Haem d_1: stereoselective synthesis of the reduced form of its parent macrocycle using the original coupling strategy

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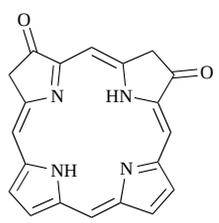
A substituted isobacteriochlorin, which corresponds structurally to the reduced metal-free macrocycle of haem d_1, has been synthesised by a stereoselective route in which the final step is a photochemical 18π-electron antarafacial cyclisation of an open-chain precursor.

Introduction

Cytochrome cd_1, an enzyme found in many denitrifying bacteria, catalyses the four-electron reduction of nitrite to N_2O. It carries two haem residues, one covalently linked (haem *c*) and the other held noncovalently. The latter, named haem d_1, was first detected[1] in 1961 but isolated much more recently by Timkovich's group.[2] Only minute amounts of haem d_1 were available but the spectroscopic data pointed to its being a tetrapyrrolic iron complex. After some early confusion about the nature of the macrocycle, Chang[3] showed that it is a derivative of 3,8-dioxoisobacteriochlorin, the parent macrocycle having structure **1**. This conclusion was based on comparison of synthetic model systems[4] with the demetallated and esterified macrocycle from haem d_1. Finally, the proposed structures **2** and **3** for haem d_1 and its demetallated ester, respectively, were given overwhelming support[5] although both lacked stereochemical definition at C-2 and C-7.



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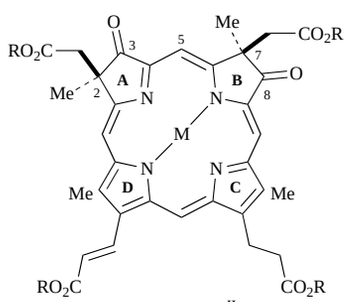
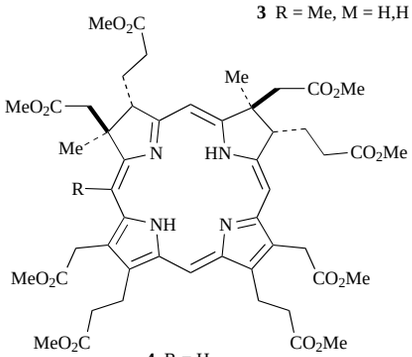


2 R = H, M = Fe^{II}
3 R = Me, M = H,H



4 R = H
5 R = Me

Synthetic confirmation that the ester of the ligand has gross structure **3**, without stereochemical information, came from Chang and Wu's synthesis[6] of a mixture of all the racemic diastereoisomers corresponding to gross structure **3**. One of these was identical, apart from being a racemate, with the ester derived from haem d_1. Montforts *et al.*[7] then made a partial synthesis yielding all the diastereoisomers of the related macrocycle having the acrylate side-chain of **3** reduced, to show that the methyl groups at C-2 and C-7 are *syn*-oriented. Thus haem d_1 has the absolute configuration **2** or it is the corresponding enantiomer. It was essential to determine the absolute configuration of haem d_1 so as to know its stereochemical relationship to several other C-methylated tetrapyrrolic substances which are important as enzymic cofactors and biosynthetic intermediates. This topic will be fully discussed in the section on 'Biosynthesis' in the third member[8] of the present set of papers. These will describe the way the stereochemical problem was solved by total stereoselective synthesis of the ester **3**.

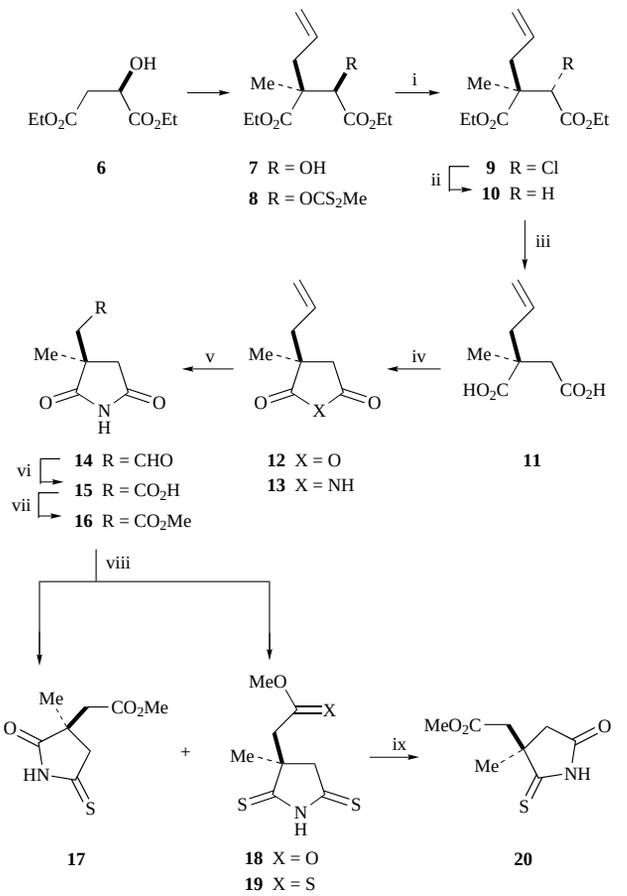
Results and discussion

A synthesis of isobacteriochlorins has been developed[9] in Cambridge in which the conditions are sufficiently mild to be compatible with the acetate and propionate side-chains present in the natural isobacteriochlorins (see **3**–**5**). This route has been successfully used for the synthesis of sirohydrochlorin octamethyl ester[10] **4** and of the corresponding 20-methyl analogue[11] **5**; both these materials were important for research[12] on the biosynthesis of vitamin B_{12}. The key step in all these syntheses is a photochemical 18π-electron antarafacial cyclisation of an open-chain precursor which, for the initial target molecule **47** in the present research, needs to have structure **46** (Scheme 4). It was envisaged that the oxo functions at C-3 and C-8 could be introduced into **47** at the end of the synthesis to afford **48**.

Scheme 4 shows the planned construction of the open-chain intermediate **46** by condensation of the western building block **44** with the eastern one **45**. In ways to be described later, ring A of the western block **44** and ring B of the eastern component **45** were to be derived from monothioimides **17** and **20** made from a common precursor, the (*R*)-succinimide **16**. The synthesis of this imide is illustrated in Scheme 1.

Synthesis of the monothioimides 17 and 20

Those steps leading to the succinate ester **10** from diethyl (*R*)-malate **6** by double alkylation to yield **7** and removal of the hydroxy group *via* the xanthate ester **8** have been briefly outlined;[11] the experimental details will be given in the full paper to be published on that topic. The deoxygenation step has now been improved for large scale preparations by conversion of **7** first into the chloride **9** using carbon tetrachloride and triphenylphosphine specifically in acetonitrile. Presumably inversion occurs as illustrated but this was not confirmed since we simply wanted to remove the halide reductively. This was achieved using zinc and acetic acid and when the two steps were carried through without isolation of **9**, the yield of the succinate **10** was consistently 60–70% overall from the malate **6** on a multi-gram scale.



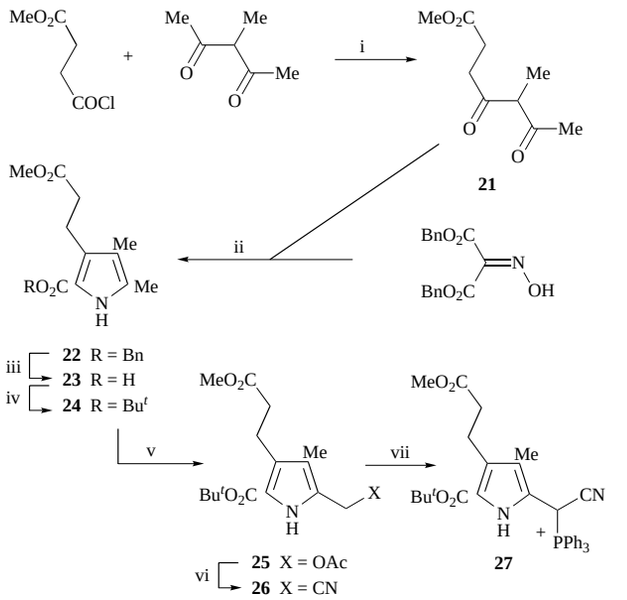
Scheme 1 *Reagents:* i, CCl_4, PPh_3; ii, Zn, HOAc; iii, KOH; iv, heat, urea; v, RuO_2, $NaIO_4$; vi, chromic acid; vii, CH_2N_2; viii, Lawesson's reagent; ix, $HgCl_2$ in aq. MeCN

In our earlier work,[13] the conversion of substituted succinate esters into the corresponding imides had required several steps which here would have involved the anhydride **12**. This process has now been considerably simplified by hydrolysis of the ester **10** to the acid **11** which is heated at 110 °C with an excess of urea[14] to give the imide **13** directly in over 90% yield. This approach was subsequently used in the synthesis of other isobacteriochlorins.[11] All that now remained was to cleave the allyl side-chain of **13** to give the acetate function of the imide **15**. This conversion was carried out using ruthenium dioxide–sodium periodate under carefully defined conditions. Some aldehyde **14** always accompanied the acid **15**, so the crude product was further oxidised with chromic acid to afford the pure product **15** consistently in >90% yield. This acid **15** was first prepared by Dr P. Guerry for a different purpose using a different approach and his work will be described separately. Treatment of the acid **15** with diazomethane in tetrahydrofuran then yielded the ester **16** in upto 95% yield free from the small amount of N-methylated imide formed when the solvent was methanol.

The next steps involved coupling the succinimide **16**, in a suitably activated state, to the pyrrole units which were to form rings C and D of the final macrocycle **47**. The original strategy for the coupling process[10,11,15,16] required, for the present work, prior conversion of the imide **16** into the two monothioimides **17** and **20**. Accordingly, the imide **16** was heated with Lawesson's reagent[17] in boiling toluene to yield the 4-monothioimide **17** in 48–68% yield together with some dithioimide **18**, a valuable product (see below) in 9–21% yield. When the imide **16** was heated in toluene with a large excess of Lawesson's reagent, the dithioimide **18** was produced in 90% yield together with the 4-monothioimide **17** and the trithio product **19**, both in variable small amounts. However, the three thioimides **17**, **18** and **19** were readily separable and the last two could be converted into the required 1-monothioimide **20** in 70–80% yield by controlled hydrolysis using mercuric chloride in aqueous acetonitrile. Both monothioimides **17** and **20** were thus readily available.

