.68, 34.83 and 36.72 (11 × CH_2 and CBr_3), 51.39, 51.53, 51.75, 51.92 and 53.09 (OMe), 65.59 (OCH_2Ph), 76.49 (OCH_2CBr_3), 83.38 (C-4), 116.07, 116.34, 118.29, 122.04, 122.33, 127.84, 130.49, 131.20, 136.11 and 138.80 (C=C) and 158.10, 160.11, 161.81, 170.82, 171.12, 172.12, 172.45, 173.39 and 173.47 (C=O and C=N); *m*/*z* (FD) 1173, 1175, 1177, 1179 and 1181 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1-phenylseleno-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin 31

A solution of chloropyrrolenine **30** (210 mg, 178 μmol) in dry degassed dichloromethane (5 cm^3) was stirred with a solution of selenophenol[16] (314 mg, 2.0 mmol) in dichloromethane (3 cm^3) at room temperature under argon for 30 min, then added to saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with dichloromethane (4 × 15 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave *phenylselenopyrrolenine* **31** (78 mg, 34%) as a gum (Found: C, 47.7; H, 4.55; N, 3.3. $C_{52}H_{56}Br_3N_3O_{16}Se$ requires C, 48.1; H, 4.35; N, 3.25%); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 1715, 1695, 1160 and 1070; δ_H($CDCl_3$, 400 MHz) 2.28–2.58 (14 H, m, 3 × CH_2CH_2 and C$H_A$$H_BCCH_A$$H_B$), 3.09–3.17 (6 H, m, 2 × CH_2CO_2 and $CH_AH_BCCH_AH_B$), 3.53, 3.58, 3.62 and 3.76 (18 H, 4 × s, 6 × OMe), 3.66 and 3.82 (each 1 H, d, *J* 17, CH_2CO_2), 5.07 and 5.12 (each 1 H, d, *J* 12, CH_2CBr_3), 5.22 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 7.26–7.37 and 7.41–7.43 (10 H, m, 2 × Ph) and 9.67 and 9.96 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.98, 20.43, 20.55, 29.19, 30.08, 30.33, 30.61, 31.07, 32.22, 34.83, 35.00 (11 × CH_2), 51.39, 51.49, 51.72, 53.02 (OMe), 65.41 (OCH_2Ph), 76.68 (OCH_2CBr_3), 85.72 (C-4), 115.88, 116.09, 118.17, 121.73, 122.07, 127.93, 128.10, 128.35, 129.00, 129.65, 130.53, 131.46, 135.32, 136.36, 141.50 and 154.90 (C=C) and 158.53, 160.15, 171.28, 171.86, 172.11, 172.57, 173.30 and 173.54 (C=O and C=N); *m*/*z* (FD) 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303 and 1304 (ratio 4:11:5:14:12:20:14:9:7:4, M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1-phenylseleno-4,5-dihydrodipyrrin 32

Dipyrrolic lactam **29**[11] (80 mg, 80 μmol) was reacted with phos-

gene, as described above for the synthesis of **30**, followed by selenophenol, as described above for the synthesis of **31**. Purification by PLC, eluting with methanol–diethyl ether (1 : 40), gave the *phenylselenopyrrolenine* **32** (42 mg, 49%) as a gum (Found: M^+, 1123.3248. $C_{57}H_{61}N_3O_{16}{}^{80}Se$ requires *M*, 1123.3217); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 1715, 1700, 1170 and 1065; $\delta_H(CDCl_3$, 400 MHz) 2.26–2.35, 2.40–2.52 and 2.80–3.22 (18 H, m, 3 × CH_2CH_2, CH_2CCH_2 and CH_2CO_2), 3.47 (2 H, s, CH_2CO_2), 3.53, 3.54, 3.57, 3.59, 3.61 and 3.70 (each 3 H, s, OMe), 3.65 and 3.83 (each 1 H, d, *J* 17, CH_2CO_2), 5.22 and 5.28 (each 1 H, d, *J* 13, CH_2Ph), 5.22 and 5.31 (each 1 H, d, *J* 13, CH_2Ph), 7.27–7.39 (15 H, m, 3 × Ph) and 9.68 and 9.71 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.00, 20.50, 29.20, 30.18, 30.31, 30.62, 31.07, 32.17, 34.69 and 34.84 (CH_2), 51.32, 51.44, 51.68, 51.74 and 52.87 (OMe), 65.38 and 65.45 (OCH_2Ph), 85.85 (C-4), 115.49, 117.16, 118.16, 121.72, 122.11, 125.00, 127.91, 128.09, 128.36, 128.38, 129.65, 129.70, 129.80, 135.34, 136.43 and 141.51 (C=C) and 154.89, 160.12, 160.18, 171.27, 171.88, 172.17, 172.60, 173.29 and 173.61 (C=O and C=N); *m*/*z* (FD) 1123 (M^+ for ^{80}Se, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 36

A solution of lactam **35**[8] (52 mg, 53 μmol) in benzene (3 cm^3) was heated at reflux with Lawesson's reagent (12 mg, 29 μmol) under argon for 45 min and then evaporated under reduced pressure. Purification on a column of silica gel PF_{254} (5 × 1 cm), eluting with dichloromethane and then diethyl ether, gave *thiolactam* **36** (43 mg, 81%) as an oil (Found: M^+, 999.3428. $C_{51}H_{57}N_3O_{16}S$ requires *M*, 999.3459); λ_{max}(EtOH)/nm 281; $\nu_{max}(CHCl_3)/cm^{-1}$ 3430, 3300, 2950, 1720s, 1690, 1570, 1435, 1180 and 1075; $\delta_H(CDCl_3$, 400 MHz) 2.45–2.51 (8 H, m) and 2.89–3.01 (4 H, m, 3 × CH_2CH_2), 2.82 and 3.06 (each 2 H, d, *J* 15, 2 × 4-CH_2), 3.32 and 3.50 (each 2 H, d, *J* 17, CH_2CO_2), 3.49 (2 H, s, CH_2CO_2), 3.55 and 3.72 (each 3 H, s, OMe), 3.60 and 3.64 (each 6 H, s, 2 × OMe), 5.20 and 5.27 (each 2 H, d, *J* 12, CH_2Ph), 7.28–7.39 (10 H, m, Ph), 9.46 (1 H, br s, NH) and 9.62 (2 H, br s, NH); $\delta_C(CDCl_3$, 100.57 MHz, DEPT) 20.68 (3 C), 29.61 (2 C), 31.01 (3 C), 31.67 and 34.64 (2 C, CH_2), 51.45 (2 C), 52.27 (2 C) and 52.99 (1 C, OMe), 66.00 (2 × OCH_2), 74.16 (C-4), 115.90, 118.33, 128.90 (br) and 130.24 (each 2 C, pyrrole-C), 128.00, 128.15 and 128.40 (phenyl-CH), 135.98 (phenyl-C), 143.23 and 147.84 (C=C), 160.65 (2 C), 171.05, 172.80 (2 C), 173.44 and 173.57 (2 C, C=O) and 197.50 (C=S); *m*/*z* (FD) 999 (M^+, 100%).

4-[4-(2-Methoxycarbonylethyl)-3-(methoxycarbonylmethyl)-pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 38

A solution of lactam dibenzyl ester **35**[8] (100 mg) in methanol (5 cm^3) was stirred with 10% palladium-on-charcoal (10 mg) under an atmosphere of hydrogen until uptake of gas ceased (45 min), then filtered through Celite and evaporated. A solution of the residue in trifluoroacetic acid (5 cm^3) was allowed to stand for 7 h at room temperature under argon, then added to water (50 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The extract was washed with 5% aqueous sodium hydrogen carbonate (30 cm^3), dried and evaporated. Purification on a short column of silica gel PF_{254} (5 × 2.5 cm diam.), eluting with diethyl ether–methanol (19 : 1), gave *lactam* **38** (59 mg, 81%) as a gum (Found: M^+, 715.2950. $C_{35}H_{45}N_3O_{13}$ requires *M*, 715.2952); λ_{max} end absorption only; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3350br, 2950, 1720, 1685, 1440, 1175 and 1010; $\delta_H(CDCl_3$, 400 MHz) 2.41 and 2.46 (each 2 H, m, 2-CH_2CH_2), 2.49 and 2.66 (each 4 H, m, 2 × $CH_2CH_2CO_2$), 2.72 and 2.95 (each 2 H, d, *J* 15, CH_2CCH_2), 3.25 and 3.38 (each 2 H, d, *J* 16, 2 × CH_2CO_2), 3.48 (2 H, s, 3-CH_2), 3.62 and 3.79 (each 3 H, s, OMe), 3.64 and 3.66 (each 6 H, s, 2 × OMe), 6.33 (2 H, d, *J* 3, 2 × α-H), 7.57 (1 H, br s, lactam-NH) and 8.75 (2 H, br s, 2 × pyrrole-NH); *m*/*z* (FD) 715 (M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 40

