Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 7.[1,2] Synthesis of (±)-Bonellin Dimethyl Ester

Alan R. Battersby,* Christopher J. Dutton, and Christopher J. R. Fookes
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

The dimethyl ester of the green marine pigment, bonellin, has been synthesized in racemic form by a rational photochemical route. The two propionate residues of this biologically active pigment have been introduced synthetically in differentiated form which opens the way to the synthesis of the naturally occurring amino acid derivatives of bonellin.

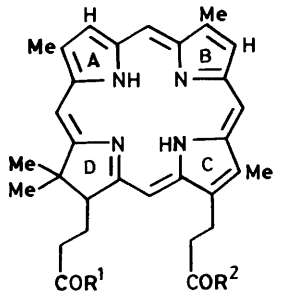
Bonellin (**1**) is the green pigment of a marine echurian worm, *Bonellia viridis*, which lives on the sea bottom of the Gulf of Pozzuoli near Naples. This pigment possesses remarkable biological properties. Initially, the larvae of *B. viridis* are sexually undifferentiated but on contact with bonellin they develop into males; the larvae which elude this contact grow into female worms.[3] In addition, bonellin has anti-tumour activity.[4] The structure of bonellin[5] (**1**) turned out to be novel in that it was the first representative of a new class, the *C*-methylated chlorins; the absolute configuration of bonellin is not known. The striking biological properties of bonellin and the inaccessibility of its natural source combined to make structure (**1**) an important target for synthesis.

We planned to use our general photochemical method which was described in the preceding paper.[1] Also described there were the syntheses of two model *C*-methylated chlorins (**5**) and (**6**) which are closely related to bonellin. Based on this experience, we planned to construct bonellin dimethyl ester (**2**) from the two building blocks (**7**) and (**8**). The synthesis of the eastern block (**8**) will be described first, see Scheme 1.

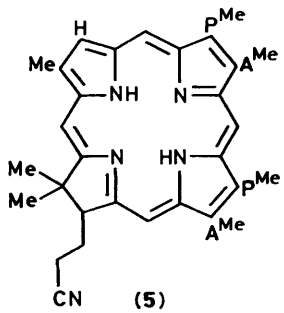
The Eastern Building Block.—Ring C of bonellin dimethyl ester (**2**) was planned to be derived from the pyrrolone (**12**). This is a known substance[6] but as the previous route to it used liquid hydrogen cyanide and high temperature–pressure hydrogenation, we sought an alternative. As described more fully in the preceding paper,[1] pyrrolones can be produced, albeit often as mixtures, by suitable oxidation of pyrroles. In order to avoid such mixtures, a study was made of the oxidation of the pyrrole[7] (**9**) with *m*-chloroperbenzoic acid. The product formed in high yield was not the expected pyrrolone (**10**) but its hydroxy derivative (**11**). This could be reduced with triethylsilane[8] in trifluoroacetic acid to yield directly the required product (**12**). Thus, removal of the t-butyl group and decarboxylation had also occurred as hoped under the acidic conditions.

The other component required was the aldehyde (**14**) which could be prepared by oxidation of the known pyrrole[9] (**13**) using lead tetra-acetate though initially the yield was low. Since it was found that the best yields were obtained with black lead tetra-acetate (white when pure), the effect of adding lead dioxide to the tetra-acetate was tested. This improved the yield which became optimum when 1.1 mol equiv. each of lead dioxide and tetra-acetate were used. These conditions have since been applied very successfully for the preparation of other aldehydes from methylpyrroles.

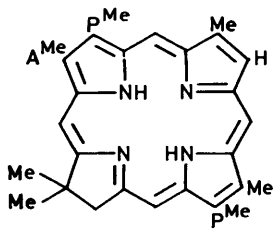
Condensation of the foregoing components (**12**) and (**14**) was best achieved in aqueous methanolic potassium hydroxide. The fact that the propionate ester was hydrolysed under these conditions turned out to be an advantage since the potassium salt of the acid corresponding to ester (**15**) precipitated in high yield. Re-esterification of the side-chain using diazomethane afforded *ca.* 90% of the desired bicyclic lactam (**15**). A standard



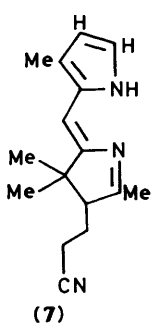
(**1**) $R^1 = R^2 = OH$ (**3**) $R^1 = NH_2, R^2 = OMe$
(**2**) $R^1 = R^2 = OMe$ (**4**) $R^1 = NH_2, R^2 = OH$



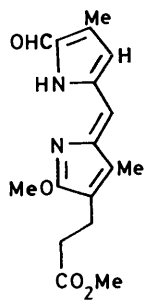
(**5**)



(**6**)

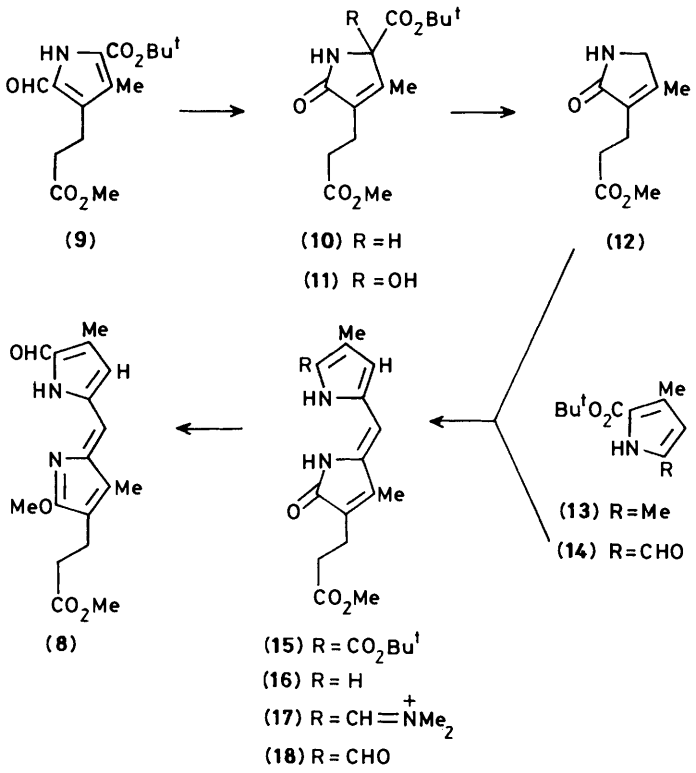


(**7**)



(**8**)

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



Scheme 1.

acid-catalysed deprotection-decarboxylation then afforded the α-free system (**16**) which was formylated using benzoyl chloride and dimethylformamide. The extended amidine (**17**), which is the intermediate in this Vilsmeier step, proved to be difficult to hydrolyse but after much experimentation, it was achieved on alumina to give the aldehyde (**18**) in 83% overall yield. Because this aldehyde was very sparingly soluble, attempts to convert it into the imino ether (**8**) using trimethyloxonium tetrafluoroborate were fruitless. This problem was overcome by first forming the complex between the aldehyde (**18**) and boron trifluoride (which was soluble) and then adding the methylating reagent; the eastern building block (**8**) was then obtained in 74% yield.