Synthesis of the east and west building blocks

The pyrrole **24** required for the further synthetic stages had been prepared earlier[18] but occasional difficulties caused by unwanted by-products led us to develop the improved route shown in Scheme 2. This pyrrole was then converted into the



Scheme 2 *Reagents:* i, $Mg(OMe)_2$ then H_3O^+; ii, Zn, HOAc; iii, H_2, Pd; iv, Bu^tOH, DCC; v, $Pb(OAc)_4$, HOAc; vi, NaCN, DMF; vii, SO_2Cl_2 then PPh_3

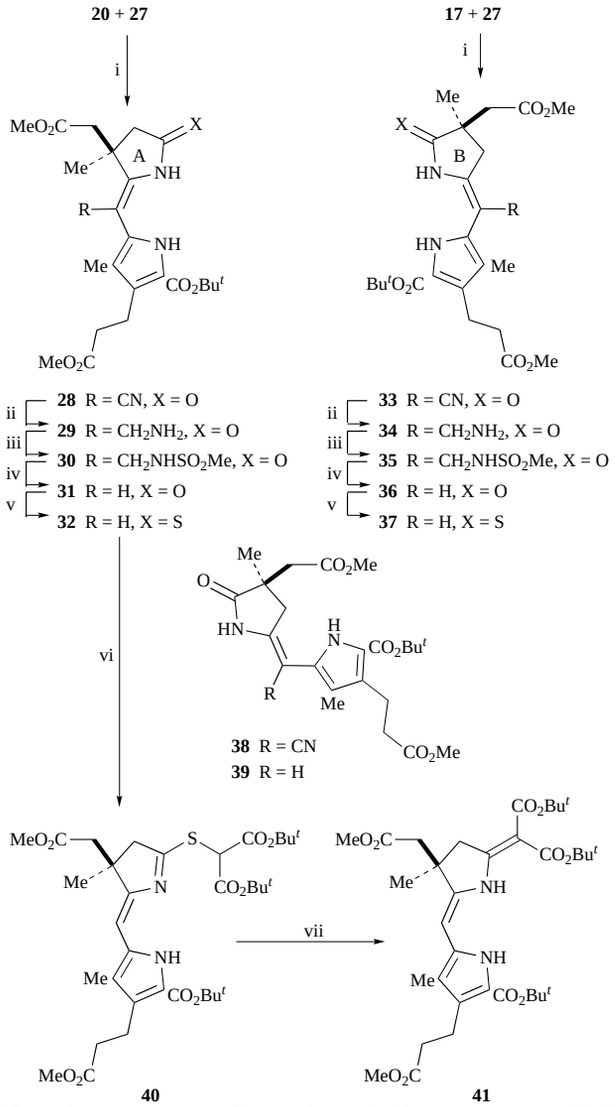
phosphonium salt **27**, first prepared and characterised by Collins[19] for a different project; details will be given in the full paper on that topic.

The stage was now set for coupling the 4-monothioimide **17** with the phosphonium salt **27** under the base catalysed conditions devised earlier.[16] The product, in 60–90% yield, was almost entirely a single geometric isomer, shown to be the *E*-isomer **33** (Scheme 3) by the marked bathochromic shift of its UV absorption spectrum by *N*,*N*′-chelation of zinc(II) ions.[20] Such chelation is not possible with the *Z*-isomer **38**, which was probably represented by trace amounts of an uncharacterised byproduct. It was essential to use freshly prepared phosphonium salt **27** for this coupling step; storage, even for a few days, led to a seriously reduced yield.

Similar coupling of the 1-monothioimide **20** with the same salt **27** proved to be more difficult and only by using an excess of **20** was an acceptable conversion into the pure *E*-isomer **28** achieved. The yield was up to 58% based on the phosphonium salt used.

The nitrile function in the phosphonium salt **27** is essential[16] for successful coupling with the foregoing monothioimides and now this group had to be removed from the products **28** and **33**. A general approach was devised in Cambridge based on a retro-Mannich reaction as the key step; it has been fully described.[21] Scheme 3 shows the conversions involved, which are **28** ⟶ **29** ⟶ **30** ⟶ **31** for the western block and **33** ⟶ **34** ⟶ **35** ⟶ **36** for the eastern unit. Several comments are needed on these sequences of reactions.

(i) The nitrile group in such coupled products had earlier been reduced to a primary amine by catalytic hydrogenation.[21] This requires scrupulous elimination of all traces of sulfur-containing materials remaining from earlier stages. Accordingly, reduction by cobalt(II) borohydride was used in one case[22] and although the latter method gave lower yields than the best

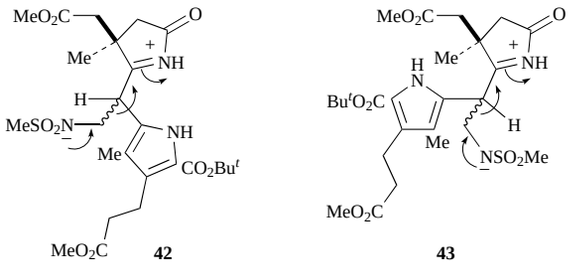


Scheme 3 *Reagents:* i, Bu^{t}OK, PPh_3; ii, $CoCl_2$, $NaBH_4$; iii, $MeSO_2Cl$, DMAP; iv, heat, $(EtNHCH_2)_2$; v, Lawesson's reagent; vi, $(Bu^tO_2C)_2$-CHBr, DBU; vii, PPh_3, DBU

catalytic reductions, its convenience led us to study it further. Following clues from the work of Heinzman and Ganem,[23] conditions were developed which consistently afforded both **30** and **35** in 45–55% yield over the two steps of reduction and methylsulfonylation. This compares favourably with the highest yields from the catalytic approach.

(ii) The key reverse-Mannich step, here **30** ⟶ **31** and **35** ⟶ **36**, eliminates the fragment CH_2=N–SO_2Me which was trapped in related cases[21,24] using excess of *N*,*N*′-dimethylethylenediamine to avoid formation of unwanted by-products. These conditions were modified for the present work; heating the sulfonamide **30** in *N*,*N*-dimethylformamide (DMF) with 10 equiv. of *N*,*N*′-diethylethylenediamine gave 78–85% of the single *Z*-isomer **31**. Similarly, **35** afforded 70–78% of a mixture of the *Z*-isomer **36** and its *E*-analogue **39**. These were separated for characterisation but the mixture could be used directly for the further synthetic steps. Interestingly, although the *E*-isomer **33** and the *Z*-isomer **36** (having the *same* illustrated double bond configuration) showed the normal bathochromic shift of their UV absorption spectra when zinc(II) ions were added, this did not occur for the intermediate *Z*-sulfonamide **35**. Exactly the same phenomenon was observed for the western series where the spectra of **28** and **31** were shifted by zinc(II) ions but that of **30** was not. A possible explanation is that the steric bulk of the CH_2NHSO_2Me group causes the pyrrole rings of **30** and **35** to be twisted too far out of plane with the double bond for significant chelation of the zinc ion to occur.

(iii) The formation of a single *Z*-isomer **31** from **30** in the reverse-Mannich step can be understood by considering the conformations **42** and **43** respectively required for formation of



the *Z*- and *E*-isomers. The latter conformation is clearly disfavoured by steric interactions between the quaternary centre and the substituted pyrrole ring.

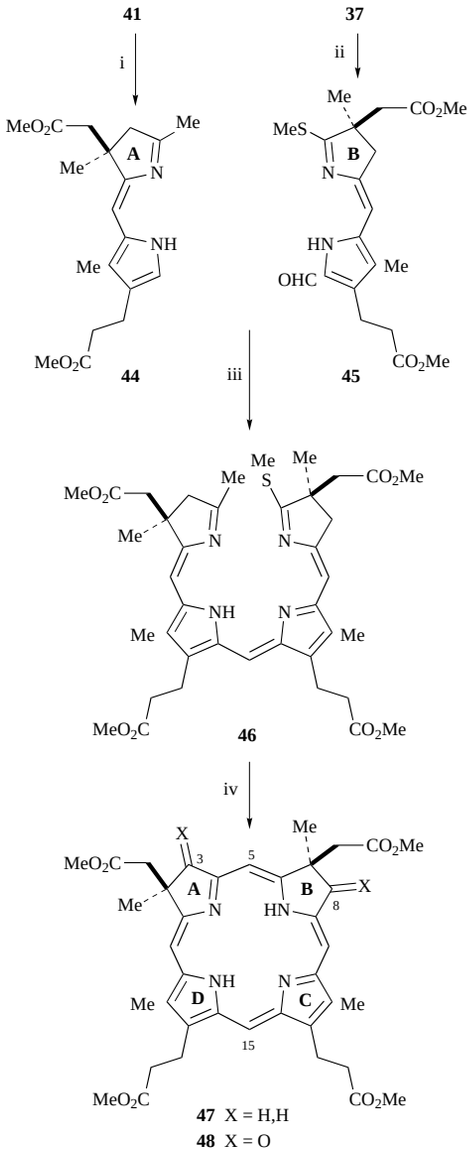
The nitrile-free lactams **31** and **36**, prepared above, can provide all the atoms of the target isobacteriochlorin **47** save two, those at C-5 and C-15. These were introduced by methods developed during earlier research[10,11,16,21,22,24] which have either been described with complete experimental detail or will be fully published in the near future. Therefore, the description here will be brief. Heating the eastern lactam **36** in toluene with Lawesson's reagent afforded up to a 60% yield of the thiolactam **37** which reacted with trimethyl orthoformate (TMOF) and trifluoroacetic acid (TFA) to generate the formyl thioimino ether **45** (Scheme 4) in yields of 70–89%. The formyl group of this product provides C-15 of the final macrocycle **47**. It should be noted that in this 'one pot' process, TMOF carried out both methylation at sulfur and formylation of the pyrrole following cleavage of the *tert*-butyl ester and decarboxylation by TFA. The eastern building block was now fully built.

Again Lawesson's reagent was used to convert the western lactam **31** into the corresponding thiolactam **32**; yields of 89–96% were obtained under strictly controlled conditions. The atom which eventually becomes C-5 of **45** was then introduced in the form of di-*tert*-butyl 2-bromomalonate, which reacted with the thiolactam **32** to form the *S*-malonyl derivative **40**. This, without isolation, was used directly for the sulfur-extrusion step,[25] brought about under basic conditions by hot triphenylphosphine, so forming 66% of the enamine **41**. This is the immediate precursor of the western building block **44** but the latter is unstable and so was generated as described below from the storable enamine **41** just in advance of its use.

Synthesis of the macrocycle 47

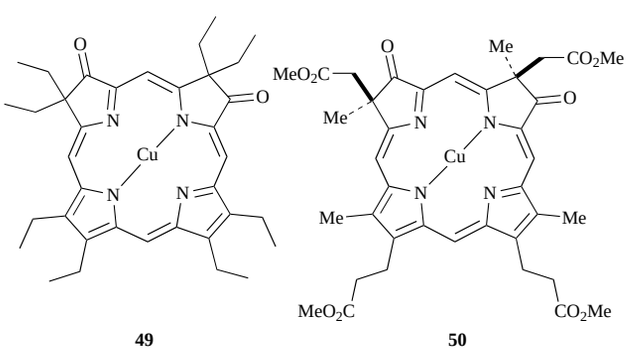
Treatment of the enamine **41** with TFA cleaved the three *tert*-butyl ester groups and the resultant tricarboxylic acid was fully decarboxylated by being heated with sodium acetate and acetic acid. The western block **44** so formed in 56–67% yield underwent acid-catalysed condensation with the eastern block **45**, used in *ca*. 50% excess, to generate the *seco*-system **46** as a deep blue protonated form. After neutralisation of the mixture with diisopropylethylamine, it was degassed and irradiated for several days to effect photochemical ring-closure of the *seco*-system **46** to form the isobacteriochlorin **47**. Under the best conditions, the yield of the macrocycle **47** was 25–26% over the two steps of condensation and cyclisation; this product was characterised by NMR and UV–visible spectroscopy and by mass spectrometry. The UV–visible spectra showed that the isobacteriochlorin **47** is readily protonated, the protonated form showing a sharp peak at *ca*. 400 nm in both dichloromethane and methanol.

At this stage, the main aim of devising a stereoselective synthesis of the reduced macrocycle **47** of haem d_1 had been accomplished. It will be seen later that this product was correlated with that synthesised by a novel route described in the following two papers, so locking the different synthetic efforts together. In addition, the supply of isobacteriochlorin **47** from



Scheme 4 *Reagents:* i, TFA, then heat, NaOAc, HOAc; ii, $(MeO)_3CH$, TFA; iii, HCl, MeOH; iv, *hv*, TFA, Pr^i_2NEt

the present work was used to explore one possible way to introduce the 3,8-dioxo functions present in haem d_1 itself. The chosen oxidant was anhydrous copper(II) acetate, and a wide range of solvents and conditions were surveyed on a small scale. Only in acetonitrile was there formation from the macrocycle **47** of a green product showing UV–visible absorption essentially identical to that of the model copper complex **49**



prepared by Chang.[26] The mass spectrum of the green product showed peaks at *m/z* 775 and 777, of relative size characteristic of the isotopes of copper and in agreement with the structure **50**. Thus our initial plan to introduce the 3,8-dioxo system at the end of the synthesis was shown to be realisable and gave us confidence to develop a far superior method for this step described in the third paper[8] of this set.

