Haem d_1: stereoselective synthesis of the macrocycle to establish its absolute configuration as 2*R*,7*R* [1]

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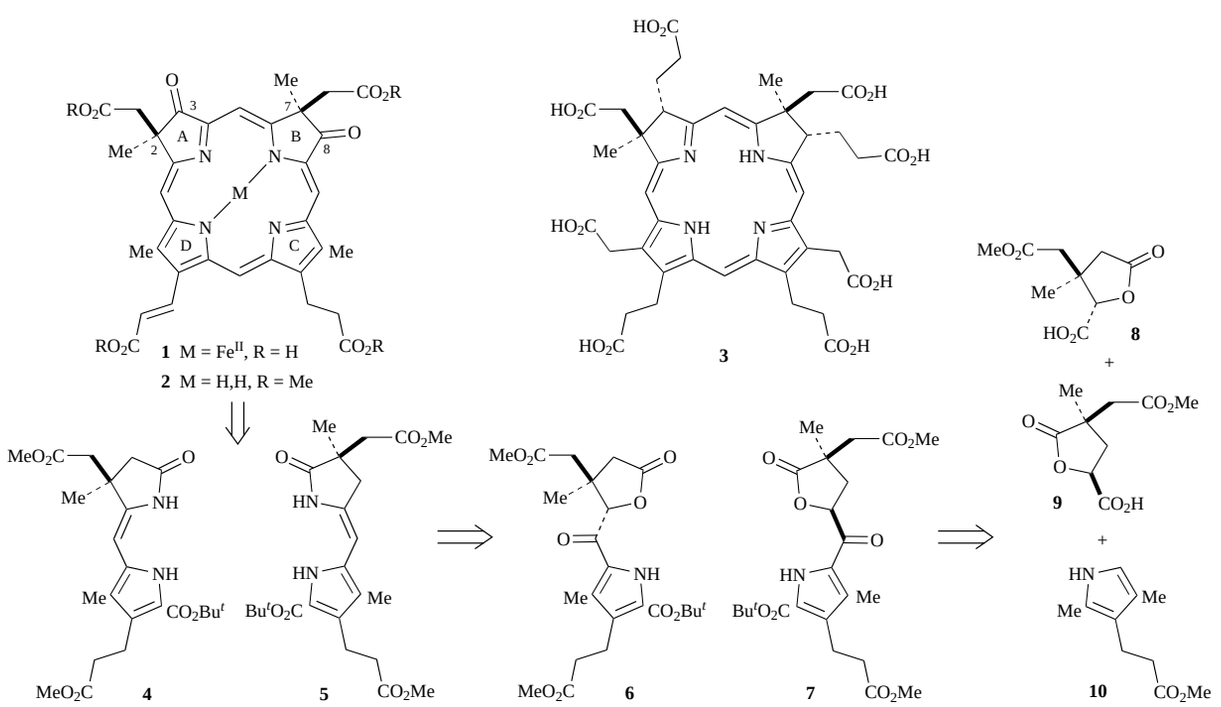
Although the gross structure of haem d_1 1 has been established, the absolute stereochemistry at C-2 and C-7 is unknown. An unambiguous stereoselective synthesis of the ester of the metal-free macrocycle corresponding to haem d_1 has been completed which establishes the absolute configuration of the natural cofactor as 2*R*,7*R*. Haem d_1 is thus shown to match stereochemically other biologically important macrocycles, *e.g.* those involved in the biosynthesis of vitamin B_{12}, which are related to isobacteriochlorins and also display 2*R*,7*R* configurations. The synthetic sequence used is based on a new procedure for assembly of the western and eastern building blocks and it serves as an efficient general route for construction of isobacteriochlorins.

Introduction

Haem d_1 is one of two different haem residues present in the bacterial enzyme cytochrome cd_1. The first[2] of this set of three papers reviewed the isolation of haem d_1 and previous work on its structure together with complete references to the literature. The outcome of all these studies was that haem d_1 was shown to have the gross structure **1** (Scheme 1), although the absolute configuration of the quaternary centres at C-2 and C-7 was unknown. Our interest in solving this stereochemical problem arose because of the work in Cambridge on precorrin-2, which is an intermediate for the biosynthesis of vitamin B_{12}[3] and a dihydro form of sirohydrochlorin, the latter having the established structure and absolute configuration[4] **3**. We felt that haem d_1 and sirohydrochlorin are probably related biosynthetically and hence that the absolute configuration at C-2 and C-7 is likely to be the same in both substances, *i.e.* 2*R*,7*R* as illustrated. The topic of biosynthesis will be revisited at the end of this paper.

The importance of establishing the absolute configuration of haem d_1 was thus clear, yet any direct approach using the natural material, *e.g.* X-ray analysis, was not possible since only microgram quantities were available. Here we describe how the problem was solved by an unambiguous stereoselective synthesis of the ester of the metal-free macrocycle of haem d_1 **2**. Although the 2*R*,7*R*-configurations were selected for the initial target molecule **2**, the synthesis was designed to allow any of the four stereoisomers of structure **2** to be constructed.

It was envisaged that the macrocycle **2** could be derived from the isobacteriochlorin **62** (Scheme 7) by introduction of the C-3 and C-8 oxo functions and the double bond in the ring D side-chain at the end of the synthesis. This substance **62** had already been synthesised in small quantities by an experimentally demanding route (see first paper[2]). It was the difficulty of scal-



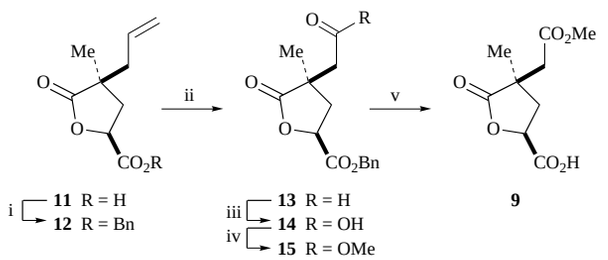
Scheme 1

ing up this synthesis that prompted the development of a new synthetic approach for assembly of the western **4** and eastern **5** units for construction of the required macrocycle **62** (Scheme 1). This new approach was described in the preceding paper.[5] For the present synthesis, the new route required construction of the ketones **6** and **7** as precursors of the lactams **4** and **5**. These ketones **6** and **7** were to be generated by acylation of the same α-free pyrrole **10** with activated forms of the lactonic acids **8** and **9** (Scheme 1).

Results and discussion

Synthesis of the lactonic acids 8 and 9

The lactone **11** (Scheme 2), readily available from L-glutamic

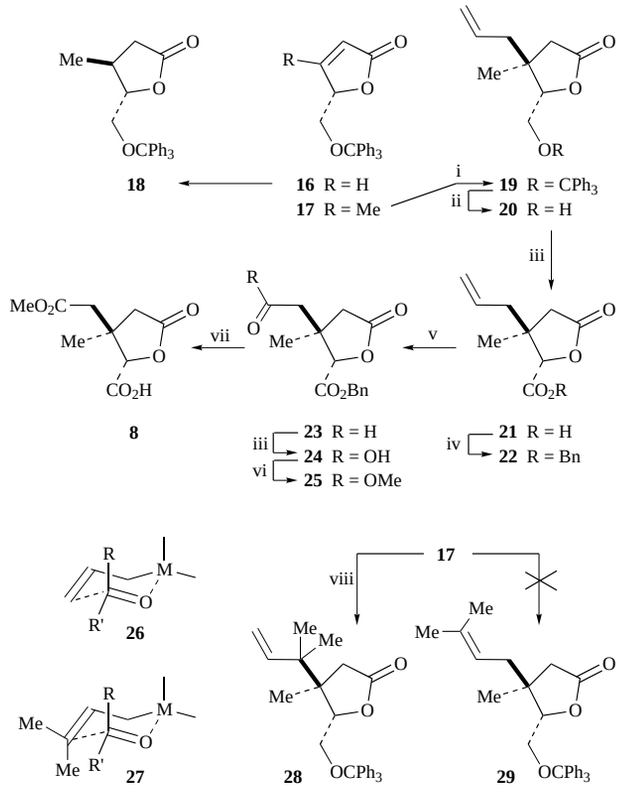


Scheme 2 *Reagents:* i, BnBr, K_2CO_3; ii, RuO_4, $NaIO_4$; iii, CrO_3, H_2SO_4; iv, CH_2N_2; v, H_2, Pd/C

acid, was in hand.[5] Oxidative cleavage of the double bond of the allyl residue in the corresponding benzyl ester **12** was achieved with ruthenium tetroxide generated *in situ*, to give a mixture of the aldehyde **13** and acid **14**. Chromic acid converted the former into the latter, which with diazomethane afforded the ester **15** in 68% yield overall. Hydrogenolysis of the benzyl group then gave the lactonic acid **9** required for ring B of the macrocycle **2**.

L-Glutamic acid was also the chosen starting material for the lactonic acid **8**, which was to provide ring A of the target molecule **2**. Ireland *et al.*[6] and Hanessian *et al.*[7] had shown that chiral butenolides such as **16** (Scheme 3) act as Michael acceptors for the addition of anions from lithium dialkylcuprates to yield *trans*-substituted lactones, *e.g.* **18**. We therefore planned to add an allyl group from a suitable allylic cuprate to the known[8] substituted butenolide **17**, derived from L-glutamic acid. However, a literature survey uncovered few successful reactions involving lower-order allylic cuprates, especially for building quaternary centres by additions to butenolides or α,β-unsaturated esters. Accordingly, the chosen reagent was the more stable and reactive higher-order cuprate, $(allyl)_2CuCNLi_2$ developed by Lipshutz *et al.*[9] This reacted with the butenolide **17** to afford the desired lactone **19** in 25% yield with complete stereocontrol (see below). The *trans*-orientation of the allyl group and the *cis*-arrangement for the methyl group relative to the trityloxymethyl group were confirmed by NOE experiments.

The main competing reaction in the foregoing process was attack at the lactonic carbonyl group to form the diallyl tertiary alcohol but, interestingly, 20% of starting material was recovered even when a large excess of allyl cuprate was used. The reason became clear when this recovered lactone was found to be fully racemised. Evidently, deprotonation at the chiral centre of the butenolide **17** was a further competing process. This last finding raised concern as to whether the desired product **19** could have been formed partly or wholly from racemised butenolide (as **17**). Accordingly, the allylation step was repeated on the recovered racemic butenolide (as **17**) to give a racemic sample of the methyl allyl system (as **19**). The ^1H NMR spectrum of this material in the presence of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III), showed two discrete singlets, from the methyl



Scheme 3 *Reagents:* i, $(allyl)_2CuCNLi_2$; ii, Amberlyst 15(H^+); iii, CrO_3, H_2SO_4; iv, BnBr, K_2CO_3; v, RuO_4, $NaIO_4$; vi, CH_2N_2; vii, H_2, Pd/C; viii, $(prenyl)_2CuCNLi_2$

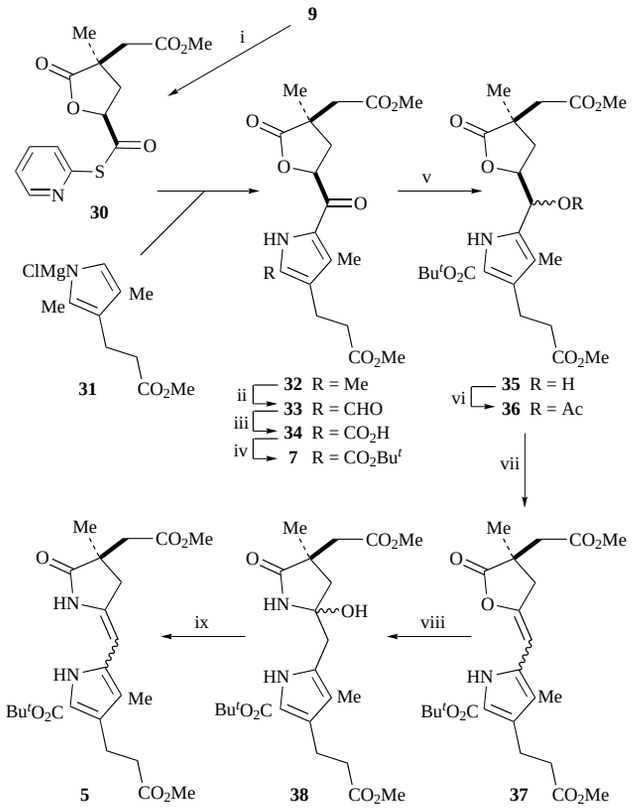
groups of the two enantiomers. Under the same conditions, the sample of **19** formed above directly from the homochiral butenolide **17** showed just one of these singlets, so proving its enantiomeric purity.

Cleavage of the trityl group from **19** afforded the alcohol **20**, which was oxidised to the acid **21** by chromic acid. The remaining steps for cleavage of the allyl group, **21** ⟶ **25** and forward to **8** (Scheme 3), were analogous to those used in Scheme 2.

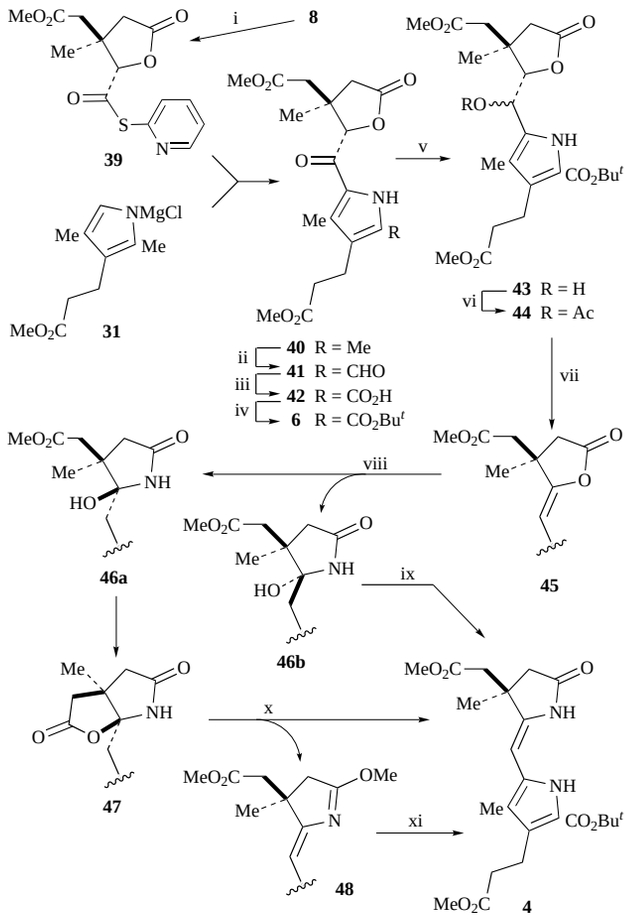
Many experiments were carried out under different conditions and with other allylic copper reagents, aiming to improve the foregoing yield of lactone **19**, but without success. However, one approach gave an interesting result. The current view[10] is that allylic organometallic reagents react with carbonyl groups *via* a cyclic chair transition state **26**. On that basis, it seemed that replacement of allyl by 3,3-dimethylallyl[9] should destabilise the system **27** by steric factors, so disfavouring 1,2-attack and thereby increasing the yield from 1,4-addition. In the event, the 1,4-product from this approach was the lactone **28** formed by allylic rearrangement, which was of no further value for the synthesis, rather than the unrearranged system **29**. These experiences, coupled with the easy availability of the butenolide **17** on a large scale and the complete stereocontrol in generating the quaternary centre of **19**, led to the view that the route to **8** in Scheme 3 was the best available.

Construction of the western and eastern lactams 4 and 5 and their conversion into the building blocks 61 and 53 for synthesis of macrocycle 62

The synthetic steps used for construction of the eastern lactam **5** are shown in Scheme 4; they followed the general methods developed in the preceding paper,[5] so the description here will be brief. The acid **9** (Scheme 2) reacted with 2,2′-dipyridyl disulfide and triphenylphosphine to yield the thioester **30**, which without isolation was added to the magnesium chloride salt **31** of pyrrole **10**. A virtually quantitative yield of the ketone **32** was obtained and its pyrrolic α-methyl group was converted



Scheme 4 *Reagents:* i, Ph_3P, dipyridyl disulfide; ii, SO_2Cl_2 then H_2O; iii, $KMnO_4$; iv, isobutene, H_2SO_4; v, $NaBH_4$; vi, Ac_2O, DMAP; vii, heat; viii, NH_3; ix, TsOH



Scheme 5 *Reagents:* i, Ph_3P, dipyridyl disulfide; ii, SO_2Cl_2 then H_2O; iii, $KMnO_4$; iv, isobutene, H_2SO_4; v, $NaBH_4$; vi, Ac_2O, DMAP; vii, heat; viii, NH_3; ix, TsOH; x, CH_2N_2, NaOMe; xi, H_3O^+

into a carboxyl residue by the steps **32** ⟶ **33** ⟶ **34** (76% overall); acid-catalysed esterification then afforded ketone **7** (80%).

Borohydride reduction of the ketone **7** gave a 1:1 mixture of the diastereoisomeric alcohols **35** in essentially quantitative yield. The corresponding acetates **36** then underwent thermal elimination of acetic acid to form the enol lactones **37** as a 1:1.2 mixture of the (*E*)- and (*Z*)-isomers in 84% yield. Aqueous ammonia converted the enol lactones smoothly into the lactam **38** as a mixture of diastereoisomers which were dehydrated under acidic catalysis to form the (*E*)- and (*Z*)-isomers of the eastern lactam **5** as a 1:1 mixture (91% yield). All the foregoing diastereoisomers and (*E*)- and (*Z*)-isomers were separated for full characterisation but could be used in admixture for preparative runs. As earlier,[2,5] the (*E*)- and (*Z*)-isomers of the lactam **5** were distinguished by the strong bathochromic shift in the UV spectrum of the illustrated (*Z*)-isomer **5** upon chelation of zinc(II) ions. Further, the two isomers of **5** were shown to be spectroscopically identical to the samples of the same materials synthesised by the original coupling strategy.[2]

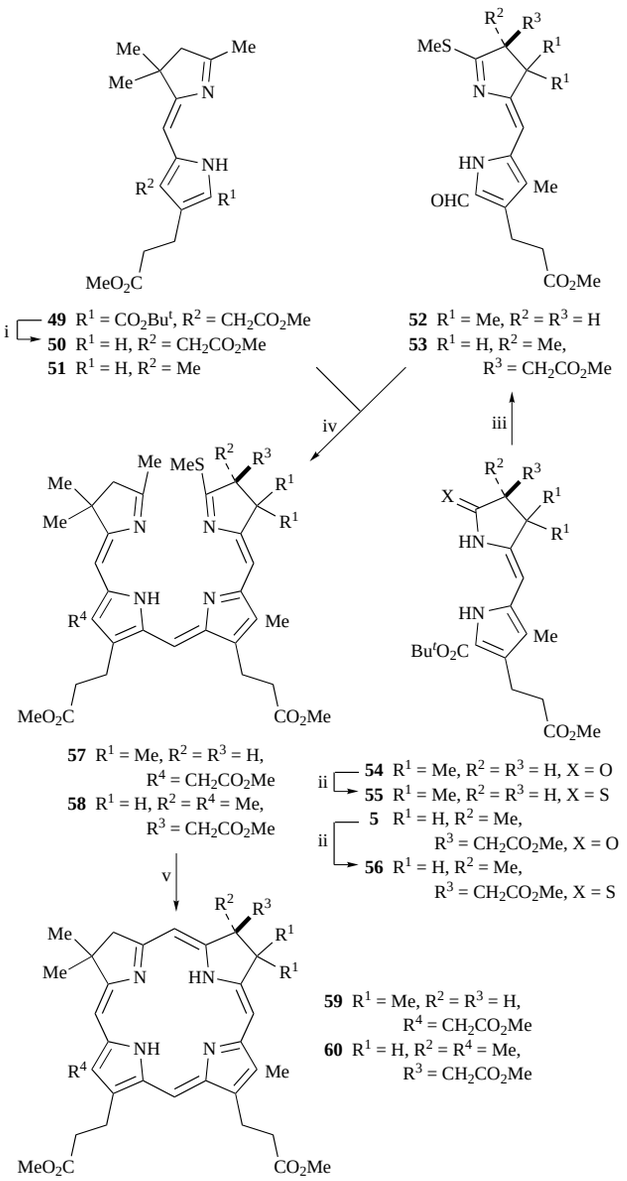
All the chemistry illustrated in Scheme 4 was first explored starting from the benzyl ester of **34** rather than the *tert*-butyl ester **7**. The benzyl esters of the entire series (analogues of **7**, **35**–**38** and **5**) were prepared and characterised; they are included in the Experimental section.

