Stereochemical Studies on Porphyrin *a*: Assignment of the Absolute Configuration of a Model Porphyrin by Degradation

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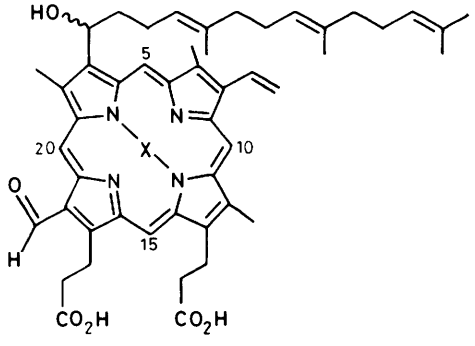
The synthesis is described of a porphyrin alcohol (**22**) which has a structure very similar to that of porphyrin *a* (**2**). The model porphyrin was resolved by separation of its camphanate esters. Ozonolysis of the 2-nitrobenzoate of each enantiomer in tritiated form gave a derivative of 2-hydroxypentanedioic acid whose configuration was determined by dilution analysis. It is demonstrated that correlation of the stereochemistry of porphyrin *a* with that of the model (**22**) will be possible by means of the ^1H and ^{19}F n.m.r. spectra of the corresponding esters with (−)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

Cytochrome c oxidase (ferrocytochrome c:O_2 oxidoreductase, EC 1.9.3.1) is one of the most important oxidases found in living systems. It occurs, not only in all animal and plant tissues, but also in many micro-organisms including some bacteria.[1] In mammals, it is the terminal enzyme in the mitochondrial respiratory chain, and is responsible for the catalysis of the reduction of molecular oxygen to water.

The monomeric enzyme (which is thought to be made up of seven subunits) has a mass of about 118 000 and contains two copper atoms and two haem molecules.[2] Initially, the two haem molecules were thought to have different chemical structures, but more recent work suggests that this is unlikely.[1,3] However they differ markedly in the co-ordination state of the metal when they are enzyme bound.[1]

The chemical structure of haem *a* (**1**) and of its metal-free form, porphyrin *a* (**2**) (so called because the enzyme was previously known as cytochrome a) has been the subject of many detailed studies[1] and has recently been proved unambiguously by total synthesis.[3]



(**1**) X = Fe
(**2**) X = H,H

Haem *a* (**1**) contains a chiral centre, the secondary alcohol at the point of attachment of the farnesylethyl side chain to the macrocycle. It is very likely that when bound to the enzyme it is optically active, although the possibility does exist that the two molecules of haem *a* present in the enzyme are opposite enantiomers, so that on isolation a more or less racemic mixture will be obtained.