Experimental

General

Most general directions are as given in ref. 16. UV–Visible spectra were recorded on a Kontron Instruments Uvikon 810P spectrophotometer in 10 mm quartz cells. Geometric isomers of the bicyclic systems discussed in the text were distinguished in most cases by the bathochromic shift observed (or not observed) when the UV–visible spectrum was recorded after the addition of a small quantity of zinc(II) acetate to the cell.[20] Standard electron impact (EI) mass spectra were recorded on A.E.I. MS30 and MS90 instruments; spectra using field desorption (FD) were recorded on an A.E.I. MS50 instrument. For all reactions involving water-sensitive reagents, glassware was flame- or microwave oven-dried, and cooled in an evacuated desiccator. All solvents were distilled before use. Where indicated, reagents or solvents were dried or purified using standard procedures.[27]

Diethyl (2*R*,3*S*)-2-allyl-3-chloro-2-methylsuccinate 9

A solution of diethyl (2*S*,3*R*)-2-allyl-3-hydroxy-2-methylsuccinate **7** (2.00 g, 8.2 mmol) and triphenylphosphine (3.76 g, 14.4 mmol) in carbon tetrachloride (50 cm^3) and acetonitrile (15 cm^3) was heated at reflux under nitrogen for 3 h and then evaporated under reduced pressure. The residue was initially purified on a short column of silica gel and then by flash chromatography, in both cases eluting with hexane–diethyl ether (4:1), to give the *chloro ester* **9** (1.59 g, 74%) as an oil (Found: C, 54.7; H, 7.4; Cl, 13.4%; M^+, 262.0983. $C_{12}H_{19}ClO_4$ requires C, 54.85; H, 7.3; Cl, 13.5%; *M*, 262.0972); ν_{max}(thin film)/cm^{-1} 1738s and 1719sh; δ_H(400 MHz) 1.25 and 1.27 (each 3 H, t, *J* 7, CH_2CH_3), 1.37 (3 H, s, CH_3), 2.38–2.49 (2 H, m, CH_2C=C), 4.15 and 4.21 (each 2 H, q, *J* 7, CH_2CH_3), 4.68 (1 H, s, CHCl), 5.07–5.15 (2 H, m, CH_2=CH) and 5.58–5.69 (1 H, m, CH_2=CH); δ_C(100 MHz) 13.62 and 13.77 (2 × CH_3CH_2), 16.83 (2-CH_3), 41.91 (CH_2C=C), 49.47 (C-2), 60.74 (C-3), 60.79 and 61.56 (2 × CH_2CH_3), 119.15 (CH_2=C), 131.88 (C=CH) and 167.88 and 172.87 (2 × C=O); *m/z* (EI) 262 (M^+, 4%), 217 (M^+ − EtO, 20), 153 (M^+ − EtO_2C − HCl, 54) and 141 (M^+ − EtO_2C-CHCl, 100).

Diethyl (*S*)-2-allyl-2-methylsuccinate 10

A suspension of zinc powder (washed successively with dilute hydrochloric acid, water and acetone and dried briefly in air before use; 9 g, 138 mmol) in a solution of chloro ester **9** (852 mg, 3.25 mmol) in glacial acetic acid (80 cm^3) was heated at reflux for 18 h, then cooled and filtered. The filtrate was evaporated under reduced pressure and the residue was redissolved in diethyl ether. This solution was washed repeatedly with saturated aqueous sodium hydrogen carbonate until no further effervescence was observed, then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with hexane–diethyl ether (4:1), to give *ester* **10** (634 mg, 86%) as an oil (Found: M^+ − OEt, 183.1008. $C_{12}H_{20}O_4$ requires *M* − OEt, 183.1021); ν_{max}(thin film)/cm^{-1} 1740s and 1640w; δ_H(400 MHz) 1.23 and 1.24 (each 3 H, t, *J* 7, CH_2CH_3), 1.24 (3 H, s, CH_3), 2.32–2.38 (2 H, m, CH_2C=C), 2.42 and 2.71 (each 1 H, d, *J* 16, CH_2CO_2), 4.09 and 4.14 (each 2 H, q, *J* 7, CH_2CH_3), 5.03–5.09 (2 H, m, CH_2=CH) and 5.67–5.78 (1 H, m, CH_2=CH); δ_C(100 MHz) 13.74 (2 × CH_3CH_2), 21.44 (CH_3), 41.75, 42.70 and 43.56 (C-2, C-3 and CH_2C=C), 59.79 and 60.13 (2 × CH_2CH_3), 118.28 (CH_2=CH), 132.79 (CH=CH_2) and 170.61 and 175.09 (2 × C=O); *m/z* (EI) 183 (M^+ − EtO, 50%), 154 (M^+ − EtO − Et, 67), 109 (M^+ − EtO_2C − EtOH, 79) and 81 (M^+ − EtO_2C − EtO_2C − H, 100).

(*S*)-2-Allyl-2-methylsuccinic acid 11

A solution of diester **10** (5.34 g, 23.4 mmol) in a mixture of aqueous potassium hydroxide (4 mol dm^{-3}; 150 cm^3) and ethanol (50 cm^3) was stirred and heated at reflux for 60 h, then cooled, acidified to pH 2 with dilute sulfuric acid and extracted with diethyl ether (5 × 150 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give the slightly impure diacid **11** (4.37 g, 108%) as an oil. This was normally carried forward without purification but for characterisation purposes it was crystallised from diethyl ether–hexane to give the pure *diacid* **11**, mp 87.5–90 °C (Found: C, 56.1; H, 6.8%; $M^+ - H_2O$, 154.0627. $C_8H_{12}O_4$ requires: C, 55.8; H, 7.0%; $M - H_2O$, 154.0630); δ_H(400 MHz) 1.28 (3 H, s, CH_3), 2.38 (2 H, d, *J* 7, CH_2C=C), 2.49 and 2.79 (each 1 H, d, *J* 17, CH_2CO_2), 5.08–5.13 (2 H, m, C*H*$_2$=CH), 5.68–5.78 (1 H, m, CH_2=C*H*) and 12.4 (2 H, br s, 2 × CO_2H); δ_C(100 MHz) 21.9 (CH_3), 41.7 and 42.8 (2 × CH_2), 44.1 (*C*CH_3), 119.1 (*C*H_2=CH), 132.7 (CH_2=*C*H) and 177.7 and 181.6 (2 × CO_2H); *m/z* (EI) 154 ($M^+ - H_2O$, 6%), 126 (62), 113 (40), 112 (32), 111 (20), 109 (36), 95 (19), 86 (38), 81 (32) and 67 ($C_5H_7^+$, 100).

(*S*)-2-Allyl-2-methylsuccinimide 13

Diacid **11** (3.44 g, 20 mmol) was fused with urea (6.13 g, 102 mmol) and the mixture was heated with stirring at 110 °C for 18 h. The cooled mixture was dissolved in water (20 cm^3) and diethyl ether (20 cm^3). The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 75 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallisation from diethyl ether–hexane gave the *imide* **13** (2.75 g, 90%), mp 81.5–83 °C (Found: C, 63.0; H, 7.1; N, 9.1%; M^+, 153.0799. Calc. for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1%; *M*, 153.0790); ν_{max}($CHCl_3$)/cm^{-1} 3400m, 3200br, 1785m, 1720s and 1645w; δ_H(400 MHz) 1.26 (3 H, s, CH_3), 2.18 and 2.39 (each 1 H, dd, *J* 13.5 and 8, CH_2C=C), 2.37 and 2.65 (each 1 H, d, *J* 18, CH_2CO), 5.07–5.11 (2 H, m, C*H*$_2$=CH), 5.56–5.70 (1 H, m, CH_2=C*H*) and 9.39 (1 H, br s, NH); δ_C(100 MHz) 23.39 (CH_3), 40.74, 41.67 and 44.56 (2 × CH_2 and *C*CH_3), 119.70 (*C*H_2=CH), 131.70 (CH_2=*C*H) and 176.83 and 183.28 (2 × *C*=O); *m/z* (EI) 153 (M^+, 25%), 138 ($M^+ - Me$, 15), 113 (8), 112 ($M^+ - CH_2$=$CHCH_2$, 7), 110 ($M^+ - CONH$, 12), 82 ($M^+ - CONHCO$, 93) and 67 ($C_5H_7^+$, 100).

(*R*)-2-(Carboxymethyl)-2-methylsuccinimide 15

Ruthenium dioxide monohydrate (120 mg, 0.79 mmol) was added to a suspension of sodium periodate (55.93 g, 261 mmol) in water (280 cm^3) and the resulting yellow suspension was stirred vigorously at 0 °C while a solution of the imide **13** (10.0 g, 65.36 mmol) in carbon tetrachloride–acetonitrile–acetic acid (2:2:1; 225 cm^3) was added dropwise over a period of 2.5 h. Stirring was continued for 5 min and the mixture was allowed to warm up to room temperature. Dichloromethane (100 cm^3) was added and the solids were removed by filtration. The layers were separated and the aqueous layer was acidified to pH 1 with dilute hydrochloric acid and extracted with ethyl acetate (6 × 200 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. A solution of the residue in acetone (250 cm^3) was stirred with excess Jones' reagent at room temperature for 15 min. Excess chromic acid was then destroyed by adding isopropyl alcohol dropwise until the colour of the solution had changed from orange to green. The mixture was diluted with water (200 cm^3), concentrated to remove acetone and extracted with ethyl acetate (6 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the acid **15** (10.49 g, 94%), mp 181–184 °C (lit.,[28] 183–186 °C) (Found: C, 49.1; H, 5.2; N, 8.2%; M^+, 171.0536. Calc. for $C_7H_9NO_4$: C, 49.1; H, 5.3; N, 8.2%; *M*, 171.0531); ν_{max}(KBr)/cm^{-1} 3600–2500br, 3300s, 1785sh, 1770s, 1730s and 1705s; δ_H(400 MHz) 1.32 (3 H, s, Me), 2.48 and 2.86 (each 1 H, d, *J* 18, CH_2), 2.68 and 2.84 (each 1 H, d, *J* 17, CH_2), 9.93 (1 H, br s, NH) and 11.0 (1 H, br s, CO_2H); δ_C(100 MHz) 25.5 (Me), 41.0 and 42.6 (2 × CH_2), 43.1 (*C*Me) and 172.7, 177.1 and 183.6 (3 × C=O); *m/z* (EI) 171 (M^+, 23%), 153 ($M - H_2O$, 7), 128 ($M - CONH$, 38), 112 ($M - CH_2$-CO_2H, 17), 100 ($M - CONHCO$, 100), 82 (15) and 72 (88).

(*R*)-2-Methoxycarbonylmethyl-2-methylsuccinimide 16

A solution of diazomethane in diethyl ether was added dropwise to a solution of acid **15** (6.93 g, 40.53 mmol) in THF (50 cm^3) at 0 °C until the yellow colour persisted. Acetic acid (1 cm^3) was added to destroy excess diazomethane and the mixture was evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with diethyl ether, to give the crude ester (7.05 g, 94%). Recrystallisation from hexane–diethyl ether gave the pure *ester* **16** as needles, mp 54–58 °C (Found: M^+, 185.0703. $C_8H_{11}NO_4$ requires *M*, 185.0688); ν_{max}($CHCl_3$)/cm^{-1} 3400m, 1790m and 1723s; δ_H(400 MHz) 1.30 (3 H, s, Me), 2.47 and 2.81 (each 1 H, d, *J* 18, CH_2), 2.55 and 2.85 (each 1 H, d, *J* 17, CH_2), 3.63 (3 H, s, OMe) and 9.15 (1 H, br s, NH); δ_C(100 MHz) 24.97 (Me), 40.42 and 41.87 (2 × *C*H_2CO), 42.41 (*C*Me), 51.67 (OMe), 171.04 (*C*O_2Me), 176.66 and 182.87 (CONHCO); *m/z* (EI) 185 (M^+, 31%), 170 ($M - Me$, 6), 154 ($M - MeO$, 36), 142 ($M - CONH$, 17), 114 ($M - CONHCO$, 81), 112 ($M - CH_2CO_2Me$, 56), 86 (31), 83 (46), 82 (67), 71 (38), 59 (66) and 55 (100).

