Haem d_1: development of a new coupling procedure leading to the synthesis of isobacteriochlorins[1]

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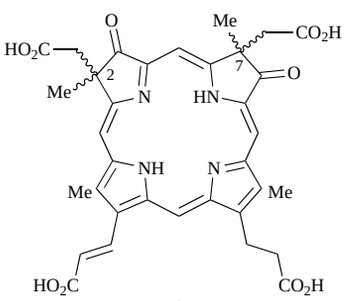
A new approach has been developed for construction of the western and eastern lactams, *e.g.* 2 and 3, needed for synthesis of isobacteriochlorins. It involves acylation of pyrroles with lactonic acids to form ketones. These are then efficiently converted into the desired lactams by a short sequence of reactions. All the steps are high yielding and simple to carry out.

Introduction

There has been considerable interest within our Cambridge group in the synthesis of isobacteriochlorins[2] because of their importance in relation to the biosynthesis of vitamin B_{12}. Also, as outlined in the preceding paper,[3] the metal-free form of haem d_1 was found[4] to be a dioxoisobacteriochlorin of gross structure **1**, although without stereochemical definition at C-2 and C-7.



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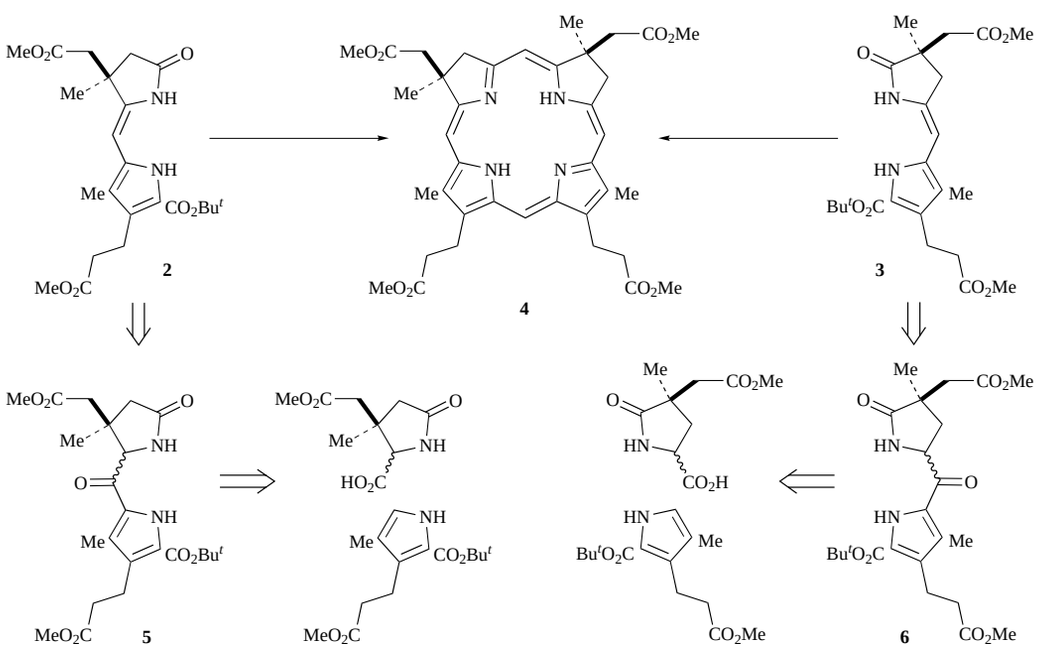
The preceding paper further described a synthesis of the macrocycle **4** (Scheme 1), the ester of one of the four possible isomers of **1** having methylenes in place of the keto groups and the acrylate side-chain reduced. The synthesis depended on the photochemical cyclisation of an open-chain precursor that in turn was constructed from the western and eastern lactams **2** and **3** respectively. These two lactams were synthesised using what we have called 'the original coupling strategy', fully described in the preceding paper.[3] Although this approach has also led to successful syntheses of several macrocycles of interest for parallel research on vitamin B_{12} biosynthesis,[5] the coupling step and the subsequent ones necessary to tailor the initial products to yield lactams such as **2** and **3** were experimentally very demanding. It was evident that the photochemical synthesis of isobacteriochlorins would be substantially improved if appropriate pyrrole and lactam units could be joined by a simpler approach which yielded the same type of pyrrolic lactam. We also wished such a new approach to be suitable for larger scale preparations and the present paper describes the development of methods which match both these requirements.

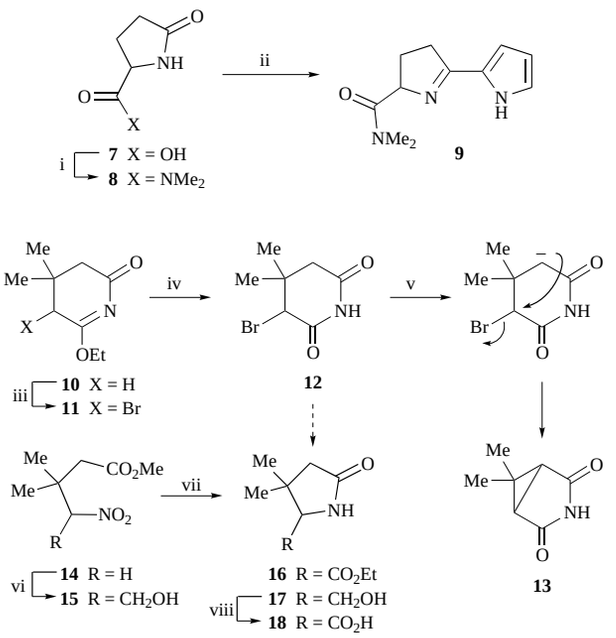
Results and discussion

The retrosynthetic analysis is shown in Scheme 1. We envisaged deriving the lactams **2** and **3** from the ketones **5** and **6**, each planned to be built by some acylation step from an α-free pyrrole and a lactam (or a precursor of a lactam) carrying an



Scheme 1

activated carboxy group. The lactam used for the first trials was DL-pyroglutamic acid **7**, which was soon found to have very awkward solubility properties. It was expected that the dimethyl analogue **18** would be more soluble and just one synthesis of its ester **16** has been reported[6] from 3,3-dimethylglutaric acid *via* the intermediates **10**, **11** and **12** (Scheme 2). Favorskii-type



Scheme 2 *Reagents:* i, $SOCl_2$ then Me_2NH; ii, $POCl_3$, pyrrole; iii, iv, see ref. 6; v, Bu^tOK; vi, $(CH_2O)_n$, KF; vii, Zn, AcOH then $TiCl_3$; viii, CrO_3, H_2SO_4

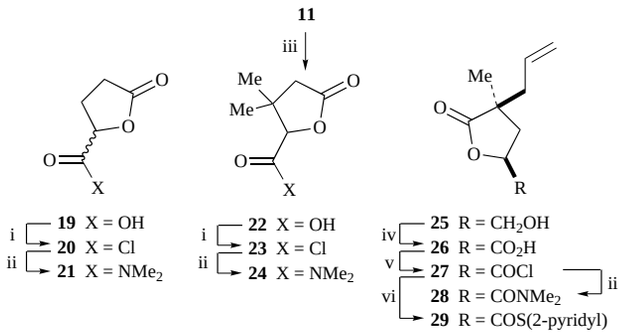
rearrangement of **12** using sodium ethoxide reportedly[6] gave the ester **16**. In our hands, these conditions yielded the cyclopropane **13** as the only isolable product (16%), clearly formed by the illustrated alternative cyclisation. When *tert*-butoxide was used as base, the yield of **13** rose to 82%. No products based on the ring-contracted system **16** were isolated from any of these experiments (but see below) so a different approach was used.

Michael addition of nitromethane to methyl 3,3-dimethylacrylate[7] readily provided the starting material **14** and fluoride ion catalysed its reaction with formaldehyde to give the alcohol **15**. Reduction of the nitro group allowed spontaneous ring-closure to **17** and final oxidation of the alcohol to the corresponding carboxylic acid **18** completed the synthesis (34% overall) which could be run on a multigram scale. As hoped, this lactam **18** was reasonably soluble in organic solvents.

Studies were then made of the Friedel–Crafts acylation of pyrroles carrying a carboxylate ester at C-2 and having a free site at C-5 (*cf*. Scheme 1) using the acid chlorides derived from lactams **7** and **18**. Either there was no ketonic product or the yield was unacceptably low. The possibility that Vilsmeier coupling might be a practical alternative fell away when treatment of a mixture of the dimethylamide **8** and pyrrole with phosphorus oxychloride yielded the imine **9** as the major product.

A strategic change was clearly needed bearing in mind these lessons from the foregoing studies: (i) any lactams related to **7** and **18** will be unsatisfactory primary building blocks and (ii) the reactivity of the pyrrolic partner must be increased. The response to (i) was to change to lactones, and (ii) was satisfied by using pyrroles carrying a C-2 methyl group in place of the deactivating ester group (*e.g.* **33**). These changes meant that the initial product of the coupling step would need modification to give a ketone of the type **5** or **6** but *a priori* the chemistry appeared feasible.

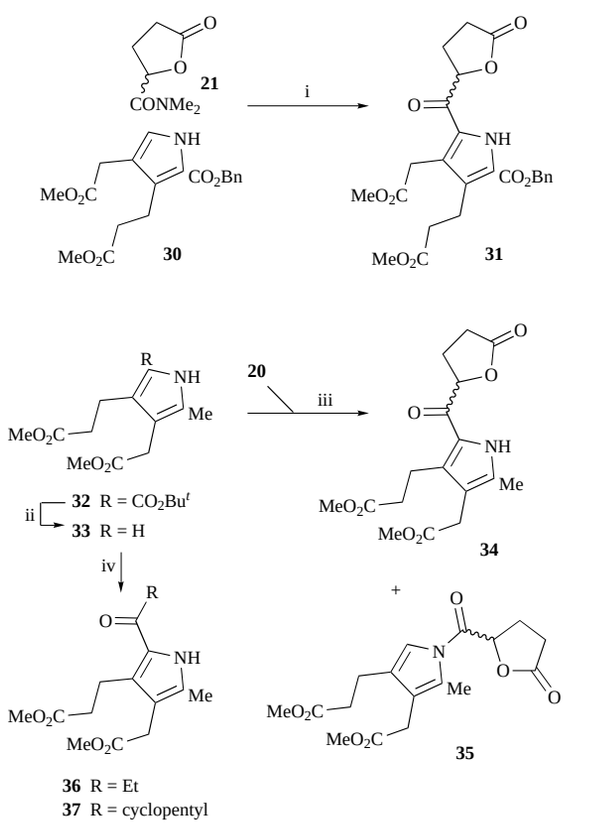
The first experiments used the lactone acid **19**, readily available[8] from L-glutamic acid. Subsequently, two further lactone acids **22** and **26** were synthesised (Scheme 3) to explore the



Scheme 3 *Reagents:* i, $SOCl_2$; ii, Me_2NH; iii, NaOH; iv, CrO_3, H_2SO_4; v, $(COCl)_2$, DMF; vi, 2-mercaptopyridine, Et_3N

scope of the acylation process and to check that the conditions used were compatible with the side-chains needed for synthesis of the macrocycle **4**. Lactone **22** was prepared by a shorter version of the published route;[6,9] simply heating the bromo imino ether **11** from Scheme 2 with aqueous sodium hydroxide yielded the acid **22**, an interesting result bearing in mind the outcome in Scheme 2. The starting material for the other lactone **26** was the alcohol **25** synthesised earlier,[2d] which was readily oxidised to the carboxylic acid by chromic acid.