Attention then turned to the synthesis of the western lactam **4** (Scheme 1). The enol lactone **45** (Scheme 5) was constructed by steps analogous to those used in Scheme 4; these were **31** + **39** ⟶ **40** and then through the illustrated series **41**–**44** to afford the single (*Z*)-isomer **45** in 42% overall yield from the acid **8**. Ammonolysis of the enol lactone **45** followed by the acid-catalysed dehydration step gave the western lactam as the single (*Z*)-isomer **4** (34% yield). The major product was the lactone lactam **47** (50%), formed from the diastereoisomer **46a** of the intermediate hydroxy lactam; the other isomer **46b** was the main source of the (*Z*)-lactam **4**. A lactone lactam similar to **47** had been encountered in the work on the total synthesis of vitamin B_{12} by Eschenmoser and Woodward.[11] Following their lead, **47** was treated with diazomethane and a catalytic quantity of sodium methoxide to generate more of lactam **4** together with its imino ether **48**. Mild acidic hydrolysis converted **48** into **4**, so that the total overall yield of **4** from the enol lactone **45** by these steps was a very satisfactory 73%. This product also was shown to be identical to that prepared earlier[2] by a different route.

The foregoing studies established practical routes for synthesis of the lactams **4** and **5** on a substantial scale. These were then converted into the building blocks **61** and **53** (Scheme 7) by the methods described in the first paper of this set.[2] Every atom required for the synthesis of the macrocycle **62** was now present in **61** and **53**; they were ready for condensation to yield the open-chain 18π-electron system followed by photochemical cyclisation to the isobacteriochlorin **62** (Scheme 7). However, we first wished to select the best conditions for these two reactions using related model compounds.

Study of the condensation and photochemical steps for synthesis of isobacteriochlorins

The first experiments were aimed at the synthesis of the isobacteriochlorin **59** (Scheme 6). The known *tert*-butyl ester[12] **49** was treated with trifluoroacetic acid (TFA) to yield **50**, one of the required halves. The other half **52** was prepared from the lactam[5] **54** *via* the thiolactam **55** (Scheme 6). Both compounds **50** and **52** were rather labile but they were quickly purified under argon with protection against light and then used directly. The best conditions found for condensation of **50** with **52** involved catalysis by TFA in methanol to yield the 18π-electron



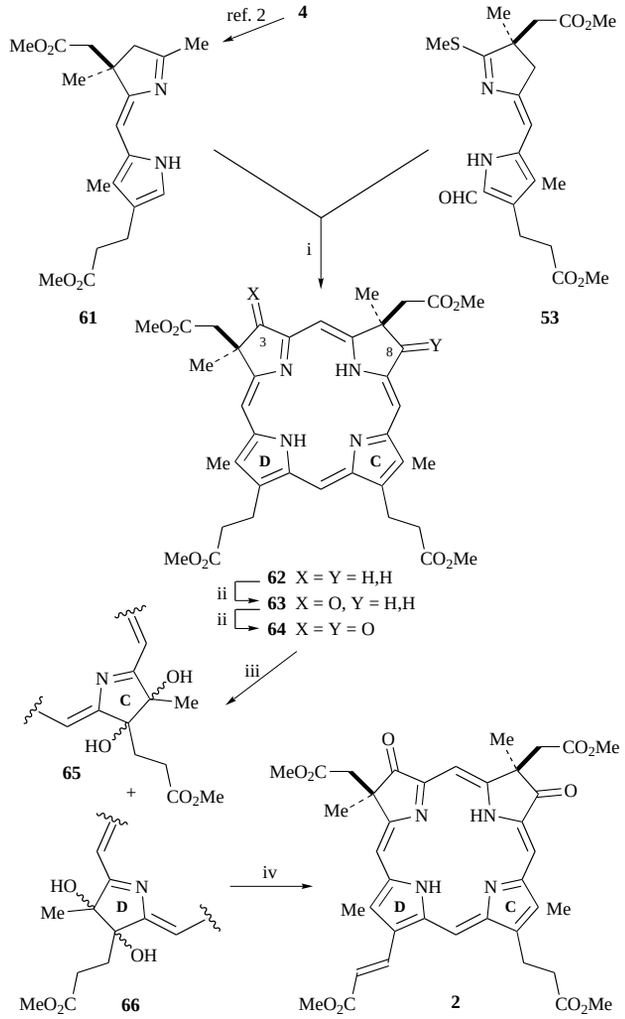
Scheme 6 *Reagents:* i, TFA; ii, Lawesson's reagent, $Pr^{i}_{2}NEt$; iii, TFA, $(MeO)_3CH$; iv, TFA, MeOH; v, *hν*

open-chain system **57**, probably as a mixture of double bond isomers. Irradiation of this product for 4 days afforded the isobacteriochlorin **59** in 47% overall yield for the two steps, a very satisfactory outcome for such a macrocyclisation process.

The macrocycle **60** is still more closely related to the target **62** (Scheme 7) for the work on haem d_1. The eastern unit **53** was prepared from lactam **5** *via* thiolactam **56** (Scheme 6). The starting material for the western unit **51** was the lactam[5] **54** and the additional carbon atom to form **51** was added to the corresponding thiolactam **55** by a sulfur-extrusion step as usual.[2] These rapidly purified materials **51** and **53** were immediately condensed together to yield **58**, followed by photochemical cyclisation under the foregoing best conditions to yield the isobacteriochlorin **60** in 55% yield. The foundation was thus well laid for synthesis of the macrocycle **62**.

Synthesis of the ester 2 of the metal-free macrocycle corresponding to haem d_1

The best conditions established by the foregoing experiments were now applied to the intermediates **61** and **53** (Scheme 7), with the latter, more readily available material used in excess. The condensation and photochemical reactions proceeded smoothly to afford the isobacteriochlorin **62** in 53% yield over the two steps; more than 100 mg of this material was synthesised in this way. Heating the macrocycle **62** for 30 min with selenium dioxide in 1,4-dioxane (an important choice of solvent) yielded a mixture of the dioxo system **64** and monooxidised material **63** (or with X and Y exchanged). The latter gave the dioxo product **64** by further treatment in the same way and when **62** was oxidised for 2 h, only dioxo system **64** was isolated (42%).



Scheme 7 *Reagents:* i, TFA, MeOH then *hν*; ii, SeO_2; iii, OsO_4; iv, HCl

The double bond was introduced into the ring D propionate side-chain by following the procedure of Chang and Wu.[13] This involved treatment of the dioxo compound **64** with osmium tetroxide to generate the two diols **65** and **66**, which underwent acid-catalysed dehydration and allylic rearrangement to yield the metal-free macrocycle of haem d_1 as its ester **2**. A smaller amount of the separable isomer having the acrylic side-chain on ring C was also isolated. That the stereoselective synthesis of the metal-free macrocycle of haem d_1 had been accomplished was shown by the identity of ester **2** with the corresponding ester derived from natural haem d_1, kindly provided by Professor R. Timkovich (Alabama). The comparisons were by UV–visible and ^{1}H NMR spectroscopy, mass spectrometry and chromatography. Importantly, the circular dichroism spectrum of the synthetic sample was virtually identical to that of the sample derived from natural sources (Fig. 1). This unambiguous synthesis firmly establishes that haem d_1 has the 2*R*,7*R* configuration also displayed by sirohydrochlorin[4] **3**, precorrin-2[3] **67**, vitamin B_{12}[3] and the nickel-containing cofactor F-430.[14] It thus appears highly probable that all these materials are members of a biosynthetically related family. Following our brief account of the above synthesis,[1] Kusch *et al*. outlined a different synthesis of the macrocycle **62** enriched in the opposite 2*S*,7*S* enantiomer.[15]

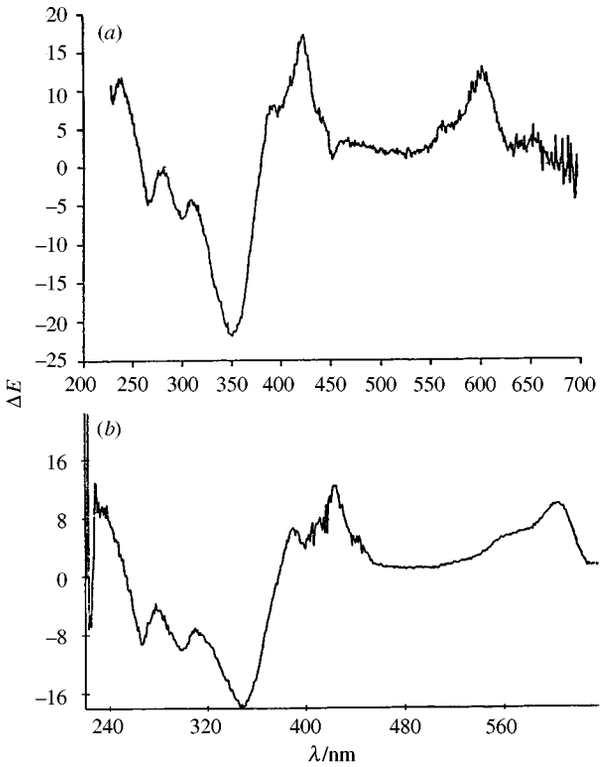
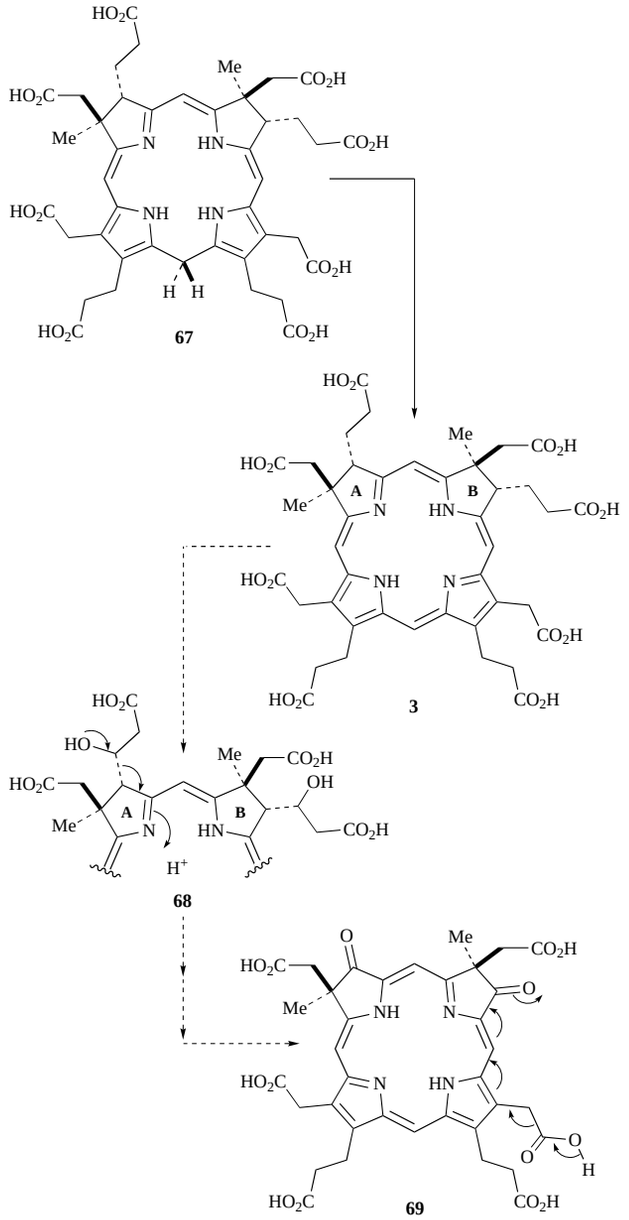


Fig. 1 Circular dichroism spectra determined in CH_2Cl_2 of (*a*) macrocycle **2** derived from natural haem d_1, measured by Timkovich's group, and (*b*) the synthetic sample of **2**, determined in Cambridge. The scales for (*a*) and (*b*) differ slightly because the instruments used were not identical.

The foregoing stereochemical relationships strengthen the view that positions C-3 and C-8, which are unsubstituted in haem d_1 **1**, still carry propionate residues in the earlier biosynthetic intermediates. Knowledge of the enzymic reactions by which the propionates are removed and their sequence will only come by pinpointing the enzymes involved. It may be helpful for this phase of research to suggest that the pathway to haem d_1 probably follows that for the biosynthesis[3] of vitamin B_{12} as far as precorrin-2 **67** (Scheme 8), and then goes forward to sirohydrochlorin **3**. Several reasonable mechanisms can be envisaged for removal of the propionate side-chains, one possibility being hydroxylation to **68**, as illustrated, followed by a reverse aldol reaction. Decarboxylation of the C-12 and C-18 acetate groups is shown in Scheme 8 as following the introduction of the C-3 and C-8 oxo-functions (see **69**) but acid-catalysed decarboxylation at the precorrin-2 stage **67** is mechanistically equally plausible. Research on the enzymes of this pathway is awaited with interest. The availability of the metal-free macrocycle of haem d_1 **2** together with the isobacteriochlorin **62** and its mono-oxo **63** and dioxo **64** derivatives from the synthesis described herein could be helpful in this endeavour.



Scheme 8

Experimental

General

General directions are as given in the first of this set of three papers.[2]

(3*S*,5*S*)-3-Allyl-5-benzyloxycarbonyl-3-methyltetrahydrofuran-2-one 12

A mixture of acid **11** (18.0 g, 97.8 mmol), anhydrous potassium carbonate (14.9 g, 108 mmol), benzyl bromide (17.4 cm^3, 147 mmol) and dry *N*,*N*-dimethylformamide (270 cm^3) was stirred for 6 h at room temperature. *tert*-Butyl methyl ether (600 cm^3) was added and the mixture was washed with water (4 × 500 cm^3), dried and evaporated under reduced pressure. Purification by column chromatography, eluting with ethyl acetate–hexane (1:7), gave the *benzyl ester* **12** (18.3 g, 68%) as an oil (Found: C, 70.1; H, 6.6%; M^+, 274.1214. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6%; *M*, 274.1205); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 and 1760 (C=O); δ_H(400 MHz, $CDCl_3$) 1.25 (3 H, s, Me), 2.21–2.35 (4 H, m, CH_2CCH_2), 4.86 (1 H, t, *J* 8, CH–O), 5.00–5.10 (2 H, m, CH=CH_2), 5.21 (2 H, br s, CH_2Ph), 5.59–5.70 (1 H, m, C*H*=CH_2) and 7.26–7.39 (5 H, m, Ph); δ_C(100 MHz, $CDCl_3$) 22.9 (Me), 36.9, 41.6 and 42.6 (CH_2CCH_2), 67.5 (CH_2Ph), 72.8 (*C*H–O), 119.9 (CH=*C*H_2), 128.7, 128.6 and 134.8 (Ph), 132.2 (*C*H=CH_2) and 169.8 and 179.8 (C=O); *m/z* (FD) 274 (M^+, 100%).

(3*R*,5*S*)-5-Benzyloxycarbonyl-3-methoxycarbonylmethyl-3-methyltetrahydrofuran-2-one 15

A solution of benzyl ester **12** (18.0 g, 65.7 mmol) in carbon tetrachloride (100 cm^3), acetonitrile (100 cm^3) and glacial acetic acid (50 cm^3) was added dropwise over 2 h to a vigorously stirred mixture of ruthenium(IV) oxide monohydrate (88 mg, 0.01 equiv.) and sodium periodate (56.2 g, 263 mmol) in water (300 cm^3) at 0 °C. The mixture was allowed to warm to room temperature, then diluted with dichloromethane (100 cm^3) and

filtered through Celite. Dichloromethane (100 cm^3) and water (100 cm^3) were added and the organic phase was separated. The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 100 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the resulting oil in acetone (400 cm^3) was treated with Jones' reagent (2.58 mol dm^{-3}; 51 cm^3, 0.131 mol) over 30 min and stirred for 2 h at room temperature. Propan-2-ol (10 cm^3) was added and the acetone was evaporated under reduced pressure. Water (300 cm^3) was added and the solution was extracted with diethyl ether (5 × 100 cm^3). The combined extracts were concentrated to 100 cm^3 under reduced pressure and extracted with saturated aqueous sodium hydrogen carbonate (3 × 100 cm^3). The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid, saturated with sodium chloride and extracted with diethyl ether (2 × 100 cm^3), ethyl acetate (2 × 100 cm^3) and dichloromethane (100 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. A solution of the resulting oil in tetrahydrofuran (300 cm^3) was stirred with an ethereal solution of diazomethane (2 equiv.) for 15 min and then the excess diazomethane was destroyed by the dropwise addition of glacial acetic acid. The solvent was evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate (5:2), gave the *methyl ester* **15** (13.6 g, 68%) as an oil (Found: C, 62.5; H, 6.1. $C_{16}H_{18}O_6$ requires C, 62.7; H, 5.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780, 1760 and 1737; δ_H(400 MHz, $CDCl_3$) 1.32 (3 H, s, Me), 2.46 (1 H, dd, *J* 13 and 9) and 2.50 (1 H, dd, *J* 13 and 8, C*H*$_2$CH–O), 2.62 and 2.72 (each 1 H, d, *J* 17, CH_2CO), 3.63 (3 H, s, OMe), 4.91 (1 H, t, *J* 8, CH–O), 5.22 and 5.25 (each 1 H, d, *J* 12, C*H*$_2$Ph) and 7.33–7.37 (5 H, m, Ph); δ_C(100 MHz, $CDCl_3$) 23.1 (Me), 37.3, 40.9 and 41.1 (CH_2CCH_2), 51.9 (OMe), 67.5 (*C*H$_2$Ph), 73.0 (CH–O), 128.5, 128.7 and 134.9 (Ph) and 169.3, 170.6 and 179.1 (C=O); *m/z* (FD) 306 (M^+, 100%).

