Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 8.[1,2] Synthesis of (±)-Faktor-I Octamethyl Ester

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Several variations have been explored of the general synthesis of chlorins which uses a photochemical ring-closure of the macrocycle as the key step. This work leads to a synthesis of (±)-Faktor-I octamethyl ester, a chlorin which arises, in the free-acid form, by aromatisation of the mono-*C*-methylated intermediate on the biosynthetic pathway to vitamin B_{12}. This synthesis confirms the structure of Faktor-I and allows labelled samples to be prepared.

Clostridium tetanomorphum produces vitamin B_{12} and this organism also yields minute quantities of a *C*-methylated chlorin, named Faktor-I, shown[3-5] to have structure (**1**). This chlorin arises by aerial oxidation of the monomethylated intermediate on the biosynthetic pathway from uroporphyrinogen-III (**3**) to vitamin B_{12} probably a tetrahydrochlorin such as (**4**) or a tautomer of that structure. It is important for our understanding of B_{12} biosynthesis (*a*) to establish that the monomethylated intermediate is in fact a tetrahydrochlorin and (*b*) to determine its structure. Yet this work and other chemical and biosynthetic studies using Faktor-I and its reduced derivatives are seriously restricted by the scarcity of Faktor-I itself. So the synthesis of its octamethyl ester (**2**) was undertaken.

Analysis of the Synthetic Problem.—We planned to base the synthesis on the novel approach to *C*-methylated chlorins which depended on the photochemical cyclisation of a seco-chlorin.[6] The mild conditions used in this method had been shown to be compatible with the base-sensitive acetate and propionate residues present in the natural pigments. Indeed, the marine pigment, bonellin dimethyl ester, had been synthesized by this photochemical approach.[7]

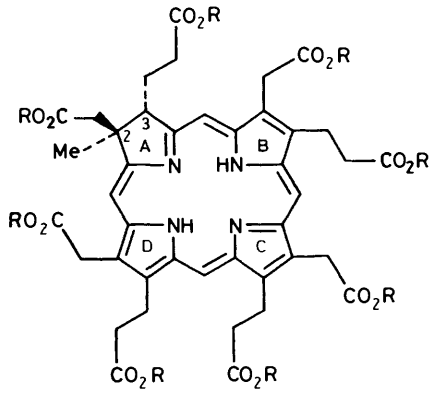
For Faktor-I ester (**2**), two mechanistically equivalent disconnections can be considered. One, between rings A and B, leads to the seco-system (**5**) and the alternative, between rings A and D, points to the seco-system (**8**) as the required intermediate. Further disconnection of seco-system (**5**) generates the building blocks (**6**) and (**7**) whereas disconnection of the other seco-system (**8**) would lead to the components (**9**) and (**10**). It seemed probable that the chemistry would drive us at some stage towards one or the other of these alternative disconnection strategies and so we wished from the outset to remain flexible.

The aim was to introduce the chiral centres of the reduced ring-A of Faktor-I ester (**2**) by using the imide (**11**). This is a known substance available in small amounts by oxidative degradation[8] of vitamin B_{12} and a synthetic route had been developed[9] which yielded multigram quantities of racemic material [as compound (**11**)]. Earlier studies had also shown[10] that model monothioimides such as (**12**) could be treated with the stabilised pyrrolomethyl phosphonium ylide (**13**) to yield the coupled product (**14**). In principle, therefore, the monothiomides (**15**) and (**18**) should be transformable in a similar way to afford the lactams (**16**) and (**19**) (Scheme 1). Clearly the nitrile function of the lactam (**16**) or (**19**) has to be removed at some subsequent stage to afford the lactam (**17**) or (**20**) and this problem will be considered later. However, another problem which had to be immediately faced on this synthetic plan was how to convert the lactam ring *e.g.* of intermediate (**17**) into the imine system present in the building block (**6**).

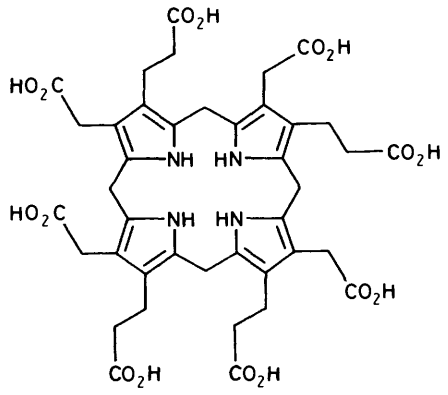
The Lactam to Imine Transformation.—The sulphur extrusion approach developed by Eschenmoser *et al.*[11] was chosen for this conversion and model studies were carried out using the available lactam[12] (**21**). This was converted into the thiolactam (**22**) by Lawesson's reagent[13] and the product treated with benzyl t-butyl bromomalonate[14] and diazabicycloundecane to yield the thioimino ether (**23**). It was used without isolation for the sulphur extrusion step to yield the malonate derivative (**24**). Two geometric isomers were observed and one could be crystallized from the mixture but studies by n.O.e. aimed at determining its configuration unambiguously were inconclusive.

Treatment of the single isomer of malonate (**24**), or of the mixed isomers, with trifluoroacetic acid gave one enamino ester (**25**) which was relatively stable and was assigned the illustrated stereochemistry by analogy with related systems.[11,14] Retention of a single ester function in the system (**25**) to be carried through the subsequent steps leading to the seco-chlorin (**26**) was expected[11,14] to hold the ring A terminus in the enamine form. Thus the π-system would be locked into the 18π-electron tautomer required for the photocyclisation process and so expedite the reaction. In practice, the enamino ester (**25**) without isolation was condensed directly with the aldehyde[6] (**7**) to yield the seco-system (**26**). Photocyclisation[6] of this seco-system then afforded the chlorin (**27**) (see Scheme 2) in 56% yield based on the aldehyde (**7**). However, the rate of photocyclisation was at least an order of magnitude slower than that experienced[6] for the seco-system (**32**) probably the result of increased steric congestion in the vicinity of the carbon–carbon bond being formed during ring-closure. Thus the benzyloxycarbonyl function at the ring A terminus afforded only a marginal yield improvement at the cost of a considerably slower reaction rate. The actual seco-system required by this approach to produce the 5-benzyloxycarbonyl derivative of Faktor-I [the enamine analogue of seco-system (**5**) carrying a benzyloxycarbonyl group at the starred centre] would be even more strongly congested. Accordingly, a modified route was examined based on the symmetrical di-t-butyl bromomalonate (**28**).

This ester (**28**) is available by bromination[15] of the trimethylsilyl ketene acetal[16] of di-t-butyl malonate. Use of this product for the sulphur extrusion procedure on the thiolactam (**22**) gave the enamine (**29**) in 50% yield although substantially more slowly than for the analogue (**24**). Treatment of the enamine (**29**) with trifluoroacetic acid then smoothly deprotected and decarboxylated all three t-butoxycarbonyl groups to yield the α-free imine (**30**); this product was identical to material prepared earlier[12] by a different method. The desired product (**30**) was accompanied (as previously[12]) by a small amount of the ketone (**31**). Condensation of the crude product (**30**) with aldehyde (**7**) gave the seco-system (**32**) and photocyclisation under the



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



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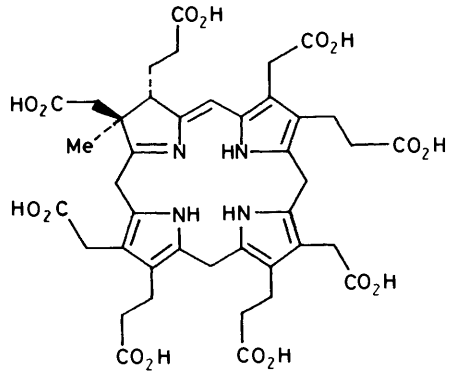

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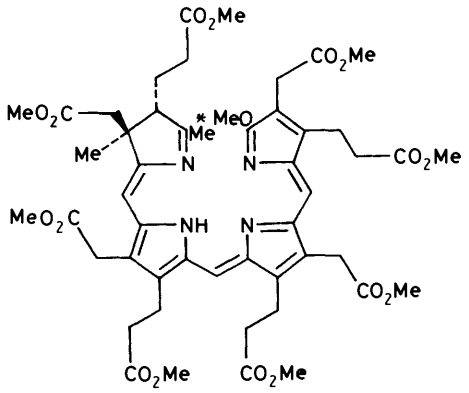

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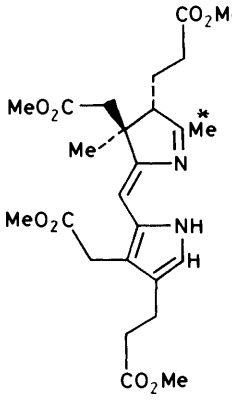

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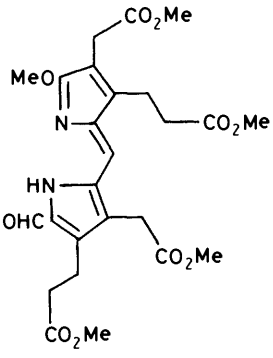

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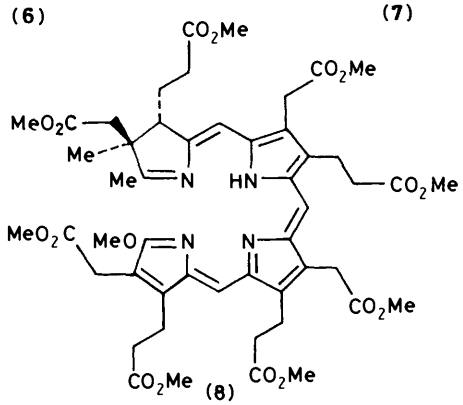

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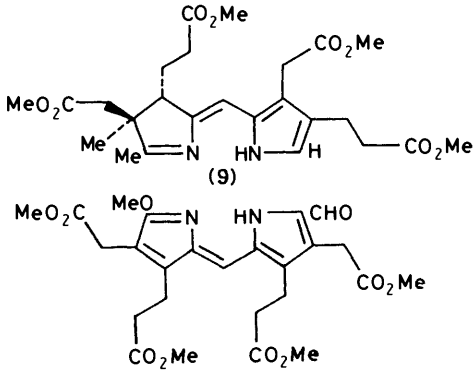