The dimethylamide **21**, prepared from acid **19**, reacted in a Vilsmeier reaction in the presence of phosphorus oxychloride even with the deactivated pyrrole **30** to give 54% of the ketone **31** (Scheme 4). The corresponding reactions using dimethyl-

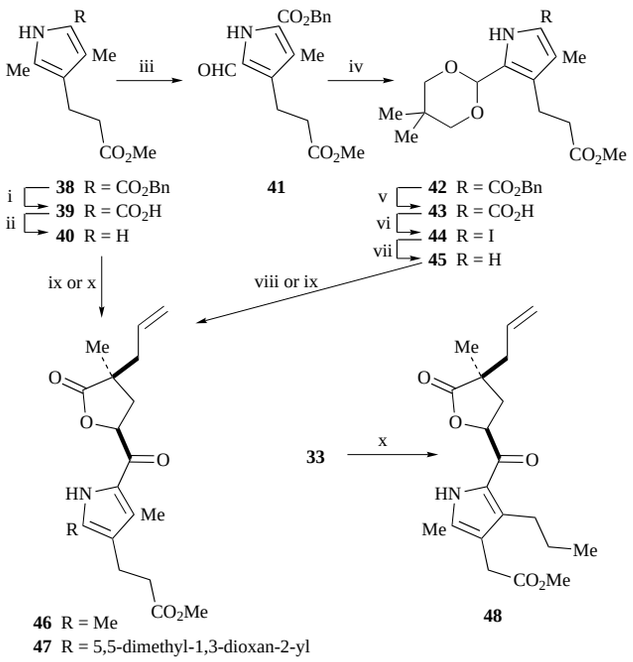


Scheme 4 *Reagents:* i, $POCl_3$; ii, TFA; iii, $AlCl_3$; iv, RCOCl, $SnCl_4$

amides **24** and **28** failed, as did a Friedel–Crafts reaction of pyrrole **30** with acid chloride **20**. Attention therefore turned to a more reactive pyrrole **33**, available from the known[2f] parent **32**. Friedel–Crafts coupling of this pyrrole with acid chloride **20** gave ketone **34**, in a much better yield of 83%, together with 10% of the *N*-acylated material **35**. The conditions for these

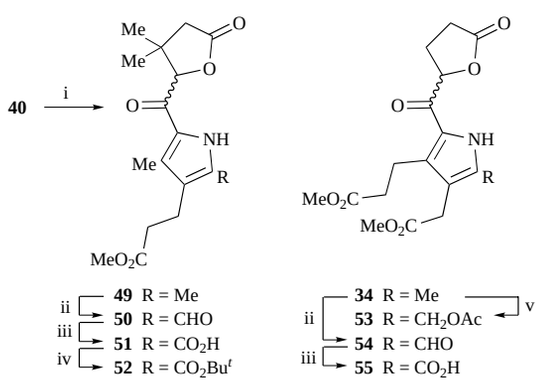
acylations had first been explored using the pyrrole **33** with propionyl chloride and separately with cyclopentanecarbonyl chloride to yield the ketones **36** and **37**, respectively, in high yield.

A second undeactivated α-free pyrrole **40** was prepared by standard steps (Scheme 5) from the known[10] ester **38**. A range



Scheme 5 *Reagents:* i, Pd–C, H_2; ii, TFA; iii, iv, v, see ref. 11; vi, I_2, KI; vii, Pt, H_2; viii, MeMgI then **27**; ix, MeMgI then **29**; x, **27**, $AlCl_3$

of experiments on the acylation process were then performed using pyrroles **33** and **40** with the lactonic acid chlorides **20**, **23** and **27** under Friedel–Crafts conditions. The results established that this approach afforded the desired ketones **34** (Scheme 4), **46** and **48** (Scheme 5) and **49** (Scheme 6) in good to high yields



Scheme 6 *Reagents:* i, **23**, $AlCl_3$; ii, SO_2Cl_2 then H_2O; iii, $KMnO_4$; iv, Bu^tOH, DCC; v, $Pb(OAc)_4$

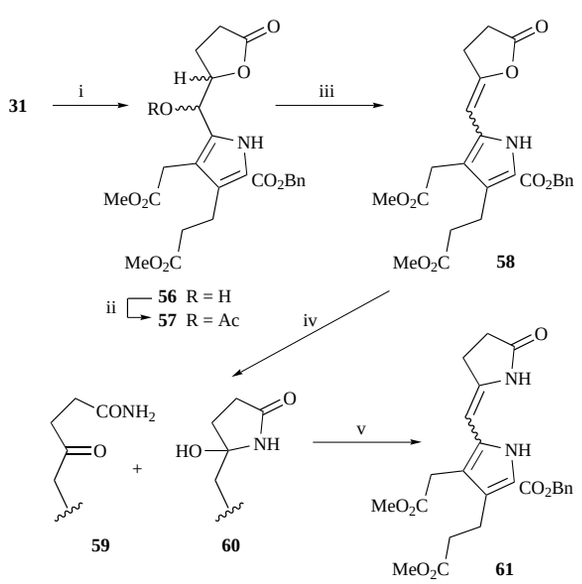
(54–90%). Nevertheless, in all cases there was formation of the undesired *N*-acylated product (4–19%). Indeed, *N*-acylation predominated (*ca*. 60% of the product) when the magnesium pyrrolyl anion derived from pyrrole **45** (Scheme 5) was treated with the acid chloride **27**. Pyrrole **45** was synthesised as earlier[11] from pyrrole **38** *via* the intermediates **41**–**44**, although some modification of the conditions was needed in our hands to obtain high yields, especially for **43** to **44** described in the Experimental section. A 'softer' acylating agent was needed and one member of this class, *S*-pyridyl thioesters, had been used by Nicolaou *et al.*[12] for *C*-acylation of pyrroles. Accordingly, the *S*-pyridyl thioester **29** was prepared from the chloride **27** and, without purification, it reacted with the pyrrolylmagnesium salt derived from **45** to give the ketone **47** in 30% yield with only a trace of *N*-acylated material. Pyrrole **45** could not be used in excess as it was precious and somewhat labile, so the readily available pyrrole **40** (4 equiv.), as its *N*-magnesium salt, was acylated with the thioester **29** to yield 78–85% of the ketone **46**, free of *N*-acylated pyrrole. Unreacted pyrrole **40** was also recovered (60%).

The foregoing work had led by this stage to the development of two high yielding coupling procedures suitable for relatively large-scale preparations. Importantly, they were also compatible with lactones carrying quaternary centres at either C-2 or C-3 of the lactone ring, as needed for the synthesis of macrocycle **4**, and a variety of pyrroles could be successfully used.

Attention then turned to transformation of lactonic ketones such as **34** and **49** (Scheme 6) into lactams related to **2** and **3** (Scheme 1). Three changes were needed: (i) oxidation of the pyrrolic methyl group to a carboxy residue with subsequent esterification, (ii) removal of the keto group to generate a double bond, (iii) conversion of the lactone into a lactam. Our view was that the order in which these steps are carried out would be critically important. The keto group must be present for the oxidation step to stabilise the pyrrole nucleus and only then should it be removed to generate an enol lactone. This is needed because the high reactivity of an enol lactone should allow the lactone-to-lactam conversion under conditions mild enough to avoid formation of amides from the side-chain esters. Thus, oxidation of the pyrrolic methyl group was studied first.

Preliminary experiments yielded the acetoxymethyl derivative **53** from ketone **34** but this proved not to be useful; it is included in the Experimental section. The best conditions found for the desired oxidation (Scheme 6) involved treatment of **34** with two equivalents of sulfuryl chloride or *tert*-butyl hypochlorite followed by hydrolysis of the halogenated products to yield the aldehyde **54**. This was oxidised to the acid **55** by permanganate in 44% overall yield from **34**. When the aldehyde **50**, formed similarly from the more substituted system **49**, was oxidised to the acid **51**, the overall yield of **51** was 82%. This acid could readily be converted into its *tert*-butyl ester **52**; task (i) above had thus been completed.

Step (ii) above was studied first on the ketone **31**, which was smoothly reduced by sodium borohydride to yield an inseparable equimolar mixture of the diastereoisomeric alcohols **56** (Scheme 7). Five standard methods for dehydration were tested



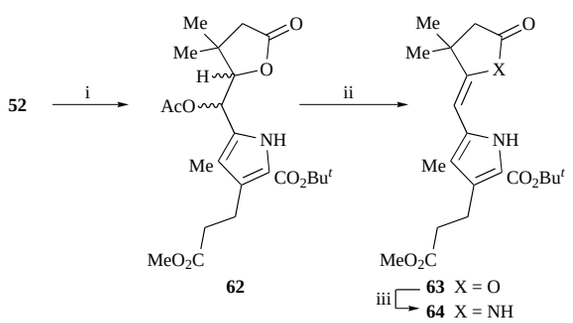
Scheme 7 *Reagents:* i, $NaBH_4$; ii, Ac_2O, DMAP; iii, heat; iv, NH_3; v, TsOH

on **56** but they gave poor yields of product. Accordingly, the alcohols **56** were acetylated and now the resultant diastereoisomers **57** were separable. When each isomer of **57** was heated

briefly under argon at 200 °C, the same mixture of the (*E*)-isomer and the (*Z*)-isomer of **58**, ratio 2.5:1, was produced in 95% yield. It was thus unnecessary in preparative runs to separate the isomeric acetates **57**, and the alcohols **56** could also be carried forward without purification allowing reproducible yields of over 80% for the two steps **31** ⟶ **57**. The configurations of the geometric isomers of **58**, and of similar lactones and lactams synthesised later in this research, were determined by NOE difference spectroscopy.

Initially the (*E*)- and (*Z*)-isomers of **58** were treated separately with aqueous ammonia[13] but the products and their ratio were essentially the same from each one and so they, and their analogues in later experiments, were used in admixture. NMR analysis indicated that the initial products were the γ-keto amide **59** and the hydroxy lactam **60**. They were not fully characterised but were used directly for acid-catalysed conversion into the desired (*E*)- and (*Z*)-lactams **61** in a ratio of 6:5. Satisfyingly, the overall yield for the five simple steps from **31** was 50–60%.

These procedures could now be tested on a system closely related to those needed for synthesis of the macrocycle **4** (Scheme 1). The lactone **52** was the ideal candidate. Reduction and acetylation afforded the acetate **62** in 90% yield (Scheme 8).



Scheme 8 *Reagents:* i, $NaBH_4$, then Ac_2O, DMAP; ii, heat; iii, NH_3 then TsOH

Thermal elimination of acetic acid gave exclusively the (*Z*)-enol lactone **63**; this steric control was discussed in the preceding paper.[3] The lactone **63** was then converted into the (*Z*)-lactam **64** (80%) by ammonia followed by treatment with acid, as above. Only two slight changes were needed when the scale of the preparation of **64** was increased to 0.5–1 g. The reduction step was carried out with portionwise addition of borohydride at lower temperature to avoid some attack at the ester groups, and the thermal elimination was best run with a stream of argon to remove the acetic acid.

In summary, an efficient procedure has been developed for coupling lactonic acids to pyrroles to yield ketones. A high yielding sequence then allows conversion of the ketones into lactams representing the western and eastern building blocks, *cf*. **2** and **3** (Scheme 1) for synthesis of isobacteriochlorins. These methods represent a substantial improvement over the 'original coupling strategy' both in terms of yields and simplicity of operation. The following paper describes their use for the stereoselective synthesis of the metal-free macrocycle of haem d_1.

Experimental

General

For general directions see the preceding paper.[3]

5-(*N*,*N*-Dimethylaminocarbonyl)pyrrolidin-2-one 8

A solution of pyroglutamic acid **7** (500 mg, 3.88 mmol) in freshly distilled thionyl chloride (5 cm^3) was heated at 40 °C for 1 h and then evaporated under reduced pressure. The residue was dissolved in dry tetrahydrofuran (5 cm^3) and added by cannula to a stirred solution of dimethylamine (1 cm^3) in dry tetrahydrofuran (10 cm^3) at −5 °C. The solution was allowed to warm to room temperature and after 4 h was evaporated under reduced pressure. The residue was purified by column chromatography, eluting with dichloromethane–methanol (9:1), and the resulting oil was triturated with ethyl acetate to give the *amide* **8** (316 mg, 52%) as crystals, mp 153–154 °C (from ethyl acetate) (Found: M^+, 156.0895. $C_7H_{12}N_2O_2$ requires *M*, 156.0899); δ_H(400 MHz, $CDCl_3$) 2.05–2.08 (1 H, m) and 2.30–2.41 (3 H, m, CH_2CH_2), 2.93 and 3.00 (each 3 H, s, NMe_2), 4.48 (1 H, dd, *J* 8 and 5, 5-H) and 6.87 (1 H, br s, NH); *m/z* (EI) 156 (M^+) and 128 (M − CO).

2-[5-(Dimethylaminocarbonyl)-4,5-dihydro-3*H*-pyrrol-2-yl]-pyrrole 9

A solution of amide **8** (100 mg, 0.64 mmol) and pyrrole (61 mm^3, 1.34 mmol) in dry dichloromethane (1 cm^3) at 0 °C was stirred with freshly distilled phosphorus oxychloride (100 mm^3, 1.1 mmol) for 2 h, then allowed to warm to room temperature and treated with a solution of sodium acetate (300 mg) in water (1 cm^3). The mixture was adjusted to pH 9 with dilute aqueous sodium hydroxide and extracted with dichloromethane (3 × 5 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the *pyrrole* **9** as a solid, mp 183–184 (from ethyl acetate) (Found: C, 64.5; H, 7.4; N, 20.6%; M^+, 205.1205. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%; *M*, 205.1215); λ_{max}(MeOH)/nm 282; ν_{max}($CHCl_3$)/cm^{-1} 3460, 1641 and 1610; δ_H(400 MHz, $CDCl_3$) 2.10 and 2.46 (each 1 H, m, CH_2CH), 2.85–2.94 and 3.08–3.12 (each 1 H, m, $CH_2C{=}N$), 2.89 and 3.15 (each 3 H, s, NMe_2), 5.02 (1 H, t, *J* 7, CHN), 6.16 (1 H, t, *J* 3), 6.54 (1 H, d, *J* 3) and 6.82 (1 H, br s, 3 × pyrrole-H) and 10.55 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 25.2 and 37.3 (CH_2CH_2), 35.2 and 35.7 (NMe_2), 71.4 (NCHCO), 109.4, 113.9, 122.6 and 127.0 (4 × pyrrole-C) and 167.7 and 171.4 (C=N and C=O); *m/z* (FD) 205 (M^+, 100%); *m/z* (EI) 205 (M^+) and 133 (M − $CONMe_2$).

