Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 4.[1,2] Development of the Photochemical Route to Isobacteriochlorins

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Pigments based on the isobacteriochlorin macrocycle are of great importance for research on the biosynthesis of vitamin B_{12}. A synthesis of the isobacteriochlorin ring system is developed in which a key step is an 18π-photochemical cyclisation. The reaction conditions are extremely mild and are demonstrated to be compatible with the reactive acetic and propionic acid residues present in the natural pigments.

The biosynthesis of vitamin B_{12}, for which a late intermediate is cobyrinic acid (**8**), involves[3] the stepwise introduction of methyl groups into tetrapyrrolic macrocycles, the first one to be methylated being uroporphyrinogen-III (**1**). The dimethylated intermediate was shown[4] to be the dihydro-system (**2**) although it had been initially isolated from B_{12}-producing organisms[5] in the aromatised form (**4**) for structure determination.[6] The latter pigment is a derivative of the isobacteriochlorin macrocycle (**9**) and it usually called sirohydrochlorin; this name is based upon the first isolation[7] of this substance as the metal-free prosthetic group of the enzyme sulphite reductase, though at that time the full structure of sirohydrochlorin was unknown. The enzyme system which produces vitamin B_{12} surprisingly places the third C-methyl group at C-20. Although it is highly probable that the true biosynthetic intermediate is the dihydroisobacteriochlorin (**3**), it was the ester (**7**) of the aromatised form (**6**) which was isolated[8] and whose structure was established.[9]

Research on the biosynthesis of vitamin B_{12} has been and is limited by the scarcity of the di- and tri-methylated isobacteriochlorins (**4**) and (**6**). Accordingly, we aimed to produce workable quantities of the corresponding esters (**5**) and (**7**) of these pigments by total synthesis. The first requirement was a rational synthesis of the isobacteriochlorin macrocycle which (*a*) allowed full control over the regiochemistry, and later stereochemistry, of the substituents and (*b*) used reaction conditions which would be compatible with the rather reactive acetate and propionate side-chains of the esters of the natural pigments (**5**) and (**7**).

No rational synthesis of the isobacteriochlorin ring-system existed prior to 1979 when a collaborative effort[10] achieved the synthesis of an octamethylated isobacteriochlorin which met requirement (*a*) but not (*b*). Two additional synthetic routes to other octamethylated isobacteriochlorins have appeared more recently[11] and a third[1] based on 3,4-dihydropyrroles, though successful, gave too modest a yield to fulfil our long-term needs. Accordingly, a completely fresh approach was initiated.

Synthesis of the Octamethylisobacteriochlorin (**10**).—The first isobacteriochlorin synthesis[10] mentioned above involved division of the macrocycle (**9**) on an east-west line so that a ring-A/ring B-unit was combined with a ring-C/ring-D unit. The present synthesis used the alternative strategy of dividing the macrocycle (**9**) north to south along its axis of symmetry. Each bicyclic building unit thus contained one pyrrolic and one reduced ring.

Our initial target was the symmetrical octamethylisobacteriochlorin (**10**). Disconnection between rings-A and B leads to the seco-system (**11**) and we hoped to effect the ring-closure (**11**) ⟶ (**10**) by nucleophilic attack from the starred methyl group (*via* the corresponding enamine) onto the electrophilic imidate residue. Further disconnection of the seco-system (**11**) leads to the western (**12**) and eastern (**13**) fragments which were expected to be joined by a standard condensation of aldehyde with pyrrole to yield (**11**).

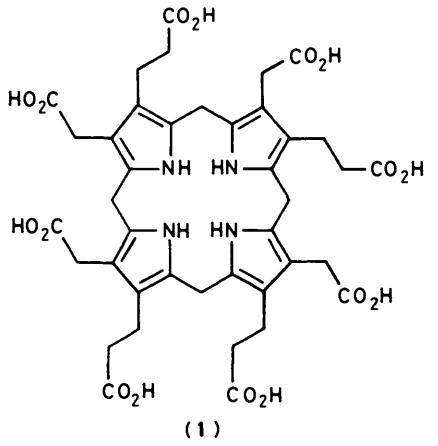
The first experiments were carried out with dihydro-derivatives of the fragments (**12**) and (**13**), *i.e.* using the building blocks (**17**) and (**25**). These were synthesized as shown in the early stages of Schemes 2 and 3; the routes depended on Michael additions to electron-deficient olefins of a nitroalkane as studied earlier for related molecules.[12,13] As an alternative to preparing the thiolactam (**22**) from the lactam (**21**), a 1,3-dipolar cycloaddition[14] of carbon disulphide to the aldonitrone[1] (**23**) was studied but the yield of thiolactam (**22**) was far inferior (24%) to that from the illustrated preparation from the lactam (**21**).

Condensation of the pyrrolic (**17**) and aldehydic (**25**) components then afforded the seco system (**30**) which was subjected to a variety of acidic and basic conditions in the presence and absence of Cu^{II} ions.[1,15] Oxygen was not excluded, in the expectation that any macrocyclic product formed would undergo aerial oxidation to the isobacteriochlorin (**10**). In the event, no detectable quantity of isobacteriochlorin was formed in any of these reactions.

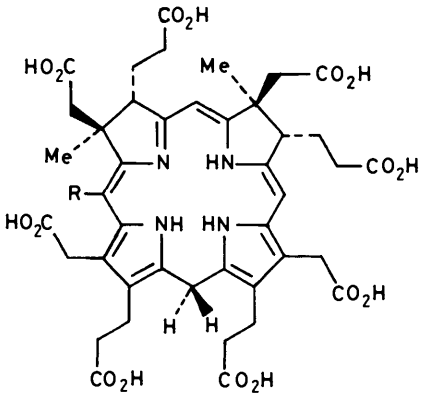
In order to increase the electrophilicity of the eastern unit for this approach, the lactam (**21**) was oxidised with lead tetra-acetate to give a mixture of two diastereoisomeric acetoxy compounds (**26**). These underwent acid-catalysed elimination of acetic acid to yield the unsaturated lactam (**27**) as a single isomer. The *Z*-geometry for the new double-bond was assigned by analogy with a closely related system of unambiguous structure (determined by *X*-ray analysis)[13] and with another relative to be described later. The unsaturated lactam (**27**) was then converted into the imidate aldehyde (**29**) as shown in Scheme 3.

Acid-catalysed condensation of the components (**17**) and (**29**) afforded the seco product (**31**) where now the reactivity of the imidate should be increased by being conjugated with the pyrromethene system of rings C and D. Certainly this product was highly labile and was used directly for experiments aimed at ring-closure which, if successful, would initially generate a dihydroisobacteriochlorin (**32**). Many reaction conditions were explored involving a variety of acids and bases with and without metal(II) ions (Zn, Cu, Ni, Pd), and some gave traces of the isobacteriochlorin (**10**). The highest yield (*ca.* 1%) resulted simply from keeping the seco system (**31**) dissolved in tetrahydrofuran.

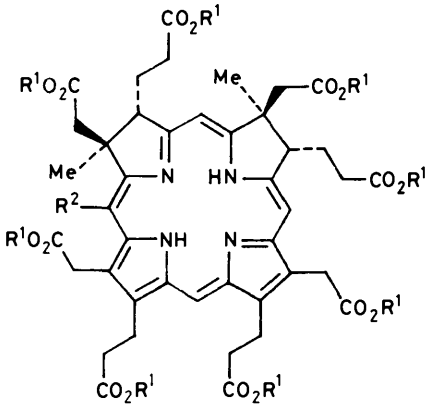
Though the foregoing experiments did not provide a practical synthesis of isobacteriochlorins, they were highly important in yielding clues which led directly to such a synthesis. The clues were (*a*) the formation of isobacteriochlorin (**10**) from the seco system (**31**) was not dependent on acid or base, and (*b*) dihydroisobacteriochlorins are aromatised more efficiently by ferricyanide than by aerial oxidation;[4] yet use of ferricyanide in the



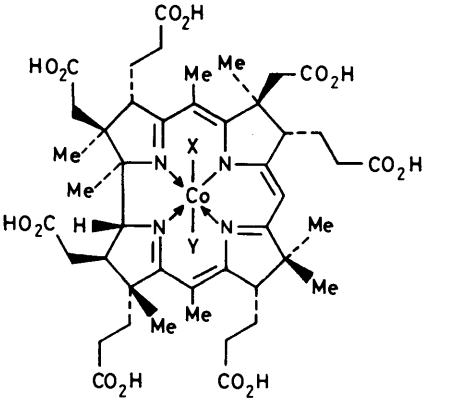
(1)



(2) R = H
(3) R = Me

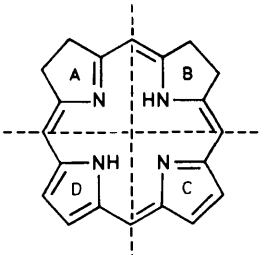


(4) $R^1 = R^2 = H$
(5) R^1 = Me, R^2 = H
(6) R^1 = H, R^2 = Me
(7) $R^1 = R^2$ = Me



(8)

Vitamin B_{12}

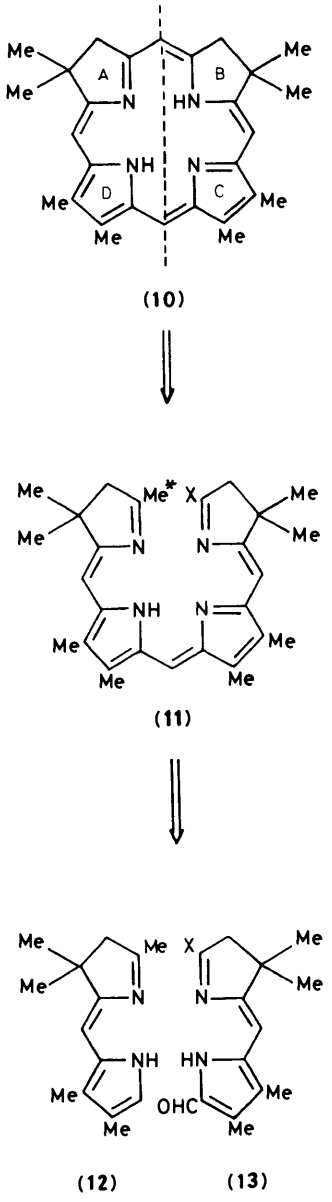


(9)

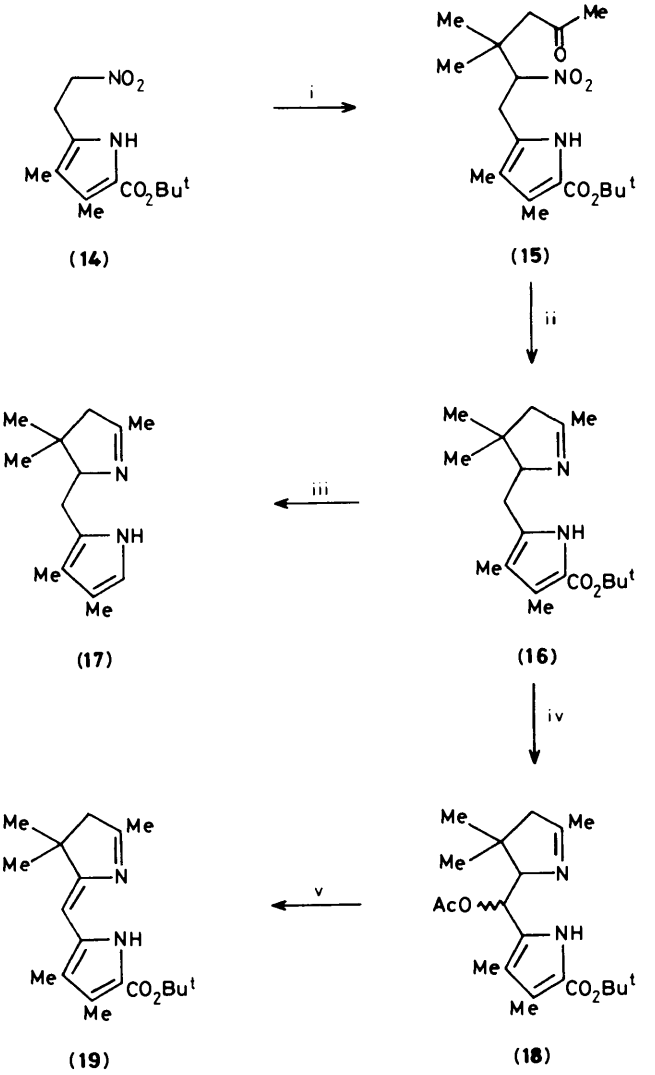
work-up of the foregoing 'best' procedure did not improve the yield. It seemed therefore that a dihydroisobacteriochlorin (**32**) was not an intermediate in the process.

