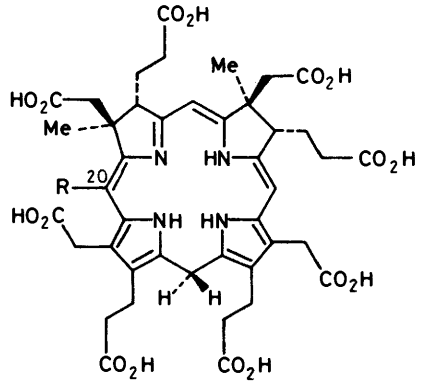
Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 9.[1,2] Synthesis of 20-Methyl and 20-Cyano Isobacteriochlorins

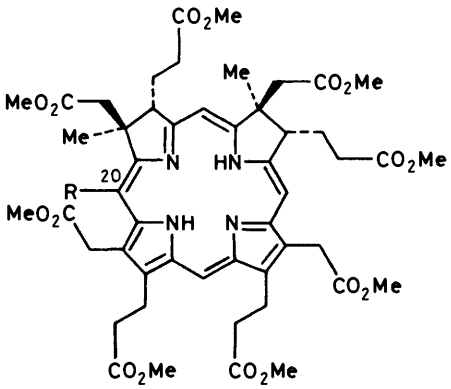
David M. Arnott, Peter J. Harrison, Graeme B. Henderson, Zhi-Chu Sheng, Finian J. Leeper, and Alan R. Battersby*
University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

Isobacteriochlorins carrying a *C*-methyl group at C-20 of the macrocycle are important for research on the biosynthesis of vitamin B_{12}. Several different approaches are studied which allow the introduction of a C-20 methyl group into model isobacteriochlorins, the most successful involving the stepwise reduction of a nitrile residue to a methyl group. Successful syntheses are described of two 20-methylisobacteriochlorins and two 20-cyanoisobacteriochlorins. All the routes used depend finally on the photochemical cyclisation of an 18π-electron open-chain precursor.

Vitamin B_{12} possesses a highly *C*-methylated macrocycle and its biosynthesis involves stepwise introduction of eight methyl groups.[3] The dimethylated intermediate[4] on the biosynthetic pathway is precorrin-2 (**1**) which is transformed into precorrin-3 (**2**) by enzymic *C*-methylation at C-20. These intermediates are dihydroisobacteriochlorins which initially were isolated[5,6] as the octamethyl esters of the corresponding aromatised isobacteriochlorins sirohydrochlorin ester (**3**) and its 20-methyl derivative (**4**) for structure determination.[7,8] Both pigments (**3**) and (**4**) are important for current and future studies on the biosynthesis of vitamin B_{12} but they are available only in limited amounts from natural sources. Our aim in Cambridge has been to construct these materials by rational synthesis.



(**1**) R = H
(**2**) R = Me



(**3**) R = H
(**4**) R = Me

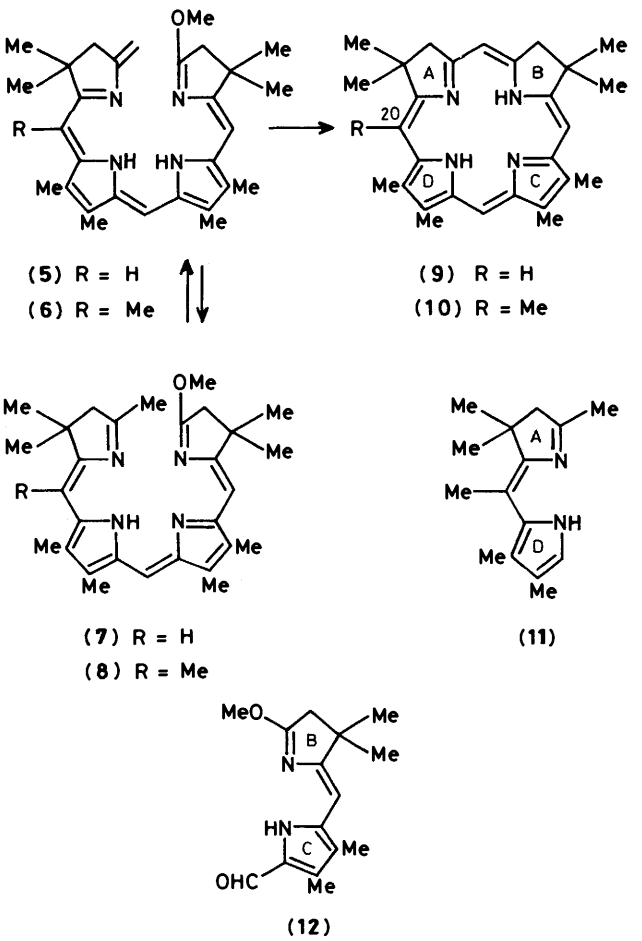
A major problem in reaching this goal was to develop methods mild enough to be compatible with the abundance of reactive acetate and propionate residues around the periphery of structures (**3**) and (**4**). That problem was solved by devising a photochemical route to the isobacteriochlorin macrocycle,[9] the strategy depending on construction of an 18 π-electron seco system (**5**)⇄(**7**), for example. This underwent photochemical ring-closure, required by the Woodward-Hoffmann rules to be an electrocyclic antarafacial process, to yield the isobacteriochlorin (**9**). The conditions throughout this synthesis were mild enough to allow the presence of acetic and propionic side chains. The power of this approach can be judged from its successful use for the synthesis[10] of sirohydrochlorin octamethyl ester (**3**), the natural dimethylated macrocycle.

The foregoing syntheses afforded isobacteriochlorins which carried no substituent at position 20. Clearly studies on the synthesis of the trimethylated pigment (**4**) must focus on ways to build in a methyl group (or a precursor of a methyl group) at the C-20 site. The present paper will describe the methods which have been developed.

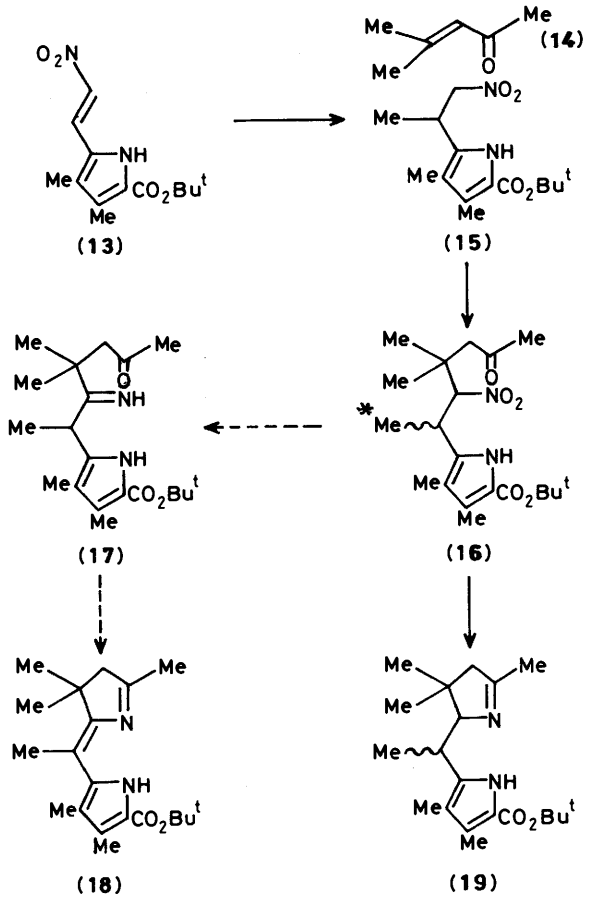
Exploratory Studies.—The initial approaches were aimed at synthesis of the nonamethylated isobacteriochlorin (**10**); an isomer of this structure was synthesized[11] by a quite different route during the course of our work. Retrosynthetic analysis of structure (**10**) leads (Scheme 1) *via* the *seco*-system (**6**)⇄(**8**) to the western A–D block (**11**) and the eastern B–C unit (**12**). The latter was already available[9] but the former was not.

In principle, synthesis of the precursor (**18**) of the western block (**11**) should be approachable by Michael addition of the ketone (**14**) to the pyrrolylnitropropane (**15**) (Scheme 2). The latter was prepared from the nitro-olefin[9] (**13**) by reaction with methyl copper[12] and this product (**15**) added smoothly to the ketone (**14**). Two separable diastereoisomers (**16**) were produced in ratio *ca.* 4:1, total 65%. The plan was to generate the nitronate anion from the isomers (**16**) followed by reduction with titanium(III) chloride[13] to the imine (**17**) as precursor of the western block (**18**). However, in sharp contrast to earlier experience with the analogue of system (**16**) lacking the starred methyl group,[9] no conditions could be found for the conversion (**16**)→(**18**). The reasons become clear from appropriate n.m.r. experiments in which the nitro compounds (**16**) were treated with MeOD–MeONa. The major diastereoisomer did not form a nitronate anion under these conditions even at 60 °C; as expected, the protons α to the carbonyl group rapidly exchanged. Similarly, there was only very slow formation of the nitronate anion from the minor diastereoisomer (6 h at 37 °C).

Reduction of the nitro ketone (**16**) with zinc–acetic acid and titanium(III) chloride yielded a single diastereoisomer (63%) of



Scheme 1.



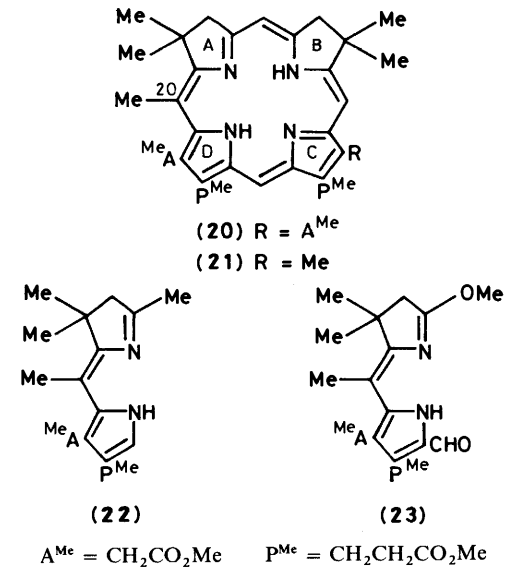
Scheme 2.

the imine (**19**). However, it was not possible to introduce the additional unsaturation required for the production of system (**18**).

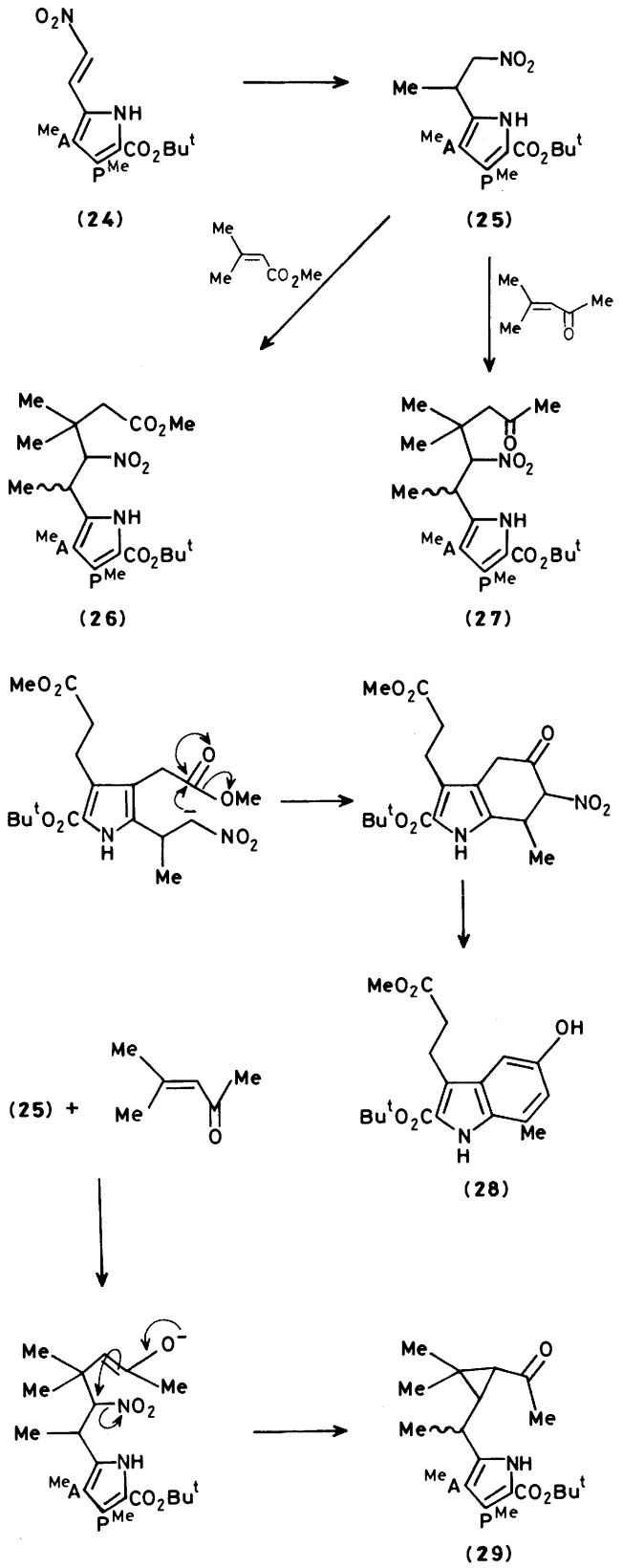
Synthesis of 20-*Methylisobacteriochlorins.*—At this stage, a change was made to model systems carrying acetate and propionate groups; the synthetic targets thus become the isobacteriochlorins (**20**) and (**21**). The latter substance having a methyl group at C-12 was included in our study because at some presently unknown stage beyond precorrin-3 (**2**) on the biosynthetic pathway to vitamin B_{12}, the 12-acetate residue is converted into a 12-methyl group by decarboxylation.

Suitable western blocks for building these isobacteriochlorins are shown as (**22**) and (**23**) and we hoped to prepare these by routes involving Michael additions. The nitropropane derivative (**25**) was prepared analogously to the work above from the known[9] nitro olefin (**24**). Attempted Michael addition of the nitropropane (**25**) to methyl 3,3-dimethylacrylate gave only *ca.* 5% of the required product (**26**). An interesting by-product was the indole (**28**) presumably formed as in Scheme 3. Use of mesityl oxide in the Michael procedure was no more successful; again only *ca.* 5% of the required material (**27**) was isolated from a complex mixture of products. One of these (30% yield) had the molecular formula $C_{25}H_{37}NO_7$ and all the spectroscopic data were consistent with the cyclopropane structure (**29**), mechanistically rationalised in Scheme 3.