3,3-Dimethylcyclopropane-1,2-dicarboximide 13

A solution of bromide **12**[6] (80 mg, 0.36 mmol) in dry *tert*-butyl alcohol (2 cm^3) was heated with a freshly prepared solution of potassium *tert*-butoxide in dry *tert*-butyl alcohol (0.33 mol dm^{-3}; 2.2 cm^3, 0.73 mmol) at 80–90 °C for 18 h, then cooled and evaporated under high vacuum, azeotroping twice with toluene (2 cm^3). A solution of the residue in water (7 cm^3) was acidified with hydrochloric acid (1 mol dm^{-3}; 1 cm^3) and extracted with ethyl acetate (4 × 5 cm^3). The combined extracts were washed with brine (4 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the imide **13** (41.3 mg, 82%) as a crystalline solid, mp 114–115 °C (from diethyl ether–hexane) (Found: M^+, 139.0632. $C_7H_9NO_2$ requires *M*, 139.0633); λ_{max}(MeOH)/nm 211 and 253; ν_{max}($CHCl_3$)/cm^{-1} 3380, 1750 and 1700; δ_H(400 MHz, $CDCl_3$) 1.24 and 1.36 (each 3 H, s, CMe_2), 2.32 (2 H, s, 2 × CH) and 7.77 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 15.8 and 26.2 (CMe_2), 34.5 (CMe_2), 35.0 (2 × CH) and 173.7 (2 × C=O); *m/z* (FD) 139 (M^+, 100%).

Methyl 5-hydroxy-3,3-dimethyl-4-nitropentanoate 15

A solution of nitro ester **14**[7] (15 g, 86 mmol) in isopropyl alcohol (15 cm^3) was stirred with paraformaldehyde (5.16 g, 172 mmol) and potassium fluoride (0.5 g, 8.6 mmol) at 30 °C for 48 h, then filtered and evaporated under reduced pressure. The residual oil was purified by column chromatography, eluting with dichloromethane–methanol (9:1), to give the *alcohol* **15** (10.5 g, 60%) as an oil, as well as the corresponding lactone (2.5 g, 14%) and starting material **14** (2.05 g, 14%) (Found: C, 47.1; H, 7.2; N, 6.7%; M^+ − OMe, 174.0761. $C_8H_{15}NO_5$ requires C, 46.8; H, 7.3; N, 6.8%; *M* − OMe, 174.0766); ν_{max}($CHCl_3$)/cm^{-1} 3400, 1730, 1550 and 1360; δ_H(400 MHz, $CDCl_3$) 1.13 and 1.17 (each 3 H, s, CMe_2), 2.32 and 2.44 (each 1 H, d, *J* 15, CH_2CO_2), 3.69 (3 H, s, OMe), 3.99 (1 H, dd, *J* 12 and 3) and 4.25 (1 H, dd,

J 12 and 10, CH_2O) and 4.93 (1 H, dd, *J* 10 and 3, $CHNO_2$); δ_C(100 MHz, $CDCl_3$) 24.2 and 24.5 (CMe_2), 35.4 (CH_2CO_2), 43.2 (CMe_2), 51.7 (OMe), 60.1 (CH_2O), 95.8 ($CHNO_2$) and 171.2 (CO_2); *m/z* (EI) 174 (M − OMe) and 158 (M − HNO_2).

5-Hydroxymethyl-4,4-dimethylpyrrolidin-2-one 17

The nitro ester **15** (3.7 g, 18 mmol) was stirred with a suspension of freshly activated zinc powder (28 g) in glacial acetic acid (200 cm^3) for 15 min at room temperature and then 75 min at 70 °C. The mixture was cooled, treated with ammonium acetate (3.56 g, 46 mmol) followed by 15% aq. titanium(III) chloride (4.6 cm^3), stirred at room temperature for 1 h and then filtered through Celite, washing well with glacial acetic acid. The filtrate and washings were evaporated under reduced pressure. A mixture of the residual oil, water (200 cm^3) and ethyl acetate (200 cm^3) was neutralised to pH 7 with saturated aqueous sodium hydrogen carbonate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (5 × 200 cm^3), then adjusted to pH 9 with further saturated aqueous sodium hydrogen carbonate and continuously extracted with ethyl acetate for 24 h. All the organic solutions were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by column chromatography, eluting with dichloromethane–methanol (9:1), to give lactam **17** (2.01 g, 78%) as an oil. For characterisation a sample of the oil was further purified by PLC, eluting with dichloromethane–methanol (9:1), to give *lactam* **17** as an oil which crystallised on cooling, mp 54–55 °C (from diethyl ether–hexane) (Found: M^+, 143.0933. $C_7H_{13}NO_2$ requires *M*, 143.0946); $\nu_{max}(CHCl_3)/cm^{-1}$ 3427 and 1696; δ_H(400 MHz, $CDCl_3$) 0.97 and 1.09 (each 3 H, s, CMe_2), 2.04 and 2.14 (each 1 H, d, *J* 17, CH_2CO), 3.24 (1 H, dd, *J* 8 and 3, CHN), 3.47 (1 H, dd, *J* 11 and 8) and 3.60 (1 H, dd, *J* 11 and 3, CH_2O), 4.30 (1 H, br s, OH) and 7.39 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 22.4 and 28.4 (CMe_2), 37.2 (CH_2CO_2), 46.0 (CMe_2), 62.1 (CHN), 85.4 (CH_2O) and 178.3 (C=O); *m/z* (FD) 143 (M^+, 100%); *m/z* (EI) 143 (M^+) and 112 (M − CH_2OH).

5-Carboxy-4,4-dimethylpyrrolidin-2-one 18

A solution of the lactam alcohol **17** (189 mg, 1.32 mmol) in acetone (5 cm^3) at 0 °C was treated with an aliquot (0.71 cm^3, 1.45 mmol) of a solution of chromium trioxide (10.3 g) in water (31 cm^3) and concentrated sulfuric acid (9 cm^3), then warmed to room temperature and stirred for 3 h. Isopropyl alcohol (1 cm^3) was added, followed after 10 min by water (10 cm^3). The acetone was evaporated under reduced pressure and the remaining aqueous liquor was adjusted to pH 2 with saturated aqueous sodium hydrogen carbonate and extracted continuously with ethyl acetate for 24 h. The extract was dried (Na_2SO_4) and evaporated under reduced pressure to give the *lactam acid* **18** as a crystalline solid, mp 200–202 °C (from ethyl acetate–methanol) (Found: M^+, 157.0729. $C_7H_{11}NO_3$ requires *M*, 157.0739); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–2200, 3240, 1740 and 1650; δ_H(400 MHz, CD_3OD) 1.09 and 1.31 (each 3 H, s, CMe_2), 2.21 (2 H, s, CH_2) and 3.92 (1 H, s, CHN); δ_C(100 MHz, CD_3OD) 24.0 and 28.3 (CMe_2), 40.0 (CH_2), 46.3 (CMe_2), 67.2 (CHN) and 173.7 and 179.6 (C=O); *m/z* (FD) 157 (M^+, 100%).

5-(Chloroformyl)tetrahydrofuran-2-one 20

A solution of acid **19**[8] (1.5 g, 11.6 mmol) in freshly distilled thionyl chloride (10 cm^3) was heated at 70 °C for 1 h, then cooled and evaporated under reduced pressure. The residue was distilled in a Kugelrohr (60–65 °C, 0.075 mmHg) to give the acid chloride **20** (1.55 g, 90%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 and 1740; δ_H(400 MHz, $CDCl_3$) 2.39–2.46 (1 H, m), 2.51–2.56 (2 H, m) and 2.64–2.71 (1 H, m, CH_2CH_2) and 5.13 (1 H, dd, *J* 9 and 4, 5-H).

5-Carboxy-4,4-dimethyltetrahydrofuran-2-one 22

A solution of imidate **10**[6] (9 g, 53 mmol) in carbon tetrachloride was treated with *N*-bromosuccinimide (9.81 g, 55 mmol) followed by benzoyl peroxide (300 mg, 2.3 mmol), heated under reflux for 9 h, then cooled, filtered through Celite, washing with more carbon tetrachloride and evaporated under reduced pressure to give the crude bromide **11**.

A solution of the above bromide **11** in aqueous sodium hydroxide (1 mol dm^{-3}; 150 cm^3) was heated under reflux for 18 h, then acidified to pH 2 with concentrated hydrochloric acid and continuously extracted with ethyl acetate overnight. The organic solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled in a Kugelrohr (145 °C, 0.05 mmHg) to give the *lactone acid* **22** (5 g, 42%) as an oil which solidified on standing, mp (unsolvated sample) 140–142 °C (Found: M^+ − CO_2H, 113.0612. $C_7H_{10}O_4$ requires *M* − CO_2H, 113.0603); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–2700, 1770 and 1730; δ_H(400 MHz, $CDCl_3$–CD_3OD) 1.07 and 1.24 (each 3 H, s, CMe_2), 2.28 and 2.42 (each 1 H, d, *J* 17, CH_2CO_2), 4.45 (1 H, s, CH−O) and 5.12 (1 H, br s, OH); δ_C(100 MHz, $CDCl_3$–CD_3OD) 22.4 and 26.8 (CMe_2), 39.4 (CMe_2), 42.2 (CH_2), 84.8 (CH−O) and 170.3 and 175.9 (2 × C=O); *m/z* (FD) 158 (M^+, 100%); *m/z* (EI) 113 (M − CO_2H, 100%).

5-Chloroformyl-4,4-dimethyltetrahydrofuran-2-one 23

A solution of acid **22** (924 mg, 5.9 mmol) in freshly distilled thionyl chloride (10 cm^3) under argon was heated at 80 °C for 90 min and then evaporated under reduced pressure. The residue was distilled in a Kugelrohr (70 °C, 0.05 mmHg) to give the acid chloride **23** as an oil; δ_H(90 MHz, $CDCl_3$) 1.3 and 1.5 (each 3 H, s, CMe_2), 2.5 and 2.6 (2 H, ABq, CH_2CO_2) and 4.8 (1 H, s, CH−O).

5-(*N*,*N*-Dimethylaminocarbonyl)-4,4-dimethyltetrahydrofuran-2-one 24

A solution of acid chloride **23** in dry tetrahydrofuran (5 cm^3) was added dropwise to a stirred solution of excess dimethylamine in dry tetrahydrofuran (5 cm^3) at −70 °C. The mixture was allowed to warm to room temperature and, after 30 min, filtered, washing the precipitate with tetrahydrofuran. The filtrate and washings were evaporated under reduced pressure and the residue was distilled in a Kugelrohr (120 °C, 0.05 mmHg) to give the *amide* **24** (574 mg, 53%) as an oil which crystallised on standing, mp 87.5–88 °C [from ethyl acetate–light petroleum (bp 60–80 °C)] (Found: C, 58.1; H, 8.3; N, 7.55%; M^+, 185.1066. $C_9H_{15}NO_3$ requires C, 58.3; H, 8.2; N, 7.55%; *M*, 185.1052); $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 and 1650; δ_H(400 MHz, $CDCl_3$) 1.11 and 1.27 (each 3 H, s, CMe_2), 2.14 and 2.72 (each 1 H, d, *J* 17, CH_2CO_2), 2.99 and 3.05 (each 3 H, s, NMe_2) and 4.91 (1 H, s, CH−O); δ_C(100 MHz, $CDCl_3$) 22.4 and 28.5 (CMe_2), 35.7 and 37.3 (NMe_2), 40.0 (CMe_2), 41.5 (CH_2), 81.6 (CH−O) and 168.2 and 176.3 (2 × C=O); *m/z* (FD) 185 (M^+, 100%).

(3*S*,5*S*)-3-Allyl-5-carboxy-3-methyltetrahydrofuran-2-one 26

A solution of alcohol **25**[2d,8] (1.9 g, 11.2 mmol) in acetone (50 cm^3) was stirred at 0 °C and an aliquot (8.6 cm^3, 22.2 mmol) of a solution of chromium trioxide (10.3 g) in concentrated sulfuric acid (9 cm^3) and water (31 cm^3) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Isopropyl alcohol (5 cm^3) was added followed, after 10 min, by water (100 cm^3). The acetone was evaporated under reduced pressure and the remaining aqueous mixture was extracted with diethyl ether (6 × 150 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was partitioned between diethyl ether (200 cm^3) and saturated aqueous sodium hydrogen carbonate (150 cm^3). The aqueous layer was washed with further diethyl ether (200 cm^3), then acidified to pH 2 using dilute sulfuric acid and extracted with diethyl ether (4 × 200 cm^3) followed by ethyl acetate (2 × 200 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under

reduced pressure to give the *acid* **26** (1.87 g, 91%) as an oil (Found: M^+, 184.0751. $C_9H_{12}O_4$ requires *M*, 184.0736); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300–2400, 1785 and 1730; δ_H(400 MHz, $CDCl_3$) 1.29 (3 H, s, Me), 2.30–2.42 (4 H, m, CH_2C-CH_2C=C), 4.89 (1 H, t, *J* 8, 5-H), 5.10–5.18 (2 H, m, CH_2=CH), 5.65–5.75 (1 H, m, CH_2=C*H*) and 9.26 (1 H, br s, CO_2H); δ_C(100 MHz, $CDCl_3$) 22.5 (Me), 36.8 (*C*H_2CH=CH_2), 41.3 (C-4), 42.9 (C-3), 72.6 (C-5), 119.9 (CH=*C*H_2), 131.9 (*C*H=CH_2) and 173.5 and 180.4 (2 × C=O); *m/z* (FD) 184 (M^+, 100%).