(*S*)-2-Methoxycarbonylmethyl-2-methyl-4-thiosuccinimide 17

The imide **16** (405 mg, 2.19 mmol) and Lawesson's reagent (1.022 g, 2.53 mmol) were heated in dry toluene (100 cm^3) at reflux for 3.75 h under argon. The cooled mixture was stirred vigorously at water pump pressure for 2 h to remove volatiles and then evaporated under reduced pressure. The residue was purified by flash chromatography, eluting first with dichloromethane and then with hexane–diethyl ether (1:1), to give the dithioimide **18** (43 mg, 9%) and the *monothioimide* **17** (300 mg, 68%) as yellow needles, mp 86–87 °C (from hexane–diethyl ether) (Found: C, 47.5; H, 5.5; N, 6.9; S, 16.1%; M^+, 201.0469. $C_8H_{11}NO_3S$ requires C, 47.7; H, 5.5; N, 7.0; S, 15.9%; *M*, 201.0460); ν_{max}($CHCl_3$)/cm^{-1} 3390w, 3140w, 1775s and 1740s; δ_H(400 MHz) 1.41 (3 H, s, Me), 2.59 and 3.02 (each 1 H, d, *J* 19, CH_2), 2.67 and 3.05 (each 1 H, d, *J* 17, CH_2), 3.66 (3 H, s, OMe) and 9.09 (1 H, br s, NH); δ_C(100 MHz) 29.2 (C*Me*), 42.1 and 43.6 (2 × *C*H_2), 49.9 (*C*Me), 51.9 (OMe), 171.1 (*C*O_2Me), 177.7 (CONH) and 219.5 (CSNH); *m/z* (EI) 201 (M^+, 89%), 170 ($M - MeO$, 50), 142 ($M - CO_2Me$, 100), 128 ($M - CH_2$-CO_2Me, 91), 114 (21), 84 (24), 71 (18), 59 (32) and 55 (43).

(*S*)-2-Methoxycarbonylmethyl-2-methyldithiosuccinimide 18

The imide **16** (526 mg, 2.84 mmol) and Lawesson's reagent (2.32 g, 5.73 mmol) were heated in dry toluene (100 cm^3) at reflux for 23 h under argon. The cooled mixture was stirred vigorously at water pump pressure for 2 h to remove volatiles and then evaporated under reduced pressure. The residue was purified by flash chromatography, eluting first with dichloromethane and then with hexane–diethyl ether (1:1), to give the *dithioimide* **18** (559 mg, 90%) as a yellow gum (Found: M^+, 217.0228. $C_8H_{11}NO_2S_2$ requires *M*, 217.0231); ν_{max}($CHCl_3$)/cm^{-1} 3370m and 1735s; δ_H(400 MHz) 1.39 (3 H, s, Me), 2.67 and 2.98 (each 1 H, d, *J* 17, CH_2), 3.05 and 3.43 (each 1 H, d, *J* 19, CH_2), 3.65 (3 H, s, OMe) and 9.95 (1 H, br s, NH); δ_C(100 MHz) 28.7 (Me), 43.4 (CH_2), 52.0 (OMe), 52.8 (*C*Me), 54.2 (CH_2), 170.9 (*C*O_2Me) and 210.7 and 219.6 (2 × C=S); *m/z* (EI) 217 (M^+, 100%), 201 ($M - O$, 7), 186 ($M - MeO$, 22), 170 ($M - CSNH$, 12), 158 ($M - CO_2Me$, 31) and 144 ($M - CH_2CO_2Me$, 77).

(*R*)-2-Methoxythiocarbonylmethyl-2-methyldithiosuccinimide 19

Lawesson's reagent (20.32 g, 50.2 mmol) and imide **16** (4.48 g, 24.2 mmol) were stirred and heated in dry toluene (130 cm^3) at reflux under argon for 19 h. After cooling, the mixture was

stirred vigorously at water pump pressure for 2 h to remove volatiles. The solution was then decanted and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting first with dichloromethane and then with hexane–diethyl ether (1:1). This achieved a partial separation of the faster running product, identified as thioester **19**, which was formed in *ca*. 15% yield (Found: M^+, 233.0016. $C_8H_{11}NOS_3$ requires *M*, 233.0003); δ_H(400 MHz) 1.40 (3 H, s, CMe), 3.00 and 3.62 (each 1 H, d, *J* 20, CH_2), 3.14 and 3.30 (each 1 H, d, *J* 16, CH_2), 4.02 (3 H, s, OMe) and 10.11 (1 H, br s, NH); δ_C(100 MHz) 28.9 (C*Me*), 53.9 (CH_2), 54.5 (*C*Me), 54.9 (CH_2), 59.0 (OMe) and 210.5, 217.8 and 218.9 (3 × C=S); *m/z* (EI) 233 (M^+, 99%), 201 (M − S, 10), 158 (M − CSOMe, 14), 144 (M − CH_2CSOMe, 100), 110 (13), 112 (13), 90 (23) and 85 (24).

The remainder of the isolated product consisted of a mixture of the dithioimide **18** and thioester **19**, which was subjected to $HgCl_2$-promoted hydrolysis according to the method described below.

(*R*)-2-Methoxycarbonylmethyl-2-methyl-1-thiosuccinimide 20

Mercuric chloride (2.6 g, 9.58 mmol) was added in portions to a stirred solution of the dithioimide **18** (1.73 g, 7.97 mmol) in a mixture of acetonitrile (60 cm^3) and water (15 cm^3), at 0 °C over 5 min. The mixture was stirred at 0 °C for 1.5 h and at room temperature for a further 2 h, then filtered (Celite). The residue was washed successively with methanol (50 cm^3), saturated methanolic hydrogen sulfide (50 cm^3) and methanol (50 cm^3). The combined filtrates were evaporated under reduced pressure to give a yellow gum, which was purified by flash chromatography, eluting with hexane–diethyl ether (55:45), to give the *monothioimide* **20** (1.12 g, 70%) as yellow needles, mp 106–106.5 °C (from hexane–diethyl ether) (Found: C, 47.4; H, 5.4; N, 6.9; S, 16.0%; M^+, 201.0475. $C_8H_{11}NO_3S$ requires C, 47.7; H, 5.5; N, 7.0; S, 15.9%; *M*, 201.0460); ν_{max}($CHCl_3$)/cm^{-1} 3390m, 3140w, 1770s and 1740s; δ_H(400 MHz) 1.33 (3 H, s, Me), 2.59 and 2.88 (each 1 H, d, *J* 17, CH_2), 2.94 and 3.20 (each 1 H, d, *J* 19, CH_2), 3.67 (3 H, s, OMe) and 9.60 (1 H, br s, NH); δ_C(100 MHz) 24.7 (C*Me*), 40.6 (CH_2), 43.7 (*C*Me), 52.1 (OMe), 52.7 (CH_2), 170.9 (CO_2Me), 183.7 (CONH) and 209.8 (CSNH); *m/z* (EI) 201 (M^+, 100%), 186 (M − Me, 7), 170 (M − MeO, 29), 169 (M − S, 33), 128 (M − CH_2CO_2Me, 81), 127 (40), 83 (33) and 55 (41).

Dibenzyl hydroxyiminomalonate

A saturated solution of sodium nitrite (40.5 g, 581 mmol) in water (90 cm^3) was added dropwise over 1 h to a mechanically stirred solution of dibenzyl malonate (54.99 g, 194 mmol) in acetic acid (33 cm^3). After a further 20 h, the mixture was diluted with diethyl ether (100 cm^3) and washed with saturated aqueous sodium hydrogen carbonate until the washings were slightly alkaline. The organic layer was washed with water (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which solidified on standing under high vacuum. The solid was broken up, shaken with hexane–diethyl ether (15:1; 250 cm^3), filtered and dried *in vacuo* to give the *oxime* (50.48 g, 83%) as a powder, mp 51.5–61 °C (Found: M^+, 313.0939. $C_{17}H_{15}NO_5$ requires *M*, 313.0950); ν_{max}($CHCl_3$)/cm^{-1} 3207br and 1742s; δ_H(250 MHz) 5.28 and 5.33 (each 2 H, s, CH_2O), 7.29–7.36 (10 H, m, 2 × Ph) and 10.19 (1 H, br s, NOH); δ_C(100 MHz) 67.8 and 68.0 (2 × CH_2O), 128.16, 128.24, 128.4 and 128.5 (10 × phenyl-CH), 134.2 and 134.3 (2 × phenyl-C), 143.6 (C=NOH) and 159.7 and 160.2 (2 × C=O); *m/z* (EI) 313 (M^+, 5%), 296 (M − OH, 2), 207 (4), 181 (4), 161 (3), 107 ($PhCH_2O^+$, 25) and 91 ($PhCH_2^+$, 100).

Methyl 5-methyl-4,6-dioxoheptanoate 21

Magnesium methoxide (10.84 g, 126 mmol) was added to a solution of 3-methylpentane-2,4-dione (13.04 g, 114 mmol) in dry diethyl ether (40 cm^3). The mixture was stirred at room temperature for 3 h and then heated at reflux for 1 h. It was then cooled to −15 °C and a solution of 3-methoxycarbonylpropanoyl chloride (20.5 g, 136 mmol) in dry diethyl ether (25 cm^3) was added. The solution was stirred for 20 h, warming up slowly to room temperature, and then acidified to pH 1 with dilute sulfuric acid (*ca*. 50 cm^3). The phases were separated and the aqueous layer was extracted with diethyl ether (75 cm^3). The organic layers were combined and stirred vigorously with aqueous ammonia (10%; 100 cm^3) for 15 min. The phases were then separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was distilled to give two main fractions, (i) dimethyl succinate bp 20–44 °C (0.1 mmHg) and (ii) *diketo ester* **21** (9.38 g, 44%) as an oil, bp 90 °C (0.1 mmHg) (Found: C, 58.1; H, 7.7%; M^+, 186.0890. $C_9H_{14}O_4$ requires C, 58.05, H, 7.6%; *M*, 186.0892); ν_{max}(thin film)/cm^{-1} 3620w, 3540w, 3450w, 1730s, 1700s and 1600m; δ_H(400 MHz) (keto form) 1.18 (3 H, d, *J* 7, *Me*CH), 2.05 (3 H, s, MeCO), 2.43–2.51 and 2.61–2.69 (each 2 H, m, CH_2CH_2), 3.51 (3 H, s, OMe) and 3.61 (1 H, q, *J* 7, C*H*Me); (enol form, distinguishable signals) 1.72 (3 H, s, MeC=C), 1.94 (3 H, s, MeCO), 3.54 (3 H, s, OMe) and 16.04 (1 H, s, OH); δ_C(100 MHz) (keto form) 11.4 (*Me*CH), 26.7 (CH_2), 27.6 (*Me*CO), 35.4 (CH_2), 50.5 (OMe), 59.8 (*C*HMe), 171.9 (CO_2Me) and 203.8 and 205.0 (2 × C=O); (enol form, distinguishable signals) 11.0 (*Me*C=C), 20.6 (*Me*CO), 27.2 and 30.9 (2 × CH_2) and 103.6 (*C*=COH); *m/z* (EI) 186 (M^+, 3%), 144 (17), 115 (M − MeCOCHMe, 100), 114 (17), 113 (M − CH_2CO_2Me, 23), 112 (28), 99 (13), 87 (MeO_2C-$CH_2CH_2^+$, 20), 59 (MeO_2C^+, 40) and 55 (68).