A solution of lactam **28**[8] (120 mg, 104 μmol) and Davy's reagent[20] **44** (16.3 mg, 57 μmol) in dry 1,2-dimethoxyethane (1 cm^3) was stirred at room temperature for 20 min and then evaporated under reduced pressure. Purification by PLC, eluting with methanol–diethyl ether (1 : 40), gave the *thiolactam* **40** (114 mg, 94%) as a gum (Found: C, 47.3; H, 4.65; N, 3.55. $C_{46}H_{52}Br_3N_3O_{16}S$ requires C, 47.0; H, 4.5, N, 3.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400, 2960, 1730, 1700, 1430 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.46–2.58 and 2.71–2.76 (12 H, m, 3 × CH_2CH_2), 2.89 and 3.20 (each 1 H, d, *J* 15) and 3.06 and 3.12 (each 1 H, d, *J* 15, CH_2CCH_2), 3.21 and 3.45 (each 1 H, d, *J* 17, CH_2CO_2), 3.57, 3.58, 3.59, 3.60, 3.61 and 3.81 (each 3 H, s, OMe), 3.57–3.81 (4 H, obscured, 2 × CH_2CO_2), 5.04 and 5.12 (each 1 H, d, *J* 12, CH_2CBr_3), 5.19 and 5.24 (each 1 H, d, *J* 12, CH_2Ph), 7.27–7.39 (5 H, m, Ph) and 9.29, 9.44 and 10.26 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.16, 20.34, 20.85, 29.20, 30.34, 30.54, 31.42, 31.79, 34.59 and 34.93 (CH_2 and CBr_3), 51.48, 51.86, 52.23, 52.53 and 53.31 (OMe), 65.64 (OCH_2Ph), 73.49 (C-4) and 76.67 (CH_2CBr_3), 115.62, 119.46, 122.14, 122.51, 129.53, 131.11, 135.25, 144.07 and 147.29 (C=C), 160.16, 161.99, 171.70, 171.78, 171.95, 172.05 and 173.70 (C=O) and 197.73 (C=S); *m*/*z* (FD) 1171, 1173, 1175, 1177 (1 : 3 : 3 : 1, M^+, 100%).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 41

A solution of tribromoethyl ester **28**[8] (100 mg, 86 μmol) in glacial acetic acid (2 cm^3) was stirred with zinc dust (200 mg) under argon at room temperature for 20 min and then filtered. The filtrate was added to aqueous sodium carbonate (15 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The combined extracts were dried and evaporated under reduced pressure. A solution of the residue in freshly distilled trifluoroacetic acid (1 cm^3) was stirred at room temperature under argon for 7 h, then poured into water (20 cm^3) and extracted with dichloromethane (4 × 15 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with 5% methanol in diethyl ether, gave the *α-free pyrrolic lactam* **41** (62 mg, 85%) as a foam (Found: C, 60.8; H, 6.0; N, 4.8. $C_{43}H_{51}N_3O_{15}$ requires C, 60.8; H, 6.05; N, 4.9%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400, 2950, 1720, 1685, 1435 and 1175; $\delta_H(CDCl_3$, 400 MHz) 2.39–2.50 (8 H, m) and 2.63–2.68 (4 H, m, 3 × CH_2CH_2), 2.74 and 3.11 (each 1 H, d, *J* 15) and 2.81 and 2.99 (each 1 H, d, *J* 15, CH_2CCH_2), 3.20 and 3.38 (each 1 H, d, *J* 16, CH_2CO_2), 3.47 and 3.55 (each 1 H, d, *J* 16, CH_2CO_2), 3.57, 3.59, 3.60, 3.63, 3.64 and 3.77 (each 3 H, s, 6 × OMe), 3.57–3.77 (2 H, obscured, CH_2CO_2), 5.17 and 5.27 (each 1 H, d, *J* 12, CH_2Ph), 6.34 (1 H, d, *J* 2, α-H), 7.28–7.38 (5 H, m, Ph) and 7.41, 8.91 and 9.54 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.14, 19.62, 20.61, 29.80, 30.43, 30.59, 30.74, 31.62, 34.69 and 34.74 (CH_2), 51.45, 51.54, 51.75, 52.04 and 52.95 (OMe), 65.68 and 66.68 (C-4 and OCH_2Ph), 112.25, 114.61, 118.99, 120.87, 121.87, 122.28, 123.25, 127.98, 128.19, 128.33, 136.00, 137.21 and 149.83 (C=C) and 160.48, 171.86, 172.38, 173.29, 173.40, 173.51 and 173.62 (C=O); *m*/*z* (FD) 849 (M^+, 100%).

General procedure for the conversion of lactams into thiolactams

A solution of the lactam (0.44 mmol) in dry benzene (24 cm^3) was heated at reflux under argon with Lawesson's reagent (95 mg, 0.23 mmol) for 45 min and then evaporated under reduced pressure. Purification by chromatography gave the thiolactam.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-thione 46

Method A. Lactam **21** was reacted with Lawesson's reagent according to the above general procedure. Purification by flash chromatography, eluting with diethyl ether, gave *thiolactam* **46** (72%) which crystallised from aqueous methanol, mp 114–116 °C (Found: C, 60.2; H, 6.2; N, 4.3%; M^+, 642.2251. $C_{32}H_{38}N_2O_{10}S$ requires C, 59.8; H, 6.0; N, 4.35%; *M*, 642.2247); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1740s, 1710, 1680, 1585, 1490, 1450, 1200 and 1065; $\delta_H(CDCl_3$, 250 MHz) 1.38 (3 H, s, 4-Me), 2.45–2.60 (6 H, m) and 2.68–2.80 (2 H, m, 2 × CH_2CH_2), 2.81 and 3.00 (each 1 H, d, *J* 15, 5-H_2), 3.32 and 3.70 (each 1 H, d, *J* 17, CH_2CO_2), 3.35 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.59, 3.62, 3.71 and 3.77 (each 3 H, s, OMe), 5.19 and 5.30 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.27–7.41 (5 H, m, Ph) and 9.13 and 10.17 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 22.43 (4-Me), 20.47, 20.53, 29.75, 31.92, 31.98, 32.72 and 34.73 (CH_2), 51.29, 51.39, 52.56 and 52.80 (OMe), 65.75 (Ph*C*H_2), 70.86 (C-4), 127.90, 128.11 and 128.34 (phenyl-CH), 115.12, 118.24, 128.80, 130.00, 136.12 and 149.95 (C=C), 160.53, 170.94 and 173.55 (C=O) and 196.52 (C=S); *m*/*z* (FD) 642 (M^+, 100%).

Method B. Dichloromethane (3 cm^3) at 0 °C was saturated with hydrogen sulfide and then stirred with a solution of the halopyrrolenines **13/14** (36 mg, 50 μmol) in dichloromethane (2 cm^3) for 1 h at room temperature. The solvent was evaporated in a stream of nitrogen. Purification by chromatography gave the thiolactam **46** (25 mg, 80%).

General procedure for desulfurisation with nickel boride

A stirred solution of nickel(II) chloride hexahydrate (1.19 g, 5 mmol) and boric acid (4.0 g) in methanol (70 ml) was cooled in ice and a solution of sodium borohydride (380 mg, 10 mmol) in water (5 ml) was added over 1 min. After 5 min the black precipitate was allowed to settle and the supernatant was decanted. The precipitate of nickel boride was washed with methanol (3 × 20 ml) decanting excess methanol after each washing and used immediately without drying.