(3*S*,5*S*)-3-Allyl-5-chloroformyl-3-methyltetrahydrofuran-2-one 27

A stirred solution of acid **26** (197 mg, 1.1 mmol) in dry dichloromethane (2 cm^3) and *N*,*N*-dimethylformamide (2 drops) at 0 °C under argon was treated dropwise with oxalyl chloride (0.188 cm^3, 2.2 mmol) and then, after 30 min, evaporated under reduced pressure. The residue was distilled in a Kugelrohr (80 °C, 0.5 mmHg) to give the acid chloride **27** as an oil; δ_H(400 MHz, $CDCl_3$) 1.31 (3 H, s, CH_3), 2.25–2.47 (4 H, m, CH_2CCH_2C=C), 5.04 (1 H, t, *J* 8, 5-H), 5.13–5.20 (2 H, m, CH=C*H*$_2$) and 5.62–5.72 (1 H, m, C*H*=CH_2).

(3*S*,5*S*)-3-Allyl-3-methyl-5-(*N*,*N*-dimethylaminocarbonyl)tetrahydrofuran-2-one 28

A stirred solution of acid **26** (197 mg, 1.1 mmol) in dry dichloromethane (2 cm^3) and *N*,*N*-dimethylformamide (2 drops) at 0 °C under argon was treated dropwise with oxalyl chloride (0.188 cm^3, 2.2 mmol). After 30 min the solution was added by cannula to dimethylamine (2 cm^3) at −70 °C. The stirred solution was allowed to warm to room temperature over 30 min and then evaporated under reduced pressure. Diethyl ether (20 cm^3) was added and the solution filtered, washing through with more diethyl ether. The ethereal solution was washed with water (30 cm^3) and the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by PLC, eluting with dichloromethane–methanol (19:1), to give the *amide* **28** (120 mg, 53%) as an oil (Found: M^+, 211.1223. $C_{11}H_{17}NO_3$ requires *M*, 211.1208); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780, 1710 and 1630; δ_H(400 MHz, $CDCl_3$) 1.22 (3 H, s, Me), 1.98 (1 H, dd, *J* 13 and 7) and 2.61 (1 H, dd, *J* 13 and 8, CH_2CH−O), 2.26 (1 H, dd, *J* 14 and 8) and 2.34 (1 H, dd, *J* 14 and 7, CH_2C=C), 2.93 and 3.06 (each 3 H, s, NMe_2), 5.01–5.11 (3 H, m, CH−O and CH_2=CH) and 5.64–5.74 (1 H, m, CH_2=C*H*); δ_C(100 MHz, $CDCl_3$) 22.9 (Me), 35.5 (*C*H_2C=C), 35.9 and 36.6 (NMe_2), 41.5 (C-4), 42.6 (C-3), 72.2 (C-5), 119.5 (CH=*C*H_2), 132.4 (*C*H=CH_2) and 167.2 and 180.0 (2 × C=O); *m/z* (EI) 211 (M^+) and 167 (M − NMe_2).

(3*S*,5*S*)-3-Allyl-3-methyl-5-(2-pyridylthiocarbonyl)tetrahydrofuran-2-one 29

Method A. A solution of the acid **26** (500 mg, 2.72 mmol), 2,2′-dipyridyl disulfide (896 mg, 4.08 mmol) and triphenylphosphine (1.07 g, 4.08 mmol) in dry toluene (18 cm^3) was left standing under argon at room temperature for 22 h. This solution was then used without further purification.

Method B. A solution of acid chloride **27** (136 mg, 0.67 mmol) and triethylamine (112 mm^3, 0.806 mmol) in dry dichloromethane (10 cm^3) was stirred with 2-mercaptopyridine (75 mg, 0.67 mmol) under argon at room temperature for 45 min, then washed with water (10 cm^3) followed by aqueous sodium hydrogen carbonate (10 cm^3), dried and evaporated under reduced pressure to give the crude thioester **29** as an oil (176 mg); λ_{max}(EtOAc)/nm 263; δ_H(400 MHz, $CDCl_3$) 1.30 (3 H, s, Me), 2.20–2.45 (4 H, m, 2 × CH_2), 4.97 (1 H, t, *J* 8, 5-H), 5.12–5.21 (2 H, m, CH=C*H*$_2$), 5.68–5.76 (1 H, m, C*H*=CH_2) and 7.32–7.35, 7.56–7.58, 7.75–7.79 and 8.65–8.66 (each 1 H, m, Ar).

Benzyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-[(5-oxotetrahydrofuran-2-yl)formyl]pyrrole-2-carboxylate 31

A solution of the amide[14] **21** (486 mg, 3.1 mmol) and the α-free pyrrole **30**[15] (1.62 g, 4.5 mmol) in dry 1,2-dichloroethane (20 cm^3) was treated with freshly distilled phosphorus oxychloride (0.43 cm^3, 4.6 mmol), heated at 95 °C for 16 h, then cooled, treated with a solution of anhydrous sodium acetate (4.5 g) in water (100 cm^3), stirred for 10 min and extracted with dichloromethane (4 × 100 cm^3). The combined extracts were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:1), to give recovered α-free pyrrole **30** (980 mg, 60%) and the *ketone* **31** (780 mg, 54%) as an oil (Found: M^+, 471.1569. $C_{24}H_{25}NO_9$ requires *M*, 471.1529); λ_{max}(MeOH)/nm 233 and 301; $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 1795, 1730 and 1660; δ_H(400 MHz, $CDCl_3$) 2.48–2.57 (6 H, m, CH_2C*H*$_2CO_2$ and C*H*$_2$C*H*$_2$CH−O), 2.99 (2 H, t, *J* 8, C*H*$_2CH_2CO_2$), 3.59 and 3.67 (each 3 H, s, OMe), 3.86 (2 H, s, CH_2CO_2), 5.33 (2 H, s, PhC*H*$_2$), 5.33–5.36 (1 H, m, CH−O), 7.33–7.42 (5 H, m, Ph) and 10.30 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 19.5 (*C*H_2-CH_2CO_2), 24.1 and 26.8 (*C*H_2CH$_2$CH−O), 30.4 (*C*H_2CO_2), 34.4 (CH_2*C*H_2CO_2), 51.6 and 52.1 (2 × OMe), 66.9 (Ph*C*H_2), 80.4 (CH−O), 123.3, 125.9, 127.9 and 130.6 (4 × pyrrole-C), 128.4, 128.5, 128.6 and 135.0 (6 × phenyl-C) and 159.7, 171.3, 173.1, 175.3 and 185.4 (5 × C=O); *m/z* (EI) 471 (M^+), 440 (M − OMe) and 359 (M − lactone ring).

4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-methylpyrrole 33

A solution of the *tert*-butyl ester **32**[2a] (300 mg, 8.85 mmol) in freshly distilled trifluoroacetic acid (10 cm^3) was stirred at room temperature under argon for 15 min and then evaporated. The resultant oil was dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate (5 cm^3), dried (Na_2SO_4) and then evaporated under reduced pressure to yield the α-free pyrrole **33** (210 mg, 99%) as a gum, which was used without further purification; δ_H(400 MHz, $CDCl_3$) 2.19 (3 H, s, 2-Me), 2.56 (2 H, t, *J* 7, CH_2C*H*$_2CO_2$), 2.75 (2 H, t, *J* 7, C*H*$_2CH_2CO_2$), 3.39 (2 H, d, *J* 0.3, CH_2CO_2), 3.66 (6 H, s, 2 × OMe), 6.39 (1 H, s, 5-H) and 7.77 (1 H, br s, NH); *m/z* (FD) 239 (M^+, 100%).

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-2-propanoylpyrrole 36

A solution of α-free pyrrole **33** (100 mg, 0.42 mmol) in dry dichloromethane (2 cm^3) was stirred with propionyl chloride (40 mm^3, 0.46 mmol) and tin(IV) chloride (53 mm^3, 0.45 mmol) at 0 °C for 30 min, then diluted with dichloromethane (5 cm^3), washed with hydrochloric acid (1 mol dm^{-3}; 5 cm^3) and brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:1), to give starting material **33** (55 mg, 55%) and *ketone* **36** (43 mg, 45%; 78% based on unrecovered starting material) as a solid, mp 93–93.5 °C (from diethyl ether–hexane) (Found: C, 61.2; H, 7.2; N, 4.5%; M^+, 295.1432. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.2; N, 4.7%; *M*, 295.1420); λ_{max}(MeOH)/nm 307; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1730 and 1620; δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7, *Me*CH_2), 2.22 (3 H, s, 5-Me), 2.53 (2 H, t, *J* 8, CH_2C*H*$_2CO_2$), 2.74 (2 H, q, *J* 7, MeC*H*$_2$), 3.03 (2 H, t, *J* 8, C*H*$_2CH_2CO_2$), 3.40 (2 H, s, CH_2CO_2), 3.65 and 3.66 (each 3 H, s, OMe) and 9.72 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.3 and 11.5 (2 × Me), 21.2 (*C*$H_2CH_2CO_2$), 29.7 (*C*H_2CO_2), 32.0 (Me*C*H_2), 35.2 (CH_2-*C*H_2CO_2), 51.6 and 51.9 (2 × OMe), 114.6, 127.0, 129.0 and 132.9 (4 × pyrrole-C) and 172.1, 173.2 and 189.8 (3 × C=O); *m/z* (FD) 295 (M^+, 100%).

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-2-(cyclopentylformyl)pyrrole 37

A solution of cyclopentanecarboxylic acid (1 cm^3) in freshly

distilled thionyl chloride (5 cm^3) was heated at 60 °C under argon for 2 h, then cooled and evaporated under reduced pressure. The residual oil was distilled in a Kugelrohr apparatus at 20 mmHg to give the acid chloride as an oil.

A solution of α-free pyrrole **33** (230 mg, 0.96 mmol) in dry 1,2-dichloroethane was treated with a solution of the above acid chloride (43 mg, 0.32 mmol) in dry 1,2-dichloroethane (0.6 cm^3) followed by tin(IV) chloride (55 mm^3, 0.48 mmol), heated at 80 °C for 30 min, then cooled, diluted with dichloromethane (10 cm^3) and washed with hydrochloric acid (1 mol dm^{-3}; 10 cm^3). The aqueous layer was extracted with dichloromethane (10 cm^3) and the combined organic layers were washed with water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with diethyl ether–hexane (2:1), and the resulting oil was triturated with diethyl ether–hexane to give the *ketone* **37** (96 mg, 88%) as a crystalline solid, mp 82.5–84 °C (from diethyl ether–hexane) (Found: M^+, 335.1734. $C_{18}H_{25}NO_5$ requires *M*, 335.1733); λ_{max}(MeOH)/nm 303; ν_{max}($CHCl_3$)/cm^{-1} 3440, 1730 and 1610; δ_H(400 MHz, $CDCl_3$) 1.57–1.64 (2 H, m), 1.68–1.80 (2 H, m) and 1.83–1.91 [4 H, m, $(CH_2)_4$], 2.22 (3 H, s, 5-Me), 2.55 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.04 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.34 (1 H, quintet, *J* 8, CHCO), 3.41 (2 H, s, CH_2CO_2), 3.66 (6 H, s, 2 × OMe) and 9.59 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.7 (5-Me), 21.2 ($CH_2CH_2CO_2$), 26.3, 29.8 and 30.5 [$(CH_2)_4$ and CH_2CO_2], 35.4 ($CH_2CH_2CO_2$), 46.5 (CHCO) 51.6 and 52.0 (2 × OMe), 115.1, 126.7, 129.6 and 132.9 (4 × pyrrole-C) and 172.1, 173.3 and 192.5 (3 × C=O); *m/z* (FD) 335 (M^+, 100%).

4-(2-Methoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylic acid 39

The benzyl ester **38**[10] (8.9 g, 28 mmol) was dissolved in tetrahydrofuran (105 cm^3) and degassed by bubbling argon through for 10 min. Triethylamine (0.5 cm^3) was added followed by 10% palladium-on-charcoal (0.9 g) and the solution was hydrogenated for 4 h, then degassed again and filtered through Celite. Evaporation of the filtrate yielded the *acid* **39** (6 g, 94%) as a solid, which needed to be stored at −20 °C; ν_{max}(Nujol)/cm^{-1} 3320, 3200–2000, 1725 and 1640; δ_H(400 MHz, $CDCl_3$) 2.22 and 2.29 (each 3 H, s, CMe), 2.43 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.70 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe) and 8.70 (1 H, br s, NH); *m/z* (EI) 225 (M^+) and 181 (M − CO_2).