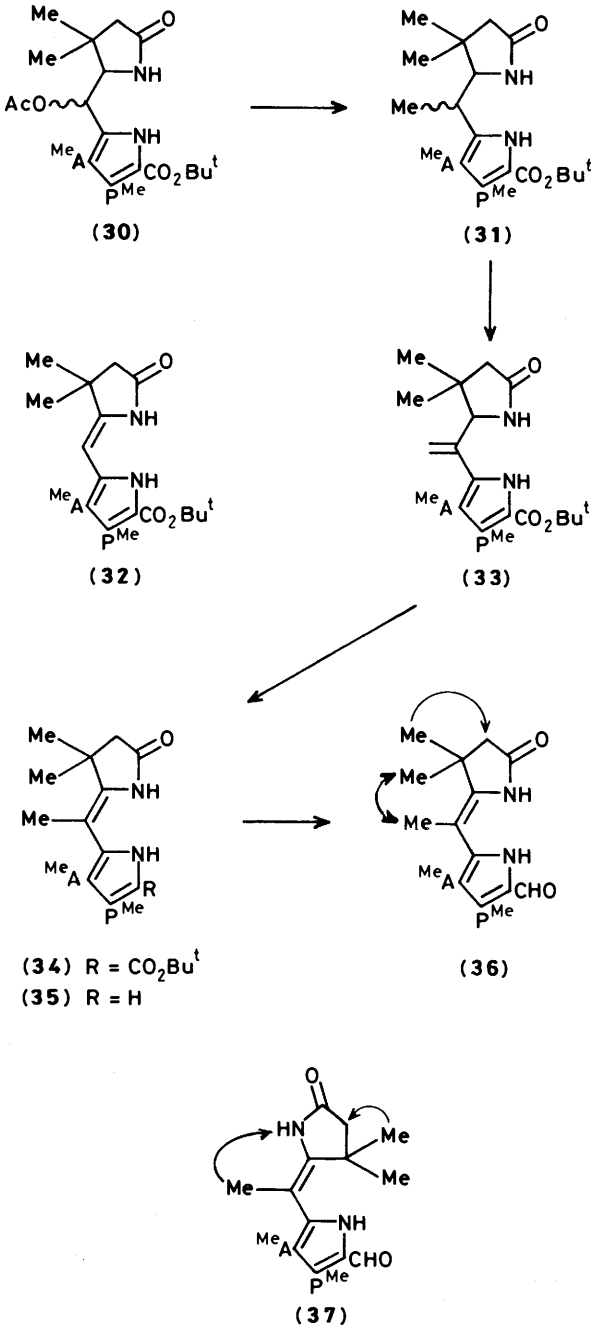
The conclusion from all the foregoing experiments is clear; the presence at the outset of what is finally to become the 20-methyl group of the isobacteriochlorin ruins synthetic approaches which in the absence of that methyl group had been very



successful. Accordingly, the late introduction of the key methyl group was studied (Scheme 4). The diastereoisomers of the previously prepared[9] acetoxy system (**30**) were separated and each was treated with lithium dimethylcuprate at −20 °C. Both gave the same two diastereoisomers of the desired product (**31**), total 77%, together with *ca.* 3% of the elimination product (**32**). By surveying a wide range of methods for introducing a double bond into the major diastereoisomer of the *C*-methylated



Scheme. 3

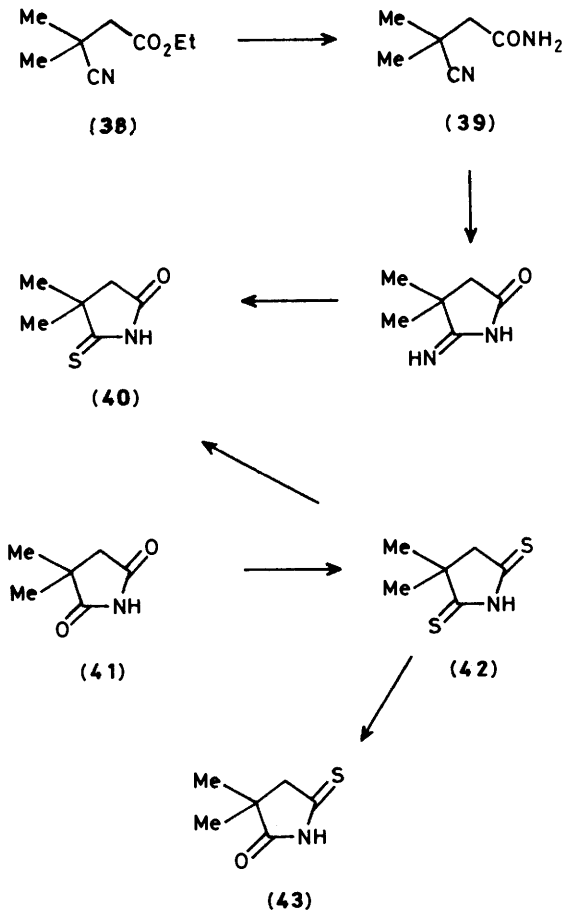


Scheme 4.

material (**31**), it was found that it could be achieved (77% yield) using t-butyl hypochlorite and potassium carbonate. However, the product was an isomer (**33**) of the desired system (**34**). Only after a very broad study of possible isomerisation methods was it found that heating the vinyl system (**33**) in a melt of benzoic acid at 160 °C gave the α-free isomerised product (**35**) in 76% yield as a 5:1 mixture of *Z*:*E* isomers.* Formylation then afforded the separable, stable *Z* aldehyde (**36**) and its *E* isomer (**37**) whose structures were assigned by n.O.e. difference measurements (the observed n.O.e.s are indicated by arrows on the structures).

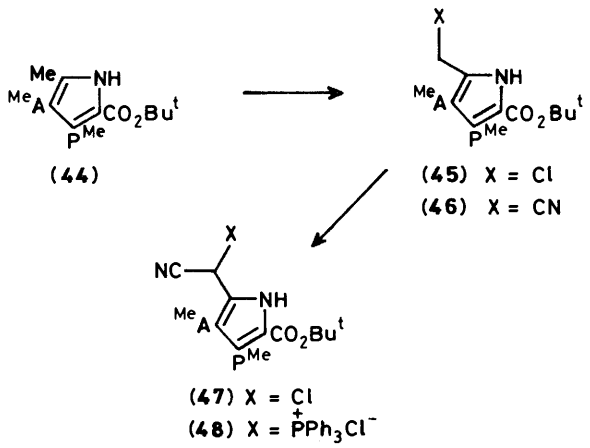
The foregoing aldehydes (**36**) and (**37**) were also obtained by a different route shown in Scheme 7. The monothioimide (**40**), required as one of the starting materials for Scheme 7, was prepared from the nitrile[14] (**38**) by the steps illustrated in

* In most cases, only the major desired isomer of the *Z* and *E* forms will be illustrated in the Schemes for economy in use of space.



Scheme 5.

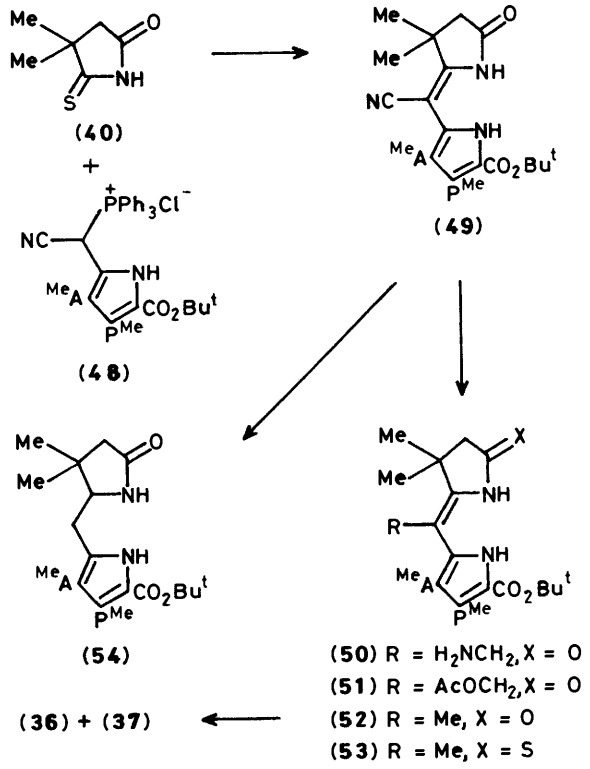
Scheme 5. During the conversion of the nitrile (**38**) into the amide (**39**), appreciable quantities of the succinimide (**41**) were also obtained and this could be converted into further quantities of the required starting material (**40**) and its isomer (**43**) *via* the dithioimide (**42**) (Scheme 5). The pyrrolic building block (**48**) was synthesized from the pyrrole[15] (**44**) by the steps shown in Scheme 6.



Scheme 6.

When the thioimide (**40**) and the phosphonium salt (**48**) were heated in toluene with potassium t-butoxide, the major product was the *E* isomer (**49**) together with a small amount of the *Z* isomer (total 83%). This step builds on the earlier work of Gossauer[16] but there may be a mechanistic difference since, unlike his case, excess of base (2 equiv.) was essential for success with ours. The mechanism of this valuable reaction is being studied.[17]

We now wished to convert the nitrile residue of system (**49**) into a methyl group and of the 12 reductive methods studied, 2 gave valuable results. In one, the nitrile (**49**) was reduced with Raney nickel and hydrogen in slightly acidic methanol. A mixture of the *Z* and *E* forms of the amine (**50**) was obtained in up to 88% yield together with small amounts (4% or less) of the *Z* and *E* *C*-methyl derivatives (**52**) and the saturated lactam (**54**) which had lost the nitrile carbon. The other reductive method used transfer hydrogenation of the nitrile (**49**) catalysed by palladium with menthene as the hydrogen source.[18] The *Z* and *E* *C*-methyl derivatives (**52**) were again formed (up to 20%) and the saturated lactam (**54**) was also produced (up to 40%).



Scheme 7.

Consideration of the possible mechanism by which the saturated lactam (**54**) is formed led to crucially important advances in subsequent synthetic work on sirohydrochlorin octamethyl ester (**3**).[10] It seems best therefore to defer mechanistic discussion of this reaction to the full paper on sirohydrochlorin.

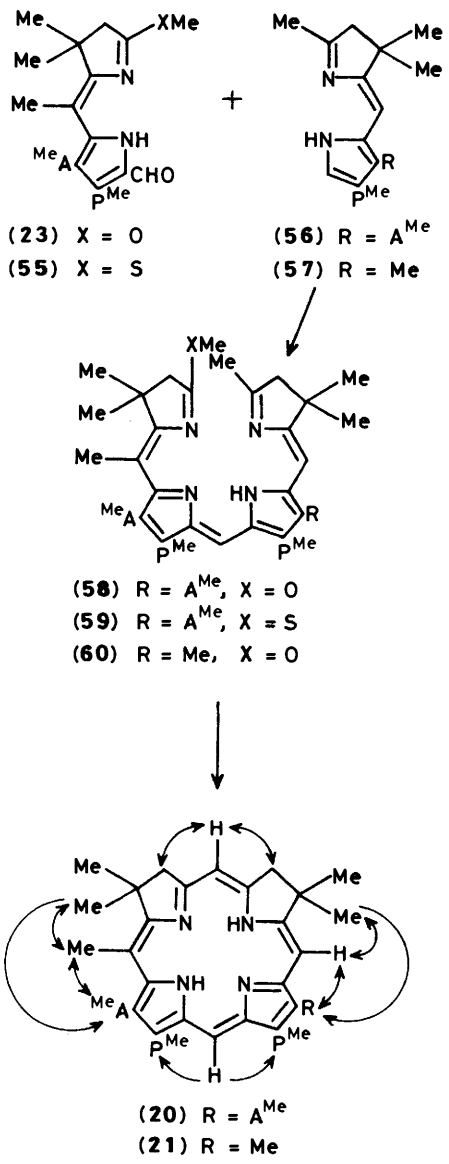
The *Z* and *E* *C*-methylated systems (**52**) were converted as earlier into the *Z* (**36**) and *E* (**37**) aldehydes which were identical with the materials described above from the first synthetic route.

Though the foregoing experiments did afford additional supplies of the aldehydes (**36**) and (**37**), the yields in the reductive step were modest or poor. A preparative alternative depended on diazotisation of the mixture of *Z* and *E* amines (**50**) in acetic acid to yield the labile *Z* and *E* allylic acetates (**51**). These were immediately hydrogenolysed over palladium to give a 2:1 mixture of the *Z* and *E* *C*-methyl products (**52**) in 50—60% overall yield from the mixed amines.

At this stage, a practical route was available to the precursor (**52**) of the western block (**23**) and its *E* isomer; a route to the

required eastern block (**56**) had been developed earlier.[9] The *O*-methylation step (**36**)→(**23**) was not possible using Meerwein's reagent (another difference from the non-C-methylated series[9]) but it was achieved, albeit in unoptimised modest yield, using methyl iodide and silver carbonate.

Condensation of the two blocks (**23**) and (**56**) then gave the seco system (**58**) which was cyclised photochemically to the 20-methylisobacteriochlorin (**20**) in unoptimised 13% overall yield from the components (**23**) and (**56**) (Scheme 8). It was

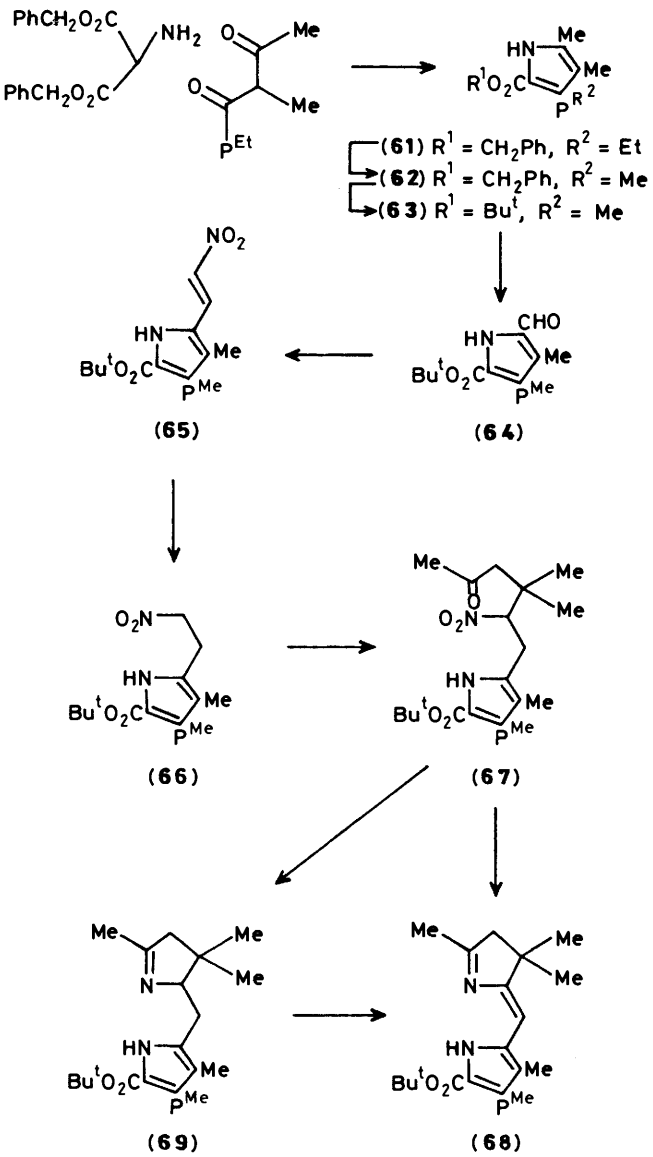


Scheme 8.

thereby demonstrated that the 20-methylated macrocycle (**20**) can be synthesized by the photochemical approach.