A solution of the thiolactam (0.2 mmol) in methanol (6 cm^3) and acetic acid (0.6 cm^3) was added to a suspension of the above nickel boride in methanol (15 cm^3). The mixture was stirred under hydrogen at room temperature for 30 min, then filtered, washing the residue with methanol (15 cm^3). The filtrate was mixed with 5% aqueous sodium hydrogen carbonate (200 cm^3), and extracted with dichloromethane (4 × 50 cm^3). The combined extracts were dried, evaporated under reduced pressure and purified by chromatography as described.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 49

The thiolactam **46** was reduced with nickel boride according to the general procedure above. Purification by PLC, eluting with ethanol–diethyl ether (1 : 9), gave *pyrrolenine* **49** (45%) as a gum (Found: M^+, 610.2535. $C_{32}H_{38}N_2O_{10}$ requires *M*, 610.2527); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3320, 2960, 2850, 1730s, 1700, 1430, 1210 and 1160; $\delta_H(CDCl_3$, 400 MHz) 1.10 (3 H, s, 4-Me), 2.23 and 3.10 (each 1 H, d, *J* 15, 5-H_2), 2.46–2.53 and 2.96–3.02 (6 H, m) and 2.61 (2 H, t, *J* 7, 2 × CH_2CH_2), 3.37 and 3.47 (each 1 H, d, *J* 17, CH_2CO_2), 3.38 and 3.48 (each 1 H, d, *J* 16, CH_2CO_2), 3.60, 3.64 and 3.69 (12 H, each s, 4 × OMe), 5.23 and 5.32 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.30–7.42 (5 H, m, Ph), 7.92 (1 H, s, 2-H) and 10.20 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.60 (4-Me), 20.43, 20.53, 29.61, 31.12, 32.15, 32.68 and 34.72 (CH_2), 51.23, 51.61, 51.76 and 52.29 (OMe), 65.46 (Ph*C*H_2), 83.30 (C-4), 115.22, 117.15, 129.72, 131.20, 137.41 and 157.85 (C=C), 127.89, 128.07 and 128.38 (C=*C*H), 160.46, 172.20 and 173.66 (C=O) and 164.78 (C-2); *m*/*z* (FD) 610 (M^+, 100%).

Amine **47** (*ca*. 5%) was also found at lower R_f. When the reaction time was extended to 15 h, *amine* **47** (51%) became the only product isolated (Found: M^+, 612.2682. $C_{32}H_{40}N_2O_{10}$ requires *M*, 612.2683); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3280, 2940, 1740s, 1700, 1450, 1260, 1160 and 1090; $\delta_H(CDCl_3$, 250 MHz) 1.16 (3 H, s, 4-Me), 2.29–2.36 (4 H, m) and 2.51 and 2.99 (each 2 H, t, *J* 7, 2 × CH_2CH_2), 2.48 and 2.58 (each 1 H, d, *J* 15, 5-H_2), 3.09–3.15 (3 H, m, CH_2CO_2 and NC*H*$_A$H$_B$), 3.37 and 3.49 (each 1 H, d, *J* 16, CH_2CO_2), 3.52 (1 H, d, *J* 15, NCH$_A$*H*$_B$), 3.59, 3.61, 3.64 and 3.65 (each 3 H, s, OMe), 5.21 and 5.32 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.27–7.42 (5 H, m, Ph) and 10.74 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 100 MHz) 20.38 (4-Me), 22.33, 25.74, 29.33, 29.97, 31.56, 33.86 and 34.61 (CH_2), 50.82, 51.09, 51.37 and 51.72 (OMe), 53.07 (C-2), 65.15 (Ph*C*H_2), 70.88 (C-4), 114.80, 116.93, 132.44, 132.55, 136.43 and 138.99 (C=C), 127.65, 128.15 and 129.60 (C=*C*H) and 160.28, 171.75, 172.03, 172.74 and 173.23 (C=O); *m*/*z* (FD) 612 (M^+, 100%).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-1-methylthio-4,5-dihydrodipyrrin 48

Thiolactam **46** (375 mg, 0.584 mmol) was dissolved in redistilled trifluoroacetic acid (10 cm^3) and distilled trimethyl orthoformate (10 cm^3) was immediately added. The solution was stirred in the dark under argon for 30 min and then evaporated under reduced pressure. The residue was twice dissolved in dichloromethane (20 cm^3) and evaporated under reduced pressure and then purified by flash chromatography (40 × 2.5 cm), eluting with diethyl ether, to give the *thioimidate* **48** (365 mg, 95%) as a gum (Found: M^+, 656.2404. $C_{33}H_{40}N_2O_{10}S$ requires *M*, 656.2403); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1720s, 1690, 1440, 1190 and 1075; $\delta_H(CDCl_3$, 400 MHz) 1.05 (3 H, s, 4-Me), 2.28 (3 H, s, S-Me), 2.30 and 2.99 (each 1 H, d, *J* 15, 5-H_2), 2.53–2.58 and 2.98–3.00 (8 H, m, 2 × CH_2CH_2), 3.39 and 3.44 (each 2 H, s, CH_2CO_2), 3.61, 3.64, 3.64 and 3.69 (each 3 H, s, OMe), 5.22 and 5.29 (each 1 H, d, *J* 12, C*H*$_2$Ph), 7.33–7.40 (5 H, m, Ph) and 10.67 (1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 12.75 (SMe), 19.9 (4-Me), 19.9, 20.55, 29.70, 31.42, 32.55, 32.77 and 34.81 (CH_2), 51.21, 51.54, 51.72 and 52.19 (OMe), 65.70 (*C*H_2Ph), 81.40 (C-4), 128.08 and 128.50 (C=*C*H), 115.21, 130.22, 136.38, 136.44 and 157.82 (C=C) and 160.39, 169.76, 172.06, 172.74 and 173.61 (C=O and C-2); *m*/*z* (FD) 656 (M^+, 100%).

9-Benzyloxycarbonyl-4-[5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin 51

Thiolactam **36** was reduced with nickel boride following the general procedure described above. Purification by PLC, eluting with diethyl ether–methanol (19 : 1), gave *pyrrolenine* **51** (33 mg, 46%) as a gum; λ_{max}(EtOH)/nm 281; $\nu_{max}(CHCl_3)$ 3420, 3320, 2950, 1725, 1685, 1445, 1435, 1255, 1175 and 1080; $\delta_H(CDCl_3$, 400 MHz) 2.33 (2 H, m), 2.48 (6 H, m) and 2.87–3.00 (4 H, m, 3 × CH_2CH_2), 2.40 and 3.10 (each 2 H, d, *J* 15, 2 × 4-CH_2), 3.32 and 3.37 (each 2 H, d, *J* 16, 2 × CH_2CO_2), 3.45 (2 H, s, CH_2CO_2), 3.58 and 3.59 (each 6 H, s, 2 × OMe), 3.58 and 3.71 (each 3 H, s, OMe), 5.26 and 5.30 (each 2 H, d, *J* 12, C*H*$_2$Ph), 7.30–7.42 (10 H, m, 2 × Ph), 7.80 (1 H, s, 2-H) and 10.03 (2 H, br s, NH); $\delta_C(CDCl_3$, 100.57 MHz) 20.60, 20.65 (2 C), 29.56 (2 C), 30.14, 31.13, 32.42 (2 C) and 34.92 (2 C, CH_2), 51.50 (2 C), 51.87, 51.98 (2 C) and 52.99 (OMe), 65.71 (2 × OCH_2), 86.13 (C-4), 115.62, 117.37, 129.85 and 130.11 (each 2 C, pyrrole-C), 128.14, 128.34, 128.57 and 136.48 (2 × Ph), 140.47 and 156.04 (C=C), 166.33 (C-2) and 160.42 (2 C), 171.36, 172.42 (2 C), 172.77 and 173.79 (2 C, C=O); *m*/*z* (FD) 967 (M^+, 100%).

2,7-Bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one 54

Iodopyrrole **12** and acetoxymethylpyrrole **53**[8] were reacted by the procedure described[11] for the synthesis of **29** except that the hydrolysis of the halopyrrolenines required 15 h. Purification by flash chromatography, eluting with 0–3% ethanol in diethyl

ether, gave *lactam* **54** (29%) as a gum (Found: M^+, 797.9630. $C_{27}H_{33}{}^{79}Br_3N_2O_{11}$ requires *M*, 797.9635); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3250, 2960, 1720s, 1430, 1210 and 1040; $\delta_H(CDCl_3$, 400 MHz) 1.40 (3 H, s, 4-Me), 2.46–2.67 (6 H, m) and 2.72 (2 H, t, *J* 7, 2 × CH_2CH_2), 2.78 and 3.14 (each 1 H, d, *J* 15, 5-H_2), 3.36 and 3.72 (each 1 H, d, *J* 17, CH_2CO_2), 3.63, 3.65, 3.68 and 3.79 (each 3 H, s, OMe), 3.63–3.79 (1 H, obscured) and 4.09 (1 H, d, *J* 17, CH_2CO_2), 4.99 and 5.13 (each 1 H, d, *J* 17, CH_2CBr_3), 6.54 (1 H, br s, lactam-NH) and 10.08 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 62.5 MHz) 24.27 (4-Me), 19.22, 19.82, 30.66, 30.93, 31.33, 33.29, 34.42 and 36.11 (CH_2 and CBr_3), 51.52, 51.85, 51.91 and 52.93 (OMe), 63.11 (C-4), 76.68 (CH_2O), 117.93, 122.60, 123.55, 129.96, 135.89 and 150.89 (C=C) and 158.78, 170.82, 171.44, 171.62 and 174.07 (C=O); *m*/*z* (FD) 798, 800, 802 and 804 (1 : 3 : 3 : 1, M^+, 100%).