An exciting interpretation in keeping with these clues, was that a small fraction of the seco system (**31**) had undergone oxidation (by air or peroxides in the solvent) to yield the conjugated product (**33**), Scheme 4. The tautomer (**34**) of (**33**) is a conjugated 18π-system which by the Woodward-Hoffman rules [16] should undergo electrocyclic ring-closure to the macrocycle (**35**) as a precursor of the isobacteriochlorin (**10**); the theory of this ring-closure will be discussed more fully below. What was clearly needed now was a rational synthesis of the seco system (**33**).

To this end, the imine (**16**) was oxidised with lead tetra-acetate (Scheme 2), and acetic acid was eliminated from the diastereoisomeric mixture of acetoxy compounds (**18**) by treatment with formic acid. A single isomer (**19**) was isolated, which was expected to have the *Z*-configuration with the bulky quaternary carbon and pyrrole substituents lying *trans*; this was proved to be true for a closely related molecule (**56**) to be



Scheme 1.



Scheme 2. i, Mesityl oxide $Bu_4N^+F^-$; ii, Zn–HOAc, then $TiCl_3$; iii, TFA iv, $Pb(OAc)_4$–HOAc; v, HCO_2H

described later. The α-free pyrrole (**12**), derived from the ester (**19**) as usual, condensed with the available aldehyde (**29**), in the presence of trimethyl orthoformate to scavenge the water formed. The reaction mixture containing the resultant seco system (**33**) was then diluted with rigorously dried and degassed tetrahydrofuran, neutralised with Hünig's base, and irradiated using tungsten lamps. The isobacteriochlorin (**10**) was isolated in an overall yield of 30% for the four steps (deprotection, decarboxylation, condensation, ring-closure) from the bicyclic components (**19**) and (**29**). This corresponds to an average yield of *ca.* 75% for each of the four stages. Thus a mild practical synthesis of the isobacteriochlorin macrocycle was available.

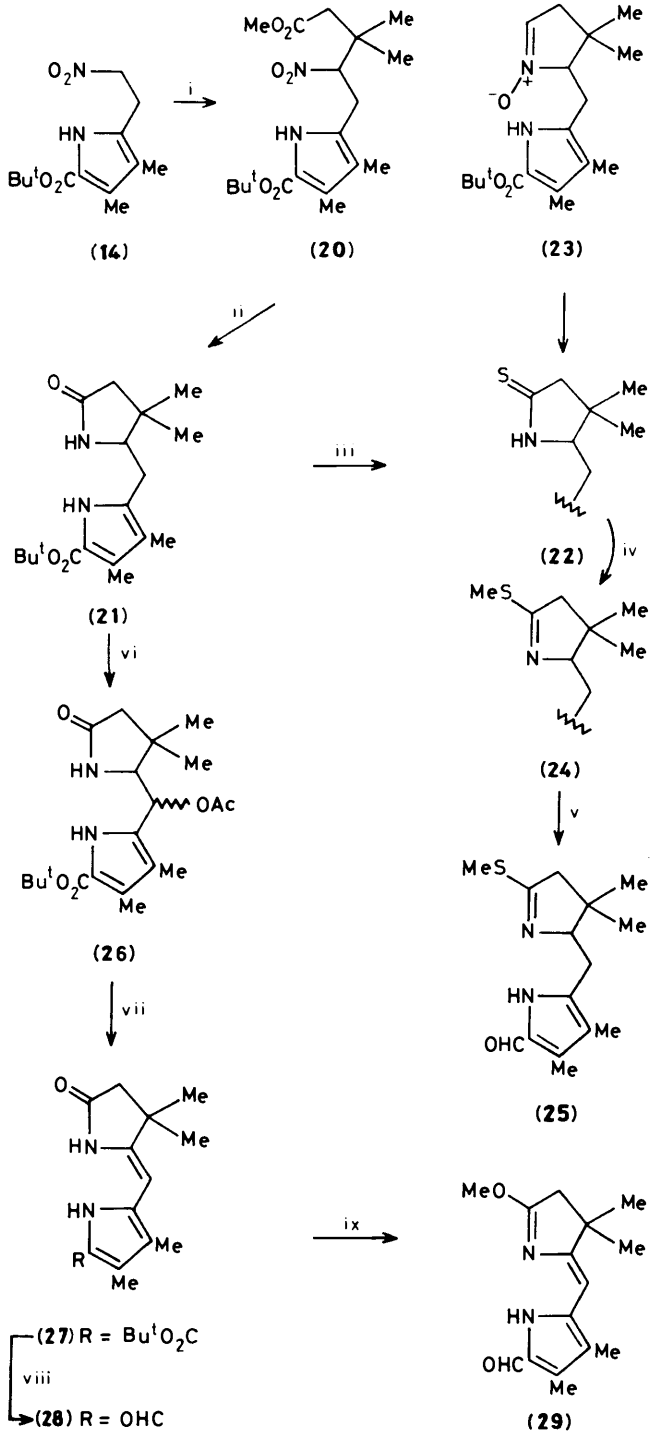
The foregoing product (**10**) was identical with the small sample prepared earlier by the exploratory nitrone route[1] and it formed excellent crystals. Accurate structural data have been acquired for this ring-system by *X*-ray analysis.[17]

In this, synthesis, the lability of the seco system (**33**) meant that it had to be generated and ring-closed without isolation. However, it was possible to isolate and characterise the closely related lactam (**36**) (see Experimental section).

Photochemical Ring-closure.—The Woodward-Hoffman rules[16] require that the two symmetry-allowed electrocyclic reorganisations of an 18π-system are (*a*) thermal, by a suprafacial (disrotatory) process or (*b*) photochemical, by an antarafacial (conrotatory) process. The antarafacial process should be strongly favoured because this requires the seco system (**34**) to adopt a helical conformation (**37**) and (**38**) in which good overlap is maintained throughout the π-system (Scheme 5). In contrast, suprafacial ring-closure involves considerable distortion of the π-system from planarity (**39**) and (**40**), resulting the loss of π-overlap.

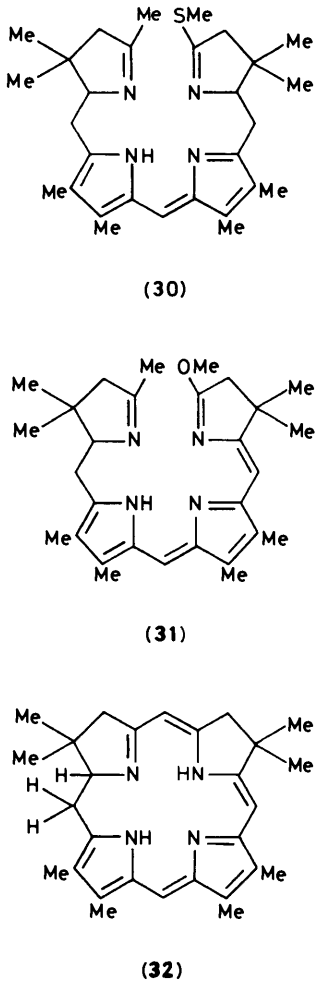
The experimental observations already described are in satisfying agreement with these considerations. The photochemical antarafacial process takes place very readily and the complementary experiment can now be added: no conversion of the seco system (**33**) into the isobacteriochlorin (**10**) takes place in the dark.

In the early stages of the foregoing work, there was concern lest the alternative 16π-electrocyclic, process (Scheme 6) might frustrate our efforts. As already described, the desired ring-closure was in fact achieved and it is interesting to consider why. The product from such a thermally-allowed 16π-ring-closure (conrotatory) is a dehydrocorrin which is crowded by having



Scheme 3. *Reagents:* i, Methyl 3,3-dimethylacrylate, $Bu_4N^+F^-$; ii, Zn–HOAc and $TiCl_3$; iii, P_2S_5; iv, MeI–K_2CO_3; v, TFA, $HC(OMe)_3$; vi, $Pb(OAc)_4$–HOAc; vii, *p*-$MeC_6H_4SO_3H$, heat; viii, TFA, $HC(OMe)_3$; ix, $Me_3O^+BF_4^-$, Hunig's base

two adjacent quaternary centres (**41**). The Zürich studies[18] on synthesis of corrinoids have provided several routes in which the key step was a 16π-thermal, conrotatory cyclisation of a seco intermediate. However, in every case of corrinoid formation, a metal ion was used as a template and this may be the critical difference from our synthesis of isobacteriochlorins. The metal template could draw C-1 and C-19 together (see Scheme 6) whereas for the ring-closure without metal-ion, the sterically