A variation of the final steps in this synthesis involved conversion using Lawesson's reagent[19] of the *Z*/*E* mixture (**52**) into the corresponding mixture of thiolactams (**53**) having a ratio *Z*:*E* of 3:1. Heating the *E* isomer in toluene caused stereochemical equilibration and more of the *Z* isomer (**53**) could be isolated. This was treated with trifluoroacetic acid and trimethyl orthoformate which caused a remarkable set of changes. Not only was the t-butyl group cleaved, the product decarboxylated and formylated but also the sulphur was methylated to produce directly the aldehydo imino thioether (**55**) in almost quantitative yield. This condensed with the eastern block (**56**) to give the seco system (**59**) which underwent photochemical ring-closure to the same 20-methylisobacteriochlorin (**20**) synthesized above but with higher yield of 23% overall (again without optimisation). The structure was confirmed by n.m.r. studies including n.O.e. difference spectra which showed the connectivities indicated by arrows on structure (**20**).

The chemistry developed above was also used for synthesis of the 12,20-dimethylisobacteriochlorin (**21**) (Scheme 8). The western block (**23**) was unchanged whilst the required eastern block was the imine (**57**) derivable from the t-butyl ester (**68**). The necessary pyrrole (**63**) was synthesized as in Scheme 9 and

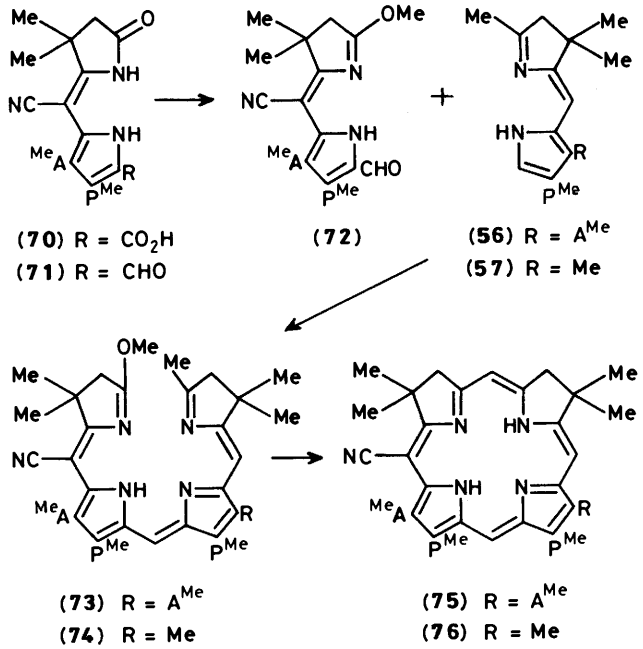


Scheme 9.

there too is shown how the steps analogous to earlier work[9] were carried out to yield the t-butyl ester (**68**). This was then converted by deprotection of the pyrrole ring into the eastern block (**57**) which under acidic catalysis condensed with the western block (**23**) to yield the seco system (**60**). Finally, photochemical ring-closure afforded the 12,20-dimethylisobacteriochlorin (**21**) though the yield in the single run

which was carried out was low (8%). Nevertheless, this experiment afforded sufficient material to act as an authentic standard for related studies[20] on the preparation of 12-methyl isobacteriochlorins.

Synthesis of 20-*Cyanoisobacteriochlorins*.—In the work so far, the methyl group destined to appear at C-20 of the final macrocycle has been generated from a nitrile residue in the early stages. A possible alternative is to carry the nitrile group through to the macrocyclic stage and then convert it into a methyl group. We therefore explored the synthesis of two 20-cyanoisobacteriochlorins (**75**) and (**76**) shown in Scheme 10.



Scheme 10.

The strategy follows closely that already discussed for the *C*-methyl series. It is therefore sufficient to comment on differences from earlier experiences. Removal of the t-butyl group from the lactam (**49**) proceeded normally but decarboxylation was very slow in neat trifluoroacetic acid and it was necessary to heat the acid (**70**) in dichloromethane with toluene-*p*-sulphonic acid. The decarboxylated product was then formylated to yield the desired *E* aldehyde (**71**) in 78% yield; this could be distinguished by n.m.r. spectroscopy from the separable *Z* isomer isolated in trace amounts (<2%). Here again it was necessary to use methyl iodide and silver carbonate to generate the imino ether (**72**); Meerwein's reagent gave complex mixtures arising in part from *N*-methylations. The imino ether (**72**) condensed with the two available eastern blocks (**56**) and (**57**) to afford the seco systems (**73**) and (**74**). Irradiation of the former yielded the 20-cyanoisobacteriochlorin (**75**) in 53% overall yield. Ring-closure was equally successful with the latter precursor (**74**) to give the 20-cyano-12-methylisobacteriochlorin (**76**) in 52% overall yield.

It is clear that the final stages in the synthesis of 20-cyano-isobacteriochlorins are very satisfactory ones and so one can, in principle, consider modification of the nitrile function at the macrocyclic stage, *e.g.* (**75**) or (**76**), to generate a *C*-methyl group. These studies lie in the future.

Experimental

Most general directions are given in ref. 21.

In addition, ^{1}H n.m.r. spectra were recorded on Varian EM360 (A), EM390 (B), CFT20 (C), and XL100 (D) and Bruker WP80 (E), WM250 (F), and WH400 (G) spectrometers. All signals are referred to tetramethylsilane as $\delta = 0$.

t-Butyl 3,4-*Dimethyl*-5-(1-*methyl*-2-*nitroethyl*)*pyrrole*-2-*carboxylate* (**15**).—Methylcopper was prepared by stirring dry cuprous iodide (1.43 g, 7.5 mmol) in dry ether (20 ml) with methyl-lithium (1.6M in ether; 4.7 ml, 7.5 mmol) at 0 °C under nitrogen for 10 min. A solution of t-butyl 3,4-dimethyl-5-(2-nitrovinyl)pyrrole-2-carboxylate (**13**)[9] (1 g, 3.76 mmol) in dry ether (40 ml) was transferred to the methylcopper reagent by a double-ended needle and the resultant mixture stirred at 5 °C for 24 h. It was then poured into aqueous ammonia–ammonium chloride (155 ml), and the aqueous layer separated and extracted with ether (3 × 40 ml); the combined organic layers were dried, filtered, and evaporated. Recrystallisation of the residue from hexane gave the *nitropropylpyrrole* (425 mg, 40%). More was obtained from the mother liquor by chromatography on silica (18 × 1.7 cm), eluting with ether–dichloromethane (1:19) (436 mg, total 861 mg, 81%), m.p. 105—106 °C (Found: C, 59.3; H, 7.8; N, 9.8. $C_{14}H_{22}N_2O_4$ requires C, 59.55; H, 7.9; N, 9.9%); $\nu_{max.}$ 3 450, 3 300, 1 670, 1 550, and 1 370 cm^{-1}; δ(D) 1.40 (3 H, d, *J* 7 Hz, CH*Me*), 1.56 (9 H, s, Bu^t), 1.95 and 2.19 (each 3 H, s, ArMe), 3.78 (1 H, sex, *J* 7 Hz, C*H*Me), 4.45 (2 H, dd, *J* 7 and 2 Hz, CH_2NO_2), and 8.60 (1 H, br s, NH); *m/z* 282 (M^+), 226 ($M^+ - C_4H_8$), and 179 (100%, $M^+ - C_4H_9NO_2$).

t-Butyl 3,4-*Dimethyl*-5-(1,3,3-*trimethyl*-2-*nitro*-5-*oxohexyl*)-*pyrrole*-2-*carboxylate* (**16**).—The foregoing nitropropyl pyrrole (**15**) (282 mg), mesityl oxide (0.58 ml), 4 Å molecular sieves (0.5 g), and tetrabutylammonium fluoride (1M in tetrahydrofuran; 1.1 ml) were stirred in dry dimethylformamide under nitrogen at 50 °C for 5 h. The cooled mixture was filtered, mixed with water (50 ml), and extracted with ether (3 × 25 ml), the combined extracts being washed with 1M hydrochloric acid (30 ml), saturated aqueous sodium hydrogen carbonate (30 ml), and brine (30 ml), dried, filtered, and evaporated. The residue by p.l.c. using ether–hexane (1:1) gave the two diastereoisomeric *nitro ketones* and a middle band containing a mixture of the faster running diastereoisomer and starting material. This mixture was rechromatographed eluting with ether–hexane (1:1 twice then 1:2) to give the faster running nitro ketone and starting material (47 mg). The combined faster running diastereoisomer of the *nitro ketone* (167 mg, 52% based on unrecovered starting material) crystallised from hexane, m.p. 120.5—122 °C (Found: C, 63.2; H, 8.7; N, 7.4%; M^+, 380.2318. $C_{20}H_{32}N_2O_5$ requires C, 63.1; H, 8.5; N, 7.4%; *M*, 380.2311); $\nu_{max.}$ 3 440, 1 710, 1 680, 1 540, and 1 360 cm^{-1}; δ(G) 1.02 and 1.04 (each 3 H, s, CMe_2), 1.20 (3 H, d, *J* 7 Hz, CH*Me*), 1.54 (9 H, s, Bu^t), 1.58 (1 H, d, *J* 18 Hz, CH_AH_BCO), 1.90 (3 H, s, MeCO), 1.98 (3 H, s, ArMe), 2.18 (1 H, d, *J* 18 Hz, CH_AH_BCO), 2.21 (3 H, s, ArMe), 3.53 (1 H, dq, *J* 11 and 7 Hz, C*H*Me), 5.53 (1 H, d, *J* 11 Hz, $CHNO_2$), and 8.31 (1 H, br s, NH); *m/z* 380 (M^+, 9%), 324 ($M^+ - C_4H_8$), and 166 (100).

The slower running diastereoisomer of the *nitro ketone* (42 mg, 13% based on unrecovered starting material) crystallised from hexane, m.p. 112—114.5 °C (Found: C, 63.4; H, 8.7; N, 7.3%; M^+, 380.2314. $C_{20}H_{32}N_2O_5$ requires C, 63.1; H, 8.5; N, 7.4%; *M*, 380.2312); $\nu_{max.}$ 3 445, 1 715, 1 545, and 1 365 cm^{-1}; δ(D) 0.91 and 1.05 (each 3 H, s, CMe_2), 1.30 (3 H, d, *J* 7 Hz, CH*Me*), 1.56 (9 H, s, Bu^t), 1.91 (3 H, s, ArMe), 2.10 (3 H, s, MeCO), 2.22 (3 H, s, ArMe), 2.31 and 2.53 (each 1 H, d, *J* 18 Hz, CH_AH_BCO), 3.26—3.54 (1 H, m, C*H*Me), 5.28 (1 H, d, *J* 6 Hz, $CHNO_2$), and 9.40 (1 H, br s, NH); *m/z* 380 (M^+, 25%), 324 ($M^+ - C_4H_8$), and 166 (100).

t-Butyl 5-(4-*Methoxycarbonyl*-1,3,3-*trimethyl*-2-*nitrobutyl*)-3,4-*dimethylpyrrole*-2-*carboxylate*.—The foregoing nitropropyl-

pyrrole (**15**) (56 mg), methyl 3-methylbut-2-enoate (0.11 ml), 4 Å molecular sieves (0.12 g), and tetrabutylammonium fluoride (1M in tetrahydrofuran; 0.22 ml) were stirred in dry dimethylformamide under argon at 50 °C for 24 h. The filtered mixture was added to water (3 ml) and extracted with ether (10 ml, 5 ml). The combined extracts were washed with 1M hydrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate (5 ml), and brine (5 ml), dried, filtered, and evaporated. The residue (48 mg) by p.l.c. eluting twice with ether–hexane (1:1) gave 7 bands. In addition to starting material (27 mg) was the desired *nitro ester* (5.5 mg, 13.5% based on unrecovered starting material) (Found: M^+, 396.2256. $C_{20}H_{32}N_2O_6$ requires M, 396.2260); δ(D) 1.01 and 1.07 (each 3 H, s, CMe_2), 1.22 (3 H, d, J 7 Hz, CH*Me*), 1.55 (9 H, s, Bu^t), 1.95 (2 H, s, CH_2CO_2), 1.99 and 2.20 (each 3 H, s, ArMe), 3.50—3.80 (1 H, m, C*H*Me), 3.63 (3 H, s, OMe), 5.37 (1 H, d, J 11 Hz, $CHNO_2$), and 8.75 (1 H, br s, NH); m/z 396 (M^+, 6%), 340 ($M^+ - C_4H_8$), and 166 (100).

t-Butyl 3,4-*Dimethyl*-5-[1-(3,3,5-*trimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*yl*)*ethyl*]*pyrrole*-2-*carboxylate* (**19**).—(*a*) The nitro ketone (**16**) (minor diastereoisomer; 38 mg) in dry methanol (1.2 ml) was stirred at 50 °C under nitrogen with sodium methoxide (16 mg) for 2.5 h. The solution was then transferred to a previously degassed solution of ammonium acetate (231 mg) and 1M aqueous titanium(III) chloride (0.5 ml) in water (2 ml) and methanol (0.5 ml), being washed in with more methanol (1 ml). After the mixture had been stirred for 21 h at 18 °C under nitrogen, it was mixed with ether (5 ml), basified with 30% aqueous ammonia (6 ml), and filtered through Celite the latter being washed well with ether. The aqueous layer was extracted with ether (10 ml) and the organic phase dried, filtered, and evaporated to afford a gum (34 mg). Fractionation by p.l.c. using methyl acetate–dichloromethane (2:3) gave *t-butyl* 3,4-*dimethylpyrrole*-5-(1,3,3-*trimethyl*-2,5-*dioxohexyl*)-2-*carboxylate* (5.5 mg) (Found: M^+, 349.2263. $C_{20}H_{31}NO_4$ requires M, 349.2253); $\nu_{max.}$ 3 440 and 1 690 cm^{-1}; δ(D) 0.99 and 1.25 (each 3 H, s, CMe_2), 1.33 (3 H, d, J 7 Hz, CH*Me*), 1.54 (9 H, s, Bu^t), 1.96 (3 H, s, ArMe), 2.09 (3 H, s, MeCO), 2.20 (3 H, s, ArMe), 2.58 and 2.92 (1 H, d, J 18 Hz, CH_AH_BCO), 4.36 (1 H, q, J 7 Hz, C*H*Me), and 8.70 (1 H, br s, NH); m/z 349 (M^+, 4%) and 166 (100%). In addition was isolated the *dihydropyrrole* (**19**) which was identical with the larger sample prepared under (*b*).