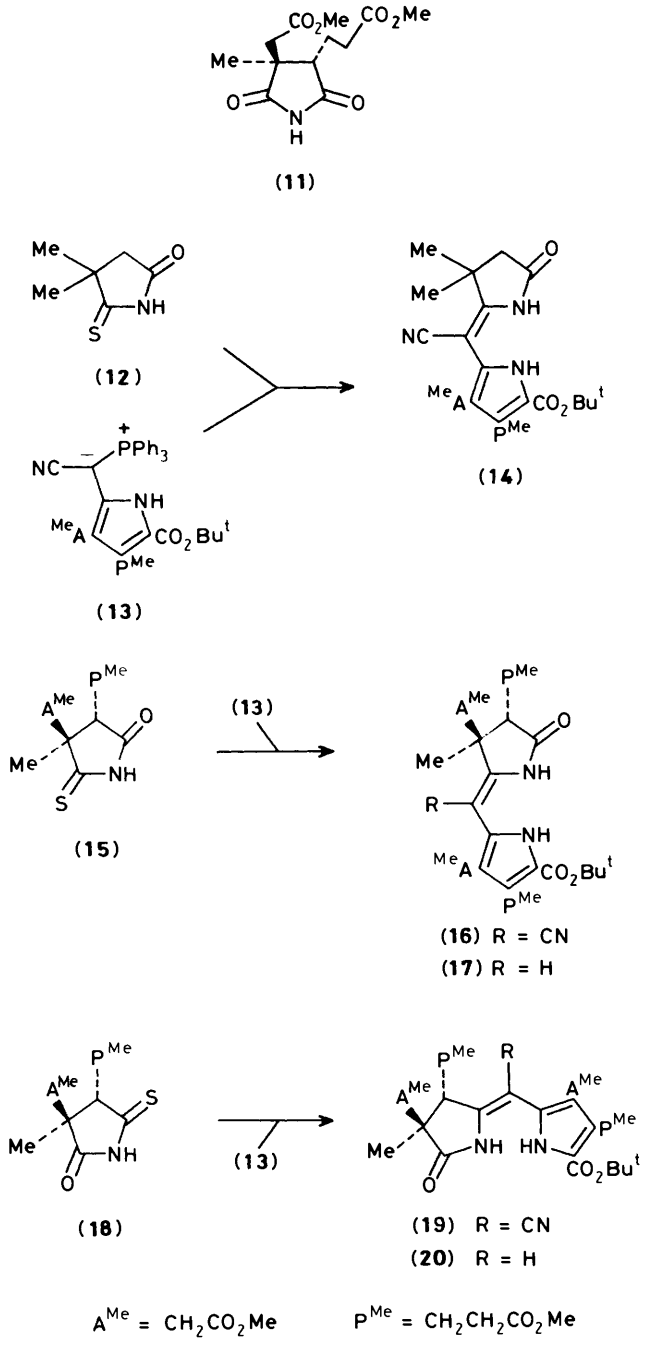
(9)

(10)

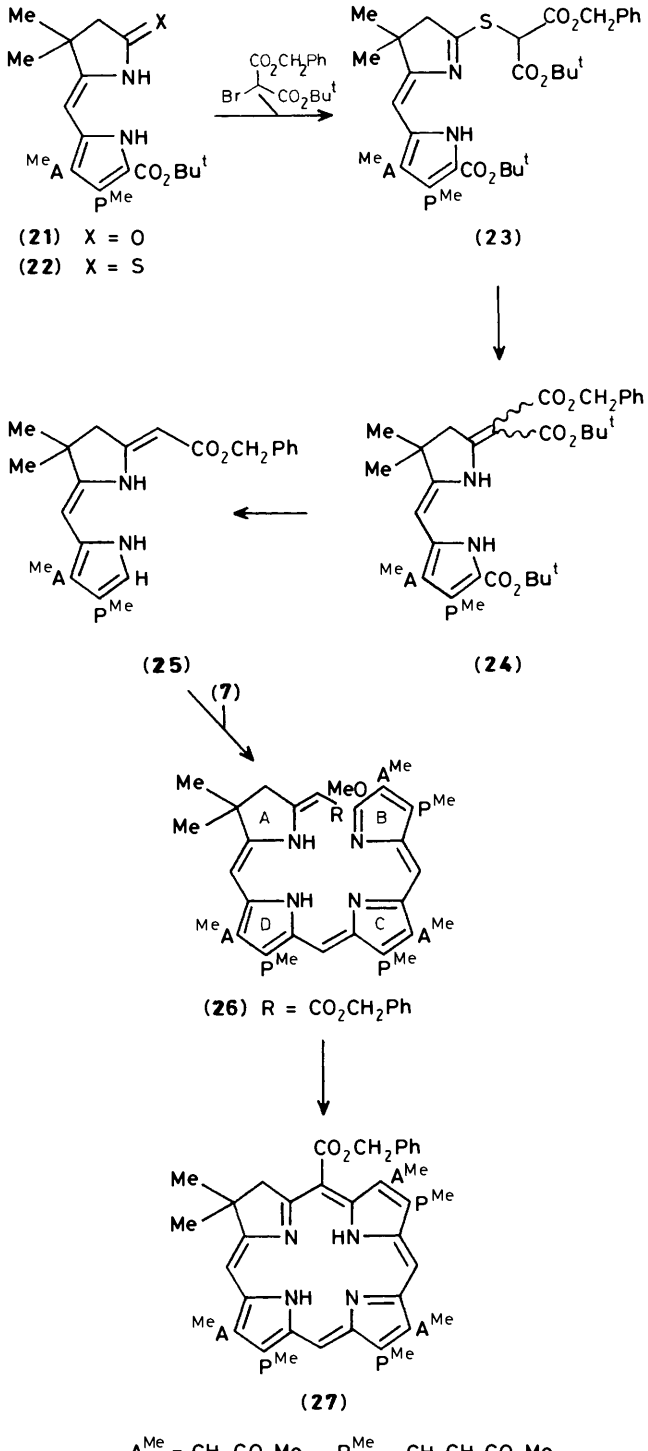
standard conditions then afforded the chlorin (**33**) (see Scheme 3) in 44% overall yield from the aldehyde (**7**). The efficiency of this compact sequence for transforming a lactam into an imine made it the method of choice for our work on the synthesis of Faktor-I ester (**2**).

It will be evident from the foregoing model studies that our initial preference was to disconnect Faktor-I ester (**2**) in a north–south direction and to proceed *via* the seco-system (**5**) rather than disconnecting east–west to go *via* the seco-system (**8**). This was because of a concern that the sulphur-extrusion process adjacent to a quaternary centre, which would be necessary for the synthesis of imine (**9**), might be a poor step. The results from the following two studies inverted that preference.

Firstly, production of the monothiomide (**18**) from the imide (**11**), using either phosphorus pentasulphide or Lawesson's



Scheme 1.



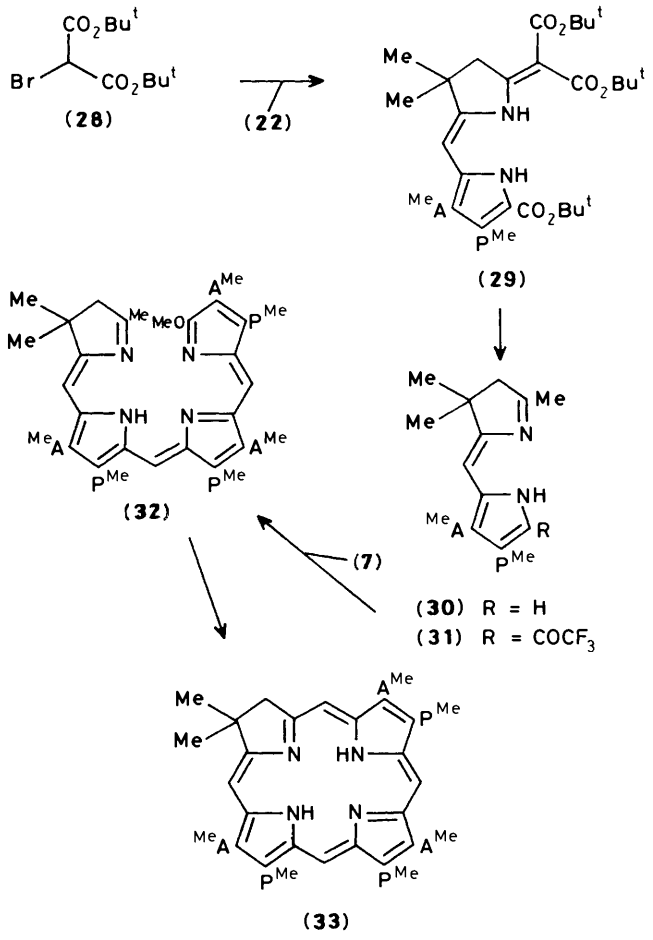
Scheme 2.

reagent, was found to be much simpler than was the production of its regioisomer (**15**).

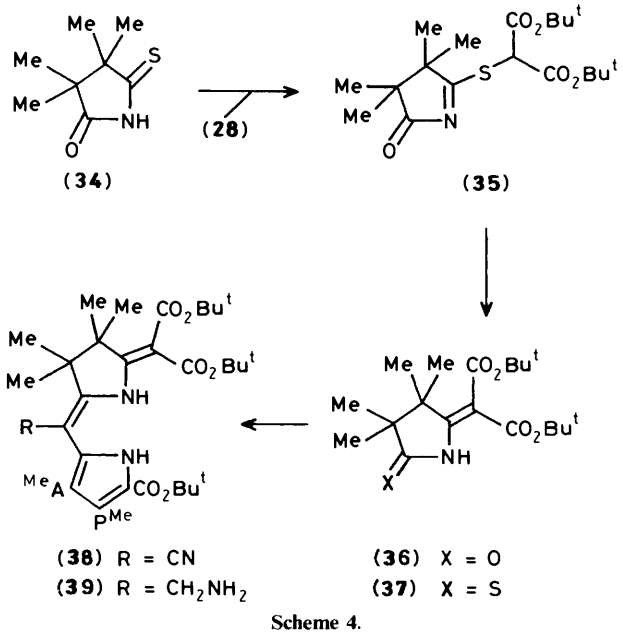
Secondly, the monothioimide (**34**), prepared as usual from the corresponding imide,[17] was alkylated with di-t-butyl bromomalonate (**28**) to yield the thioimino ester (**35**). Sulphur extrusion was then effected in almost quantitative yield to generate the enamine (**36**) (Scheme 4). Accordingly, our researches were focussed on synthesis of the seco-system (**8**) *via* the ring-A/ ring-B unit (**9**) and the ring-C/ring-D block (**10**).

The availability of the foregoing enamine (**36**) allowed us to test whether an alternative sequence would be effective for assembling a structure such as compound (**38**). The model (**36**) was converted into the thiolactam (**37**) in high yield but this gave only a poor yield of product (**38**) when it was treated under a variety of conditions with the ylide (**13**); so this alternative sequence was not pursued.