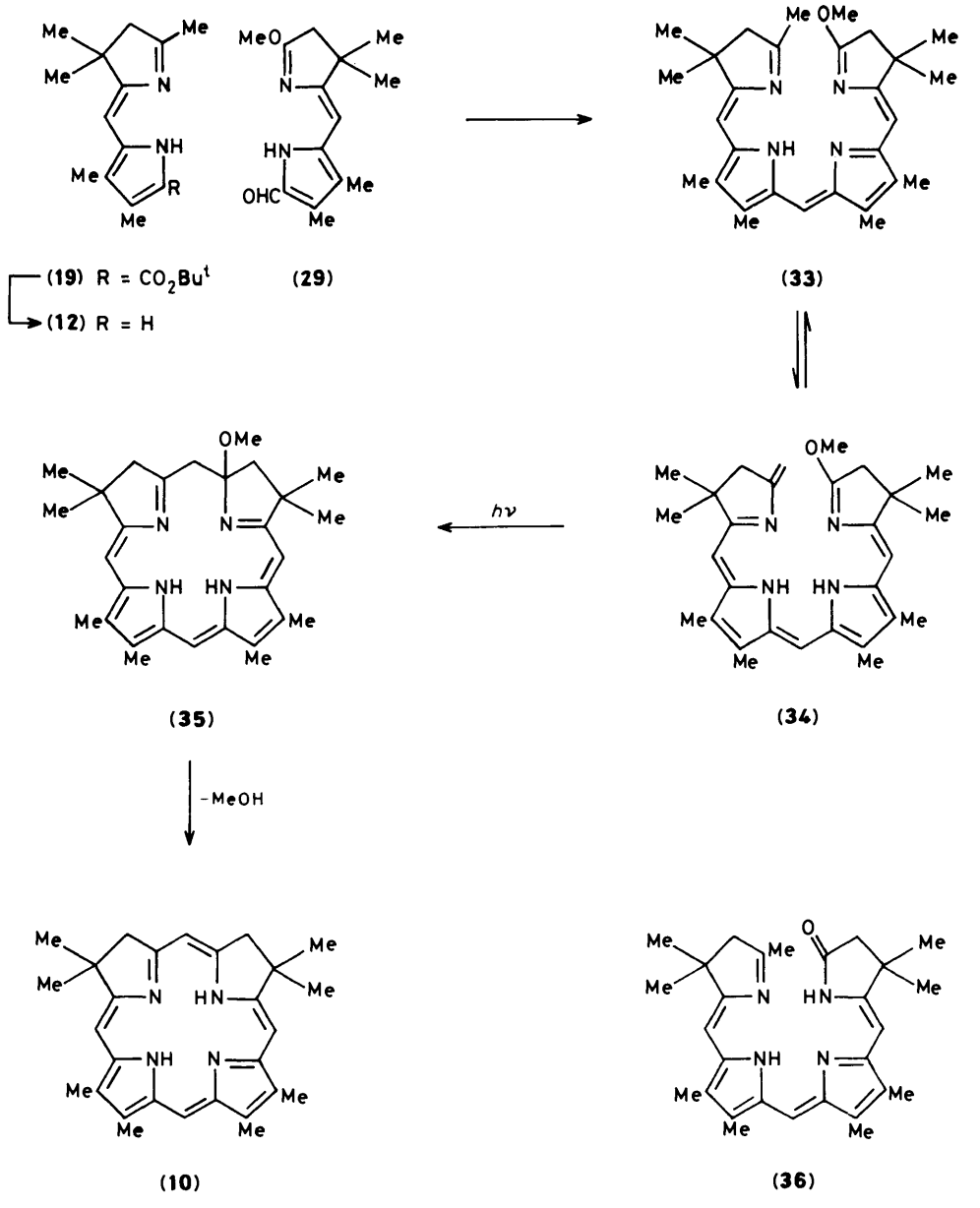


less demanding 18π-cyclisation would be expected to be favoured (Scheme 5), as was observed in our experiments.

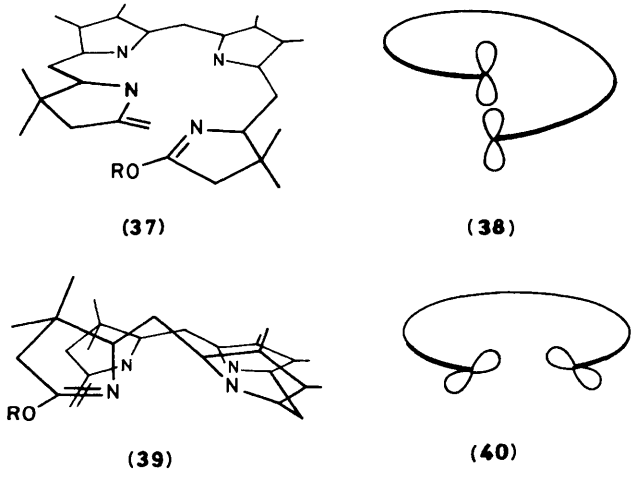
Synthesis of an Isobacteriochlorin Carrying Acetic and Propionic Acid Side-chains.—A major advantage of the photochemical route to isobacteriochlorins lies in its mild conditions which we hoped would be compatible with the acetic and propionic side-chains of the esters of the natural pigments (**5**) and (**7**). To test this prediction, a synthesis of the isobacteriochlorin (**59**) was initiated, following the same strategy used for the macrocycle (**10**).

The synthesis of the eastern building block (**50**) is shown in Scheme 7. In this route, the oxidation with lead tetra-acetate for the conversion (**46**) ⟶ (**47**) was dramatically slower than for the earlier example (**21**) ⟶ (**26**) (Scheme 3). Also the elimination of acetic acid from the acetoxy derivatives (**47**) to yield the unsaturated lactam required more drastic conditions, although the single isomer formed (**48**) was obtained in good yield. The illustrated *Z*-stereochemistry was established by demonstrating a nuclear Overhauser enhancement (13%) of the signal from the olefinic proton by irradiation at the resonance frequency corresponding to the gem-dimethyl group. The final steps from the lactam (**48**) to the aldehydo imidate (**50**) proceeded smoothly.

Synthesis of the western building block proved more troublesome. Though the Michael addition step (**44**) ⟶ (**51**) and the reductive cyclisation (**51**) ⟶ (**52**) were very satisfactory (see Scheme 7), it was not possible to obtain the acetoxy derivatives (**53**) in any acceptable yield. Presumably retardation of the rate of the desired reaction (as observed above) allowed unwanted competitive reactions to predominate (*e.g.* oxidation of the



Scheme 4.

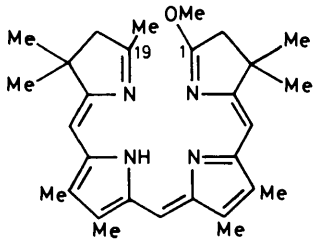


Scheme 5.

imine residue). However, reduction of the nitronate anion (**54**) from the nitro system (**51**) using buffered titanium trichloride [19] gave the required product (**56**) as a single isomer shown to have the illustrated *Z*-configuration by demonstrating a nuclear Overhauser effect (10% enhancement) between the arrowed nuclei. This product is presumably formed by ring-closure of the initially formed imine (**55**). A major by-product was the saturated imine (**52**) which had been obtained earlier.

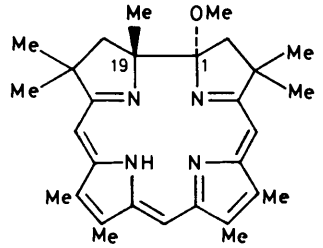
With the building blocks (**50**) and (**56**) available, the seco system (**58**) was generated as before (Scheme 7) and irradiated to form the isobacteriochlorin (**59**) in 40% overall yield from the bicyclic precursors (**50**) and (**56**). This corresponds to an average yield of *ca.* 80% for each of the four stages involved. The characteristic ^{1}H n.m.r. spectrum of this product is shown in the Figure.

These results demonstrated the power of the photochemical approach and confirmed its compatibility with the side-chains present in the esters of the natural pigments (**5**) and (**7**). Indeed, brief accounts have been published of the synthesis of the



(33)

16π Electrocyclic



(41)

Scheme 6.

natural enantiomer of sirohydrochlorin (**4**) and of its octamethyl ester (**5**) by this method,[20] together with the extension of the photochemical approach to the synthesis of natural chlorins.[21,22]

Experimental

For general directions, see ref. 12. U.v. spectra were recorded in ethanol unless otherwise stated.