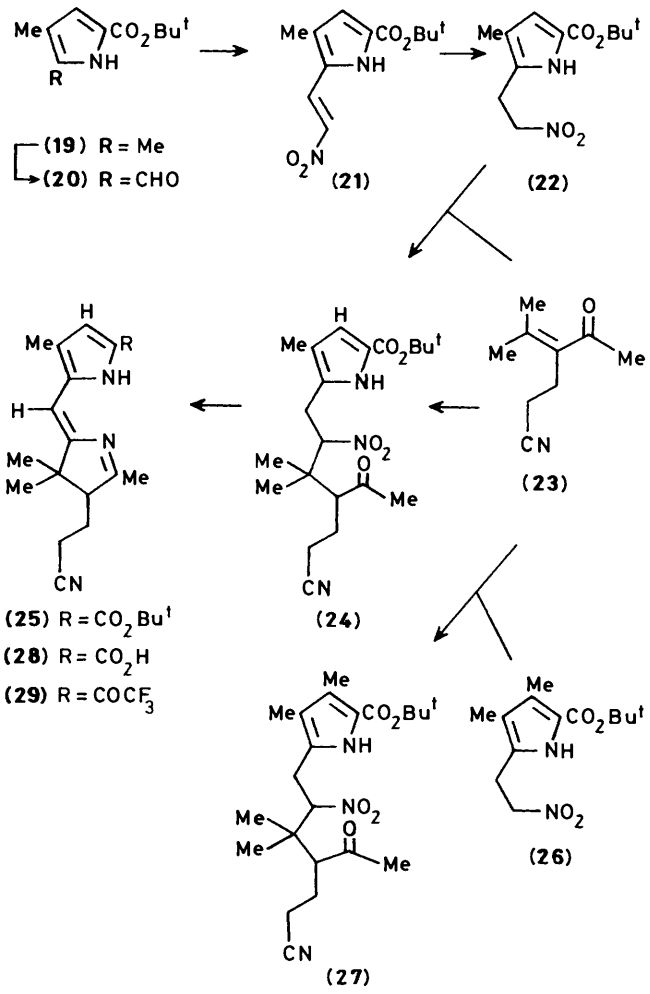
The Western Building Block.—The molecule required for the western portion of bonellin dimethyl ester (**2**) was the imine (**7**). Such unsaturated imines had been constructed earlier[10] for synthesis of isobacteriochlorins and a similar strategy was adopted for the present case as shown in Scheme 2. However, a new feature in structure (**7**) is the substituent adjacent to the *gem*-dimethyl group. This led to a study of the Michael addition of nitroethylpyrrole (**22**) to the known[11] enone (**23**) catalysed by tetrabutylammonium fluoride. A 79% yield of the mixture of diastereoisomers (**24**) was obtained which, as for related examples,[10] was converted into the nitronate anion and reduced with buffered titanium(III) chloride.[12] In this way, the required imine (**25**) was obtained in *ca.* 60% overall yield from the nitro ketone (**24**). The stereochemistry of this product (**25**) was shown to be *Z* as illustrated by n.m.r.; irradiation at δ 5.71, corresponding to the olefinic proton, caused nuclear Overhauser enhancement of the signals corresponding to both the pyrrolic methyl group and to the *gem*-dimethyl groups. The Experimental section also records details of an exploratory model experiment in which pyrrole (**26**) was successfully converted into the nitro ketone (**27**), 52%.

The foregoing nitroethylpyrrole (**22**) proved difficult to obtain in large quantity. There are good reasons (see ref. 13) why it is necessary to use the benzyl ester corresponding to pyrrole (**19**) as starting material and although hydrogenolysis of the benzyl group was straightforward, generation of the t-butyl ester of the resultant acid on a large scale was not. The Experimental section gives conditions which work satisfactorily on several tens of grams. The moderate quantities of ester (**19**) so obtained could then be converted as usual into the aldehyde (**20**) and the remaining steps to the nitroethylpyrrole (**22**) shown in Scheme 2 proceeded smoothly.

With the building blocks (**25**) and (**8**) in hand, it remained to convert the former into the α-free pyrrole (**7**) under the standard acidic conditions[1] which are used to effect t-butyl ester cleavage and decarboxylation. We expected the α-free pyrrole (**7**) to be unstable and so the total product from the acidic treatment was condensed with the aldehyde (**8**) in expectation of forming the seco-system (**35**), Scheme 3. Irradiation of the crude product under our normal conditions[1] did indeed generate the chlorin (**37**) but in totally unacceptable yield (0.24%).

The problem was found to be due to a failure to generate satisfactorily the α-free pyrrole (**7**). It was found that there was rapid formation of the acid (**28**) from the ester (**25**) in trifluoroacetic acid at room temperature but decarboxylation proved to be very slow. At higher temperatures (35—50 °C), the trifluoromethyl ketone (**29**) became the major product. Various other methods for decarboxylation of the acid (**28**) were studied but none was satisfactory. Accordingly, we decided to build ring-A into bonellin in unprotected form throughout the synthesis of the western unit. It was also recognised that success in this approach would cut the number of steps required to build the unit (**7**) from ten to five.

Synthesis of the Unprotected Western Building Block.—The starting material (**30**) was obtained by photochemical rearrangement of 4-methylpyridine 1-oxide[14] and conditions



Scheme 2.

were developed to allow batches of 20 g to be irradiated. The subsequent steps were strictly analogous to those already worked out for the protected western block (**25**) and proceeded smoothly from (**30**)→(**31**)→(**32**)→(**33**)→(**7**). A by-product in the final step was the separable saturated imine (**34**) formed by over reduction. With the required α-free pyrrole (**7**) available, the steps leading to bonellin could now be examined.

The Photochemical Cyclisation.—Acid-catalysed condensation of the α-free pyrrole (**7**) and the aldehyde (**8**) occurred readily and the seco-system (**35**) could be purified chromatographically and characterised by mass spectroscopy. This product was shown by n.m.r. to be a mixture of at least two isomers and these could arise in several ways. For example, they may be tautomers or *E*/*Z* double-bond isomers or diastereoisomers arising from the chiral centre at C-2 and the clockwise and anti-clockwise helical arrangements of the main skeleton. Since all these isomers should be suitable for the final photochemical step, the total seco-material was irradiated with light of wavelength 580 nm essentially as in the earlier model studies.[1] It proved important, however, to use proton-sponge [1,8-bis(dimethylamino)naphthalene] rather than Hunig's base in the cyclisation step. Presumably this ring-closure occurs *via* the tautomer (**36**) of the seco system (**35**) since this possesses the necessary 18π-conjugated chromophore. The photochemical ring-closure was slow and gave a 20% yield of the chlorin (**37**) after 7 days together with recovered seco-compound (**35**); the yield was over 95% based on unrecovered starting material.

All that remained was to convert the nitrile of chlorin (**37**) into a methoxycarbonyl group and this was achieved almost quantitatively using methanolic hydrogen chloride. The product (**2**) was identical, apart from its racemic nature, with authentic bonellin dimethyl ester prepared from the natural pigment and kindly provided by Professor A. Pelter and Dr. J. A. Ballantine (Swansea) whom we thank. The comparison was made by ^{1}H n.m.r., u.v.–visible, i.r., and mass spectroscopy and by chromatography. Following our preliminary accounts,[2] a second synthesis of (±)bonellin dimethyl ester was outlined,[16] based on a different approach.