2,7-Bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 55

Lactam **54** was reacted with Lawesson's reagent according to the above general procedure. The residue was purified by flash chromatography, eluting with diethyl ether, to give *thiolactam* **55** as a foam (Found: M^+, 813.9374. $C_{27}H_{33}{}^{79}Br_3N_2O_{10}S$ requires *M*, 813.9406); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1725s, 1430, 1200 and 1160; $\delta_H(CDCl_3$, 400 MHz) 1.45 (3 H, s, 4-Me), 2.57–2.80 (8 H, m, 2 × CH_2CH_2), 2.83 and 3.24 (each 1 H, d, *J* 15, 5-H_2), 3.38 and 3.72 (each 1 H, d, *J* 17, CH_2CO_2), 3.64, 3.65, 3.74 and 3.79 (each 3 H, s, OMe), 3.75 and 4.08 (each 1 H, d, *J* 17, CH_2CO_2), 5.01 and 5.11 (each 1 H, d, *J* 17, CH_2CBr_3), 8.74 (1 H, br s, thiolactam-NH) and 10.12 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 62.5 MHz) 23.04 (4-Me), 19.11, 21.08, 31.02, 31.92, 32.76, 34.13 and 36.17 (CH_2 and CBr_3), 51.51, 51.93, 52.21 and 53.02 (OMe), 70.87 (C-4), 76.74 (CH_2O), 118.14, 122.61, 123.80, 129.27, 141.96 and 149.44 (C=C), 158.80, 170.79, 171.52, 173.55 and 174.77 (C=O) and 196.55 (C=S); *m*/*z* (FD) 814, 816, 818 and 820 (1 : 3 : 3 : 1, M^+, 100%).

9-Carboxy-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-thione 56

A solution of thiolactam **55** (500 mg, 0.61 mmol) in glacial acetic acid (30 cm^3) was stirred with zinc dust (1.30 g) for 20 min, then filtered, mixed with water (50 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. Purification by flash chromatography (20 × 2 cm), eluting with ethanol–diethyl ether (1 : 9), gave *acid* **56** (302 mg, 90%) as a gum (Found: M^+, 552.1772. $C_{25}H_{32}N_2O_{10}S$ requires *M*, 552.1776); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 3400–2700, 1730s, 1650, 1450 and 1160; $\delta_H(CDCl_3$, 400 MHz) 1.23 (3 H, s, 4-Me), 2.45–2.52 and 2.67–2.72 (8 H, m, 2 × CH_2CH_2), 2.71 and 3.19 (each 1 H, d, *J* 15, 5-H_2), 3.52 and 3.58 (each 1 H, d, *J* 16, CH_2CO_2), 3.64, 3.64, 3.68 and 3.74 (each 3 H, s, OMe), 3.83 (2 H, s, CH_2CO_2) and 9.99 and 10.49 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.70 (4-Me), 19.37, 20.92, 30.94, 31.42, 32.11, 32.31 and 34.69 (CH_2), 51.65, 51.82, 52.12, 52.73 (OMe), 72.09 (C-4), 119.42, 123.13, 123.98, 129.66, 140.35, 151.99 (C=C), 164.35, 169.83, 172.55 and 173.64 (C=O) and 196.19 (C=S); *m*/*z* (FD) 552 (M^+, 100%).

2,7-Bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-1-methylthio-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin 57

Thiolactam **55** was treated with trifluoroacetic acid and trimethyl orthoformate according to the procedure described above for the synthesis of **48**. Purification by flash chromatography, eluting with diethyl ether, gave *thioimidate* **57** (92%) as a gum (Found: M^+, 827.9551. $C_{28}H_{35}{}^{79}Br_3N_2O_{10}S$ requires *M*, 827.9562); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2970, 1725 and 1180; $\delta_H(CDCl_3$, 400 MHz) 1.50 (3 H, s, 4-Me), 2.27–2.63 (9 H, m, 2 × CH_2CH_2 and 5-H_A), 2.81 (3 H, s, SMe), 3.43 (1 H, d, *J* 15, 5-H_B), 3.55 and 3.66 (each 1 H, d, *J* 16, CH_2CO_2), 3.64, 3.64, 3.65 and 3.74 (each 3 H, s, OMe), 3.74 and 3.93 (each 1 H, d, *J* 17, CH_2CO_2), 5.02 and 5.14 (each 1 H, d, *J* 12, CH_2CBr_3) and 10.05 (1 H, br s, NH); $\delta_C(CDCl_3$, 100.57 MHz) 14.71 (SMe), 19.18, 19.36, 20.19, 30.54, 31.55, 31.81, 33.04, 34.91 and 36.20 (7 × CH_2, 4-Me and CBr_3), 51.71, 51.80, 51.89 and 52.87 (OMe), 80.10 (C-4), 118.19, 122.52, 123.34, 128.22, 136.95 and 158.59 (C=C) and 159.76, 168.31, 171.42, 172.14, 173.28 and 180.03 (C=O and C-2); *m*/*z* (FD) 828, 830, 832 and 834 (1 : 3 : 3 : 1, M^+, 100%).

9-Carboxy-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-1-methylthio-4,5-dihydrodipyrrin 58

Tribromoethyl ester **57** was cleaved using zinc and acetic acid following the same procedure as for the preparation of **56**. Purification by PLC, eluting with 5% methanol in diethyl ether, gave the *carboxylic acid* **58** (95%) as a gum (Found: M^+, 566.1851. $C_{26}H_{34}N_2O_{10}S$ requires *M*, 566.1822); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400–2700, 3300, 1730, 1650 and 1180; $\delta_H(CDC1_3$, 400 MHz) 1.13 (3 H, s, 4-Me), 2.26 and 3.06 (each 1 H, d, *J* 15, 5-H_2), 2.37–2.39 (2 H, m), 2.50–2.58 (4 H, m) and 2.68 (2 H, t, *J* 8, 2 × CH_2CH_2), 2.56 (3 H, s, SMe), 3.44 (2 H, s, CH_2CO_2), 3.63, 3.65, 3.66 and 3.71 (each 3 H, s, OMe), 3.75 and 3.89 (each 1 H, d, *J* 17, CH_2CO_2) and 10.70 (1 H, br s, NH); *m*/*z* (FD) 566 (M^+, 100%).

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-2-methylthiopyrrole 62

A solution of carboxylic acid **61**[25] (1.00 g, 3.53 mmol) and thiourea (270 mg, 3.55 mmol) in ethanol–water (1 : 1; 20 cm^3) was stirred at room temperature under argon and a solution of iodine (0.1 mol dm^{-3}) in aqueous potassium iodide (0.2 mol dm^{-3}; 36 cm^3) was added dropwise. After a further 30 min, sodium hydrogen carbonate (2.0 g) was added and the mixture was extracted with dichloromethane (4 × 15 cm^3). The combined extracts were washed with water (30 ml), dried and evaporated to dryness. Without further purification, the intermediate thiourea derivative was dissolved in methanol–water (1 : 1) and sodium hydroxide (150 mg, 3.75 mmol) was added. The solution was stirred for 30 min at room temperature under argon and then methyl iodide was added. The solution was stirred for 15 h and then extracted with chloroform (4 × 15 cm^3). The combined extracts were washed with water (30 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the *methylthiopyrrole* **62** (275 mg, 27%) as an oil (Found: M^+, 285.1038. $C_{13}H_{19}NO_4S$ requires *M*, 285.1035); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3450, 2940, 1730, 1435, 1300, 1270 and 1165; $\delta_H(CDCl_3$, 400 MHz) 2.17 and 2.21 (each 3 H, s, SMe and 5-Me), 2.53 and 2.82 (each 2 H, t, *J* 8, CH_2CH_2), 3.38 (2 H, s, CH_2CO_2), 3.66 and 3.67 (each 3 H, s, OMe) and 7.88 (1 H, br s, NH); *m*/*z* (EI) 285 (M^+, 100%), 238 (55), 226 (35) and 212 (55).