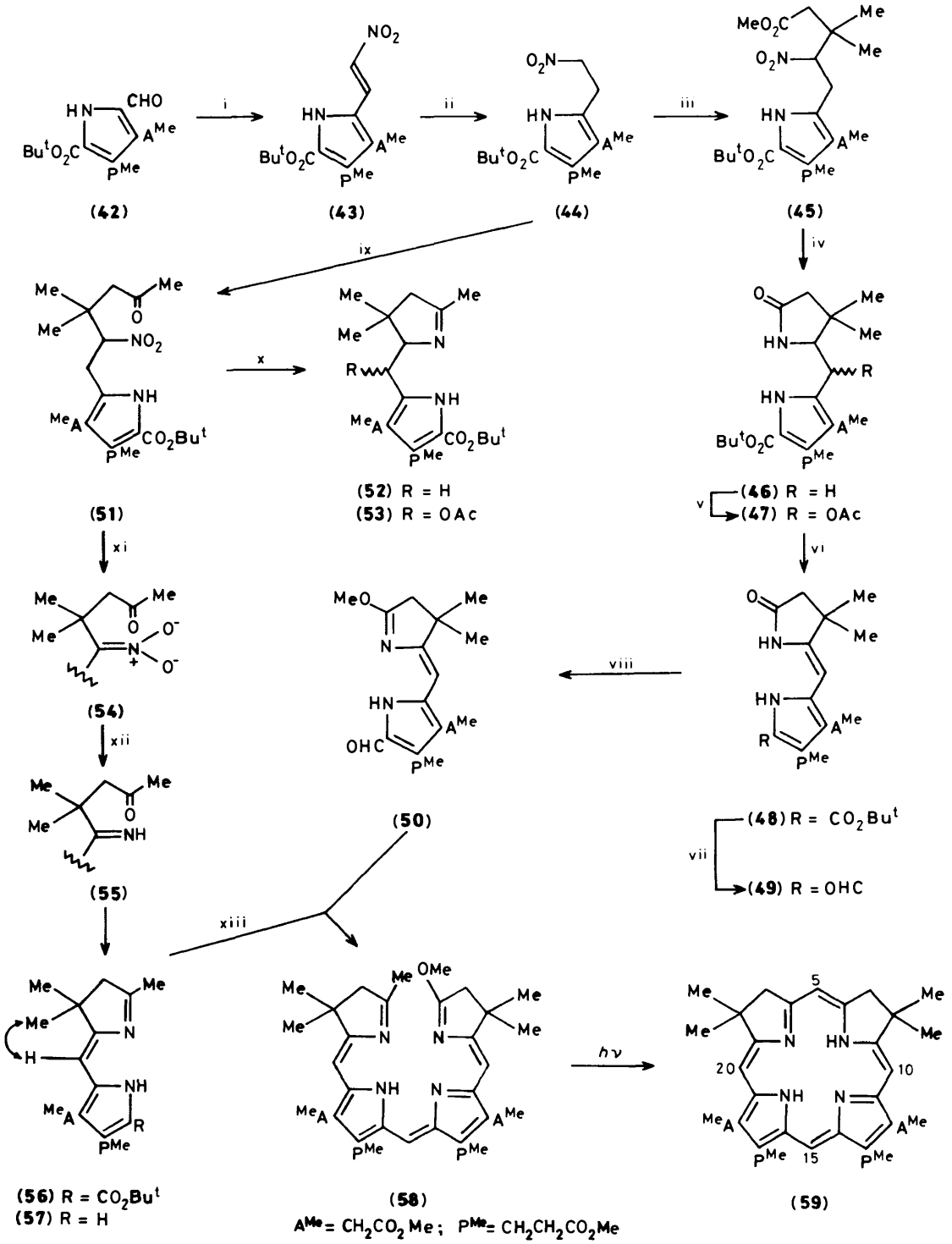
5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-3,4-*dihydro*-2,4,4-*trimethylpyrrole* (**16**).—6-(3,4-Dimethyl-5-t-butoxycarbonylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one[12] (**15**) (1.83 g, 5 mmol) was dissolved in acetic acid (75 ml), and zinc (10 g) was added with stirring and cooling to 20 °C. After 45 min, the zinc was filtered off and washed with acetic acid. Ammonium acetate (10 g) was added to the combined filtrates, which were degassed *in vacuo* and flushed with nitrogen before 15% aqueous titanium(III) chloride (20 ml, 20 mmol) was added. After the solution had been stirred for 6 h, it was evaporated and the residue was mixed with chloroform (200 ml). The aqueous layer was neutralised with 10% aqueous sodium carbonate (*ca.* 500 ml) and the white precipitate filtered off (Celite). Extraction of the aqueous layer with chloroform (3 × 150 ml) gave a combined organic solution which was washed with 5% aqueous sodium hydrogen carbonate (150 ml), dried, filtered and evaporated. The residue in chloroform was filtered through silica; the eluate afforded the *bicyclic imine* (**16**) as a gum (1.48 g, 93%) which crystallised slowly, m.p. 68—73 °C (Found: C, 71.7; H, 9.6; N, 8.8. $C_{19}H_{30}N_2O_2$ requires C, 71.7; H, 9.5; N, 8.8%). $\lambda_{max.}$ 284 nm; $\nu_{max.}$ 3 350br, 1 680, and 1 580 cm^{-1}; δ 0.92 (3 H, s, Me), 1.10 (3 H, s, Me), 1.53 [9 H, s, $C(Me)_3$], 1.91 (3 H, s, ArMe), 2.01 (3 H, d, *J* 2 Hz, MeC=N), 2.23 (3 H, s, ArMe), 2.31 (2 H, br s, $CH_2C{=}N$), 2.20—2.82 (2 H, m, CH_2CHN), 3.60 (1 H, m, CH_2CHN), and 10.15 (1 H, br s, NH); *m*/*z* 318 (6%, M^+), 245 (5, $M^+ - C_4H_9O$), 152 (27), and 110 (100).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-4,4-*dimethylpyrrolidin*-2-*one* (**21**).—Methyl 5-(3,5-dimethyl-5-t-butoxycarbonylpyrrol-2-yl)-3,3-dimethyl-4-nitropentanoate[1] (**20**) (1.65 g, 4.32 mmol) in acetic acid was stirred and treated with zinc (6.5 g). After 15 min, the mixture was warmed to 70 °C for 1 h, then cooled and mixed with ammonium acetate (0.86 g) and 15% aqueous titanium(III) chloride (1.1 ml, 1.1 mmol). After being stirred for 30 min more at 20 °C, the mixture was filtered and the zinc washed with acetic acid. The combined filtrates were evaporated (50 °C) and the residue was partitioned between ether (200 ml) and water (100 ml). The aqueous layer was acidified to pH 2 with concentrated hydrochloric acid, then separated and extracted with more ether (3 × 100 ml). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (100 ml, 50 ml) and brine (100 ml), dried, filtered, and evaporated. The residue crystallised from methanol to give the *bicyclic lactam* (**21**) (1.22 g, 88%), m.p. 199—200 °C (Found: C, 67.2; H, 8.9; N, 8.4. $C_{18}H_{28}N_2O_3$ requires C, 67.5; H, 8.8; N, 8.7%); $\lambda_{max.}$ 280 nm; $\nu_{max.}$ 3 450, 3 280br, and 1 680 cm^{-1}; δ 1.18 (3 H, s, Me), 1.21 (3 H, s, Me), 1.49 [9 H, s, $C(Me)_3$], 1.92 (3 H, s, ArMe), 2.05 (1 H, d, *J* 17 Hz, CH_AH_B CONH), 2.16 (3 H, s, ArMe), 2.41 (1 H, d, *J* 17 Hz, CH_AH_BCONH), 2.70 (2 H, m, CH_2CNH), 3.35 (1 H, dd, *J* 6, 9 Hz, CH_2CHN), 6.62 (1 H, br s, NH), and 9.90 (1 H, br s, NH); *m*/*z* 320 (8%, M^+), 247 (6, $M^+ - C_4H_9O$), 209 (39), and 153 (100).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-4,4-*dimethylpyrrolidine*-2-*thione* (**22**).—(*a*) To a stirred solution of the foregoing bicyclic lactam (**21**) (320 mg, 1 mmol) in THF (50 ml) at 50 °C under nitrogen, was added phosphorus pentasulphide (244 mg, 1.1 mmol). After 90 min, the reaction mixture was filtered (Celite) and the solids were washed with ether. The combined filtrates were shaken with 5% aqueous sodium hydrogen carbonate (20 ml, 10 ml) and brine (20 ml), dried, and evaporated. The residue, in chloroform, was filtered through alumina to give a gum which was recrystallised from hexane–ethyl acetate to give the *bicyclic thiolactam* (**22**) (259 mg, 77%).

(*b*) A solution of 5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-4,4-dimethylpyrrole 1-oxide[1] (**23**) (96 mg, 0.3 mmol) in carbon disulphide (10 ml) was heated at reflux for 7 days and then evaporated, the resultant oil being evaporated again from ether (5 ml). Crystallisation of the residue from hexane yielded the bicyclic thiolactam (**22**) (24 mg, 23.8%), m.p. 152—155 °C (Found: C, 64.2; H, 8.3; N, 8.2. $C_{18}H_{28}N_2O_2S$ requires: C, 64.25; H, 8.4; N, 8.3%); $\lambda_{max.}$ 276 nm; $\nu_{max.}$ 3 450, 3 400, 3 230br, 1 670, and 1 490 cm^{-1}; δ 1.11 (3 H, s, Me), 1.14 (3 H, s, Me), 1.47 (9 H, s, CMe_3), 1.88 (3 H, s, ArMe), 2.15 (3 H, s, ArMe), 2.59 (1 H, d, *J* 18 Hz, CH_AH_BCSNH), 2.68 (2 H, m, CH_2CHN), 2.88 (1 H, d, *J* 18 Hz, CH_AH_BCSNH), 3.57 (1 H, br t, *J* 8 Hz, CH_2CHN), 8.52 (1 H, br s, NH), and 9.53 (1 H, br s, NH); *m*/*z* 336 (30%, M^+), 263 (6, $M^+ - C_4H_9O$), 209 (23), and 152 (100).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-3,4-*dihydro*-2-*methylthio*-4,4-*dimethylpyrrole* (**24**).—A stirred solution of the foregoing thiolactam (**22**) (303 mg, 0.9 mmol) in tetrahydrofuran (THF) (25 ml) at 50 °C was treated with potassium carbonate (414 mg, 3 mmol) and methyl iodide (420 mg, 3 mmol). After 4 h, the mixture was partitioned between 5% aqueous sodium hydrogen carbonate (50 ml) and chloroform (50 ml), the aqueous layer being extracted with chloroform (2 × 25 ml). The combined extracts were dried, filtered, and evaporated and the residue was recrystallised from hexane to give the *thioimidate* (**24**) (277 mg, 87.8%), m.p. 95—97 °C (Found: C, 64.8; H, 8.7; N, 8.3. $C_{19}H_{30}N_2O_2S$ requires C, 65.1; H, 8.9; N, 8.0%); $\lambda_{max.}$ 215, 235, and 284 nm; $\nu_{max.}$ 3 380br, 1 680, and 1 585 cm^{-1}; δ 0.99 (3 H, s, Me), 1.15 (3 H, s, Me), 1.54 (9 H, s,



Scheme 7. *Reagents:* i, $MeNO_2$, $MeNH_3^+ Cl^-$, KOAc; ii, $NaBH_4$; iii, methyl 3,3-dimethylacrylate, $Bu_4N^+F^-$; iv, Zn–HOAc; v, $Pb(OAc)_4$, HOAc; vi, Heat in xylene; vii, TFA, $HC(OMe)_3$; viii, $Me_3O^+ BF_4^-$, Hunig's base; ix, mesityl oxide, $Bu_4N^+F^-$; x, Zn–HOAc; xi, NaOMe; xii, $TiCl_3$, NH_4OAc; xiii, TFA

CMe_3), 1.94 (3 H, s, ArMe), 2.26 (3 H, s, ArMe), 2.46 (2 H, br s, CH_2C=N), 2.52 (3 H, s, SMe), 2.37—2.86 (2 H, m, CH_2CHN), 3.65 (1 H, m, CH_2CHN), and 10.12 (1 H, br s, NH); *m/z* 350 (67%, M^+), 246 (25), and 216 (100).

5-(3,4-*Dimethyl*-5-*formylpyrrol*-2-*ylmethyl*)-3,4-*dihydro*-2-*methylthio*-4,4-*dimethylpyrrole* (**25**).—A solution of the foregoing thioimidate (**24**) (70 mg, 0.2 mmol) in TFA (2 ml) was kept for 10 min and then treated with trimethyl orthoformate (0.6 ml) and, after a further 15 min, with water (2 ml). The solution was allowed to stand for a further 30 min before admixture with 1M aqueous ammonia (30 ml) and chloroform (20 ml). The basic aqueous layer was separated and extracted with more chloroform (10 ml), the combined organic layers being dried, filtered, and evaporated. The residue was fractionated by p.l.c. (1 mm plate, eluted with 10% methanol in chloroform) to yield the *formyl thioimidate* (**25**) (52 mg, 93.4%),

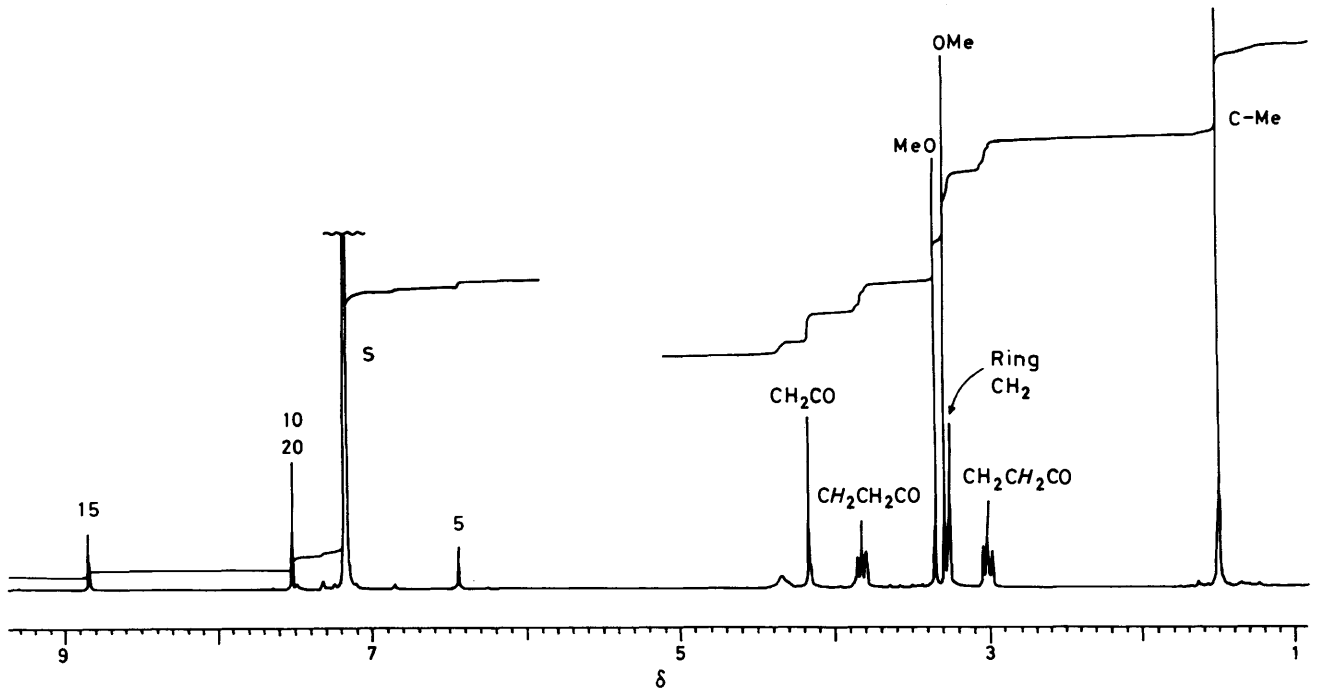


Figure. ^{1}H-N.m.r. spectrum at 250 MHz of the isobacteriochlorin (**59**) run in C_6D_6; S is signal from solvent

m.p. 108—109 °C from hexane (41.9 mg, 75.3%) (Found: M^+, 278.1460. $C_{15}H_{22}N_2OS$ requires: M^+, 278.1452); $\lambda_{max.}$ 313 nm; $\nu_{max.}$ 3 340br, 1 630, and 1 590 cm^{-1}; δ 1.02 (3 H, s, Me), 1.18 (3 H, s, Me), 1.97 (3 H, s, ArMe), 2.26 (3 H, s, ArMe), 2.52 (2 H, s, CH_2C=N), 2.63 (3 H, s, SMe), 2.30—2.95 (2 H, m, CH_2CHN), 3.73 (1 H, dd, *J* 4, 10 Hz, CH_2CHN), 9.50 (1 H, s, CHO), and 10.60 (1 H, br s, NH); *m/z* 278 (19%, M^+), and 142 (100).