Benzyl 3-(2-methoxycarbonylethyl)-4,5-dimethylpyrrole-2-carboxylate 22

A mixture of zinc dust (13 g; washed successively with dilute hydrochloric acid, water and acetone and dried briefly in air before use), sodium acetate (13 g) and a solution of dibenzyl hydroxyiminomalonate (18.53 g, 59.2 mmol) in 75% aqueous acetic acid (25 cm^3) were added simultaneously to a stirred solution of the diketo ester **21** (10.5 g, 56.5 mmol) in glacial acetic acid (40 cm^3) at 80 °C. The rate of this addition was controlled so that the ensuing reaction was contained within the reaction vessel. After the initial exotherm had subsided, the mixture was heated at reflux with vigorous stirring for 1 h and then filtered. The solids were washed repeatedly with diethyl ether. The combined filtrate and washings were shaken with portions of 10% aqueous sodium hydroxide (100 cm^3) until the aqueous layer was clearly alkaline. The organic layer was then washed with brine (100 cm^3), followed by water (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with hexane–diethyl ether (3:1), to give pyrrole **22** (5.17 g, 29%) as needles, mp 92.5–94.5 °C (from ethanol; lit.,[29] 93–95 °C) (Found: C, 68.65; H, 6.7; N, 4.2%; M^+, 315.1453. Calc. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.7; N, 4.4%; *M*, 315.1465); λ_{max}(MeOH)/nm 286 and 233; ν_{max}($CHCl_3$)/cm^{-1} 3450s, 3310m, 1728s, 1688sh and 1670s; δ_H(300 MHz) 1.92 and 2.15 (each 3 H, s, CMe), 2.48 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.00 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.61 (3 H, s, OMe), 5.26 (2 H, s, $PhCH_2$), 7.30–7.40 (5 H, m, Ph) and 8.66 (1 H, br s, NH); δ_C(100 MHz) 8.4 and 11.2 (2 × C*Me*), 20.8 ($CH_2CH_2CO_2$), 34.8 ($CH_2CH_2CO_2$), 51.3 (OMe), 65.5 (CH_2Ph), 115.9, 116.6, 130.2 and 130.5 (4 × pyrrole-C), 127.9, 128.0 and 128.3 (5 × phenyl-CH), 136.2 (phenyl-C), 161.0 (CO_2Bn) and 173.5 (CO_2Me); *m/z* (EI) 315 (M^+, 41%), 224 (M − $PhCH_2$, 14), 206 (6), 198 (14), 192 (50) and 91 ($PhCH_2^+$, 100).

tert-Butyl 3-(2-methoxycarbonylethyl)-4,5-dimethylpyrrole-2-carboxylate 24

A solution of the benzyl ester **22** (14.58 g, 46.3 mmol) in THF (120 cm^3) was stirred with 10% palladium-on-carbon (1.1 g) under hydrogen at room temperature and pressure for 20 h and then filtered, washing with further small quantities of THF. *tert*-Butyl alcohol (20 cm^3, 15.72 g, 212 mmol) was added to the filtrate, followed by dicyclohexylcarbodiimide (DCC) (19 g, 92 mmol). The mixture was stirred at room temperature for 24 h,

and the precipitated dicyclohexylurea was filtered off. The filtrate was evaporated under reduced pressure and the residue redissolved in diethyl ether (50 cm^3) and filtered again. The filtrate was again evaporated under reduced pressure and the residue was purified by flash chromatography to give the *tert*-butyl ester **24** as a solid (8.60 g, 66%), mp 95–96 °C (from hexane–diethyl ether; lit.,[30] 99–100 °C) (Found: C, 63.9; H, 8.3; N, 4.85%; M^+, 281.1629. Calc. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0%; *M*, 281.1627); λ_{max}(MeOH)/nm 284 and 247; ν_{max}($CHCl_3$)/cm^{-1} 3450m, 3310w, 1728s and 1665s; δ_H(300 MHz) 1.55 (9 H, s, Bu^t), 1.92 and 2.18 (each 3 H, s, CMe), 2.50 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.97 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.66 (3 H, s, OMe) and 9.27 (1 H, br s, NH); δ_C(100 MHz) 8.5 and 11.3 (2 × C*Me*), 21.0 ($CH_2CH_2CO_2$), 28.4 (CMe_3), 35.1 ($CH_2CH_2CO_2$), 51.3 (OMe), 80.3 (CMe_3), 116.2, 117.7, 128.8 and 129.4 (4 × pyrrole-*C*), 161.2 (CO_2Bu^t) and 173.7 (CO_2Me); *m/z* (EI) 281 (M^+, 77%), 225 ($M^+ - C_4H_8$, 73), 194 ($M^+ - CH_2CH_2CO_2Me$, 38), 179 ($M^+ - CO_2Bu^t - H$, 38), 165 ($M^+ - CO_2Bu^t - Me$, 100), 152 (39), 134 (33), 122 (45) and 108 (26).

(3*R*,4*E*)-9-*tert*-Butoxycarbonyl-5-cyano-8-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 28

A solution of freshly sublimed potassium *tert*-butoxide in dry *tert*-butyl alcohol (0.5 mol dm^{-3}; 1.4 cm^3, 0.7 mmol) was added to a stirred suspension of monothioimide **20** (235 mg, 1.17 mmol) and the phosphonium salt **27** (225 mg, 0.37 mmol) in dry toluene (35 cm^3) at room temperature under argon. The resulting yellow solution was heated at reflux for 4 h, during which time the colour changed from yellow to dark red. The reaction mixture was poured into saturated aqueous ammonium chloride (50 cm^3), the phases were separated and the aqueous layer was extracted with dichloromethane (4 × 50 cm^3). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by PLC, eluting with hexane–ethyl acetate (1:1), to give the starting monothioimide (154 mg, 0.766 mmol), and the *lactam* **28** (95 mg, 54%) as a gum (Found: M^+, 473.2168. $C_{24}H_{31}N_3O_7$ requires *M*, 473.2161); λ_{max}(MeOH)/nm 293 infl, 275 infl and 253; [+Zn(OAc)$_2$] 373, 304 infl, 280 and 252; ν_{max}($CHCl_3$)/cm^{-1} 3420m, 3370m, 2195s, 1755sh, 1720s, 1675s, 1620s and 1615m; δ_H(400 MHz) 1.49 (9 H, s, Bu^t), 1.59 (3 H, s, 3-Me), 1.87 (3 H, s, 7-Me), 2.41 and 2.83 (each 1 H, d, *J* 18.3, CH_2CO_2), 2.46 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.78 and 3.42 (each 1 H, d, *J* 17.8, CH_2CONH), 2.92 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.63 and 3.66 (each 3 H, s, OMe) and 8.33 and 9.17 (each 1 H, br s, NH); δ_C(100 MHz) 8.9 (7-Me), 20.6 ($CH_2CH_2CO_2$), 26.4 (3-Me), 28.2 (CMe_3), 34.6 ($CH_2CH_2CO_2$), 40.5, 41.6 and 43.2 (CH_2C-MeCH$_2$), 51.4 and 51.7 (2 × OMe), 75.5 (C-5), 81.3 (CMe_3), 117.1, 119.9, 121.3 and 121.5 (4 × pyrrole-C), 128.9 (CN), 160.4 (CO_2Bu^t), 164.7 (C-4), 170.7 and 173.4 (2 × CO_2Me) and 174.5 (CONH); *m/z* (EI) 473 (M^+, 11%), 417 ($M - C_4H_8$, 100) and 357 ($M - C_4H_8 - CH_3CO_2H$, 60).

(3*R*,4*Z*)-9-*tert*-Butoxycarbonyl-5-methylsulfonamidomethyl-8-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 30

Anhydrous cobalt(II) chloride (700 mg, 5.38 mmol) was added to a solution of the nitrile **28** (100 mg, 0.21 mmol) in dry methanol (20 cm^3). The stirred suspension was cooled to 0 °C and sodium borohydride (210 mg, 5.53 mmol) was added in portions over 15 min. The resulting black suspension was stirred for 3 h, then a further quantity of sodium borohydride (260 mg, 6.84 mmol) was added over 15 min. After a further 2 h, the mixture was acidified to pH 2 with dilute hydrochloric acid and stirred at room temperature for 45 min. The resulting pink solution was diluted with dichloromethane (30 cm^3) and made alkaline by the addition of 10% aqueous sodium hydrogen carbonate (40 cm^3). The resulting pink precipitate was filtered off and washed with dichloromethane (20 cm^3). The two phases of the filtrate were separated and the aqueous phase was extracted with dichloromethane (4 × 50 cm^3). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was redissolved in dry dichloromethane (20 cm^3), and methanesulfonyl chloride (81 mm^3, 120 mg, 1.05 mmol) and 4-dimethylaminopyridine (154 mg, 1.26 mmol) were added. The mixture was stirred under argon at room temperature for 30 min, then diluted with dichloromethane (30 cm^3), washed with dilute hydrochloric acid (30 cm^3) followed by saturated aqueous sodium hydrogen carbonate (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by PLC, eluting with dichloromethane–methyl acetate (7:3), to give the (Z)-*sulfonamide* **30** (56 mg, 48%) as a gum (Found: M^+, 555.2235. $C_{25}H_{37}N_3O_9S$ requires *M*, 555.2250); λ_{max}(MeOH)/nm 282 and 230; [+Zn(OAc)$_2$] 282 and 227; ν_{max}($CHCl_3$)/cm^{-1} 3430m, 3390m, 1720s, 1660s and 1565w; δ_H(400 MHz) 1.44 (9 H, s, Bu^t), 1.48 (3 H, s, 3-Me), 1.81 (3 H, s, 7-Me), 2.37–2.45 (3 H, m, $CH_2CH_2CO_2$ and CHHCONH), 2.55 (3 H, s, $MeSO_2$), 2.69 (1 H, d, *J* 16, CHHCO$_2$), 2.87–2.94 (4 H, m, $CH_2CH_2CO_2$, CHHCO$_2$ and CHHCONH), 3.62 and 3.64 (each 3 H, s, OMe), 3.98 (2 H, br m, CH_2NHSO_2), 5.49 (1 H, br s, CH_2NHSO_2) and 9.50 (2 H, s, 2 × NH); δ_C(100 MHz) 8.9 (7-Me), 20.8 ($CH_2CH_2CO_2$), 28.2 (CMe_3), 28.3 (3-Me), 34.8 ($CH_2CH_2CO_2$), 39.7 ($MeSO_2$), 40.1, 43.1, 44.0 and 45.0 (CH_2NH and CH_2CCH_2), 51.4 and 51.95 (2 × OMe), 81.1 (CMe_3), 100.2 (C-5), 118.4, 120.6, 128.4 and 128.6 (4 × pyrrole-C), 147.7 (C-4), 160.9 (CO_2Bu^t), 171.1 and 173.5 (2 × CO_2Me) and 174.1 (CONH); *m/z* 555 (M^+, 36%), 499 ($M^+ - C_4H_8$, 20), 491 (21), 455 (15), 435 (23), 404 (17) and 392 (100).

A further band isolated from the PLC (8 mg) was thought to contain the (*E*)-isomer (as indicated by mass spectrometry) but was not pure (by ^{1}H NMR spectroscopy).