9-Carboxy-1-methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 63

A solution of benzyl ester **18** (126 mg, 197 μmol) in methanol (10 cm^3) was stirred with 10% palladium-on-charcoal (20 mg) under hydrogen until uptake of gas ceased (*ca.* 1.5 h), then filtered and evaporated under reduced pressure. Purification by PLC, eluting with 5% ethanol in diethyl ether, gave *acid* **63** (94 mg, 87%) as a gum (Found: M^+, 550.2149. $C_{26}H_{34}N_2O_{11}$ requires *M*, 550.2163); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400–2400, 2940, 1730, 1660, 1435, 1260 and 1170; $\delta_H(CDCl_3$, 400 MHz) 1.11 (3 H, s, 4-Me), 2.30 and 3.02 (each 1 H, d, *J* 15, 5-H_2), 2.44–2.61 (6 H, m) and 2.99–3.03 (2 H, m, 2 × CH_2CH_2), 3.40 (2 H, s, CH_2CO_2), 3.42 and 3.47 (each 1 H, d, *J* 17, CH_2CO_2), 3.63, 3.63, 3.64, 3.70 and 3.95 (each 3 H, s, OMe) and 10.54 (1 H, br s, NH); *m*/*z* (FD) 550 (M^+, 100%).

1-Methoxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 64

A solution of carboxylic acid **63** (77 mg, 0.14 mmol) in dry dichloromethane (5 cm^3) was stirred with toluene-*p*-sulfonic acid (39 mg, 0.21 mmol) under argon at room temperature for 24 h, then washed with water (3 × 5 cm^3), dried and evaporated under reduced pressure. Purification by PLC, eluting with 10% ethanol in diethyl ether, gave the *methoxypyrrolenine* **64** (62 mg, 88%) as a gum (Found: M^+, 506.2354. $C_{25}H_{34}N_2O_9$ requires *M*, 506.2264); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400, 2950, 1725s, 1680, 1440, 1265 and 1165; $\delta_H(CDCl_3$, 250 MHz) 1.02 (3 H, s, 4-Me), 2.18 and 2.96 (each 1 H, d, *J* 15, 5-H_2), 2.41–2.57 and 2.70–2.76 (8 H, m, 2 × CH_2CH_2), 3.37 (4 H, s, 2 × CH_2CO_2), 3.62, 3.62, 3.63, 3.68 and 3.90 (each 3 H, s, OMe), 6.41 (1 H, d, *J* 2, 9-H) and 9.44 (1 H, br s, NH); *m*/*z* (FD) 506 (M^+, 100%).

9-Benzyloxycarbonyl-4-[3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2,2,2-tribromoethoxycarbonyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 66

Lactam **65**[8] was reacted with Lawesson's reagent as described in the general procedure above. Purification by flash chromatography, eluting with 2% ethanol in diethyl ether, gave *thiolactam* **66** (71%) as a gum (Found: C, 47.1; H, 4.5; N, 3.5. $C_{46}H_{52}Br_3N_3O_{16}S$ requires C, 47.0; H, 4.5; N, 3.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3440, 3300, 2960, 1730s, 1700, 1430, 1250 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.44–2.52 (9 H, m), 2.68–2.72 (2 H, m) and 2.89–2.94 (2 H, m, 4-CH_AH_B and 2 × CH_2CH_2), 2.91 and 3.11 (each 1 H, d, *J* 15, 4-CH_2), 3.24 (1 H, d, *J* 15, 4-CH_AH_B), 3.41 (1 H, d, *J* 17, C$H_AH_BCO_2$), 3.58, 3.58, 3.64, 3.65, 3.70 and 3.74 (each 3 H, s, OMe), 3.58–3.74 (3 H, obscured, $CH_AH_BCO_2$ and CH_2CO_2), 3.87 and 3.90 (each 1 H, d, *J* 17, CH_2CO_2), 5.00–5.03 (2 H, m, CH_2CBr_3), 5.18 and 5.26 (each 1 H, d, *J* 12, CH_2Ph), 7.27–7.37 (5 H, m, Ph) and 9.35, 10.00 and 10.20 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.15, 20.62, 29.26, 29.52, 29.58, 30.68, 30.92, 31.00, 31.18, 31.51, 34.50, 34.61 and 35.93 (CH_2 and CBr_3), 51.93, 51.48, 51.77, 51.93, 52.42 and 53.03 (OMe), 66.06 (*C*H_2Ph), 73.99 and 76.76 (C-4 and O*C*H_2CBr_3), 115.63, 118.11, 118.33, 122.72, 123.54, 128.79, 130.10, 135.82, 143.41 and 147.56 (C=C), 127.94, 128.09 and 128.32 (phenyl-CH), 158.52, 171.49, 173.36, 173.46 and 173.54 (C=O) and 197.40 (C=S); *m*/*z* (FD) 1171, 1173, 1175 and 1177 (1 : 3 : 3 : 1, M^+, 100%).

Acid-catalysed fragmentation of the thiolactam acid 67 derived from tribromoethyl ester 66

A solution of the tribromoethyl ester **66** (126 mg, 0.107 mmol) in acetic acid (3 cm^3) was stirred with zinc dust (260 mg) for 20 min and then filtered. The filtrate was diluted with water (10 cm^3) and extracted with dichloromethane (5 × 10 cm^3). The combined extracts were washed with water (2 × 10 cm^3), dried and evaporated under reduced pressure. Purification by PLC, using methanol–diethyl ether (3 : 17), gave the acid **67** (87 mg, 89%); *m*/*z* (FD) 909.

A solution of acid **67** (50 mg) in dry dichloromethane (5 ml) was stirred at room temperature with toluene-*p*-sulfonic acid (13.6 mg) under argon in the dark for 20 h. TLC then showed essentially one product in addition to baseline material. The product was isolated by PLC, eluting with ethanol–diethyl ether (1 : 9), and identified as the dipyrromethane **68** by comparison with an authentic sample synthesised as below.

1-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)dipyrromethane 68

A solution of iodide **69**[11] (112 mg, 155 μmol) in methanol (10 cm^3) was stirred with Adams catalyst (10 mg) and sodium acetate (100 mg) under hydrogen until uptake of gas ceased (*ca.* 2 h). The catalyst was then filtered off and the filtrate evaporated under reduced pressure. The residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3) and the aqueous layer was further extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure. Purification by PLC, eluting with diethyl ether, gave the α-*free dipyrromethane* **68** (62 mg, 67%) as a light-sensitive gum (Found: M^+, 596.2351. $C_{31}H_{36}N_2O_{10}$ requires *M*, 596.2370); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3350, 2950, 1730, 1690, 1430, 1250 and 1170; $\delta_H(CDCl_3$, 400 MHz) 2.47–2.53 (4 H, m), 2.72 (2 H, t, *J* 8) and 3.00 (2 H, t, *J* 8, 2 × CH_2CH_2), 3.49 and 3.64 (each 2 H, s, CH_2CO_2), 3.57, 3.57, 3.60 and 3.74 (each 3 H, s, OMe), 3.79 (2 H, s, 5-H_2), 5.23 (2 H, s, CH_2Ph), 6.42 (1 H, d, *J* 2, 9-H), 7.26–7.40 (5 H, m, Ph) and 9.35 and 10.20 (each 1 H, br s, NH); *m*/*z* (FD) 596 (M^+, 100%).

9-Carboxy-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 73

A solution of benzyl ester **21** (3.95 g, 6.31 mmol) in methanol (50 cm^3) was stirred with 10% palladium-on-charcoal (100 mg) in the dark under hydrogen until uptake of gas ceased (4 h), then filtered through Celite, washing with methanol (20 cm^3), and evaporated under reduced pressure to give the *acid* **73** (2.80 g, 83%), mp 177–178 °C (from methanol) (Found: C, 55.8; H, 6.0; N, 5.1. $C_{25}H_{32}N_2O_{11}$ requires C, 56.0; H, 6.0; N, 5.2%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 3200–2400, 2950, 1730s, 1680 and 1420; $\delta_H(CDCl_3$, 250 MHz) 1.01 (3 H, s, 4-Me), 2.59–2.64 and 3.04–3.07 (8 H, m, 2 × CH_2CH_2), 2.35 and 3.17 (each 1 H, d, *J* 15, 5-H_2), 3.47 (2 H, s, CH_2CO_2), 3.47 and 3.55 (each 1 H, d, *J* 16, CH_2CO_2), 3.62, 3.64, 3.65 and 3.72 (each 3 H, s, OMe) and 9.45 and 10.30 (each 1 H, br s, NH); $\delta_C(CDCl_3$, 62.5 MHz) 19.99 (4-Me), 19.56, 20.72, 30.01, 31.01, 31.57, 34.23 and 34.77 (CH_2), 51.33, 51.54, 51.94 and 52.50 (OMe), 65.01 (C-4), 117.42, 120.34, 129.92, 130.90, 133.86 and 154.67 (C=C) and 165.44, 169.34, 171.95, 173.16, 173.71 and 174.25 (C=O); *m*/*z* (FD) 536 (M^+, 100%).