(*b*) The foregoing nitro ketone (**16**) (major diastereoisomer; 190 mg) and zinc dust (3 g) were stirred in glacial acetic acid (50 ml) at 50 °C for 2.25 h under nitrogen. Ammonium acetate (1 g) was added to the cooled mixture, followed by 15% aqueous titanium(III) chloride solution (1.25 ml) and the whole stirred at 18 °C for 4.5 h. The filtered solution and washings (with acetic acid) were evaporated and the residue was partitioned between ether (35 ml), water (20 ml), and 30% aqueous ammonia (30 ml). The organic phase from the filtered mixture was dried and evaporated to a gum (150 mg). Purification by p.l.c. using methyl acetate–dichloromethane (2:3) gave the *dihydropyrrole* (**19**) (single diastereoisomer) as a gum (105 mg, 63%) (Found: M^+, 332.2460. $C_{20}H_{32}N_2O_2$ requires M, 332.2463); $\nu_{max.}$(CCl_4) 3 555, 3 460, 2 950, 1 680, and 1 575 cm^{-1}; δ(D) 0.93 and 1.07 (each 3 H, s, CMe_2), 1.08 (3 H, d, J 7 Hz, CH*Me*), 1.55 (9 H, s, Bu^t), 1.93 (3 H, s, ArMe), 2.08 (3 H, d, J 1.5 Hz, N=CMe), 2.23 (3 H, s, ArMe), 2.32 (2 H, br s, $N{=}CCH_2$), 2.95—3.15 (1 H, m, C*H*Me), 3.75 (1 H, br m, CHN), and 9.80 (1 H, br s, NH); m/z 332 (M^+, 9%) and 166 (100).

t-Butyl 3,4-*Dimethyl*-5-[1-(3,3,5-*trimethyl*-1-*oxido*-3,4-*dihydro*-2H-*pyrrol*-2-*yl*)*ethyl*]*pyrrole*-2-*carboxylate*.—The foregoing nitro ketone (**16**) (major diastereoisomer; 76 mg) in glacial acetic acid (3 ml) was stirred with zinc dust (0.4 g) at 18 °C for 1.5 h. The zinc was filtered off and washed with acetic acid and the filtrate evaporated. The residue was shaken with dichloromethane (20 ml) and 30% aqueous ammonia (10 ml) and the organic phase was dried, filtered, and evaporated. Purification of the residue by p.l.c. using methyl acetate–dichloromethane (1:1) gave the foregoing dihydropyrrole (8 mg), while the major, lower band was the *dihydropyrrole*-N-*oxide* as a gum (single diastereoisomer) (58 mg, 83%) (Found: M^+, 348.2414. $C_{20}H_{32}N_2O_3$ requires M, 348.2413); $\nu_{max.}$ 3 175, 1 670, and 1 620 cm^{-1}; δ(D) 1.04 (3 H, d, J 7 Hz, CH*Me*), 1.17 and 1.23 (each 3 H, s, CMe_2), 1.56 (9 H, s, Bu^t), 1.93 (3 H, s, ArMe), 2.13 (3 H, d, J 1.5 Hz, N=CMe), 2.25 (3 H, s, ArMe), 2.50 (2 H, br m, $N{=}CCH_2$), 3.20—3.40 (1 H, m, C*H*Me), 3.90 (1 H, br m, CHN), and 11.83 (1 H, br s, NH); m/z 348 (M^+, 8%), 275, and 166 (100).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-(1-*methyl*-2-*nitroethyl*)*pyrrole*-2-*carboxylate* (**25**).—A solution of the nitrovinylpyrrole[9] (**24**) (1 g, 2.52 mmol) in dry ether (40 ml) was transferred by a double-ended needle to a solution of methylcopper (5.04 mmol) in ether (prepared as before), being washed in with a further portion of ether (20 ml). Stirring was continued at 5 °C for 24 h. The mixture was then added to aqueous ammoniacal ammonium chloride (125 ml) and extracted with ether (4 × 30 ml). The combined extracts were dried and evaporated to give a gum which crystallised from ether–hexane to yield the *nitropropylpyrrole* (**25**) as yellow needles (446 mg, 43%). More product (199 mg) and starting material (50 mg) were obtained after p.l.c. of the mother liquors eluting twice with ether–dichloromethane (1:9) (total 645 mg, 65% based on unrecovered starting material), m.p. 120—124 °C (Found: C, 55.4; H, 6.8; N, 6.6%; M^+, 412.1873. $C_{19}H_{28}N_2O_8$ requires C, 55.3; H, 6.8; N, 6.8%; M, 412.1846); $\nu_{max.}$ 3 500, 3 400, 1 715, 1 665, 1 535, and 1 350 cm^{-1}; δ(B) 1.36 (3 H, d, J 7 Hz, CH*Me*), 1.53 (9 H, s, Bu^t), 2.43—2.66 (2 H, m, $CH_2CH_2CO_2$), 2.83—3.10 (2 H, m, $CH_2CH_2CO_2$), 3.50 (2 H, s, CH_2CO_2), 3.66 and 3.70 (each 3 H, s, OMe), 3.66—3.91 (1 H, m, C*H*Me), 4.33—4.76 (2 H, m, CH_2NO_2), and 9.0 (1 H, br s, NH); m/z 412 (M^+, 4%), 353, 297, 266, and 237 (100).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-(4-*methoxycarbonyl*-1,3,3-*trimethyl*-2-*nitrobutyl*)-*pyrrole*-2-*carboxylate* (**26**).—The foregoing nitropropylpyrrole (**25**) (50 mg), 4 Å molecular sieves (0.1 g), tetrabutylammonium fluoride (1M in tetrahydrofuran; 0.15 ml), and methyl 3-methylbut-2-enoate (0.1 ml), were stirred in dry dimethylformamide (0.5 ml) at 80 °C under argon for 5.5 h. The mixture was then poured into water (15 ml), extracted with ether (3 × 5 ml), the extracts being washed with 1M hydrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate (5 ml), and brine (5 ml), dried, and evaporated. The residue (33 mg) by p.l.c. using ether–dichloromethane (1:9) gave starting material (9.5 mg), a blue fluorescent band [6.8 mg, an hydroxyindole (**28**), see below], and the title *nitro ester* (4.6 mg). This was combined with other samples from other runs and rechromatographed as before to give the pure *nitro ester* (**26**) (single diastereoisomer, 3 mg) as a yellow gum (Found: M^+, 526.2521. $C_{25}H_{38}N_2O_{10}$ requires M, 526.2527); δ(F) 1.02 and 1.06 (each 3 H, s, CMe_2), 1.23 (3 H, d, J 7 Hz, CH*Me*), 1.54 (9 H, s, Bu^t), 1.57 and 2.03 (each 1 H, d, J 16 Hz, $CH_AH_BCO_2$), 2.54 (2 H, t, J 7 Hz, $CH_2CH_2CO_2$), 2.95 (2 H, m, $CH_2CH_2CO_2$), 3.46 and 3.55 (each 1 H, d, J 16 Hz, $ArCH_AH_BCO_2$), 3.63, 3.64, and 3.66 (each 3 H, s, OMe), 3.55—3.64 (1 H, m, C*H*Me), 5.42 (1 H, d, J 10 Hz, $CHNO_2$), and 9.03 (1 H, br s, NH); m/z 526 (M^+, 18%) and 236 (100).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-(1,3,3-*trimethyl*-2-*nitro*-5-*oxohexyl*)*pyrrole*-2-*carboxylate* (**27**).—Dry dimethylformamide (2 ml), 4 Å

molecular sieves (0.2 g), and tetrabutylammonium fluoride (1M in tetrahydrofuran; 0.12 ml) were stirred at 18 °C under argon for 20 min. The foregoing nitropropylpyrrole (**25**) (50 mg) in dry dimethylformamide (0.5 ml) was then added followed by mesityl oxide (70 μl) and the mixture was stirred at 18 °C for 27 h and then at 50 °C for 2.5 h. The mixture was poured into water (10 ml), extracted with ether (15 ml, 2 × 12 ml) and the combined extracts were washed with 1M hydrochloric acid (10 ml), saturated aqueous sodium hydrogen carbonate (10 ml), and brine (10 ml), dried, and evaporated. The residue (22 mg) by p.l.c. using ether–dichloromethane (3:17) gave, in addition to starting material (2 mg), the title *nitro ketone* (**27**) as a gum (1.5 mg; single diastereoisomer) (Found: M^+, 510.2606. $C_{25}H_{38}N_2O_9$ requires M, 510.2578); δ(F) 1.00 and 1.05 (each 3 H, s, CMe_2), 1.22 (3 H, d, J 7 Hz, CH*Me*), 1.55 (9 H, s, Bu^t), 1.66 (1 H, d, J 18 Hz, CH_AH_BCO), 1.92 (3 H, s, MeCO), 2.23 (1 H, d, J 18 Hz, CH_AH_BCO), 2.56 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 2.96 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 3.48 (1 H, d, J 16 Hz, $ArCH_AH_BCO_2$), 3.57 (1 H, d, J 16 Hz, $CH_AH_BCO_2$), 3.50—3.60 (1 H, m, CHMe), 3.64 and 3.68 (each 3 H, s, OMe), 5.56 (1 H, d, J 11 Hz, $CHNO_2$), and 8.70 (1 H, br s, NH); m/z 510 (M^+, 2%), 390, 264, and 238 (100).

Performing the reaction at a higher concentration [as above but in dimethylformamide (0.5 ml)] and at 80 °C for 5.5 h gave none of the desired nitro ketone (**27**). Work-up as before gave the *hydroxyindole* (**28**) (4 mg) (see below) and the *acylcyclopropane* (**29**) (19 mg) as a gum (Found: M^+, 463.2592. $C_{25}H_{37}NO_7$ requires M, 463.2570); $\nu_{max.}$ 3 450, 1 730, 1 680, and 1 200 cm^{-1}; δ(F) 1.22 and 1.27 (each 3 H, s, CMe_2), 1.23 (3 H, d, J 7 Hz, CH*Me*), 1.41 (1 H, dd, J 11 and 8 Hz, MeCHCH), 1.54 (9 H, s, Bu^t), 1.77 (1 H, d, J 8 Hz, CHCOMe), 2.02 (3 H, s, MeCO), 2.51 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 2.90 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 3.38 and 3.53 (each 1 H, d, J 16 Hz, $CH_AH_BCO_2$), 3.4—3.5 (1 H, m, CHMe), 3.64 and 3.66 (each 3 H, s, OMe), and 8.67 (1 H, br s, NH); m/z 463 (M^+, 5%), 407 ($M^+ - C_4H_8$), and 406 (100).

t-Butyl 5-Hydroxy-3-(2-methoxycarbonylethyl)-7-methylindole-2-carboxylate (**28**).—The blue fluorescent product above was the *5-hydroxyindole* (**28**) (Found: M^+, 333.1574. $C_{18}H_{23}NO_5$ requires M, 333.1576); $\nu_{max.}$(CCl_4) 3 625, 3 475, 3 400—3 150, 1 745, and 1 700 cm^{-1}; $\lambda_{max.}$ 207, 230, 301, and 340sh nm; δ(F) 1.61 (9 H, s, Bu^t), 2.42 (3 H, s, ArMe), 2.62 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 3.28 (2 H, t, J 8 Hz, $CH_2CH_2CO_2$), 3.65 (3 H, s, OMe), 4.74 (1 H, br s, OH), 6.72 and 6.88 (each 1 H, s, ArH), and 8.48 (1 H, br s, NH); m/z 333 (M^+, 20%), 277 ($M^+ - C_4H_8$), and 107 (100).

t-Butyl 5-[1-(3,3-Dimethyl-5-oxopyrrolidin-2-yl)ethyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**31**).—Lithium dimethylcuprate (4.15 mmol) was prepared as follows: methyl-lithium (1.6M in ether; 5.2 ml, 8.3 mmol) was added to a vigorously stirred suspension of dry cuprous iodide (789 mg, 4.15 mmol) in dry ether (10 ml) under argon at −20 °C. This solution was added by a double-ended needle to a solution of the diastereoisomeric acetoxy compounds[9] (**30**) (422 mg, 0.83 mmol) in dry ether (45 ml) under argon. After being stirred at −20 °C for 1.5 h, the mixture was poured into aqueous ammonia–ammonium chloride (100 ml) and extracted with ether (3 × 50 ml). The combined extracts were dried and evaporated, the residue being purified by p.l.c. using ether–methanol (24:1) to give the two diastereoisomers of the *methyl lactam* (**31**) as gums. The major diastereoisomer, upper band (192 mg, 50%), crystallised from ether, m.p. 135—137 °C (Found: C, 62.3; H, 8.1; N, 5.9%; M^+, 464.2519. $C_{24}H_{36}N_2O_7$ requires C, 62.05; H, 7.8; N, 6.0%; M, 464.2522); $\nu_{max.}$ 3 440, 1 735, 1 690, and 1 200 cm^{-1}; δ(F) 1.11 and 1.25 (each 3 H, s, CMe_2), 1.27 (3 H, d, J 7 Hz, CH*Me*), 1.55 (9 H, s, Bu^t), 2.02 and 2.25 (each 1 H, d, J 17 Hz, CH_AH_BCONH), 2.50 (2 H, t, J 7 Hz, $CH_2CH_2CO_2$), 2.87—2.98 (3 H, m, $CH_2CH_2CO_2$ and CHMe), 3.38 (1 H, d, J 10 Hz, CHN), 3.44 (2 H, s, CH_2CO_2), 3.64 and 3.67 (each 3 H, s, OMe), and 5.62 and 8.99 (each 1 H, br s, NH); m/z 464 (M^+), 353 ($M^+ - C_6H_9NO$), and 297 (353 − C_4H_8, 100%). The minor diastereoisomer, lower band (105 mg, 27%), was a resin (Found: M^+, 464.2504. $C_{24}H_{36}N_2O_7$ requires M, 464.2522); $\nu_{max.}$ 3 440, 1 735, 1 690, and 1 200 cm^{-1}; δ(F) 0.94 and 1.07 (each 3 H, s, CMe_2), 1.26 (3 H, d, J 7 Hz, CH*Me*), 1.54 (9 H, s, Bu^t), 2.14 and 2.20 (each 1 H, d, J 17 Hz, CH_AH_BCONH), 2.53 (2 H, t, J 7.5 Hz, $CH_2CH_2CO_2$), 2.96 (2 H, t, J 7.5 Hz, $CH_2CH_2CO_2$), 3.08 (1 H, m, CHMe), 3.42 (1 H, d, J 6 Hz, CHN), 3.45 (2 H, s, CH_2CO_2), 3.64 and 3.66 (each 3 H, s, OMe), and 6.42 and 9.00 (each 1 H, br s, NH); m/z 353 ($M^+ - C_6H_9NO$) and 297 (353 − C_4H_8, 100%).

A high R_F by-product (15 mg) was the known[9] *unsaturated lactam* (**32**) (Found: M^+, 448.2212. $C_{23}H_{32}N_2O_7$ requires M, 448.2210) which was spectroscopically and chromatographically identical with the earlier sample.