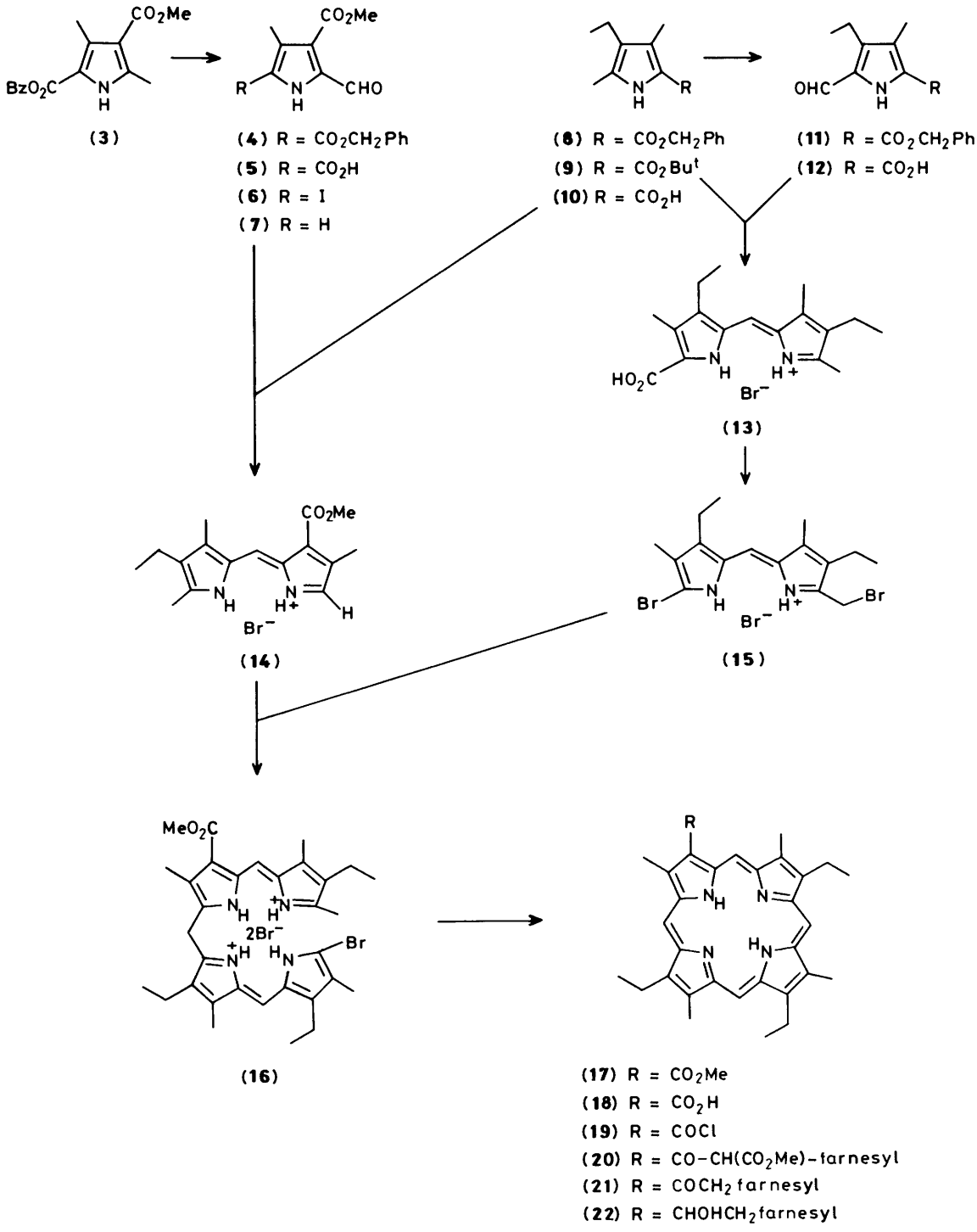
Any study aimed at the elucidation of the absolute stereochemistry of haem *a* (**1**) is hampered by the susceptibility of this chiral centre to racemisation,[4] which can occur under acidic conditions and possibly under basic conditions also, due to the electron-withdrawing formyl group. As a result it is uncertain whether haem *a* can be isolated in optically active form. In two studies[5,6] haem *a*, isolated by different extraction procedures, has been claimed to be optically active but the two samples had o.r.d. curves which were the mirror image of each other. No satisfactory explanation for these results is available. However it has been shown[3] by h.p.l.c. that both extraction procedures yield, after demetallation, samples of porphyrin *a* which are seriously impure.

One possible source of optical activity other than the chiral secondary alcohol could be introduced if the metal had different ligands on either side of the porphyrin ring. Because of this possibility it would be safer to study the stereochemistry of the metal-free porphyrin *a* (**2**), but a problem still to be faced is that the normal conditions for the removal of iron from a porphyrin are strongly acidic[7] and would be certain to racemise the chiral centre.

It is clear that isolation of optically active porphyrin *a* from natural sources will not be easy, but once that has been achieved there will remain the problem of assigning the absolute stereochemistry. Our plan was to synthesize a model porphyrin closely related to porphyrin *a* and to resolve it. With the optically active materials in hand, the way would be open (a) to determine their absolute configurations by degradation, (b) to develop methods for the correlation of the configurations of the model porphyrin with porphyrin *a* itself, and (c) to study the optical stability of the enantiomers of the model system. We report here our results from studies (a) and (b).

Synthesis of the Model Porphyrin.—The very small quantities of porphyrin *a* (**2**) which could reasonably be obtained from natural sources precluded extensive direct studies on its stereochemistry and although porphyrin *a* is now available synthetically,[3] it was decided to simplify the synthesis by working on a model porphyrin which had only alkyl substituents. Accordingly porphyrin (**22**) was chosen as the synthetic target.

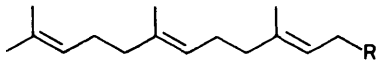
A previously used method for the attachment of side-chains to a porphyrin nucleus has involved porphyrin acid chlorides such as (**19**).[3,8,9] The porphyrin ester (**17**) has been synthesized by Kenner and co-workers[10] and essentially the same procedure was employed in the present study. Starting with the four pyrroles (**3**), (**8**), (**9**), and (**11**) (all available by Knorr pyrrole synthesis followed by appropriate modifications of the side-chains[11]) the pyrromethenes (**14**) and (**15**) were synthesized as shown in Scheme 1. Coupling of the two pyrromethenes using a tin(IV) ion as template gave the *a,c*-biladiene (**16**), which was cyclised thermally to the porphyrin ester (**17**) in 52% yield. Hydrolysis of the ester with sodium hydroxide in pyridine followed by treatment with oxalyl chloride gave the acid chloride (**19**).