(3*R*,5*S*)-5-Carboxy-3-methoxycarbonylmethyl-3-methyltetrahydrofuran-2-one 9

A solution of benzyl ester **15** (13.62 g, 44.5 mmol) in methanol (400 cm^3) was stirred under an atmosphere of hydrogen with 10% palladium-on-carbon (750 mg) for 3 h and then filtered through Celite. The methanol was evaporated under reduced pressure to give the *carboxylic acid* **9** (9.53 g, 99%) as a crystalline solid, mp 118–124 °C (Found: C, 49.9; H, 5.5. $C_9H_{12}O_6$ requires C, 50.0; H, 5.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1762, 1736 and 1724; δ_H(400 MHz, $CDCl_3$) 1.35 (3 H, s, Me), 2.49 (1 H, dd, *J* 13 and 8.5) and 2.55 (1 H, dd, *J* 13 and 9, C*H*$_2$CH–O), 2.66 and 2.81 (each 1 H, d, *J* 17, CH_2CO), 3.69 (3 H, s, OMe), 4.95 (1 H, t, *J* 8.5, C*H*–O) and 5.30 (1 H, br s, CO_2H); δ_C(100 MHz, $CDCl_3$) 23.1 (Me), 37.7, 41.1 and 41.9 (CH_2CCH_2), 51.8 (OMe), 73.3 (CH–O) and 171.1, 171.4 and 179.8 (C=O).

(4*S*,5*S*)-4-Allyl-4-methyl-5-triphenylmethoxymethyltetrahydrofuran-2-one 19

A suspension of copper(I) cyanide (2.42 g, 27 mmol) in dry tetrahydrofuran at −78 °C under argon was stirred with a solution of methyllithium in diethyl ether (1.4 mol dm^{-3}; 38.6 cm^3, 54 mmol). The resultant solution was allowed to warm to 0 °C over 30 min, then cooled to −78 °C again, treated with allyltri-*n*-butylstannane (16.8 cm^3, 54 mmol), allowed to warm to 0 °C over 30 min and then cooled again to −78 °C. A solution of butenolide **17**[8] (5 g, 13.5 mmol) in dry tetrahydrofuran (30 cm^3) at −78 °C was added over 1 min. After 30 min at −78 °C saturated aqueous ammonium chloride (200 cm^3) was added, followed by concentrated aqueous ammonia (200 cm^3) and ethyl acetate (300 cm^3). The organic phase was separated, washed with brine and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–diethyl ether, gave recovered butenolide **17** (1 g) and *allyl lactone* **19** (1.11 g, 25% based on unrecovered **17**) as a crystalline solid, mp 105–107 °C (Found: M^+, 412.2047. $C_{28}H_{28}O_3$ requires *M*, 412.2038); $[\alpha]_D$ +43.3 (*c* 1.12, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1775; δ_H(400 MHz, $CDCl_3$) 0.91 (3 H, s, Me), 2.15 (2 H, d, *J* 8, CH_2C=C), 2.43 and 2.56 (each 1 H, d, *J* 17, CH_2CO), 3.14 and 3.43 (each 1 H, dd, *J* 10.5 and 4, CH_2O), 4.28 (1 H, t, *J* 4, CH–O), 5.06–5.12 (2 H, m, CH=C*H*$_2$), 5.63–5.72 (1 H, m, C*H*=CH_2) and 7.22–7.46 (15 H, m, Ph); δ_C(100 MHz, $CDCl_3$) 19.4 (Me), 41.3, 41.8 and 44.6 (CH_2CCH_2), 63.6 (CH_2O), 84.9 (CH–O), 87.4 (*C*Ph$_3$), 119.6 (CH=C*H*$_2$), 127.1, 127.9, 128.6 and 143.3 (Ph), 132.6 (*C*H=CH_2) and 176.4 (C=O); *m/z* (FD) 412 (M^+, 100%).

(4*S*,5*S*)-4-Allyl-5-hydroxymethyl-4-methyltetrahydrofuran-2-one 20

A solution of lactone **19** (6.9 g, 16.7 mmol) in dry methanol (150 cm^3) was heated under reflux with Amberlyst 15(H^+) resin (1.5 g) for 1.5 h, then filtered through a short column of basic alumina and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate (1:1), gave the *alcohol* **20** (2.64 g, 93%) as an oil (Found: M^+ − CH_2OH, 139.0763. $C_9H_{14}O_3$ requires *M* − CH_2OH, 139.0759); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1775; δ_H(400 MHz, $CDCl_3$) 1.08 (3 H, s, Me), 2.15 (2 H, d, *J* 7, CH_2C=C), 2.37 (2 H, s, CH_2CO), 3.27 (1 H, t, *J* 6, OH), 3.69–3.81 (2 H, m, C*H*$_2$OH) 4.20 (1 H, dd, *J* 5 and 3, CH–O), 5.05–5.12 (2 H, m, CH=C*H*$_2$) and 5.65–5.76 (1 H, m, C*H*=CH_2); δ_C(100 MHz, $CDCl_3$) 19.5 (Me), 41.1, 41.8 and 44.4 (CH_2CCH_2), 61.4 (CH_2OH), 86.9 (CH–O), 119.6 (CH=*C*H$_2$), 132.6 (*C*H=CH_2) and 176.8 (C=O); *m/z* (FD) 170 (M^+, 100%).

(4*S*,5*S*)-4-Allyl-5-carboxy-4-methyltetrahydrofuran-2-one 21

A solution of alcohol **20** (2.54 g, 15 mmol) in acetone (150 cm^3) was treated with Jones' reagent (2.58 mol dm^{-3}; 11.6 cm^3, 29.9 mmol) over 30 min and then stirred for 12 h at room temperature. Propan-2-ol (10 cm^3) was added and the acetone was evaporated under reduced pressure. Water (300 cm^3) was added and the solution was extracted with diethyl ether (5 × 100 cm^3). The combined extracts were concentrated under reduced pressure to 100 cm^3 and extracted with saturated aqueous sodium hydrogen carbonate (3 × 100 cm^3). The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid, then saturated with sodium chloride and extracted with diethyl ether (2 × 100 cm^3), ethyl acetate (2 × 100 cm^3) and dichloromethane (100 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give the *carboxylic acid* **21** (2.75 g, 100%) as an oil (Found: M^+, 184.0722. $C_9H_{12}O_4$ requires *M*, 184.0736); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785 and 1735; δ_H(400 MHz, $CDCl_3$) 1.13 (3 H, s, Me), 2.30 (2 H, d, *J* 7, CH_2C=C), 2.40 and 2.48 (each 1 H, d, *J* 17, CH_2CO), 4.64 (1 H, s, CH–O), 5.12–5.20 (2 H, m, CH=C*H*$_2$), 5.70–5.77 (1 H, m, C*H*=CH_2) and 10.45 (1 H, br s, CO_2H); δ_C(100 MHz, $CDCl_3$) 20.7 (Me), 39.7, 42.6 and 43.5 (CH_2CCH_2), 82.47 (CH–O), 120.57 (CH=*C*H$_2$), 131.72 (*C*H=CH_2) and 172.54 and 175.50 (C=O); *m/z* (FD) 184 (M^+, 100%).

(4*S*,5*S*)-4-Allyl-5-benzyloxycarbonyl-4-methyltetrahydrofuran-2-one 22

A mixture of acid **21** (2.70 g, 14.7 mmol), potassium carbonate (2.43 g, 17.6 mmol) and benzyl bromide (8.73 cm^3) in dry *N*,*N*-dimethylformamide (150 cm^3) was stirred for 6 h at room temperature, then evaporated under high vacuum. Water (50 cm^3) was added and the mixture was extracted with ethyl acetate (100 cm^3 then 3 × 50 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. Purification by column chromatogaphy, eluting with ethyl acetate–hexane, gave the *benzyl ester* **22** (3.07 g, 76%) as an oil (Found: M^+, 274.1193. $C_{16}H_{18}O_4$ requires *M*, 274.1205); $\nu_{max}(CHCl_3)/cm^{-1}$ 1795 and 1750; δ_H(400 MHz, $CDCl_3$) 0.98 (3 H, s, Me), 2.25 (2 H, d, *J* 7, CH_2C=C), 2.40 (2 H, m, C*H*$_2$CO), 4.63 (1 H, s, CH–O), 5.11–5.28 (4 H, m, CH=C*H*$_2$ and C*H*$_2$Ph), 5.67–5.78 (1 H, m,

C*H*=CH_2) and 7.33–7.41 (5 H, m, Ph); δ_C(100 MHz, $CDCl_3$) 20.6 (Me), 39.6, 42.8 and 43.9 (CH_2CCH_2), 67.3 (CH_2Ph), 82.6 (CH−O), 120.5 (CH=CH_2), 128.6, 128.7 and 134.6 (Ph), 131.8 (*C*H=CH_2) and 168.4 and 175.0 (C=O); *m/z* (FD) 274 (M^+, 100%).

(4*S*,5*S*)-5-Benzyloxycarbonyl-4-methoxycarbonylmethyl-4-methyltetrahydrofuran-2-one 25

A solution of benzyl ester **22** (2.43 g, 8.87 mmol) in carbon tetrachloride (23 cm^3), acetonitrile (23 cm^3) and glacial acetic acid (12 cm^3) was added dropwise over 2 h to a vigorously stirred mixture of ruthenium(IV) oxide monohydrate (30 mg) and sodium periodate (7.59 g, 35.5 mmol) in water (70 cm^3) at 0 °C. The solution was allowed to warm to room temperature, diluted with dichloromethane (50 cm^3) and filtered through Celite. Dichloromethane (50 cm^3) and water (50 cm^3) were added and the organic phase was separated. The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 50 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the resulting oil in acetone (100 cm^3) was treated with Jones' reagent (2.58 mol dm^{-3}; 3.5 cm^3, 9.01 mmol) over 30 min and stirred for 2 h at room temperature. Propan-2-ol (5 cm^3) was added and the acetone was evaporated under reduced pressure. Water (100 cm^3) was added and the solution was extracted with diethyl ether (5 × 50 cm^3). The combined extracts were concentrated to 50 cm^3 under reduced pressure and extracted with saturated aqueous sodium hydrogen carbonate (3 × 50 cm^3). The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid, saturated with sodium chloride and extracted with diethyl ether (2 × 50 cm^3), ethyl acetate (2 × 50 cm^3) and dichloromethane (50 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. A solution of the resulting oil in tetrahydrofuran (75 cm^3) was treated with an ethereal solution of diazomethane (2 equiv.) and stirred for 15 min. The diazomethane was then destroyed by the dropwise addition of glacial acetic acid and the solvent was evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate (3:1), gave the *methyl ester* **25** (2.32 g, 86%) as an oil (Found: M^+, 306.1102. $C_{16}H_{18}O_6$ requires *M*, 306.1103); ν_{max}($CHCl_3$)/cm^{-1} 1800 and 1740; δ_H(400 MHz, $CDCl_3$) 1.03 (3 H, s, Me), 2.51 and 2.70 (each 1 H, d, *J* 17.5, 3-H_2), 2.54 and 2.59 (each 1 H, d, *J* 15.5, CH_2CO_2Me), 3.65 (3 H, s, OMe), 4.86 (1 H, s, CH−O), 5.17–5.24 (2 H, m, CH_2Ph) and 7.33–7.35 (5 H, s, Ph); δ_C(100 MHz, $CDCl_3$) 20.7 (Me), 40.2, 41.4 and 42.2 (CH_2CCH_2), 51.8 (OMe), 67.4 (CH_2Ph), 82.1 (CH−O), 128.6, 128.7 and 134.5 (Ph) and 167.7, 170.5 and 174.2 (C=O); *m/z* (FD) 306 (M^+, 100%).

(4*S*,5*S*)-5-Carboxy-4-methoxycarbonylmethyl-4-methyltetrahydrofuran-2-one 8

A solution of benzyl ester **25** (2.80 g, 9.15 mmol) in methanol (100 cm^3) was stirred under an atmosphere of hydrogen with 10% palladium-on-carbon (250 mg) for 3 h at room temperature then filtered through Celite. The methanol was evaporated under reduced pressure to give the *carboxylic acid* **8** (1.97 g, 100%) as an oil (Found: $M^+ - CO_2H$, 171.0669. $C_9H_{12}O_6$ requires *M* − CO_2H, 171.0657); ν_{max}($CHCl_3$)/cm^{-1} 1795 and 1735; δ_H(400 MHz, $CDCl_3$) 1.19 (3 H, s, Me), 2.54 and 2.78 (each 1 H, d, *J* 17.5, 3-H_2), 2.60 and 2.68 (1 H, d, *J* 16, CH_2CO_2Me), 3.67 (3 H, s, OMe), 4.91 (1 H, s, CH−O) and 9.24 (1 H, br s, CO_2H); δ_C(100 MHz, $CDCl_3$) 20.8 (Me), 40.5, 41.1 and 41.9 (CH_2CCH_2), 52.0 (OMe), 82.1 (CH−O), 170.9, 171.3 and 175.1 (C=O); *m/z* (FD) 216 (M^+, 100%).

(4*R*,5*S*)-4-Methyl-4-(1,1-dimethylprop-2-enyl)-5-triphenylmethoxymethyltetrahydrofuran-2-one 28

Butenolide **17**[8] (110 mg, 0.298 mmol) was reacted with (prenyl)$_2$CuCNLi$_2$ as described above for the preparation of allyl lactone **19**. The prenyl cuprate was prepared from a solution of methyllithium (1.28 cm^3, 1.79 mmol), copper(I) cyanide (80 mg, 0.893 mmol) and prenyltri-*n*-butylstannane (619 μl, 1.79 mmol) in dry tetrahydrofuran (1 cm^3) and a solution of butenolide **17** in tetrahydrofuran (0.7 cm^3) was added. Work up and purification by PLC gave the *lactone* **28** (104 mg, 79%) as a crystalline solid, mp 108–110 °C (Found: M^+, 440.2321. $C_{30}H_{32}O_3$ requires *M*, 440.2351); ν_{max}($CHCl_3$)/cm^{-1} 1765; δ_H(400 MHz, $CDCl_3$) 0.93, 0.95, 0.97 (each 3 H, s, Me), 2.40 and 2.70 (each 1 H, d, *J* 18, CH_2CO), 3.07 (1 H, dd, *J* 10.5 and 4) and 3.47 (1 H, dd, *J* 10.5 and 3, CH_2O), 4.56 (1 H, t, *J* 3.5, CH−O), 4.98–5.05 (2 H, m, CH=CH_2), 5.75 (1 H, dd, *J* 17 and 11, C*H*=CH_2) and 7.21–7.50 (15 H, m, Ph); δ_C(100 MHz, $CDCl_3$) 17.1, 22.1 and 22.5 (3 × Me), 39.5 (CH_2CO), 41.3 and 46.4 (Me*C*−*C*Me_2), 63.6 (CH_2O), 82.9 (CH−O), 87.3 (CPh_3), 114.2 (CH=CH_2), 127.0, 127.8, 128.5 and 143.4 (Ph), 143.3 (*C*H=CH_2) and 176.7 (C=O); *m/z* (FD) 440 (M^+, 100%).

4-(2-Methoxycarbonylethyl)-2-[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-3,5-dimethylpyrrole 32

A solution of acid **9** (5 g, 23 mmol), 2,2′-dipyridyl disulfide (7.64 g, 34.7 mmol) and triphenylphosphine (9.1 g, 34.7 mmol) in dry toluene (150 cm^3) was kept under argon at room temperature for 22 h to give a solution containing thioester **30**. A solution of methylmagnesium chloride in diethyl ether (3 mol dm^{-3}; 31 cm^3, 93 mmol) was added to a stirred solution of α-free pyrrole **10**[5] (16.8 g, 92.3 mmol) in dry toluene (400 cm^3) and dry tetrahydrofuran (5 cm^3) at −78 °C under argon. This solution was allowed to warm for 10 min with vigorous stirring and then cooled to −78 °C and the above thioester solution was then added *via* double-ended needle under a positive pressure of argon over a period of 30 min. The solution was stirred at −78 °C for a further 1.5 h, then treated with saturated aqueous ammonium chloride (10 cm^3) and allowed to warm to room temperature. Diethyl ether (300 cm^3), saturated aqueous ammonium chloride (200 cm^3) and water (200 cm^3) were then added. The organic phase was separated, washed with 10% aqueous potassium carbonate (200 cm^3) and then water (200 cm^3), dried and evaporated under reduced pressure. Column chromatography, eluting with hexane–ethyl acetate, gave recovered *a*-free pyrrole **10** (8.40 g, 50%) and *ketone* **32** (8.28 g, 94%) as a gum (Found: M^+, 379.1612. $C_{19}H_{25}NO_7$ requires *M*, 379.1631); λ_{max}(MeOH)/nm 314; ν_{max}($CHCl_3$)/cm^{-1} 3445, 1781, 1731 and 1620; δ_H(400 MHz, $CDCl_3$) 1.37, 2.27 and 2.33 (each 3 H, s, Me), 2.36–2.44 (3 H, m, CH_2CH_2CO and CH_AH_BCH−O), 2.61–2.73 (4 H, m, CH_2CH_2CO, CH_AH_BCH−O and CH_AH_B-CO), 2.88 (1 H, d, *J* 17.5, CH_AH_BCO), 3.65 and 3.66 (each 3 H, s, OMe), 5.09 (1 H, t, *J* 8, CH−O) and 9.63 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.5 and 11.6 (Ar–Me), 19.1 (CH_2CH_2-CO), 22.8 (C*Me*), 34.6 (CH_2CH_2CO), 37.2, 40.8 and 41.1 (CH_2CCH_2), 51.5 and 52.0 (OMe), 79.0 (CH−O), 121.4, 124.1, 131.4 and 134.1 (pyrrole-C) and 171.5, 173.3, 179.5 and 182.4 (C=O); *m/z* (FD) 379 (M^+, 100%); *m/z* (EI) 379 (M^+), 348 (M − OMe) and 306 (M − CH_2CO_2Me).