When the separated diastereoisomers (**30**) were treated as above, each gave the same mixture of products (**31**).

t-Butyl 5-[1-(3,3-Dimethyl-5-oxopyrrolidin-2-yl)vinyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**33**).—A solution of the major diastereoisomer of the foregoing lactam (**31**) (69.6 mg) in carbon tetrachloride (7.5 ml) was cooled to 0 °C, and anhydrous potassium carbonate (207 mg, 1.5 mmol) was added under argon followed by t-butyl hypochlorite (100 mg). The mixture was stirred at 0 °C for 6.5 h, and then filtered, being washed with dichloromethane. The filtrate was evaporated and the residue by p.l.c. using ether–methanol (19:1) gave the exo-*methylene lactam* (**33**) (54 mg, 78%), m.p. 114—117 °C (from ether) (Found: M^+, 462.2328. $C_{24}H_{34}N_2O_7$ requires M, 462.2366); δ(G) 0.85 and 1.02 (each 3 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 2.24 (2 H, br s, CH_2CONH), 2.55 (2 H, t, J 7 Hz, $CH_2CH_2CO_2$), 2.95 (2 H, m, $CH_2CH_2CO_2$), 3.49 and 3.58 (each 1 H, d, J 16 Hz, $CH_AH_BCO_2$), 3.64 and 3.68 (each 3 H, s, OMe), 4.29 (1 H, br s, CHN), 5.41 and 5.42 (each 1 H, s, C=CH_2), and 6.50 and 9.00 (each 1 H, br s, NH); m/z 462 (M^+, 40%), 406 ($M^+ - C_4H_8$), and 374 (100).

Z- and E-5-[1-(3,3-Dimethyl-5-oxopyrrolidin-2-ylidene)ethyl]-2-formyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole (**36**) *and* (**37**).—The foregoing *exo*-methylene lactam (**33**) (25 mg), benzoic acid (35 mg), and hydroquinone (5 mg) were sealed in a glass tube under argon and heated at 160 °C for 6.5 h. The contents of the tube were fractionated by p.l.c. using ether–methanol (24:1) to give the unsaturated lactams (**35**) (15 mg, 76%) as a mixture of geometric isomers (Z:E, 5:1). For the Z isomer, δ(G) (CD_2Cl_2) 1.47 (6 H, s, CMe_2), 1.95 (3 H, s, C=CMe), 2.42 (2 H, s, CH_2CONH), 2.57 (2 H, m, $CH_2CH_2CO_2$), 2.70 (2 H, m, $CH_2CH_2CO_2$), 3.34 (2 H, s, CH_2CO_2), 3.68 and 3.69 (each 3 H, s, OMe), 6.57 (1 H, d, J 3 Hz, ArH), and 7.35 and 7.86 (each 1 H, br s, NH).

For the E isomer δ(G) (CD_2Cl_2) 0.99 (6 H, s, CMe_2), 1.84 (3 H, s, C=CMe), 2.34 (2 H, s, CH_2CONH), 2.57 (2 H, m, $CH_2CH_2CO_2$), 2.70 (2 H, m, $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.65 and 3.66 (each 3 H, s, CO_2Me), 6.53 (1 H, d, J 2.5 Hz, ArH), and 7.70 and 8.05 (each 1 H, br s, NH).

The foregoing mixture (33 mg) was stirred at 17 °C under argon with trifluoroacetic acid (3.5 ml) and trimethyl orthoformate (1.5 ml) for 15 min. Water (3.5 ml) was added and the solution was stirred for 30 min and then shaken with dichloromethane (12 ml) and 30% aqueous ammonia. The organic layer was washed with brine (10 ml), dried, and evaporated. The residue by p.l.c. using chloroform–methanol

(19:1) gave the title *formyl lactams* as gums; the *Z* isomer (**36**) was at higher R_F (19.2 mg, 54%) and the *E* isomer (**37**) at lower R_F (11 mg, 31%).

For the *Z* isomer (**36**): (Found: M^+, 390.1781. $C_{20}H_{26}N_2O_6$ requires *M*, 390.1790); $\nu_{max.}$ 3 440, 3 225br, 1 720, 1 670, and 1 640 cm^{-1}; $\lambda_{max.}$ 240 and 310 nm [unchanged by the addition of $Zn(OAc)_2$]; δ(G) (CD_2Cl_2) 1.48 (6 H, s, CMe_2), 1.98 (3 H, s, C=CMe), 2.42 (2 H, s, CH_2CONH), 2.61 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.02 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.40 (2 H, s, CH_2CO_2), 3.68 and 3.70 (each 3 H, s, OMe), 7.14 and 9.09 (each 1 H, br s, NH), and 9.65 (1 H, s, CHO); irradiation of the signal at 1.48 p.p.m. gave n.O.e.'s at 1.98 and 2.42 p.p.m.; irradiation of the signals at 1.98 p.p.m. gave a n.O.e. at 1.48 p.p.m.; *m/z* 390 (M^+, 100%) and 276 (90).

For the *E* isomer (**37**): (Found: M^+ 390.1790. $C_{20}H_{26}N_2O_6$ requires *M*, 390.1790); $\nu_{max.}$ 3 440, 3 225, 1 720, 1 670, and 1 640 cm^{-1}; $\lambda_{max.}$ 234 and 308 nm [unchanged by the addition of $Zn(OAc)_2$]; δ(G) (CD_2Cl_2) 1.01 (6 H, s, CMe_2), 1.82 (3 H, s, C=CMe), 2.34 (2 H, s, CH_2CONH), 2.62 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.06 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.44 (2 H, s, CH_2CO_2), 3.65 and 3.68 (each 3 H, s, OMe), 7.56 and 8.99 (each 1 H, br s, NH), and 9.65 (1 H, s, CHO); irradiation of the signal at 1.01 p.p.m. gave a n.O.e. at 2.34 p.p.m.; irradiation of the signal at 1.82 p.p.m. gave n.O.e.'s at 7.56 and 8.99; *m/z* 390 (M^+, 100%) and 276 (85).

Ethyl 3-Cyano-3-methylbutyrate (**38**).—Ethyl isopropylidenemalonate[22] (40 g) in 95% ethanol (500 ml) was heated for 7 h at 80 °C with potassium cyanide (14 g) added in water (50 ml). The precipitate was filtered off and washed with ethanol (150 ml) and the combined filtrates were acidified with 3M hydrochloric acid (100 ml). (**CARE**: Air was drawn through the solution *via* hypochlorite traps to remove HCN.) The solution was concentrated, diluted with water (100 ml), and extracted with dichloromethane (2 × 75 ml, 50 ml). The extracts were washed with 10% aqueous sodium carbonate (50 ml), dried, and evaporated and the residue was distilled through a Vigreux column (20 cm). Three fractions were collected: (*a*) 60—74 °C (mostly 68—70 °C)/0.6 mmHg (12.7 g, 41%); (*b*) 74—93 °C/0.6 mmHg (2.55 g); (*c*) 96—111 °C/0.6 mmHg (5.89 g). N.m.r. spectroscopy showed fraction (*a*) to be the *nitrile ester* (**38**) + *ca.* 7% starting material; (*b*) was the nitrile ester + *ca.* 21% starting material; (*c*) contained unwanted materials. For fraction (*a*): (Found M^+, 155.0945. $C_8H_{13}NO_2$ requires *M*, 155.0946); $\nu_{max.}$(film) 2 995, 2 245, and 1 740 cm^{-1}; δ(A) 1.30 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.50 (6 H, s, 2 × Me), 2.56 (2 H, s, CH_2CO_2), and 4.22 (2 H, q, *J* 7 Hz, CO_2CH_2Me); *m/z* 155 (M^+, 2%) and 110 (100).

3-Cyano-3-methylbutyramide (**39**).—Ethyl 3-cyano-3-methylbutyrate (**38**) (1 g) was stirred with aqueous 2M potassium hydroxide (10 ml) for 45 min at 18 °C and the homogeneous solution was extracted with ether (3 × 5 ml), the extracts being discarded. After the aqueous layer had been acidified with aqueous 3M sulphuric acid (7 ml), it was extracted with ethyl acetate (5 × 10 ml) to give the carboxylic acid. This in dry benzene (10 ml) was chilled to 0 °C, thionyl chloride (1 ml) was added, and the mixture was heated at 60 °C for 30 min, and then evaporated. The residual acid chloride was dissolved in dry tetrahydrofuran (3 ml) and added slowly to a solution of liquid ammonia (2 ml) in dry tetrahydrofuran (10 ml) at −78 °C. After the mixture had warmed to 17 °C, it was evaporated and the residue extracted with boiling acetone (10 ml). The filtered extracts were evaporated and the residue was chromatographed on silica using ethyl acetate to yield 2,2-*dimethylsuccinimide* (**41**) (101 mg), m.p. 106—107 °C (from ether) (Found: C, 56.5; H, 7.1; N, 10.9. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%); $\nu_{max.}$ 3 405, 3 205, 1 790, and 1 720 cm^{-1}; δ(A) 1.37 (6 H, s, 2 × Me), 2.62 (2 H, s, CH_2), and 8.73 (1 H, br s, NH); *m/z* 127 (M^+) and 100.

Further elution of the column with ethyl acetate–methanol (4:1) gave the *amide* (**39**) (339 mg, 42%), m.p. 106—108 °C (from ethyl acetate–ether) (Found: C, 57.1; H, 7.9; N, 22.3. $C_6H_{10}N_2O$ requires C, 57.1; H, 8.0; N, 22.2%); $\nu_{max.}$ 3 525, 3 410, 2 240w, 1 690, and 1 595 cm^{-1}; δ(B) 1.48 (6 H, s, 2 × Me), 2.45 (2 H, s, CH_2), and 5.83 (1 H, br s, NH); *m/z* 127 (*M* + 1), 126 (M^+), and 59 (100%).

Both the above products were visualised on t.l.c. plates by placing them in chlorine for 2 min followed by spraying with an aqueous solution of sodium iodide and starch.

4,4-Dimethyl-5-thioxopyrrolidin-2-one (**40**).—The foregoing amide (**39**) (1 g) in dry ethanol (20 ml) was stirred with a freshly prepared solution of sodium ethoxide (2M; 20 ml) for 1.75 h. The residue after evaporation was extracted with ethyl acetate–methanol and the soluble material was chromatographed on silica eluting first with ethyl acetate which removed yellow material. Elution with ethyl acetate–methanol (3:1) gave the intermediate iminopyrrolidone (890 mg, 89%), m.p. 242—244 °C; $\nu_{max.}$(Nujol mull) 3 300, 1 690, and 1 530 cm^{-1}; δ(B) (C_5D_5N) 1.32 (6 H, s, 2 × Me), 2.55 (2 H, s, CH_2), and 5.0 (2 H, br s, 2 × NH); *m/z* 126 (M^+), 111 and 56 (100%).

This product (1.76 g) was stirred in dry pyridine (130 ml) as hydrogen sulphide gas was passed through the solution for 1.5 h. The solution was then boiled for 15 min while nitrogen was passed through it. The pyridine was evaporated and totally removed by evaporation of added toluene (twice); the residue was then crystallised from ether-hexane to give the *monothioimide* (**40**) as yellow needles (1.59 g, 79.9%), m.p. 135—136 °C (Found: C, 50.2; H, 6.5; N, 10.0; S, 22.6. C_6H_9NOS requires C, 50.3; H, 6.3; N, 9.8; S, 22.4%); $\nu_{max.}$(CCl_4) 3 400, 3 200, 1 790, 1 770, 1 730, 1 425, and 1 170 cm^{-1}; δ(B) 1.37 (6 H, s, 2 × Me), 2.60 (2 H, s, CH_2), and 8.95 (1 H, br s, NH); *m/z* 143 (M^+), 128 (M^+ − Me), and 56.

3,3-Dimethylpyrrolidine-2,5-dithione (**42**).—A solution of 3,3-dimethylsuccinimide (1.27 g) and Lawesson's reagent (4.04 g) in dry toluene (40 ml) was heated at reflux under argon for 1.5 h and then evaporated. The residue was chromatographed on silica using dichloromethane–methanol (1:0, then 49:1, then 19:1). Crystallisation of the product eluted with dichloromethane from ether–hexane gave the *dithioimide* (1.3 g, 81%), m.p. 78—79 °C (Found: C, 45.0; H, 5.7; N, 8.5; S, 40.1%; M^+, 159.0174. $C_6H_9NS_2$ requires C, 45.2; H, 5.7; N, 8.8; S, 40.3%; *M*, 159.0176); δ 1.40 (6 H, s, CMe_2) and 3.08 (2 H, s, CH_2CS).

3,3-Dimethyl-5-thioxopyrrolidin-2-one (**43**) *and Its Isomer* (**40**).—A suspension of the foregoing dithione (120 mg) and sodium hydride (19 mg) in dry tetrahydrofuran (5 ml) was stirred under argon at 20 °C for 1 h. Methyl iodide (0.05 ml) in tetrahydrofuran (1 ml) was then added and after the mixture had been stirred for 1 h, water (5 ml) was added and stirring was continued for 1 h at 50 °C. The products were extracted into chloroform which was washed with water, dried, and evaporated. Fractionation of the residue by p.l.c. using ether–hexane (3:7) gave starting material (9.7 mg, 7.8%), the *monothioimide* (**43**) as pale yellow needles (20 mg), m.p. 143—144 °C (from ether–hexane), and the regioisomer (**40**), m.p. 135—136 °C (from ether–hexane). The last material was identical with that from the preparation described above.

For the thione (**43**): (Found: C, 50.5; H, 6.4; N, 9.8; S, 22.5%; M^+, 143.0404. C_6H_9NOS requires C, 50.3; H, 6.3; N, 9.8; S, 22.3%; *M*, 143.0408); δ 1.32 (6 H, s, CMe_2) and 2.98 (2 H, s, CH_2CS); δ_C(CD_2Cl_2) 25.0 (Me), 42.8 (CH_2), and 55.2 (C-3).

For the thione (**40**): (Found: C, 50.4; H, 6.3; N, 9.9; S, 22.3%; M^+, 143.0408. C_6H_9NOS requires C, 50.3; H, 6.3; N, 9.8; S,

22.3%; *M*, 143.0408); δ 1.42 (6 H, s, CMe_2) and 2.68 (2 H, s, CH_2CO); $\delta_C(CD_2Cl_2)$ 29.4 (Me), 45.1 (CH_2), 49.6 (C-3), 178.3 (C=O), and 223.1 (C=S).