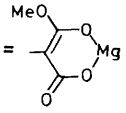


Scheme 1.

The (*E,E*)-farnesylmalonate (**29**) required for attachment of the side-chain to the porphyrin acid chloride has previously been prepared from farnesol[9] but the separation of pure (*E,E*)-farnesol from the mixture of isomers available at the time can be difficult.[12] Instead we chose to prepare (**29**) from pure (*E,E*)-farnesyl acetone* (**23**). Various attempts to obtain the carboxylic acid (**24**) by a haloform reaction were not successful so an alternative method using a reverse Claisen condensation[13] was investigated. A methoxycarbonyl group was introduced using sodium hydride and dimethyl carbonate to give the ester (**25**) and the reverse Claisen was effected in the presence of potassium cyanide and methanol. This reaction was very slow at 50 °C (300 h) but could not be heated further because loss of the methoxycarbonyl group[14] to reform the ketone (**23**) then predominated. Although the yield of the methyl ester (**27**) was

* A gift from F. Hoffmann-La Roche, Switzerland.



(23) R = CH_2COMe
(24) R = CH_2CO_2H
(25) R = $CH_2COCH_2CO_2Me$
(26) R = $CH_2COCH(Me)CO_2Me$
(27) R = CH_2CO_2Me
(28) R = $CH(CO_2Me)_2$
(29) R = $CH(CO_2H)CO_2Me$
(30) R = 

good under these conditions (70%), the purification of the product proved difficult. In an alternative procedure, the β-keto ester (**25**) was monomethylated using methyl iodide and potassium carbonate to give the keto ester (**26**). Nitrosation of (**26**) with methyl nitrite and sodium methoxide[15] was accompanied by cleavage to yield the methyl ester (**27**). The overall yield for these two reactions was lower than for the other method but the product was much more readily purified.

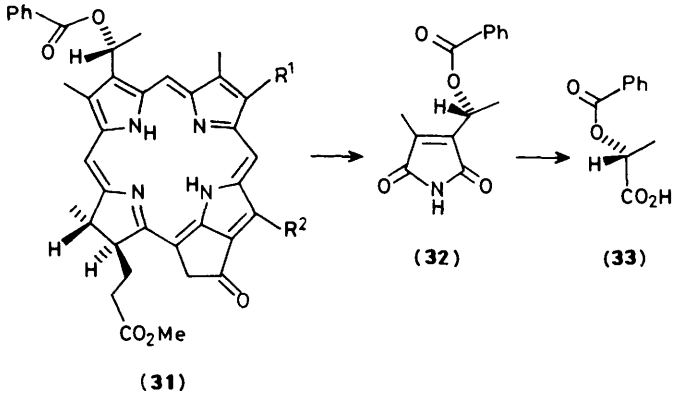
In order to compare the purity of (**27**) with that of a previously prepared sample[16] of the farnesylmalonate diester (**28**), it was methoxycarbonylated, again with sodium hydride and dimethyl carbonate. The resulting diester (**28**) gave a single peak on gas chromatography identical with that of (**28**) previously prepared from farnesol.[16] To obtain the monoester (**29**), the enolate of the ester (**27**) was generated using lithium *N*-isopropylcyclohexylamide (LICA) at −78 °C and then quenched with carbon dioxide. Careful acidification gave the monoester (**29**) which could not be purified by chromatography without decomposition and so was used crude in the next reaction.

The magnesium chelate (**30**) was formed by reaction of (**29**) with 2 equivalents of isopropylmagnesium bromide using 1,10-phenanthroline as an indicator to show the end point of the reaction. A very large excess of the chelate (**30**) was required for the reaction with the porphyrin acid chloride since the yield dropped markedly if less than a 20-fold excess was used. The unused side-chain could be recovered if necessary. The resulting porphyrin β-keto ester (**20**) was demethoxycarbonylated with lithium iodide and 12-crown-4 in pyridine at reflux. Reduction of the resultant porphyrin ketone (**21**) with sodium borohydride in methanol then afforded the desired model porphyrin alcohol (**22**) in 31% overall yield from the porphyrincarboxylic acid (**18**).