Co-occurring with bonellin (**1**) in *B. viridis* are various amino acid conjugates of bonellin. For example, structure (**38**) shows the dimethyl ester of the conjugate derived from bonellin (**1**) and valine, the latter being attached specifically to the ring-D propionic acid residue. It was therefore of interest for future synthetic work on these conjugates to examine a transformation of the nitrile group of chlorin (**37**) which would preserve the differentiation of the two propionate side-chains. To this end, chlorin (**37**) was treated with boron trifluoride–diethylether in acetic acid.[15] The products were the desired amide (**3**), 59% together with the corresponding acid (**4**), 27%; the latter could be re-esterified essentially quantitatively to give the amide (**3**).

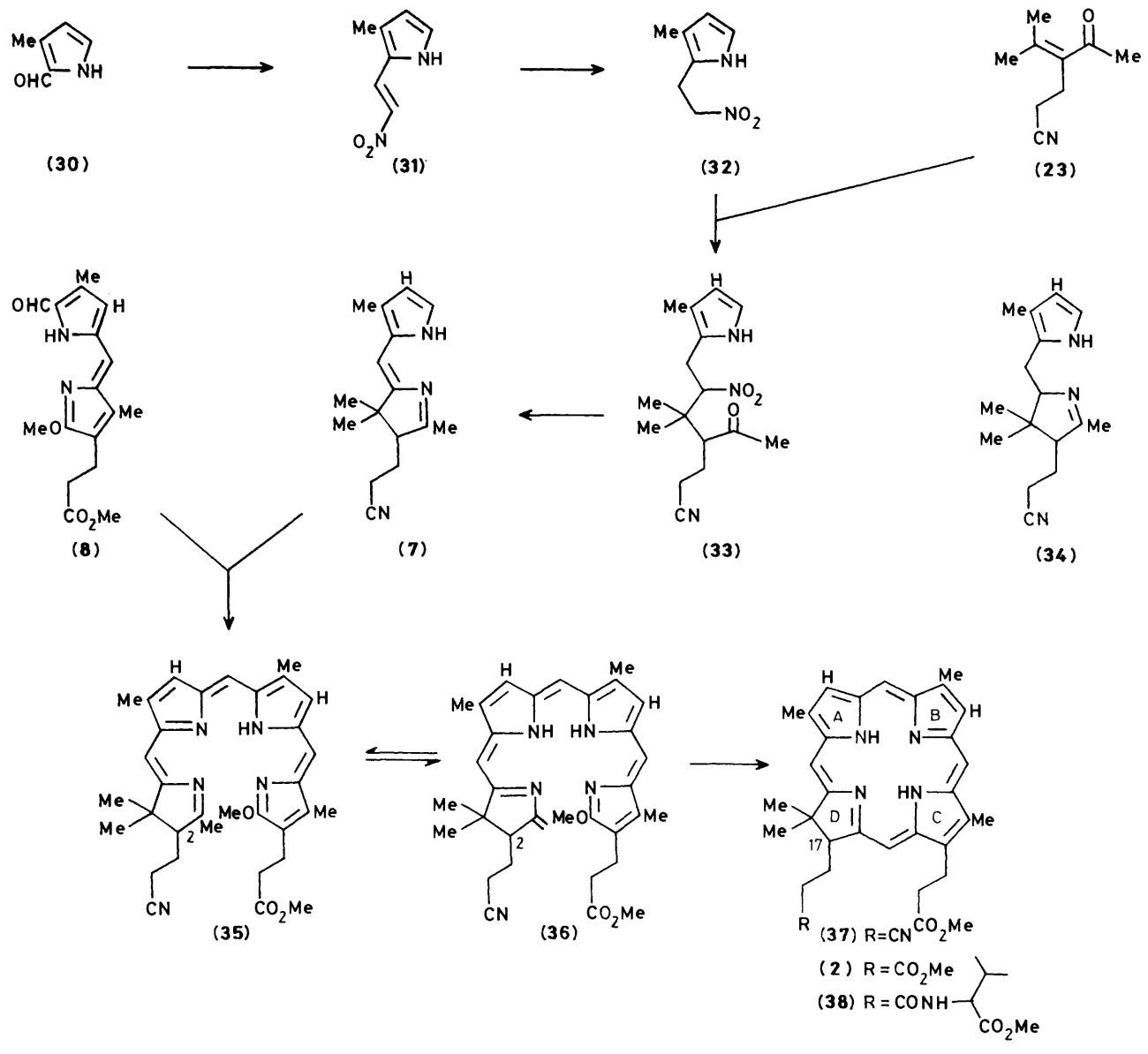
Further obvious steps should allow the amino acid conjugates [*e.g.* (**38**)] to be synthesized but this phase remains for future study.

Experimental

For general directions, see ref. 17

t-Butyl 2,5-*Dihydro*-2-*hydroxy*-4-(2-*methoxycarbonylethyl*)-3-*methyl*-5-*oxopyrrole*-2-*carboxylate* (**11**).—The formyl ester[7] (**9**) (15 g) and *m*-chloroperbenzoic acid (32.5 g, about 80% purity) were stirred at 0 °C in chloroform (150 ml) for 10 min and then allowed to warm to room temperature. An exothermic reaction ensued, the solvent refluxed, and after 2 h, the precipitated *m*-chlorobenzoic acid was filtered off and washed with chloroform (50 ml). The filtrate was then washed thrice with buffer (pH 7.5) made from 0.3M potassium hydroxide and 0.3M potassium dihydrogen phosphate (800 ml). The washings were back-extracted with chloroform (100 ml) and the combined organic layers were dried and evaporated. The residue was crystallised from diethyl ether–hexane and the mother liquors were chromatographed (65 g silica) eluting with 5% increasing to 10% methanol in chloroform which gave more crude product as an oil (4.8 g). This oil in dichloromethane (150 ml) was treated with potassium fluoride (dried at 100 °C *in vacuo*, 0.1 mmHg, 1.2 g) to precipitate the remaining acids.[18] After stirring for 5 h, the filtered solution was evaporated and the residue was crystallised from diethyl ether–hexane. All the crystalline *title compound* (**11**) was combined (total: 9.2 g, 60%), m.p. 86—87 °C (Found: C, 56.0; H, 7.0; N, 4.7. $C_{14}H_{21}NO_6$ requires C, 56.2; H, 7.1; N, 4.7%); $\nu_{max.}$ 3 430 (NH), 3 190 (OH), 1 735 (ester), 1 725 (ester), and 1 690 cm^{-1} (lactam); δ_H 6.6 (1 H, br s, NH), 4.55 (1 H, s, OH), 3.55 (3 H, s, MeO), 2.5 (4 H, s, CH_2CH_2CO), 1.85 (3 H, s, CMe), and 1.5 (9 H, s, CMe_3); *m*/*z* 300 (M + H$^+$).