5-Formyl-4-(2-methoxycarbonylethyl)-2-[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-3-methylpyrrole 33

Freshly distilled sulfuryl chloride (3.6 cm^3, 45 mmol) in dry dichloromethane (170 cm^3) was added over 4 min to a stirred solution of ketone **32** (8.5 g, 22.4 mmol) in dry dichloromethane (255 cm^3) at −5 °C under argon. The solution was stirred for 10 min and then evaporated under reduced pressure. Acetone (150 cm^3) and water (300 cm^3) were added and the solution was stirred for 15 min. More water (200 cm^3) was added and the mixture was extracted with dichloromethane (500 cm^3 then 2 × 200 cm^3). The combined extracts were dried and evaporated under reduced pressure to give crude aldehyde **33** (9.00 g) as a foam, which was used in the next step without

further purification (Found: M^+, 393.1421. $C_{19}H_{23}NO_8$ requires *M*, 393.1424); λ_{max}(MeOH)/nm 246 and 315; ν_{max}($CHCl_3$)/cm^{-1} 3940, 3000, 1800, 1740 and 1660; δ_H(400 MHz, $CDCl_3$) 1.38 and 2.33 (each 3 H, s, Me), 2.39 (1 H, dd, *J* 13 and 7.5) and 2.71 (1 H, dd, *J* 13 and 10, CH_2CH−O), 2.56 (2 H, t, *J* 8, CH_2CH_2CO), 2.66 and 2.86 (each 1 H, d, *J* 18, CH_2CO), 3.06 (2 H, t, *J* 8, CH_2CH_2CO), 3.63 and 3.64 (each 3 H, s, OMe), 5.17 (1 H, dd, *J* 10 and 7.5, CH−O), 9.89 (1 H, s, CHO) and 10.48 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.3 (3-Me), 18.5 (CH_2CH_2CO), 23.1 (C*Me*), 34.5 (CH_2CH_2CO), 36.1, 40.8 and 41.9 (CH_2CCH_2), 51.5 and 51.9 (OMe), 78.1 (CH−O), 128.9, 129.6 and 130.9 (pyrrole-C) and 171.2, 172.6, 178.9, 180.6 and 186.2 (C=O); *m/z* (FD) 393 (M^+, 100%).

3-(2-Methoxycarbonylethyl)-5-[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-methylpyrrole-2-carboxylic acid 34

A solution of potassium permanganate (6.11 g, 38.7 mmol) in water (167 cm^3) and acetone (122 cm^3) was added over 2 h at room temperature to a solution of formylpyrrole **33** (9 g) in acetone (200 cm^3). The mixture was stirred for a further 3 h and then the acetone was evaporated under reduced pressure. Dichloromethane (150 cm^3), water (100 cm^3) and sodium metabisulfite (25 g) were added. Concentrated hydrochloric acid was added dropwise until the pH of the aqueous layer was 1. The organic phase was then separated and the aqueous phase was saturated with sodium chloride and extracted with dichloromethane (2 × 100 cm^3). The combined organic extracts were evaporated under reduced pressure. Saturated aqueous sodium hydrogen carbonate (400 cm^3) was added and the mixture was extracted with dichloromethane (100 cm^3). The organic extract was evaporated under reduced pressure to give recovered formylpyrrole **33** (1.43 g). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid, extracted with dichloromethane (4 × 200 cm^3), then saturated with sodium chloride and further extracted with dichloromethane (2 × 100 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give the *carboxylic acid* **34** (6.32 g) as a foam. The recovered formyl pyrrole **33** (1.43 g) was oxidised as described above to give further *acid* **34** (678 mg; total yield 7.00 g, 76% from ketone **32**) (Found: M^+, 409.1371. $C_{19}H_{23}NO_9$ requires *M*, 409.1373); λ_{max}(MeOH)/nm 230 and 305; ν_{max}($CHCl_3$)/cm^{-1} 3450, 2980, 1800, 1740 and 1660; δ_H(400 MHz, $CDCl_3$) 1.38 (3 H, s, CMe), 2.33 (3 H, s, 4-Me), 2.41 (1 H, dd, *J* 13 and 8) and 2.70 (1 H, dd, *J* 13 and 9, CH_2CH−O), 2.54 (2 H, t, *J* 8, CH_2CH_2CO), 2.65 and 2.83 (each 1 H, d, *J* 17, CH_2CO), 3.06 (3 H, t, *J* 8, CH_2CH_2CO), 3.63 and 3.66 (each 3 H, s, OMe), 5.24 (1 H, dd, *J* 9 and 8, CH−O) and 10.34 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.7 (4-Me), 19.6 (CH_2CH_2CO), 23.3 (C*Me*), 34.3 (CH_2CH_2CO), 36.3, 40.8 and 41.0 (CH_2CCH_2), 51.6 and 52.0 (OMe), 78.1 (CH−O), 122.6, 128.1, 130.0 and 130.8 (pyrrole-C) and 164.6, 171.0, 173.5, 179.1 and 185.9 (C=O); *m/z* (FD) 409 (M^+, 100%).

tert-Butyl 3-(2-methoxycarbonylethyl)-5-[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-methylpyrrole-2-carboxylate 7

Concentrated sulfuric acid (150 mm^3) was added dropwise to a solution of acid **34** (6.32 g, 15.5 mmol) in isobutene (25 cm^3) and dry chloroform (50 cm^3). The reaction vessel was then sealed and the mixture was stirred for 36 h. Saturated aqueous sodium hydrogen carbonate (5 cm^3) was added and the isobutene was evaporated under a stream of argon. Saturated aqueous sodium hydrogen carbonate (100 cm^3) was added and the mixture was extracted with dichloromethane (60 cm^3 then 2 × 100 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate, gave the tert-*butyl ester* **7** (5.75g, 80%) as an oil (Found: M^+, 465.1995. $C_{23}H_{31}NO_9$ requires *M*, 465.1999); λ_{max}(MeOH)/nm 233 and 305; ν_{max}($CHCl_3$)/cm^{-1} 3435, 2955, 1790, 1735 and 1645; δ_H(400 MHz, $CDCl_3$) 1.37 (3 H, s, CMe), 1.55 (9 H, s, Bu^t), 2.32 (3 H, s, 4-Me), 2.39 (1 H, dd, *J* 13 and 8) and 2.65 (1 H, dd, *J* 13 and 9, CH_2CH−O), 2.50 (2 H, t, *J* 8, CH_2CH_2CO), 2.63 and 2.80 (each 1 H, d, *J* 17, CH_2CO), 3.01 (2 H, t, *J* 8, CH_2CH_2CO) 3.60 and 3.65 (each 3 H, s, OMe), 5.18 (1 H, dd, *J* 8 and 9, CH−O) and 10.11 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.7 (4-Me), 19.7 (CH_2CH_2CO), 23.4 (C*Me*), 28.2 (CMe_3), 34.6, 36.6, 40.6 and 41.0 (CH_2CH_2CO and CH_2CCH_2), 51.5 and 51.9 (OMe), 78.3 (CH−O), 82.3 (CMe_3), 124.9, 126.7, 128.6 and 130.0 (pyrrole-C) and 159.5, 170.7, 173.2, 178.7 and 185.3 (C=O); *m/z* (FD) 465 (M^+, 100%).

Benzyl 3-(2-methoxycarbonylethyl)-5-[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-methylpyrrole-2-carboxylate

A mixture of acid **34** (1 g, 2.44 mmol), anhydrous potassium carbonate (610 mg, 6.22 mmol) and freshly distilled benzyl bromide (875 cm^3, 7.36 mmol) in dry *N*,*N*-dimethylformamide (40 cm^3) was stirred for 12 h at room temperature under argon. *tert*-Butyl methyl ether (200 cm^3) was then added and the mixture was washed with water (3 × 75 cm^3), dried and evaporated under reduced pressure. Purification by column chromatography, eluting with dichloromethane–ethyl acetate (12:1), gave the *benzyl ester* (corresponding to *tert*-butyl ester **7**) (920 mg, 75%) as a solid, mp 89–90 °C (Found: C, 62.6; H, 5.7; N, 2.9%; M^+, 499.1829. $C_{26}H_{29}NO_9$ requires C, 62.5; H, 5.85; N, 2.8%; *M*, 499.1842); λ_{max}(MeOH)/nm 233 and 304; ν_{max}($CHCl_3$)/cm^{-1} 3440, 2950, 1800, 1735 and 1650; δ_H(400 MHz, $CDCl_3$) 1.37 (3 H, s, CMe), 2.33 (3 H, s, 4-Me), 2.39 (1 H, dd, *J* 13 and 8) and 2.68 (1 H, dd, *J* 13 and 9, CH_2CH−O), 2.49 (2 H, t, *J* 8, CH_2CH_2CO), 2.63 and 2.80 (each 1 H, d, *J* 17, CH_2CO), 3.03–3.07 (2 H, m, CH_2CH_2CO), 3.53 and 3.62 (each 3 H, s, OMe), 5.20 (1 H, dd, *J* 9 and 8, CH−O), 5.33 (2 H, s, CH_2Ph), 7.32–7.43 (5 H, m, Ph) and 10.22 (1 H, br s, NH); δ_C(67.7 MHz, $CDCl_3$) 10.8 (4-Me), 19.8 (CH_2CH_2CO), 23.4 (C*Me*), 34.4 (CH_2CH_2CO), 36.4, 40.7 and 41.1 (CH_2CCH_2), 51.7 and 52.0 (OMe), 60.7 (CH_2Ph), 78.3 (CH−O), 123.2, 127.3, 128.1, 128.3, 128.7, 129.9 and 135.3 (pyrrole-C and Ph) and 160.0, 170.8, 173.2, 178.9 and 185.7 (C=O); *m/z* (FD) 499 (M^+, 100%).

tert-Butyl 3-(2-methoxycarbonylethyl)-5-hydroxy[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]methyl-4-methylpyrrole-2-carboxylate 35

A solution of *tert*-butyl ester **7** (5.74 g, 12.3 mmol) in dry tetrahydrofuran (150 cm^3) under argon was treated with sodium borohydride (155 mg, 4.10 mmol) portionwise over 30 min with the temperature maintained at −5 °C, then warmed to room temperature over 5 min, mixed with dilute hydrochloric acid (0.5 mol dm^{-3}; 210 cm^3) and extracted with dichloromethane (4 × 100 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give the diastereoisomeric *alcohols* **35** as an oil (*ca.* 5.74 g, 100%). These alcohols were generally used as a mixture in the next reaction but for characterisation they were separated by PLC using 5% MeOH in CH_2Cl_2.

Lower R_f diastereoisomer (Found: M^+, 467.2132. $C_{23}H_{33}NO_9$ requires *M*, 467.2155); λ_{max}(MeOH)/nm 272; ν_{max}($CHCl_3$)/cm^{-1} 3440, 2950, 1775, 1730 and 1680; δ_H(400 MHz, $CDCl_3$) 1.25 (3 H, s, CMe), 1.52 (9 H, s, Bu^t), 1.86 (1 H, dd, *J* 13 and 7) and 2.21 (1 H, dd, *J* 13 and 10, CH_2CH−O), 1.97 (3 H, s, 4-Me), 2.47 (2 H, t, *J* 8, CH_2CH_2CO), 2.56 and 2.75 (each 1 H, d, *J* 17, CH_2CO), 2.92–2.96 (2 H, m, CH_2CH_2CO), 3.54 (1 H, d, *J* 4, OH), 3.64 and 3.66 (each 3 H, s, OMe), 4.66–4.68 and 4.84–4.86 (each 1 H, m, C*H*C*H*OH) and 9.28 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.9 (4-Me), 20.6 (CH_2CH_2CO), 23.5 (C*Me*), 28.3 (CMe_3), 34.9, 35.4, 40.9 and 41.8 (CH_2CH_2CO and CH_2CCH_2), 51.4 and 51.9 (OMe), 68.3 (CHOH), 79.7 (*C*HCHOH), 81.0 (CMe_3), 117.5, 120.3, 128.2 and 129.0 (pyrrole-C) and 160.8, 171.3, 173.7 and 179.8 (C=O); *m/z* (FD) 467 (M^+, 100%).

Higher R_f diastereoisomer (Found: M^+, 467.2147); λ_{max} (MeOH)/nm 273; $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 2980, 1780, 1740 and 1685; δ_H(400 MHz, $CDCl_3$) 1.25 (3 H, s, CMe), 1.52 (9 H, s, Bu^t), 1.75 (1 H, dd, *J* 13 and 7, CH_AH$_B$CH−O), 1.97 (3 H, s, 4-Me), 2.43–2.49 (3 H, m, CH$_A$$H_B$CH−O and CH$_2CH_2$CO), 2.57 and 2.75 (each 1 H, d, *J* 17, CH$_2$CO), 2.90–2.98 (2 H, m, CH_2CH$_2$CO), 3.56 (1 H, d, *J* 2.5, OH), 3.64 and 3.67 (each 3 H, s, OMe), 4.58–4.63 and 5.23–5.25 (each 1 H, m, C*H*C*H*OH) and 9.20 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.7 (4-Me), 20.6 (*C*H$_2$CH$_2$CO), 23.5 (C*Me*), 28.4 (C*Me*$_3$), 32.9, 35.0, 41.0 and 41.8 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.5 and 52.0 (OMe), 66.7 (*C*HOH), 78.4 (*C*HCHOH), 80.9 (*C*Me$_3$), 115.8, 119.6, 128.6 and 128.8 (pyrrole-C) and 161.0, 171.5, 173.6 and 180.1 (C=O); *m/z* (FD) 467 (M^+, 100%).

Benzyl 3-(2-methoxycarbonylethyl)-5-hydroxy[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]methyl-4-methylpyrrole-2-carboxylate

The benzyl ester (corresponding to *tert*-butyl ester **7**) (385 mg, 0.772 mmol) was reduced in the same way as described for **7** to give the diastereoisomeric *alcohols* (the benzyl esters corresponding to *tert*-butyl esters **35**) as an oil (*ca.* 385 mg, 100%). They were separated by PLC using 2% MeOH in CH_2Cl_2.

Lower R_f diastereoisomer (Found: M^+, 501.1965. $C_{26}H_{31}NO_9$ requires *M*, 501.1999); λ_{max}(MeOH)/nm 278; $\nu_{max}(CHCl_3)/cm^{-1}$ 3444, 2955, 2931, 1775, 1733, 1698 and 1603; δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, s, CMe), 1.88 (1 H, dd, *J* 13 and 7) and 2.27 (1 H, dd, *J* 13 and 10, CH_2CH−O), 1.99 (3 H, s, 4-Me), 2.46 (2 H, t, *J* 8, CH$_2$CH_2CO), 2.57 and 2.78 (each 1 H, d, *J* 17, CH$_2$CO), 2.97–3.01 (2 H, m, CH_2CH$_2$CO), 3.20 (1 H, d, *J* 4, OH), 3.61 and 3.67 (each 3 H, s, OMe), 4.63–4.65 and 4.84–4.86 (each 1 H, m, C*H*C*H*OH), 5.26 and 5.30 (each 1 H, d, *J* 12, CH_2Ph), 7.31–7.40 (5 H, m, Ph) and 9.26 (1 H, br s, NH); δ_C(67.7 MHz, $CDCl_3$) 8.9 (4-Me), 20.4 (*C*H$_2$CH$_2$CO), 23.6 (C*Me*), 34.6, 35.4, 40.9 and 41.7 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.5 and 51.9 (OMe), 66.0 and 68.4 (*C*H$_2$Ph and CHOH), 79.5 (*C*HCHOH), 117.7, 118.6, 128.1, 128.4, 128.6, 130.0 and 136.0 (pyrrole-C and Ph) and 160.7, 171.4, 173.6 and 179.7 (C=O); *m/z* (FD) 501 (M^+, 100%).

Higher R_f diastereoisomer (Found: M^+, 501.1998); λ_{max} (MeOH)/nm 279; $\nu_{max}(CHCl_3)/cm^{-1}$ 3444, 3020, 1775, 1733, 1688 and 1602; δ_H(400 MHz, $CDCl_3$) 1.25 (3 H, s, CMe), 1.74 (1 H, dd, *J* 13 and 7, CH_AH$_B$CHCHOH), 1.97 (3 H, s, 4-Me), 2.43–2.49 (3 H, m, CH$_A$$H_B$CHCHOH and CH$_2CH_2$CO), 2.56 and 2.74 (each 1 H, d, *J* 17, CH$_2$CO), 2.95–3.00 (2 H, m, CH_2CH$_2$CO), 3.53 (1 H, br s, OH), 3.60 and 3.68 (each 3 H, s, OMe), 4.59–4.64 (1 H, m, C*H*CHOH), 5.23–5.31 (3 H, m, CHC*H*OH and CH_2Ph), 7.29–7.39 (5 H, m, Ph) and 9.24 (1 H, br s, NH); δ_C(67.7 MHz, $CDCl_3$) 8.8 (4-Me), 20.4 (*C*H$_2$-CH$_2$CO), 23.6 (C*Me*), 32.5, 34.6, 41.0 and 41.7 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.4 and 52.0 (OMe), 65.8 and 66.6 (*C*H$_2$Ph and CHOH), 78.1 (*C*HCHOH), 116.0, 117.9, 128.1, 128.3, 129.4, 130.4 and 136.1 (pyrrole-C and Ph) and 160.7, 171.6, 173.5 and 180.0 (C=O); *m/z* (FD) 501 (M^+, 100%).

***tert*-Butyl 3-(2-methoxycarbonylethyl)-5-acetoxy[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]-methyl-4-methylpyrrole-2-carboxylate 36**

A solution of alcohols **35** (5.74 g, 12.3 mmol) in dry dichloromethane (200 cm^3) was treated with 4-dimethylaminopyridine (3.05 g, 25 mmol) and then acetic anhydride (4.65 cm^3, 49.3 mmol), and stirred for 15 min. Water (200 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 cm^3). The combined organic layers were washed with brine (100 cm^3), dried and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate (1.5:1), gave the diastereoisomeric *acetoxy lactones* **36** as a foam (6.15 g, 98%). The acetoxy lactones were used as a mixture for the next reaction but were separated for characterisation by PLC using hexane–ethyl acetate (2:1).

Lower R_f diastereoisomer (Found: M^+, 509.2227. $C_{25}H_{35}NO_{10}$ requires *M*, 509.2261); λ_{max}(MeOH)/nm 273; $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1790, 1740 and 1690; δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, s, CMe), 1.53 (9 H, s, Bu^t), 2.01 (3 H, s, 4-Me), 2.06–2.10 (5 H, m, CH_2CH−O and Ac), 2.47 (2 H, t, *J* 8, CH$_2$-CH_2CO), 2.51 (2 H, s, CH$_2$CO), 2.94 (2 H, t, *J* 8, CH_2CH$_2$CO), 3.57 and 3.63 (each 3 H, s, OMe), 4.70–4.75 (1 H, m, AcO-CHC*H*), 6.04 (1 H, d, *J* 3.8, AcOC*H*) and 8.89 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.7 (4-Me), 20.5 and 20.8 (*C*H$_2$-CH$_2$CO and *Me*CO$_2$), 22.9 (C*Me*), 28.3 (C*Me*$_3$), 34.9, 35.6, 40.7 and 41.4 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.4 and 51.6 (OMe), 67.6 (AcO*C*H), 77.0 (AcOCH*C*H), 81.2 (*C*Me$_3$), 119.6, 121.1, 124.6 and 127.7 (pyrrole-C) and 160.5, 169.5, 170.4, 173.5 and 179.0 (C=O); *m/z* (FD) 509 (M^+, 100%).