9-Formyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 74

A solution of carboxylic acid **73** (950 mg, 1.77 mmol) in redistilled trifluoroacetic acid (20 cm^3) under argon in the dark was stirred at room temperature for 75 min, then cooled to 0 °C and treated with trimethyl orthoformate (20 cm^3). After a further 40 min at 0 °C the solution was poured into 10% aqueous sodium carbonate (200 cm^3) and extracted with dichloromethane (4 × 75 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by flash chromatography (25 × 2 cm), eluting with 0–4% ethanol in diethyl ether, gave *aldehyde* **74** (664 mg, 72%), which crystallised from dichloromethane–diethyl ether, mp 84–85 °C (Found: C, 57.4; H, 6.45; N, 5.1. $C_{25}H_{32}N_2O_{10}$ requires C, 57.7; H, 6.2; N, 5.4%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1740s, 1690, 1440 and 1100; $\delta_H(CDCl_3$, 250 MHz) 1.31 (3 H, s, 4-Me), 2.49–2.57 (6 H, m) and 2.99 (2 H, t, *J* 8, 2 × CH_2CH_2), 2.76 and 3.05 (each 1 H, d, *J* 15, 5-H_2), 3.37 and 3.49 (each 1 H, d, *J* 16, CH_2CO_2), 3.40 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.63, 3.72 and 3.77 (12 H, each s, 4 × OMe), 7.41 (1 H, br s, lactam-NH), 9.51 (1 H, s, CHO) and 10.62 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 62.5 MHz) 23.25 (4-Me), 19.25, 19.67, 29.65, 30.74, 31.37, 33.85 and 35.77 (CH_2), 51.46, 51.52, 52.27 and 52.66 (OMe), 63.44 (C-4), 116.15, 128.75, 133.39, 133.85, 135.38 and 151.36 (C=C), 170.39, 171.69, 172.50, 172.78 and 173.39 (C=O) and 177.38 (CHO); *m*/*z* (FD) 520 (M^+, 100%).

Reaction of formyl lactam 74 with Lawesson's reagent

Formyl lactam **74** (27 mg, 52 μmol) was reacted with Lawesson's reagent following the general procedure described above. The residue was purified by PLC, eluting with ethanol–ether (1 : 9), to give two higher R_f compounds: (i) at lower R_f, *thioformyl lactam* **75** (15 mg, 53%) as an oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3300, 2950, 1735s, 1700, 1440 and 1150; $\delta_H(CDCl_3$, 250 MHz) 1.38 (3 H, s, 4-Me), 2.46–2.60 (6 H, m) and 2.97 (2 H, t, *J* 7, 2 × CH_2CH_2), 2.81 and 3.00 (each 1 H, d, *J* 15, 5-H_2), 3.33 and

3.70 (each 1 H, d, *J* 17, CH_2CO_2), 3.38 and 3.54 (each 1 H, d, *J* 16, CH_2CO_2), 3.64, 3.75 and 3.80 (12 H, each s, 4 × OMe), 7.15 (1 H, br s, lactam-NH), 10.21 (1 H, br s, pyrrole-NH) and 10.57 (1 H, s, CHS); *m*/*z* (FD) 536 (M^+, 100%); (ii) at higher R_f, *thioformyl thiolactam* **79** (7 mg, 24%) as a gum (Found: M^+, 522.1543. $C_{25}H_{32}N_2O_8S_2$ requires *M*, 552.1600); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3250, 2950, 1730s, 1450, 1300, 1140 and 990; $\delta_H(CDCl_3$, 250 MHz) 1.43 (3 H, s, 4-Me), 2.49–2.82 and 2.93–2.98 (8 H, m, 2 × CH_2CH_2), 2.87 and 3.03 (each 1 H, d, *J* 15, 5-H_2), 3.34 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.39 and 3.79 (each 1 H, d, *J* 16, CH_2CO_2), 3.65, 3.81 and 3.82 (12 H, each s, 4 × OMe), 9.03 and 10.23 (each 1 H, br s, NH) and 10.60 (1 H, s, CHS); *m*/*z* (FD) 552 (M^+, 100%).

Reaction of formyl lactam **74** (114 mg, 220 μmol) with Lawesson's reagent (91 mg, 220 μmol) as above gave thioformyl thiolactam **79** (51%).

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-2-thioformylpyrrole 60

A solution of aldehyde **59**[13] (260 mg, 0.97 mmol) in dry benzene (10 ml) was heated at reflux with Lawesson's reagent (215 mg, 0.53 mmol) under argon in the dark for 45 min and then evaporated under reduced pressure. Purification by flash chromatography (20 × 2 cm), eluting with dichloromethane, gave *thioaldehyde* **60** (198 mg, 72%) as red blocks, mp 112–113 °C (from diethyl ether–hexane) (Found: C, 55.0; H, 6.1; N, 4.85; S, 11.3%; M^+, 283.0874. $C_{13}H_{17}NO_4S$ requires C, 55.1; H, 6.05; N, 4.9; S, 11.3%; *M*, 283.0878); $\lambda_{max}(CH_2Cl_2)$/nm 399 (strong) and 310; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2940, 1740s, 1490, 1430 and 1160; $\delta_H(CDCl_3$, 400 MHz) 2.24 (3 H, s, 5-Me), 2.48 and 3.00 (each 2 H, m, CH_2CH_2), 3.44 (2 H, s, CH_2CO_2), 3.68 and 3.71 (each 3 H, s, OMe), 9.35 (1 H, br s, NH) and 10.50 (1 H, s, CHS); δ_C ($CDCl_3$, 62.5 MHz) 12.23 (5-Me), 19.60, 29.66 and 35.49 (CH_2), 51.67 and 52.06 (OMe), 117.60, 133.04, 140.10 and 142.10 (pyrrole-C), 171.24 and 172.54 (C=O) and 194.42 (CH=S); *m*/*z* 283 (M^+, 100%), 250, 224, 209, 164 and 150.

9-Formyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-thione 80

A solution of thioformyl thiolactam **79** (51 mg, 92 μmol) in dimethylformamide (2 cm^3) was stirred with morpholine (2 drops) and water (10 drops) under argon in the dark for 20 h, then evaporated under reduced pressure. Purification by PLC, eluting with 7% ethanol in diethyl ether, gave *formyl thiolactam* **80** (26 mg, 53%) as a gum (Found: M^+, 536.1835. $C_{25}H_{32}N_2O_9S$ requires *M*, 536.1829); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2950, 1730s, 1695, 1440, 1175 and 1090; $\delta_H(CDCl_3$, 400 MHz) 1.36 (3 H, s, 4-Me), 2.54–2.74 (6 H, m) and 3.01 (2 H, t, *J* 7, 2 × CH_2CH_2), 2.81 and 3.07 (each 1 H, d, *J* 15, 5-H_2), 3.42 and 3.52 (each 1 H, d, *J* 16, CH_2CO_2), 3.46 and 3.62 (each 1 H, d, *J* 18, CH_2CO_2), 3.64, 3.65, 3.77 and 3.78 (each 3 H, s, OMe), 9.43 (1 H, br s, thiolactam-NH), 9.47 (1 H, s, CHO) and 10.68 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 62.5 MHz) 22.05 (4-Me), 19.19, 20.90, 29.80, 31.08, 31.93, 33.13 and 35.97 (CH_2), 51.54, 51.63, 52.64 and 52.86 (OMe), 71.08 (C-4), 115.88, 128.86, 133.43, 133.63, 141.43 and 149.79 (C=C), 170.56, 172.80, 172.91 and 173.73 (C=O), 177.31 (CHO) and 196.44 (C=S); *m*/*z* (FD) 536 (M^+, 100%).

9-Formyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 82

A solution of thiolactam **80** (45 mg, 84 μmol) in methanol (3 cm^3) was heated at reflux with freshly prepared Raney nickel (one small spatula) for 20 min, then filtered, washing with methanol, and evaporated under reduced pressure. The residue was purified by PLC to give the *pyrrolenine* **82** (15 mg, 52% based on unrecovered **80**) as a gum (Found: M^+, 504.2110. $C_{25}H_{32}N_2O_9$ requires *M*, 504.2108); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2950, 1730s, 1640, 1570, 1435, 1260, 1200 and 1170; $\delta_H(CDCl_3$, 400 MHz) 1.09 (3 H, s, 4-Me), 2.21 and 3.14 (each 1 H, d, *J* 15, 5-H_2), 2.48–2.52 and 2.56–2.65 (8 H, m, 2 × CH_2CH_2), 3.39 and 3.45 (each 1 H, d, *J* 16, CH_2CO_2), 3.43 and 3.48 (each 1 H, d, *J* 16, CH_2CO_2), 3.64, 3.65, 3.67 and 3.73 (each 3 H, s, OMe), 7.94 (1 H, s, 2-H), 9.56 (1 H, s, CHO) and 10.44 (1 H, br s, NH); *m*/*z* (FD) 504 (M^+, 100%).