3-(2-*Methoxycarbonylethyl*)-4-*methylpyrrol*-2(5H)-*one* (**12**).—The oxopyrrole ester (**11**) (100 mg) was dissolved in trifluoroacetic acid (0.4 ml) with triethylsilane (38.8 mg) under argon. After 18 h at 18 °C, more triethylsilane (38.8 mg) was added and the mixture was heated at 45 °C for 3 h. The solution was then evaporated, toluene was added and evaporated, and the residue was purified by p.l.c. eluting with methanol–



Scheme 3.

chloroform (1:9); crystallisation from diethyl ether–hexane gave the pyrrolone (53 mg, 87%), m.p. 71—76 °C (lit.,[6] 76—79 °C) (Found: C, 58.8; H, 7.2; N, 7.7%; M^+, 183.0884. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.2; N, 7.7%; M^+, 183.0895); $\nu_{max.}$ 3 195 (NH), 1 730 (ester), 1 675 (lactam), and 1 650 cm^{-1} (C=C); $\lambda_{max.}(CH_2Cl_2)$ 231 nm; δ_H 7.7 (1 H, br s), 3.7 (2 H, s), 3.6 (3 H, s), 2.55 (4 H, s), and 2.0 (3 H, s); *m/z* 183 (M^+).

t-Butyl 5-Formyl-3-methylpyrrole-2-carboxylate (**14**).—A solution of the dimethylpyrrole[9] (**13**) (1 g) in acetic acid (40 ml) and acetic anhydride (5 drops) was stirred at 18 °C with lead dioxide (1.35 g) and lead tetra-acetate (2.5 g) for 60 h and then filtered. The filtrate was shaken with water (200 ml) and dichloromethane (3 × 50 ml), the combined organic layers were washed with aqueous sodium hydrogen carbonate (100 ml), dried, and evaporated. The residue in tetrahydrofuran (15 ml) and water (10 ml) was heated under reflux for 6 h then diluted with water (40 ml) and the product was extracted into dichloromethane (3 × 100 ml). The combined organic layers were washed with dilute aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml), dried, and evaporated. Chromatography of the residue on silica (11.7 g) using 3:1 hexane–dichloromethane with a gradient of diethyl ether from 0 to 4% gave the *title compound* (**14**) (0.5 g, 50%), m.p. 81—83 °C (from hexane) (Found: C, 63.2; H, 7.2; N, 6.5. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%); $\nu_{max.}$ 3 210 (NH), 2 850 (CH), 1 710 (aldehyde), and 1 650 cm^{-1} (ester); δ_H 9.5 (1 H, s), 9.45 (1 H, br s), 6.65 (1 H, d, *J* 3 Hz), 2.35 (3 H, s), and 1.6 (9 H, s); *m/z* 209 (M^+).

t-Butyl 1,10-Dihydro-2-(2-methoxycarbonylethyl)-3,8-dimethyl-1-oxodipyrrin-9-carboxylate (**15**).—The formyl ester (**14**) (100 mg) and the pyrrolone (**12**) (126 mg) with potassium hydroxide (335 mg) were stirred in water (1.25 ml) and methanol (0.25 ml) for 4.5 h and then diluted with water (5 ml). After acidification using sulphur dioxide, the yellow solid was collected, washed with water, and dried. It was slurried in methanol (0.7 ml) and treated at 0 °C with a solution of diazomethane [prepared from Diazald (0.72 g)] in diethyl ether (10 ml). After the mixture had warmed to 18 °C, it was stirred for 1 h and the yellow solid was filtered off and washed with ice-cold

diethyl ether to give the *title compound* (**15**) (160 mg, 89%), m.p. 249—250 °C (from diethyl ether) (Found: C, 64.1; H, 6.9; N, 7.4. $C_{20}H_{26}N_2O_5$ requires C, 64.1; H, 7.0; N, 7.5%); $\nu_{max.}$ 3 420 (NH), 3 170, 3 130, 3 100 (NH), 1 740 (methyl ester), 1 660 (2 × C=O), and 1 570 cm^{-1} C=C); $\lambda_{max.}(CH_2Cl_2)$ 374, 393, 272, and 260 nm; $\lambda_{max.}[Zn(OAc)_2]$ 374, 430, 264, and 258 nm; δ_H 9.05 (1 H, br s), 8.3 (1 H, br s), 6.1 (1 H, br s), 5.7 (1 H, br s), 3.5 (3 H, s), 2.55 (4 H, br s), 2.2 (3 H, s), 2.0 (3 H, s), and 1.55 (9 H, s); *m/z* 374 (M^+).

2-(2-*Methoxycarbonylethyl*)-3,8-*dimethyldipyrrin*-1(10H)-*one* (**16**).—The oxodipyrrin ester (**15**) (100 mg) was heated under reflux in sulphuric acid (1M in methanol–water, 3:1, 12 ml) for 4 h, then diluted with water, and extracted with dichloromethane (4 × 20 ml). The combined organic layers were washed with dilute aqueous sodium hydrogen carbonate (50 ml), dried, and evaporated, the residue being purified by p.l.c. on silica (eluting with 3:7 methyl acetate–dichloromethane). Crystallisation from diethyl ether–hexane gave the *title compound* (**16**) (40 mg, 51%), m.p. 202—203 °C (Found: C, 65.8; H, 6.7; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%); $\nu_{max.}$ 3 350 (NH), 3 150 (NH), 1 725 (ester), 1 660 (lactam), 1 630 (C=C), and 1 600 cm^{-1} (C=C); $\lambda_{max.}(CH_2Cl_2)$ 382, 391sh, and 235w nm; δ_H 10.68 (1 H, br s), 10.06 (1 H, br s), 6.80 (1 H, t, *J* 3 Hz), 6.27 (1 H, t, *J* 3 Hz), 6.07 (1 H, s), 3.66 (3 H, s), 2.66 (4 H, s), and 2.11 (6 H, s); *m/z* 274 (M^+, 100%), 243 (5), and 214 (80).

1,10-*Dihydro*-2-(2-*methoxycarbonylethyl*)-3,8-*dimethyl*-1-*oxodipyrrin*-9-*carbaldehyde* (**18**).—The α-free dipyrrinone (**16**) (0.88 g) in dimethylformamide (50 ml) at 0 °C under argon was treated dropwise with benzoyl chloride (1.76 ml) and the mixture stirred at 0 °C for 1 h followed by 0.5 h at 18 °C then poured into ice–water and extracted with dichloromethane (2 × 40 ml). The aqueous layer was basified to pH 8 with solid sodium hydrogen carbonate and extracted with dichloromethane (3 × 100 ml). All the combined organic layers were dried, filtered through a plug of alumina (30 g) to give a yellow band and a brown band. The latter was eluted with 5% methanol in dichloromethane and discarded. The alumina carrying the yellow material was removed and slurried with dichloromethane, treated with boron trifluoride–diethyl ether (3 ml) and the pigment was eluted from the alumina with 15% methanol in dichloromethane. The eluant was washed with aqueous sodium hydrogen carbonate (100 ml) then dried, and evaporated. The residue crystallised from dichloromethane to give the *title compound* (**18**) (0.8 g, 83%), m.p. > 300 °C (Found: C, 63.6; H, 6.1; N, 9.1. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%); $\nu_{max.}$ 3 300 (NH), 1 710 (ester), 1 660 (2 × C=O), and 1 590 cm^{-1} (C=C); δ_H(DMSO, 250 MHz) 11.75 (1 H, br s), 10.0 (1 H, s), 9.6 (1 H, s), 6.8 (1 H, br s), 6.1 (1 H, s), 3.6 (3 H, s), 2.3 (3 H, s), 2.1 (3 H, s), and 2.2—2.8 (4 H, m); *m/z* 302 (M^+, 95%) and 242 (100).