Higher R_f diastereoisomer (Found: M^+, 509.2309); λ_{max} (MeOH)/nm 271; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2960, 1770, 1740 and 1680; δ_H(400 MHz, $CDCl_3$) 1.22 (3 H, s, CMe), 1.53 (9 H, s, Bu^t), 1.88 (1 H, dd, *J* 13 and 7, CH_AH$_B$CH−O), 2.01–2.11 (7 H, m, CH$_A$$H_B$CH−O, Ac and 4-Me), 2.44–2.48 (2 H, m, CH$_2$CH_2CO), 2.55 and 2.72 (each 1 H, d, *J* 17, CH$_2$CO), 2.93 (2 H, t, *J* 8, CH_2CH$_2$CO), 3.63 and 3.65 (each 3 H, s, OMe), 4.77–4.80 (1 H, m, AcOCHC*H*), 5.92 (1 H, d, *J* 6, AcOC*H*) and 9.08 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.7 (4-Me), 20.6 and 20.8 (*C*H$_2$CH$_2$CO and *Me*CO$_2$), 23.3 (C*Me*), 28.3 (C*Me*$_3$), 34.9, 35.7, 40.7 and 41.5 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.4 and 51.8 (OMe), 68.1 (AcO*C*H), 76.8 (AcOCH*C*H), 81.3 (*C*Me$_3$), 119.3, 121.1, 125.9 and 127.8 (pyrrole-C) and 160.6, 169.8, 170.8, 173.5 and 179.1 (C=O); *m/z* (FD) 509 (M^+, 100%).

Benzyl 3-(2-methoxycarbonylethyl)-5-acetoxy[(2*S*,4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-yl]-methyl-4-methylpyrrole-2-carboxylate

The alcohols (the benzyl esters corresponding to *tert*-butyl esters **35**) (385 mg, 0.772 mmol) were acetylated as described above for **35** to give the diastereoisomeric *acetoxy lactones* (the benzyl esters corresponding to *tert*-butyl esters **36**) as oils. They were separated by flash chromatography on silica eluting with hexane–ethyl acetate (1.5:1).

Lower R_f diastereoisomer (134 mg, 32%) (Found: M^+ − AcOH, 483.1883. $C_{28}H_{33}NO_{10}$ requires *M* − AcOH, 483.1893); λ_{max}(MeOH)/nm 276; $\nu_{max}(CHCl_3)/cm^{-1}$ 3020, 1780, 1736 and 1602; δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, s, CMe), 2.01–2.11 (8 H, m, CH_2CH−O, Ac and 4-Me), 2.43–2.49 (4 H, m, CH$_2$CO and CH$_2$CH_2CO), 2.98 (2 H, t, *J* 8, CH_2CH$_2$CO), 3.51 and 3.59 (each 3 H, s, OMe), 4.73–4.78 (1 H, m, AcOCHC*H*), 5.24–5.31 (2 H, m, CH_2Ph), 6.02 (1 H, d, *J* 4, AcOC*H*), 7.27–7.39 (5 H, m, Ph) and 9.08 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.6 (4-Me), 20.3 and 20.7 (*C*H$_2$CH$_2$CO and *Me*CO$_2$), 22.8 (C*Me*), 34.6, 35.6, 40.7 and 41.4 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.3 and 51.6 (OMe), 65.9 and 67.7 (*C*H$_2$Ph and AcO*C*H), 76.9 (AcO-CH*C*H), 119.4, 119.9, 125.5, 128.1, 128.2, 128.5, 129.3 and 135.9 (pyrrole-C and Ph) and 160.5, 169.5, 170.3, 173.3 and 178.9 (C=O); *m/z* (FD) 543 (M^+, 100%).

Higher R_f diastereoisomer (284 mg, 67%) (Found: M^+ − AcOH, 483.1881); λ_{max}(MeOH)/nm 276; $\nu_{max}(CHCl_3)/cm^{-1}$ 3025, 1780, 1736 and 1603; δ_H(400 MHz, $CDCl_3$) 1.24 (3 H, s, CMe), 1.87 (1 H, dd, *J* 13 and 7, CH_AH$_B$CH−O), 2.01–2.13 (7 H, m, CH$_A$$H_B$CH−O, Ac and 4-Me), 2.44 (2 H, t, *J* 8, CH$_2$CH_2CO), 2.55 and 2.73 (each 1 H, d, *J* 17, CH$_2$CO), 2.97 (2 H, t, *J* 8, CH_2CH$_2$CO), 3.59 and 3.63 (each 3 H, s, OMe), 4.81–4.87 (1 H, m, AcOCHC*H*), 5.28 and 5.32 (each 1 H, d, *J* 12, CH_2Ph), 5.95 (1 H, d, *J* 6, AcOC*H*), 7.28–7.40 (5 H, m, Ph) and 9.38 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.6 (4-Me), 20.4 and 20.7 (*C*H$_2$CH$_2$CO and *Me*CO$_2$), 23.3 (C*Me*), 34.6, 35.7, 40.6 and 41.5 (CH$_2$*C*H$_2$CO and *C*H$_2$*CC*H$_2$), 51.4 and 51.7 (OMe), 66.1 and 68.1 (*C*H$_2$Ph and AcO*C*H), 76.7 (AcOCH*C*H), 119.3, 119.6, 127.0, 128.2, 128.2, 128.5, 129.5 and 135.8 (pyrrole-C

and Ph) and 160.7, 169.8, 170.7, 173.3 and 179.1 (C=O); *m/z* (FD) 543 (M^+, 100%).

tert-Butyl 3-(2-methoxycarbonylethyl)-5-[(4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-ylidene]-methyl-4-methylpyrrole-2-carboxylate 37

The acetoxy lactones **36** (2.05 g, 4.03 mmol) were heated at 200 °C for 5 min under a stream of argon. Purification by column chromatography, eluting with hexane–ethyl acetate (5:2), gave (E)- and (Z)-*enol lactones* **37** as an oil (1.52 g, 84%). The enol lactones were used as a mixture for the next reaction but were separated for characterisation by PLC using hexane–ethyl acetate (1.7:1).

Lower R_f isomer (Found: M^+, 449.2022. $C_{23}H_{31}NO_8$ requires *M*, 449.2050); λ_{max}(MeOH)/nm 244, 278 and 312; ν_{max}($CHCl_3$)/cm^{-1} 3460, 3000, 1810, 1735 and 1690; δ_H(400 MHz, $CDCl_3$) 1.35 (3 H, s, CMe), 1.55 (9 H, s, Bu^t), 2.00 (3 H, s, 4-Me), 2.51 (2 H, t, *J* 8, CH_2CH_2CO), 2.65 and 2.84 (each 1 H, d, *J* 17, CH_2CO), 2.77 (1 H, d, *J* 16.5) and 3.20 (1 H, dd, *J* 16.5 and 1.7, CH_2C=C), 2.96–3.00 (2 H, m, CH_2CH_2CO), 3.64 and 3.67 (each 3 H, s, OMe), 5.54 (1 H, br s, C=CH) and 9.43 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.6 (4-Me), 20.6 (CH_2CH_2CO), 24.1 (CMe), 28.4 (CMe_3), 34.9 (CH_2CH_2CO), 38.6, 40.7 and 40.8 (CH_2CCH_2), 51.4 and 52.0 (OMe), 80.6 (CMe_3), 94.5 (C=CH), 118.0, 120.0, 126.4 and 128.2 (pyrrole-C), 144.2 (C=CH) and 160.3, 170.7, 173.7 and 177.4 (C=O); *m/z* (FD) 449 (M^+, 100%).

Higher R_f isomer (Found: M^+, 449.2042); λ_{max}(MeOH)/nm 244 and 299; ν_{max}($CHCl_3$)/cm^{-1} 3490, 3000, 1800, 1735, and 1680; δ_H(400 MHz, $CDCl_3$) 1.34 (3 H, s, CMe), 1.55 (9 H, s, Bu^t), 1.97 (3 H, s, 4-Me), 2.49 (2 H, t, *J* 8, CH_2CH_2CO), 2.63 and 2.89 (each 1 H, d, *J* 17, CH_2CO), 2.86 (1 H, d, *J* 16) and 3.24 (1 H, dd, *J* 16 and 2.4, CH_2C=C), 2.96 (2 H, t, *J* 8, CH_2CH_2CO), 3.66 and 3.68 (each 3 H, s, OMe), 6.21 (1 H, br s, C=C*H*) and 8.42 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.8 (4-Me), 20.7 (CH_2CH_2CO), 24.7 (CMe), 28.3 (CMe_3), 34.9 (CH_2CH_2CO), 37.5, 40.9 and 41.4 (CH_2CCH_2), 51.4 and 52.1 (OMe), 81.1 (CMe_3), 96.7 (C=CH), 119.7, 120.3, 126.5 and 128.5 (pyrrole-C), 147.7 (C=CH) and 161.0, 170.7, 173.4 and 177.8 (C=O); *m/z* (FD) 449 (M^+, 100%).

Benzyl 3-(2-methoxycarbonylethyl)-5-[(4*R*)-4-methoxycarbonylmethyl-4-methyl-5-oxotetrahydrofuran-2-ylidene]-methyl-4-methylpyrrole-2-carboxylate

The acetoxy lactones (the benzyl esters corresponding to *tert*-butyl esters **36**) (75 mg, 0.138 mmol) were heated at 200 °C for 5 min under a stream of argon. Purification by PLC, eluting with hexane–ethyl acetate (1:1), gave the higher R_f (E)-*enol lactone* (28 mg, 42%) and the lower R_f (Z)-*enol lactone* (30 mg, 45%) (the benzyl esters corresponding to *tert*-butyl esters **37**) as oils.

(*Z*)-Isomer (Found: M^+, 483.1895. $C_{26}H_{29}NO_8$ requires *M*, 483.1893); ν_{max}($CHCl_3$)/cm^{-1} 3459, 2955, 1807, 1734 and 1693; δ_H(400 MHz, $CDCl_3$) 1.34 (3 H, s, CMe), 1.99 (3 H, s, 4-Me), 2.49 (2 H, t, *J* 8, CH_2CH_2CO), 2.65 and 2.85 (each 1 H, d, *J* 17, CH_2CO), 2.77 (1 H, d, *J* 17) and 3.19 (1 H, dd, *J* 17 and 1.8, CH_2C=C), 3.01 (2 H, t, *J* 8, CH_2CH_2CO), 3.60 and 3.66 (each 3 H, s, OMe), 5.30 (2 H, s, CH_2Ph), 5.54 (1 H, s, C=CH), 7.27–7.43 (5 H, m, Ph) and 9.51 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.5 (4-Me), 20.4 (CH_2CH_2CO), 24.1 (CMe), 34.6 (CH_2CH_2CO), 38.5, 40.6 and 40.7 (CH_2CCH_2), 51.3 and 52.0 (OMe), 65.5 (CH_2Ph), 94.3 (C=CH), 118.2, 118.25, 127.3, 127.9, 128.4, 129.7 and 136.2 (pyrrole-C and Ph), 144.8 (C=CH) and 160.2, 170.6, 173.5 and 177.4 (C=O); *m/z* (FD) 483 (M^+, 100%).

(*E*)-Isomer (Found: M^+, 483.1877); λ_{max}(MeOH)/nm 243 and 315; ν_{max}($CHCl_3$)/cm^{-1} 3450, 2955, 1860, 1735 and 1680; δ_H(400 MHz, $CDCl_3$) 1.33 (3 H, s, CMe), 1.96 (3 H, s, 4-Me), 2.46 (2 H, t, *J* 8, CH_2CH_2CO), 2.64 and 2.87 (each 1 H, d, *J* 17, CH_2CO), 2.84 (1 H, dd, *J* 16 and 1.4) and 3.24 (1 H, dd, *J* 16, 2.5, CH_2C=C), 2.97–3.01 (2 H, m, CH_2CH_2CO), 3.61 and 3.66 (each 3 H, s, OMe), 5.29 (2 H, s, CH_2Ph), 6.19 (1 H, br s, C=CH), 7.30–7.39 (5 H, m, Ph) and 8.57 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.9 (4-Me), 20.6 (CH_2CH_2CO), 24.7 (CMe), 34.7 (CH_2CH_2CO), 37.5, 40.9 and 41.4 (CH_2CCH_2), 51.4 and 52.1 (OMe), 66.0 (CH_2Ph), 96.6 (C=CH), 118.6, 120.0, 127.5, 128.1, 128.15, 128.5, 130.1 and 136.0 (pyrrole-C and Ph), 148.4 (C=CH) and 161.0, 170.8, 173.4 and 177.8 (C=O); *m/z* (FD) 483 (M^+, 100%).

(2*R*)-9-*tert*-Butoxycarbonyl-4-hydroxy-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3,4,5-tetrahydrodipyrrin-1(10*H*)-one 38

A solution of enol lactones **37** (4.20 g, 9.35 mmol) in tetrahydrofuran (100 cm^3) at room temperature was treated with concentrated aqueous ammonia (60 cm^3) dropwise over 5 min, stirred for 75 min, mixed with brine (100 cm^3) and extracted with dichloromethane (200 cm^3 then 3 × 200 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give *lactam alcohols* **38** as a foam, which was used without further purification in the next reaction, but for characterisation the isomers were separated by PLC using 5% MeOH in CH_2Cl_2.

Lower R_f diastereoisomer (Found: $M^+ - H_2O$, 448.2224. $C_{23}H_{34}N_2O_8$ requires $M - H_2O$, 448.2210); λ_{max}(MeOH)/nm 280; ν_{max}($CHCl_3$)/cm^{-1} 3690, 3440, 3340, 1745, 1720 and 1700; δ_H(400 MHz, $CDCl_3$) 1.32 (3 H, s, 2-Me), 1.50 (9 H, s, Bu^t), 1.93 (4 H, m, 3-H_A and 7-Me), 2.29 (1 H, d, *J* 14, 3-H_B), 2.38 (1 H, d, *J* 16, CH_AH_BCO), 2.43–2.50 (3 H, m, CH_2CH_2CO and CH_AH_BCO), 2.91–2.95 (2 H, m, CH_2CH_2CO), 2.99 (2 H, s, 5-H_2), 3.57 and 3.64 (each 3 H, s, OMe), 4.59 (1 H, br s, OH), 7.37 (1 H, br s, lactam-NH) and 9.69 (1 H, br s, pyrrole-NH); δ_C(100 MHz, $CDCl_3$) 8.8 (7-Me), 21.0 (CH_2CH_2CO), 25.5 (2-Me), 28.4 (CMe_3), 35.1 (CH_2CH_2CO), 37.4 (C-5), 41.4 and 42.5 (CH_2CO and C-2), 45.7 (C-3), 51.4 and 51.5 (OMe), 80.8 (CMe_3), 86.2 (C-4), 118.2, 119.4, 127.7 and 128.2 (pyrrole-C) and 161.4, 171.6, 173.7 and 180.9 (C=O); *m/z* (FD) 466 (M^+, 100%).

Higher R_f diastereoisomer (Found: $M^+ - H_2O$, 448.2197); λ_{max}(MeOH)/nm 280; ν_{max}($CHCl_3$)/cm^{-1} 3690, 3630, 3440, 1725, 1690 and 1605; δ_H(400 MHz, $CDCl_3$) 0.99 (3 H, s, 2-Me), 1.50 (9 H, s, Bu^t), 1.94 (3 H, s, 7-Me), 2.08 and 2.20 (each 1 H, d, *J* 15, 3-H_2), 2.42 and 2.84 (each 1 H, d, *J* 18, CH_2CO), 2.44–2.48 (2 H, m, CH_2CH_2CO), 2.89–2.99 (4 H, m, CH_2CH_2CO and 5-H_2), 3.63 (6 H, s, 2 × OMe), 5.04 (1 H, br s, OH), 7.10 (1 H, br s, lactam-NH) and 9.60 (1 H, br s, pyrrole-NH); δ_C(100 MHz, $CDCl_3$) 8.9 (7-Me), 20.9 (CH_2CH_2CO), 26.8 (2-Me), 28.4 (CMe_3), 35.1 (CH_2CH_2CO), 37.2 (C-5), 41.6 and 41.7 (CH_2CO and C-2), 46.9 (C-3), 51.4 and 52.1 (OMe), 80.6 (CMe_3), 85.9 (C-4), 117.9, 119.3, 127.6 and 128.0 (pyrrole-C) and 161.1, 173.5, 173.7 and 179.8 (C=O); *m/z* (FD) 466 (M^+, 100%).

(2*R*)-9-Benzyloxycarbonyl-4-hydroxy–8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3,4,5-tetrahydrodipyrrin-1(10*H*)-one

A solution of the (*Z*)-enol lactone (the benzyl ester corresponding to *tert*-butyl ester **37**) (80 mg, 0.166 mmol) in tetrahydrofuran (3 cm^3) at −10 °C was treated with concentrated aqueous ammonia (0.5 cm^3) dropwise over 20 min, then stirred for 40 min at room temperature, mixed with water (15 cm^3) and extracted with dichloromethane (20 cm^3 then 2 × 10 cm^3). The combined extracts were dried and evaporated under reduced pressure to give a mixture of the *lactam alcohols* (the benzyl esters corresponding to *tert*-butyl esters **38**), which was used without further purification in the next reaction, but for characterisation the isomers were separated by PLC using 5% MeOH in CH_2Cl_2.

Lower R_f diastereoisomer (Found: $M^+ - H_2O$, 482.2056. $C_{26}H_{32}N_2O_8$ requires $M - H_2O$, 482.2053); ν_{max}($CHCl_3$)/cm^{-1} 3690, 3430, 1730, 1700 and 1605; δ_H(400 MHz, $CDCl_3$) 1.31 (3 H, s, 2-Me), 1.92–1.95 (4 H, m, 3-H_A and 7-Me), 2.30 (1 H, d, *J* 14, 3-H_B), 2.36 (1 H, d, *J* 16.5, CH_AH_BCO), 2.42–2.50 (3 H, m, CH_AH_BCO and CH_2CH_2CO), 2.95–2.98 (4 H, m, CH_2CH_2CO and 5-H_2), 3.54 and 3.60 (each 3 H, s, OMe), 4.13 (1 H, br s,

OH), 5.23 (2 H, s, CH_2Ph), 7.21 (1 H, br s, lactam-NH), 7.26–7.36 (5 H, m, Ph) and 9.81 (1 H, br s, pyrrole-NH); δ_C(67.7 MHz, $CDCl_3$) 8.9 (7-Me), 20.8 (*C*H_2CH$_2$CO), 25.8 (2-Me), 34.8 (CH$_2$*C*H$_2$CO), 38.4 (C-5), 41.2 and 42.3 (*C*H_2CO and C-2), 45.8 (C-3), 51.3 and 51.4 (OMe), 65.8 (*C*H_2Ph), 86.0 (C-4), 117.9, 118.8, 128.1, 128.2, 128.3, 128.4, 129.8 and 136.1 (pyrrole-C and Ph) and 161.2, 171.7, 173.8 and 180.8 (C=O); *m/z* (FD) 500 (M^+, 100%).