3-(2-Methoxycarbonylethyl)-2,4-dimethylpyrrole 40

The acid **39** (13.31 g, 59 mmol) was dissolved in freshly distilled trifluoroacetic acid (100 cm^3) and nitrogen was then blown rapidly through the solution for 30 min to evaporate the trifluoroacetic acid. A solution of the residual oil in dichloromethane (200 cm^3) was washed successively with water (2 × 200 cm^3), saturated aqueous sodium hydrogen carbonate (150 cm^3) and brine (150 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the α-free pyrrole **40** (9.44 g, 83%) as an oil; λ_{max}(MeOH)/nm 210; ν_{max}(CH_2Cl_2)/cm^{-1} 3480 and 1730; δ_H(400 MHz, $CDCl_3$) 2.03 and 2.17 (each 3 H, s, CMe), 2.46 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.72 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.67 (3 H, s, OMe), 6.34 (1 H, s, 5-H) and 7.63 (1 H, br s, NH).

General procedure for the Friedel–Crafts reaction between α-free pyrroles and acid chlorides

A solution of the acid chloride (0.21 mmol) in dry 1,2-dichloroethane (0.33 cm^3) was added to a solution of the α-free pyrrole (0.63 mmol) in dry 1,2-dichloroethane (2 cm^3) at −25 °C and a solution of aluminium(III) chloride in nitrobenzene (1 mol dm^{-3}; 0.32 cm^3, 0.32 mmol) was added. The mixture was stirred under argon for 6 h whilst it warmed to room temperature, then diluted with dichloromethane (5 cm^3) and washed with hydrochloric acid (1 mol dm^{-3}; 5 cm^3). The aqueous layer was extracted with dichloromethane (2 × 5 cm^3) and the combined organic layers were washed with water (5 cm^3) and brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (2:1) or with dichloromethane–methanol (19:1), to give the *C*-acyl and *N*-acyl pyrroles as oils.

3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-2-(5-oxotetrahydrofuran-2-yl)formylpyrrole 34. The above procedure using α-free pyrrole **33** and acid chloride **20** gave the *C*-acyl pyrrole **34** (83%) (Found: M^+, 351.1338. $C_{17}H_{21}NO_7$ requires *M*, 351.1318); λ_{max}(MeOH)/nm 306; ν_{max}($CHCl_3$)/cm^{-1} 3441, 1790, 1734 and 1626; δ_H(400 MHz, $CDCl_3$) 2.26 (3 H, s, 5-Me), 2.53–2.60 (6 H, m, $CH_2CH_2CO_2$ and CH_2CH_2CH−O), 3.02 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.45 (2 H, s, CH_2CO_2), 3.64 and 3.67 (each 3 H, s, OMe), 5.30 (1 H, br s, CH−O) and 9.57 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.8 (5-Me), 21.2 ($CH_2CH_2CO_2$), 24.9 and 27.0 (CH_2CH_2CH−O), 29.3 (CH_2CO_2), 34.0 ($CH_2CH_2CO_2$), 51.5 and 52.0 (2 × OMe), 80.2 (CH−O), 116.0, 124.4, 134.3 and 135.4 (4 × pyrrole-C) and 171.8, 173.5, 176.5 and 182.4 (4 × C=O); *m/z* (FD) 351 (M^+, 100%); *m/z* (EI) 351 (M^+), 320 (M^+ − OMe) and 292 (M − CO_2Me).

Also obtained was the *N*-acyl pyrrole **35** (10%); λ_{max}(MeOH)/nm 246; ν_{max}($CHCl_3$)/cm^{-1} 1792 and 1733; δ_H(400 MHz, $CDCl_3$) 2.42 (3 H, s, 5-Me), 2.52–2.65 (8 H, m, CH_2CH_2CH−O and $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.67 and 3.68 (each 3 H, s, OMe), 5.49 (1 H, t, *J* 6, CH−O) and 6.81 (1 H, s, 2-H); δ_C(100 MHz, $CDCl_3$) 13.3 (5-Me), 20.4 ($CH_2CH_2CO_2$), 25.2 and 26.6 (CH_2CH_2CH−O), 29.5 (CH_2CO_2), 35.5 ($CH_2CH_2CO_2$), 51.8 and 52.1 (2 × OMe), 75.7 (CH−O), 114.9, 118.4, 127.1 and 131.2 (4 × pyrrole-C) and 167.0, 171.5, 173.2 and 175.7 (4 × C=O); *m/z* (FD) 351 (M^+, 100%).

2-(4-Allyl-4-methyl-5-oxotetrahydrofuran-2-yl)formyl-3,5-dimethyl-4-(2-methoxycarbonylethyl)pyrrole 46. *Method A.*—The above procedure using α-free pyrrole **40** and acid chloride **27** gave the *C*-acyl pyrrole **46** (62%) (Found: M^+, 347.1751. $C_{19}H_{25}NO_5$ requires *M*, 347.1733); λ_{max}(MeOH)/nm 314; ν_{max}($CHCl_3$)/cm^{-1} 3442, 1778, 1731 and 1621; δ_H(400 MHz, $CDCl_3$) 1.30 (3 H, s, Me), 2.20–2.36 (3 H, m, CH_2C=C and CH_AH_BCH−O), 2.25 and 2.31 (each 3 H, s, Ar*Me*), 2.40 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.52 (1 H, dd, *J* 13 and 8, CH_AH_BCH−O), 2.71 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe), 5.07–5.12 (2 H, m, CH=CH_2), 5.24 (1 H, br s, CH−O), 5.65–5.73 (1 H, m, C*H*=CH_2) and 9.40 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.5 and 11.6 (2 × ArMe), 22.8 ($CH_2CH_2CO_2$), 34.6 ($CH_2CH_2CO_2$), 36.4 , 41.6 and 42.6 (CH_2CCH_2), 51.5 (OMe), 119.6 (CH=CH_2), 121.7, 125.3, 130 (br) and 132.3 (4 × pyrrole-C), 134.7 (CH=CH_2) and 173.2, 180.2 and 182.4 (3 × C=O); *m/z* (FD) 347 (M^+, 100%); *m/z* (EI) 347 (M^+) and 209 (M − lactone ring).

Also obtained was a by-product showing UV and IR absorption indicating it was the corresponding *N*-acylpyrrole (9%), but full characterisation was not carried out.

Method B.—A solution of methylmagnesium chloride in diethyl ether (3 mol dm^{-3}; 3.63 cm^3) was added to a stirred solution of α-free pyrrole **40** (1.97 g, 10.9 mmol) in dry toluene (48 cm^3) and dry tetrahydrofuran (2 cm^3) at −78 °C under argon. This solution was allowed to warm for 10 min with vigorous stirring and then cooled down to −78 °C again. The solution of thioester **29** was then added by 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 quenched with saturated aqueous ammonium chloride (2 cm^3) and allowed to warm to room temperature. Diethyl ether (50 cm^3), saturated aqueous ammonium chloride (30 cm^3) and water (30 cm^3) were then added. The organic phase was separated, washed with 10% aqueous potassium carbonate (30 cm^3) and then water (30 cm^3), dried and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with hexane–ethyl acetate, to give the *C*-acyl pyrrole **46** as a gum (736 mg, 78%).

2-(4-Allyl-4-methyl-5-oxotetrahydrofuran-2-yl)formyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methyl-pyrrole 48. The general procedure above using α-free pyrrole **33**

and acid chloride **27** gave the *C*-acyl pyrrole **48** (54%) (Found: M^+, 405.1786. $C_{21}H_{27}NO_7$ requires *M*, 405.1788); λ_{max}(MeOH)/nm 311; ν_{max}($CHCl_3$)/cm^{-1} 3440, 1780 and 1734; δ_H(400 MHz, $CDCl_3$) 1.28 (3 H, s, Me), 2.23 (3 H, s, 5-Me), 2.25–2.34 (2 H, m, CH_2C=C), 2.51–2.57 (4 H, m, CH_2CH−O and $CH_2CH_2CO_2$), 3.01 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.49 (2 H, s, CH_2CO_2), 3.61 and 3.65 (each 3 H, s, OMe), 5.07–5.11 (2 H, m, CH=CH_2), 5.15 (1 H, t, *J* 7, CH−O), 5.61–5.72 (1 H, m, C*H*=CH_2) and 9.64 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.9 (ArMe), 21.2 (CH_2-CH_2CO_2), 22.6 (C*Me*), 29.3 (CH_2CO_2), 33.7 ($CH_2CH_2CO_2$), 36.5, 41.5 and 42.5 (CH_2CCH_2), 51.5 and 52.0 (2 × OMe), 78.5 (CH−O), 115.9, 124.7, 132.0 and 134.8 (4 × pyrrole-C), 120.0 (CH=CH_2), 135.1 (*C*H=CH_2) and 171.9, 173.7, 179.9 and 182.3 (4 × C=O); *m/z* (FD) 405 (M^+, 100%); *m/z* (EI) 405 (M^+), 374 (M − OMe) and 345 (M − $MeCO_2H$).

Also obtained was the corresponding *N*-acyl pyrrole (18%); λ_{max}(MeOH)/nm 245; δ_H(400 MHz, $CDCl_3$) 1.33 (3 H, s, Me), 2.18–2.49 (2 H, m, CH_2C=C), 2.41 (3 H, s, 5-Me), 2.53–2.64 (4 H, m, $CH_2CH_2CO_2$ and CH_2CH−O), 2.71 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.67 (6 H, s, 2 × OMe), 5.10–5.16 (2 H, m, CH=CH_2), 5.34 (1 H, t, *J* 8, CH−O), 5.63–5.81 (1 H, m, C*H*=CH_2) and 6.83 (1 H, s, 2-H); *m/z* (FD) 405 (M^+, 100%).

4-(2-Methoxycarbonylethyl)-3,5-dimethyl-2-(3,3-dimethyl-5-oxotetrahydrofuran-2-yl)formylpyrrole 49. The general procedure above using α-free pyrrole **40** and acid chloride **23** gave the *C*-acyl pyrrole **49** (90%), mp 136.5–137.5 °C [from ethyl acetate–light petroleum (bp 60–80 °C)] (Found: C, 63.7; H, 7.2; N, 4.2%; M^+, 321.1574. $C_{17}H_{23}NO_5$ requires C, 63.5; H, 7.2; N, 4.35%; *M*, 321.1576); λ_{max}(MeOH)/nm 316; ν_{max}($CHCl_3$)/cm^{-1} 3436, 1784, 1731 and 1614; δ_H(400 MHz, $CDCl_3$–CD_3OD) 0.81 and 1.14 (each 3 H, s, CMe_2), 2.05 and 2.11 (each 3 H, s, ArMe), 2.10 and 2.44 (each 1 H, d, *J* 17, CH_2CMe_2), 2.23 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.51 (2 H, t, *J* 8, C$H_2CH_2CO_2$), 3.45 (3 H, s, OMe) and 5.06 (1 H, br s, CH−O); δ_C(100 MHz, $CDCl_3$) 10.4 and 11.2 (2 × ArMe), 18.7 ($CH_2CH_2CO_2$), 22.0 and 27.3 (CMe_2), 34.1 ($CH_2CH_2CO_2$), 40.2 and 41.4 (CH_2CMe_2), 50.9 (OMe), 85.5 (CH−O), 121.6, 126.9, 127.1 and 127.4 (4 × pyrrole-C) and 173.4, 177.5 and 182.6 (3 × C=O); *m/z* (FAB) 322 (MH^+); *m/z* (FD) 321 (M^+, 100%).

Also obtained was the isomeric *N*-acyl pyrrole (4%) (Found: M^+, 321.1553); λ_{max}(MeOH)/nm 249; ν_{max}($CHCl_3$)/cm^{-1} 1790 and 1713; δ_H(400 MHz, $CDCl_3$) 1.06 and 1.35 (each 3 H, s, CMe_2), 2.01 (3 H, d, *J* 1, 3-Me), 2.27 and 2.67 (each 1 H, d, *J* 17, CH_2CMe_2), 2.41 (3 H, s, 5-Me), 2.41 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.67 (2 H, t, *J* 8, C$H_2CH_2CO_2$), 3.66 (3 H, s, OMe), 5.14 (1 H, s, CH−O) and 6.67 (1 H, s, 2-H); δ_C(100 MHz, $CDCl_3$) 10.4 and 13.3 (2 × ArMe), 19.4 ($CH_2CH_2CO_2$), 23.0 and 28.5 (CMe_2), 34.3 ($CH_2CH_2CO_2$), 40.7 and 41.3 (CH_2CMe_2), 51.7 (OMe), 83.5 (CH−O), 115.1, 123.8, 125.0 and 129.6 (4 × pyrrole-C) and 167.4, 173.1 and 175.5 (3 × C=O); *m/z* (FD) 321 (M^+, 100%); *m/z* (EI) 321 (M^+), 290 (M − OMe) and 248 (M − CH_2CO_2Me).