1-*Methoxy*-2-(2-*methoxycarbonylethyl*)-3,8-*dimethyldipyrrin*-9-*carbaldehyde* (**8**).—The lactam (**18**) (110 mg) was slurried in dichloromethane (60 ml) with boron trifluoride–diethyl ether (100 μl) and stirred until it had dissolved. Then trimethyloxonium tetrafluoroborate (0.5 g) was added, the solution stirred under argon for 24 h, then washed with dilute aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was purified by p.l.c., eluting with 15% methyl acetate in dichloromethane to give the *title compound* (**8**) (85 mg, 74%), m.p. 110—112 °C (from hexane) (Found: C, 64.4; H, 6.6; N, 8.7. $C_{17}H_{20}N_2O_4$ requires C, 64.5; H, 6.4; N, 8.9%); $\nu_{max.}$ 3 300 (NH), 1 730 (ester), 1 640 (C=O), and 1 370 cm^{-1} (CO); $\lambda_{max.}$(MeOAc) 405, 386, and 258 nm; $\delta_H(CD_2Cl_2$, 400 MHz) 11.6 (1 H, br s), 9.7 (1 H, s), 6.35 (1 H, s), 6.29 (1 H, d, *J* 2 Hz), 4.1 (3 H, s), 3.65 (3 H, s), 2.63 (2 H, t, *J* 7 Hz), 2.5 (2 H, t, *J* 7 Hz), 2.35 (3 H, s), and 2.1 (3 H, s); *m/z* 316 (M^+, 100%), 301 (10, *M* − Me), 287 (12, *M* − CHO), 285 (12, *M* − MeO), and 243 (20, *M* − CH_2CO_2Me).

4-*Acetyl*-7-(3,4-*dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-5,5-*dimethyl*-6-*nitroheptanenitrile* (**27**).—The nitroethylpyrrole[10] (**26**) (1.34 g) and the nitrile (**23**) (1.3 g) with tetrabutylammonium fluoride (1M in tetrahydrofuran, 5 ml) were stirred together in dimethylformamide (20 ml) with 4 Å molecular sieves (2.5 g) for 22 h at 50 °C under argon. The mixture was diluted with water and extracted with diethyl ether (3 × 100 ml) and the extracts were washed with 1M hydrochloric acid (150 ml), aqueous sodium hydrogen carbonate (5%, 150 ml), and brine (150 ml), then dried, and evaporated. Chromatography (15 g silica), eluting with 2:1 hexane–dichloromethane and a gradient of diethyl ether from 0–30% gave the *nitro ketone* (**27**) as a mixture of diastereoisomers (1.2 g, 57%). Crystallisation from hexane–diethyl ether gave a single diastereoisomer (0.4 g), m.p. 170—171.5 °C (Found: C, 63.2; H, 7.9; N, 10.0. $C_{22}H_{33}N_3O_5$ requires 63.0; H, 7.9; N, 10.0%); $\nu_{max.}$ 3 410 (NH), 2 250 (CN), 1 720 (ketone), 1 700 (ester), 1 550 (NO_2), and 1 370 cm^{-1} (NO_2); δ_H(400 MHz) 8.65 (1 H, br s), 4.62 (1 H, dd, *J* 12 and 2 Hz), 3.37 (1 H, dd, *J* 12 and 15 Hz), 3.08 (1 H, dd, *J* 15 and 2 Hz), 2.92 (1 H, dd, *J* 10 and 2 Hz), 2.5 (2 H, m), 2.36 (3 H, s), 1.8—2.2 (2 H, m), 2.19 (3 H, s), 1.9 (3 H, s), 1.55 (9 H, s), 1.25 (3 H, s), and 1.05 (3 H, s); *m/z* 419 (M^+).

t-*Butyl* 4,5-*Dimethylpyrrole*-2-*carboxylate* (**19**).—Benzyl 4,5-dimethylpyrrole-2-carboxylate[19] (40 g) was stirred under hydrogen in tetrahydrofuran (400 ml), with 10% palladium on charcoal (2.1 g) for 19 h and the solution was then filtered. t-Butyl alcohol (350 ml) and 4-dimethylaminopyridine (4 g) followed by dicyclohexylcarbodi-imide (60 ml) were added to the filtrate and dichloromethane washings, the mixture was stirred for 24 h at 18 °C, and then filtered. The filtrate was evaporated and the residue was chromatographed in hexane–diethyl ether (1:1) on alumina (200 g) finally eluting with diethyl ether. Further chromatography on silica (200 g) and again on alumina (200 g) with diethyl ether in both cases gave an oil which crystallised from diethyl ether–hexane to give the *title compound* (**19**) (31.7 g, 98%), m.p. 120—122 °C (Found: C, 67.7; H, 8.9; N, 7.2. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); $\nu_{max.}$ 3 315 (NH) and 1 665 cm^{-1} (C=O); δ_H 9.35 (1 H, br s), 6.5 (1 H, d, *J* 3 Hz), 2.2 (3 H, s), 2.0 (3 H, s), and 1.6 (9 H, s); *m/z* 195 (M^+, 30%) and 139 (100, *M* − Bu^t).

t-*Butyl* 5-*Formyl*-4-*methylpyrrole*-2-*carboxylate* (**20**).—The dimethylpyrrole (**19**) (7.1 g) was stirred with lead tetra-acetate (18 g) and lead dioxide (10 g) in acetic acid (300 ml) at 18 °C for 60 h. The stirred mixture was diluted with water (200 ml), gently heated for 3.5 h, diluted with more water (500 ml), and extracted with dichloromethane (2 × 1 l). The combined organic layers were dried, evaporated to low volume, and filtered through silica (50 g), eluting with diethyl ether to give the *title compound* (**20**) (6.2 g, 82%), m.p. 78—79 °C (from hexane) (Found: C, 63.2; H, 7.2; N, 6.6. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%); $\nu_{max.}$ 3 275 (NH), 2 750 (CH of aldehyde), and 1 670 cm^{-1} (C=O); δ_H 9.8 (1 H, br s), 9.7 (1 H, s), 6.75 (1 H, d, *J* 3 Hz), 2.4 (3 H, s), and 1.55 (9 H, s); *m/z* 209 (M^+).