Higher R_f diastereoisomer (Found: $M^+ - H_2O$, 482.2067); ν_{max}($CHCl_3$)/cm^{-1} 3695, 3425, 1730, 1700 and 1605; δ_H(400 MHz, $CDCl_3$) 1.10 (3 H, s, 2-Me), 1.96 (3 H, s, 7-Me), 2.13 and 2.24 (each 1 H, d, *J* 15, 3-H$_2$), 2.43 and 2.88 (each 1 H, d, *J* 18, CH$_2$CO), 2.45–2.49 (2 H, m, CH$_2$C*H*$_2$CO), 2.93 (2 H, m, 5-H$_2$), 2.97–3.03 (2 H, m, C*H*$_2$CH$_2$CO), 3.61 and 3.67 (each 3 H, s, OMe), 5.16 (1 H, br s, OH), 5.27 (2 H, s, C*H*$_2$Ph), 6.21 (1 H, br s, lactam-NH), 7.30–7.40 (5 H, m, Ph) and 9.43 (1 H, br s, pyrrole-NH); δ_C(67.7 MHz, $CDCl_3$) 9.9 (7-Me), 20.8 (*C*H$_2$-CH$_2$CO), 27.6 (2-Me), 34.8 (CH$_2$*C*H$_2$CO), 37.7 (C-5), 41.2 and 41.7 (*C*H$_2$CO and C-2), 48.4 (C-3), 51.3 and 52.2 (OMe), 65.7 (*C*H$_2$Ph), 85.3 (C-4), 118.7, 119.3, 127.9, 128.0, 128.2, 128.5, 129.6 and 136.2 (pyrrole-C and Ph) and 160.8, 173.6, 173.8 and 179.2 (C=O); *m/z* (FD) 500 (M^+, 100%)

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

A solution of lactam alcohols **38** [from enol lactones **37** (4.20 g, 9.35 mmol)] in dichloromethane (200 cm^3) was stirred with toluene-*p*-sulfonic acid (25 mg) at room temperature for 35 min. Saturated aqueous sodium hydrogen carbonate (150 cm^3) was then added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 75 cm^3) and the combined organic layers were dried and evaporated under reduced pressure. Purification by column chromatography, eluting with dichloromethane–ethyl acetate (3:1), gave the (E)- and (Z)-*lactams* **5** as a foam (3.82 g, 91% from the enol lactones **37**). For characterisation the isomers were separated by PLC and were identical to the compounds previously synthesised.[2]

(2*R*)-9-Benzyloxycarbonyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-one

A solution of the lactam alcohols (the benzyl esters corresponding to *tert*-butyl esters **38**) [from (*Z*)-enol lactone (80 mg, 0.166 mmol)] in dichloromethane (4 cm^3) was stirred with toluene-*p*-sulfonic acid (*ca.* 1 mg) at −10 °C for 15 min and then evaporated under reduced pressure. Purification by PLC, eluting with hexane–ethyl acetate (1:1), gave the lower R_f (E)-*lactam* (22 mg, 27%) and the higher R_f (Z)-*lactam* (28 mg, 35%) (the benzyl esters corresponding to *tert*-butyl esters **5**) as oils.

(*E*)-Isomer (Found: M^+, 482.2049. $C_{26}H_{30}N_2O_7$ requires *M*, 482.2053); λ_{max}(MeOH)/nm 228 and 325; ν_{max}($CHCl_3$)/cm^{-1} 3460, 3410, 1730, 1670 and 1565; δ_H(400 MHz, $CDCl_3$) 1.28 (3 H, s, 2-Me), 1.95 (3 H, s, 7-Me), 2.47 (2 H, t, *J* 8, CH$_2$C*H*$_2$CO), 2.57 and 2.81 (each 1 H, d, *J* 17, CH$_2$CO), 2.74 (1 H, dd, *J* 16 and 1.5) and 3.14 (1 H, dd, *J* 16 and 2, 3-H$_2$), 2.98–3.00 (2 H, m, C*H*$_2$CH$_2$CO), 3.61 and 3.65 (each 3 H, s, OMe), 5.30 (2 H, s, C*H*$_2$Ph), 5.75 (1 H, br s, 5-H), 7.30–7.41 (5 H, m, Ph), 8.38 and 8.53 (each 1 H, br s, NH); δ_C(67.7 MHz, $CDCl_3$) 8.9 (7-Me), 20.7 (*C*H$_2$CH$_2$CO), 25.0 (2-Me), 34.8 (CH$_2$*C*H$_2$CO), 37.9, 40.8 and 42.1 (*C*H$_2$*CC*H$_2$), 51.4 and 51.8 (OMe), 65.9 (*C*H$_2$Ph), 93.0 (C-5), 117.8, 118.7, 128.0, 128.5, 129.9 and 130.1 (pyrrole-C and Ph), 136.2 (C-4) and 160.9, 171.2, 173.4 and 179.7 (C=O); *m/z* (FD) 482 (M^+, 100%).

(*Z*)-Isomer (Found: M^+, 482.2067); λ_{max}(MeOH)/nm 227 and 313; [+Zn(OAc)$_2$] 236 and 361; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1735, 1675 and 1440; δ_H(400 MHz, $CDCl_3$) 1.28 (3 H, s, 2-Me), 1.94 (3 H, s, 7-Me), 2.43 (2 H, t, *J* 8, CH$_2$C*H*$_2$CO), 2.58 and 2.82 (each 1 H, d, *J* 17, CH$_2$CO), 2.65 and 3.06 (each 1 H, d, *J* 16, 3-H$_2$), 2.97 (2 H, t, *J* 8, C*H*$_2$CH$_2$CO), 3.59 and 3.63 (each 3 H, s, OMe), 5.18 (2 H, s, C*H*$_2$Ph), 5.30 (1 H, br s, 5-H), 7.25–7.32 (5 H, m, Ph), 9.03 and 9.32 (each 1 H, br s, NH); δ_C(67.7 MHz, $CDCl_3$) 9.2 (7-Me), 20.8 (*C*H$_2$CH$_2$CO), 24.3 (2-Me), 34.7 (CH$_2$*C*H$_2$CO), 39.3, 40.8 and 41.9 (*C*H$_2$*CC*H$_2$), 51.5 and 51.8 (OMe), 66.0 (*C*H$_2$Ph), 91.5 (C-5), 118.3, 128.1, 128.2, 128.4, 129.1, 130.9, 136.1 (pyrrole-C and Ph), 138.1 (C-4) and 160.8, 171.3, 173.7 and 180.1 (C=O); *m/z* (FD) 482 (M^+, 100%).

4-(2-Methoxycarbonylethyl)-2-[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]formyl-3,5-dimethylpyrrole 40

A mixture of acid **8** (1.08 g, 4.98 mmol), 2,2-dipyridyl disulfide (1.65 g, 7.47 mmol) and triphenylphosphine (1.96 g, 7.47 mmol) in dry toluene (32 cm^3) was stirred under argon at room temperature for 22 h to give a solution containing thioester **39**. A solution of methylmagnesium chloride in diethyl ether (3 mol dm^{-3}; 6.64 cm^3, 19.9 mmol) was added to a stirred solution of the α-free pyrrole **10**[5] (3.6 g, 19.9 mmol) in dry toluene (86 cm^3) and dry tetrahydrofuran (4 cm^3) at −78 °C under argon. The solution was allowed to warm for 10 min with vigorous stirring and was then cooled again to −78 °C. The above thioester solution was then added *via* double-ended needle under a positive pressure of argon over a period of 30 min. The solution was stirred at −78 °C for 1.5 h, then treated with saturated aqueous ammonium chloride (5 cm^3), warmed to room temperature and mixed with diethyl ether (150 cm^3), saturated aqueous ammonium chloride (100 cm^3) and water (100 cm^3). The organic phase was separated, washed with 10% aqueous potassium carbonate (100 cm^3) then water (100 cm^3), dried and evaporated under reduced pressure. Column chromatography, eluting with hexane–ethyl acetate, gave the *ketone* **40** (1.64 g, 87%) as a gum (Found: M^+, 379.1608. $C_{19}H_{25}NO_7$ requires *M*, 379.1631); λ_{max}(MeOH)/nm 315; ν_{max}($CHCl_3$)/cm^{-1} 3440, 3340, 2920, 1790, 1725 and 1620; δ_H(400 MHz, $CDCl_3$) 1.09 (3 H, s, CMe), 2.24 and 2.30 (each 3 H, s, Ar–*Me*), 2.36–2.69 (8 H, m, CH$_2$CH$_2$CO and CH$_2$CCH$_2$), 3.60 and 3.71 (each 3 H, s, OMe), 5.51 (1 H, s, CH–O) and 10.07 (1 H, s, NH); δ_C(100 MHz, $CDCl_3$) 11.3 and 11.7 (Ar–*Me*), 19.1 (*C*H$_2$CH$_2$CO), 20.8 (C*Me*), 34.5 (CH$_2$*C*H$_2$CO), 40.8, 41.7 and 42.2 (*C*H$_2$*CC*H$_2$), 51.5 and 52.1 (OMe), 83.6 (CH–O), 121.8, 125.5, 132.0 and 133.9 (pyrrole-C), 173.2 (2 C) and 175.0 and 181.9 (C=O); *m/z* (FD) 379 (M^+, 100%).

5-Formyl-4-(2-methoxycarbonylethyl)-2-[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]formyl-3-methylpyrrole 41

A solution of ketone **40** (777 mg, 2.05 mmol) in dry dichloromethane (23 cm^3) at −5 °C was treated with a solution of freshly distilled sulfuryl chloride (338 mm^3, 4.20 mmol) in dry dichloromethane (16 cm^3) over 1 min, then stirred at −5 °C for 30 min and evaporated under reduced pressure. The residue was stirred with acetone (20 cm^3) and water (10 cm^3) for 30 min, then the acetone was evaporated under reduced pressure and the residual aqueous solution was extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried and evaporated under reduced pressure to give the *aldehyde* **41** (650 mg, 81%) as an oil (Found: M^+, 393.1445. $C_{19}H_{23}NO_8$ requires *M*, 393.1424); λ_{max}(MeOH)/nm 247 and 316; ν_{max}($CHCl_3$)/cm^{-1} 3420, 3280, 2950, 1800, 1720 and 1655; δ_H(400 MHz, $CDCl_3$) 1.13 (3 H, s, CMe), 2.34 (3 H, s, 3-Me), 2.42 and 2.83 (each 1 H, d, *J* 17, C*H*$_2$CO), 2.51–2.59 (4 H, m, CH$_2$CO and CH$_2$C*H*$_2$CO), 3.06 (2 H, t, *J* 7, C*H*$_2$CH$_2$CO), 3.63 and 3.83 (each 3 H, s, OMe), 5.74 (1 H, s, CH–O), 9.92 (1 H, s, CHO) and 10.95 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.5 (3-Me), 18.5 (*C*H$_2$CH$_2$CO), 20.9 (C*Me*), 34.7 (CH$_2$*C*H$_2$CO), 40.6, 41.9 and 42.3 (*C*H$_2$*CC*H$_2$), 51.7 and 52.6 (OMe), 83.23 (CH–O), 129.8, 130.2, 131.4 and 131.5 (pyrrole-C) and 172.6, 172.9, 179.3, 180.4 and 186.7 (C=O); *m/z* (FD) 393 (M^+, 100%).

3-(2-Methoxycarbonylethyl)-5-[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-methylpyrrole-2-carboxylic acid 42

A solution of potassium permanganate (720 mg, 4.55 mmol) in water (54 cm^3) and acetone (37 cm^3) was added to a solution of formylpyrrole **41** (1.12 g, 2.85 mmol) in acetone (65 cm^3) at 0 °C over 6 h. The mixture was stirred for 4 h at 0 °C and then for 8 h at room temperature. The acetone was evaporated under reduced pressure and dichloromethane (75 cm^3), water (50 cm^3) and sodium metabisulfite (3 g) were added. Concentrated hydrochloric acid was added dropwise until the pH of the aqueous layer was 1 and the organic phase was separated. The aqueous phase was saturated with sodium chloride and extracted with dichloromethane (2 × 50 cm^3). The combined organic layers were evaporated under reduced pressure and saturated aqueous sodium hydrogen carbonate (100 cm^3) was added. This mixture was extracted with dichloromethane (50 cm^3) and the extract was dried and evaporated under reduced pressure to give unreacted formylpyrrole **41** (80 mg). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid, extracted with dichloromethane (4 × 50 cm^3), saturated with sodium chloride and further extracted with dichloromethane (2 × 50 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give the *carboxylic acid* **42** (908 mg, 88%) as a foam (Found: $M^+ - CO_2H$, 364.1387. $C_{19}H_{23}NO_9$ requires $M - CO_2H$, 364.1396); λ_{max}(MeOH)/nm 231 and 307; $\nu_{max}(CHCl_3)/cm^{-1}$ 3300, 3100, 1800, 1720 and 1660; δ_H(400 MHz, $CDCl_3$) 1.14 (3 H, s, CMe), 2.37 (3 H, s, 4-Me), 2.52 and 2.63 (each 1 H, d, *J* 17, CH_2CO), 2.54–2.60 (3 H, m, CH_AH_BCO and CH_2CH_2CO), 2.83 (1 H, d, *J* 17, CH_AH_BCO), 3.08 (2 H, t, *J* 7.7, CH_2CH_2CO), 3.67 and 3.80 (each 3 H, s, OMe), 5.68 (1 H, s, CH–O) and 10.85 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.6 (4-Me), 19.6 (CH_2CH_2CO), 20.9 (C*Me*), 34.3 (CH_2CH_2CO), 40.6, 42.1 and 42.2 (CH_2CCH_2), 51.6 and 52.3 (OMe), 83.8 (CH–O), 122.9, 129.0, 130.5 and 131.2 (pyrrole-C) and 164.8, 172.5, 173.4, 174.5 and 186.0 (C=O); *m/z* (FD) 409 (M^+, 100%).

***tert*-Butyl 3-(2-methoxycarbonylethyl)-5-[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-methylpyrrole-2-carboxylate 6**

Concentrated sulfuric acid (35 mm^3) was added dropwise to a mixture of acid **42** (1.43 g, 3.50 mmol), isobutene (6 cm^3) and chloroform (12 cm^3). The reaction vessel was then sealed and the mixture was stirred for 48 h. Saturated aqueous sodium hydrogen carbonate (2 cm^3) was then added and the isobutene was evaporated under a stream of argon. Saturated aqueous sodium hydrogen carbonate (30 cm^3) was then added and the mixture was extracted with dichloromethane (30 cm^3 then 2 × 50 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. Purification by column chromatography, eluting with hexane–ethyl acetate, gave the tert-*butyl ester* **6** (1.29 g, 79%) as an oil (Found: M^+, 465.1990. $C_{23}H_{31}NO_9$ requires *M*, 465.1999); λ_{max}(MeOH)/nm 235 and 308; $\nu_{max}(CHCl_3)/cm^{-1}$ 3425, 3315, 1800, 1720 and 1660; δ_H(400 MHz, $CDCl_3$) 1.13 (3 H, s, CMe), 1.59 (9 H, s, Bu^t), 2.34 (3 H, s, 4-Me), 2.45 and 2.62 (each 1 H, d, *J* 17.5, CH_2CO), 2.48–2.52 (2 H, m, CH_2CH_2CO), 2.54 and 2.78 (each 1 H, d, *J* 17, CH_2CO), 3.00–3.04 (2 H, m, CH_2CH_2CO), 3.64 and 3.77 (each 3 H, s, OMe), 5.64 (1 H, s, CH–O) and 10.50 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 10.6 (4-Me), 19.7 (CH_2CH_2CO), 20.7 (CMe), 28.2 (CMe_3), 34.5 (CH_2CH_2CO), 40.5, 41.7 and 42.2 (CH_2CCH_2), 51.4 and 52.3 (OMe), 82.3 (CMe_3), 83.3 (CH–O), 125.3, 127.6, 129.2 and 130.5 (pyrrole-C) and 159.4, 172.4, 173.1, 174.4 and 185.5 (C=O).

***tert*-Butyl 3-(2-methoxycarbonylethyl)-5-hydroxy[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]methyl-4-methylpyrrole-2-carboxylate 43**

A solution of *tert*-butyl ester **42** (1.04 g, 2.23 mmol) in dry tetrahydrofuran (32 cm^3) under argon was treated with sodium borohydride (143 mg, 3.79 mmol) portionwise over 3 h with the temperature maintained at −5 °C, then stirred for a further 30 min, treated with dilute hydrochloric acid (0.5 mol dm^{-3}; 20 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried and evaporated under reduced pressure to give the diastereoisomeric *alcohols* **43** (*ca.* 1.04 g, 100%) as an oil, which was used without further purification in the next reaction, but for characterisation the isomers were separated by PLC using hexane–diethyl ether–methanol (3:3:1).

Lower R_f diastereoisomer (Found: M^+, 467.2176. $C_{23}H_{33}NO_9$ requires *M*, 467.2155); λ_{max}(MeOH)/nm 276; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2950, 1785, 1730 and 1685; δ_H(400 MHz, $CDCl_3$) 1.38 (3 H, s, CMe), 1.51 (9 H, s, Bu^t), 2.00 (3 H, s, 4-Me), 2.22 and 2.34 (each 1 H, d, *J* 15.5, CH_2CO), 2.45–2.50 (2 H, m, CH_2CH_2CO), 2.55 and 2.73 (each 1 H, d, *J* 17, CH_2CO), 2.89–2.96 (3 H, m, OH and CH_2CH_2CO), 3.64 (6 H, s, 2 × OMe), 4.63 (1 H, d, *J* 3, CHCHOH), 4.95 (1 H, br s, CHOH) and 9.30 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 5.4 (4-Me), 20.2 (C*Me*), 20.6 (CH_2CH_2CO), 29.7 (CMe_3), 35.0 (CH_2CH_2CO), 40.8, 41.9 and 43.5 (CH_2CCH_2), 51.5 and 51.8 (OMe), 64.7 (CHOH), 81.1 (CMe_3), 87.0 (CHCHOH), 117.3, 120.4, 128.1 and 129.9 (pyrrole-C) and 160.7, 171.1, 173.7 and 175.7 (C=O).