1,3,3,7,8,12,13,17,17-*Nonamethyl*-19-*methylthio*-2,3,4,5,15,16,17,18-*octahydrobilin* (**30**).—The imine (**16**) (6.4 mg, 0.02 mmol) was dissolved in TFA (0.5 ml). After 10 min, a solution of the formyl thioimidate (**25**) (5.6 mg, 0.02 mmol) in methanol (0.5 ml) was added. After a further 15 min, a u.v./visible spectrum of the reaction mixture indicated that no formyl thioimidate (**25**) remained, and analytical t.l.c. revealed the major component to be a yellow spot just above the baseline (5% methanol and 5% acetic acid in chloroform). The solution was concentrated under reduced pressure to give the crude trifluoroacetate salt of the tetracyclic imine-thioimidate (**30**) as an orange gum; $\lambda_{max.}$ 485 nm. This material was used for many attempts at ring-closure under a wide variety of conditions outlined in the text.

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethylene*)-4,4-*dimethylpyrrolidin*-2-*one* (**27**).—The lactam (**21**) (320 mg, 1.0 mmol) in acetic acid (20 ml) was treated with lead tetra-acetate (665 mg, 1.5 mmol), at 40 °C under nitrogen. After being stirred for 1 h, the solution was treated with ethylene glycol (10 drops) and concentrated under reduced pressure (50 °C) to give a mixture of the diastereomeric acetoxy compounds (**26**); δ 0.91 (3 H, s, Me), 1.08 (3 H, s, Me), 1.59 (9 H, s, CMe_3), 2.09 (6 H, br s, OCOMe and ArMe), 2.20 (3 H, s, ArMe), 2.27 (2 H, s, CH_2CONH), 3.82 [1 H, d, *J* 8 Hz, CH(OAc)C*H*N], 5.73 [1 H, d, *J* 8 Hz, C*H*(OAc)CHN], 7.53 (1 H, br s, NH), and 9.28 (1 H, br s, NH).

This mixture in dichloromethane (20 ml) was washed with water (20 ml) and 5% aqueous sodium hydrogen carbonate (10 ml), dried, and filtered. The filtrate was heated at reflux with toluene-*p*-sulphonic acid (9.5 mg, 0.05 mmol) for 2 h, then cooled and washed with 5% aqueous sodium hydrogen carbonate (10 ml), dried, filtered, and evaporated. The residue crystallised from methanol (1 ml) to yield the *unsaturated lactam* (**27**) (234 mg, 73.5%), m.p. 187—189 °C. (Found: C, 68.0; H, 8.2; N, 8.5. $C_{18}H_{26}N_2O_3$ requires: C, 67.9; H, 8.2; N, 8.8%); $\lambda_{max.}$ 215 and 312 nm; $\nu_{max.}$ 3 450, 3 410, 1 720, and 1 680 cm^{-1}; δ 1.36 (6 H, s, 2 × Me), 1.54 [9 H, s, C(Me)$_3$], 1.92 (3 H, s, ArMe), 2.22 (3 H, s, ArMe), 2.41 (2 H, s, CH_2CONH), 5.24 (1 H, br s, C=CH), 8.40 (1 H, br s, NH), and 8.91 (1 H, br s, NH); *m/z* 318 (31%, M^+), 262 (100, $M^+ - C_4H_8$), 244 (34).

5-(5-*Formyl*-3,4-*dimethylpyrrol*-2-*ylmethylene*)-4,4-*dimethylpyrrolidin*-2-*one* (**28**).—The foregoing lactam (**27**) (159 mg, 0.5 mmol) was dissolved in TFA (5 ml) and after 15 min was mixed with trimethyl orthoformate (1.5 ml). After a further 15 min, water (5 ml) was added, the solution was kept for 30 min, then shaken with chloroform (50 ml) and 1M aqueous ammonia (50 ml). More 1M aqueous ammonia (*ca.* 20 ml) was added until the aqueous layer was basic. The organic layer was dried, filtered, and evaporated and the residue by p.l.c. (2 × 1 mm plates, eluted with 10% methanol in chloroform) gave the yellow *formyl lactam* (**28**) (106 mg, 86.1%), m.p. 221—222 °C (Found: C, 68.1; H, 7.4; N, 11.3. $C_{14}H_{18}N_2O_2$ requires C, 68.3; H, 7.4; N, 11.4%); $\lambda_{max.}$243 and 356 nm; $\nu_{max.}$ 3 320br, 1 720, 1 665, and 1 605 cm^{-1}; δ 1.36 (6 H, s, 2 × Me), 1.98 (3 H, s, ArMe), 2.26 (3 H, s, ArMe), 2.40 (2 H, s, CH_2CONH), 5.28 (1 H, s, C=CH), 9.47 (1 H, s, CHO), and 10.81 (2 H, br s, 2 × NH); *m/z* 246 (100%, M^+), 231 (77), 203 (19), and 162 (39).

5-(5-*Formyl*-3,4-*dimethylpyrrol*-2-*ylmethylene*)-3,4-*dihydro*-2-*methoxy*-4,4-*dimethylpyrrole* (**29**).—The foregoing formyl lactam (**28**) (113 mg, 0.46 mmol) in dichloromethane (20 ml), under argon, was treated with Hunig's base (0.8 ml, 4.6 mmol) and trimethyloxonium tetrafluoroborate (681 mg, 4.6 mmol), and stirred for 1 h at 20 °C. The mixture was partitioned between dichloromethane (20 ml) and water (40 ml) and the residue from the dichloromethane was chromatographed (2 × 1 mm plates, eluted with 10% methanol in chloroform) to give the *formyl imidate* (**29**) (62.2 mg, 52%) which slowly crystallised, m.p. 132—134 °C. Starting material (**28**) was also recovered (35.9 mg, 31.7%) (Found: C, 69.5; H, 7.4; N, 10.6.

$C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%); $\lambda_{max.}$ 245 and 376 nm; $\nu_{max.}$ 3 360br, 1 620, and 1 590 cm^{-1}; δ 1.32 (6 H, s, 2 × Me), 2.02 (3 H, s, ArMe), 2.25 (3 H, s, ArMe), 2.54 (2 H, s, CH_2C=N), 4.05 (3 H, s, OMe), 5.54 (1 H, s, C=CH), 9.49 (1 H, s, CHO), and 10.90 (1 H, br s, NH); *m/z* 260 (100%, M^+) and 245 (28, M^+ − Me).

19-*Methoxy*-1,3,3,7,8,12,13,17,17-*nonamethyl*-2,3,4,5,17,18-*hexahydrobilin* (**31**).—(*a*) The imine (**16**) (16 mg, 0.05 mmol) in TFA (0.5 ml) was treated, after 10 min, with a solution of the formyl lactam (**28**) (12.3 mg, 0.05 mmol) in methanol (2 ml). After a further 15 min, the solution was diluted with dichloromethane (10 ml), washed with water (5 ml) and 5% aqueous sodium hydrogen carbonate (5 ml), dried, and evaporated. The residue was purified by p.l.c. (2 × 0.25 mm indicator-free plates, eluted with 10% methanol in chloroform) to give the seco system as a gum (21.5 mg, 96%); $\lambda_{max.}$($CHCl_3$) 296 and 508 nm, moving in acid to 304 and 555 nm; *m/z* 446 (100% M^+ for $C_{28}H_{38}N_4O$).

This intermediate (9.8 mg, 0.022 mmol) in chloroform (2 ml) was treated with a solution of zinc(II) acetate dihydrate (9.7 mg, 0.044 mmol) in methanol (1 ml). The solution was then diluted with chloroform (5 ml), washed with water (10 ml), dried, and evaporated to give the corresponding zinc(II) complex; $\lambda_{max.}$($CHCl_3$) 320, 550sh, and 589 nm; *m/z* 510 (M^+ for $C_{28}H_{36}N_4O^{66}Zn$) and 508 (M^+ for $C_{28}H_{36}N_4O^{64}Zn$).

This complex was pumped at high vacuum overnight after which it was treated in dichloromethane (5 ml) with Hunig's base (0.04 ml, 0.23 mmol) and trimethyloxonium tetrafluoroborate (68.5 mg, 0.46 mmol), and stirred for 15 min under argon. It was mixed with dichloromethane (5 ml), washed with 0.5M aqueous hydrochloric acid (10 ml) and 2% aqueous sodium hydrogen carbonate (10 ml), filtered, and evaporated. P.l.c. (0.25 mm indicator-free plate, eluted with 15% methanol in chloroform) on the residue gave a mixture of protonated and unprotonated forms of the seco-system (**31**) (2.2 mg, 21.7%) as a slow-running purple band.

(*b*) The imine (**16**) (7 mg, 0.022 mmol), under argon, in TFA (0.1 ml) was treated, after 10 min, with a solution, also under argon, of the formyl imidate (**29**) (5.6 mg, 0.022 mmol) and trimethyl orthoformate (0.1 ml) in methanol (1 ml). After a further 10 min, the mixture was shaken with 10% aqueous sodium carbonate (10 ml) and dichloromethane (10 ml), the separated aqueous layer being extracted with more dichloromethane (10 ml). The combined organic layers were dried, filtered, and evaporated to give the seco system (**31**) as a gum; $\lambda_{max.}$(CH_2Cl_2) 290 and 508 nm, moving on acidification to 310, 370, 540sh, and 584 nm; *m/z* 460 (100%, M^+ for $C_{29}H_{40}N_4O$) and 458 (33, M^+ − 2 H).

The seco system (**31**) was used for many ring-closure experiments as summarised in the text.