Resolution of the Model Porphyrin.—At this stage it was necessary to resolve the two enantiomers of the porphyrin alcohol in order to assign their stereochemistry. Previous work on porphyrin *a* had shown that esterification was possible with, for example, acetyl chloride in pyridine[3] but camphanyl chloride* had failed to react,[16] presumably because the secondary alcohol is unusually hindered. We have reinvestigated this problem and found that by using 3 equivalents of 4-dimethylaminopyridine to act as both base and catalyst, a variety of diastereoisomers of the model porphyrin could be prepared and the separation of the respective pairs rapidly examined by h.p.l.c. From this study it was found that the diastereoisomers of the (−)-camphanate (**34**)* gave the best separation. It was hoped that the same separation could be achieved by preparative t.l.c.; however initially decomposition of the esters was observed until it was discovered that this could be minimised if the preparative t.l.c. was run with both the solvent system (ether–hexane, 1:3) and the atmosphere saturated with ammonia vapour and if the bands were rapidly extracted after the elution had been completed. Once the diastereoisomers had been at least partially separated the diastereoisomeric excess (d.e.) of each sample could be readily determined by h.p.l.c. Eventually, the optimum separation was obtained by continuous elution, which yielded one essentially pure diastereoisomer and the other at 80% purity.

Hydrolysis of each diastereoisomer in turn, with aqueous potassium hydroxide in tetrahydrofuran, afforded the corresponding porphyrin alcohol enantiomers (**22**). Re-esterification of each to the (−)-camphanate diastereoisomers and redetermination of the d.e. by h.p.l.c. of the reaction mixture, showed that under the conditions of both the hydrolysis and the esterification no significant racemisation had occurred.

Correlation of the Model Porphyrin with a Chiral Standard.—Three general types of reaction have been discussed in the literature[17] for the degradation of porphyrins: (i) reductive degradation of *meso*-free porphyrins, with hydriodic acid in acetic acid in the presence of formaldehyde, to generate 2,5-dimethylpyrroles; (ii) oxidative cleavage of porphyrins with basic potassium permanganate to give pyrrole-2,5-dicarboxylic acids which can be esterified with diazomethane for ease of handling and purification; (iii) oxidative cleavage with chromic acid in sulphuric acid which yields the corresponding maleimides. The latter degradation was used by Brockmann and Tacke-Karimdadian[18] in their assignment of the stereochemistry of the hydroxyethyl side-chain of the bacteriochlorophylls *d*. Chromic acid oxidation of the benzoate (**31**) gave the maleimide (**32**) without loss of configurational purity. The imide (**32**) was further degraded by ozonolysis to a lactic acid derivative (**33**) (Scheme 2).



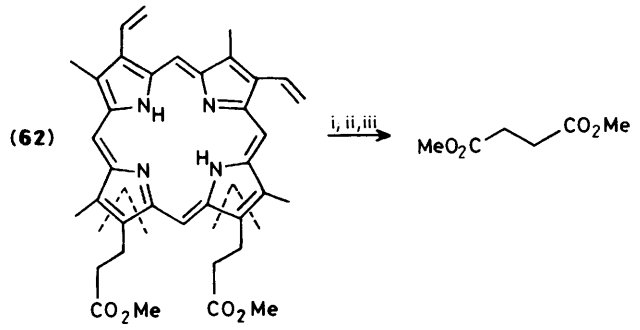
(31) (32) (33)

Scheme 2.

In our case we needed to be sure about the fate of the farnesyl side-chain under the degradative conditions and it seemed best if oxidative cleavage of the double bonds could also be effected so as to produce a derivative of optically active 2-hydroxypentanedioic acid (**49**), both enantiomers of which are known. We therefore investigated direct ozonolysis of the porphyrin.

To our knowledge ozonolysis of porphyrins has not been reported in the literature, so first the optimum conditions were determined for the degradation of protoporphyrin IX dimethyl

* Throughout, reference is made to the derivatives of ω-camphanic acid (−)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid.



Scheme 3. *Reagents:* i, O_3 at −78 °C; ii, H_2O_2–MeOH; iii, CH_2N_2

ester (**62**) (Scheme 3). On ozonolysis at −78 °C of a solution of this porphyrin in dichloromethane, a rapid colour change from deep purple to greenish brown was observed and the strong red fluorescence was completely destroyed (*ca.* 10 min). A variety of mild oxidative work-up procedures were assessed, and found to be inadequate, before it was recognised that fairly vigorous conditions would be required. Heating at reflux in a mixture of aqueous 100 vol. hydrogen peroxide–methanol (1 : 1), followed by evaporation and esterification was most promising, affording dimethyl succinate in 43% yield. Slightly milder conditions were found using aqueous performic acid at reflux for a few minutes. Although this resulted in a drop in the yield of dimethyl succinate (26%), the milder conditions were found to be advantageous when the ozonolysis of derivatives of cyclopent-2-enol (below) was being investigated and so these conditions were used in all subsequent degradations.