Higher R_f diastereoisomer (Found: M^+, 467.2182); λ_{max} (MeOH)/nm 278; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 2950, 1785, 1735 and 1675; δ_H(400 MHz, $CDCl_3$) 1.22 (3 H, s, CMe), 1.47 (9 H, s, Bu^t), 1.93 (3 H, s, 4-Me), 2.38–2.45 (3 H, m, CH_2CH_2CO and CH_AH_BCO), 2.50 and 2.75 (each 1 H, d, *J* 15.5, CH_2CO), 2.68 (1 H, d, *J* 17, CH_AH_BCO), 2.85–2.89 (2 H, m, CH_2CH_2CO), 3.60 and 3.62 (each 3 H, s, OMe), 3.89 (1 H, d, *J* 3, OH), 4.35 (1 H, d, *J* 8, CHCHOH), 4.88 (1 H, dd, *J* 8 and 3, CHOH) and 9.26 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.7 (4-Me), 19.1 (C*Me*), 20.5 (CH_2CH_2CO), 28.2 (CMe_3), 34.9 (CH_2CH_2CO), 40.8 (1 C) and 42.7 (2 C, CH_2CCH_2), 51.4 and 51.6 (OMe), 65.3 (CHOH), 81.1 (CMe_3), 86.0 (CHCHOH), 117.5, 119.4, 128.6 and 131.3 (pyrrole-C) and 161.2, 171.4, 173.7 and 175.1 (C=O).

***tert*-Butyl 3-(2-methoxycarbonylethyl)-5-acetoxy[(2*S*,3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-yl]-methyl-4-methylpyrrole-2-carboxylate 44**

A solution of alcohols **43** (1.04 g, 2.23 mmol) in dry dichloromethane (40 cm^3) was treated with 4-dimethylaminopyridine (544 mg, 4.45 mmol) and then acetic anhydride (840 mm^3, 8.91 mmol), stirred for 15 min and then mixed with water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 cm^3). The combined organic layers were washed with brine (20 cm^3), dried and evaporated. Purification by column chromatography, eluting with hexane–diethyl ether (1:3), gave the diastereoisomeric *acetoxy lactones* **44** as an oil (1.07 g, 94%), used as a mixture in the next reaction but separated for characterisation by PLC using hexane–diethyl ether (2.5:1).

Lower R_f diastereoisomer (Found: M^+, 509.2278. $C_{25}H_{35}NO_{10}$ requires *M*, 509.2261); λ_{max}(MeOH)/nm 274; $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 2980, 1790, 1735 and 1680; δ_H(400 MHz, $CDCl_3$) 1.06 (3 H, s, CMe), 1.53 (9 H, s, Bu^t), 2.03 and 2.06 (each 3 H, s, 4-Me and Ac), 2.26 and 2.72 (each 1 H, d, *J* 17.5, CH_2CO), 2.45–2.52 (3 H, m, CH_2CH_2CO and CH_AH_BCO), 2.60 (1 H, d, *J* 15.5, CH_AH_BCO), 2.89–2.97 (2 H, m, CH_2CH_2CO), 3.62 and 3.69 (each 3 H, s, OMe), 4.66 (1 H, d, *J* 6, CHCHOAc), 5.93 (1 H, d, *J* 6, CHOAc) and 8.97 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.8 (4-Me), 19.5 and 20.9 (CMe and *Me*CO), 20.5 (CH_2CH_2CO), 28.3 (CMe_3), 34.9 (CH_2CH_2CO), 40.7, 42.0 and 42.8 (CH_2CCH_2), 51.4 and 51.9 (OMe), 65.6 (CHOAc), 81.2 (CMe_3), 85.1 (CHCHOAc), 119.8, 121.1, 125.7 and 127.9 (pyrrole-C) and 160.4, 169.0, 170.6, 173.5 and 173.9 (C=O).

Higher R_f diastereoisomer (Found: M^+, 509.2300); λ_{max}

(MeOH)/nm 270; ν_{max}($CHCl_3$)/cm^{-1} 3420, 2930, 1790, 1730 and 1685; δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, s, 4-Me), 1.55 (9 H, s, Bu^t), 2.00 and 2.24 (each 1 H, d, *J* 16, CH_2CO), 2.04 and 2.08 (each 3 H, s, 4-Me and Ac), 2.44 and 2.74 (each 1 H, d, *J* 17, CH_2CO), 2.46–2.50 (2 H, m, CH_2CH_2CO), 2.92–2.98 (2 H, m, CH_2CH_2CO), 3.65 and 3.66 (each 3 H, s, OMe), 4.86 (1 H, d, *J* 5.5, CHCHOAc), 5.97 (1 H, d, *J* 5.5, CHOAc) and 9.09 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.8 (4-Me), 20.5 and 21.0 (C*Me* and *Me*CO), 20.6 (CH_2CH_2CO), 28.3 (CMe_3), 35.0 (CH_2CH_2CO), 40.6, 41.9 and 42.0 (CH_2CCH_2), 51.5 and 52.0 (OMe), 65.5 (CHOAc), 81.3 (CMe_3), 84.5 (CHCHOAc), 119.6, 121.3, 125.6 and 127.6 (pyrrole-C) and 160.5, 169.2, 170.9, 173.5 and 174.1 (C=O).

tert-Butyl (*Z*)-3-(2-methoxycarbonylethyl)-5-[(3*S*)-3-methoxycarbonylmethyl-3-methyl-5-oxotetrahydrofuran-2-ylidene]-methyl-4-methylpyrrole-2-carboxylate 45

The acetoxy lactones **44** (251 mg, 0.493 mmol) were heated at 200 °C for 5 min under a stream of argon. The resulting oil was purified by PLC, eluting with diethyl ether–hexane (3:1), to give the (Z)-*enol lactone* **45** (202 mg, 91%) as an oil (Found: M^+, 449.2066. $C_{23}H_{31}NO_8$ requires *M*, 449.2049); λ_{max}(MeOH)/nm 213, 242 and 312; ν_{max}($CHCl_3$)/cm^{-1} 3450, 2930, 1815, 1730 and 1680; δ_H(400 MHz, $CDCl_3$) 1.42 (3 H, s, CMe), 1.53 (9 H, s, Bu^t), 1.98 (3 H, s, 4-Me), 2.47–2.51 (2 H, m, CH_2CH_2CO), 2.55 and 2.99 (each 1 H, d, *J* 18, CH_2CO), 2.67 (2 H, s, CH_2CO), 2.94–2.98 (2 H, m, CH_2CH_2CO), 3.63 and 3.64 (each 3 H, s, OMe), 5.45 (1 H, s, CH=C) and 9.39 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.6 (4-Me), 20.5 (CH_2CH_2CO), 27.5 (C*Me*), 28.3 (CMe_3), 34.8 (CH_2CH_2CO), 39.8, 40.6 and 44.1 (CH_2CCH_2), 51.3 and 51.8 (OMe), 80.6 (CMe_3), 91.8 (CH=C), 118.5, 120.2, 126.0 and 128.2 (pyrrole-C), 154.3 (CH=*C*) and 160.2, 170.5, 171.3 and 173.6 (C=O).

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

Concentrated aqueous ammonia (16 drops) was added over 1 h to a stirred solution of enol lactone **45** (200 mg, 0.445 mmol) in tetrahydrofuran (20 cm^3) at 0 °C. The solution was stirred for a further 1 h at 0 °C and then brine (50 cm^3) and dichloromethane (60 cm^3) were added. The organic phase was separated and the remaining aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with dichloromethane (2 × 20 cm^3). The combined organic layers were dried and evaporated under reduced pressure. A solution of the resulting oil in dichloromethane (15 cm^3) was stirred with toluene-*p*-sulfonic acid (10 mg) at room temperature for 1 h and then washed with water (10 cm^3), dried and evaporated under reduced pressure. PLC, eluting with 5% methanol in dichloromethane, gave the (Z)-*lactam* **4** as an oil (67 mg, 34%), identical to the compound prepared previously,[2] and the *lactone lactam* **47** (96 mg, 50%) as an oil (Found: M^+, 434.2065. $C_{22}H_{30}N_2O_7$ requires *M*, 434.2053); λ_{max}(MeOH)/nm 277; ν_{max}($CHCl_3$)/cm^{-1} 3400, 3240, 1785 and 1725; δ_H(400 MHz, $CDCl_3$) 1.41 (3 H, s, lactone-Me), 1.46 (9 H, s, Bu^t), 1.96 (3 H, s, pyrrole-Me), 2.42–2.49 (3 H, m, CH_2CH_2CO and CH_AH_B), 2.55 (1 H, d, *J* 17, CH_AH_B), 2.59 and 2.76 (each 1 H, d, *J* 18, CH_2), 2.85–2.95 (2 H, m, CH_2CH_2CO), 3.01 and 3.09 (each 1 H, d, *J* 15, CH_2), 3.65 (3 H, s, OMe), 7.31 (lactam-NH) and 9.78 (pyrrole-NH); δ_C(100 MHz, $CDCl_3$) 8.7 (pyrrole-Me), 20.6 (lactam-Me), 21.1 (CH_2CH_2CO), 28.2 (CMe_3), 30.6 (pyrrole-CH_2), 35.1 (CH_2CH_2CO), 42.9, 43.3 and 44.7 (CH_2CCH_2), 51.3 (OMe), 80.9 (CMe_3), 101.0 (O–C–N), 118.6, 119.7, 125.2 and 128.1 (pyrrole-C) and 161.2, 173.5, 173.5 and 174.4 (C=O).

Conversion of lactam lactone 47 into lactam 4

An ethereal solution of diazomethane (6 cm^3) was added over 2 h to a solution of the lactam lactone **47** (96 mg, 0.221 mmol) and a catalytic amount of sodium methoxide (*ca.* 0.3 mg) in methanol (6 cm^3). The solution was evaporated to give the crude imino ether **48** containing lactam **4**. Pure **48** was isolated chromatographically (Found: M^+, 462.2370. $C_{24}H_{34}N_2O_7$ requires *M*, 462.2366); λ_{max}(MeOH)/nm 229 and 346; ν_{max}($CHCl_3$)/cm^{-1} 3360, 1730, 1675 and 1600; δ_H(400 MHz, $CDCl_3$) 1.32 (3 H, s, CMe), 1.52 (9 H, s, Bu^t), 2.02 (3 H, s, pyrrole-Me), 2.48–2.61 (5 H, m, CH_2CH_2CO, CH_2C=N and CH_AH_BCO), 2.99–3.03 (2 H, m, CH_2CH_2CO), 3.05 (1 H, d, *J* 18, CH_AH_B-CO), 3.64, 3.65 and 4.05 (each 3 H, s, OMe), 5.29 (1 H, s, C=C*H*) and 10.78 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.6 (pyrrole-Me), 20.6 (CH_2CH_2CO), 27.6 (C*Me*), 28.5 (CMe_3), 34.9 (CH_2CH_2CO), 43.1, 43.8 and 44.4 (CH_2CCH_2), 51.4, 51.6 and 56.6 (OMe), 79.8 (CMe_3), 98.6 (C=CH), 117.1, 118.7, 128.9 and 130.4 (pyrrole-C), 157.6 (*C*=CH), 160.5, 171.5 and 173.9 (C=O) and 177.3 (N=C).

A solution of the crude imino ether in acetone (6 cm^3) and water (2 cm^3) was stirred with toluene-*p*-sulfonic acid (10 mg) for 10 h at room temperature. Saturated aqueous sodium hydrogen carbonate (10 cm^3) and dichloromethane (20 cm^3) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 10 cm^3) and the combined organic extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with hexane–ethyl acetate (3:1), gave *lactam* **4** (74 mg, 75%).

9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-3,3,7-trimethyl-2,3-dihydrodipyrrin–1(10*H*)-thione 55

A solution of the lactam **54**[5] (100 mg, 0.256 mmol) in dry dimethoxyethane (5 cm^3) was treated with Lawesson's reagent (288 mg, 0.713 mmol) and dry diisopropylethylamine (90 mm^3, 0.518 mmol), heated under reflux for 45 min, then cooled and evaporated under reduced pressure. The residue was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:2), to give the *thiolactam* **55** (91 mg, 87%) as an oil (Found: M^+, 406.1901. $C_{21}H_{30}N_2O_4S$ requires *M*, 406.1926); λ_{max}(MeOH)/nm 221, 271 and 343; [+$Zn(OAc)_2$] 258 and 394; ν_{max}(CH_2Cl_2)/cm^{-1} 3439, 3380, 1733 and 1680; δ_H(400 MHz, $CDCl_3$) 1.32 (6 H, s, CMe_2), 1.50 (9 H, s, Bu^t), 1.93 (3 H, s, 7-Me), 2.50 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.87 (2 H, s, CH_2CS), 2.94 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.67 (3 H, s, OMe), 5.32 (1 H, s, CH=C) and 9.00 and 9.53 (each 1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 9.3 (7-Me), 20.8 (CH_2CH_2CO), 28.3 (CMe_2 and CMe_3), 34.9 (CH_2CH_2CO), 41.5 (CMe_2), 51.5 (OMe), 57.1 (CH_2CS), 81.1 (CMe_3), 91.4 (CH=C), 118.5, 120.5, 127.4 and 129.2 (pyrrole-C), 152.8 (CH=*C*), 160.9 and 173.6 (C=O) and 203.9 (C=S); *m/z* (FD) 406 (M^+, 100%).

13,17-Bis(2-methoxycarbonylethyl)-18-methoxycarbonylmethyl-2,2,8,8,12-pentamethylisobacteriochlorin 59

A solution of thiolactam **55** (12 mg, 30 μmol) in dry trifluoroacetic acid (1 cm^3) was stirred at room temperature for 90 min, then treated with trimethyl orthoformate (160 mm^3), stirred for a further 20 min and evaporated under a stream of argon. PLC, eluting with diethyl ether–hexane (1:1), gave the formyl thioimino ether **52** (7.7 mg, 75%) as an oil; λ_{max}(MeOH)/nm 265 and 392; δ_H(400 MHz, CD_2Cl_2) 1.26 (6 H, s, CMe_2), 2.06 (3 H, s, ArMe), 2.55 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.69 (3 H, s, SMe), 2.72 (2 H, s, CH_2CSMe), 3.01 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.63 (3 H, s, OMe), 5.65 (1 H, s, CH=C), 9.54 (1 H, s, CHO) and 10.82 (1 H, br s, NH).

The imine **49**[12] (31 mg, 69 μmol) was stirred in dry trifluoroacetic acid (1 cm^3) for 1 h at room temperature. The solvent was then evaporated under a stream of argon. A solution of the residue in dichloromethane (10 cm^3) was washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with diethyl ether–light petroleum (bp 60–80 °C) (3:1), to give the imine **50** (7 mg, 30%) as an oil. (The purification of this product was carried out as quickly as

possible and the product stored at −20 °C for no more than 8 h before being used in the next reaction.)

A solution of the imine **50** (7 mg, 20 μmol) in dry methanol (0.7 cm^3) was added to the formyl thioimino ether **52** (7.7 mg, 22 μmol) and then dry trifluoroacetic acid (36 mm^3) was added. The solution was stirred at room temperature in the dark for 1 h, during which time a green–blue colour developed. Dry tetrahydrofuran (5 cm^3) was added followed by dry diisopropylethylamine (150 mm^3), which resulted in a change of colour to deep blue. The solution was then mixed with a solution of diisopropylethylammonium trifluoroacetate (200 mg) in dry toluene (1 cm^3), transferred to a glass tube and the total volume made up to 40 cm^3 with dry tetrahydrofuran. The solution was then subjected to four cycles of freeze-pump-thaw degassing and the tube was sealed under high vacuum and irradiated for 120 h, during which time the solution turned a deep purple–red colour and developed a bright orange fluorescence. The tube was opened and the solution was diluted with dichloromethane (25 cm^3), washed with hydrochloric acid (0.2 mol dm^{-3}; 25 cm^3) and then saturated aqueous sodium hydrogen carbonate (10 cm^3), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by PLC, eluting with methyl acetate–dichloromethane (1:9), to give the *isobacteriochlorin* **59** (6 mg, 47%) as a purple solid (Found: M^+, 628.3267. $C_{36}H_{44}N_4O_6$ requires *M*, 628.3261); λ_{max}(MeOH)/nm 272, 368, 544 and 587; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3433, 3368, 1733, 1692 and 1644; δ_H(400 MHz, $CDCl_3$) 1.47 and 1.50 (each 6 H, s, 2 × CMe_2), 2.69 (3 H, s, 12-Me), 2.84 and 3.04 (each 2 H, t, *J* 7.5, CH_2CH_2CO), 3.24, 3.28 and 3.35 (each 3 H, s, OMe), 3.28 and 3.30 (each 2 H, s, 3- and 7-H_2), 3.73 and 3.86 (each 2 H, t, *J* 7.5, $CH_2CH_2CO_2$), 4.19 (2 H, s, 18-CH_2CO), 6.50 (1 H, s, 5-H), 7.33 and 7.56 (each 1 H, s, 10- and 20-H) and 8.86 (1 H, s, 15-H).

(2*R*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-2,3-dihydrodipyrrin-1(10*H*)-thione 56

A solution of the lactam **5** (137 mg, 0.306 mmol) in dry toluene (13 cm^3) was treated with Lawesson's reagent (379 mg, 0.94 mmol) and dry diisopropylethylamine (0.16 cm^3, 0.92 mmol) and heated under reflux for 45 min, then cooled, diluted with dichloromethane (50 cm^3), washed with hydrochloric acid (1 mol dm^{-3}; 25 cm^3) and then brine (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with ethyl acetate–light petroleum (1:3), to give a mixture of the (E)- and (Z)-*thiolactams* **56** (60 mg, 46%; ratio 3:1) as an oil. For characterisation, the isomers were separated by PLC eluting with diethyl ether–hexane (3:2).

(*E*)-Isomer (lower R_f): λ_{max}(MeOH)/nm 252 and 361; δ_H(400 MHz, $CDCl_3$) 1.35 (3 H, s, 2-Me), 1.56 (9 H, s, Bu^t), 1.98 (3 H, s, 7-Me), 2.50 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.67 (1 H, d, *J* 17, CH_AH_BCO), 2.89–3.02 (4 H, m, $CH_2CH_2CO_2$, CH_AH_BCO and 3-H_A), 3.35 (1 H, dd, *J* 16 and 2, 3-H_B), 3.65 and 3.66 (each 3 H, s, OMe), 5.91 (1 H, br s, CH=C) and 8.50 and 9.19 (each 1 H, br s, NH); *m/z* (FD) 464 (M^+, 100%).