Synthesis of (±)-*Faktor-I Octamethyl Ester.*—Much of the extensive development work and model studies, which were necessary before a successful synthesis of the northern block (**9**) was achieved, were carried out in relation to the synthesis of sirohydrochlorin octamethyl ester.[18] Those details and the

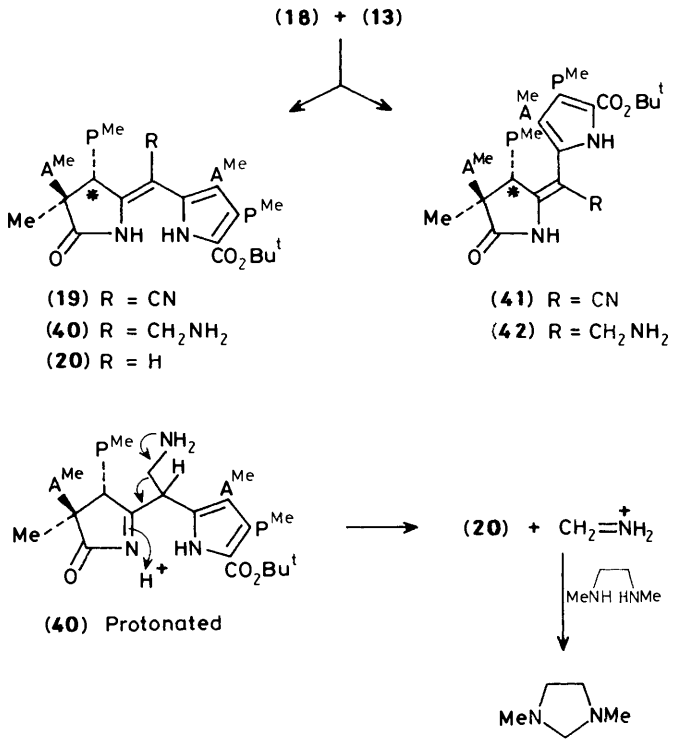


Scheme 3.



Scheme 4.

relevant discussion will be given in our full paper on that topic and only the direct key steps from the racemic imide[9] (**11**) to the racemic northern block (**9**) will be concisely described here; for simplicity, the structures show one enantiomer throughout.

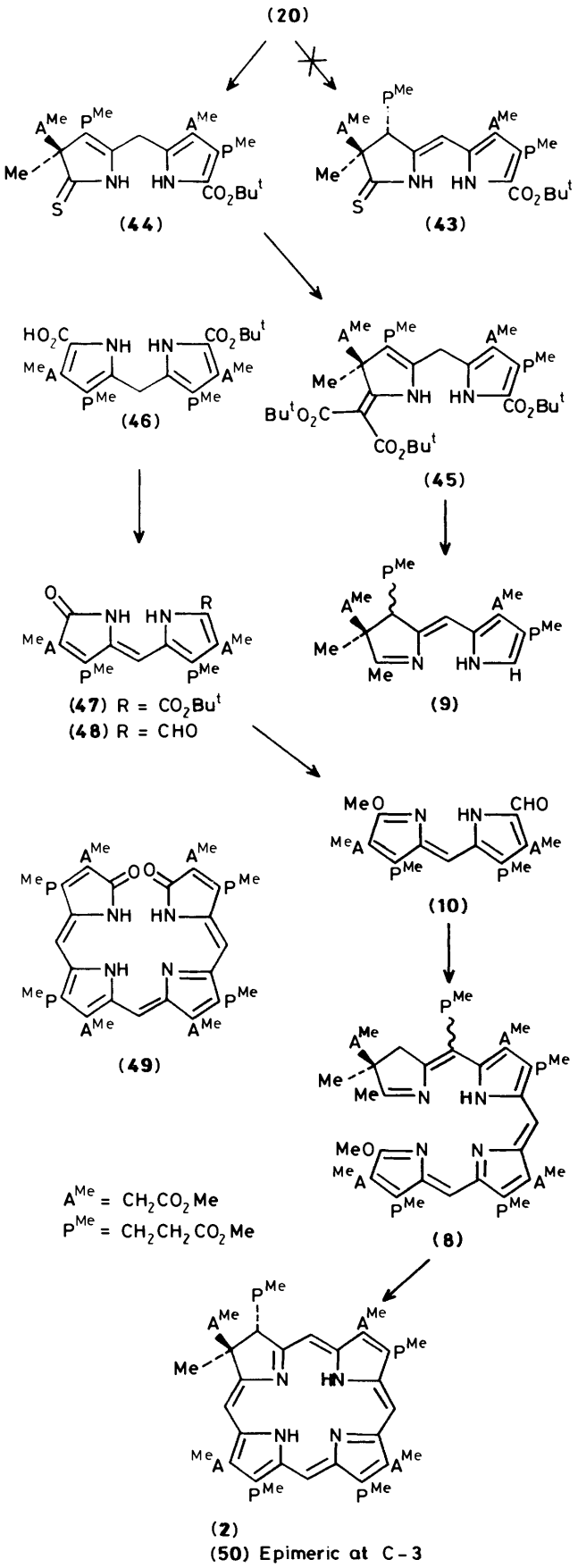


Scheme 5.

It was found that for preparation of the monothioimide (**18**), using Lawesson's reagent, highly pure (±)-imide[9] (**11**) was essential; then the desired product (**18**) could be obtained in good yield by exact control of the reaction conditions. With somewhat more vigorous conditions than the ideal ones for generating the isomer (**18**), increasing quantities of the corresponding dithioimide were formed in addition to the monothio product (**18**). This product (**18**) was coupled with ylide (**13**) to afford the (*E*)-lactam (**19**) in 75% yield together with 11% of its (*Z*)-isomer (**41**) (Scheme 5). Both products were found by n.m.r. spectroscopy to be epimerically pure at the starred centre. Hydrogenation of the pure (*E*)-lactam (**19**) over W-2 Raney nickel gave a mixture of the (*Z*)-amine (**40**) and its (*E*)-isomer (**42**) in up to 86% yield. Although the reduction was somewhat sensitive to the activity of the catalyst, the variable yields are probably due to the difficulty of desorbing the products from the nickel. These products were not separated but were heated directly in anisole with *N,N*-dimethyl-1,2-diaminoethane. The latter traps the one-carbon fragment which is eliminated in the desired reverse-Mannich reaction (see Scheme 5). This process afforded the precursor (**20**) of the required northern block (**9**) in 47% yield as a single product; there is thus a considerable simplification of the stereochemical problem in this step. The (*Z*)-lactam (**41**) could also be carried through the foregoing stages to afford the same final product (**20**). There is thus no need to separate the (*E*)- and (*Z*)-lactams (**19**) and (**41**).

In parallel with the foregoing hydrogenation experiments, it was shown that the nitrile (**38**) could also be reduced over W-2 Raney nickel to give, 65% yield, an 8:1 mixture of the (*Z*)-amine (**39**) and its (*E*)-isomer. Gratifyingly, there was no sign of any product in which the double-bond to the malonate residue had been reduced; however, this approach was not carried further because of the successes described below.

Treatment of the (*Z*)-lactam (**20**) with Lawesson's reagent in hot toluene rapidly gave a thiolactam (70% yield) of the composition expected for structure (**43**). However, the ^{1}H n.m.r. spectrum of this product showed no olefinic proton and its true



Scheme 6.

structure, the tautomer with the endocyclic double-bond (**44**), was established by its 2D homonuclear *J*-correlated spectrum (COSY) and by the heteronuclear polarisation transfer ^{13}C spectrum (DEPT). This tautomerisation was not regarded as a major problem since it seemed possible, indeed probable, that the reverse migration back into conjugation would occur at a later stage, *e.g.* in forming the seco system (**8**). Accordingly, the bromomalonate (**28**) was used with the thiolactam (**44**) in the sulphur extrusion sequence to give, in so far unoptimised modest yield, the enamine (**45**) still displaying the endocyclic double bond.

The synthesis of the southern block (**10**) started with the readily available dipyrromethane dicarboxylic acid [19] (**46**). This was treated with 2 mol equiv. of bromine in formic acid buffered with sodium formate followed by basic work-up [6] to afford the bicyclic lactam (**47**) in 50% yield. Deprotection and formylation of the latter by treatment first with trifluoroacetic acid and then with added trimethyl orthoformate gave 86% of the aldehyde (**48**). A small amount of a blue by-product was identified as the bis-lactam (**49**). Preparation of the southern component was then completed by treatment of the lactam (**48**) with trimethyloxonium tetrafluoroborate and Hunig's base to give the aldehyde (**10**).

With the northern (**45**) and southern (**10**) building blocks available, their conversion into the seco-system (**8**) was studied. To make best use of the more valuable northern precursor (**45**), the condensation step was carried out using the aldehyde (**10**) in considerable excess. Deprotection and decarboxylation of the tri-t-butyl ester (**45**) in trifluoroacetic acid followed by direct condensation of the product (**9**) with the aldehyde (**10**), also in trifluoroacetic acid, afforded the intense purple–red colour familiar to us from the earlier model studies. This colour indicated that the conjugated seco-system (**8**) had indeed been formed, confirming that the expected double-bond migration had occurred. This product was then irradiated under the standard conditions to give, in 34% overall yield [for four steps based on the limiting northern component (**45**)], a 3.2:1 mixture of (±)-Faktor-I octamethyl ester (**2**) and its separable 3-epimer [20] (**50**) (Scheme 6). Both products were shown by n.m.r., u.v.–visible, and mass spectroscopy to be identical, apart from their racemic nature, with authentic samples isolated [20] from *Clostridium tetanomorphum*.

The impact of the foregoing work can be judged by the fact that more (±)-Faktor-I octamethyl ester (**2**) was produced in the first small-scale synthetic run than had been isolated *in total* as optically active material (*ca.* 300 μg) during our extensive studies over several years on the natural source. The larger synthetic sample also allowed the ^1H n.m.r. signal to be assigned for the methine proton at C-3 of Faktor-I ester (**2**), previously not located. Decoupling studies and a COSY spectrum showed the signal for the 3-H proton to lie at δ 4.95 underneath a group of resonances from the methylenes of the three acetate side-chains other than that at C-2.

The synthesis of (±)-Faktor-I ester (**2**) gives rigorous confirmation of the structure of this pigment. It also allows labelled samples to be prepared and opens the door to investigations of the structure of the putative tetrahydrochlorin [(**4**) or a tautomer] which is believed to be the true intermediate on the biosynthetic pathway to vitamin B_{12}. These studies are in progress.

Experimental

For general directions, see ref. 21. In addition, u.v. spectra were run in methanol, drying of solutions was over anhydrous sodium sulphate or magnesium sulphate and evaporations were under reduced pressure <40 °C, unless otherwise stated. ^1H N.m.r. spectra were recorded on Varian EM 360 (A), EM 390

(B) and Bruker WH 250 (C) and WH 400 (D) spectrometers. For spectra runs on spectrometers A and B, tetramethylsilane or the residual proton signal from the solvent were used as standards whereas for C and D, the solvent signal was used. Unless otherwise stated, solutions for n.m.r. were in $CDCl_3$.

t-Butyl 1,2,3,10-*Tetrahydro*-8-(2-*methoxycarbonylethyl*)-7-*methoxycarbonylmethyl*-3,3-*dimethyl*-1-*thioxodipyrrin*-9-*carboxylate* (**22**).—A solution of the lactam (**21**) (0.72 g) and Lawesson's reagent (0.33 g) in dry toluene (85 ml) was heated at reflux under argon for 15 min. The solution was evaporated and the residue was chromatographed on silica H (30 g) eluting with ether–hexane (2:1) to give the *title compound* (**22**) as yellow needles (0.64 g 86%), m.p. 158—160 °C (from methyl acetate–hexane) (Found: C, 59.5; H, 7.0; N, 6.05; S, 7.1%; M^+, 464.1942. $C_{23}H_{32}N_2O_6S$ requires C, 59.5; H, 7.0; N, 6.0; S, 6.9%; *M*, 464.1981); $\nu_{max.}$(CH_2Cl_2) 3 680, 3 450br, 3 386, 1 736, 1 679, and 1 464 cm^{-1}; $\lambda_{max.}$ 330 and 268 nm; δ(A) 1.30 (6 H, s, Me_2C), 1.51 (9 H, s, Me_3C), 2.30—3.13 (4 H, m, CH_2CH_2), 2.83 (2 H, s, 2-CH_2), 3.37 (2 H, s, CH_2CO_2), 3.63 and 3.69 (each 3 H, s, 2 × CO_2Me), 5.22 (1 H, s, C=CH), and 9.08 and 10.03 (each 1 H, br s, 2 × NH); *m/z* (e.i.) 464 (26%, M^+), 408 (100, $M - C_4H_8$), 376 (23), and 364 (18, $M - C_4H_8 - CO_2$).