The following ^{13}C spectra were run in CD_2Cl_2 for comparison: 2,5-dioxopyrrolidine (succinimide), δ_C 29.9 (CH_2) and 178.4 (C=O). 3,3,4,4-Tetramethylpyrrolidine-2,5-dione, δ_C 21.4 (Me), 48.3 (C-3 and C-4), and 183.1 (C=O). 3,3-Dimethylpyrrolidine-2,5-dione δ_C 25.3 (Me), 41.4 (C-3), 44.5 (CH_2), and 176.7 and 184.3 (C=O).

t-Butyl 5-Cyanomethyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**46**).—Sulphuryl chloride (3 g, 22.4 mmol), was added dropwise to a vigorously stirred solution of t-butyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate[15] (**44**) (6.8 g, 20 mmol) in dry dichloromethane (200 ml) containing anhydrous potassium carbonate (26 g) at 0 °C. The resultant mixture was stirred at 0 °C for 10 min and at 18 °C for 15 min and then filtered. Evaporation of the filtrate gave the chloromethylpyrrole (**45**) which in dry DMF (60 ml) was stirred with sodium cyanide (2 g, 40.8 mmol) at 18 °C for 4.5 h. The mixture was shaken with ether (300 ml) and water (300 ml) and the aqueous layer was further extracted with ether (2 × 100 ml, 1 × 150 ml). The combined organic layers were washed with water (300 ml) and brine (300 ml), dried, and evaporated. Chromatography (160 g; t.l.c. grade silica) using 5—10% MeOAc–CH_2Cl_2 then gave the *cyanomethylpyrrole* (**46**) as a gum (6.44 g, 88%) (Found: M^+, 364.1667. $C_{18}H_{24}N_2O_6$ requires *M*, 364.1634); δ(C) 1.53 (9 H, s, Bu^t), 2.43 (2 H, m, $CH_2CH_2CO_2$), 2.85 (2 H, m, $CH_2CH_2CO_2$), 3.47 (2 H, s, CH_2CO_2), 3.62 and 3.65 (each 3 H, s, OMe), 3.76 (2 H, s, CH_2CN), and 9.52 (1 H, br s, NH); *m/z* 364 (M^+, 3%), 308 ($M^+ - C_4H_8$), 276, and 248 (100).

[5-t-Butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrol-2-yl]cyanomethyltriphenylphosphonium Chloride (**48**).—A solution of the foregoing cyanomethylpyrrole (**46**) (44.7 mg, 0.12 mmol) in dichloromethane (2 ml) was stirred with potassium carbonate (166 mg, 1.2 mmol) during dropwise addition of sulphuryl chloride (17.6 mg, 0.13 mmol). The reaction mixture was stirred for a further 10 min, filtered through Celite, and evaporated to give the crude chlorocyanomethylpyrrole (**47**) as an oil; δ 1.60 (9 H, s, Bu^t), 2.55 (2 H, m, $CH_2CH_2CO_2$), 3.00 (2 H, m, $CH_2CH_2CO_2$), 3.56 (2 H, s, CH_2CO_2), 3.63 and 3.67 (each 3 H, s, OMe), 5.87 (1 H, s, CHCN), and 9.56 (1 H, br s, NH).

A solution of this product (**47**) [from 73.1 mg, 0.20 mmol of cyanomethylpyrrole (**46**)] in ether (10 ml) was treated dropwise with a solution of triphenylphosphine (57.7 mg, 0.22 mmol) in ether (2 ml). After 20 h, the precipitated *phosphonium salt* (**48**) was collected and washed with ether (40 ml) [96.9 mg, 73.3% from the cyanomethylpyrrole (**46**)], m.p. 139—175 °C (decomp.) (Found: C, 65.2; H, 5.8; Cl, 5.2; N, 4.1; P, 4.7. $C_{36}H_{38}ClN_2O_6P$ requires C, 65.4; H, 5.8; Cl, 5.4; N, 4.2; P, 4.7%); $\nu_{max.}$ 3 100br, 2 240w, 1 730, 1 690, and 1 440 cm^{-1}; $\delta(CD_2Cl_2)$ 1.47 (9 H, s, Bu^t), 2.53 (2 H, m, $CH_2CH_2CO_2$), 2.78 (2 H, m, $CH_2CH_2CO_2$), 3.14 (2 H, m, CH_2CO_2), 3.42 and 3.60 (each 3 H, s, OMe), and 7.50—8.00 (16 H, m, $CHPPh_3$).

t-Butyl 5-[Cyano(3,3-dimethyl-5-oxopyrrolidin-2-ylidene)methyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**49**).—Potassium t-butoxide solution was prepared by heating clean potassium (4.4 g) in dry t-butyl alcohol (200 ml) at reflux under argon until all the potassium had dissolved. This solution (25 ml) was added dropwise under argon to a stirred suspension of the foregoing monothioimide (**40**) (1.61 g) and the phosphonium salt (**48**) (5.29 g) in dry toluene (400 ml). The mixture was stirred at 18 °C for 5 min and then heated under reflux for 8.5 h. It was cooled, shaken with saturated aqueous ammonium chloride (70 ml), diluted with water (500 ml), and extracted with dichloromethane (4 × 100 ml). The combined extracts were dried and evaporated, and the residue was purified by flash chromatography using dichloromethane–methyl acetate (9:1) to give the (E)-*cyano lactam* (**49**) as a foam (2.78 g, 73%) (Found: M^+, 473.2162. $C_{24}H_{31}N_3O_7$ requires *M*, 473.2162); $\nu_{max.}(CCl_4)$ 3 450, 3 275, 2 210, 1 750, 1 700, and 1 650 cm^{-1}; $\lambda_{max.}$(MeOH) 251 and 275sh: [+$Zn(OAc)_2$] 247, 280, 294, 303, and 363 nm; δ_H(D) 1.55 (9 H, s, Bu^t), 1.63 (6 H, s, CMe_2), 2.51 (2 H, s, CH_2CONH), 2.52 (2 H, m, $CH_2CH_2CO_2$), 2.90 (2 H, m, $CH_2CH_2CO_2$), 3.40 (2 H, s, CH_2CO_2), 3.65 and 3.71 (each 3 H, s, OMe), and 8.60 and 8.98 (each 1 H, br s, NH); δ_C(F)($CDCl_3$), 20.8 (t, $CH_2CH_2CO_2$), 26.9 (q, CMe_2), 28.5 (q, CMe_3), 30.2 (t, CH_2CO_2), 34.8 (t, $CH_2CH_2CO_2$), 40.1 (s, CMe_2), 45.85 (t, CH_2CONH), 51.5 and 52.6 (both q, 2 × CO_2Me), 74.7 (s, CMe_3), 81.9 (s, C=C–CN), 117.2, 117.4, 122.3, 123.0, and 129.15 (each s, 4 × pyrrole–C and CN), 160.2 (2 C, s, C=CCN and CO_2Bu^t), and 172.8, 173.4, and 174.05 (each s, C=O); *m/z* 473 (M^+, 15%), 417 ($M^+ - C_4H_8$, 100), and 385.

The *Z* isomer was also isolated (0.4 g, 10%), m.p. 200—203 °C (Found: M^+, 473.2162. $C_{24}H_{31}N_3O_7$ requires *M*, 473.2162); $\nu_{max.}$ 3 440, 3 390, 2 190, 1 735, 1 680, and 1 620 cm^{-1}; $\lambda_{max.}$(EtOH) 252 and 267sh; [+$Zn(OAc)_2$] 252 and 267sh nm; δ(D) 1.16 (6 H, s, CMe_2), 1.57 (9 H, s, Bu^t), 2.48 (2 H, s, CH_2CONH), 2.50 (2 H, m, $CH_2CH_2CO_2$), 2.93 (2 H, m, $CH_2CH_2CO_2$), 3.48 (2 H, s, CH_2CO_2), 3.64 and 3.67 (each 3 H, s, OMe), and 8.03 and 8.80 (each 1 H, br s, NH); *m/z* 473 (M^+, 12%), 417 ($M^+ - C_4H_8$, 100), and 385.

t-Butyl 5-[1-(3,3-Dimethyl-5-oxopyrrolidin-2-ylidene)ethyl]-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**52**).—(*a*) To a solution of the nitrile (**49**) (100 mg) in methanol–water–acetic acid (80:20:1) (50 ml) was added *freshly prepared* Raney nickel (*ca.* 350 mg) and the mixture was stirred at 18 °C under hydrogen until reduction was complete (12—36 h). The solution was filtered through Celite and the catalyst washed several times with methanol (*ca.* 300 ml). The filtrate was evaporated (at *ca.* 10 °C) and the residue was purified by p.l.c. on silica gel using dichloromethane–methanol (9:1) to give the separated isomeric amines (**50**) (total 86 mg, 85%).

Z Isomer: *m/z* 477 (f.d.); $\lambda_{max.}$(MeOH) 280; [+$Zn(OAc)_2$] 290 nm; δ 1.50 (6 H, s, CMe_2), 1.57 (9 H, s, Bu^t), 2.43 (2 H, s, CH_2CO), 2.55 (2 H, m, $CH_2CH_2CO_2$), 2.91 (2 H, m, $CH_2CH_2CO_2$), 3.40 (2 H, s, CH_2CO_2), 3.67 and 3.72 (each 3 H, s, OMe), 3.78 (2 H, br s, CH_2NH_2), and 7.51 and 10.11 (each 1 H, br, NH).

E Isomer: *m/z* 477 (f.d.); $\lambda_{max.}$(MeOH) 280 nm; [+$Zn(OAc)_2$] no shift; δ 1.03 (6 H, s, CMe_2), 1.57 (9 H, s, Bu^t), 2.34 (2 H, s, CH_2CO), 2.54 (2 H, m, $CH_2CH_2CO_2$), 2.97 (2 H, m, $CH_2CH_2CO_2$), 3.52 (2 H, s, CH_2CO_2), 3.64 and 3.73 (each 3 H, s, OMe), 3.76 (2 H, br, CH_2NH_2), 5.4 (br, NH), and 9.15 (1 H, br, NH).

Other fractions from the plates afforded small amounts of the *Z* and *E* forms of the *C*-methyl system (**52**), typically 2—3% and also the saturated lactam (**54**), typically 4%. These products were identified by comparison with authentic samples (see later).

A solution of the foregoing mixed *Z* and *E* amines (**50**) (303 mg) in acetic acid (6 ml) and tetrahydrofuran (20 ml) was stirred at 50 °C during the addition of a solution of isopentyl nitrite (95 mg) in tetrahydrofuran (2 ml). The mixture was stirred at 50 °C for 10 min and then evaporated at 20 °C to 7 ml and diluted with acetic acid (6 ml). Acetic anhydride (6 ml) then 10% palladium on charcoal (130 mg) were added and the mixture was stirred under hydrogen until hydrogenolysis was complete (3 h). The solution was filtered through Celite and evaporated to leave an oil which was fractionated by p.l.c. using dichloromethane–

methanol (19:1) to give the *Z* isomer (**52**) and the *E* isomer (ratio 5:2; combined yield, 159 mg, 54%).

Z Isomer (**52**): m.p. 148—150 °C (from dichloromethane–hexane) (Found: M^+, 462.2366. $C_{24}H_{34}N_2O_7$ requires *M*, 462.2366); $\lambda_{max.}$ 282 and 230 nm [unchanged by the addition of $Zn(OAc)_2$]; $\delta(CD_2Cl_2)$ 1.47 (6 H, s, CMe_2), 1.58 (9 H, s, Bu^t), 1.96 (3 H, s, MeC=C), 2.41 (2 H, s, CH_2CO), 2.56 (2 H, m, $CH_2CH_2CO_2$), 2.92 (2 H, m, $CH_2CH_2CO_2$), 3.38 (2 H, s, CH_2CO_2), 3.67 and 3.69 (each 3 H, s, OMe), 7.09 (1 H, br, NH), and 8.65 (1 H, br, NH).

E *Isomer*: m.p. 201—205 °C (from dichloromethane–hexane) (Found: M^+, 462.2361. $C_{24}H_{34}N_2O_7$ requires *M*, 462.2366); $\delta(CD_2Cl_2)$ 0.983 (6 H, s, CMe_2), 1.54 (9 H, s, Bu^t), 1.78 (3 H, s, MeC=C), 2.30 (2 H, s, CH_2CO), 2.54 (2 H, m, $CH_2CH_2CO_2$), 2.93 (2 H, m, $CH_2CH_2CO_2$), 3.39 (2 H, s, CH_2CO_2), 3.61 and 3.64 (each 3 H, s, OMe), 7.54 (1 H, br, NH), and 8.75 (1 H, br, NH).

(*b*) The following is a representative example of one of the many sets of conditions tested. The nitrile (**49**) (251 mg) and 10% palladium on charcoal (106 mg) were degassed under argon and then suspended in *p*-menth-1-ene (10 ml) containing Hunig's base (5 ml). The mixture was heated under reflux for 7 h and then filtered and evaporated. Fractionation of the residue by p.l.c. using dichloromethane–ether (3:1) gave recovered starting material (87 mg, 35%), the *Z* and *E* isomers of the *C*-methyl system (**52**) (total 49 mg, 20%), and the saturated lactam (**54**) (28.5 mg, 12%). The former products were identical with those from method (*a*).

The *Z* and *E* isomers of the *C*-methyl system (**52**) from both methods (*a*) and (*b*) were converted into the formyl derivatives (**36**) and (**37**) to establish identity with the earlier preparations.

2-*Formyl*-5-[1-(5-*methoxy*-3,3-*dimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*ylidene*)*ethyl*]-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole* (**23**).—The *Z* isomer of the formyl lactam (**36**) (23.6 mg) in dry benzene (5 ml) was stirred at 18 °C in the dark under argon with silver carbonate (80 mg). After 4.5 h, methyl iodide (1.5 ml) was added and stirring was continued for 67 h. The supernatant was removed by pipette, the solid washed with benzene (8 ml), and the solution was evaporated to a gum which by p.l.c. using ether–methanol (19:1) gave the *formyl imidate ester* (**23**) as a gum (9 mg, 37%) together with starting material (7 mg, 30%) (53% based on unrecovered starting material) (Found: M^+, 404.1941. $C_{21}H_{28}N_2O_6$ requires *M*, 404.1948); $\delta(F)(CD_2Cl_2)$ 1.44 (6 H, s, CMe_2), 2.16 (3 H, s, C=CMe), 2.59 (2 H, m, $CH_2CH_2CO_2$), 2.61 (2 H, s, $CH_2C{=}N$), 3.06 (2 H, m, $CH_2CH_2CO_2$), 3.37 (2 H, s, CH_2CO_2), 3.66 and 3.70 (each 3 H, s, CO_2Me), 4.02 (3 H, s, N=C–OMe), and 9.60 (1 H, s, CHO).

t-Butyl 5-[1-(3,3-*Dimethyl*-5-*thioxopyrrolidin*-2-*ylidene*)-*ethyl*]-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-*pyrrole*-2-*carboxylate* (**53**).—A solution of the *C*-methyl lactam (**52**) (108 mg) and Lawesson's reagent (50 mg) in toluene (5 ml) was stirred at 100 °C for 15 min and then evaporated. The residue was purified by flash column chromatography using dichloromethane–diethyl ether (from 1:0 to 0:1) to give the *Z* and *E* isomers of the title *thiolactam* in a ratio of 3:1 (combined yield 100 mg, 89%).