It was realised that the vigorous oxidative work-up procedure would necessitate the protection of the secondary alcohol of the model porphyrin (**22**) to avoid oxidation at this site also. It would be helpful to use a protecting group which would furnish a crystalline 2-hydroxypentanedioate derivative because the quantity of degradation product expected was too small to allow direct determination of its stereochemistry. Instead dilution analysis of a radioactive sample would have to be carried out, by recrystallisation of samples of a suitable derivative, heavily diluted with unlabelled (*R*) and (*S*) enantiomers.

Rather than use the valuable porphyrin alcohol (**22**) in studies to determine the best protecting group, it was decided to investigate the ozonolysis, under the same conditions, of a simpler compound which would yield the same product. Therefore the synthesis of various derivatives of cyclopent-2-enol (**41**) was undertaken.

Preparation of Cyclopentenol Derivatives.—Several procedures have been described [19] for the preparation of cyclopent-2-enol (**41**) in high yield from commercially available cyclopent-2-enone, though most quote yields based on g.c. Cyclopent-2-enol is a volatile liquid (b.p. 78 °C 59 mmHg) and when prepared by these methods was difficult to purify. The esters prepared from cyclopent-2-enol always contained minor impurities which were extremely difficult to remove, even by recrystallisation. This route to cyclopent-2-enol was, therefore, avoided whenever possible, the derivatives usually being prepared by the following method. Cyclopentene oxide was ring-opened by treatment with one equivalent of dimethyl-t-butylsilyltrifluoromethanesulphonate and a slight excess of 1,8-diazabicyclo[5.4.0]undec-7-ene, to give the allylic silyl ether (**42**).[20,21] Addition of tetrabutylammonium fluoride led to smooth cleavage of the protecting group to give cyclopent-2-enol (**41**). In the presence of 4 Å molecular sieves, esterification could then be achieved *in situ* in the usual fashion with 4-dimethylaminopyridine and the respective acid chloride.

Table 1. Yields of pentanedioate derivatives by ozonolysis of the corresponding cyclopent-2-enol derivatives under porphyrin degradation conditions

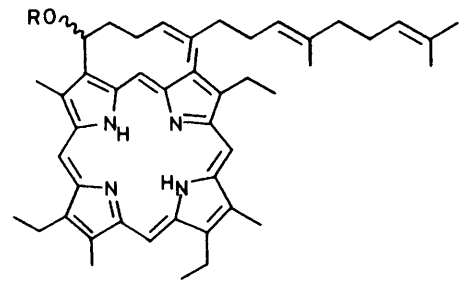
Cyclopent-2-enol derivative	Yield (%)
2-Cyclopentenol (**41**)	0
Dimethyl-t-butylsilyl ether (**42**)	0
(−)-Camphanate (**44**)	0
3,5-Dinitrobenzoate (**43**)	0
Benzoate (**45**)	12
4-Bromobenzoate (**46**)	20
2,6-Dinitrobenzoate (**47**)	84
2-Nitrobenzoate (**48**)	72

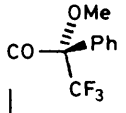
As expected, ozonolysis of cyclopent-2-enol itself under the standard porphyrin degradation conditions led to over-oxidation. The major product from the sequence was dimethyl succinate and no trace of the desired pentanedioate could be found by t.l.c. The same result was obtained with the silyl protected alcohol (**42**) and the pair of (−)-camphanate diastereoisomers (**44**). Next, the 3,5-dinitrobenzoate (**43**) was investigated because (i) an electron-deficient benzene ring should be less susceptible to ozonolysis and (ii) the dimethyl ester (**51**) of the expected product had been found to be a suitably crystalline compound (see later). However none of the desired pentanedioate (**51**) was obtained in this case either. It is likely that the 3,5-dinitrobenzoyl protecting group failed because the esters are particularly susceptible to hydrolysis. Degradation of both the simple benzoate (**45**) and the 4-bromobenzoate (**46**) did afford the respective dimethyl pentanedioates (**53**) and (**54**) in moderate yield. Benzoate esters with *ortho* substituents should be more resistant to hydrolysis and consequently the 2,6-dinitrobenzoate (**47**) was tested and gave a very satisfactory 84% yield of the required product (**55**). The 2-nitrobenzoate (**48**) also gave a reasonable yield of the corresponding product (**56**) (Table 1).

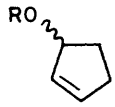
Preparation of the Pentanedioate Derivatives.—In certain cases it was necessary to prepare the dimethyl pentanedioate derivatives to facilitate the identification of the respective degradation products. When this was the only reason for carrying out the preparation, the racemic derivatives were synthesized by reduction of dimethyl 2-oxopentanedioate with sodium borohydride. Careful acidification with 10% aqueous ammonium chloride followed by acylation then provided the required derivatives with minimal lactonisation.