5-*Benzyloxycarbonyl*-8,13,17-*tris*(2-*methoxycarbonylethyl*)-7,12,18-*tris*(*methoxycarbonylmethyl*)-2,2-*dimethylchlorin* (**27**).—A stirred solution of the thioxodipyrrin ester (**22**) (160 mg) and benzyl t-butyl bromomalonate (227 mg) in dry toluene (12.5 ml) was treated at 18 °C under argon with diazabicycloundecane (105 μl, 107 mg). After 1 h, triphenylphosphine (445 mg) was added and the mixture heated at reflux under argon for 1.25 h. The cooled solution was evaporated at 0.3 Torr and the residue was chromatographed on silica H (30 g) eluting with 0—5% methyl acetate in dichloromethane to give a 1:1 mixture of the 1-(*E*) and 1-(*Z*) isomers of the *enamine* (**24**) as a gum (158 mg, 67%). One isomer crystallised from the mixture as needles (54.3 mg, 23%), m.p. 128.5—131 °C; $\nu_{max.}$ 3 448, 3 292br, 1 729, 1 679, 1 642, and 1 570 cm^{-1}; $\lambda_{max.}$ 317, 276, and 238 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 405, 312infl, 293, and 236 nm; δ(D, C_6D_6) 0.82 (6 H, s, Me_2C), 1.44 (9 H, s, C=CCO_2CMe_3), 1.52 (9 H, s, 9-CO_2CMe_3), 2.82 (2 H, t, *J* 7.9 Hz, CH_2CH_2), 2.90 (2 H, s, 2-CH_2), 3.28 and 3.35 (each 3 H, s, 2 × CO_2Me), 3.33 (2 H, t, *J* 7.9 Hz, CH_2CH_2), 3.47 (2 H, s, CH_2CO_2), 5.14 (1 H, s, C=CH), 5.27 (2 H, s, $PhCH_2$), 7.07—7.36 (5 H, m, Ph), and 8.73 and 11.23 (each 1 H, br s, 2 × NH); δ(D, C_6D_6) for the non-crystalline isomer: 0.85 (6 H, s, Me_2C), 1.48 (9 H, s, C=CCO_2CMe_3), 1.52 (9 H, s, 9-CO_2CMe_3), 2.87 (2 H, t, *J* 8 Hz, CH_2CH_2), 2.90 (2 H, s, 2-CH_2), 3.28 and 3.35 (each 3 H, s, 2 × CO_2Me), 3.36 (2 H, m, CH_2CH_2), 3.50 (2 H, s, CH_2CO_2), 5.16 (2 H, s, $PhCH_2$), 5.19 (1 H, s, C=CH), 7.07—7.35 (5 H, m, Ph), and 8.78 and 11.11 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 680 (100% M^+).

A solution of the foregoing crystalline enamine (**24**) (20 mg) in dry trifluoroacetic acid (0.2 ml) was kept under argon at 18 °C for 3 h and then evaporated. A solution of the aldehyde[6] (**7**) (10 mg) in dichloromethane (3 ml) was added, the dichloromethane was evaporated under an argon stream and more dry trifluoroacetic acid (0.2 ml) was added. The dark green solution was kept at 18 °C for 3 h then diluted with dry, deoxygenated tetrahydrofuran (50 ml) under argon and neutralised with dry Hünig's base (0.44 ml). The solution was transferred under argon into a thick-walled glass tube, thoroughly degassed by three cycles of 'freeze-pump-thaw' at high vacuum (<0.3 Torr) and the tube sealed whilst evacuated. The solution was then irradiated at 20 °C with visible light (tungsten; 1000 W array; 12 cm) through a solution filter of aqueous sodium dichromate (0.04M; mean path length 6 cm) for 90 h.

The contents of the tube were evaporated to *ca.* 5 ml, diluted with dichloromethane (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic layer was dried and evaporated. The residue was purified by p.l.c. [successively, 2 × 0.25 mm plates eluted with methyl acetate–dichloromethane (1:9) followed by 1 × 0.25 mm plate, eluted with methyl acetate–dichloromethane (3:22)] to give the *benzyloxycarbonyl chlorin* (**27**) as a dark green gum [10.2 mg by u.v. assay, 55.5% based on the aldehyde (**7**)]. Crystallisation from dichloromethane–methanol gave dark needles, m.p. 136.5—137.5 °C (Found: C, 64.6; H, 6.1; N, 6.0. $C_{51}H_{56}N_4O_{14}$ requires C, 64.55; H, 5.95; N, 5.9%); $\nu_{max.}$ 3 330, 1 727, 1 608w, and 1 586w cm^{-1}; $\lambda_{max.}$(MeOAc) 649 (4.80), 619 (3.55), 597 (3.61), 550 (3.21), 524 (3.30), 498 (4.15), 492sh (4.14), 394 (5.28), 348infl (4.57), 291.5sh (4.14), and 281.5sh nm (4.17); δ(D, CD_2Cl_2) −2.18 and −1.83 (each 1 H, br s, 2 × NH), 1.91 (6 H, s, Me_2C), 3.18—3.32 (6 H, m, 3 × $CH_2CH_2CO_2$), 3.66, 3.67, 3.68, 3.72, 3.76, and 3.77 (each 3 H, s, 6 × CO_2Me), 4.18 (2 H, t, *J* 7.8 Hz, $CH_2CH_2CO_2$), 4.24 (2 H, s, 3-CH_2), 4.27 (2 H, t, *J* 8.3 Hz, $CH_2CH_2CO_2$), 4.31 (2 H, t, *J* 7.9 Hz, $CH_2CH_2CO_2$), 4.80, 4.88, and 4.93 (each 2 H, s, 3 × CH_2CO_2), 5.80 (2 H, s, CH_2Ph), 7.43—7.69 (5 H, m, Ph), 8.83 (1 H, s, 20-H), and 9.75 and 9.90 (each 1 H, s, 10-H and 15-H); *m/z* (f.d.) 948 (100% M^+).

Di-t-butyl Bromomalonate (**28**).—Butyl-lithium (1.6M solution in hexane) was added dropwise to a stirred solution of di-t-butyl malonate (1.1 g) in dry tetrahydrofuran (10 ml) containing a small crystal of 1,10-phenanthroline at −78 °C under argon until a red–brown colour persisted. After a further 2 min, chlorotrimethylsilane (0.72 ml, 0.62 g) was added and stirring was continued at −78 °C for 10 min, then for 40 min while warming to 0 °C. A solution of bromine in carbon tetrachloride (1M; 5.2 ml) was then added dropwise with stirring until the bromine colour persisted. After a further 5 min, the solvent was evaporated and the residue was mixed with dichloromethane (50 ml) and water (40 ml). The aqueous layer was extracted with more dichloromethane (2 × 15 ml) and the combined methylene dichloride solutions were washed with water (25 ml), dried, and evaporated. P.l.c. eluting with dichloromethane–ether–hexane (1:1:18) gave the *bromomalonate* (**28**) as an oil (0.82 g, 54.6%); $\nu_{max.}$(film) 1 735 cm^{-1}; δ(A) 1.44 (18 H, s, 2 × Me_3C) and 4.52 (1 H, s, CHBr); *m/z* (e.i.) 294/296 (10%, M^+, 239/241 (56, $M - C_4H_7$), 223/225 (58, $M - C_4H_7O$), 194/196 (22, $M - C_4H_8 - CO_2$), 147/149 (15, 223/225 − C_4H_8), 138/140 (8, 194/196 − C_4H_8), 120/122 (45, $BrCH_2CHO^+$), and 115 (100).

t-Butyl 1,2,3,10-*Tetrahydro*-8-(2-*methoxycarbonylethyl*)-7-*methoxycarbonylmethyl*-3,3-*dimethyl*-1-[*bis*(*t-butoxycarbonyl*)-*methylene*]*dipyrrin*-9-*carboxylate* (**29**).—A stirred solution of the thioxodipyrrin ester (**22**) (280 mg) and di-t-butyl bromomalonate (**28**) (215 mg) in dry toluene (25 ml) was treated at 18 °C under argon with diazabicycloundecane (110 μl, 112 mg). After 1.3 h, triphenylphosphine (0.79 g) and diazabicycloundecane (70 μl, 71 mg) were added and the mixture was heated under reflux under argon for 7.5 h. It was then evaporated at 0.3 Torr and the residue was chromatographed on silica H (30 g), eluting with 0—8% methyl acetate in dichloromethane to give the *enamine* (**29**) (160 mg, 41%), m.p. 141—143 °C (from ether–hexane) (Found: C, 63.3; H, 7.8; N, 4.5. $C_{34}H_{50}N_2O_{10}$ requires C, 63.1; H, 7.8; N, 4.3%); $\nu_{max.}$ 3 452, 3 314br, 1 730, 1 681, 1 644, and 1 580 cm^{-1}; $\lambda_{max.}$ 332, 328sh, 272, 239sh, and 232 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 401, 320sh, 292, 239sh, and 232 nm; δ(D, C_6H_6) 0.84 (6 H, s, Me_2C), 1.49, 1.53, and 1.56 (each 9 H, s, 3 × Me_3C), 2.83 (2 H, t, *J* 8.0 Hz, CH_2CH_2), 2.86 (2 H, s, 2-CH_2), 3.29 and 3.35 (each 3 H, s, 2 × CO_2Me), 3.29—3.35 (2 H, m, CH_2CH_2), 3.47 (2 H, s, CH_2CO_2), 5.11 (1 H, s, C=CH), and 8.69 and 10.95 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 646 (100%, M^+).