Z Isomer (**53**): (Found: M^+, 478.2148. $C_{24}H_{34}N_2O_6S$ requires *M*, 478.2137); $\delta(CD_2Cl_2)$ 1.42 (6 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 1.94 (3 H, s, MeC=C), 2.57 (2 H, m, $CH_2CH_2CO_2$), 2.89 (2 H, s, CH_2CS), 2.90 (2 H, m, $CH_2CH_2CO_2$), 3.36 (2 H, s, CH_2CO_2), 3.64 and 3.69 (each 3 H, s, OMe), 8.67 (1 H, br, NH), and 8.74 (1 H, br, NH).

E *Isomer*: m.p. 85—90 °C (decomp.) (from ether) (Found: M^+, 478.2145. $C_{24}H_{34}N_2O_6S$ requires *M*, 478.2137); $\delta(CD_2Cl_2)$ 0.95 (6 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 1.87 (3 H, s, MeC=C), 1.54 (2 H, m, $CH_2CH_2CO_2$), 2.78 (2 H, s, CH_2CS), 2.93 (2 H, m, $CH_2CH_2CO_2$), 3.39 (2 H, s, CH_2CO_2), 3.61 and 3.69 (each 3 H, s, OMe), and 8.88 (2 H, br, 2 × NH).

The same ratio of *Z* and *E* isomeric thiolactams was obtained by treating the *E* lactam [isomer of (**52**)] under the above conditions.

When a solution of the separated *E* thiolactam was heated in toluene at reflux for 30 min, the equilibrated mixture of *Z* and *E* isomers in the ratio 3:1 respectively was produced which could be separated as above.

5-[1-(3,3-*Dimethyl*-5-*methylthio*-3,4-*dihydro*-2H-*pyrrol*-2-*ylidene*)*ethyl*]-2-*formyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole* (**55**).—A solution of the foregoing *Z*-thioamide (**53**) (54 mg) in freshly distilled trifluoroacetic acid (1.5 ml) was stirred at 18 °C under nitrogen for 40 min, then trimethyl orthoformate (0.2 ml) was added. After being stirred at 18 °C for 10 min, the solution was evaporated to dryness to give an oil which crystallised; this was shown to be essentially pure *imino thioether* and it was used directly for the next stage [under (*b*) below]; *m/z* 420 (f.d.); $\delta(CD_2Cl_2)$ 1.39 (6 H, s, CMe_2), 2.17 (3 H, s, MeC=C), 2.55 (2 H, m, $CH_2CH_2CO_2$), 2.64 (3 H, s, SMe), 2.74 (2 H, s, CH_2CS), 3.01 (2 H, m, $CH_2CH_2CO_2$), 3.64 and 3.68 (each 3 H, s, OMe), 3.69 (2 H, s, CH_2CO_2), 9.60 (1 H, s, CHO), and 12.31 (1 H, br, NH); δ_C(assignments using DEPT pulse sequence) 13.6 and 14.6 (3 × CMe), 17.9 ($CH_2CH_2CO_2$), 26.3 (SMe), 30.1 (CH_2CO_2), 35.2 ($CH_2CH_2CO_2$), 42.8 (CMe_2), 50.6 and 51.0 (OMe), 54.07 ($CH_2C{=}N$), 110.1, 114.1, 126.65, 132.8, and 137.5 (4 × pyrrole–C and C=C–N), 158.7 (C=*C*–N), 171.3 and 171.9 (CO_2), 175.6 (CHO), and 176.3 (C=N).

13,17-*Bis*(2-*methoxycarbonylethyl*)-12,18-*bis*(*methoxycarbonylmethyl*)-2,2,8,8,20-*pentamethylisobacteriochlorin* (**20**).—(*a*) *The oxygen series.* The imine (**56**) was generated as previously[9] from the corresponding 5-t-butoxycarbonyl derivative[9] (28 mg) which was dissolved in trifluoroacetic acid (2 ml) and kept under argon for 2 h. The solution was evaporated to dryness in a stream of nitrogen and the residue was evacuated (0.05 mmHg) for 1 h. To this was added under argon, using a gas-tight syringe, a solution of the foregoing imino ether (**23**) (8.8 mg) in dry methanol (1 ml) containing trimethyl orthoformate (0.15 ml). 10% Trifluoroacetic acid in methanol (5 drops) was then added, a deep blue colour developed and after 15 min, 10% Hunig's base in methanol (0.1 ml) was added. The mixture was then then washed into a glass tube using degassed tetrahydrofuran (35 ml) and after several freeze-pump-thaw series, the tube was sealed. It was irradiated through an aqueous dichromate filter by 5 × 100 W tungsten lamps for 137 h and the contents of the tube were then evaporated. The residue in dichloromethane (20 ml) was washed with 0.2M hydrochloric acid and 1% aqueous sodium hydrogen carbonate and the organic solution was dried and evaporated. The residue was purified by chromatography on silica using dichloromethane–methyl acetate (1:0 then 19:1 then 9:1). The middle eluant yielded the product which was further purified by p.l.c. using ether–methyl acetate (9:1) to yield the 20-*methylisobacteriochlorin* (**20**) as a dark red-violet solid (2 mg, 13%); full characterisation given under (*b*).

(*b*) *The sulphur series.* All operations were carried out under strictly anhydrous conditions and under argon. A solution of the *imino thioether* (**55**) (16 mg) and the imine[9] (**56**) (20 mg) in trifluoroacetic acid (0.4 ml) was stirred at 18 °C for 3 h and then evaporated. The residue was dissolved in tetrahydrofuran (25 ml) to give a blue solution which became red when Hunig's base (*ca.* 0.1 ml) was added. This solution was transferred to a glass tube, diluted with tetrahydrofuran (to *ca.* 100 ml) and after thorough degassing by freeze-pump-thaw, the tube was sealed and irradiated at 30 °C as under (*a*) for 16 h.

The tube's contents were evaporated and the residue was purified as under (*a*) to yield the 20-*methylisobacteriochlorin* (6.4 mg, 26%), m.p. 152—155 °C (from dichloromethane–hexane) (Found: M^+, 700.3476. $C_{39}H_{48}N_4O_8$ requires *M*, 700.3472); $\lambda_{max.}(CH_2Cl_2)$ 640, 590, 546, 402, 374, 358sh, and 268; (MeCN) 640, 588, 542, 398, 370, 358sh, and 268 nm; $\delta(CD_2Cl_2)$ 1.64 (*6 H, s*, 8-CMe_2), 1.71 (6 H, s, 2-CMe_2), 2.81 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 2.89 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 2.93 (3 H, s, 20-Me), 3.58 (2 H, s, 7-CH_2), 3.59 (2 H, s, 3-CH_2), 3.59 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.64 (6 H, s, 2 × OMe), 3.68 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.72 and 3.76 (each 3 H, s, OMe), 4.23 (2 H, s, 12-CH_2CO_2), 4.32 (2 H, s, 18-CH_2CO_2), 6.64 (1 H, s, 5-H), 7.11 (1 H, s, 10-H), and 8.38 (1 H, s, 15-H).

This product was shown to be identical with that from method (*a*).

(E)-t-*Butyl* 3-(2-*Methoxycarbonylethyl*)-4-*methyl*-5-(2-*nitrovinyl*)*pyrrole*-2-*carboxylate* (**65**).—To t-butyl 3-(2-methoxycarbonylethyl)-4,5-dimethylpyrrole-2-carboxylate[15] (**63**) (8.78 g) in glacial acetic acid (30 ml) was added lead tetra-acetate (30 g) during 5 min and the mixture was heated for 3.25 h at 65 °C. More lead tetra-acetate (5 g) was then added and the mixture heated at 70 °C for a further 30 min. After addition of ethylene glycol (4 ml), the mixture was poured into water (200 ml) and extracted with dichloromethane (40 ml, 2 × 30 ml). The extracts gave an oil which was dissolved in tetrahydrofuran (50 ml) and water (50 ml) and heated under reflux for 2.5 h. After cooling, ether (50 ml) was added and the organic layer was washed with aqueous sodium hydrogen carbonate (3 × 25 ml), then brine (30 ml), dried, and evaporated to give the *formylpyrrole* (**64**) (9.78 g) as an oil which was used directly in the next stage; $\nu_{max.}(CCl_4)$ 3 460, 3 440, 1 740, 1 705, and 1 655 cm^{-1}; δ(B)(CCl_4), 1.53 (9 H, s, Bu^t), 2.30 (3 H, s, ArMe), 2.43 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 2.93 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.58 (3 H, s, OMe), 9.73 (1 H, s, CHO), and 9.98 (1 H, br s, NH).

The foregoing formylpyrrole (**64**) (9.72 g) was stirred in dry methanol (60 ml) for 5 h with potassium acetate (3.94 g), methylamine hydrochloride (2.22 g), and nitromethane (4.07 g). The mixture was poured into water (300 ml) and extracted with dichloromethane (100 ml, 4 × 50 ml) to give an oil which by chromatography on silica using dichloromethane–ether (19:1) gave the *nitrovinylpyrrole* (**65**) as orange needles (5.33 g), m.p. 128.5—130 °C (from methyl acetate–hexane) (Found: C, 56.9; H, 6.3; N, 8.3. $C_{16}H_{22}N_2O_6$ requires C, 56.8; H, 6.5; N, 8.3%); $\nu_{max.}(CCl_4)$ 3 450, 3 290, 1 740, 1 690, 1 670, 1 628, 1 510, and 1 330 cm^{-1}; δ(B) 1.59 (9 H, s, Bu^t), 2.18 (3 H, s, ArMe), 2.53 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 2.96 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.25 (2 H, t, *J* 7.5 Hz, $CH_2CH_2NO_2$), 3.63 (3 H, s, OMe), 4.48 (2 H, t, *J* 7.5 Hz, $CH_2CH_2NO_2$), and 9.05 (1 H, br s, NH); *m*/*z* 340 (M^+) and 284 ($M^+ - C_4H_8$).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methyl*-5-(2-*nitroethyl*)*pyrrole*-2-*carboxylate* (**66**).—Sodium borohydride (1.2 g) was stirred with the foregoing nitrovinylpyrrole (**65**) (5.2 g) in absolute ethanol (250 ml) for 45 min. The residue from evaporation was dissolved in water (250 ml), acidified with acetic acid (*ca.* 4 ml) and the precipitated solid was recrystallised from aqueous methanol to give the *nitroethylpyrrole* (**66**) as yellow needles (4.07 g, 78%), m.p. 112.5—114 °C (Found: C, 56.4; H, 7.3; N, 8.4. $C_{16}H_{24}N_2O_6$ requires C, 56.5; H, 7.1; N, 8.2%); $\nu_{max.}(CCl_4)$ 3 445, 3 305, 1 738, 1 685, 1 658, 1 435, and 1 365 cm^{-1}; δ(B) 1.53 (9 H, s, Bu^t), 1.93 (3 H, s, ArMe), 2.46 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 2.96 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.25 (2 H, t, *J* 7.5 Hz, $CH_2CH_2NO_2$), 3.63 (3 H, s, OMe), 4.48 (2 H, t, *J* 7.5 Hz, $CH_2CH_2NO_2$), and 9.05 (1 H, br s, NH); *m*/*z* 340 (M^+) and 284 ($M^+ - C_4H_8$).

t-Butyl 5-(3,3-*Dimethyl*-2-*nitro*-5-*oxohexyl*)-3-(2-*methoxycarbonylethyl*)-4-*methylpyrrole*-2-*carboxylate* (**67**).—The foregoing nitroethylpyrrole (**66**) (1.83 g) in dry dimethylformamide (75 ml) was stirred with 4 Å molecular sieves (3 g) under argon for 4 h with mesityl oxide (2.16 g) and tetrabutylammonium fluoride (1M in tetrahydrofuran; 5.4 ml). The mixture was poured into water (150 ml) and extracted with ether (50 ml, 3 × 30 ml). The extracts were washed with 1M hydrochloric acid (50 ml), 5% aqueous sodium hydrogen carbonate (50 ml), and brine (50 ml), dried, and evaporated. After the product had been kept under high vacuum for 24 h to remove mesityl oxide, it was crystallised from methyl acetate–hexane to give the *nitro ketone* (**67**) (1.54 g). The material in the mother liquor was chromatographed on silica using dichloromethane–methyl acetate (19:1) to give more product (0.33 g; total 1.87 g, 79%), m.p. 117—118 °C (Found: C, 60.1; H, 7.8; N, 6.5%; M^+, 438.2361. $C_{22}H_{34}N_2O_7$ requires C, 60.2; H, 7.8; N, 6.4%; *M*, 438.2366); $\nu_{max.}(CCl_4)$ 3 440, 1 740, 1 720, 1 685, 1 440, and 1 365 cm^{-1}; δ(B) 1.10 and 1.23 (each 3 H, s, CMe_2), 1.52 (9 H, s, Bu^t), 1.90 (3 H, s, ArMe), 2.12 (3 H, s, MeCO), 2.25—2.72 (4 H, m, $CH_2CH_2CO_2$ and CH_2COMe), 2.85—3.42 (4 H, m, $CH_2CH_2CO_2$ and CH_2CHNO_2), 3.62 (3 H, s, OMe), 5.08 (1 H, dd, *J* 10.5 and 3 Hz, $CHNO_2$), and 8.67 (1 H, br s, NH); *m*/*z* 438 (M^+, 40%), 336, and 278 (100).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methyl*-5-(3,3,5-*trimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*yl*)*methylpyrrole*-2-*carboxylate* (**69**).—The foregoing nitro ketone (**67**) (440 mg) in glacial acetic acid (16 ml) was stirred with zinc dust (1.84 g) for 45 min. The zinc was filtered off, ammonium acetate (1.84 g) added to the filtrate, and the latter degassed and 15% aqueous titanium(III) chloride (4 ml) added to it. This solution was stirred under nitrogen for 5.5 h after which water (20 ml), dichloromethane (40 ml), and Hyflo-supercel (3 spatulas) were added to it and the mixture basified with 30% aqueous ammonia solution (120 ml). The layers in the filtered mixture were separated and the aqueous layer was extracted with dichloromethane; the combined extracts were then washed with 5% aqueous sodium hydrogen carbonate (50 ml), dried, and evaporated. The residue by p.l.c. using methyl acetate–dichloromethane (1:1) gave the *imine* (**69**) as a gum (334 mg, 86%) (Found: M^+, 390.2487. $C_{22}H_{34}N_2O_4$ requires *M*, 390.2518); $\nu_{max.}(CCl_4)$ 3 345, 1 740, 1 690, and 1 650 cm^{-1}; δ(B) 0.90 and 1.08 (each 3 H, s, CMe_2), 1.50 (9 H, s, Bu^t), 1.92 (3 H, s, ArMe), 1.98 (3 H, d, *J* 3 Hz, N=CMe), 2.30 (2 H, br s, CH_2C=N), 2.35—2.60 (4 H, m, $CH_2CH_2CO_2$ and CH_2CHN), 3.00 (2 H, m, $CH_2CH_2CO_2$), 3.50 (1 H, m, CHN), 3.61 (3 H, s, OMe), and 10.25 (1 H, br s, NH); *m*/*z* 390 (M^+), 281, 224, and 110 (100%).