For the optically active series, the disodium salts of (*R*)-and (*S*)-2-hydroxypentanedioic acid (**49**) are both commercially available but they are however, rather expensive, so the (*S*)-disodium salt was usually prepared by opening the lactone ring of (*S*)-2-oxotetrahydrofuran-5-carboxylic acid (**59**). This compound was obtained from (*S*)-glutamic acid by treatment with nitrous acid, a reaction that is known [22] to proceed with complete retention of configuration.

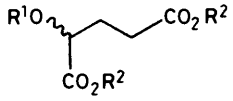
Disodium 2-hydroxypentanedioate proved to be surprisingly difficult to esterify cleanly, due mainly to competing lactonisation of the product. Eventually it was found that the dimethyl ester (**50**) could be prepared in good yield by converting the disodium salt into the disilver salt and then heating this salt in iodomethane at reflux.[23] If the alcohol was immediately protected by acylation, lactonisation of this labile intermediate could be largely avoided. Accordingly, the alcohol was treated with the requisite substituted benzoyl chloride in the presence of 3 equivalents of 4-dimethylaminopyridine to achieve rapid protection. By this method both enantiomers of the 3,5-dinitrobenzoate (**51**) could be prepared in good yield



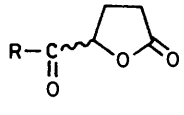
(22) R = H
(34) R = camphanyl
(35) R = 3,5-dinitrobenzoyl
(36) R = 2,6-dinitrobenzoyl
(37) R = 2-nitrobenzoyl
(38) R = CO-CH_2O-menthyl
(39) R = COCH(Et)Ph
(40) R = 



(41) R = H
(42) R = $SiMe_2Bu^t$
(43) R = 3,5-dinitrobenzoyl
(44) R = camphanyl
(45) R = benzoyl
(46) R = 4-bromobenzoyl
(47) R = 2,6-dinitrobenzoyl
(48) R = 2-nitrobenzoyl



(49) R^1 = R^2 = H
(50) R^1 = H, R^2 = Me
(51) R^1 = 3,5-dinitrobenzoyl, R^2 = Me
(52) R^1 = 3,5-dinitrobenzoyl, R^2 = H
(53) R^1 = benzoyl, R^2 = Me
(54) R^1 = 4-bromobenzoyl, R^2 = Me
(55) R^1 = 2,6-dinitrobenzoyl, R^2 = Me
(56) R^1 = 2-nitrobenzoyl, R^2 = Me
(57) R^1 = 2,6-dinitrobenzoyl, R^2 = CH_2Ph
(58) R^1 = 2,6-dinitrobenzoyl, R^2 = p-C_6H_4Br



(59) R = OH
(60) R = NHC_6H_4Br-p
(61) R = OC_6H_4Br-p

Scheme 4.

from the respective disodium salts and they were highly crystalline, which would have made them suitable for the proposed dilution analysis.

The esterification giving the 2,6-dinitrobenzoate (**55**) was slow under the standard conditions but on raising the temperature the desired benzoate (**55**) was produced in reasonable yield. Under these conditions, a considerable quantity of 1,3-dinitrobenzene was also obtained. This side reaction did not appear to affect adversely the yield of desired product, but did make purification more difficult. The mechanism of its formation remains obscure, though it presumably arises from decomposition of the acid chloride. However, although the (*R,S*)-2,6-dinitrobenzoate (**55**) was a relatively easy compound to recrystallise, the pure enantiomers could not, under any circumstances, be induced to form crystals. Extension of the silver salt method to the preparation of the dibenzyl ester proved to be only slightly less efficient than for the preparation of the dimethyl ester. However, the dibenzyl derivative (**57**) also failed to crystallise. Substituted dibenzyl esters could also be prepared by this route if acetone was used as the solvent. However, none of the derivatives prepared (4-nitrobenzyl, 4-bromobenzyl, 3,5-dinitrobenzyl) proved to be crystalline.

It was found that the stability of the 2,6-dinitrobenzoate ester to hydrolysis permitted the methyl esters to be selectively hydrolysed to give the diacid, which was converted into the (*S*)-di-4-bromophenyl ester (**58**) by treatment with 4-bromophenol, dicyclohexylcarbodi-imide (DCC), and 4-dimethylaminopyridine. This derivative proved to be crystalline.

The (*S*)-enantiomer of the 2-nitrobenzoate dimethyl ester (**56**) also failed to crystallise. This time mild hydrolysis led to complete saponification to the (*S*)-hydroxy diacid (**49**). As was mentioned before, the diesters of (**49**) are not easy to make because of competing lactonisation. Indeed neutralisation of the reaction mixture followed by distillation (200 °C, 0.3 mmHg)

afforded the crystalline (*S*)-lactone carboxylic acid (**59**). These crystals were rather hygroscopic but a suitable crystalline derivative, the 4-bromoanilide (**60**) was soon found.