8,13,17-*Tris*(2-*methoxycarbonylethyl*)-7,12,18-*tris*(*methoxycarbonylmethyl*)-2,2-*dimethylchlorin* (**33**).—The foregoing enamine (**29**) (20.8 mg) in dry trifluoroacetic acid (0.2 ml) was kept at 18 °C under argon for 3 h and then evaporated under an argon stream. A solution of the aldehyde (**7**) (10.2 mg) in dichloromethane (3 ml) was added, the solvent was evaporated under argon, and the residue was treated again with dry trifluoroacetic acid (0.2 ml). After 3 h, the purple–red solution was diluted with dry, deoxygenated tetrahydrofuran (60 ml) under argon and the deep turquoise solution was neutralised with dry Hunig's base (0.45 ml). The resulting green solution was transferred under argon into a thick-walled glass tube, degassed by four cycles of 'freeze-pump-thaw' at high vacuum (< 0.3 Torr) and the tube sealed whilst under high vacuum. The solution was irradiated at 20 °C with visible light (tungsten; 1000 W array; 12 cm) through a solution filter of aqueous sodium dichromate (0.04M; mean path length 6 cm) for 28 h.

The contents of the tube were evaporated to *ca.* 5 ml, dichloromethane (50 ml) was added, and the solution was washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml), dried, and evaporated. The residue was purified by p.l.c. [2 × 0.25 mm plates, eluted with methyl acetate–dichloromethane (3:22)] to give the *chlorin* (**33**) [6.95 mg by u.v. assay, 43.4% based on the aldehyde (**7**)] which crystallised from dichloromethane–methanol to give dark needles. This was identical by m.p. and full spectroscopic comparison with an authenic sample.[6]

2,2,3,3-*Tetramethylmonothiosuccinimide* (**34**).—(With Dr. P. J. Harrison). 2,2,3,3-Tetramethylsuccinimide (207 mg) and Lawesson's reagent (322 mg) were heated under reflux in dry toluene (10 ml), under argon for 1.25 h. The cooled mixture was evaporated and chromatography of the residue on silica H (10 g), eluting with 0—6% methyl acetate in dichloromethane, gave two fractions. The second fraction, obtained using 2% methyl acetate in dichloromethane gave the desired *monothiosuccinimide* (**34**) as pale yellow needles (149 mg, 65.3%) which could be further purified by sublimation under reduced pressure, m.p. 102—105 °C (sublimes) (Found: C, 56.2; H, 7.4; N, 8.1; S, 18.6. $C_8H_{13}NOS$ requires C, 56.1; H, 7.6; N, 8.2; S, 18.7%); $\nu_{max.}$ 3 390, 3 200br, 1 755, 1 469, and 1 421 cm^{-1}; δ(A) 1.20 and 1.28 (each 6 H, s, 2 × Me_2C) and 9.65 (1 H, br s, NH), *m/z* (e.i.) 171 (100%, M^+), 156 (36, *M* − Me), 128 (12), 102 (12), 97 (22), 84 (24), 70 (17), and 69 (35).

The fraction eluted with dichloromethane yielded 2,2,3,3-*tetramethyldithiosuccinimide* as yellow prisms (74.5 mg, 28.7%), m.p. 92.5—94.5 °C (from ether–pentane) (Found: C, 51.5; H, 7.0; N, 7.5; S, 34.0. $C_8H_{13}NS_2$ requires C, 51.3; H, 7.0; N, 7.5; S, 34.5%); $\nu_{max.}$ 3 376, 3 155br, 1 432, 1 395, and 1 376 cm^{-1}; δ(A) 1.27 (12 H, s, 4 × Me) and 11.56 (1 H, br s, NH); *m/z* (e.i.) 187 (100%, M^+), 172 (47, *M* − Me), 154 (28), 113 (40), 86 (72), 85 (50), 71 (40), 69 (31), and 59 (73).

3,3,4,4-*Tetramethyl*-5-*bis*(*t-butoxycarbonyl*)*methylene*-2-*pyrrolidone* (**36**).—Diazabicycloundecane (228 μl, 232 mg) was added to a stirred solution of the monothioimide (**34**) (262 mg) and di-t-butyl bromomalonate (**28**) (0.5 g) in dichloromethane (20 ml) under argon at 18 °C. After 1.5 h, the solvent was evaporated and the residue in dry toluene (23 ml) was mixed with triphenylphosphine (1.21 g) and diazabicycloundecane (230 μl, 234 mg). The mixture was heated at reflux under nitrogen for 15 min, cooled, neutralised with glacial acetic acid and evaporated at 0.3 Torr. Chromatography of the residue on silica H (15 g) eluting with ether–hexane (3:7) gave the *pyrrolidone* (**36**) (536 mg, 99%). It was further purified either by sublimation under reduced pressure or by slow evaporation of a solution in cold pentane, m.p. 130—144 °C (sublimes) (Found: 64.8; H, 8.6; N, 3.8. $C_{19}H_{31}NO_5$ requires C, 64.6; H, 8.8; N, 4.0%); $\nu_{max.}$ 1 724, 1 696, and 1 607 cm^{-1}; δ(A) 1.08 and 1.24 (each 6 H, s, 2 × Me_2C), 1.48 and 1.53 (each 9 H, s, 2 × Me_3C), and 10.15 (1 H, br s, NH), *m/z* (e.i.) 353 (100%, M^+), 297 (23, $M - C_4H_8$), 280 (9, $M - C_4H_9O$), 241 (100, $M - 2 \times C_4H_8$), 224 (40), 223 (32), 208 (38), 205 (44), and 57 (57, $C_4H_9^+$).

3,3,4,4-*Tetramethyl*-5-[*bis*(*t-butoxycarbonyl*)*methylene*]-*pyrrolidine*-2-*thione* (**37**).—A solution of the foregoing pyrrolidone (**36**) (117 mg) and Lawesson's reagent (153 mg) in dry toluene (10 ml) was heated at reflux under nitrogen for 1 h. The cooled mixture was evaporated and the residue was purified by p.l.c. [2 × 1 mm plates, eluted with ether–hexane (1:4)] to give the *thiolactam* (**37**) as pale yellow needles (147 mg, 79%), m.p. 145.5—146.5 °C (from cold ether) (Found: C, 61.7; H, 8.35; N, 3.8; S, 9.0. $C_{19}H_{31}NO_4S$ requires C, 61.8; H, 8.5; N, 3.8; S, 8.7%), $\nu_{max.}$ 3 302, 1 712, 1 678, 1 618, 1 474, 1 451, and 1 436 cm^{-1}; $\lambda_{max.}(CH_2Cl_2)$ 321 and 236 nm; δ(A) 1.16 and 1.23 (each 6 H, s, 2 × Me_2C), 1.50 and 1.53 (each 9 H, s, 2 × Me_3C), and 11.60 (1 H, br, NH); *m/z* (e.i.) 369 (50%, M^+), 313 (5, $M - C_4H_8$), 296 (15, $M - C_4H_9O$), 269 (7, $M - CO_2 - C_4H_8$), 257 (100, $M - 2 \times C_4H_8$), 239 (63, 257 − H_2O), 57 (41, $C_4H_9^+$); *m** 265.5 (369→313), 222 (257→239).

t-Butyl (E)-5-*Cyano*-1,2,3,10-*tetrahydro*-8-(2-*methoxycarbonylethyl*)-7-*methoxycarbonylmethyl*-2,2,3,3-*tetramethyl*-1-[*bis*(*t-butoxycarbonyl*)*methylene*]*dipyrrin*-9-*carboxylate* (**38**).—A 0.84M solution of potassium t-butoxide in t-butyl alcohol (0.26 ml) was added to a stirred suspension of the phosphonium salt[10] (**13**) (98 mg) in dry toluene (6 ml) containing the foregoing thiolactam (**37**) (55 mg) at 18 °C under argon and the resulting solution was heated under reflux for 5.5 h. The cooled mixture was evaporated under reduced pressure (0.3 Torr) and the residue was purified by p.l.c. [2 × 1 mm plates, eluted with ether–hexane (2:1)] to give the *nitrile* (**38**) [31 mg, 29.9%, 94.3% based on the unrecovered thiolactam (**37**)] as a gum (Found: M^+, 699.3732. $C_{37}H_{53}N_3O_{10}$ requires *M*, 699.3730); $\nu_{max.}(CH_2Cl_2)$ 3 430, 3 270br, 2 202, 1 731, 1 677, and 1 604 cm^{-1}; $\lambda_{max.}$ 322 and 276 nm; $\lambda_{max.}[Zn(OAc)_2]$ 430, 307, and 281sh nm; δ(D, CD_2Cl_2) 1.19 and 1.34 (each 6 H, s, 2 × Me_2C), 1.41, 1.49, and 1.56 (each 9 H, s, 3 × Me_3C), 2.57 (2 H, t, *J* 8.2 Hz, $CH_2CH_2CO_2$), 3.01 (2 H, t, *J* 8.2 Hz, $CH_2CH_2CO_2$), 3.39 (2 H, s, CH_2CO_2), 3.61 and 3.65 (each 3 H, s, 2 × CO_2Me), and 8.96 and 11.15 (each 1 H, br s, 2 × NH); *m/z* 699 (60%, M^+), 643 (4, $M - C_4H_8$); 626 (12, $M - C_4H_9O$), 599 (4, $M - CO_2 - C_4H_8$), 587 (3, $M - 2 \times C_4H_8$), 531 (100, 587 − C_4H_8), and 469 (51, 531 − CO_2 − H_2O); *m** 591.5 (699→643), 480 (587→531), and 414 (531→469).

t-Butyl (Z)-5-*Aminomethyl*-1,2,3,10-*tetrahydro*-8-(2-*methoxycarbonylethyl*)-7-*methoxycarbonylmethyl*-2,2,3,3-*tetramethyl*-1-[*bis*(*t-butoxycarbonyl*)*methylene*]*dipyrrin*-9-*carboxylate* (**39**).—A solution of the nitrile (**38**) (37.3 mg) in methanol–water–acetic acid (80:19:1; 5 ml) was stirred at 18 °C with W-2 Raney nickel under hydrogen for 16 h and the solution was then filtered through Celite. The Raney nickel was washed well with methanol (100 ml), then glacial acetic acid (100 ml), and the total filtrate was evaporated under reduced pressure (0.3 Torr); the last traces of acetic acid and water were removed by addition and evaporation of toluene (*ca.* 3 ml). The residual gum was purified by p.l.c [1 mm plate, eluted with methanol–dichloromethane (1:9)] to give the (*Z*)-isomer of the *amine* (**39**) (21.6 mg, 57.6%) as an amorphous solid (Found: M^+, 703.4038. $C_{37}H_{57}N_3O_{10}$ requires *M*, 703.4043); $\nu_{max.}$ 3 442, 3 282br, 1 729, 1 675, 1 646, and 1 591 cm^{-1}; $\lambda_{max.}$ 324 and 277 nm; $\lambda_{max.}[Zn(OAc)_2]$ 336 and 289 nm; δ(C) 1.13 and 1.21 (each 6 H, s, 2 × Me_2), 1.40, 1.48, and 1.52 (each 9 H, s, 3 × Me_3C), 2.02 (2 H, br, NH_2), 2.57 (2 H, t, *J* 8.2 Hz, $CH_2CH_2CO_2$), 3.01 (2 H, br s, $CH_2CH_2CO_2$), 3.34 (2 H, br s, CH_2CO_2), 3.61 and

3.66 (each 3 H, s, 2 × CO_2Me), 3.65—3.86 (2 H, br, CH_2NH_2), and 9.83 and 10.10 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 703 (100%, M^+).