t-*Butyl* 4-*Methyl*-5-(2-*nitrovinyl*)*pyrrole*-2-*carboxylate* (**21**).—A solution of the formyl ester (**20**) (7 g) with potassium acetate (11.8 g), methylamine hydrochloride (4 g), and nitromethane (6.8 g) in dry methanol (100 ml) was stirred at 18 °C for 6 h, then diluted with water (350 ml), and extracted with dichloromethane (3 × 250 ml). The extracted material was chromatographed on

silica (75 g), eluting with hexane–dichloromethane (2:1) and a gradient of diethyl ether from 0 to 6% to give the *nitrovinylpyrrole* (**21**) (9.95 g, 82%), m.p. 164—165 °C (from hexane–diethyl ether) (Found: C, 57.4; H, 6.6; N, 10.9. $C_{12}H_{16}N_2O_4$ requires C, 57.1; H, 6.4; N, 11.1%); $\nu_{max.}$ 3 275 (NH), 1 660 (C=O), 1 550 (NO_2), and 1 325 cm^{-1} (NO_2); δ_H 10.2 (1 H, br s), 8.0 (1 H, d, *J* 16 Hz), 7.4 (1 H, d, *J* 16 Hz), 6.65 (1 H, d, *J* 3 Hz), 2.25 (3 H, s), and 1.55 (9 H, s); *m/z* 252 (M^+, 25%), 196 (35), 157 (67), 153 (65), and 135 (100).

t-Butyl 4-Methyl-5-(2-nitroethyl)pyrrole-2-carboxylate (**22**).—Sodium borohydride was added to a stirred solution of the nitrovinylpyrrole (**21**) (240 mg) in dry methanol (10 ml) and acetic acid (3 drops) at 0 °C until no further colour change occurred. After 1.5 h at 18 °C, 0.5M hydrochloric acid (40 ml) was added and the suspension was extracted with dichloromethane (2 × 30 ml). The combined extracts were washed with dilute aqueous sodium hydrogen carbonate, dried, and evaporated. Trituration of the residue with diethyl ether gave the *nitroethylpyrrole* (**22**) (237 mg, 98%), m.p. 129—131 °C (from diethyl ether) (Found: C, 56.5; H, 7.1; N, 10.7. $C_{12}H_{18}N_2O_4$ requires C, 56.7; H, 7.1; N, 11.0%); $\nu_{max.}$ 3 280 (NH), 1 665 (C=O), 1 555 (NO_2), and 1 340 cm^{-1} (NO_2); δ_H 9.4 (1 H, br s), 6.5 (1 H, d, *J* 3 Hz), 4.4 (2 H, t, *J* 7 Hz), 3.25 (2 H, t, *J* 7 Hz), 2.0 (3 H, s), and 1.55 (9 H, s); *m/z* 254 (M^+).

4-*Acetyl*-7-(3-*methyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-5,5-*dimethyl*-6-*nitroheptanenitrile* (**24**).—The nitroethylpyrrole (**22**) (1.75 g), the nitrile (**23**) (1.75 g) and tetrabutylammonium fluoride (1M in tetrahydrofuran, 10 ml) in dry dimethylformamide (50 ml) was stirred for 44 h at 50 °C. The solvent was then evaporated off and the residue in 3% ethyl acetate–dichloromethane (250 ml) was washed with water (500 ml), dilute hydrochloric acid (250 ml), dilute aqueous sodium hydrogen carbonate (250 ml), and finally brine (250 ml). The dried solution was evaporated and the residue (4.3 g) was chromatographed on silica (25 g) eluting with hexane–dichloromethane (2:1) with a gradient of ether from 0 to 75% to give the *nitro ketone* (**24**) as a mixture of diastereoisomers (2.2 g, 79%). Crystallisation from diethyl ether–hexane gave one diastereoisomer, m.p. 138—140 °C (Found: M^+, 405.2250. $C_{21}H_{31}N_3O_5$ requires *M*, 405.2263); $\nu_{max.}$ 3 380 (NH), 2 240 (CN), 1 720 (ketone), 1 700 (ester), 1 550 (NO_2), and 1 365 cm^{-1} (NO_2); $\lambda_{max.}$ 274 nm; δ_H 8.82 (1 H, br s), 6.55 (1 H, d, *J* 3 Hz), 4.64 (1 H, dd, *J* 12 and 2 Hz), 3.41 (1 H, dd, *J* 12 and 15 Hz), 3.1 (1 H, dd, *J* 15 and 2 Hz), 2.95 (1 H, dd, *J* 10 and 2 Hz), 2.52 (2 H, m), 2.38 (3 H, s), 2.0 (3 H, s), 1.8—2.2 (2 H, m), 1.53 (9 H, s), 1.25 (3 H, s), and 1.05 (3 H, s); *m/z* 405 (M^+).

t-Butyl 2-(2-*Cyanoethyl*)-1,3,3,7-*tetramethyldipyrrin*-9-*carboxylate* (**25**).—The nitro ketone (**24**) (1.9 g) and sodium methoxide (673 mg) in methanol (16.8 ml) and tetrahydrofuran (8.4 ml) was stirred for 40 min at 18 °C under argon. This mixture was then injected into titanium(III) chloride solution (15% w/v in water; 26 ml) with tetrahydrofuran (25.2 ml), ammonium acetate (5.9 g), and water (5 ml), stirred for 20 h at 18 °C under argon, and then extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml), dried, and evaporated. The residue was chromatographed on silica (19 g) eluting with hexane–dichloromethane (2:1) and a gradient of diethyl ether from 0 to 15% to give the *title compound* (**25**) (1 g, 60%) (Found: M^+, 355.2264. $C_{21}H_{29}N_3O_2$ requires *M*, 355.2260): $\nu_{max.}$ 3 450 (NH), 2 240 (CN), and 1 690 cm^{-1} (C=O); $\lambda_{max.}$ 342 and 229 nm; $\lambda_{max.}$[+$Zn(OAc)_2$] 373 and 229 nm; δ_H 11.05 (1 H, br s), 6.61 (1 H, d, *J* 3 Hz), 5.71 (1 H, s), 2.56 (1 H, dd, *J* 8 and 5 Hz), 2.45 (4 H, m), 2.25 (3 H, s), 2.12 (3 H, s), 1.56 (9 H, s), 1.26 (3 H, s), and 1.15 (3 H, s); *m/z* 355 (M^+).

3-*Methylpyrrole*-2-*carbaldehyde* (**30**).—4-Methylpyridine 1-oxide (5 g) and copper(II) sulphate (100 g) in water (800 ml) were irradiated with stirring and cooling for 40 h using a medium-pressure mercury vapour lamp. The mixture was extracted with diethyl ether (3 × 150 ml), the combined layers were dried, and evaporated to low volume. This was filtered through silica (50 g) eluting with diethyl ether to give the title compound (**30**) (0.86 g, 17%), m.p. 90—92 °C (from diethyl ether–hexane) (lit.,[14] 90—92 °C) (Found: C, 65.7; H, 6.4; N, 12.7. Calc. for C_6H_7NO: C, 66.0; H, 6.5; N, 12.8%); $\nu_{max.}$ 3 250 (NH), 2 850 (CH), and 1 615 cm^{-1} (C=O); δ_H 10.0 (1 H, br, s), 9.55 (1 H, d, *J* 2 Hz), 6.95 (1 H, m), 6.05 (1 H, m), and 2.3 (3 H, s); *m/z* 109 (M^+, 100%) and 89 (80, *M* − CHO).