It was necessary to show that no racemisation or inversion of the chiral centre had occurred during the course of the several reactions leading to the (*S*)-anilide (**60**). Using the chiral shift reagent [Eu(hfc)$_3$],[24] the C-2 protons for the two enantiomers in racemic (**60**) were only poorly resolved even when decoupling of the adjacent protons was used. However in the corresponding ester (**61**) (made in the same way), the C-2 protons were sufficiently well resolved for it to be shown that no significant racemisation had occurred in the optically active series. Comparison of this product by the n.m.r. method with a sample of (*S*)-ester (**61**) derived directly from (*S*)-glutamic acid eliminated the possibility that complete inversion had occurred. It was thus established that the entire sequence from (**56**) to (**60**) had been achieved with retention of configuration.

In order to test that the planned dilution analysis procedure was effective, dimethyl 2-oxopentanedioate was reduced with tritiated sodium borohydride to give racemic [2-^{3}H]alcohol (**50**) which was acylated to give the three compounds (**51**), (**55**), and (**56**). Each of these was diluted with the corresponding unlabelled (*S*)-enantiomer and the esters (**55**) and (**56**) were converted into the crystalline derivatives (**58**) and (**60**), respectively. In all three cases it was found that the specific activity fell to *ca.* 50% of the original value after several recrystallisations and then remained steady, indicating that this process was successful in removing the (*R*)-enantiomer.

Absolute Stereochemistry of the Model Porphyrin.—The results with the cyclopentenol derivatives indicated that the best derivative for protection of the porphyrin alcohol (**22**) during the oxidative degradation would be the 2,6-dinitrobenzoyl group. Unfortunately, all attempts to prepare this ester (**36**) failed. Under the standard conditions, at reflux in dichloromethane, the alcohol was recovered unchanged after 24 h. In dipolar aprotic solvents the porphyrin alcohol slowly decomposed with no apparent formation of the required ester, and attempted acylation with the acylium cation (generated by treatment of the acid chloride with silver tetrafluoroborate in acetonitrile[25]) led to immediate quenching of the porphyrin chromophore.

The 2-nitrobenzoyl group was chosen as an alternative protecting group because it should still have some resistance to hydrolysis while not being quite as hindered as the 2,6-dinitrobenzoyl group. It was hoped, therefore, that esterification of the porphyrin alcohol would again be possible. In fact, esterification proceeded rapidly and smoothly in the presence of 4-dimethylaminopyridine at room temperature. The porphyrin (**37**) was, however, rather unstable and although its presence could be detected by analytical t.l.c., attempted purification by preparative t.l.c. was unsuccessful. A two-dimensional t.l.c. plate showed that the ester, which was considerably less polar than the porphyrin alcohol, decomposed to a mixture of the porphyrin alcohol and a slightly less polar compound, identified as the dehydration product by field desorption (f.d.) mass spectroscopy. F.d. mass spectroscopy also confirmed that the only porphyrinic material present in the reaction mixture after 15 min was the 2-nitrobenzoate. After a mild wash with aqueous base, u.v. assay, using an estimated molar absorption coefficient, suggested that the yield was almost quantitative.

To obtain the tritiated porphyrin alcohol (**22**), the ketone (**21**) was reduced with tritiated sodium borohydride and the enantiomers were separated as their camphanates as described above. The alcohol obtained by hydrolysis of the higher R_F camphanate was converted into its 2-nitrobenzoate and ozonolysed. After the standard degradation sequence, the residue was divided into two, one half was diluted with the unlabelled (*R*)-enantiomer of (**56**) and the other half with the 'cold' (*S*)-enantiomer. Each half was then purified by chromatography and the residual activity determined. The two samples were then converted, in parallel experiments, into the respective 4-bromoanilides (**60**) by the previously described procedure and purified by chromatography. The activity of each sample was then redetermined before recrystallisation to constant activity. The specific activity of each of the samples was determined, during the dilution analysis, after every third recrystallisation. After each sample had been recrystallised 12 times a clear picture emerged (Table 2). Whilst the specific activity of the (*S*)-anilide dropped to *ca.* 5% of its original value, the specific activity of the (*R*)-enantiomer actually rose slightly at first, presumably because the initial activity had been determined on slightly impure non-crystalline material, and then fell to *ca.* 97% of its maximum value. The yield from the degradation, determined from the retained activity, was a remarkable 23% and the final specific activities corresponded to *ca.* 90% enantiomeric excess (e.e.) for the original porphyrin, assuming that no racemisation had occurred during the degradation and derivatisation procedures.