2-[(2*S*,4*S*)-4-Allyl-4-methyl-5-oxotetrahydrofuran-2-yl]formyl-4-(2-methoxycarbonylethyl)-3-methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)pyrrole 47

A mixture of carboxylic acid **43**[11] (375 mg, 1.15 mmol), sodium hydrogen carbonate (217 mg, 2.58 mmol), dichloromethane (15 cm^3) and water (15 cm^3) was vigorously stirred and an aqueous solution (12.2 cm^3) containing iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added quickly. After 10 min 10% aqueous sodium thiosulfate was added dropwise until the brown colour disappeared. The organic layer was separated, washed with water, dried and evaporated under reduced pressure. A solution of the residual oil in diethyl ether (10 cm^3) was passed through a short column of alumina, which was then eluted with further diethyl ether (20 cm^3). The combined ethereal solutions were evaporated under reduced pressure to give the iodopyrrole **44** (312 mg, 66%) as an oil; δ_H(400 MHz, $CDCl_3$) 0.76 and 1.23 (each 3 H, s, CMe_2), 1.93 (3 H, s, 3-Me), 2.45 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.77 (2 H, t, *J* 8, C$H_2CH_2CO_2$), 3.60 and 3.68 (each 2 H, d, *J* 11, 2 × OCH_2), 3.65 (3 H, s, OMe), 5.44 (1 H, s, O−CH−O) and 8.27 (1 H, br s, NH); *m/z* (FD) 407 (M^+, 100%).

A suspension of platinum oxide (40 mg) in dichloromethane (8 cm^3) was stirred under an atmosphere of hydrogen for 2 h and then a solution of the iodopyrrole **44** (340 mg, 0.84 mmol) and triethylamine (175 mm^3, 0.92 mmol) in dichloromethane (12 cm^3) was added. The mixture was stirred under the atmosphere of hydrogen for 4 h at room temperature and then filtered through Celite. The filtrate was washed with water (10 cm^3), dried and evaporated under reduced pressure to give the unstable α-free pyrrole **45** (220 mg, 94%) as an oil; δ_H(400 MHz, $CDCl_3$) 0.76 and 1.23 (each 3 H, s, CMe_2), 2.00 (3 H, s, 3-Me), 2.48 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.77 (2 H, t, *J* 8, C$H_2CH_2CO_2$), 3.62 and 3.69 (each 2 H, d, *J* 11, 2 × OCH_2), 3.66 (3 H, s, OMe), 5.47 (1 H, s, O−CH−O), 6.45 (1 H, s, 2-H) and 8.19 (1 H, br s, NH); *m/z* (FD) 281 (M^+, 100%).

Method A. A solution of methylmagnesium iodide in diethyl ether (1 mol dm^{-3}; 254 μl, 0.254 mmol) was added dropwise to a stirred solution of the α-free pyrrole **45** (65 mg, 0.231 mmol) in dry tetrahydrofuran (10 cm^3) under argon at −15 °C. After a further 10 min a solution of acid chloride **27** (47 mg, 0.231 mmol) in dry tetrahydrofuran (4 cm^3) was added, followed after a further 45 min by water (10 cm^3). The mixture was warmed to room temperature and extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried and evaporated under reduced pressure. Purification by PLC, eluting with hexane–diethyl ether, gave the C-*acylpyrrole* **47** (19 mg, 17%) as an oil (Found: M^+, 447.2267. $C_{24}H_{33}NO_7$ requires *M*, 447.2257); λ_{max}(MeOH)/nm 302; δ_H(400 MHz, $CDCl_3$) 0.78, 1.24 and 1.31 (each 3 H, s, Me), 2.20–2.37 (6 H, m, 3-Me, CH_2C=C and C$H_A$$H_B$CH−O), 2.45–2.57 (3 H, m, CH_AH_BCH−O and CH_2-CH_2CO_2), 2.79 (2 H, t, *J* 8, C$H_2CH_2CO_2$), 3.62 and 3.74 (each 2 H, d, *J* 11, 2 × OCH_2), 3.65 (3 H, s, OMe), 5.07–5.13 (2 H, m, CH=CH_2), 5.24 (1 H, t, *J* 8, CH−O), 5.52 (1 H, s, O−CH−O), 5.64–5.74 (1 H, m, C*H*=CH_2) and 9.62 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.13 (3-Me), 18.93 (CH_2CH_2CO), 21.79, 22.87 and 22.92 (3 × Me), 30.29 (CH_2CH_2CO), 34.79 (CMe_2), 36.25, 41.58 and 42.53 (CH_2CCH_2), 51.58 (OMe), 77.20 (CH−O), 77.43 (2 × CH_2O), 95.20 (O−CH−O), 119.84 (CH=CH_2), 121.66, 124.02, 125.45 and 132.65 (pyrrole-C), 132.24 (*C*H=CH_2) and 173.44, 179.83 and 184.02 (C=O); *m/z* (FD) 447 (M^+, 100%).

Also obtained was the isomeric *N*-acyl pyrrole (39 mg, 38%) as an oil (Found: M^+, 447.2287); λ_{max}(MeOH)/nm 257 and 298; ν_{max}($CHCl_3$)/cm^{-1} 1785, 1732 and 1642; δ_H(400 MHz, $CDCl_3$) 0.74, 1.26 and 1.30 (each 3 H, s, Me), 1.97 (3 H, s, 3-Me), 2.20 (1 H, dd, *J* 14 and 8, C$H_A$$H_B$CH−O), 2.31 (1 H, dd, *J* 7 and 14) and 2.38 (1 H, dd, *J* 8 and 14, CH_2C=C), 2.52–2.60 (3 H, m, CH_AH_BCH−O and CH_2CH_2CO), 2.98–3.04 (2 H, m, CH_2CH_2CO), 3.60–3.70 (7 H, m, 2 × OCH_2 and OMe), 5.09–5.17 (2 H, m, CH=CH_2), 5.33 (1 H, t, *J* 8, CH_2CH−O), 5.66–5.74 (1 H, m, C*H*=CH_2), 5.52 (1 H, s, O−CH−O) and 6.62 (1 H, s, 2-H); δ_C(100 MHz, $CDCl_3$) 9.95 (3-Me), 20.39 (CH_2CH_2CO), 21.96, 23.24 and 23.31 (3 × Me), 30.26 (CH_2CH_2CO), 34.89 (CMe_2), 36.65, 41.64 and 42.69 (CH_2CCH_2), 51.54 (OMe), 73.35 (CH−O), 78.07 and 78.14 (each CH_2O), 97.50 (O−CH−O), 120.09 (CH=CH_2), 117.27, 124.28, 128.73 and 129.65 (pyrrole-C), 132.15 (*C*H=CH_2) and 166.00, 173.70 and 179.38 (C=O); *m/z* (FD) 447 (M^+, 100%).

Method B. A solution of methylmagnesium iodide in diethyl ether (1 mol dm^{-3}; 0.833 cm^3, 0.833 mmol) was added to a stirred solution of the α-free pyrrole **45** (234 mg, 0.833 mmol) in dry tetrahydrofuran (5 cm^3) at −40 °C under argon. The temperature was increased to −20 °C over 10 min and then cooled to −78 °C. A solution of thioester **29** (230 mg, 0.833 mmol) in dry tetrahydrofuran (2.5 cm^3) was added dropwise using a double-ended needle. The mixture was stirred for 30 min, then quenched with water (5 cm^3) and warmed to room temperature,

diluted with more water (40 cm^3) and extracted with diethyl ether (50 cm^3 then 2 × 20 cm^3). The combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with hexane–diethyl ether, to give the *C*-acyl pyrrole **47** (110 mg, 30%) and the *N*-acyl pyrrole (35 mg, 9%).

5-Acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-2-(5-oxotetrahydrofuran-2-yl)formylpyrrole 53

A solution of ketone **34** (19 mg, 54 μmol) in acetic acid (1.5 cm^3) was stirred with lead tetraacetate (26 mg, 59 μmol) for 24 h. A further portion of lead tetraacetate (13 mg, 30 μmol) was added, followed after a further 4 h by water (3 cm^3). The mixture was adjusted to pH 6 with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (4 × 5 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with dichloromethane–methanol (9:1), to give the *acetoxymethylpyrrole* **53** (13.2 mg, 59%) as an oil (Found: M^+, 409.1353. $C_{19}H_{23}NO_9$ requires *M*, 409.1373); λ_{max}(MeOH)/nm 261 and 302; ν_{max}($CHCl_3$)/cm^{-1} 3434, 1790, 1736 and 1645; δ_H(400 MHz, $CDCl_3$) 2.08 (3 H, s, Ac), 2.54–2.61 (6 H, m, $CH_2CH_2CO_2$ and CH_2CH_2CH–O), 3.02 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.56 (2 H, s, CH_2CO_2), 3.64 and 3.67 (each 3 H, s, OMe), 5.07 (2 H, s, CH_2O), 5.29 (1 H, br s, CH–O) and 9.95 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.8 and 20.9 (CH_3CO and $CH_2CH_2CO_2$), 24.6 and 27.0 (CH_2CH_2CH–O), 29.1 (CH_2CO_2), 33.8 ($CH_2CH_2CO_2$), 51.6 and 52.2 (2 × OMe), 57.0 (OCH_2), 80.8 (CH–O), 117.6, 125.9, 131.5 and 133.6 (4 × pyrrole-C) and 171.4, 171.6, 173.5, 175.6 and 183.7 (5 × C=O).

5-Formyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-2-(5-oxotetrahydrofuran-2-yl)formylpyrrole 54

A solution of the methyl pyrrole **34** (24 mg, 68 μmol) in dry dichloromethane (1 cm^3) was cooled to −5 °C. A solution of freshly distilled sulfuryl chloride (11 mm^3, 138 μmol) in dry dichloromethane (0.5 cm^3) was added over 3 min. The solution was stirred for a further 10 min and then evaporated under reduced pressure. The residual oil was stirred with acetone (2 cm^3) and water (4 cm^3) for 30 min, then the acetone was evaporated and the remaining aqueous liquor was extracted with dichloromethane (3 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with dichloromethane–methanol (19:1), to give the *aldehyde* **54** (19.2 mg, 77%) as an oil (Found: M^+, 365.1115. $C_{17}H_{19}NO_8$ requires *M*, 365.1111); λ_{max}(MeOH)/nm 246 and 304; ν_{max}($CHCl_3$)/cm^{-1} 3416, 1793, 1737 and 1662; δ_H(400 MHz, $CDCl_3$) 2.56–2.65 (6 H, m, CH_2CH_2CH–O and $CH_2CH_2CO_2$), 3.04 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.63 and 3.71 (each 3 H, s, OMe), 3.66 (2 H, s, CH_2CO_2), 5.41 (1 H, t, *J* 6, CH–O), 9.82 (1 H, s, CHO) and 10.34 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.2 ($CH_2CH_2CO_2$), 24.0 and 26.7 (CH_2CH_2CH–O), 28.9 (CH_2CO_2), 33.6 ($CH_2CH_2CO_2$), 51.7 and 52.5 (2 × OMe), 80.4 (CH–O), 125.0, 128.9, 131.6 and 133.5 (4 × pyrrole-C) and 171.0, 173.3, 175.3, 180.2 and 185.8 (5 × C=O); *m/z* (EI) 365 (M^+), 337 (M − CO) and 306 (M − CO_2Me).

4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-5-(5-oxotetrahydrofuran-2-yl)formylpyrrole-2-carboxylic acid 55

A solution of the aldehyde **54** (19.2 mg, 53 μmol) in acetone was stirred with an aliquot (0.8 cm^3, 107 μmol) of a solution of potassium permanganate (0.474 g) in water (13 cm^3) and acetone (9.5 cm^3) for 3 h. Dichloromethane (10 cm^3), water (10 cm^3) and sodium metabisulfite (100 mg) were added followed by concentrated hydrochloric acid until both layers were colourless. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 cm^3). The combined organic layers were washed with brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was dissolved in diethyl ether (5 cm^3) and extracted with saturated aqueous sodium hydrogen carbonate (5 cm^3). The aqueous layer was washed with diethyl ether (5 cm^3), then acidified to pH 2 with concentrated hydrochloric acid and extracted with dichloromethane (3 × 10 cm^3). These organic extracts were combined, washed with brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the *acid* **55** (11.4 mg, 57%) as a foam (Found: M^+, 381.1050. $C_{17}H_{19}NO_9$ requires *M*, 381.1060); λ_{max}(MeOH)/nm 231 and 302; ν_{max}($CHCl_3$)/cm^{-1} 3431, 1792, 1734 and 1663; δ_H(400 MHz, $CDCl_3$) 2.54–2.59 (6 H, m, CH_2CH_2CH–O and $CH_2CH_2CO_2$), 3.01 (2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.64 and 3.70 (each 3 H, s, OMe), 3.90 (2 H, s, CH_2CO_2), 5.45 (1 H, t, *J* 5, CH–O), 5.57 (1 H, br s, OH) and 10.40 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.5 ($CH_2CH_2CO_2$), 24.4 and 27.0 (CH_2CH_2CH–O), 29.7 (CH_2CO_2), 33.7 ($CH_2CH_2CO_2$), 51.7 and 52.3 (2 × OMe), 80.5 (CH–O), 123.8, 124.2, 127.8 and 133.7 (4 × pyrrole-C) and 163.0, 172.1, 173.6, 176.0 and 185.5 (5 × C=O); *m/z* (FD) 381 (M^+, 100%); *m/z* (EI) 381 (M^+), 349 (M − MeOH) and 337 (M − CO_2).