The unstable, slightly less polar (*E*)-isomer was also isolated (2.7 mg, 7.2%) (Found: M^+, 703.4010. $C_{37}H_{57}N_3O_{10}$ requires *M*, 703.4043); $\lambda_{max.}$ 315 and 276 nm [unchanged by $Zn(OAc)_2$]; *m/z* (f.d.) 703 (100%, M^+).

(±)-4α-(2-*Methoxycarbonylethyl*)-3β-*methoxycarbonylmethyl*-3α-*methyl*-5-*thioxo*-2-*pyrrolidone* (**18**).—(±)-2α-(2-Methoxycarbonylethyl)-3β-methoxycarbonylmethyl-3α-methylsuccinimide (**11**) (97.4 mg) and Lawesson's reagent (303 mg) were heated at reflux in dry toluene (12 ml) under argon. After 12 h, the cooled reaction mixture was evaporated (0.3 Torr) and a solution of the residue in dichloromethane (5 ml) was filtered and evaporated. Fractionation of this residue by p.l.c. [4 × 1 mm plates eluted continuously with ether–hexane (1:1)] gave two bands. The lower R_F band yielded the (±)-*monothioimide* (**18**) (37.9 mg, 36.7%) which crystallised from ether–hexane as pale yellow needles, m.p. 117—119 °C (Found: C, 50.05; H, 5.95; N, 4.7%; M^+, 287.0830. $C_{12}H_{17}NO_5S$ requires C, 50.15; H, 5.95; N, 4.9%; *M*, 287.0827); $\nu_{max.}$ 3 392, 1 762, 1 733, and 1 439 cm^{-1}; δ(C) 1.12 (3 H, s, 3-Me), 1.77 (1 H, m, $CH_aH_bCH_2CO_2$), 2.21 (1 H, m, $CH_aH_bCH_2CO_2$), 2.61 (1 H, d, *J* 17.7 Hz, $CH_aH_bCO_2$), 2.69 (2 H, m, $CH_2CH_2CO_2$), 2.86 (1 H, d, *J* 17.7 Hz, $CH_aH_bCO_2$), 3.07 (1 H, dd, *J* 5.2 and 7.6 Hz, 3-H), 3.62 and 3.63 (each 3 H, s, 2 × CO_2Me), and 9.90 (1 H, br s, NH); *m/z* 287 (50%, M^+), 256 (41, *M* − MeO), 255 (38, *M* − MeOH), 227 (21, *M* − HCO_2Me), 214 (27, *M* − CH_2CO_2Me), 182 (100), 154 (67), and 128 (72).

The higher R_F band gave (±)-3α-(2-*methoxycarbonylethyl*)-4β-*methoxycarbonylmethyl*-4α-*methylpyrrolidine*-2,5-*dithione* as a yellow gum (58.4 mg, 53.6%) (Found: M^+, 303.0611. $C_{12}H_{17}NO_4S_2$ requires *M*, 303.0599); $\nu_{max.}$ 3 377, 3 193br, 1 738, and 1 448 cm^{-1}; δ(C) 1.19 (3 H, s, 4-Me), 1.87 (1 H, m, $CH_aH_bCH_2CO_2$), 2.17 (1 H, m, $CH_aH_bCH_2CO_2$), 2.67 (1 H, d, *J* 17.5 Hz, $CH_aH_bCO_2$), 2.74 (2 H, m, $CH_2CH_2CO_2$), 3.04 (1 H, d, *J* 17.5 Hz, $CH_aH_bCO_2$), 3.32 (1 H, dd, *J* 4.7 and 7.9 Hz, 3-H), 3.63 and 3.64 (each 3 H, s, 2 × CO_2Me), and 10.78 (1 H, br s, NH); *m/z* 303 (100%, M^+), 272 (42, *M* − MeO), 271 (54, *M* − MeOH), 230 (31, *M* − CH_2CO_2Me), 198 (70), 170 (29), 144 (26), 135 (40), and 69 (84).

(±)-*t-Butyl* (E)- *and* (Z)-5-*Cyano*-1,2,3,10-*tetrahydro*-3α,8-*bis*(2-*methoxycarbonylethyl*)-2β,7-*bis*(*methoxycarbonylmethyl*)-2α-*methyl*-1-*oxodipyrrin*-9-*carboxylate* (**19**).—(With Dr. P. J. Harrison). A suspension of the phosphonium chloride[10] corresponding to ylide (**13**) (80 mg) in dry toluene (6 ml) containing the (±)-monothioimide (**18**) (31.5 mg) was stirred at 18 °C under argon during the addition of a 0.83M solution of potassium t-butoxide in t-butyl alcohol (0.20 ml) and the resulting solution was heated at reflux under argon. After 3.5 h, the cooled mixture was treated with saturated aqueous ammonium chloride (1.5 ml) then shaken with water (10 ml) and dichloromethane (10 ml). The organic layer was separated, the aqueous layer extracted with dichloromethane (2 × 10 ml), and the combined organic fractions were dried and evaporated to dryness. The residue by p.l.c. (1 mm plate, eluted with 12% methyl acetate in dichloromethane) gave the (±)-(E)-*nitrile* and the (±)-(Z)-*nitrile* (**19**) and (**41**), respectively, as gums (51.4 mg, 76% and 7.1 mg, 10.5%, respectively), the (*E*)-isomer having the higher R_F.

The (*E*)-isomer: (Found: M^+, 617.2593. $C_{30}H_{39}N_3O_{11}$ requires *M*, 617.2584); $\nu_{max.}$ 3 436, 3 300br, 2 210, 1 739, 1 690, 1 635, and 1 574 cm^{-1}; $\lambda_{max.}$ 274sh and 254 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 370, 306sh, 294sh, 283, and 251 nm; δ(D) 1.28 (3 H, s, 2-Me), 1.54 (9 H, s, Me_3C), 2.20 (2 H, m, 3-$CH_2CH_2CO_2$), 2.47—2.57 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.55 (1 H, d, *J* 16.3 Hz, 2-$CH_aH_bCO_2$), 2.60 (1 H, d, *J* 16.3 Hz, 2-$CH_aH_bCO_2$), 2.90 (2 H, t, *J* 7.9 Hz, 8-$CH_2CH_2CO_2$), 3.41 (1 H, d, *J* 16.8 Hz, 7-$CH_aH_bCO_2$), 3.44 (1 H, m, 3-H), 3.52 (1 H, d, *J* 16.8 Hz, 7-$CH_aH_bCO_2$), 3.65 and 3.71 (each 3 H, s, 2 × CO_2Me), 3.67 (6 H, s, 2 × CO_2Me), and 8.96 and 9.14 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 617 (100%, M^+).

The (*Z*)-isomer: (Found: M^+, 617.2593. $C_{30}H_{39}N_3O_{11}$ requires *M*, 617.2584); $\nu_{max.}$ 3 430, 3 385, 2 209, 1 732, 1 690, and 1 634 cm^{-1}; $\lambda_{max.}$ 277infl and 255 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 277infl and 255 nm; δ(D) 1.25 (3 H, s, 2-Me), 1.56 (9 H, s, Me_3C), 1.85, 2.01, and 2.13 (each 1 H, m, 3-$CH_2CH_aH_bCO_2$), 2.52 (1 H, d, *J* 15.0 Hz, 2-$CH_aH_bCO_2$), 2.54—2.60 (3 H, m, 8-$CH_2CH_2CO_2$ and 3-$CH_2CH_aH_bCO_2$), 2.73 (1 H, d, *J* 15.0 Hz, 2-$CH_aH_bCO_2$), 2.95 (2 H, m, 8-$CH_2CH_2CO_2$), 3.49 (1 H, d, *J* 16.8 Hz, 7-$CH_aH_bCO_2$), 3.55 (1 H, d, *J* 16.8 Hz, 7-$CH_aH_bCO_2$), 3.58, 3.64, 3.65, and 3.69 (each 3 H, s, 4 × CO_2Me), 3.60 (1 H, m, 3-H), and 8.24 and 9.67 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 617 (100%, M^+).

(±)-*t-Butyl* (Z)-5-*Aminomethyl*-1,2,3,10-*tetrahydro*-3α,8-*bis*(2-*methoxycarbonylethyl*)-2β,7-*bis*(*methoxycarbonylmethyl*)-2-*methyl*-1-*oxodipyrrin*-9-*carboxylate* (**40**).—A solution of the foregoing (±)-nitrile (**19**) (85.5 mg) in methanol–water–acetic acid (80:19:1; 20 ml) was stirred with W-2 Raney nickel at 18 °C under hydrogen for 13 h. The solution was then filtered (Celite) and the nickel was washed sequentially with methanol (200 ml), triethylamine (30 ml), methanol (30 ml), glacial acetic acid (60 ml), and finally more methanol (30 ml). Each separate filtrate was evaporated under reduced pressure (0.3 Torr) and the combined residues by p.l.c. [2 × 1 mm plates, eluted with methanol–dichloromethane (1:9)] gave the (±)-*amine* (**40**) as a gum (55 mg, 64%) (Found: M^+, 621.2799. $C_{30}H_{43}N_3O_{11}$ requires *M*, 621.2897); $\nu_{max.}$(CH_2Cl_2) 3 387br, 1 731, and 1 676 cm^{-1}; $\lambda_{max.}$ 284 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 307 nm; δ(C) 1.26 (3 H, s, 2-Me), 1.55 (9 H, s, Me_3C), 1.86 (1 H, m, 3-$CH_aH_bCH_2CO_2$), 2.02 (1 H, m, 3-$CH_aH_bCH_2CO_2$), 2.39 (2 H, t, *J* 7.9 Hz, 8-$CH_2CH_2CO_2$), 2.44 (2 H, s, 2-CH_2CO_2), 2.53 (2 H, t, *J* 7.7 Hz, 3-$CH_aH_bCH_2CO_2$), 2.91 (2 H, t, *J* 7.9 Hz, 8-$CH_2CH_2CO_2$), 3.20 (2 H, br, NH_2), 3.33 (1 H, d, *J* 17.1 Hz, 7-$CH_aH_bCO_2$), 3.34—3.44 (1 H, m, 3-H), 3.40 (1 H, d, *J* 17.1 Hz, 7-$CH_aH_bCO_2$), 3.63—3.70 (2 H, br, CH_2N), 3.66, 3.665, 3.68, and 3.73 (each 3 H, s, 4 × CO_2Me), and 8.01 and 10.57 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 622 (100%, M^+ + 1) and 621 (70, M^+).

The (*E*)-amine (**42**) was also formed in this reduction and, for preparative work, was not separated from the foregoing (*Z*)-isomer (**40**).