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethylene*)-3,4-*dihydro*-2,4,4,-*trimethylpyrrole* (**19**).—The imine (**16**) (95.4 mg, 0.3 mmol) in acetic acid (6 ml) was treated with lead tetraacetate (0.2 g, 0.45 mmol). After 30 min, the mixture was treated with ethylene glycol (5 drops) and the residual oil from evaporation was dissolved in dichloromethane (10 ml) and the solution washed with water (10 ml, 5 ml) and 5% aqueous sodium hydrogen carbonate (5 ml). The organic layer was dried, filtered, and treated with formic acid (140 mg, 3 mmol). After 18 h, the solution was washed with 5% aqueous sodium hydrogen carbonate (10 ml), dried, and evaporated; the residue in dichloromethane was passed through a short silica column to give the *unsaturated imine* (**19**) as a gum (48.3 mg, 51%) which crystallised and had m.p. 152.5—154 °C (Found: M^+, 316.2134. $C_{19}H_{28}N_2O_2$ requires M^+, 316.2151); $\lambda_{max.}$ 228 and 349 nm; $\nu_{max.}$ 3 350br, 1 680, and 1 600 cm^{-1}; δ 1.21 (6 H, s, 2 × Me), 1.57 [9 H, s, C(Me)$_3$], 2.01 (3 H, s, ArMe), 2.19 (3 H, br s, CH_3C=N), 2.24 (3 H, s, ArMe), 2.49 (2 H, br s, CH_2C=N), 5.58 (1 H, br s, C=CH), and 11.07 (1 H, br s, NH); *m/z* 316 (27%, M^+), 260 (100, M^+ − C_4H_8), 245 (17), and 207 (30).

2,2,8,8,12,13,17,18-*Octamethylisobacteriochlorin* (**10**).—All glassware was rigorously dried and all operations prior to the final work-up were conducted under argon, with total exclusion of air and moisture.

The bicyclic imine (**19**) (6.4 mg, 0.02 mmol) was dissolved in TFA (0.05 ml) and the solution treated, after 10 min, with a solution of the formyl imidate (**29**) (5.2 mg, 0.02 mmol) and trimethyl orthoformate (0.1 ml) in methanol (0.9 ml). After a further 10 min, analytical t.l.c. showed the major component to be a turquoise spot just above the baseline (10% methanol in dichloromethane), corresponding to the protonated form of the seco system (**33**). The reaction mixture was either worked up at this stage (*a*), or used directly in the next step (*b*).

(*a*) Two thirds of the reaction mixture were partitioned between 5% aqueous sodium hydrogen carbonate (10 ml) and dichloromethane (10 ml), the organic layer being dried, filtered, and evaporated to give the seco system (**33**) as a purple gum; $\lambda_{max.}$(CH_2Cl_2) 352 and 564 nm, shifted on addition of acid to 348, 615, and 668 nm.

(*b*) The remaining third of the above reaction mixture was diluted into degassed THF (15 ml), and Hunig's base was added dropwise until the solution had turned from turquoise to purple; and solution was then irradiated (100 W tungsten lamp, 10 cm), with stirring, for 2 h. The residue from evaporation of the solution to *ca.* 2 ml was diluted with dichloromethane (5 ml), washed with 0.1M aqueous hydrochloric acid (5 ml) and 1% aqueous sodium hydrogen carbonate (5 ml), dried, filtered and evaporated. The product was purified by p.l.c. (0.25 mm indicator-free plate, eluted with dichloromethane) to give the *isobacteriochlorin* (**10**), yield by u.v. assay: 30.2%. The combined products from a number of such experiments were recrystallised from methanol–dichloromethane to give dark red rhombohedra, m.p. (decomp.) >230 °C (Found: C, 78.6; H, 8.1; N, 13.1%; M^+, 426.2786. $C_{28}H_{34}N_4$ requires C, 78.8; H, 8.0; N, 13.1%; M^+, 426.2784); $\lambda_{max.}$($MeCO_2Me$) 350sh (ε 60 700 dm^3 mol^{-1} cm^{-1}), 364 (95 700), 374 (82 300), 395 (40 900), 474 (5 500), 506 (9 600), 540 (16 700), 581 (27 600), and 632nm (7 500); $\nu_{max.}$ 3 370, 3 260br, 1 640sh, and 1 605 cm^{-1}; δ(CD_3COCD_3) 1.75 (12 H, s, 4 × Me), 2.81 (6 H, s, 2 × ArMe), 2.92 (6 H, s, 2 × ArMe), 3.81 (4 H, s, 2 × CH_2), 6.98 (1 H, br s, 5-H), 7.45 (2 H, s, 10-H and 20-H), and 8.52 (1 H, s, 15-H); *m/z* 426 (100%, M^+), and 411 (34, M^+ − CH_3).

1,3,3,7,8,12,13,17,17-*Nonamethyl*-2,3,17,18-*tetrahydrobilin*-19(24H)-*one* (**36**).—The unsaturated imine (**19**) (12.6 mg, 0.04 mmol) in TFA (0.1 ml), under argon was treated, after 10 min, with a solution of the formyl lactam (**28**) (9.8 mg, 0.04 mmol) and trimethyl orthoformate (1 drop) in methanol (1 ml). After a further 10 min, the green solution was diluted with dichloromethane (20 ml), washed with 5% aqueous sodium hydrogen carbonate (10 ml), dried, filtered, and evaporated. P.l.c. (3 × 0.25 mm indicator-free plates, eluted with dichloromethane) yielded from the major purple band, the *seco-lactam* (**36**) as a red solid (10.3 mg, 58%) (Found: M^+, 444.2887. $C_{28}H_{36}N_4O$ requires: M^+, 444.2889); $\lambda_{max.}$(CH_2Cl_2) 324 and 570 nm, shifting on acidification to 316, 580, and 600 nm; $\nu_{max.}$ 3 300br, 1 735, 1 715, 1 640, and 1 605 cm^{-1}; δ 1.29 (6 H, s, 2 × Me), 1.36 (6 H, s, 2 × Me), 2.01 (6 H, s, 2 × ArMe), 2.10 (3 H, s, ArMe), 2.15 (3 H, br s, CH_3C=N), 2.17 (3 H, s, ArMe), 2.30 (2 H, s, CH_2CONH), 2.48 (2 H, br s, CH_2C=N), and 5.51, 5.81, and 6.73 (1 H, s, 1 H, br s, 1 H, s, respectively, 3 × C=CH); *m/z* 444 (100%, M^+), and 429 (69).

t-Butyl 5-Formyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (**42**).—(*a*) *Using lead tetra-acetate.* t-Butyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate (16.95 g, 50 mmol) in acetic acid (50 ml) at 60 °C was treated with lead tetra-acetate (25 g, 56 mmol), which caused the temperature to rise to *ca.* 75 °C. After 30 min, when t.l.c. showed complete conversion into the monoacetoxy compound, a second portion of lead tetra-acetate (26.3 g, 59 mmol) was added and the mixture was warmed to 70 °C for 3 h and then 80 °C for a further 2 h. A further portion of lead tetra-acetate (12.5 g, 28 mmol) was added and heating at 80 °C continued for 1 h. The mixture was then treated with ethylene glycol, cooled, diluted with water (300 ml), and extracted with dichloromethane (3 × 50 ml). The combined organic layers were washed with water (50 ml), filtered, and evaporated to give the crude *bis*acetoxy compound; δ 1.58 [9 H, s, $C(Me)_3$], 2.29 (6 H, s, 2 × OCOMe), 2.54 (2 H, m, $CH_2CH_2CO_2$), 3.02 (2 H, m, $CH_2CH_2CO_2$), 3.63 (8 H, br s, CH_2CO_2 and 2 × OMe), 7.65 [1 H, s, $CH(OAc)_2$], and 9.24 (1 H, br s, NH).

This product in THF (75 ml) and water (75 ml) was heated at reflux for 2 h, the cooled mixture was then extracted with ether (75 ml) and the organic solution was washed with aqueous sodium hydrogen carbonate (3 × 50 ml) and brine (50 ml). It was dried, filtered, and evaporated to yield the crude formyl pyrrole (**42**) as an oil.

(*b*) *By halogenation.* A solution of the methylpyrrole (1.02 g, 3 mmol) in dichloromethane (30 ml) was stirred vigorously at 0 °C with potassium carbonate (4.55 g, 33 mmol) during dropwise addition of sulphuryl chloride (850 mg, 6.3 mmol). The mixture was stirred for 10 min at 0 °C and 10 min at 20 °C before filtration through Celite and evaporation to yield the crude dichloromethyl pyrrole; δ 1.59 [9 H, s, $C(Me)_3$], 2.53 (2 H, m, $CH_2CH_2CO_2$), 2.97 (2 H, m, $CH_2CH_2CO_2$), 3.51 (2 H, s, CH_2CO_2), 3.58 (3 H, s, OMe), 3.61 (3 H, s, OMe), 6.81 (1 H, s, $CHCl_2$), and 9.38 (1 H, br s, NH).

A solution of this product in acetone (30 ml) and water (15 ml) was kept for 1 h before dilution with water (30 ml) and extraction with dichloromethane (3 × 20 ml). The combined organic layers were washed with 5% aqueous sodium hydrogen carbonate (20 ml), dried, filtered, and evaporated. The residue crystallised from ether (8 ml) and hexane (10 ml) to give the *formylpyrrole* (**42**) (803 mg, 75.8%), m.p. 114—115.5 °C; $\lambda_{max.}$ 232 and 304 nm; $\nu_{max.}$ 3 430, 1 735, 1 700, and 1 660 cm^{-1}; δ 1.60 [9 H, s, $C(Me)_3$], 2.56 (2 H, m, $CH_2CH_2CO_2$), 3.00 (2 H, m, $CH_2CH_2CO_2$), 3.59 (3 H, s, OMe), 3.63 (3 H, s, OMe), 3.77 (2 H, s, CH_2CO_2), 9.62 (1 H, s, CHO), and 9.88 (1 H, br s, NH); *m/z* 353 (13%, M^+ for $C_{17}H_{23}NO_7$), 297 (78, $M^+ - C_4H_8$), 265 (100), and 237 (94).

t-Butyl 3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2-nitrovinyl)pyrrole-2-carboxylate (**43**).—The foregoing crude formylpyrrole (**42**) (2.68 g, 7.45 mmol), prepared by method (*a*), nitromethane (0.93 g, 15.2 mmol), methylamine hydrochloride (0.51 g, 7.6 mmol), and potassium acetate (0.82 g, 8.4 mmol) were stirred together in methanol (10 ml). After 5 h, the mixture was diluted with water (50 ml) and extracted with dichloromethane (20 ml, 2 × 10 ml). The combined organic layers were washed with water (10 ml), dried, filtered, and evaporated, the residue being passed through a short silica column in dichloromethane. The product crystallised from methanol (8 ml) to yield the *nitrovinylpyrrole* (**43**) as orange–yellow prisms (1.3 g, 44%), m.p. 124—126.5 °C (Found: C, 54.6; H, 6.4; N, 7.3. $C_{18}H_{24}N_2O_8$ requires C, 54.5; H, 6.1; N, 7.1%). $\lambda_{max.}$ 263 and 384 nm; $\nu_{max.}$ 3 420, 3 280br, 1 730, 1 685, and 1 625 cm^{-1}; δ 1.55 [9 H, s, $C(Me)_3$], 2.54 (2 H, m, $CH_2CH_2CO_2$), 2.98 (2 H, m, $CH_2CH_2CO_2$), 3.61 (5 H, s, CH_2CO_2 and OMe), 3.70 (3 H, s, OMe), 7.40 (1 H, d, *J* 13 Hz, CH=C*H*NO_2), 7.70 (1 H, d, *J* 13 Hz, C*H*=$CHNO_2$), 10.03 (1 H, br s, NH); *m/z* 396 (66%, M^+), 340 (14, $M^+ - C_4H_8$), 323 (22, $M^+ - C_4H_9O$), and 249 (100).