3-*Methyl*-2-(2-*nitrovinyl*)*pyrrole* (**31**).—The formylpyrrole (**30**) (2.1 g) in methanol (40 ml) was stirred with potassium acetate (2.3 g), methylamine hydrochloride (1.3 g), and nitromethane (2.6 g) for 25 h at 18 °C under argon. The mixture was poured into water (100 ml), extracted with dichloromethane (3 × 50 ml), and the combined organic layers were dried and evaporated. The residue in diethyl ether was filtered through silica (50 g), eluting with more diethyl ether to give the *nitrovinylpyrrole* (**31**) (2.56 g, 88%), m.p. 131—132 °C (from diethyl ether–hexane) (Found: C, 55.0; H, 5.0; N, 18.3. $C_7H_8N_2O_2$ requires C, 55.2; H, 5.3; N, 18.4%); $\nu_{max.}$ 3 280 (NH), 1 595 (NO_2), and 1 375 cm^{-1} (NO_2); $\lambda_{max.}$ 407 nm; δ_H 9.0 (1 H, br s), 7.95 (1 H, d, *J* 13 Hz), 7.3 (1 H, d, *J* 13 Hz), 6.9 (1 H, t, *J* 2.4 Hz), 6.05 (1 H, t, *J* 2.4 Hz), and 2.2 (3 H, s); *m/z* 152 (M^+).

4-*Acetyl*-5,5-*dimethyl*-7-(3-*methylpyrrol*-2-*yl*)-6-*nitroheptanenitrile* (**33**).—A stirred solution of the nitrovinylpyrrole (**31**) (2.28 g) in methanol (50 ml) and acetic acid (0.5 ml) was treated at 0 °C with sodium borohydride until the yellow colour disappeared. The mixture was poured into saturated aqueous ammonium chloride, the pH was adjusted to 7—8 by the addition of phosphoric acid and extracted with dichloromethane (4 × 40 ml). The combined extracts were dried, filtered quickly through silica (25 g), and evaporated to give the *nitroethylpyrrole* (**32**) which was used without delay, δ_H 8.15 (1 H, br s), 6.5 (1 H, t, *J* 3 Hz), 5.85 (1 H, t, *J* 3 Hz), 4.35 (2 H, t, *J* 7 Hz), 3.15 (2 H, t, *J* 7 Hz), and 2.0 (3 H, s); *m/z* 154 (M^+, 90%), 107 (100, *M* − HNO_2), and 94 (90, *M* − CH_2NO_2).

This product (2.28 g) and the nitrile (**23**) (2.3 g) in dimethylformamide (55 ml) with tetrabutylammonium fluoride (1M in THF, 18.5 ml) were stirred at 50 °C for 22 h and then evaporated. A solution of the residue in dichloromethane (50 ml) was washed with saturated aqueous ammonium chloride (100 ml) and dilute aqueous sodium hydrogen carbonate (100 ml), then dried, and evaporated. The residue was chromatographed on silica (50 g) in 2:1 hexane–dichloromethane with a gradient of diethyl ether from 0—60% to give the *nitro ketone* (**33**) (2.6 g, 57% over two steps) as a mixture of diastereoisomers (Found: M^+, 305.1733. $C_{16}H_{23}N_3O_3$ requires *M*, 305.1739); $\nu_{max.}$(CCl_4) 3 475 (NH), 3 400 (NH), 2 950 (CH), 2 250 (CN), 1 700 (C=O), 1 530 (NO_2), and 1 360 cm^{-1} (NO_2); δ_H *major diastereoisomer*: 8.0 (1 H, br s), 6.45 (1 H, br s), 5.8 (1 H, br s), 4.52 (1 H, dd, *J* 9 and 3.5 Hz), 2.8—3.65 (4 H, m), 2.1—2.7 (3 H, m), 2.25 (3 H, s), 1.95 (3 H, s), 1.2 (3 H, s), and 1.15 (3 H, s); *minor diastereoisomer*: 8.8 (1 H, br s), 6.7 (1 H, br s), 6.0 (1 H, br s), 4.52 (1 H, dd, *J* 9 and 3.5 Hz), 2.8—3.65 (4 H, m), 2.1—2.7 (3 H, m), 2.2 (3 H, s), 1.95 (3 H, s), 1.05 (3 H, s), and 1.15 (3 H, s); *m/z* 305 (M^+).

2-(2-*Cyanoethyl*)-2,3-*dihydro*-1,3,3,7-*tetramethyldipyrrin* (**7**).—The nitro ketone (**33**) (260 mg) in methanol (3.5 ml) was stirred with sodium methoxide (123 mg) in tetrahydrofuran (1.7 ml) under argon at 18 °C for 35 min. Then aqueous titanium(III) chloride (15%, 6.5 ml) with water (0.9 ml), ammonium acetate

(1.07 g), and tetrahydrofuran (5 ml) were injected and the solution was stirred for 4 h before extraction with dichloromethane (3 × 25 ml). The combined extracts were washed with dilute aqueous sodium hydrogen carbonate under argon, then dried, and evaporated at 18 °C. The residue purified by p.l.c. with methyl acetate–dichloromethane (1:9) to give the air-sensitive *unsaturated imine* (**7**) (83 mg, 38%) which was stored under argon at 4 °C in methyl acetate solution (Found: M^+, 255.1730. $C_{16}H_{21}N_3$ requires M, 255.1735); $\nu_{max.}(CH_2Cl_2)$ 3 460 (NH), 2 900 (CH), 2 250 (CN), 1 735 (imine), and 1 690 cm^{-1} (C=C); $\lambda_{max.}$(MeOAc) 342 and 251 nm; δ_H 10.3 (1 H, br s), 6.6 (1 H, t, *J* 3 Hz), 5.8 (1 H, t, *J* 3 Hz), 5.6 (1 H, s), 1.7—2.6 (5 H, m), 2.2 (3 H, s), 2.15 (3 H, s), 1.3 (3 H, s), and 1.15 (3 H, s); *m/z* 255 (M^+).

A lower R_F band afforded the *saturated imine* (**34**); $\nu_{max.}(CH_2Cl_2)$ 3 590 (NH), 3 460 (NH), 2 900 (CH), 2 250 (CN), 1 735 (imine), and 1 690 cm^{-1} (imine); $\lambda_{max.}(CH_2Cl_2)$ 232, 301, and 339 nm; δ_H 8.75 (1 H, br s), 6.7 (1 H, t, *J* 3 Hz), 5.95 (1 H, t, *J* 3 Hz), 1.4—2.8 (8 H, m), 2.15 (3 H, s), 1.95 (3 H, s), 1.25 (3 H, s), and 1.1 (3 H, s); *m/z* 256 ($M - 1^+$).

2-(2-*Cyanoethyl*)-2,3-*dihydro*-19-*methoxy*-18-(2-*methoxycarbonylethyl*)-1,3,3,7,12,17-*hexamethylbilin* (**35**).—The imino ether (**8**) (4 mg) and the unsaturated imine (**7**) (6.5 mg) in trifluoroacetic acid (0.2 ml) were kept under argon at 0 °C for 25 min, then allowed to warm to 18 °C. The solvent was removed at 0.1 mmHg and the residue was purified by p.l.c. eluting with methanol–dichloromethane (1:9) to give the blue *bilin* (**35**) (5 mg, 71%) (Found: M^+, 533.307. $C_{33}H_{39}N_5O_3$ requires M, 533.305); $\lambda_{max.}$(THF) 640.397, and 300 nm; $\delta_H(CDCl_3$, 400 MHz) 11.5 (1 H, br s), 6.4 (1 H, s), 6.3 (1 H, s), 6.1 (1 H, s), 5.2 (1 H, s), 5.1 (1 H, s), 4.12 (3 H, s), 3.65 (3 H, s), 2.3—2.7 (5 H, m), 2.19 (3 H, s), 2.16 (3 H, s), 2.14 (3 H, s), 2.11 (3 H, s), 1.22 (3 H, s), and 1.2 (3 H, s); *m/z* 553 (M^+).