(*Z*)-Isomer (higher R_f): λ_{max}(MeOH)/nm 269 and 350; [+$Zn(OAc)_2$] 256 and 383; δ_H(400 MHz, $CDCl_3$) 1.35 (3 H, s, 2-Me), 1.56 (9 H, s, Bu^t), 1.96 (3 H, s, 7-Me), 2.52 (2 H, t, *J* 8, CH_2CH_2CO), 2.72 and 2.85 (each 1 H, d, *J* 17, CH_2CO), 2.81 (1 H, d, *J* 17) and 3.23 (1 H, dd, *J* 17 and 2, 3-H_2), 2.98 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.66 and 3.67 (each 3 H, s, OMe), 5.44 (1 H, br s, CH=C) and 8.63 and 9.11 (each 1 H, br s, NH).

(2*R*)-8-(2-Methoxycarbonylethyl)-2-methoxycarbonylmethyl-2,7-dimethyl-1-methylthio–2,3-dihydrodipyrrin-9-carbaldehyde 53

A solution of thiolactam **56** (60 mg, 0.129 mmol) in dry trifluoroacetic acid (3 cm^3) was stirred in the dark for 45 min, then treated with trimethyl orthoformate (160 mm^3), stirred for 30 min, mixed with water (5 cm^3) and extracted with dichloromethane (25 cm^3 then 10 cm^3). The combined organic extracts were washed with 10% aqueous ammonia (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with diethyl ether, to give the (Z)-*formyl thioimino ether* **53** (7.9 mg, 15%) and the (E)-*formyl thioimino ether* (40.2 mg, 77%), as oils.

(*Z*)-Isomer (higher R_f): λ_{max}(MeOH)/nm 222, 266 and 389; δ_H(400 MHz, C_6D_6) 1.02 (3 H, s, 2-Me), 1.86 (3 H, s, 7-Me), 2.15–2.39 (5 H, m, CH_2CH_2CO, CH_2CO and 3-H_A), 2.87 (2 H, t, *J* 8, CH_2CH_2CO), 2.93 (1 H, dd, *J* 17 and 1, 3-H_B), 3.22 (6 H, s) and 3.28 (3 H, s, 2 × OMe and SMe), 5.63 (1 H, br s, CH=C), 9.76 (1 H, s, CHO) and 10.73 (1 H, br s, NH).

(*E*)-Isomer (lower R_f): λ_{max}(MeOH)/nm 222, 265 and 380; δ_H(400 MHz, C_6D_6) 0.94 (3 H, s, 2-Me), 1.75 (3 H, s, 7-Me), 2.18–2.30 (4 H, m, CH_2CH_2CO and 2 × CH_AH_B), 2.25 (3 H, s, SMe), 2.46 (1 H, d, *J* 18, CH_AH_B), 2.78 (2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.09 (1 H, d, *J* 17, CH_AH_B), 3.22 and 3.28 (each 3 H, s, OMe), 6.78 (1 H, br s, CH=C), 9.07 (1 H, br s, NH) and 9.72 (1 H, s, CHO); *m/z* (FD) 406 (M^+, 100%).

tert-Butyl 1-[bis(*tert*-butoxycarbonyl)methylene]-8-(2-methoxycarbonylethyl)-3,3,7-trimethyl-1,2,3,10-tetrahydrodipyrrin-9-carboxylate

A solution of thiolactam **55** (73 mg, 0.18 mmol) in dry dichloromethane (10 cm^3) was treated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.13 cm^3, 0.876 mmol) followed by a solution of di-*tert*-butyl bromomalonate (88 mg, 0.298 mmol) in dry dichloromethane (2 cm^3), stirred for 2 h at room temperature and evaporated under reduced pressure and dried under high vacuum. Dry toluene (15 cm^3) and triphenylphosphine (200 mg) were added and the mixture was heated at 110 °C for 90 min, then cooled, diluted with diethyl ether (50 cm^3), washed with hydrochloric acid (1 mol dm^{-3}; 50 cm^3) then brine (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with diethyl ether–hexane (1:1), to give the *enamine* (54 mg, 51%) as a foam (Found: M^+, 588.3457. $C_{32}H_{48}N_2O_8$ requires *M*, 588.3411); λ_{max}(MeOH)/nm 273 and 338; [+$Zn(OAc)_2$] 239, 326 and 407; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3626, 3448, 1733, 1686 and 1651; δ_H(400 MHz, $CDCl_3$) 1.26 (6 H, s, CMe_2), 1.47, 1.49 and 1.54 (each 9 H, s, Bu^t), 1.93 (3 H, s, 7-Me), 2.54 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.93 (2 H, s, 2-H_2), 3.01 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.66 (3 H, s, OMe), 5.22 (1 H, s, CH=C) and 8.53 and 10.47 (each 1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 9.4 (7-Me), 20.7 ($CH_2CH_2CO_2$), 28.3, 28.4, 28.5 and 28.8 (3 × CMe_3 and CMe_2), 34.7 ($CH_2CH_2CO_2$), 39.3 and 46.4 (C-2 and -3), 51.4 (OMe), 80.0, 80.3 and 80.5 (3 × CMe_3), 89.1 and 95.2 (C-5 and N−C=*C*), 117.9, 119.6, 128.3 and 129.6 (pyrrole-C), 151.8 and 160.3 (C-1 and -4) and 163.9, 166.9, 167.9 and 173.8 (C=O); *m/z* (FD) 588 (M^+, 100%).

(7*R*)-13,17-Bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-2,2,7,12,18-pentamethylisobacteriochlorin 60

The above enamine (54 mg, 92 μmol) was stirred in dry trifluoroacetic acid (2 cm^3) for 40 min in the dark. The solvent was then evaporated under a stream of argon and the residue was dissolved in dry toluene (5 cm^3) and re-evaporated under reduced pressure. A solution of the residual oil in dry toluene (5 cm^3) was treated with anhydrous sodium acetate (150 mg) followed by glacial acetic acid (5 drops), heated at 80 °C for 2 h and then filtered through glass wool. The filtrate was evaporated under reduced pressure and the residual oil was purified by PLC, eluting with diethyl ether, to give the imine **51** (20.2 mg, 76%) as an oil (this purification was performed as rapidly as possible to avoid decomposition and the product was stored at −20 °C for no more than 8 h before being used in the next reaction); λ_{max}(MeOH)/nm 248 and 337; δ_H(400 MHz, CD_2Cl_2) 1.19 (6 H, s, CMe_2), 2.03 (3 H, s, ArMe), 2.17 (3 H, s, MeC=N), 2.50–2.55 (4 H, m, CH_2CH_2CO and CH_2C=N), 2.71 (2 H, t, *J* 8, CH_2CH_2CO), 3.64 (3 H, s,

OMe), 5.67 (1 H, s, CH=C), 6.51 (1 H, d, *J* 2, ArH) and 10.48 (1 H, br s, NH).

A solution of the imine **51** (20.2 mg, 69 μmol) in dry methanol (2 cm^3) was stirred with formyl thioimino ether **53** (32.9 mg, 81 μmol) at room temperature in the dark and dry trifluoroacetic acid (126 mm^3) was added, which caused a blue colour to develop. The solution was stirred for 3 h, then dry tetrahydrofuran (10 cm^3) was added followed by diisopropylethylamine (0.6 cm^3), which resulted in a change of colour to deep red. The solution was then mixed with a solution of diisopropylethylammonium trifluoroacetate (700 mg) in dry toluene (3 cm^3), transferred to a glass tube, made up to a total volume of 40 cm^3 with dry tetrahydrofuran and subjected to four cycles of freeze-pump-thaw degassing. The tube was sealed under high vacuum and then irradiated for 132 h, during which time the solution turned to a deep purple–red colour and gave a bright orange fluorescence. The tube was opened and the solution was diluted with dichloromethane (25 cm^3), washed with hydrochloric acid (0.2 mol dm^{-3}; 25 cm^3) then saturated aqueous sodium hydrogen carbonate (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual gum was purified by PLC on plates free of fluorescent indicator, eluting with methyl acetate–dichloromethane (1:9), to give the *isobacteriochlorin* **60** (23.8 mg, 55%) as a purple solid (Found: M^+, 628.3261. $C_{36}H_{44}N_4O_6$ requires *M*, 628.3261); λ_{max}(MeOH)/nm 275, 367, 396, 508, 542, 582 and 633; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3368, 3278, 1734 and 1644; δ_H(400 MHz, $CDCl_3$) 1.48 (6 H, s, CMe_2), 1.60 (3 H, s, 7-Me), 2.72 and 2.75 (each 3 H, s, 12- and 18-Me), 2.80 (1 H, d, *J* 7, CH_AH_BCO), 2.85–2.91 (5 H, m, 2 × CH_2-CH_2CO_2 and CH_AH_BCO), 3.24 (3 H, s, OMe), 3.25 (6 H, s, 2 × OMe), 3.37 (2 H, s, 3-H_2), 3.58 and 4.14 (each 1 H, d, *J* 17, 8-H_2), 3.79 (4 H, t, *J* 7, $CH_2CH_2CO_2$), 6.60 (1 H, s, 5-H), 7.44 and 7.54 (each 1 H, s, 10- and 20-H) and 8.93 (1 H, s, 15-H); δ_C(100 MHz, $CDCl_3$) 10.4 and 10.6 (12-Me and 18-Me), 21.5 and 21.6 (CH_2CH_2CO), 27.1 (7-Me), 30.0 (CMe_2), 36.7 (2 × CH_2CH_2CO), 42.5, 44.9, 45.3 and 47.6 (CH_2CO, C-2, C-7 and C-8), 50.9, 51.0 and 51.1 (OMe), 63.7 (C-3), 89.0 (C-5), 92.0 and 94.7 (C-10 and C-20), 105.6 (C-15), 126.0, 127.0, 134.7, 136.6, 137.4, 144.7, 147.2, 152.2, 159.1 and 162.1 (12 × aromatic-C) and 169.8, 171.2 and 173.2 (C=O).

(2*R*,7*R*)-13,17-Bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-2,7,12,18-tetramethylisobacteriochlorin 62

A solution of imine **61** (19 mg, 55 μmol) in dry methanol (3 cm^3) was stirred with formyl thioimino ether **53** (45 mg, 0.11 mmol) at room temperature in the dark and dry trifluoroacetic acid (126 mm^3) was added, which caused a blue–green colour to develop. The solution was stirred for 3 h, then treated with dry tetrahydrofuran (10 cm^3) followed by diisopropylethylamine (564 mm^3), which resulted in a colour change to deep red, then mixed with a solution of diisopropylethylammonium trifluoroacetate (500 mg) in dry toluene (3 cm^3), transferred to a glass tube, made up to a total volume of 40 cm^3 with dry tetrahydrofuran, and subjected to four cycles of freeze-pump-thaw degassing. The tube was then sealed and irradiated for 90 h, during which time the solution became a deep purple–red colour and gave a bright orange fluorescence. The tube was opened and the solution was diluted with dichloromethane (40 cm^3), washed with dilute hydrochloric acid (0.5 mol dm^{-3}; 30 cm^3) then saturated aqueous sodium hydrogen carbonate (40 cm^3), dried and evaporated under reduced pressure. Purification by PLC on plates free of fluorescent indicator, eluting with dichloromethane–methyl acetate (10:1), gave the isobacteriochlorin **62** as a purple gum (20 mg, 53%), with identical spectroscopic data to those reported previously;[2] δ_C(100 MHz, $CDCl_3$) 10.5 (12- and 18-Me), 21.15 and 21.2 (CH_2CH_2CO), 27.5 and 28.5 (2- and 7-Me), 36.5 (2 × CH_2CH_2CO), 45.0, 45.2 (2 C), 46.1, 47.3 and 49.5 (2 × CH_2CO and C-2, -3, -7 and -8), 51.55 (2 × OMe), 51.6 (2 × OMe), 89.9 (C-5), 92.4 and 93.1 (C-10 and -20), 103.3 (C-15), 125.3, 127.0, 132.0, 134.9, 135.5, 137.3, 142.5, 146.8, 152.6, 162.7, 163.1 and 167.3 (12 × aromatic-C), 171.6 and 171.9 (C=O) and 173.5 (2 × C=O).

(2*R*,7*R*)-13,17-Bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-2,7,12,18-tetramethyl-3,8-dioxoisobacteriochlorin 64

A mixture of the isobacteriochlorin **62** (34 mg, 50 μmol) and selenium dioxide (600 mg) was heated under reflux in dry 1,4-dioxane (30 cm^3) for 2 h. The solution was then evaporated under reduced pressure and dichloromethane (20 cm^3) was added. This solution was filtered and evaporated under reduced pressure. Purification by PLC, eluting with hexane–methyl acetate (1:1) and then methyl acetate–dichloromethane (1:10), gave the *dioxoisobacteriochlorin* **64** (15 mg, 42%) as a green solid (Found: M^+, 714.2901. $C_{38}H_{42}N_4O_{10}$ requires *M*, 714.2901); $\lambda_{max}(CHCl_3)$/nm 401, 416, 436, 540, 591 and 637; δ_H(400 MHz, $CDCl_3$) 1.84 and 1.85 (each 3 H, s, 2- and 7-Me), 3.08 and 3.13 (each 3 H, s, 12- and 18-Me), 3.10–3.16 (4 H, m, 2 × CH_2CH_2CO), 3.27, 3.32, 3.58 and 3.62 (each 3 H, s, OMe), 3.73 and 3.78 (each 1 H, d, *J* 17, CH_2CO), 3.74 and 3.88 (each 1 H, d, *J* 17.5, CH_2CO), 4.14–4.21 (4 H, m, CH_2CH_2CO) and 8.45, 8.67, 9.38 and 9.56 (each 1 H, s, C=CH); δ_C(100 MHz, $CDCl_3$) 10.9 and 11.1 (12- and 18-Me), 21.41 and 21.44 (CH_2CH_2CO), 23.4 and 23.9 (2- and 7-Me), 36.3 (2 × CH_2-CH_2CO), 41.7 and 42.0 (CH_2CO), 49.4 and 51.8 (C-2 and -7), 51.6 (2 × OMe), 51.72 and 51.75 (OMe), 91.2 and 91.4 (C=*C*H), 96.7 (2 × C=*C*H), 131.5, 131.8, 132.1, 135.4, 136.2, 138.0, 139.1, 144.7, 144.9, 145.6, 160.9 and 165.2 (12 × aromatic-C), 170.3 and 170.5 (CO_2), 173.2 (2 × CO_2) and 207.3 (2 × C=O).

When the foregoing reaction was run for only 0.5 h, the blue mono-oxo system **63** accompanied **64** (ratio 1:2) and was separated from it by PLC using hexane–methyl acetate (1:1) (Found: M^+, 700.3110. $C_{38}H_{44}N_4O_9$ requires *M*, 700.3108); λ_{max} ($CHCl_3$)/nm 377, 385, 412, 436, 548, 590 and 642; δ_H(400 MHz, $CDCl_3$) 1.58 and 1.86 (each 3 H, s, 2- and 7-Me), 2.86 and 3.00 (each 3 H, s, 12- and 18-Me), 2.93 (4 H, t, *J* 7.5, 2 × CH_2-CH_2CO), 3.12 (1 H, d, *J* 15, CH_AH_BCO), 3.17–3.21 (4 H, m, CH_AH_BCO and OMe), 3.61 (3 H, s, OMe), 3.64 (6 H, s, 2 × OMe), 3.39 and 3.50 (each 1 H, d, *J* 17, CH_2CO), 3.75 and 3.81 (each 2 H, t, *J* 7.5, CH_2CH_2CO), 3.89 and 4.44 (each 1 H, d, *J* 17.5, 3- or 8-H_2) and 7.06, 7.44, 8.63 and 8.69 (each 1 H, s, C=CH); *m/z* (FD) 700 (M^+, 100%).

Further oxidation of the mono-oxo system **63**, as above, converted it into **64**, the identification being by spectroscopic and chromatographic comparison.

(2*R*,7*R*)-17-(2-methoxycarbonylethenyl)-13-(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-2,7,12,18-tetramethyl-3,8-dioxoisobacteriochlorin 2

An aliquot (5.6 cm^3) of a solution of osmium tetroxide (100 mg) in dry dichloromethane (71.5 cm^3) and dry pyridine (1.43 cm^3) was stirred with dioxoisobacteriochlorin **64** (11 mg, 15.4 μmol) in the dark, under argon, at room temperature for 20 h. Methanol (5 cm^3) was then added and hydrogen sulfide bubbled into the solution. The black precipitate was removed by filtration through Celite and the filtrate was evaporated under reduced pressure. PLC gave recovered dioxoisobacteriochlorin **64** (8 mg) and a mixture of diols **65** and **66** (1.5 mg). A solution of the diols in benzene (5 cm^3) was treated with concentrated hydrochloric acid (4 drops), heated under reflux for 3.5 h and then evaporated under reduced pressure. Purification by PLC, eluting with benzene–methyl acetate (10:1), gave metal-free haem d_1 methyl ester **2** as a green solid (0.4 mg, 13% based on unrecovered **64**) and its isomer with the acrylate side-chain on ring C (0.13 mg, 4% based on unrecovered **64**).

Metal-free haem d_1 methyl ester **2** (Found: M^+, 712.2746. $C_{38}H_{40}N_4O_{10}$ requires *M*, 712.2744); $\lambda_{max}(CHCl_3)$/nm 422, 445, 610 and 660; δ_H(400 MHz, $CDCl_3$) 1.78 and 1.80 (each 3 H, s, 2- and 7-Me), 3.05 (2 H, t, *J* 7.5, CH_2CH_2CO), 3.14, 3.18, 3.25, 3.32, 3.62 and 4.00 (each 3 H, s, 12- and 18-Me and 4 × OMe),

3.70 and 3.80 (each 1 H, d, *J* 18, CH_2CO), 3.76 (2 H, s, CH_2CO), 4.06–4.10 (2 H, m, CH_2CH_2CO), 6.91 and 8.98 (each 1 H, d, *J* 16, CH=CH) and 8.27, 8.43, 9.22 and 9.45 (each 1 H, s, C=CH). This product was identical with a sample of **2** derived from natural haem d_1 by full spectroscopic and CD comparison.

(2*R*,7*R*)-13-(2-Methoxycarbonylethenyl)-17-(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-2,7,12,18-tetramethyl-3,8-dioxoisobacteriochlorin. (Found: M^+, 712.2785); $\lambda_{max}(CHCl_3)$/nm 419, 443, 537, 572, 603 and 650; δ_H(400 MHz, $CDCl_3$) 1.78 and 1.79 (each 3 H, s, 2- and 7-Me), 3.06 (2 H, t, *J* 7.5, CH_2CH_2CO), 3.14, 3.16, 3.18 and 3.40 (each 3 H, s, 12- and 18-Me and 2 × OMe), 3.62–3.84 (7 H, m, OMe and 2 × CH_2CO), 4.00 (3 H, s, OMe), 4.04 (2 H, t, *J* 7.5, CH_2CH_2CO), 6.94 and 9.04 (each 1 H, d, *J* 16, CH=CH) and 8.22, 8.39, 9.27 and 9.41 (each 1 H, s, C=CH).

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