3-(2-Methoxycarbonylethyl)-4-methyl-5-(3,3-dimethyl-5-oxotetrahydrofuran-2-yl)formylpyrrole-2-carboxylic acid 51

A solution of the methylpyrrole **49** (2.61 g, 8.13 mmol) in dry dichloromethane (80 cm^3) at 0 °C was treated with a solution of freshly distilled sulfuryl chloride (1.37 cm^3, 16.2 mmol) in dry dichloromethane (15 cm^3) over 5 min, then stirred for 2.5 h and evaporated under reduced pressure. The residual oil was stirred with water (100 cm^3) and acetone (50 cm^3) for 10 min, then some of the acetone (*ca.* 30 cm^3) was evaporated under reduced pressure. The remaining solution was extracted with dichloromethane (3 × 100 cm^3). The combined extracts were washed with brine (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude aldehyde **50** as an oil; δ_H(400 MHz, $CDCl_3$) 1.02 and 1.42 (each 3 H, s, CMe_2), 2.35 (3 H, s, ArMe), 2.40 and 2.52 (each 1 H, d, *J* 17, CH_2CMe_2), 2.57 (2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.07 (2 H, m, $CH_2CH_2CO_2$), 3.64 (3 H, s, OMe), 5.05 (1 H, s, CH–O), 9.89 (1 H, s, CHO) and 10.10 (1 H, br s, NH); *m/z* (FD) 335 (M^+, 100%); *m/z* (EI) 335 (M^+), 306 (M − CHO), 304 (M − OMe) and 276 (M − CO_2Me).

The above aldehyde **50** was dissolved in acetone (120 cm^3) and an aliquot (120 cm^3, 16 mmol) of a solution of potassium permanganate (2.844 g) in water (78 cm^3) and acetone (57 cm^3) was added over 10 min. The resultant solution was stirred for 8 h and the acetone was then evaporated under reduced pressure. Water (100 cm^3), dichloromethane (200 cm^3) and sodium metabisulfite (10 g) were added, followed by concentrated hydrochloric acid until both layers were colourless. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were washed with brine (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual foam was dissolved in diethyl ether (100 cm^3) and extracted with saturated aqueous sodium hydrogen carbonate (100 cm^3). The aqueous layer was washed with diethyl ether (100 cm^3), then acidified to pH 2 with concentrated hydrochloric acid and extracted with dichloromethane (5 × 100 cm^3). These extracts were combined, washed with brine (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the *acid* **51** (2.16 g, 76%) as a foam. The ethereal layer was washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was oxidised again with potassium permanganate as described above to give more of the *acid* **51** (160 mg, 6%, total yield 82%) (Found: M^+, 351.1333. $C_{17}H_{21}NO_7$ requires *M*, 351.1318); λ_{max}(MeOH)/nm 230 and 306; ν_{max}($CHCl_3$)/cm^{-1} 3500–2500, 3436, 1790, 1730 and 1649; δ_H(400 MHz, $CDCl_3$) 1.00 and 1.39 (each 3 H, s, CMe_2), 2.32 (3 H, s, 4-Me), 2.39 and 2.52 (each 1 H, d, *J* 17, CH_2CMe_2), 2.55 (2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.05 (2 H, t, *J* 7, $CH_2CH_2CO_2$), 3.64 (3 H, s, OMe), 5.15 (1 H, s, CH–O), 8.06 (1 H, br s, OH) and 10.33 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.1 (4-Me), 19.6 ($CH_2CH_2CO_2$), 22.5 and 27.2

(CMe_2), 34.3 ($CH_2CH_2CO_2$), 41.4 and 42.5 (CH_2CMe_2), 51.7 (OMe), 87.6 (CH–O), 122.9, 128.9, 129.6 and 131.4 (4 × pyrrole-C) and 164.3, 173.6, 175.3 and 186.5 (4 × C=O); *m/z* (FD) 351 (M^+, 100%); *m/z* (EI) 351 (M^+), 335 (M − O) and 320 (M − OMe).

***tert*-Butyl 3-(2-methoxycarbonylethyl)-4-methyl-5-(3,3-dimethyl-5-oxotetrahydrofuran-2-yl)formylpyrrole-2-carboxylate 52**

A solution of acid **51** (2.56 g, 7.3 mmol) in dry dichloromethane (30 cm^3) and dry *tert*-butyl alcohol (30 cm^3) was stirred with a solution of *N*,*N*′-dicyclohexylcarbodiimide (1.95 g, 9.5 mmol) in dry *tert*-butyl alcohol (20 cm^3) for 12 h, then filtered through Celite and evaporated under reduced pressure. The residual oil was purified by column chromatography, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:2), to give the *tert*-*butyl ester* **52** (2.14 g, 72%) as a foam (Found: M^+, 407.1914. $C_{21}H_{29}NO_7$ requires *M*, 407.1944); λ_{max}(EtOAc)/nm 306; ν_{max}($CHCl_3$)/cm^{-1} 3440, 1791, 1733 and 1646; δ_H(400 MHz, $CDCl_3$) 1.01 and 1.40 (each 3 H, s, CMe_2), 1.57 (9 H, s, Bu^t), 2.33 (3 H, s, 4-Me), 2.37 and 2.52 (each 1 H, d, *J* 17, CH_2CMe_2), 2.51 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.01 (2 H, m, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe), 5.04 (1 H, s, CH–O) and 10.00 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.3 (4-Me), 19.8 ($CH_2CH_2CO_2$), 22.6 and 27.3 (CMe_2), 28.2 (CMe_3), 34.6 ($CH_2CH_2CO_2$), 41.4 and 42.6 (CH_2CMe_2), 51.5 (OMe), 82.6 (CMe_3), 87.6 (CH–O), 125.1, 128.4, 128.7 and 128.9 (4 × pyrrole-C) and 159.4, 173.2, 174.6 and 185.9 (4 × C=O).

Benzyl 5-[hydroxy(5-oxotetrahydrofuran-2-yl)methyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate 56

The ketone **31** (312 mg, 0.66 mmol) was dissolved in methanol (5 cm^3) and cooled to 0 °C. Sodium borohydride (26 mg, 0.69 mmol) was added portionwise over 5 min and the solution was stirred for a further 10 min. Hydrochloric acid (0.1 mol dm^{-3}; 10 cm^3) was added and the mixture was extracted with dichloromethane (20 cm^3 then 2 × 15 cm^3). The combined extracts were washed with brine (15 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give an oil (306 mg, 98%), which was used in the next reaction without further purification. For characterisation the oil was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:1), to give a mixture of the diastereoisomeric *alcohols* **56** as an oil (*ca.* 90%) (Found: $M^+ - H_2O$, 455.1615. $C_{24}H_{27}NO_9$ requires $M - H_2O$, 455.1580); λ_{max}(MeOH)/nm 274; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1780, 1730 and 1710; δ_H(400 MHz, $CDCl_3$) 2.06–2.21 (2 H, m), 2.25–2.31 (2 H, m) and 2.39–2.68 (8 H, m, CH_2CH_2CH–O and $CH_2CH_2CO_2$), 2.94–2.98 (4 H, t, *J* 8, $CH_2CH_2CO_2$), 3.45–3.69 (4 H, m, CH_2CO_2), 3.58 and 3.67 (each 6 H, s, OMe), 3.78 and 3.97 (each 1 H, br s, OH), 4.77 (2 H, m, CH_2CH–O), 5.07 (1 H, d, *J* 3, CHOH), 5.23–5.30 (5 H, m, CHOH and $PhCH_2$), 7.24–7.42 (10 H, m, Ph) and 9.44 and 9.64 (each 1 H, br s, NH); *m/z* (FD) 473 (M^+, 100%); *m/z* (EI) 473 (M^+) and 455 (M − H_2O).

Benzyl 5-[acetoxy(5-oxotetrahydrofuran-2-yl)methyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate 57

A solution of the crude alcohols **56** (306 mg, 0.65 mmol) in dry dichloromethane (15 cm^3) was stirred with 4-dimethylaminopyridine (153 mg, 1.25 mmol) and acetic anhydride (0.1 cm^3, 1.1 mmol) for 15 min, then diluted with dichloromethane (20 cm^3) and washed with water (15 cm^3). The aqueous phase was extracted with dichloromethane (3 × 20 cm^3) and the combined organic layers were washed with brine (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:1), to give a 1:1 mixture of the diastereoisomeric *acetates* **57** (280 mg, 82% from ketone **31**). For characterisation the diastereoisomers were separated by PLC, developing two times with ethyl acetate–light petroleum (bp 60–80 °C) (2:1).

Higher R_F diastereoisomer (Found: $M^+ - MeCO_2H$, 455.1600. $C_{26}H_{29}NO_{10}$ requires $M - MeCO_2H$, 455.1580); λ_{max}($CHCl_3$)/nm 269; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1785, 1735 and 1710; δ_H(400 MHz, $CDCl_3$) 2.07 (3 H, s, Ac), 2.28–2.62 (6 H, m, CH_2CH_2CH–O and $CH_2CH_2CO_2$), 2.90–3.02 (2 H, m, $CH_2CH_2CO_2$), 3.56 and 3.66 (each 1 H, d, *J* 16, CH_2CO_2), 3.60 and 3.66 (each 3 H, s, OMe), 4.88 (1 H, m, CH_2CH–O), 5.29 and 5.32 (each 1 H, d, *J* 12, $PhCH_2$), 5.89 (1 H, d, *J* 3, AcOCH), 7.30–7.43 (5 H, m, Ph) and 9.33 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.2 and 20.8 ($MeCO_2$ and $CH_2CH_2CO_2$), 24.0 and 27.9 (CH_2CH_2CH–O), 29.2 (CH_2CO_2), 34.6 ($CH_2CH_2CO_2$), 51.4 and 52.1 (2 × OMe), 66.2 ($PhCH_2$), 67.7 (AcOCH), 79.9 (CH_2CH–O), 117.0, 119.8 and 129.3 (3 × pyrrole-C), 128.2, 128.3, 128.6 and 128.7 (5 × phenyl-CH and pyrrole-C), 135.7 (phenyl-C) and 160.3, 169.7, 172.3, 173.4 and 175.9 (5 × C=O); *m/z* (FD) 515 (M^+, 100%).

Lower R_F diastereoisomer (Found: $M^+ - MeCO_2H$, 455.1576); λ_{max}($CHCl_3$)/nm 269; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1790, 1740 and 1710; δ_H(400 MHz, $CDCl_3$) 2.10 (3 H, s, Ac), 1.97–2.07 (1 H, m), 2.25–2.32 (2 H, m) and 2.43–2.53 (3 H, m, CH_2CH_2CH–O and $CH_2CH_2CO_2$), 2.95–2.99 (2 H, m, $CH_2CH_2CO_2$), 3.56 and 3.62 (each 1 H, d, *J* 16, CH_2CO_2), 3.60 and 3.66 (each 3 H, s, OMe), 4.87 (1 H, m, CH_2CH–O), 5.29 (2 H, s, $PhCH_2$), 5.97 (1 H, d, *J* 3, AcOCH), 7.33–7.42 (5 H, m, Ph) and 9.13 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.2 and 20.8 ($MeCO_2$ and $CH_2CH_2CO_2$), 23.5 and 27.6 (CH_2CH_2-CH–O), 29.4 (CH_2CO_2), 34.5 ($CH_2CH_2CO_2$), 51.4 and 52.1 (2 × OMe), 66.3 ($PhCH_2$), 67.8 (AcOCH), 80.0 (CH_2CH–O), 117.6, 120.2, 126.5 and 129.6 (4 × pyrrole-C), 128.3, 128.4 and 128.6 (5 × phenyl-CH), 135.7 (phenyl-C) and 160.2, 169.5, 171.9, 173.4 and 175.9 (5 × C=O); *m/z* (FD) 515 (M^+, 100%).

Benzyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(5-oxotetrahydrofuran-2-ylidene)methylpyrrole-2-carboxylate 58

The lower R_F acetate **57** (45 mg, 87 μmol) was heated at 200 °C for 15 min, then cooled under argon and finally under high vacuum. The residual oil was purified by PLC, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (2:1), to give the (E)-*alkene* **58** (4.3 mg, 11%) and the (Z)-*alkene* (23 mg, 58%) as oils.