(±)-*t-Butyl* (E)-1,2,3,10-*Tetrahydro*-3α,8-*bis*(2-*methoxycarbonylethyl*)-2β,7-*bis*(*methoxycarbonylmethyl*)-2α-*methyl*-1-*oxodipyrrin*-9-*carboxylate* (**20**).—A solution of the foregoing amine (**40**) (55.7 mg) in anisole (7 ml) containing *N,N'*-dimethylethylenediamine (0.19 ml) was heated at 90 °C under argon for 9 h, then cooled and evaporated (0.3 Torr). The residue was purified by p.l.c. [1 mm plate, eluted with methanol–dichloromethane (1:9)] to give the (±)-*lactam* (**20**) as a gum (24.9 mg, 46.9%) (Found: M^+, 592.2636. $C_{29}H_{40}N_2O_{11}$ requires *M*, 592.2632); $\nu_{max.}$(CH_2Cl_2) 3 438, 1 733, and 1 678 cm^{-1}; $\lambda_{max.}$ 302sh and 288 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 352, 306sh, and 272 nm; δ(C) 1.15 (3 H, s, 2-Me), 1.53 (9 H, s, Me_3C), 1.92 (2 H, m, 3-$CH_2CH_2CO_2$), 2.45—2.57 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.51 (1 H, d, *J* 16.5 Hz, 2-$CH_aH_bCO_2$), 2.79 (1 H, d, *J* 16.5 Hz, 2-$CH_aH_bCO_2$), 2.93 (2 H, t, *J* 8.0 Hz, 8-$CH_2CH_2CO_2$), 3.15 (1 H, dt, *J* 1.7 and 7.3 Hz, 3-H), 3.40 (1 H, d, *J* 16.0 Hz, 7-$CH_aH_bCO_2$), 3.47 (1 H, d, *J* 16.0 Hz, 7-$CH_aH_bCO_2$), 3.64, 3.65, 3.67, and 3.70 (each 3 H, s, 4 × CO_2Me), 5.32 (1 H, d, *J* 1.7 Hz, C=CH), and 8.74 and 8.98 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 592 (100%, M^+).

A mixture of the (*Z*)- and (*E*)-amines (**40**) and (**42**) could be

used for the above preparation to give an unchanged yield of the lactam (**20**).

(±)-*t-Butyl* 5,8,9,10-*Tetrahydro*-2,7-*bis*(2-*methoxycarbonylethyl*)-3,8-*bis*(*methoxycarbonylmethyl*)-8-*methyl*-9-*thioxodipyrrin*-1-*carboxylate* (**44**).—A solution of Lawesson's reagent (22.8 mg) and the foregoing lactam (**20**) (16 mg) in dry toluene (4 ml) was heated at reflux under argon for 30 min then cooled and evaporated (0.3 Torr). The residue was purified by p.l.c. (1 mm plate, eluted with 8% methyl acetate in dichloromethane) to give the (±)-*thiolactam* (**44**) as a gum (11.5 mg) (Found: M^+, 608.2403. $C_{29}H_{40}N_2O_{10}S$ requires M, 608.2403); $\nu_{max.}$ 3 342br, 1 728, 1 685. and 1 478 cm^{-1}; $\lambda_{max.}$(MeOAc) 322 and 275 nm; δ(C) 1.23 (3 H, s, 8-Me), 1.51 (9 H, s, Me_3C), 2.50 (2 H, t, J 8.0 Hz, 2-$CH_2CH_2CO_2$), 2.54—2.63 (4 H, m, 7-$CH_2CH_2CO_2$), 2.67 (1 H, d, J 16.5 Hz, 8-$CH_aH_bCO_2$), 2.93 (2 H, t, J 8.0 Hz, 2-$CH_2CH_2CO_2$), 3.05 (1 H, d, J 16.5 Hz, 8-$CH_aH_bCO_2$), 3.50 (1 H, d, J 16.6 Hz, 3-$CH_aH_bCO_2$), 3.53 (3 H, s, 8-CO_2Me), 3.54 (1 H, d, J 16.6 Hz, 3-$CH_aH_bCO_2$), 3.63 (1 H, d, J 16.6 Hz, 5-CH_aH_b), 3.65 (3 H, s, 2-CO_2Me), 3.77 (1 H, d, J 16.6 Hz, 5-CH_aH_b), 3.77 (3 H, s, 7-CO_2Me), 3.79 (3 H, s, 3-CO_2Me), and 9.74 and 10.10 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 608 (100%, M^+).

(±)-*t-Butyl* 5,8,9,10-*Tetrahydro*-2,7-*bis*(2-*methoxycarbonylethyl*)-3,8-*bis*(*methoxycarbonylmethyl*)-8-*methyl*-9-[*bis*(*t-butoxycarbonyl*)*methylene*]*dipyrrin*-1-*carboxylate* (**45**).—A solution of the foregoing thiolactam (**44**) (10.4 mg), and di-t-butyl bromomalonate (**28**) (8.2 mg) in dichloromethane (1 ml) was stirred at 18 °C under argon with diazabicycloundecane (4.2 μl, 4.3 mg) for 1 h and then evaporated. The residue in dry toluene (1 ml) was mixed with diazabicycloundecane (5 μl, 5.1 mg) and triphenylphosphine (23.8 mg) and was heated at reflux under argon for 3 h. The cooled solution was neutralised with glacial acetic acid (1 drop) and evaporated (0.3 Torr). The residue by p.l.c. [1 mm plate, eluted with ether–hexane (55:45)] gave the (±)-*enamine* (**45**) as a gum (2.9 mg, 21.5%) (Found: M^+, 790.3884. $C_{40}H_{58}N_2O_{14}$ requires M, 790.3887); $\nu_{max.}$ 3 333, 1 731, 1 687, 1 649, and 1 571 cm^{-1}; $\lambda_{max.}$(CH_2Cl_2) 336 and 273 nm; δ(D) 1.36 (3 H, s, 8-Me), 1.44, 1.48, and 1.51 (each 9 H, s, 3 × Me_3C), 2.35—2.44 (4 H, m, 7-$CH_2CH_2CO_2$), 2.54 (2 H, t, J 8.1 Hz, 2-$CH_2CH_2CO_2$), 2.66 (1 H, d, J 17.4 Hz, 8-$CH_aH_bCO_2$), 2.98 (2 H, t, J 8.1 Hz, 2-$CH_2CH_2CO_2$), 3.42 (1 H, d, J 17.4 Hz, 8-$CH_aH_bCO_2$), 3.45 (1 H, d, J 15.8 Hz, 3-$CH_aH_bCO_2$), 3.49 (1 H, d, J 15.8 Hz, 3-$CH_aH_bCO_2$), 3.53 (1 H, d, J 17.0 Hz, 5-CH_aH_b), 3.63, 3.66, 3.67, and 3.69 (each 3 H, s, 4 × CO_2Me), 3.72 (1 H, d, J 17.0 Hz, 5-CH_aH_b), and 9.54 and 9.86 (each 1 H, br s, 2 × NH); *m/z* (f.d.) 790 (100%, M^+).

t-Butyl 1,10-*Dihydro*-3,7-*bis*(2-*methoxycarbonylethyl*)-2,8-*bis*(*methoxycarbonylmethyl*)-1-*oxodipyrrin*-9-*carboxylate* (**47**).—5,10-Dihydro-3,7-bis(2-methoxycarbonylethyl)-2,8-bis(methoxycarbonylmethyl)-9-t-butoxycarbonyldipyrrin-1-carboxylic acid[19] (**46**) (60.7 mg) and sodium formate (27.5 mg) were stirred together in dry formic acid (0.2 ml) at 0 °C under argon during the addition of a solution of 1.03M bromine in formic acid (0.20 ml). After 15 min at 0 °C, the mixture was warmed to 18 °C during 5 min, then poured into ice–water (1 ml) and dichloromethane (10 ml). Saturated brine (10 ml) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (2 × 10 ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (15 ml) and the aqueous washings back-extracted with more dichloromethane (5 ml). The combined organic fractions were dried, evaporated, and the residue was washed with ether to leave a yellow solid which was recrystallised from dichloromethane–ether to yield the *title compound* (**47**) as yellow needles (24.5 mg, 42.5%), m.p. 195—196.5 °C (Found: C, 58.4; H, 6.3; N, 4.8. $C_{28}H_{36}N_2O_{11}$ requires C, 58.3; H, 6.3; N, 4.9%); $\nu_{max.}$ 3 436, 3 340, 1 738, and 1 698 cm^{-1}; $\lambda_{max.}$ 402sh, 386, 259, and 253sh nm; $\lambda_{max.}$[$Zn(OAc)_2$] 441, 425sh, and 266 nm; δ(D) 1.53 (9 H, s, Me_3C), 2.49 (2 H, t, J 7.5 Hz, 7-$CH_2CH_2CO_2$), 2.61 (2 H, t, J 7.5 Hz, 3-$CH_2CH_2CO_2$), 2.86 (2 H, t, J 7.5 Hz, 3-$CH_2CH_2CO_2$), 2.90 (2 H, t, J 7.5 Hz, 7-$CH_2CH_2CO_2$), 3.62, 3.64, 3.65, 3.67, and 3.69 (4 × 3 H, and 1 × 2 H, s, 4 × CO_2Me and 2-CH_2CO_2), 3.78 (2 H, s, 8-CH_2CO_2), 6.22 (1 H, s, C=CH), and 10.01 and 10.34 (each 1 H, br s, 2 × NH); *m/z* 576 (26%, M^+), 520 (100, $M - C_4H_8$), 489 (14, $M - C_4H_8 - MeO$), 476 (54, $M - C_4H_8 - CO_2$), 400 (15), 373 (29), 343 (28), and 329 (28); *m** 469.5 (576→520).

1,10-*Dihydro*-3,7-*bis*(2-*methoxycarbonylethyl*)-2,8-*bis*(*methoxycarbonylmethyl*)-1-*oxodipyrrin*-9-*carbaldehyde* (**48**).—A solution of the foregoing oxodipyrrin ester (**47**) (56 mg) in dry trifluoroacetic acid (4 ml) was stirred at 50 °C under argon for 1.1 h, then cooled to 0 °C, and treated with trimethyl orthoformate (0.18 ml). Stirring was continued for 20 min at 0 °C, then water (4 ml) was added, and the resulting solution was stirred for 15 min more whilst warming to 18 °C. It was then shaken with dichloromethane (10 ml) and water (5 ml), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried, evaporated, and the green–yellow residue was washed with ether to leave a yellow solid; recrystallisation from dichloromethane–ether gave the *title compound* (**48**) as yellow needles (42 mg, 85.7%), m.p. 184—186.5 °C (Found: C, 57.35; H, 5.5; N, 5.4. $C_{24}H_{28}N_2O_{10}$ requires: C, 57.1; H, 5.6; N, 5.55%); $\nu_{max.}$ 3 336, 2 850, 1 738, 1 705, and 1 680 cm^{-1}; $\lambda_{max.}$ 416sh, 392, and 269 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 456, 430, 414infl, and 279 nm; δ(D) 2.55 (2 H, t, J 7.2 Hz, $CH_2CH_2CO_2$), 2.64 (2 H, t, J 7.6 Hz, $CH_2CH_2CO_2$), 2.89—2.97 (4 H, m, 2 × $CH_2CH_2CO_2$), 3.57 and 3.83 (each 2 H, s, 2 × CH_2CO_2), 3.63, 3.67, 3.69, and 3.71 (each 3 H, s, 4 × CO_2Me), 6.25 (1 H, s, C=CH), 9.73 (1 H, s, CHO), and 10.20 and 10.60 (each 1 H, br, 2 × NH); *m/z* 504 (100%, M^+), 472 (23, M − MeOH), 447 (35), 446 (96), 445 (39, $M - CO_2Me$), 371 (53), 357 (47), 343 (42), 335 (84), and 285 (78).