Bonellin Mononitrile Methyl Ester (**37**).—The unsaturated imine (**7**) (9 mg) and the imino ether (**8**) (6.5 mg) in trifluoroacetic acid were kept at 18 °C under argon for 1.5 h and the solution was then evaporated under reduced pressure. The colour changed from purple to blue and the remaining trifluoracetic acid was removed by the addition of toluene (3 × 20 ml) and evaporating the resulting solution under reduced pressure. The blue residue was dissolved in tetrahydrofuran (80 ml) containing 1,8-bis(dimethylamino)naphthalene, (25 mg) which had been degassed by passing argon for 3 h. This solution was further degassed by three cycles of 'freeze/pump/thaw' at high vacuum (0.1 mmHg) and then sealed under vacuum in a thick-walled glass tube. The tube was irradiated for 1 week by a 1 000 W array of tungsten bulbs, through a water-cooled liquid filter of aqueous sodium dichromate. The contents of the tube were then evaporated and the residue in dichloromethane was washed with dilute aqueous sodium hydrogen carbonate, dried, and the solution evaporated. The residue was chromatographed on silica (5 g) in dichloromethane containing some methyl acetate to elute the green chlorin band. Addition of methanol to the solvent then caused elution of the seco-imino ether (**35**) as a blue band (7.5 mg). The chlorin was further purified by p.l.c. with hexane–diethyl ether (3:7) to give *bonellin mononitrile methyl ester* (**37**) (2.16 mg, 20.2%, 97% based on unrecovered starting material) (Found: M^+, 521.2777. $C_{32}H_{35}N_5O_2$ requires M, 521.2791); $\nu_{max.}(CHCl_3)$ 3 325 (NH), 2 900 (CH), 2 250 (CN), 1 730 (C=O), 1 610 (C=C), 1 150 (OMe), and 870 cm^{-1} (CH, β-free); $\lambda_{max.}$(MeOAc) 639, 606, 581, 514, 490, 481, and 383 nm; $\delta_H(CD_2Cl_2$, 400 MHz) 9.8 (1 H, s), 9.71 (1 H, s), 9.03 (2 H, s), 8.92 (1 H, s), 8.75 (1 H, s), 4.66 (1 H, m), 4.28 (2 H, m), 3.7 (3 H, s), 3.61 (3 H, s), 3.58 (3 H, s), 3.55 (3 H, s), 3.23 (2 H, t, *J* 8 Hz), 2.75 (1 H, m), 2.5 (2 H, m), 2.32 (1 H, m), 2.22 (3 H, s), 1.87 (3 H, s), and −2.52 (2 H, br s); *m/z* 521 (M^+).

(±)-*Bonellin Dimethyl Ester* (**2**).—A slight vacuum was applied to the flask containing a stirred solution of the nitrile (**37**) (1 mg) in methanol (1 ml) and a balloon of hydrogen chloride gas was attached *via* a tap. The flask was placed in an ice–water bath and the tap to the balloon was opened. After 45 min, the balloon had collapsed and was replaced with another balloon of hydrogen chloride gas and stirring was continued for a further 30 min. The flask was sealed and stirring continued for 16 h at 18 °C. The reaction mixture was then added dropwise to a stirred solution of sodium hydrogen carbonate, ice, and water, which was extracted with dichloromethane; the combined organic layers were dried and evaporated. The residue was purified by p.l.c. with hexane–diethyl ether (1:2) to give bonellin dimethyl ester (**2**) as dark needles with a purple lustre (0.93 mg, 88%), m.p. 154—156 °C (from pentane–diethyl ether). The synthetic material was identical with the natural material by u.v.–visible, i.r., n.m.r., and mass spectroscopy and by chromatography (Found: M^+, 554.2874. $C_{33}H_{38}N_4O_4$ requires M, 554.2892); $\nu_{max.}(CHCl_3)$ 3 675 (NH), 3 325 (NH), 2 900 (CH), 1 720 (C=O), 1 605 (C=C), and 860 cm^{-1} (CH, β-free); $\lambda_{max.}(CHCl_3)$ 394, 641, 620, 590, 539, 521, 494, and 488 nm; $\delta_H(CD_2Cl_2$, 400 MHz) 9.75 (1 H, s), 9.65 (1 H, s), 9.0 (1 H, s), 8.99 (1 H, s), 8.9 (1 H, s), 8.71 (1 H, s), 4.53 (1 H, t, *J* 7 Hz), 4.25 (2 H, t, *J* 8 Hz), 3.7 (3 H, s), 3.57 (3 H, s), 3.56 (3 H, s), 3.54 (3 H, s), 3.52 (3 H, s), 3.2 (2 H, t, *J* 8 Hz), 2.6 (1 H, m), 2.48 (2 H, m), 2.28 (1 H, m), 2.16 (3 H, s), 1.85 (3 H, s), and −2.55 (2 H, br s); *m/z* 554 (M^+).

Bonellin Monoamide Methyl Ester (**3**).—The nitrile (**37**) (2 mg) in acetic acid (1 ml) was warmed to 70 °C under argon in the dark. Then boron trifluoride–diethyl ether (10 μl) was added and heating continued for 20 min after which the temperature was raised to 90 °C and more boron trifluoride–diethylether (20 μl) was added and heating continued for 3 h. The cooled reaction mixture was added dropwise to ice-cold aqueous sodium hydrogen carbonate (75 ml) and extracted with dichloromethane (3 × 30 ml), the combined organic layers being dried and evaporated. Purification of the product by p.l.c. eluting with methyl acetate–dichloromethane (7:13) gave *bonellin monoamide methyl ester* (**3**) (1.22 mg, 59%) and the corresponding acid (**4**) (0.55 mg, 27%). The latter could be re-esterified in 1.5% sulphuric acid in methanol overnight at 18 °C to give more *methyl ester* (total 1.78 mg, 86%) (Found: M^+, 539.2897. $C_{32}H_{37}N_5O_3$ requires M, 539.2896); $\lambda_{max.}(CH_2Cl_2)$ 641, 608, 582, 531, 525, 498, 494sh, and 393 nm; $\delta_H(CD_2Cl_2$, 400 MHz) 9.78 (1 H, s), 9.69 (1 H, s), 9.09 (1 H, s), 9.01 (1 H, br s), 8.93 (1 H, s) 8.74 (1 H, br s), 4.56 (1 H, t, *J* 6 Hz), 4.28 (2 H, m), 3.61 (3 H, s), 3.60 (3 H, s), 3.57 (3 H, s), 3.55 (3 H, s), 3.24 (2 H, t, *J* 7 Hz), 2.77 (1 H, m), 2.44 (2 H, m), 2.22 (1 H, m), 2.20 (3 H, s), 1.85 (3 H, s), and −2.53 (2 H, br s); *m/z* 539 (M^+).

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