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methyl*-5-(3,3,5-*trimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*ylidene*)*methylpyrrole*-2-*carboxylate* (**68**).—(*a*) The foregoing imine (**69**) (120 mg) in glacial acetic acid (8 ml) was stirred with lead tetra-acetate (0.2 g) for 4 h and then ethylene glycol (12 drops) was added and the mixture evaporated. A solution of the residue in dichloromethane (20 ml) was washed with water (20 ml then 10 ml) and 5% aqueous sodium hydrogen carbonate (10 ml), dried, and filtered. The filtrate was stirred with formic acid (158 mg) for 20 h and then washed with 5% aqueous sodium hydrogen carbonate (25 ml), dried, and evaporated. The residue by p.l.c. using dichloromethane–methanol (9:1) gave the *unsaturated imine* (**68**) as a gum (59 mg, 49%) (Found: M^+, 388.2353. $C_{22}H_{32}N_2O_4$ requires *M*, 388.2362); $\nu_{max.}(CCl_4)$ 3 360, 1 740, 1 690, 1 640, and 1 595 cm^{-1}; δ(C) 1.19 (6 H, s, CMe_2), 1.55 (9 H, s, Bu^t), 2.03 (3 H, s, ArMe), 2.20 (3 H, s, N=CMe), 2.50 (2 H, s, CH_2C=N), 2.52 (2 H, m, $CH_2CH_2CO_2$), 3.02 (2 H, m, $CH_2CH_2CO_2$), 3.64 (3 H, s, OMe), 5.65 (1 H, s, HC=C), and 11.20 (1 H, br s, NH); *m*/*z* 388 (M^+, 25%), 364, and 332 ($M^+ - C_4H_8$, 100).

(*b*) The above nitro ketone (**67**) (110 mg) in dry tetrahydrofuran (0.5 ml) and dry methanol (1 ml) was stirred with sodium methoxide (34 mg) under nitrogen for 25 min. This solution was injected into a previously degassed solution of ammonium acetate (0.35 g) and 15% aqueous titanium(III) chloride (1.4 ml) in water (1.5 ml), being washed in with more tetrahydrofuran (1.5 ml). The mixture was stirred for 5 h, extracted with ether (2 × 15 ml, 10 ml) and the extracts were washed with 5% aqueous sodium hydrogen carbonate (15 ml) and brine (15 ml), dried, and evaporated. The residue was purified by p.l.c. as above to give the *unsaturated imine* (**68**) (50 mg, 51%) identical with that from (*a*) above.

13,17-*Bis*(2-*methoxycarbonylethyl*)-18-*methoxycarbonylmethyl*-2,2,8,8,12,20-*hexamethylisobacteriochlorin* (**21**).—All glassware was baked overnight prior to use and the tetrahydrofuran was freshly distilled from potassium and degassed by passage of argon for 3 h.

The foregoing imine (**68**) (22 mg) was stirred with trifluoroacetic acid (0.35 ml) for 50 min under argon. Then a solution of the formyl imidate ester (**23**) (7 mg) in dry methanol (1 ml) and trimethyl orthoformate (0.25 ml) was transferred into the above solution through a double-ended needle. After the solution had been stirred for 15 min, dry degassed tetrahydrofuran (10 ml) and Hunig's base (*ca.* 0.6 ml) were added and the solution was transferred under argon to a thick-walled tube, being washed in with tetrahydrofuran (30 ml). The solution was degassed by three cycles of 'freeze/pump/thaw' at 0.1 mmHg and then sealed *in vacuo* and irradiated through a liquid filter of sodium dichromate solution with water-cooling for 70 h by a 1 000 W array of tungsten bulbs. The contents of the tube were evaporated and the residue was dissolved in dichloromethane (50 ml) and washed with 0.2M hydrochloric acid (20 ml) and saturated aqueous sodium hydrogen carbonate (20 ml), dried, and evaporated. The residue by p.l.c. (indicator-free silica plates with concentration zone) using dichloromethane–methyl acetate (9:1) yielded the 20-*methylisobacteriochlorin* (**21**), as a purple gum (0.85 mg, 7.6%) (Found: M^+, 642.3417. $C_{37}H_{46}N_4O_6$ requires M, 642.3417); $\lambda_{max.}$(CH_2Cl_2), 304, 358sh, 373, 403, 540sh, 596, and 638 nm; δ(G)(CD_2Cl_2) 1.69 and 1.76 (each 6 H, s, CMe_2), 2.81 (3 H, s, 12-Me), 2.82 and 2.90 (each 2 H, m, 2 × $CH_2CH_2CO_2$), 3.00 (3 H, s, 20-Me), 3.6—3.7 (14 H, m, 2 × OMe, 2 × $CH_2CH_2CO_2$, 3-CH_2, and 7-CH_2), 3.76 (3 H, s, OMe), 4.32 (2 H, br s, CH_2CO_2), 6.77 (1 H, s, 5-H), 7.22 (1 H, s, 10-H), and 8.52 (1 H, br s, 15-H).

5-[*Cyano*(3,3-*dimethyl*-5-*oxopyrrolidin*-2-*ylidene*)*methyl*]-2-*formyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole* (**71**).—A solution of the (*E*)-cyano lactam (**49**) (236 mg) in trifluoroacetic acid (3 ml) was stirred at 0 °C under argon for 5 min and then evaporated. The resultant acid (**70**) in dichloromethane (12 ml) was heated under reflux with a solution of toluene-*p*-sulphonic acid monohydrate (205 mg) in methanol (3 ml) for 20 h and then evaporated. The residual gum in trifluoroacetic acid (9 ml) was stirred with trimethyl orthoformate (5 ml) at 0 °C under argon for 15 min and then diluted with water (9 ml). After being stirred for a further 30 min, the mixture was diluted with dichloromethane (70 ml) and basified with aqueous 30% ammonia (28 ml). The organic layer was dried and evaporated and the residue was purified by p.l.c. using first dichloromethane–methanol (9:1) and then ether–methanol (93:7) to give the (E)-*formyl cyanolactam* (**72**) as a gum (156 mg, 78%) (Found: M^+, 401.1566. $C_{20}H_{23}N_3O_6$ requires M, 401.1587); $\nu_{max.}$ 3 440, 3 250, 2 215, 1 745, and 1 630 cm^{-1}; $\lambda_{max.}$(MeOH) 254 and 305; [+$Zn(OAc)_2$] 262, 300, 388, and 403 nm; δ(C) 1.65 (6 H, s, CMe_2), 2.53 (2 H, s, CH_2CONH), 2.54 (2 H, m, $CH_2CH_2CO_2$), 3.00 (2 H, m, $CH_2CH_2CO_2$), 3.44 (2 H, s, CH_2CO_2), 3.66 and 3.73 (each 3 H, s, OMe), 8.64 and 9.52 (each 1 H, br s, NH), and 9.67 (1 H, s, CHO); *m/z* 401 (M^+, 100%) and 369.

The minor product was the *Z* isomer of the formyl cyanolactam as a gum (3.5 mg, 1.7%) (Found: M^+, 401.1594. $C_{20}H_{23}N_3O_6$ requires M, 401.1587); $\nu_{max.}$ 3 440, 3 240, 2 210, 1 745, 1 655, and 1 625 cm^{-1}; $\lambda_{max.}$(MeOH) 255 and 298; [+$Zn(OAc)_2$] 256 and 298 nm; δ(C) 1.16 (6 H, s, CMe_2), 2.49 (2 H, s, CH_2CONH), 2.62 (2 H, m, $CH_2CH_2CO_2$), 3.08 (2 H, s, $CH_2CH_2CO_2$), 3.49 (2 H, s, CH_2CO_2), 3.65 and 3.69 (each 3 H, s, OMe), 8.16 and 9.21 (each 1 H, s, NH), and 9.72 (1 H, s, CHO); *m/z* 401 (M^+, 100%) and 369.

5-[*Cyano*(3,3-*dimethyl*-5-*methoxy*-3,4-*dihydro*-2H-*pyrrol*-2-*ylidene*)*methyl*]-2-*formyl*-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole* (**72**).—The foregoing (*E*)-formyl cyanolactam (**71**) (40 mg) in dry benzene (4.5 ml) was stirred at 18 °C in the dark with silver carbonate (69 mg) for 1.5 h. Methyl iodide (1.5 ml) was added and stirring was continued for 47 h; the supernatant was then removed, filtered through Celite, washed through with more benzene, and evaporated. The residue was purified by p.l.c. using ether–methanol (19:1) to give the *imidate* (**72**) as a gum (13.8 mg, 33%) (Found: M^+, 415.1760. $C_{21}H_{25}N_3O_6$ requires M, 415.1743); δ(E)(CD_2Cl_2), 1.60 (6 H, s, CMe_2), 2.65 (2 H, m, $CH_2CH_2CO_2$), 2.77 (2 H, s, $CH_2C{=}N$), 3.06 (2 H, m, $CH_2CH_2CO_2$), 3.66 and 3.73 (each 3 H, s, 2 × CO_2Me), 3.90 (2 H, s, CH_2CO_2), 4.21 (3 H, s, MeOC=N), 9.69 (1 H, s, CHO), and 11.75 (1 H, br s, NH); *m/z* 415 (M^+, 100%) and 356.

20-*Cyano*-13,17-*bis*(2-*methoxycarbonylethyl*)-12,18-*bis*-(*methoxycarbonylmethyl*)-2,2,8,8-*tetramethylisobacteriochlorin* (**75**).—The precautions were as for the earlier isobacteriochlorin synthesis.

The α-free pyrrole (**56**), derived as earlier from the corresponding t-butyloxycarbonyl derivative (22.3 mg), in trifluoroacetic acid (0.25 ml) was mixed under argon with the foregoing imidate ester (**72**) (14.3 mg) dissolved in dry methanol (1.4 ml) and trimethyl orthoformate (0.15 ml) and washed in with methanol (0.5 ml). After being stirred for 30 min, the mixture was diluted with dry, degassed tetrahydrofuran (6 ml) containing Hunig's base (*ca.* 0.5 ml) and then transferred into a thick walled tube, being washed in with more tetrahydrofuran (35 ml). The solution was degassed by three cycles of 'freeze/pump/thaw' at 0.1 mmHg and then sealed *in vacuo*. The tube was irradiated by a 1000 W array of tungsten bulbs, through a filter of aqueous sodium dichromate, with water cooling for 114 h. The residue from evaporation of the tube contents was dissolved in dichloromethane (50 ml), washed with 0.2M hydrochloric acid (20 ml) and 3% aqueous sodium hydrogen carbonate (20 ml), dried, and evaporated. The residue was chromatographed on a column of indicator free t.l.c.-grade silica (3 cm × 1 cm) eluting with 0—10% methyl acetate in dichloromethane. The fractions which were fluorescent under long wavelength u.v. light were combined, concentrated, and rechromatographed on indicator-free silica plates with concentration zone, eluting with dichloromethane–methyl acetate (9:1). Three bands were observed: a high R_F olive green band (f.d.m.s., M^+, 717), the purple major product band, and a low R_F blue band corresponding to seco-*lactam* (Found: M^+, 729.3366. $C_{39}H_{47}N_5O_9$ requires M, 729.3373).

The major band was extracted with methyl acetate to give the 20-*cyanoisobacteriochlorin* (**75**) as a purple gum (13 mg, 53%) which crystallised from dichloromethane overlayered with methanol as dark purple, lustrous needles, m.p. 204.5—207 °C (Found: M^+, 711.3250. $C_{39}H_{45}N_5O_8$ requires M, 711.3268); $\nu_{max.}$ 2 380, 2 190, 1 735, and 1 605 cm^{-1}; $\lambda_{max.}$(CH_2Cl_2) 280 ($\varepsilon_{max.}$ 16 149 $dm^3\ mol^{-1}\ cm^{-1}$), 376 (129 248), 405 (62 017), 487 (7 846), 515 (8 544), 540 (11 178), 581 (18 030), and 630 nm

(11 661); δ(G)(CD_2Cl_2), 1.73 and 1.98 (each 6 H, s, CMe_2), 2.91 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 2.98 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 3.65, 3.66, and 3.76 (each 3 H, s, OMe), 3.77 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 3.80 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 3.81 (3 H, s, OMe), 3.82 and 3.92 (each 2 H, s, 3-CH_2 and 7-CH_2), 4.36 and 4.69 (each 2 H, s, CH_2CO_2), 7.16 (1 H, s, 5-H), 7.47 (1 H, s, 10-H), and 8.78 (1 H, s, 15-H).

20-*Cyano*-13,17-*bis*(2-*methoxycarbonylethyl*)-18-*methoxycarbonylmethyl*-2,2,8,8,12-*pentamethylisobacteriochlorin* (**76**).—The imine t-butyl ester (**68**) (18 mg) was stirred with trifluoroacetic acid (0.23 ml) under argon for 30 min. Into this solution was transferred a solution of the foregoing imidate ester (**72**) (11 mg) in dry methanol (1.2 ml) and trimethylorthoformate (0.14 ml) being washed in with more methanol (0.5 ml). The rest of the synthesis was run as for the foregoing example (**75**) to yield the *isobacteriochlorin* (**76**) (9 mg, 52%) which crystallised from dichloromethane over-layered with methanol as dark purple, lustrous needles, m.p. 213—215 °C (Found: M^+, 653.3224. $C_{37}H_{43}N_5O_6$ requires *M*, 653.3213); $\nu_{max.}$ 3 525, 2 380, 2 190, 1 730, and 1 605 cm^{-1}; $\lambda_{max.}$(CH_2Cl_2), 281 ($\varepsilon_{max.}$ 8 831 dm^3 mol^{-1} cm^{-1}), 376 (151 970), 405 (961 837), 429 (4 599), 487 (9 321), 515 (9 653), 545 (9 408), 584 (15 756), and 628 nm (18 117); $\lambda_{max.}$(MeCN) 280, 374, 403, 482sh, 512, 544, 582, and 626 nm; [+NaOH] 222, 274, 384, 402, 554, 595, and 625 nm; δ(F)(CD_2Cl_2) 1.77 and 2.01 (each 6 H, s, CMe_2), 2.94 (3 H, s, 12-Me), 2.97 (4 H, m, 2 × $CH_2CH_2CO_2$), 3.63, 3.65 and 3.82 (each 3 H, s, OMe), 3.84 (4 H, m, 2 × $CH_2CH_2CO_2$), 3.90 and 4.00 (each 2 H, s, 3-CH_2 and 7-CH_2), 4.75 (2 H, s, CH_2CO_2), 7.31 (1 H, s, 5-H), 7.58 (1 H, s, 10-H), and 8.87 (1 H, s, 15-H).

A small amount of the *seco* lactam (f.d.m.s. M^+, 671), was obtained as a lower R_F blue band.

Acknowledgements

Grateful acknowledgement is made to the S.E.R.C. for Studentships (to D. M. A. and P. J. H.), the S.E.R.C. and Roche Products Ltd. for financial support, Dr. C. J. R. Fookes for help with the early experiments and Professor Wang Yu, Shanghai, for arranging leave of absence for Z.-C. S.

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Received 10*th May* 1988; *Paper* 8/01840E