9-Cyano-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 78

A solution of formyl lactam **74** (191 mg, 0.367 mmol) in methanol (10 cm^3) was treated with hydroxylamine hydrochloride (45 mg, 0.65 mmol), sodium acetate (54 mg, 0.66 mmol) and water (10 drops), heated at reflux under argon for 45 min and then evaporated under reduced pressure. The residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3) and the aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried and evaporated under reduced pressure to give crude oximes **76**.

Without further purification, the oximes **76** were dissolved in dry acetonitrile (3 cm^3) and added to a mixture of dimethylformamide (71 mg, 75 μl, 0.97 mmol) and freshly distilled phosphorus oxychloride (120 mg, 0.80 mmol) in dry acetonitrile (2 cm^3) at −23 °C. The solution was stirred at −23 °C for 20 min and then at room temperature for 1 h, poured into 5% aqueous sodium hydrogen carbonate (25 cm^3) and extracted with dichloromethane (4 × 20 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with 10% ethanol in diethyl ether, gave the *nitrile* **78** (142 mg, 74%) as a gum (Found: M^+, 517.2065. $C_{25}H_{31}N_3O_9$ requires *M*, 517.2060); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2960, 2210, 1725s, 1690, 1435, 1100 and 1065; $\delta_H(CDCl_3$, 400 MHz) 1.29 (3 H, s, 4-Me), 2.50–2.66 and 2.81–2.85 (8 H, m, 2 × CH_2CH_2), 2.77 and 3.02 (each 1 H, d, *J* 15, 5-H_2), 3.33 and 3.47 (each 1 H, d, *J* 16, CH_2CO_2), 3.40 and 3.59 (each 1 H, d, *J* 17, CH_2CO_2), 3.64, 3.65, 3.70 and 3.77 (each 3 H, s, OMe), 7.53 (1 H, br s, lactam-NH) and 10.43 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 100 MHz) 23.15 (4-Me), 19.53, 20.12, 29.62, 30.59, 31.15, 33.36 and 34.27 (CH_2), 51.55, 51.64, 52.24 and 52.74 (OMe), 63.63 (C-4), 98.93, 113.95, 114.36, 130.29, 132.67, 135.39 and 151.55 (C=C and C≡N) and 170.74, 171.89, 172.28, 172.81 and 173.70 (C=O); *m*/*z* (FD) 517 (M^+, 100%).

9-Cyano-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-thione 81

Lactam **78** was reacted with Lawesson's reagent according to the above general procedure. The residue was purified by flash chromatography, eluting with diethyl ether, to give *thiolactam* **81** (88%) as a gum (Found: M^+, 533.1820. $C_{25}H_{31}N_3O_8S$ requires *M*, 533.1832); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3300, 2960, 2220, 1730s, 1450 and 1000; $\delta_H(CDCl_3$, 400 MHz) 1.41 (3 H, s, 4-Me), 2.52–2.81 (6 H, m) and 2.84 (2 H, t, *J* 8, 2 × CH_2CH_2), 2.91 and 3.05 (each 1 H, d, *J* 15, 5-H_2), 3.33 and 3.53 (each 1 H, d, *J* 16, CH_2CO_2), 3.39 (1 H, d, *J* 17, $CH_AH_BCO_2$), 3.64, 3.68, 3.78 and 3.80 (each 3 H, s, 4 × OMe), 3.64–3.80 (1 H, obscured, CH_A-H_BCO_2), 8.95 (1 H, br s, lactam-NH) and 10.18 (1 H, br s, pyrrole-NH); $\delta_C(CDCl_3$, 100 MHz) 23.10 (C-4), 20.16, 21.14, 29.77, 30.84, 31.45, 32.72 and 34.53 (CH_2), 51.79, 51.94, 52.93 and 53.16 (OMe), 70.96 (C-4), 98.81, 113.79, 129.97, 132.92, 142.2 and 148.97 (C=C and C≡N), 171.67, 172.94, 173.42 and 174.52 (C=O) and 196.19 (C=S); *m*/*z* (FD) 533 (M^+, 100%).

9-Cyano-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin 83

Thiolactam **81** was reduced with nickel boride according to the general procedure above. Purification by PLC, eluting with ethanol–diethyl ether (1:9), gave *pyrrolenine* **83** (40% based on unrecovered **81**) as a gum (Found: M^+, 501.2108. $C_{25}H_{31}N_3O_8$ requires *M*, 501.2111); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350, 2960, 2220, 1725s, 1690, 1440 and 1150; $\delta_H(CDCl_3$, 400 MHz) 1.07 (3 H, s,

4-Me), 2.14 and 3.10 (each 1 H, d, *J* 15, 5-H_2), 2.51 and 2.66 (6 H, m) and 2.86 (2 H, t, *J* 8, 2 × CH_2CH_2), 3.40–3.43 (4 H, m, 2 × CH_2CO_2), 3.66, 3.67 and 3.73 (12 H, each s, 4 × OMe), 7.95 (1 H, s, 2-H) and 10.45 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.39 (4-Me), 20.28, 20.51, 29.71, 31.21, 32.24, 32.66 and 34.47 (CH_2), 51.50, 51.70, 51.87 and 52.35 (OMe), 83.3 (C-4), 97.88, 114.04, 114.7, 132.62, 132.92, 137.6 and 158.0 (C=C and C≡N), 164.9 (C-2), 170.08, 171.65, 171.71 and 172.71 (C=O), *m*/*z* (FD) 501 (M^+, 100%).

9-Formyl-4-[5-formyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 86

Hydrogenation of dibenzyl ester **29** and decarboxylation–formylation of the resulting diacid **85** was carried out using similar procedures to those used for **21→73→74** except that the hydrogenation required 3 h and decarboxylation required 6.5 h. Purification by flash chromatography, eluting with 0–5% ethanol in diethyl ether, gave the *dialdehyde* **86** (72% over both steps) as a gum (Found: M^+, 771.2862. $C_{37}H_{45}N_3O_{15}$ requires *M*, 771.2851); ν_{max}(CH_2Cl_2)/cm^{-1} 3280, 2950, 1730, 1640, 1460, 1250 and 1070; δ_H($CDCl_3$, 400 MHz) 2.41–2.55 (6 H, m), 2.72 (2 H, t, *J* 7) and 2.91–2.98 (4 H, m, 3 × CH_2CH_2), 2.52 and 3.18 (each 1 H, d, *J* 15, 4-CH_2), 2.85 and 3.08 (each 1 H, d, *J* 15, 4-CH_2), 3.25 and 3.47 (each 1 H, d, *J* 16, CH_2CO_2), 3.62, 3.63, 3.64, 3.67, 3.68 and 3.83 (each 3 H, s, 6 × OMe), 3.62–3.83 (4 H, obscured, 2 × CH_2CO_2), 7.63 (1 H, br s, lactam-NH), 9.50 (2 H, s, 2 × CHO) and 10.14 and 10.46 (each 1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 62.5 MHz) 19.10, 19.26, 19.68, 29.60, 30.93, 31.03, 31.73, 31.96, 32.10 and 34.64 (CH_2), 51.56, 51.68, 52.19, 52.29 and 53.01 (OMe), 66.66 (C-4), 116.30, 122.96, 129.05, 129.75, 132.03, 132.73, 137.40 and 149.83 (C=C), 170.46, 171.11, 172.29, 172.87, 173.31 and 173.38 (C=O) and 177.60 and 177.79 (CHO); *m*/*z* (FD) 771 (M^+, 100%).

9-Cyano-4-[5-cyano-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 87

Dialdehyde **86** was reacted with hydroxylamine hydrochloride and then phosphorus oxychloride following an analogous procedure to that employed for **74→76→78**. Purification by flash chromatography, eluting with 2% ethanol in diethyl ether, gave the *dinitrile* **87** (50%) as a gum (Found: M^+, 765.2845. $C_{37}H_{43}N_5O_{13}$ requires *M*, 765.2857); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2960, 2220, 1725s, 1695, 1435, 1200 and 1170; δ_H($CDCl_3$, 400 MHz) 2.39–2.60 (8 H, m), 2.67 (2 H, t, *J* 7) and 2.78 (2 H, t, *J* 8, 3 × CH_2CH_2), 2.71 and 3.15 (each 1 H, d, *J* 15, 4-CH_2), 2.82 and 3.00 (each 1 H, d, *J* 15, 4-CH_2), 3.18 and 3.43 (each 1 H, d, *J* 16, CH_2CO_2), 3.55 (2 H, s, CH_2CO_2), 3.64, 3.64, 3.68, 3.69, 3.69 and 3.83 (each 3 H, s, 6 × OMe), 3.64–3.83 (2 H, obscured, CH_2CO_2) and 7.74, 9.97 and 10.21 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.25, 19.90, 20.20, 29.30, 30.63, 30.68, 30.87, 32.24 and 34.33 (CH_2), 51.69, 51.83, 52.06, 52.22, 52.55 and 53.31 (OMe), 66.38 (C-4), 99.17, 100.72, 113.66, 113.91, 114.65, 121.25, 125.89, 128.29, 128.92, 129.68, 132.87, 137.76 and 149.90 (C=C and C≡N), 170.83, 171.70, 172.15, 172.87, 172.89, 173.59 and 174.21 (C=O); *m*/*z* (FD) 765 (M^+, 100%).