t-Butyl 3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2-nitroethyl)pyrrole-2-carboxylate (**44**).—A stirred solution of the foregoing nitrovinylpyrrole (**43**) (3.96 g, 10 mmol) in methanol (100 ml) and DMF (10 ml) containing acetic acid (0.60 g, 10 mmol) was treated rapidly with sodium borohydride, portionwise, until no further colour change occurred, the reaction mixture then being pale yellow. It was cooled to 0 °C, acidified to pH 2 with concentrated hydrochloric acid (*ca.* 6 ml), then diluted with water (200 ml) and extracted with ether (2 × 100 ml). The combined organic layers were washed with 5% aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml), dried, filtered, and evaporated. Crystallisation of the residue from methanol gave the *nitroethylpyrrole* (**44**) (3.37 g, 84.6%), m.p. 114—115.5 °C (Found: C, 54.5; H, 6.3; N, 6.9. $C_{18}H_{26}N_2O_8$ requires C, 54.3; H, 6.6; N, 7.0%); $\lambda_{max.}$ 275 nm; $\nu_{max.}$ 3 430, 1 730, 1 680, and 1 550 cm^{-1}; δ 1.55 (9 H, s, CMe_3), 2.52 (2 H, m, $CH_2CH_2CO_2$), 2.97 (2 H, m, $CH_2CH_2CO_2$), 3.25 (2 H, t, *J* 7 Hz, $CH_2CH_2NO_2$), 3.42 (2 H, s, CH_2CO_2), 3.62 (6 H, s, 2 × OMe), 4.53 (2 H, t, *J* 7 Hz, $CH_2CH_2NO_2$), and 9.17 (1 H, br s, NH); *m/z* 398 (32%, M^+), 311 (36), 296 (52), and 264 (100).

Methyl 5-[4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-5-t-butoxycarbonylpyrrol-2-yl]-3,3-dimethyl-4-nitropentanoate (**45**).—The foregoing nitroethylpyrrole (**44**) (1.19 g, 3 mmol), methyl 3,3-dimethylacrylate (1.71 g, 15 mmol), tetrabutylammonium fluoride (1M solution in THF; 3.1 ml, 3.1 mmol) and 4Å molecular sieves (1.5 g) were stirred together in DMF (30 ml) at 50 °C, under argon, for 8.5 h. The cooled reaction mixture was diluted with water (120 ml) and extracted with ether (4 × 30 ml), the combined extracts being washed with 1M aqueous hydrochloric acid (30 ml), 5% aqueous sodium hydrogen carbonate (30 ml), and brine (30 ml), dried, and evaporated. The residue crystallised from ether (6 ml) to yield the *nitro ester* (**45**) as brown prisms (0.921 g, 60%), m.p. 117—118.5 °C (Found: C, 52.6; H, 6.9; N, 5.3. $C_{24}H_{36}N_2O_{10}$ requires C, 56.2; H, 7.1; 5.5%); $\lambda_{max.}$ 276 nm; $\nu_{max.}$ 3 420, 1 730, 1 680, and 1 550 cm^{-1}; δ 1.13 (3 H, s, Me), 1.18 (3 H, s, Me), 1.54 (9 H, s, CMe_3), 2.43 (2 H, s, CH_2CO_2), 2.51 (2 H, m, $CH_2CH_2CO_2$), 2.96 (2 H, m, $CH_2CH_2CO_2$), 3.19 (2 H, m, CH_2CHNO_2), 3.44 (2 H, s, $ArCH_2CO_2$), 3.65 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.72 (3 H, s, OMe), 5.03 (1 H, dd, *J* 3, 8 Hz, CH_2CHNO_2), and 8.99 (1 H, br s, NH); *m/z* 512 (14%, M^+), 465 (22), 425 (23), and 409 (100).

5-[4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl]-4,4-dimethylpyrrolidin-2-one (**46**).—A stirred solution of the foregoing nitro ester (**45**) (256 mg, 0.5 mmol) in acetic acid (10 ml) was treated with zinc (0.65 g, 10 mmol) at 20 °C for 20 min and then at 70 °C for 1 h. The cooled mixture was treated with ammonium acetate (77 mg, 1 mmol) and 15% aqueous titanium(III) chloride (0.05 ml, 0.05 mmol), and stirred for a further 4 h. The zinc was then filtered off (Celite) and washed well with acetic acid, the filtrate being evaporated (50 °C) and the residue partitioned between chloroform (25 ml) and water (25 ml). The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, separated, and extracted with additional chloroform (10 ml). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (25 ml), dried, and evaporated. Recrystallisation of the residue from hexane–methyl acetate gave the *lactam* (**46**) (205 mg, 91%), m.p. 151—153 °C (Found: C, 61.4; H, 7.4; N, 6.3. $C_{23}H_{34}N_2O_7$ requires C, 61.3; H, 7.5; N, 6.2%); $\lambda_{max.}$ 276 nm; $\nu_{max.}$ 3 460, 3 320br, 1 740, and 1 700 cm^{-1}; δ 1.16 (3 H, s,

Me), 1.20 (3 H, s, Me), 1.48 (9 H, s, CMe_3), 2.09 (1 H, d, *J* 16 Hz, CH_AH_BCONH), 2.34 (1 H, d, *J* 16 Hz, CH_AH_BCONH), 2.50 (2 H, m, $CH_2CH_2CO_2$), 2.72 (2 H, m, CH_2CHN), 2.90 (2 H, m, $CH_2CH_2CO_2$), 3.40 (1 H, m, CH_2CHN), 3.44 (2 H, br s, CH_2CO_2), 3.66 (3 H, s, OMe), 3.69 (3 H, s, OMe), 6.81 (1 H, br s, NH), and 9.96 (1 H, br s, NH); *m/z* 450 (4%, M^+), 363 (14), 339 (90), and 283 (100).

5-[4-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethylene*]-4,4-*dimethylpyrrolidin*-2-*one* (**48**).—A solution of the foregoing lactam (**46**) (315 mg, 0.7 mmol) in acetic acid (14 ml) was stirred at 60 °C, under argon, with lead tetra-acetate (620 mg, 1.4 mmol). After 24 h, the mixture was treated with ethylene glycol (10 drops) and evaporated (50 °C). The residue in chloroform (50 ml) was washed with water (2 × 25 ml) and 5% aqueous sodium hydrogen carbonate (25 ml), dried, filtered, and evaporated to give a mixture of the diastereomeric acetoxy compounds (**47**). The less polar diastereoisomer showed δ 1.10 (3 H, s, Me), 1.29 (3 H, s, Me), 1.57 [9 H, s, $C(Me)_3$], 2.05 (3 H, s, OCOMe), 2.21 (2 H, s, CH_2CONH), 2.50 (2 H, m, $CH_2CH_2CO_2$), 2.94 (2 H, m, $CH_2CH_2CO_2$), 3.61 (2 H, br s, CH_2CO_2), 3.67 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.75 [1 H, d, *J* 10 Hz, $CH(OAc)CHN$], 5.62 (1 H, br s, NH), 5.68 [1 H, d, *J* 10 Hz, $CH(OAc)CHN$], and 9.06 (1 H, br s, NH).

The more polar diastereoisomer showed δ 1.08 (3 H, s, Me), 1.10 (3 H, s, Me), 1.56 (9 H, s, CMe_3), 2.08 (3 H, s, OCOMe), 2.11 (1 H, d, *J* 16 Hz, CH_AH_BCONH), 2.33 (1 H, d, *J* 16 Hz, CH_AH_BCONH), 2.52 (2 H, m, $CH_2CH_2CO_2$), 2.97 (2 H, m, $CH_2CH_2CO_2$), 3.59 [3 H, br s, CH_2CO_2 and $CH(OAc)CHN$], 3.66 (3 H, s, OMe), 3.70 (3 H, s, OMe), 5.85 [1 H, d, *J* 5 Hz, $CH(OAc)CHN$], 6.42 (1 H, br s, NH), and 9.15 (1 H, br s, NH).

This mixture of acetoxy compounds (**47**) in xylene (14 ml) was heated at reflux for 90 min, part (*ca.* 7 ml) of the solvent being distilled off during the following 30 min. The solution was then cooled and evaporated (50 °C), the residue being filtered through a short silica column using 2% and 5% methyl acetate in dichloromethane as eluant. This afforded the *unsaturated bicyclic lactam* (**48**) as a foam (270 mg, 86%), which crystallised from dichloromethane–hexane, m.p. 126—127 °C (Found: C, 61.2; H, 7.1; N, 6.2%; M^+, 448.2211. $C_{23}H_{32}N_2O_7$ requires C, 61.6; H, 7.2; N, 6.3%; M^+, 448.2210); $\lambda_{max.}$ 304 nm; $\nu_{max.}$ 3 450br, 1 730, and 1 680 cm^{-1}; δ 1.35 (6 H, s, 2 × Me), 1.56 (9 H, s, CMe_3), 2.39 (2 H, s, CH_2CONH), 2.51 (2 H, m, $CH_2CH_2CO_2$), 2.95 (2 H, m, $CH_2CH_2CO_2$), 3.42 (2 H, s, CH_2CO_2), 3.68 (3 H, s, OMe), 3.75 (3 H, s, OMe), 5.20 (1 H, br s, C=CH), 8.48 (1 H, br s, NH), and 8.63 (1 H, br s, NH); *m/z* 448 (17%, M^+), 392 (100, $M^+ - C_4H_8$), and 360 (30).

5-[5-*Formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethylene*]-4,4-*dimethylpyrrolidin*-2-*one* (**49**).—The foregoing unsaturated bicyclic lactam (**48**) (203 mg, 0.45 mmol) in TFA (5 ml) was treated, after 15 min, with trimethyl orthoformate (1.5 ml). After a further 15 min, water (5 ml) was added and the solution was kept for 30 min. It was then diluted with chloroform (50 ml) and 1M aqueous ammonia (50 ml), more 1M aqueous ammonia being added until the aqueous layer became basic. The organic layer was dried, filtered, and evaporated and p.l.c. of the residue (3 × 1 mm plates, eluted with 10% methanol in chloroform) gave the *formyl lactam* (**49**) as a gum (153 mg, 90%), which crystallised from dichloromethane–hexane, m.p. 96—97.5 °C. (Found: C, 60.9; H, 6.4; N, 7.8; M^+, 376.1636. $C_{19}H_{24}N_2O_6$ requires C, 60.6; H, 6.4; N, 7.4%; M^+, 376.1634); $\lambda_{max.}$ 244 and 347 nm; $\nu_{max.}$ 3 440, 3 320, 1 730, 1 670, and 1 610 cm^{-1}; δ 1.37 (6 H, s, 2 × Me), 2.43 (2 H, s, CH_2CONH), 2.62 (2 H, m, $CH_2CH_2CO_2$), 3.09 (2 H, m, $CH_2CH_2CO_2$), 3.51 (2 H, s, CH_2CO_2), 3.67 (3 H, s, OMe), 3.69 (3 H, s, OMe), 5.35 (1 H, s, C=CH), 9.06, 9.34, 9.56 (each 1 H, each br s, 2 × NH and CHO); *m/z* 376 (100%, M^+), 344 (33, $M^+ - CH_3OH$), 302 (30), and 260 (50).