(3*R*,4*Z*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 31

A solution of the sulfonamide **30** (602 mg, 1.09 mmol) in dry DMF (35 cm^3) was stirred with dry *N*,*N*′-diethylethylenediamine (1.55 cm^3, 1.26 g, 10.85 mmol) at 120 °C under argon for 2 h, then cooled and evaporated under high vacuum. The residue was purified by flash chromatography, eluting with methyl acetate–dichloromethane (3:7), to give the (Z)-*lactam* **31** (468 mg, 78%) as a foam (Found: M^+, 448.2189. $C_{23}H_{32}N_2O_7$ requires *M*, 448.2209); λ_{max}(MeOH)/nm 308 and 227; [+Zn(OAc)$_2$] 358, 270 and 234; ν_{max}($CHCl_3$)/cm^{-1} 3435m, 3260br, 1735sh, 1720s, 1670s and 1565w; δ_H(400 MHz) 1.39 (3 H, s, 3-Me), 1.51 (9 H, s, Bu^t), 1.92 (3 H, s, 7-Me), 2.38 and 2.89 (each 1 H, d, *J* 18, CH_2CONH), 2.46–2.50 (2 H, m, $CH_2CH_2CO_2$), 2.62 and 2.67 (each 1 H, d, *J* 16, CH_2CO_2), 2.93–2.97 (2 H, m, $CH_2CH_2CO_2$), 3.65 and 3.66 (each 3 H, s, OMe), 5.21 (1 H, s, 5-H) and 8.56 and 9.08 (each 1 H, br s, NH); δ_C(100 MHz) 9.1 (7-Me), 20.8 ($CH_2CH_2CO_2$), 28.1 (3-Me), 28.3 (CMe_3), 34.9 ($CH_2CH_2CO_2$), 40.4, 42.6 and 44.4 (CH_2CCH_2), 51.4 and 51.6 (2 × OMe), 80.7 (CMe_3), 89.8 (C-5), 118.1, 120.1, 127.8 and 128.9 (4 × pyrrole-C), 146.8 (C-4), 161.0 (CO_2Bu^t), 170.9 and 173.6 (2 × CO_2CH_3) and 176.0 (CONH); *m/z* 448 (M^+, 48%), 392 ($M^+ - C_4H_8$, 100), 332 ($M^+ - C_4H_8 - MeO_2CH$, 56) and 318 (17).

(3*S*,4*Z*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-thione 32

A solution of lactam **31** (254 mg, 0.567 mmol), dry Hünig's base (295 mm^3, 220 mg, 1.7 mmol) and Lawesson's reagent (940 mg, 2.32 mmol) in dry 1,2-dimethoxyethane (25 cm^3) was stirred and heated at reflux under argon for 45 min, then cooled and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting first with dichlorometh-

ane and then with hexane–ethyl acetate (1:1), to give the (Z)-*thiolactam* **32** as a gum (234 mg, 89%) (Found: M^+, 464.1973. $C_{23}H_{32}N_2O_6S$ requires *M*, 464.1981); λ_{max}(MeOH)/nm 338 and 272; [+Zn(OAc)$_2$] 392 and 262; ν_{max}($CHCl_3$)/cm^{-1} 3440w, 3385w, 1730s, 1670s, 1600w and 1560w; δ_H(400 MHz) 1.37 (3 H, s, 3-Me), 1.42 (9 H, s, Bu^t), 1.89 (3 H, s, 7-Me), 2.43–2.47 (2 H, m, $CH_2CH_2CO_2$), 2.57 and 2.64 (each 1 H, d, *J* 15.5, CH_2CO_2), 2.86–2.90 (2 H, m, $CH_2CH_2CO_2$), 2.88 and 3.26 (each 1 H, d, *J* 18.5, CH_2C=S), 3.63 and 3.64 (each 3 H, s, OMe), 5.33 (1 H, s, 5-H) and 9.55 and 10.13 (each 1 H, br s, NH); δ_C(100 MHz) 9.0 (7-Me), 20.7 ($CH_2CH_2CO_2$), 26.8 (3-Me), 28.2 (CMe_3), 34.9 ($CH_2CH_2CO_2$), 42.9 (C-3), 44.1 (CH_2CO_2), 51.4 and 51.6 (2 × OMe), 54.9 (CH_2C=S), 81.0 (CMe_3), 92.5 (C-5), 118.6, 120.4, 127.5 and 129.0 (4 × pyrrole-C), 150.2 (C-4), 161.0 (CO_2Bu^t), 170.7 and 173.5 (2 × CO_2Me) and 203.5 (C=S); *m/z* 464 (M^+, 29%) and 408 ($M^+ - C_4H_8$, 100).

A very small amount of the (*E*)-isomer was also obtained but it was contaminated with inseparable impurities and could not be fully characterised. The following NMR signals could be seen: δ_H(400 MHz) 1.86 (s, 3-CH_3), 3.62 (s, OMe), 5.86 (s, 5-H) and 9.25 and 10.55 (each br s, NH); δ_C(100 MHz) 20.7 ($CH_2CH_2CO_2$), 27.0 (3-Me), 28.3 (CMe_3), 42.6 (C-3), 43.5 (CH_2CO_2), 51.9 (OMe), 96.2 (C-5) and 202.3 (C=S).

(2*R*,4*E*)-9-*tert*-Butoxycarbonyl-5-cyano-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 33

A solution of freshly sublimed potassium *tert*-butoxide in dry *tert*-butyl alcohol (0.5 mol dm^{-3}; 2.1 cm^3, 1.05 mmol) was added to a stirred suspension of monothioimide **17** (130 mg, 0.647 mmol) and phosphonium salt **27** (580 mg, 0.96 mmol) in dry toluene (30 cm^3) at room temperature under argon. The resulting yellow solution was heated at reflux for 2 h, during which time the colour changed from yellow to dark red. A further quantity of the solution of potassium *tert*-butoxide in *tert*-butyl alcohol (0.8 cm^3, 0.4 mmol) was added, followed by triphenylphosphine (125 mg, 0.48 mmol). The mixture was stirred and heated at reflux for a further 3 h and then poured into saturated aqueous ammonium chloride (50 cm^3). The phases were separated and the aqueous layer was extracted with dichloromethane (4 × 50 cm^3). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with hexane–ethyl acetate (1:1), and then by PLC, eluting with the same solvent, to yield the *lactam* **33** (275 mg, 90%) as a gum (Found: M^+, 473.2179. $C_{24}H_{31}N_3O_7$ requires *M*, 473.2161); λ_{max}(MeOH)/nm 297 and 246; [+Zn(OAc)$_2$] 371, 287 and 248; ν_{max}($CHCl_3$)/cm^{-1} 3400w,br, 2205w, 1735s, 1680m and 1640s; δ_H(400 MHz) 1.27 (3 H, s, 2-Me), 1.49 (9 H, s, Bu^t), 1.94 (3 H, s, 7-Me), 2.48 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.57 and 2.81 (each 1 H, d, *J* 17, CH_2CO_2), 2.92 and 3.22 (each 1 H, d, *J* 18, 3-H_2), 2.94 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.64 (6 H, s, 2 × OMe) and 8.48 and 9.21 (each 1 H, br s, NH); δ_C(100 MHz) 9.2 (7-Me), 20.7 ($CH_2CH_2CO_2$), 25.1 (2-Me), 28.3 (CMe_3), 34.7 ($CH_2CH_2CO_2$), 39.1, 40.6 and 41.5 (CH_2CMeCH_2), 51.5 and 51.9 (2 × OMe), 77.7 (C-5), 81.4 (CMe_3), 117.0, 119.8, 121.0 and 121.6 (4 × pyrrole-C), 129.0 (CN), 155.4 (C-4), 160.5 (CO_2Bu^t), 171.0 and 173.5 (2 × CO_2Me) and 181.0 (CONH); *m/z* (EI) 473 (M^+, 40%), 417 ($M^+ - C_4H_8$, 100) and 357 ($M^+ - CO_2Bu^t$ − Me, 30).

(2*R*,4*Z*)-9-*tert*-Butoxycarbonyl-5-methylsulfonamidomethyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 35

Anhydrous cobalt(II) chloride (9.01 g, 69 mmol) was added to a solution of the nitrile **33** (1.356 g, 2.87 mmol) in dry methanol (20 cm^3). The stirred suspension was cooled to 0 °C and sodium borohydride (2.82 g, 74 mmol) was added in portions over 10 min. The resulting black suspension was stirred under argon for 45 min and then a further quantity of sodium borohydride (2.7 g, 71 mmol) was added. After a further 2.5 h at 0 °C, the mixture was acidified to pH 1 with dilute hydrochloric acid and stirred at room temperature for a further 3.5 h to allow the complexes to decompose. The resulting pink solution was shaken with saturated aqueous sodium hydrogen carbonate (250 cm^3), diluted with dichloromethane (200 cm^3) and filtered through Celite. The solid was washed with dichloromethane (3 × 200 cm^3) and the aqueous phase separated and extracted with dichloromethane (3 × 200 cm^3). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure at 25–30 °C. The residue was redissolved in dry dichloromethane (100 cm^3), and methanesulfonyl chloride (1.33 cm^3, 1.97 g, 17.2 mmol) and 4-dimethylaminopyridine (2.45 g, 20 mmol) were added. The mixture was stirred under argon at room temperature for 20 min and then diluted with dichloromethane (100 cm^3), washed with dilute hydrochloric acid (100 cm^3) and saturated aqueous sodium hydrogen carbonate (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with dichloromethane–methyl acetate (7:3), to give the *sulfonamide* **35** as a mixture of *E* and *Z* isomers (753 mg, 47%). For characterisation, the isomers could be separated by PLC, eluting with the same solvent.

For the (*Z*)-isomer (Found: M^+, 555.2289. $C_{25}H_{37}N_3O_9S$ requires *M*, 555.2250); λ_{max}(MeOH)/nm 291 and 235; [+Zn(OAc)$_2$] 291; ν_{max}($CHCl_3$)/cm^{-1} 3430sh, 3390m, 1725s, 1670s and 1570w; δ_H(400 MHz) 1.22 (3 H, s, 2-Me), 1.44 (9 H, s, Bu^t), 1.99 (3 H, s, 7-Me), 2.44 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.50 and 2.72 (each 1 H, d, *J* 17.0, CH_2CO_2) and 2.81 and 3.11 (each 1 H, d, *J* 16.8, 3-H_2), 2.84 (3 H, s, $MeSO_2$), 2.96 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.65 and 3.66 (each 3 H, s, OMe), 3.91 (2 H, d, *J* 5.6, CH_2NH), 4.98 (1 H, br t, *J* 5.6, CH_2NH) and 7.13 and 9.24 (each 1 H, br s, NH); δ_C(100 MHz) 9.3 (7-Me), 20.8 ($CH_2CH_2CO_2$), 24.9 (2-Me), 28.2 (CMe_3), 34.8 ($CH_2CH_2CO_2$), 36.5 (CH_2NH), 40.4 ($MeSO_2$), 40.6 and 43.7 (C-3 and CH_2CO_2), 41.9 (C-2), 51.4 and 51.6 (2 × OMe), 80.9 (CMe_3), 99.8 (C-5), 118.4, 120.5, 128.3 and 128.6 (4 × pyrrole-C), 139.1 (C-4), 160.9 (CO_2Bu^t), 171.3 and 173.5 (2 × CO_2Me) and 180.7 (CONH); *m/z* 555 (M^+, 16%) and 499 ($M - C_4H_8$, 28).