9-Cyano-4-[5-cyano-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-thione 88

Lactam **87** was reacted with Lawesson's reagent following the general procedure described above. Purification by flash chromatography, eluting with 2% ethanol in diethyl ether, gave the *thiolactam* **88** (67%) as a gum (Found: M^+, 781.2632. $C_{37}H_{43}N_5O_{12}S$ requires *M*, 781.2629); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2950, 2220, 1730s, 1440, 1270 and 1000; δ_H($CDCl_3$, 400 MHz) 2.49–2.82 (13 H, m, 3 × CH_2CH_2 and 4-C$H_A$$H_B$), 2.89 and 3.10 (each 1 H, d, *J* 15, 4-CH_2), 3.22 and 3.50 (each 1 H, d, *J* 16, CH_2CO_2), 3.29 (1 H, d, *J* 15, 4-C$H_A$$H_B$), 3.56 (2 H, s, CH_2CO_2), 3.64, 3.67, 3.70, 3.73, 3.75 and 3.86 (each 3 H, s, 6 × OMe), 3.64–3.86 (2 H, obscured, CH_2CO_2), 9.31, 9.61 and 10.07 (each 1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 19.17, 20.17, 21.25, 29.28, 30.34, 30.72, 30.85, 31.11, 31.74, 34.15 and 34.47 (CH_2), 51.79, 52.25, 52.32, 52.87 and 53.49 (OMe), 73.48 (C-4), 99.15, 100.90, 113.58, 113.82, 114.31, 121.33, 126.03, 128.46, 129.26, 133.01, 143.81 and 147.91 (C=C and C≡N), 170.84, 172.06, 172.86, 173.36, 173.93 and 174.85 (C=O) and 197.20 (C=S); *m*/*z* (FD) 781 (M^+, 100%).

9-Cyano-4-[5-cyano-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin 89

Thiolactam **88** was reduced with nickel boride following the general procedure described above, except that the reaction time was increased to 2.5 h. Purification by normal phase HPLC on a Kontron S5W column, eluting with hexane–ethyl acetate (1:1), gave the *pyrrolenine* **89** (14%) as a gum (Found: M^+, 749.2908. $C_{37}H_{43}N_5O_{12}$ requires *M*, 749.2908); ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 2950, 2220, 1730s, 1695, 1440, 1200 and 1175; δ_H($CDCl_3$, 400 MHz) 2.29 and 3.19 (each 1 H, d, *J* 15, 4-C$H_A$$H_B$), 2.41–2.50, 2.55–2.65 and 2.86 (13 H, m, 3 × CH_2CH_2 and 4-C$H_A$$H_B$), 3.07 (1 H, d, *J* 15, 4-C$H_A$$H_B$), 3.29 and 3.40 (each 1 H, d, *J* 16, CH_2CO_2), 3.49 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.59 (2 H, s, CH_2CO_2), 3.63, 3.65, 3.67, 3.70, 3.74 and 3.83 (each 3 H, s, OMe), 7.81 (1 H, s, N=C–H) and 10.16 and 10.35 (each 1 H, br s, NH); *m*/*z* (FD) 749 (M^+, 100%).

Hydrolysis of the ester groups of pyrrolenines 83 and 89

A solution of pyrrolenine **83** (44 mg, 88 μmol) in dry degassed methanol (1 cm^3) was treated with degassed aqueous potassium hydroxide (4 mol dm^{-3}; 1 cm^3) and then shaken under argon in the dark at room temperature for 15 h. A sample was then removed and prepared for NMR analysis by four times evaporating *in vacuo* and redissolving the residue in D_2O (1 cm^3); δ_H(D_2O, 400 MHz, relative to HOD signal at 4.77 ppm) 1.14 (3 H, s, 4-Me), 2.12, 2.25, 2.43, 2.62 (each 2 H, t, *J* 8, 2 × CH_2CH_2), 2.60 and 3.01 (each 1 H, d, *J* 15, 5-H_2), 3.18 and 3.27 (each 2 H, d, *J* 16, 2 × CH_2CO_2) and 7.79 (1 H, s, 2-H).

The remainder of the solution was then washed with diethyl ether (2 × 2 cm^3) and evaporated *in vacuo*. The residue was dissolved in acetic acid (400 μl), and methanol (4 cm^3) and diethyl ether (10 cm^3) were added. The mixture was treated with diazomethane at room temperature until the yellow colour persisted, stirred for a further hour and then evaporated under reduced pressure. Purification by PLC gave the starting pyrrolenine **83** as the major product (20 mg, 46% recovery).

For enzymatic studies, the pyrrolenine **89** was hydrolysed under exactly the same conditions.

Crystal data for 60 §

$C_{13}H_{17}NO_4S$, *M* = 283.34. Monoclinic, *a* = 8.367(4), *b* = 19.764(8), *c* = 18.672(4) Å, *β* = 95.16(3)°, *V* = 1428.2(11) $Å^3$ [from centring angles for 25 reflections (40 ⩽ 2*θ* ⩽ 50°, *λ* = 1.541 84 Å, *T* = 290 K)], space group $P2_1/a$ (Alt. $P2_1/c$, No. 14), *Z* = 4, D_x = 1.318 g cm^{-3}, red block, 0.38 × 0.35 × 0.19 mm, *μ*(Cu-K*α*) = 2.111 mm^{-1}.

§ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/200.

Data collection and processing
Siemens P3 diffractometer, $\omega/2\theta$ scans, graphite-monochromated Cu-Kα *X*-radiation; 2255 reflections measured ($9 \leqslant 2\theta \leqslant 115°$), 1959 unique [merging $R = 0.018$], giving 1809 with $F \geqslant 4\sigma(F)$ and 1959 which were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

Structure solution and refinement
Automatic direct methods[35] (all non-H atoms). Full-matrix least-squares refinement[35] with all non-H atoms anisotropic; H atoms were included at geometrically calculated positions and thereafter allowed to ride on their respective parent atoms at a distance of 0.98 Å. The weighting scheme selected gave satisfactory agreement analyses. Final R_f [$F \geqslant 4\sigma(F)$] = 0.0459, wR_2 [all data] = 0.1310, $S[F^2] = 1.03$ for 187 refined parameters. An extinction correction[35] refined to 0.0065(10) and the final ΔF synthesis showed no peaks above 0.33 e Å^{-3}.

Crystal data for 77 §
$C_{27}H_{35}N_3O_{11}$, $M = 577.58$. Monoclinic, $a = 7.517(3)$, $b = 18.551(5)$, $c = 20.760(8)$ Å, $\beta = 94.30(3)°$, $V = 2887(2)$ Å^3 [from centring angles for 25 reflections ($40 \leqslant 2\theta \leqslant 50°$, $\lambda = 1.541\,84$ Å, $T = 290$ K)], space group $P2_1/c$ (No. 14), $Z = 4$, $D_x = 1.329$ g cm^{-3}, colourless block, $0.41 \times 0.38 \times 0.25$ mm, μ(Cu-Kα) = 0.875 mm^{-1}.

Data collection and processing
Siemens P3 diffractometer, $\omega/2\theta$ scans, graphite-monochromated Cu-Kα *X*-radiation; 4195 reflections measured ($6 \leqslant 2\theta \leqslant 115°$), 3938 unique [merging $R = 0.013$], giving 3441 with $F \geqslant 4\sigma(F)$ and 3938 which were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

Structure solution and refinement
Automatic direct methods[35] (all non-H atoms). Full-matrix least-squares refinement[35] with all non-H atoms anisotropic; H atoms were included at geometrically calculated positions and thereafter allowed to ride on their respective parent atoms at a distance of 0.98 Å. The weighting scheme selected gave satisfactory agreement analyses. Final R [$F \geqslant 4\sigma(F)$] = 0.0437, wR_2 [all data] = 0.1284, $S[F^2] = 1.03$ for 391 refined parameters. The final ΔF synthesis showed no peaks above 0.38 e Å^{-3}.

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