5-[5-*Formyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrol*-2-*ylmethylene*]-3,4-*dihydro*-2-*methoxy*-4,4-*dimethylpyrrole* (**50**).—A stirred solution of the foregoing formyl lactam (**49**) (116 mg, 0.31 mmol) in dichloromethane (20 ml) was treated, under argon, with Hunig's base (0.8 g, 6.2 mmol) and trimethyloxonium tetrafluoroborate (0.91 g, 6.2 mmol). After 2 h, the mixture was diluted with dichloromethane (20 ml), washed with water (2 × 40 ml), dried, and evaporated. Preparative t.l.c. of the residue (2 × 1 mm plates, eluted with 6% methanol in chloroform) gave the *formyl imidate* (**50**) as a gum (78.8 mg, 65.3%), m.p. 90.5—92 °C from dichloromethane–hexane. Starting material (**49**) (11.3 mg, 9.7%) was also recovered (Found: C, 61.1; H, 7.0; N, 7.2%; M^+, 390.1794. $C_{20}H_{26}N_2O_6$ requires C, 61.5; H, 6.7; N, 7.2%; M^+, 390.1791); $\lambda_{max.}$ 246 and 372 nm; $\nu_{max.}$ 3 340, 1 730, 1 630, and 1 590 cm^{-1}; δ 1.29 (6 H, s, 2 × Me), 2.55 (2 H, s, $CH_2C=N$), 2.61 (2 H, m, $CH_2CH_2CO_2$), 3.07 (2 H, m, $CH_2CH_2CO_2$), 3.52 (2 H, s, CH_2CO_2), 3.64 (3 H, s, OMe), 3.66 (3 H, s, OMe), 4.10 (3 H, s, $CH_3OC=N$), 5.64 (1 H, s, C=CH), 8.68 (1 H, br s, NH), and 9.53 (1 H, s, CHO); *m/z* 390 (100%, M^+) and 331 (34).

t-Butyl 5-(3,3-*Dimethyl*-2-*nitro*-5-*oxohexyl*)-3-(2-*methoxycarbonylethyl*)-4-*methoxycarbonylmethylpyrrole*-2-*carboxylate* (**51**).—The nitroethylpyrrole (**44**) (1.2 g, 3 mmol), mesityl oxide (1.47 g, 15 mmol), tetrabutylammonium fluoride (1M solution in THF; 3.1 ml, 3.1 mmol) and 4Å molecular sieves (1.5 g) were stirred together in DMF (30 ml) for 3 h. The mixture was then diluted with water (120 ml) and extracted with ether (4 × 30 ml), the combined organic extracts being washed with 1M aqueous hydrochloric acid (30 ml), 5% aqueous sodium hydrogen carbonate (30 ml), and brine (30 ml), and dried. The residue from evaporation crystallised from hexane–methyl acetate to give the *nitro ketone* (**51**) as pale yellow prisms (1.09 g, 73.3%), m.p. 110.5—112.5 °C (Found: C, 58.1; H, 7.2; N, 5.6. $C_{24}H_{36}N_2O_9$ requires C, 58.1; H, 7.3; N, 5.6%); $\lambda_{max.}$ 276 nm; $\nu_{max.}$ 3 430, 1 725, 1 680, and 1 545 cm^{-1}; δ 1.13 (3 H, s, Me), 1.23 (3 H, s, Me), 1.56 [9 H, s, $C(Me)_3$], 2.16 (3 H, s, COMe), 2.47 (1 H, d, *J* 17 Hz, CH_AH_BCO), 2.52 (2 H, m, $CH_2CH_2CO_2$), 2.63 (1 H, d, *J* 17 Hz, CH_AH_BCO), 2.99 (2 H, m, $CH_2CH_2CO_2$), 3.18 (2 H, m, CH_2CHNO_2), 3.47 (2 H, s, CH_2CO_2), 3.68 (3 H, s, OMe), 3.72 (3 H, s, OMe), 5.21 (1 H, dd, *J* 3, 8 Hz, CH_2CHNO_2), and 9.00 (1 H, br s, NH); *m/z* 496 (14%, M^+), 449 (19), 393 (70), and 336 (100).

5-[4-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethyl*]-3,4-*dihydro*-2,4,4-*trimethylpyrrole* (**52**).—A stirred solution of the foregoing nitro ketone (**51**) (99 mg, 0.2 mmol) in acetic acid (4 ml) was treated for 1 h at 20 °C with zinc (0.39 g, 6 mmol). Ammonium acetate (30 mg, 0.4 mmol) and 15% aqueous titanium(III) chloride (0.04 ml, 0.04 mmol) were added, and stirring was continued for 6 h. The mixture was filtered (Celite) and the zinc washed with acetic acid, the combined filtrates being evaporated (50 °C). The residue was partitioned between water (10 ml) and chloroform (10 ml), the aqueous layer was made basic with potassium carbonate, and the two layers were filtered. The separated aqueous layer was extracted with more chloroform (5 ml), and the combined organic layers were filtered, washed with 5% aqueous sodium hydrogen carbonate (10 ml), dried, and evaporated. The residue crystallised from methanol to give the *imine* (**52**) (57 mg, 63%), m.p. 149.5—150.5 °C (Found: C, 64.4; H, 7.9; N, 6.0. $C_{24}H_{36}N_2O_6$ requires C, 64.3; H, 8.1; N, 6.2%); $\lambda_{max.}$ 280 nm; $\nu_{max.}$ 3 350br, 1 730, 1 680, and 1 580 cm^{-1}; δ 0.94 (3 H, s, Me), 1.13 (3 H, s, Me), 1.56 (9 H, s, CMe_3), 2.04 (3 H, d, *J* 2 Hz, $CH_3C=N$), 2.35 (2 H, br s, $CH_2C=N$), 2.56 (4 H, m,

$CH_2CH_2CO_2$ and CH_2CHN), 3.03 (2 H, m, $CH_2CH_2CO_2$), 3.46 (2 H, s, CH_2CO_2), 3.57 (1 H, m, CH_2CHN), 3.65 (3 H, s, OMe), 3.66 (3 H, s, OMe), and 9.41 (1 H, br s, NH); *m/z* 448 (58%, M^+), 375 (20, $M^+ - C_4H_9O$), 361 (30), and 339 (33).

5-[4-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethylene*]-3,4-*dihydro*-2,4,4-*trimethylpyrrole* (**56**). A solution of the nitro ketone (**51**) (248 mg, 0.5 mmol) in THF (1 ml) and methanol (2 ml) was mixed with sodium methoxide (54 mg, 1 mmol), stirred for 5 min, and then added, dropwise, to a stirred solution of ammonium acetate (0.69 g, 9 mmol) and 15% aqueous titanium(III) chloride (3 ml, 3.0 mmol) in water (3 ml) and THF (3 ml), under argon. The resulting solution was kept for 5.5 h, then extracted with ether (2 × 25 ml, 10 ml), and the combined organic layers were washed with 5% aqueous sodium hydrogen carbonate (25 ml), brine (25 ml), and dried. The residue from evaporation was filtered through a short silica column (5 g) with 2% methyl acetate in dichloromethane as eluant to yield the pale yellow *unsaturated imine* (**56**) (71 mg, 32%), m.p. 115—116 °C from hexane–methyl acetate (Found: 64.5; H, 7.7; N, 6.4. $C_{24}H_{34}N_2O_6$ requires C, 64.5; H, 7.7; N, 6.3%); $\lambda_{max.}$ 228 and 344 nm; $\nu_{max.}$ 3 340, 1 735, 1 690, and 1 600 cm^{-1}; δ 1.20 (6 H, s, 2 × Me), 1.57 (9 H, s, CMe_3), 2.24 (3 H, br s, CH_3C=N); 2.53 (2 H, br s, CH_2C=N), 2.60 (2 H, m, $CH_2CH_2CO_2$), 3.05 (2 H, m, $CH_2CH_2CO_2$), 3.55 (2 H, s, CH_2CO_2), 3.66 (6 H, s, 2 × OMe), 5.73 (1 H, br s, C=CH), and 8.64 (1 H, br s, NH); *m/z* 446 (30%, M^+) and 390 (100, $M^+ - C_4H_8$).

13,17-*Bis*(2-*methoxycarbonylethyl*)-12,18-*bis*(*methoxycarbonylmethyl*)-2,2,8,8-*tetramethylisobacteriochlorin* (**59**).—All operations, prior to work-up, were performed under argon with carefully dried glassware.

The unsaturated imine (**56**) (42.5 mg, 0.095 mmol) in TFA (0.5 ml) was kept at *ca.* 20 °C for 90 min and then mixed with a solution of the formyl imidate (**50**) (35.9 mg, 0.092 mmol) and trimethyl orthoformate (0.5 ml) in methanol (4.5 ml). The resulting green solution was kept for 30 min before dilution into degassed THF (30 ml), Hunig's base being added dropwise until the solution changed from turquoise to purple (about 2.5 ml). The flask and stirred contents were immersed in an ice–water bath and irradiated (5 × 200 W tungsten lamps, 15 cm) for 65 min. The solution was then evaporated to *ca.* 8 ml and diluted with dichloromethane (100 ml) before being washed with 0.2M aqueous hydrochloric acid (10 ml) and 1% aqueous sodium hydrogen carbonate (2 × 50 ml) and dried. The residue from evaporation was chromatographed on silica H (2 g) using dichloromethane and then 2% methyl acetate in dichloromethane as eluants. Finally, p.l.c. (0.25 mm indicator-free plate, eluted with 10% methyl acetate in dichloromethane) gave the *isobacteriochlorin* (**59**) (25.5 mg, 40.3%). Recrystallisation from methanol–dichloromethane gave dark red prisms, m.p. 204—206 °C (Found: C, 66.5; H, 7.0; N, 8.2%; M^+, 686.3333. $C_{38}H_{46}N_4O_8$ requires C, 66.5; H, 6.8; N, 8.2%; M^+, 686.3315); $\lambda_{max.}$(MeOAc) 337sh (ε 33 500 $dm^3\ mol^{-1}\ cm^{-1}$), 355sh (65 700), 371 (94 500), 396sh (33 300), 476 (5 100), 506 (9 400), 542 (18 300), 583 (30 300), and 635 nm (2 300); $\nu_{max.}$ 3 360w, 3 260w, 1 730, 1 640, and 1 600 cm^{-1}; δ(C_6D_6) 1.54 (12 H, s, 4 × Me), 3.05 (4 H, t, *J* 8 Hz, 2 × $CH_2CH_2CO_2$), 3.30 (4 H, s, 2 × 3-H and 2 × 7-H), 3.33 (6 H, s, 2 × OMe), 3.40 (6 H, s, 2 × OMe), 3.86 (4 H, t, *J* 8 Hz, 2 × $CH_2CH_2CO_2$), 4.20 (4 H, s, 2 × CH_2CO_2), 6.48 (1 H, br s, 5-H), 7.56 (2 H, s, 10-H and 20-H), and 8.88 (1 H, s, 15-H); *m/z* 686 (100%, M^+), 671 (4, $M^+ - Me$), 655 (3), and 627 (7).

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