For the (*E*)-isomer (Found: M^+, 555.2213); δ_H(400 MHz) 1.21 (3 H, s, 2-Me), 1.54 (9 H, s, Bu^t), 1.87 (3 H, s, 7-Me), 2.34 and 2.71 (each 1 H, d, *J* 17) and 2.48 and 2.78 (each 1 H, d, *J* 17, CH_2CCH_2), 2.50 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.85 (3 H, s, $MeSO_2$), 2.96 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.62 and 3.65 (each 3 H, s, OMe), 3.92 and 3.94 (each 1 H, d, *J* 6, CH_2NH), 5.93 (1 H, br t, *J* 6, CH_2NH) and 9.42 and 9.63 (each 1 H, br s, NH); δ_C(100 MHz) 9.7 (7-Me), 21.0 ($CH_2CH_2CO_2$), 24.8 (2-Me), 28.4 (CMe_3), 35.0 ($CH_2CH_2CO_2$), 38.1 (CH_2NH), 40.6, 40.7 and 43.6 ($MeSO_2$ and CH_2CCH_2), 41.7 (C-2), 51.5 and 51.8 (2 × OMe), 81.0 (CMe_3), 100.7 (C-5), 117.9, 119.9, 128.4 and 130.1 (4 × pyrrole-C), 140.0 (C-4), 161.0 (CO_2Bu^t), 171.5 and 173.7 (2 × CO_2Me) and 182.4 (CONH); *m/z* 555 (M^+, 58%), 499 ($M - C_4H_8$, 68), 487 (52), 476 ($M - SO_2Me$, 10), 460 ($M - MeSO_2NH_2$, 26), 448 ($M - MeSO_2NCH_2$, 16) and 404 ($M - MeSO_2NH_2 - C_4H_8$, 100).

(2*R*,4*Z*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 36

A solution of the sulfonamide **35** (745 mg, 1.34 mmol) and dry *N*,*N*′-diethylethylenediamine (1.92 cm^3, 1.56 g, 13.4 mmol) in dry DMF (60 cm^3) was stirred at 120 °C under argon for 2 h, then cooled and evaporated under high vacuum. The residue was purified by flash chromatography, eluting with methyl acetate–dichloromethane (3:7), to give the *lactam* **36** (468 mg, 78%) as a mixture of isomers. For characterisation the isomers could be separated on a small scale by PLC, using the same solvent system, to give the (*Z*)- and (*E*)-isomers in a ratio of 1:2.6.

For the (*Z*)-isomer (Found: M^+, 448.2205. $C_{23}H_{32}N_2O_7$ requires *M*, 448.2209); λ_{max}(MeOH)/nm 308 and 228;

[+Zn(OAc)$_2$] 356, 309, 279 and 231; ν_{max}(CHCl$_3$)/cm^{-1} 3430br, 3410sh, 1730sh, 1720s, 1670s and 1560w; δ_H(400 MHz) 1.29 (3 H, s, 2-Me), 1.51 (9 H, s, Bu^t), 1.94 (3 H, s, 7-Me), 2.46–2.50 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.62 and 2.82 (each 1 H, d, *J* 17, CH$_2$CO$_2$), 2.65 (1 H, dd, *J* 16 and 1) and 3.05 (1 H, dd, *J* 16 and 2, 3-H$_2$), 2.93–2.97 (2 H, m, C*H*$_2$CH$_2$CO$_2$), 3.63 and 3.65 (each 3 H, s, OMe), 5.30 (1 H, br s, 5-H) and 9.03 and 9.17 (each 1 H, br s, NH); δ_C(100 MHz) 9.1 (7-Me), 20.9 (*C*H$_2$CH$_2$CO$_2$), 24.1 (2-Me), 28.3 (C*Me*$_3$), 35.0 (CH$_2$*C*H$_2$CO$_2$), 39.8, 40.5 and 41.8 (CH$_2$CCH$_2$), 51.4 and 51.6 (2 × OMe), 80.8 (*C*Me$_3$), 91.9 (C-5), 117.8, 119.9, 128.3 and 128.8 (4 × pyrrole-C), 135.4 (C-4), 161.1 (*C*O$_2$Bu^t), 171.5 and 173.7 (2 × *C*O$_2$Me) and 182.1 (CONH); *m/z* 448 (M$^+$, 21%), 392 (M$^+$ − C$_4$H$_8$, 100) and 332 (M$^+$ − C$_4$H$_8$ − HCO$_2$Me, 19).

For the (*E*)-isomer (Found: M$^+$, 448.2206); λ_{max}(MeOH)/nm 326, 244infl and 228; [+Zn(OAc)$_2$] 326, 245infl and 224; ν_{max}(CHCl$_3$)/cm^{-1} 3460m, 3410m, 1720s, 1665s and 1560w; δ_H(400 MHz) 1.27 (3 H, s, 2-Me), 1.54 (9 H, s, Bu^t), 1.94 (3 H, s, 7-Me), 2.46–2.50 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.55 (1 H, d, *J* 17, C*H*HCO$_2$), 2.74–2.82 (2 H, m, CH*H*CO$_2$ and 3-H$_A$), 2.93–2.97 (2 H, m, C*H*$_2$CH$_2$CO$_2$), 3.14 (1 H, dd, *J* 16 and 2, 3-H$_B$), 3.64 (6 H, s, 2 × OMe), 5.75 (1 H, br s, 5-H) and 8.52 and 8.58 (each 1 H, br s, NH); *m/z* 448 (M$^+$, 20%), 392 (M$^+$ − C$_4$H$_8$, 100) and 332 (M$^+$ − C$_4$H$_8$ − HCO$_2$Me, 18).

(2*R*,4*Z*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-thione 37

Lawesson's reagent (2.14 g, 5.53 mmol) and Hünig's base (250 mm^3, 185 mg, 1.43 mmol) were added to a stirred solution of the lactam **36** (443 mg, 0.99 mmol) in dry toluene (75 cm^3) under argon. The mixture was heated at reflux for 30 min, then allowed to cool and evaporated under reduced pressure. The residue was purified initially by flash chromatography, eluting first with dichloromethane and then with dichloromethane–methyl acetate (4:1), and then by PLC, eluting with hexane–ethyl acetate (1:1), to give the (Z)- and (E)-*thiolactams* **37** as a yellow gum (combined yield 274 mg, 60%).

The product at higher R_f was the (*Z*)-isomer (Found: 464.1944. C$_{23}$H$_{32}$N$_2$O$_6$S requires 464.1981); λ_{max}(MeOH)/nm 352, 271 and 217; [+Zn(OAc)$_2$] 378 and 261; ν_{max}(CHCl$_3$)/cm^{-1} 3420w, 3360w, 1730s, 1670m and 1595w; δ_H(400 MHz) 1.35 (3 H, s, 2-Me), 1.55 (9 H, s, Bu^t), 1.96 (3 H, s, 7-Me), 2.49–2.53 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.72 and 2.84 (each 1 H, d, *J* 17, CH$_2$CO$_2$), 2.80 (1 H, dd, *J* 1.4 and 16, C*H*HC=C), 2.95–2.99 (2 H, m, C*H*$_2$CH$_2$CO$_2$), 3.23 (1 H, dd, *J* 2.1 and 16, CH*H*C=C), 3.66 and 3.67 (each 3 H, s, OMe), 5.45 (1 H, br s, 5-H) and 9.03 and 9.55 (each 1 H, br s, NH); δ_C(100 MHz) 8.8 (7-Me), 20.7 (*C*H$_2$CH$_2$CO$_2$), 27.5 (2-Me), 28.3 (C*Me*$_3$), 34.9 (CH$_2$*C*H$_2$CO$_2$), 38.6 and 43.3 (*C*H$_2$CO$_2$ and *C*H$_2$C=C), 40.1 (C-2), 51.4 and 51.6 (2 × OMe), 81.1 (*C*Me$_3$), 95.5 (C-5), 119.7, 120.0, 128.5 and 128.7 (4 × pyrrole-C), 138.8 (C-4), 161.1 (*C*O$_2$Bu^t), 171.2 and 173.6 (2 × *C*O$_2$Me) and 205.8 (C=S); *m/z* 464 (M$^+$, 25%) and 408 (M$^+$ − C$_4$H$_8$, 100).

The product at lower R_f was the (*E*)-isomer: λ_{max}(MeOH)/nm 359, 253 and 220; [+Zn(OAc)$_2$] 362 and 253; ν_{max}(CHCl$_3$)/cm^{-1} 3460m, 3380m, 3190br, 1730s, 1665s and 1560m; δ_H(400 MHz) 1.36 (3 H, s, 2-Me), 1.55 (9 H, s, Bu^t), 1.96 (3 H, s, 7-Me), 2.47–2.51 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.71 (1 H, d, *J* 15, C*H*HCO$_2$), 2.90 (1 H, dd, *J* 1.6 and 16, C*H*HC=C), 2.94–2.98 (3 H, m, C*H*$_2$CH$_2$CO$_2$ and CH*H*CO$_2$), 3.33 (1 H, dd, *J* 2.3 and 16, CH*H*C=C), 3.64 and 3.66 (each 3 H, s, OMe), 5.96–5.97 (1 H, m, 5-H) and 8.59 and 10.18 (each 1 H, br s, NH). The (*E*)-isomer was converted into the (*Z*)-isomer when dissolved in CDCl$_3$ (freshly filtered through basic alumina) at such a rate that it was impossible to obtain a clean ^{13}C NMR spectrum in this solvent, which is the one used for most of the other compounds. It was possible, however, to identify some signals belonging to the (*E*)-isomer which were present in the ^{13}C spectrum of the (*Z*)-isomer described above: δ_C(100 MHz) 9.2 (7-Me), 20.9 (*C*H$_2$CH$_2$CO$_2$), 28.4 (C*Me*$_3$), 81.2 (*C*Me$_3$) and 93.1 (C-5).

tert-Butyl (3*R*,4*Z*)-1-[bis(*tert*-butoxycarbonyl)methylene]-8-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3,7-dimethyl-1,2,3,10-tetrahydrodipyrrin-9-carboxylate 41

A solution of di-*tert*-butyl bromomalonate in dry dichloromethane (0.18 mol dm^{-3}; 7.5 cm^3, 1.35 mmol) was mixed with a solution of thiolactam **32** (370 mg, 0.8 mmol) in dry dichloromethane (40 cm^3) and dry 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (650 mm^3, 662 mg, 4.35 mmol) and stirred at room temperature under argon for 1 h. A further quantity of the di-*tert*-butyl bromomalonate solution (2.5 cm^3, 0.45 mmol) was then added. After a further 30 min, the solution was evaporated under reduced pressure and the residue was redissolved in dry toluene (50 cm^3). Triphenylphosphine (1.99 g, 7.6 mmol) was added, and the resulting solution was heated at reflux under argon for 1 h. A further quantity of dry DBU (400 mm^3, 407 mg, 2.67 mmol) was added and heating continued for a further 1.25 h. The reaction mixture was cooled, diluted with diethyl ether (100 cm^3) and washed, first with hydrochloric acid (1 mol dm^{-3}) saturated with sodium chloride (30 cm^3), and then with brine (30 cm^3). The organic phase was dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was purified by PLC, eluting with hexane–ethyl acetate (1:1), to give, at lower R_f value, the (Z)-*enamine* **41** (342 mg, 66%) as a foam (Found: M$^+$, 646.3423. C$_{34}$H$_{50}$N$_2$O$_{10}$ requires *M*, 646.3464); λ_{max}(MeOH)/nm 338, 275 and 233; [+Zn(OAc)$_2$] 405, 334, 291 and 228sh; ν_{max}(CHCl$_3$)/cm^{-1} 3450m, 3300br, 1730s, 1685sh, 1675s, 1645s and 1580s; δ_H(400 MHz) 1.34 (3 H, s, 3-Me), 1.46, 1.49 and 1.54 (each 9 H, s, Bu^t), 1.92 (3 H, s, 7-Me), 2.52–2.56 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.58 (2 H, s, CH$_2$CO$_2$), 2.95 and 3.38 (each 1 H, d, *J* 18, CH$_2$C=C), 2.99–3.03 (2 H, m, C*H*$_2$CH$_2$CO$_2$), 3.63 and 3.66 (each 3 H, s, OMe), 5.21 (1 H, s, 5-H) and 8.56 and 10.52 (each 1 H, br s, N*H*); δ_C(100 MHz) 9.4 (7-Me), 20.7 (*C*H$_2$CH$_2$CO$_2$), 27.7 (3-Me), 28.3, 28.37 and 28.43 (3 × C*Me*$_3$), 34.7 (CH$_2$*C*H$_2$CO$_2$), 40.9 (C-3), 44.21 and 44.24 (*C*H$_2$CO$_2$ and *C*H$_2$C=C), 51.5 and 51.7 (2 × OMe), 80.0, 80.4 and 80.6 (3 × *C*Me$_3$), 89.8 (C-5), 95.3 [*C*(CO$_2$Bu^t)$_2$], 118.1, 119.8, 128.0 and 129.6 (4 × pyrrole-C), 149.7 (C-4), 160.4, 163.6 and 166.6 (3 × *C*O$_2$Bu^t), 167.9 (C-1) and 170.9 and 173.8 (2 × *C*O$_2$Me); *m/z* (FD) 646 (M$^+$, 100%).