(*Z*)-Alkene (lower R_F) (Found: M^+, 455.1585. $C_{24}H_{25}NO_8$ requires *M*, 455.1580); λ_{max}(EtOAc)/nm 251, 271, 309 and 322; ν_{max}(CH_2Cl_2)/cm^{-1} 3456, 1819, 1785, 1735 and 1693; δ_H(400 MHz, $CDCl_3$) 2.54 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.73 (2 H, t, *J* 9, C=CCH$_2$CH$_2$), 3.00–3.07 (4 H, m, $CH_2CH_2CO_2$ and C=CCH_2-CH_2), 3.49 (2 H, s, CH_2CO_2), 3.61 and 3.65 (each 3 H, s, OMe), 5.31 (2 H, s, $PhCH_2$), 5.59 (1 H, t, *J* 1, CH=C), 7.31–7.43 (5 H, m, Ph) and 9.60 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.3 ($CH_2CH_2CO_2$), 25.8 and 26.8 (CH_2CH_2C=C), 29.6 (CH_2CO_2), 34.6 ($CH_2CH_2CO_2$), 51.4 and 52.1 (2 × OMe), 65.8 ($PhCH_2$), 93.6 (CH=C–O), 115.1, 119.7 and 130.1 (3 × pyrrole-C), 128.1, 128.2 and 128.6 (5 × phenyl-CH and pyrrole-C), 136.1 (phenyl-C), 147.9 (CH=*C*–O) and 160.1, 171.9, 173.2 and 173.6 (4 × C=O); *m/z* (EI) 455 (M^+).

(*E*)-Isomer (higher R_F) (Found: M^+, 455.1585); λ_{max}(EtOAc)/nm 304; ν_{max}(CH_2Cl_2)/cm^{-1} 3460, 1806, 1735 and 1685; δ_H(400 MHz, $CDCl_3$) 2.52 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.78 (2 H, t, *J* 9, C=CCH$_2$CH$_2$), 2.99 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.11 (2 H, td, *J* 9 and 2, C=CCH_2CH$_2$), 3.46 (2 H, s, CH_2CO_2), 3.61 and 3.66 (each 3 H, s, OMe), 5.30 (2 H, s, $PhCH_2$), 6.17 (1 H, t, *J* 2, CH=C), 7.33–7.38 (5 H, m, Ph) and 8.61 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.5 ($CH_2CH_2CO_2$), 24.8 and 27.3 (CH_2CH_2C=C), 29.6 (CH_2CO_2), 34.6 ($CH_2CH_2CO_2$), 51.5 and 52.1 (2 × OMe), 66.3 ($PhCH_2$), 95.8 (CH=C–O), 117.2, 119.1, 120.6 and 130.7 (4 × pyrrole-C), 128.2, 128.3 and 128.6 (5 × phenyl-CH), 135.8 (phenyl-C), 151.5 (CH=*C*–O) and 160.6, 171.7, 173.4 and 173.4 (4 × C=O); *m/z* (EI) 455 (M^+).

9-Benzyloxycarbonyl-8-(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-2,3-dihydrodipyrrin-1(10*H*)-one 61

A solution of (*E*)-lactone **58** (16.8 mg, 37 μmol) in tetrahydrofuran (1 cm^3) at 0 °C was treated dropwise with concentrated aqueous ammonia (1 cm^3), stirred for 15 min and then evaporated under reduced pressure. Water (10 cm^3) was added and the mixture was extracted with dichloromethane (3 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the residual oil and one crystal of toluene-*p*-sulfonic acid in dry toluene (1 cm^3) was stirred for 15 min and then mixed with water (5 cm^3) and saturated aqueous sodium hydrogen carbonate (5 cm^3) and extracted with dichloromethane (2 × 10 cm^3). The combined extracts were washed with brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by PLC, eluting with dichloromethane–methanol (19:1), to give the (E)-*lactam* **61** (4.3 mg, 26%), the (Z)-*lactam* (5.1 mg, 30 %) and the amide **59** (5.1 mg, 29%).

(*Z*)-Lactam (higher R_F) (Found: M^+, 454.1750. $C_{24}H_{26}N_2O_7$ requires *M*, 454.1740); λ_{max}(MeOH)/nm 229 and 304; ν_{max}(CH_2Cl_2)/cm^{-1} 3689, 3435, 1735 and 1682; δ_H(400 MHz, $CDCl_3$) 2.46–2.54 (4 H, m, $CH_2CH_2CO_2$ and CH_2CONH), 2.86 (2 H, t, *J* 7, CH_2CH_2CONH), 2.95 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.43 (2 H, s, CH_2CO_2), 3.61 and 3.72 (each 3 H, s, OMe), 5.20 (1 H, s, C*H*=C), 5.27 (2 H, s, PhCH_2), 7.32–7.37 (5 H, m, Ph) and 8.68 and 8.73 (each 1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.7 ($CH_2CH_2CO_2$), 26.2 and 30.1 (CH_2CH_2CONH), 29.2 (CH_2CO_2), 34.5 ($CH_2CH_2CO_2$), 51.4 and 52.4 (2 × OMe), 66.1 (PhCH_2), 89.6 (*C*H=C–N), 115.4, 118.5, 130.2 and 130.7 (4 × pyrrole-C), 128.3, 128.4 and 128.6 (5 × phenyl-CH), 135.9 (phenyl-C), 142.2 (CH=*C*–N) and 160.6, 173.2, 173.5 and 178.2 (4 × C=O); *m/z* (FD) 454 (M^+, 100%).

(*E*)-Lactam (lower R_F) (Found: M^+, 454.1769); λ_{max}(MeOH)/nm 230 and 321; ν_{max}($CHCl_3$)/cm^{-1} 3418, 1732 and 1682; δ_H(400 MHz, $CDCl_3$) 2.52 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.62 (2 H, t, *J* 8, CH_2CONH), 2.90–3.05 (4 H, m, $CH_2CH_2CO_2$ and CH_2CH_2CONH), 3.45 (2 H, s, CH_2CO_2), 3.60 and 3.65 (each 3 H, s, OMe), 5.30 (2 H, s, PhCH_2), 5.73 (1 H, s, C*H*=C), 7.32–7.40 (5 H, m, Ph) and 7.60 and 8.60 (each 1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 20.5 ($CH_2CH_2CO_2$), 24.7, 29.4 and 29.7 (CH_2CH_2CONH and CH_2CO_2), 34.7 ($CH_2CH_2CO_2$), 51.4 and 52.1 (2 × OMe), 66.1 (PhCH_2), 92.0 (*C*H=C–N), 115.7 and 116.2 (2 × pyrrole-C), 128.2, 128.6, 130.7 and 131.0 (5 × phenyl-CH and 2 × pyrrole-C), 136.0 (phenyl-C), 140.3 (CH=*C*–N) and 160.7, 172.0, 173.5 and 176.7 (4 × C=O); *m/z* (FD) 454 (M^+, 100%).

***tert*-Butyl 5-[acetoxy(3,3-dimethyl-5-oxotetrahydrofuran-2-yl)methyl]-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate 62**

A solution of *tert*-butyl ester **52** (2.43 g, 5.97 mmol) in methanol (25 cm^3) at 0 °C was treated with sodium borohydride (240 mg, 6.24 mmol) portionwise over 12 min, stirred for 15 min, then diluted with water (100 cm^3) and hydrochloric acid (1 mol dm^{-3}; 10 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined extracts were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a mixture of the diastereomeric *alcohols* (*ca.* 100%) as a foam; λ_{max}(MeOH)/nm 276; ν_{max}(CH_2Cl_2)/cm^{-1} 1785, 1736 and 1683; δ_H(400 MHz, $CDCl_3$) 1.17 and 1.27 (each 3 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 2.00 (3 H, s, 4-Me), 2.30 and 2.40 (each 1 H, d, *J* 17, CH_2CMe_2), 2.50 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.96 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe), 4.24 (1 H, d, *J* 7, CMe_2-C*H*–O), 4.93 (1 H, d, *J* 7, C*H*OH) and 8.97 (1 H, br s, NH); *m/z* (FD) 409 (M^+, 100%).

A solution of the above alcohols in dry dichloromethane (50 cm^3) was treated with 4-dimethylaminopyridine (1.42 g, 11.52 mmol) followed by acetic anhydride (3.1 cm^3, 53 mmol), stirred for 15 min, then diluted with water (50 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by column chromatography, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (2:3), to give a mixture of the diastereoisomeric *acetates* **62** (2.49 g, 92%) as a foam (Found: $M^+ - CH_3CO_2H$, 391.1989. $C_{23}H_{33}NO_8$ requires $M - CH_3CO_2H$, 391.1995); λ_{max}(MeOH)/nm 272; ν_{max}($CHCl_3$)/cm^{-1} 3431, 1789, 1736 and 1685; δ_H(400 MHz, $CDCl_3$) 0.99 and 1.27 (each 3 H, s, CMe_2), 1.54 (9 H, s, Bu^t), 2.04 and 2.07 (each 3 H, s, 4-Me and Ac), 2.10 and 2.34 (each 1 H, d, *J* 17, CH_2CMe_2), 2.48 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.93 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.63 (3 H, s, OMe), 4.44 (1 H, d, *J* 6, Me_2CCH–O), 5.93 (1 H, d, *J* 6, AcOC*H*) and 8.93 (1 H, br s, NH); *m/z* (FD) 451 (M^+, 100%).

***tert*-Butyl (*Z*)-3-(2-methoxycarbonylethyl)-4-methyl-5-(3,3-dimethyl-5-oxotetrahydrofuran-2-ylidene)methylpyrrole-2-carboxylate 63**

The acetates **62** (2.08 g, 4.61 mmol) were heated at 200 °C for 15 min under a stream of argon, then allowed to cool under argon and dried under high vacuum to give (Z)-*alkene* **63** (*ca.* 1.80 g, 100%), essentially pure by NMR spectroscopy (Found: M^+, 391.2008. $C_{21}H_{29}NO_6$ requires *M*, 391.1995); λ_{max}(EtOAc)/nm 309; ν_{max}(CH_2Cl_2)/cm^{-1} 3465, 1811, 1733 and 1684; δ_H(400 MHz, $CDCl_3$) 1.38 (6 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 2.01 (3 H, s, 4-Me), 2.51 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.58 (2 H, s, CH_2CMe_2), 2.99 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe), 5.48 (1 H, s, CH=C) and 9.41 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 8.7 (4-Me), 20.5 ($CH_2CH_2CO_2$), 28.0 (CMe_2), 28.4 (CMe_3), 34.9 ($CH_2CH_2CO_2$), 39.6 and 42.3 (CH_2CMe_2), 51.4 (OMe), 80.7 (CMe_3), 91.1 (*C*H=C–O), 118.3, 120.1, 126.3 and 128.3 (4 × pyrrole-C), 156.5 (CH=*C*–O) and 160.3, 171.6 and 173.7 (3 × C=O).

(*Z*)-9-*tert*-Butoxycarbonyl-8-(2-methoxycarbonylethyl)-3,3,7-trimethyl-2,3-dihydrodipyrrin-1(10*H*)-one 64

A solution of the lactone **63** prepared above (1.80 g, 4.6 mmol) in tetrahydrofuran (25 cm^3) at 0 °C was treated with concentrated aqueous ammonia (25 cm^3) dropwise over 1 min and stirred for 1 h. The tetrahydrofuran was evaporated under reduced pressure and the residual aqueous liquor was diluted with water (10 cm^3) and brine (50 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. A solution of the residual oil in dry dichloromethane (50 cm^3) was stirred with toluene-*p*-sulfonic acid (75 mg, 0.44 mmol) for 10 min, then diluted with water (100 cm^3) and saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined extracts were washed with brine (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:2), to give the (Z)-*lactam* **64** (1.17 g, 65% from **62**) as a solid, mp 124–125 °C (from diethyl ether–hexane) (Found: C, 64.7; H, 7.8; N, 7.3%; M^+, 390.2161. $C_{21}H_{30}N_2O_5$ requires C, 64.6; H, 7.75; N, 7.2%; *M*, 390.2155); λ_{max}(MeOH)/nm 226 and 303; [+ $Zn(OAc)_2$] 281 and 354; ν_{max}(CH_2Cl_2)/cm^{-1} 3440, 1728 and 1681; δ_H(400 MHz, $CDCl_3$) 1.33 (6 H, s, CMe_2), 1.51 (9 H, s, Bu^t), 1.93 (3 H, s, 7-Me), 2.40 (2 H, s, 2-H_2), 2.49 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 2.96 (2 H, t, *J* 8, $CH_2CH_2CO_2$), 3.66 (3 H, s, OMe), 5.24 (1 H, s, 5-H) and 8.37 and 8.89 (each 1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 9.2 (7-Me), 20.9 ($CH_2CH_2CO_2$), 28.4 (CMe_3), 28.9 (CMe_2), 34.9 ($CH_2CH_2CO_2$), 39.1 and 45.0 (C-2 and C-3), 51.5 (OMe), 80.8 (CMe_3), 89.1 (C-5), 117.9, 119.9, 128.1 and 129.1 (4 × pyrrole-C), 149.2 (C-4) and 160.9, 173.7 and 176.1 (3 × C=O); *m/z* (FD) 390 (M^+, 100%).

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