The residue from the above ether washings gave by p.l.c. (0.25 mm plate, eluted with 8% methyl acetate in dichloromethane) 3,7,13,17-*tetrakis*(2-*methoxycarbonylethyl*)-2,8,12,18-*tetrakis*(*methoxycarbonylmethyl*)*bilin*-1,19(21H,24H)-*dione* (**49**) as a blue gum (2 mg, 4.3%) (Found: M^+, 962.3408. $C_{47}H_{54}N_4O_{18}$ requires M, 952.3432); $\nu_{max.}$ 3 424, 1 735, 1 704, and 1 584 cm^{-1}; $\lambda_{max.}$(CH_2Cl_2) 653, 373, 315sh, and 271sh nm; δ(D, CD_2Cl_2) 2.54 (4 H, t, J 7.6 Hz, 2 × $CH_2CH_2CO_2$), 2.66 (4 H, t, J 7.6 Hz, 2 × $CH_2CH_2CO_2$), 2.86 (8 H, t, J 7.6 Hz, 4 × $CH_2CH_2CO_2$), 3.32 (4 H, s, 2 × CH_2CO_2), 3.64, 3.67, 3.68, and 3.69 (total 28 H, each s, 8 × CO_2Me and 2 × CH_2CO_2), 6.12 (2 H, s, 5-H and 15-H), 6.85 (1 H, s, 10-H), 8.05—8.25 (1 H, br, NH). Two NH not observed; *m/z* (f.d.) 962 (M^+, 100%).

1-*Methoxy*-3,7-*bis*(2-*methoxycarbonylethyl*)-2,8-*bis*(*methoxycarbonylmethyl*)*dipyrrin*-9-*carbaldehyde* (**10**).—A stirred mixture of the foregoing oxodipyrrin ester (**48**) (9.8 mg) and trimethyloxonium tetrafluoroborate (72.5 mg) in dichloromethane (1.5 ml) was treated with Hünig's base (80 μl, 59.4 mg) and 18 °C under argon. After a further 45 min, the solution was filtered, evaporated, and the residue purified p.l.c. [0.25 mm plate, eluted with methyl acetate–dichloromethane (1:4)]. The yellow high R_F band gave the *title compound* (**10**) as a yellow gum (5.5 mg, 54%) (Found: M^+, 518.1900. $C_{25}H_{30}N_2O_{10}$ requires M, 518.1900); $\nu_{max.}$(CCl_4) 3 300br w, 3 050, 2 857w, 1 745, and 1 650 cm^{-1}; $\lambda_{max.}$ 422, 404, and 266 nm; $\lambda_{max.}$[$Zn(OAc)_2$] 459, 313, 278, and 274 nm; δ(D) 2.55 (2 H, t, J

7.5 Hz, $CH_2CH_2CO_2$), 2.59 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 2.86 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 2.93 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$), 3.41 (2 H, s, 2-CH_2CO_2), 3.64, 3.66, 3.69, and 3.70 (each 3 H, s, 4 × CO_2Me), 3.77 (2 H, s, 8-CH_2CO_2), 4.11 (3 H, s, 1-OMe), 6.56 (1 H, s, C=CH), 9.71 (1 H, s, CHO), and 11.97 (1 H, br s, NH); *m/z* (f.d.) 518 (100%, M^+).

(±)-3α,8,13,17-*Tetrakis*(2-*methoxycarbonylethyl*)-2β,7,12,18-*tetrakis*(*methoxycarbonylmethyl*)-2α-*methylchlorin* [(±)-*Faktor-I Octamethyl Ester*] (**2**).—The enamine (**45**) (2.9 mg) in dry trifluoroacetic acid (0.1 ml) was kept at 18 °C under argon for 3 h and then evaporated in an argon stream. A solution of the aldehyde (**10**) (4.5 mg) in dichloromethane (1 ml) was added to the residue and the green solution was then evaporated under an argon stream. The residue was dissolved in dry trifluoroacetic acid (0.15 ml) and after 2.5 h, the purple–red solution was diluted into dry, deoxygenated tetrahydrofuran (25 ml) under argon which caused a colour change to deep green–blue. Neutralisation of this solution with dry Hünig's base (0.34 ml) produced a further colour change to a deep green. The solution was transferred under argon into a thick-walled glass tube, degassed by four cycles of 'freeze-pump-thaw' at high vacuum (<0.3 Torr) and the evacuated tube was sealed. The solution was irradiated for 22 h at 18 °C with visible light (tungsten; 1 200 W array; 18 cm distance) through a solution filter of aqueous 0.04M sodium dichromate, mean path length 10 cm.

The solution was largely evaporated and the concentrate (*ca.* 1 ml) with dichloromethane (15 ml) was washed with saturated aqueous sodium hydrogen carbonate (15 ml) and water (15 ml), dried, and evaporated. The residue was purified by p.l.c. [0.25 mm plate, eluted with methyl acetate–dichloromethane (3:17)] to give a mixture of (±)-*Faktor-I octamethyl ester* (**2**) and its 3-epimer (**50**); the latter was removed by repetitive p.l.c.[20] [0.25 mm plates, eluted continuously with ether–chloroform (4:1)] to give the pure chlorin as a dark green gum [0.92 mg, 26% over the four steps based on compound (**45**)]. This product was identical, apart from its racemic nature, with authentic Faktor-I octamethyl ester[20] by t.l.c., h.p.l.c., u.v.–visible, and 400 MHz ^{1}H n.m.r. spectroscopy and field desorption mass spectroscopy (Found: M^+, 958.3836. $C_{49}H_{58}N_4O_{16}$ requires *M*, 958.3847); $\lambda_{max.}$(MeOAc) 644 (rel. int. 0.291), 615 (0.020), 592 (0.022), 542 (0.010), 523 (0.015), 498 (0.071), 489 (0.068), 393 (1.0), 348infl (0.169), 292sh (0.079), and 280 (0.086) nm; δ(D, CD_2Cl_2) −2.37 (2 H, br s, 2 × NH), 2.28 (3 H, s, 2-Me), 2.27—2.69 (4 H, m, 3-$CH_2CH_2CO_2$), 2.94 (1 H, d, *J* 15.0 Hz, 2-$CH_aH_bCO_2$), 3.06 (1 H, d, *J* 15.0 Hz, 2-$CH_aH_bCO_2$), 3.22, 3.27, and 3.28 (each 2 H, t, *J* 7.8 Hz, 8-, 13-, and 17-$CH_2CH_2CO_2$), 3.48, 3.56, 3.68, 3.76, 3.79, and 3.80 (each 3 H, s, 6 × CO_2Me), 3.67 (6 H, s, 2 × CO_2Me), 4.22, 4.34, and 4.36 (each 2 H, t, *J* 7.8 Hz, 8-, 13-, and 17-$CH_2CH_2CO_2$), 4.91 (2 H, s, 12-CH_2CO_2), 4.95 (1 H, m, 3-H), 4.96 (2 H, s, 18-CH_2CO_2), 4.97 (2 H, ABq, *J* 16.2 Hz, 7-$CH_aH_bCO_2$), 8.88 (1 H, s, 20-H), 9.01 (1 H, s, 5-H), 9.83 (1 H, s, 10-H), and 9.85 (1 H, s, 15-H); *m/z* (f.d.) 958 (100%, M^+).

The (±)-3-epimer (**50**) was also collected as a green gum [0.28 mg, 8.1% based on compound (**45**)] and identified by n.m.r. with a sample from natural sources enriched in 3-epi-Faktor-I octamethyl ester.[20]

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References

1 Part 7, A. R. Battersby, C. J. Dutton, and C. J. R. Fookes, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper.
2 Preliminary account in part. S. P. D. Turner, M. H. Block, Z.-C. Sheng, S. C. Zimmerman, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1985, 583.
3 R. Deeg, H.-P. Kriemler, K.-H. Bergmann, and G. Müller, *Hoppe-Seyler's Z. Physiol. Chem.*, 1977, **358**, 339.
4 K.-H. Bergmann, R. Deeg, K. D. Gneuss, H.-P. Kriemler, and G. Müller, *Hoppe-Seyler's Z. Physiol. Chem.*, 1977, **358**, 1315.
5 M. Imfeld, D. Arigoni, R. Deeg, and G. Müller, in 'Vitamin B_{12},' eds. B. Zagalak and W. Freidrich, de Gruyter, Berlin, 1979, p. 315.
6 A. R. Battersby, C. J. Dutton, C. J. R. Fookes, and S. P. D. Turner, *J. Chem. Soc., Chem. Commun.*, 1983, 1235; *J. Chem. Soc., Perkin Trans. 1*, 1988, 1557.
7 A. R. Battersby, C. J. Dutton and C. J. R. Fookes, *J. Chem. Soc., Chem. Commun.*, 1983, 1237 and ref. 1.
8 T. L. Bogard and A. Eschenmoser, unpublished work, E.T.H., Zürich.
9 A. R. Battersby and S. W. Westwood, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1679.
10 D. M. Arnott, A. R. Battersby, P. J. Harrison, G. B. Henderson, and Z.-C. Sheng, *J. Chem. Soc., Chem. Commun.*, 1984, 525.
11 A. Eschenmoser, and C. E. Winter, *Science*, 1977, **196**, 1410; V. Rasetti, Diss. ETH 6462, Zürich, 1979.
12 P. J. Harrison, C. J. R. Fookes, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1981, 797; P. J. Harrison, Z.-C. Sheng, C. J. R. Fookes, and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1667.
13 S. Scheibye, B. S. Pedersen, and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 229.
14 M. H. Block, Ph.D. Thesis, Cambridge, 1985.
15 R. H. Reuss and A. Hassner, *J. Org. Chem.*, 1974, **39**, 1785; L. Blanco, P. Amice, and J. M. Conia, *Synthesis*, 1976, 194.
16 E. W. Colvin, 'Silicon in Organic Synthesis,' Butterworths, London, 1981, p. 214.
17 A. F. Bickel and W. A. Waters, *Rec. Trav. Chim. Pays-Bas*, 1950, **69**, 1490.
18 M. H. Block, S. C. Zimmerman, G. B. Henderson, S. P. D. Turner, S. W. Westwood, F. J. Leeper, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1985, 1061.
19 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2413.
20 A. R. Battersby and S. Seo, *J. Chem. Soc., Perkin Trans. 1*, 1983, 3049.
21 A. R. Battersby, C. J. R. Fookes, and R. J. Snow, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2725.

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