Usually there was so little of the (*E*)-isomer formed (ratio *Z*:*E*, *ca.* 25:1) that it was not practical to isolate it in a pure form. On one occasion, however, a sample of the (*Z*)-isomer was found to have partially isomerised, presumably due to storage in a slightly acidic environment. This mixture was purified by TLC, eluting with hexane–diethyl ether (1:1), to give, at higher R_f value, a sample of the (*E*)-isomer as a foam; δ_H(400 MHz) 1.19 (3 H, s, 3-Me), 1.49, 1.50 and 1.54 (each 9 H, s, Bu^t), 1.87 (3 H, s, 7-Me), 2.40 and 2.44 (each 1 H, d, *J* 16, CH$_2$CO$_2$), 2.49–2.53 (2 H, m, CH$_2$C*H*$_2$CO$_2$), 2.95–2.99 (2 H, m, C*H*$_2$CH$_2$-CO$_2$Me), 2.95 and 3.40 (each 1 H, d, *J* 18.5, CH$_2$C=C), 3.64 and 3.65 (each 3 H, s, OMe), 5.67 (1 H, s, 5-H) and 9.06 and 10.38 (each 1 H, br s, NH); δ_C(100 MHz) 9.3 (7-Me), 20.9 (*C*H$_2$CH$_2$CO$_2$), 27.5 (3-Me), 28.3, 28.4 and 28.5 (3 × C*Me*$_3$), 35.0 (CH$_2$*C*H$_2$CO$_2$), 40.7 (C-3), 43.5 and 46.55 (*C*H$_2$CO$_2$ and *C*H$_2$C=C), 51.5 and 51.9 (2 × OMe), 79.9, 80.3 and 80.6 (3 × *C*Me$_3$), 89.7 [*C*(CO$_2$Bu^t)$_2$], 93.7 (C-5), 119.17, 119.24, 126.1 and 128.6 (4 × pyrrole-C), 151.7 (C-4), 160.7, 164.0 and 166.8 (3 × *C*O$_2$Bu^t), 168.4 (C-1) and 171.5 and 173.7 (2 × *C*O$_2$Me).

(3*R*,4*Z*)-8-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-1,3,7-trimethyl-2,3-dihydrodipyrrin 44

The tri-*tert*-butyl ester **41** (100 mg, 0.155 mmol) was stirred in dry TFA (5 cm^3) under argon in the dark for 40 min. The TFA was removed by evaporation under high vacuum, finally azeotroping with dry toluene (4 × 5 cm^3) to remove residual traces. The residue was dissolved in dry toluene (15 cm^3), treated with

anhydrous sodium acetate (270 mg, 3.29 mmol) and glacial acetic acid (10 drops), heated at reflux under argon in the dark for 130 min, then cooled, filtered through cotton wool and evaporated at 20 °C under high vacuum. The residue was purified as rapidly as possible by PLC, eluting with diethyl ether, to give the *imine* **44** (35.5 mg, 66%) as a gum (Found: M + H^+, 347.1979. $C_{19}H_{26}N_2O_4$ requires *M* + H^+, 347.1971); $\lambda_{max}(CH_2Cl_2)$/nm 337; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3350br, 1730s and 1595w; δ_H(400 MHz, C_6D_6) 1.09 (3 H, s, 3-Me), 1.73 (3 H, s, 7-Me), 2.05 and 2.75 (each 1 H, d, *J* 19, $CH_2C{=}N$), 2.08 (3 H, s, 1-Me), 2.23 and 2.29 (each 1 H, d, *J* 15, CH_2CO_2), 2.49 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.87 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.24 and 3.34 (each 3 H, s, OMe), 5.80 (1 H, s, 5-H), 6.44 (1 H, d, *J* 2, 9-H) and 10.73 (1 H, br s, NH); *m/z* (EI) 347 (M + H^+, 29%), 319 (M − CHN, 82), 303 (M + H − CO_2, 28), 287 (M − CO_2Me, 44), 261 (25), 189 (83) and 165 ($C_9H_{11}NO_2$, 92).

(2*R*,4*Z*)-9-Formyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-1-methylthio-2,3-dihydrodipyrrin 45

The thiolactam **37** (80 mg, 0.177 mmol) was stirred in dry TFA (5 cm^3) under argon in the dark for 45 min. Trimethyl orthoformate (200 mm^3) was added and then, after a further 15 min, water (3 cm^3) was added. After a final 10 min, the mixture was diluted with dichloromethane (50 cm^3), washed with 10% aqueous ammonia (40 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure at 25 °C. The residue was purified by PLC, eluting with dichloromethane–methyl acetate (7:3), to give the *thioimino ether* **45** (64 mg, 89%) as a gum (Found: M^+, 406.1557. $C_{20}H_{26}N_2O_5S$ requires *M*, 406.1562); $\lambda_{max}(CH_2Cl_2)$/nm 386, 379 and 264; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3510w, 3465w, 3390w, 1740s, 1625s and 1525m; δ_H(400 MHz, CH_2Cl_2) 1.33 (3 H, s, 2-Me), 2.03 (3 H, s, 7-Me), 2.55 (3 H, s, SMe), 2.55 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.60 and 2.66 (each 1 H, d, *J* 16, CH_2CO_2), 2.83 and 3.26 (each 1 H, dd, *J* 16 and 2, $CH_2C{=}C$), 3.01 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.647 and 3.653 (each 3 H, s, OMe), 6.52 (1 H, t, *J* 2, 5-H), 8.84 (1 H, br s, NH) and 9.52 (1 H, s, CHO); *m/z* (EI) 406 (M^+, 100%), 391 (M − Me, 3), 377 (M − CHO, 5), 375 (7), 359 (M − SMe, 8) and 347 (M − CO_2Me, 16).

13,17-Bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-2,7,12,18-tetramethylisobacteriochlorin 47

For the condensation and photochemical cyclisation steps, the following procedures were used. All apparatus was dried before use. Starting materials were vacuum-dried at less than 0.1 mmHg for a minimum of 30 min. All solvents and reagents were dried and purified. All transfers were carried out using a double-ended needle (cannula), driven by a small pressure of argon. All reactions were carried out under argon, taking the utmost care to exclude water and air. Light was also excluded except during the photochemical cyclisation step. Irradiations were performed using a 1000 W array of tungsten light bulbs, at an average distance of 10 cm from the tubes which were submerged in aqueous potassium dichromate (0.04 mol dm^{-3}) maintained at below 30 °C. Macrocyclic materials were stored in the dark under argon at −18 °C.

A solution of the imine **44** (35 mg, 0.101 mmol) in methanol (5 cm^3) was added by cannula to the formyl imino thioether **45** (58 mg, 0.143 mmol) under argon at room temperature. Saturated methanolic hydrogen chloride (5 drops) was added to the stirred solution, producing an immediate deep blue coloration. The solution was stirred for 3 h at room temperature under argon in the dark. During this time diisopropylethylammonium trifluoroacetate was prepared by adding TFA (0.35 cm^3, 518 mg, 4.55 mmol) to a solution of Hünig's base (0.4 cm^3, 297 mg, 2.3 mmol) in toluene (5 cm^3). Excess TFA was removed by evaporation under high vacuum, azeotroping with further toluene. The residual liquid was heated at 120 °C under high vacuum (0.1 mmHg) until evidence of sublimation was seen (about 5 min). After cooling, the salt was redissolved in toluene (2 cm^3) under argon.

The reaction mixture was diluted with THF (20 cm^3), neutralised with Hünig's base (0.8 cm^3) (the colour changed at this point from intense blue to a deep purple–red), added to the solution of diisopropylethylammonium trifluoroacetate in toluene in a thick-walled glass tube and diluted with THF to a total volume of 40 cm^3. It was subjected to four cycles of freeze–pump–thaw degassing and then sealed under high vacuum and irradiated for 15 days.

The tube was opened and the solvent was evaporated under reduced pressure. A solution of the residue in dichloromethane (40 cm^3) was washed with hydrochloric acid (0.5 mol dm^{-3}; 30 cm^3) and then saturated aqueous sodium hydrogen carbonate (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by PLC on two PLC plates (Merck, 2 mm thickness), eluting continuously with methyl acetate–dichloromethane (16:84). Extraction of the pink–purple band with a bright orange fluorescence near the top of the plate with methyl acetate gave the *isobacteriochlorin* **47** (13.4 mg, 19%) as a purple gum (Found: M^+, 686.3311. $C_{38}H_{46}N_4O_8$ requires *M*, 686.3315); λ_{max}(free base in CH_2Cl_2)/nm 632 (ε/dm^3 mol^{-1} cm^{-1} 6200), 585 (15 700), 543 (10 300), 510 (6700), 399 (36 000), 376 (infl, 56 900) and 368 (66 250); (+ acid) 625 (20 500), 583 (8900), 544 (4400), 491 (4800), 404 (57 000), 382 (39 400) and 369 (43 400); $\nu_{max}(CCl_4)$/cm^{-1} 3365w, 1740s, 1640w, 1605m and 1510w; δ_H(400 MHz, CD_2Cl_2) 1.78 (3 H, s, 7-Me), 1.80 (3 H, s, 2-Me), 2.86 (3 H, s, 12-Me), 2.90 (3 H, s, 18-Me), 2.93 and 2.94 (each 2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.06 and 3.13 (each 1 H, d, *J* 15, 7-CH_2CO_2), 3.08 and 3.17 (each 1 H, d, *J* 15, 2-CH_2CO_2), 3.63 and 3.64 (each 3 H, s, OMe), 3.66 (6 H, s, 2 × OMe), 3.755 and 3.775 (each 2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.84 and 4.27 (each 1 H, d, *J* 17, 8-H_2), 3.86 and 4.32 (each 1 H, d, *J* 17, 3-H_2), 6.92 (1 H, s, 5-H), 7.44 (1 H, s, 20-H), 7.57 (1 H, s, 10-H) and 8.57 (1 H, s, 15-H); *m/z* (FD) 686 (M^+, 100%).

Oxidation of isobacteriochlorin 47

A solution of isobacteriochlorin **47** (1 mg, 1.46 μmol) in dry acetonitrile (1 cm^3) was stirred and heated at reflux with $Cu(OAc)_2$ (7 mg, 38 mmol) under an atmosphere of oxygen in the dark for 18 h. The resulting green solution was cooled, diluted with dry dichloromethane (5 cm^3), decanted from the solids and evaporated under reduced pressure. The residue was purified by PLC, eluting with dichloromethane–methyl acetate (4:1), to give two main products. The product at higher R_f value (0.8) was green; $\lambda_{max}(CH_2Cl_2)$/nm 389 (59) 401 (54), 429 (88), 577 (14) and 617 (46); *m/z* 775 and 777 (M^+). The product at lower R_f value (0.7) was blue; $\lambda_{max}(CH_2Cl_2)$/nm 372 infl, 390 infl, 401 (100%), 422 infl, 498 (4.7), 536 (10.7), 582 (16.4) and 617 (47.4). This second, blue product was converted into the first, green product by further heating with $Cu(OAc)_2$ as above.

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