Table 2. Relative specific activities of anilides (**60**)[a]

Porphyrin camphanate	High R_F		Low R_F	
Enantiomer of (**56**) used for dilution	(*S*)	(*R*)	(*S*)	(*R*)
Anilide (**60**), crude	100	100	100	100
3rd Recryst.	15	107	102	15
6th Recryst.	5	104	104	5
9th Recryst.	5	104	103	5
12th Recryst.	5	105	103	5

[a] The specific activities are expressed as a percentage of the activities of the anilides before any recrystallisation.

The entire sequence was then repeated, starting from the tritiated lower R_F (−)-camphanate (**34**) and the complementary result obtained (Table 2). Again, the retained activity, this time of the (*S*)-anilide, rose slightly at first and then fell to *ca.* 98% of its maximum value, whilst the specific activity of the (*R*)-enantiomer dropped rapidly to *ca.* 5% of its original value. The final specific activities corresponded, once more, to an e.e. of *ca.* 90% for the original porphyrin, though this time the degradation yield, based on retained specific activity, was lower (4%).

These two results, in conjunction with evidence gained from the chiral shift experiments, proved categorically that the higher R_F (−)-camphanate diastereoisomer (**34**) correlates with the (*R*)-4-bromoanilide and hence with the (*R*)-enantiomer of the model porphyrin and *vice versa* for the lower R_F (−)-camphanate diastereoisomer which is therefore the (*S*)-enantiomer.

Correlation of Porphyrin a *with the Model.*—Circular dichroism (c.d.) was considered as a possibility for correlating the stereochemistry of porphyrin *a* with that of the model porphyrin. However, in practice this method proved ineffective because porphyrins have very large molar extinction coefficients. With such strong absorption, spectra have to be obtained on very dilute solutions forcing the spectrometer to work at the limit of its sensitivity.[26] C.d. spectra of the (−)-menthoxyacetate diastereoisomers (**38**), separated by h.p.l.c., were recorded, but only poorly resolved, faint maxima were observed.

N.m.r. methods for distinguishing the enantiomers were tried next. The diasteroisomers of the 2-phenylbutanoates[27] (**39**) were disappointing because they proved to be completely inseparable by reverse-phase h.p.l.c., eluting with 100%

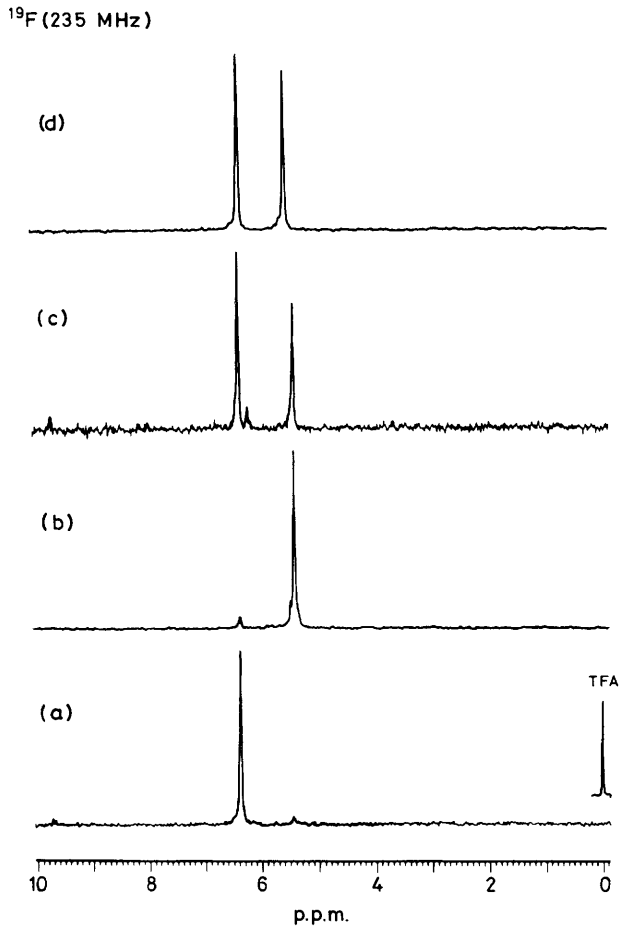


Figure 1. 235 MHz ^{19}F N.m.r. spectra of (−)-MPTA esters derived from (a), (*S*)-model porphyrin (**22**); (b), (*R*)-(**22**); (c), (*RS*)-(**22**); (d) Dimethyl ester of (*RS*)-porphyrin *a* (**2**). Chemical shifts are measured in p.p.m. downfield from external trifluoroacetic acid

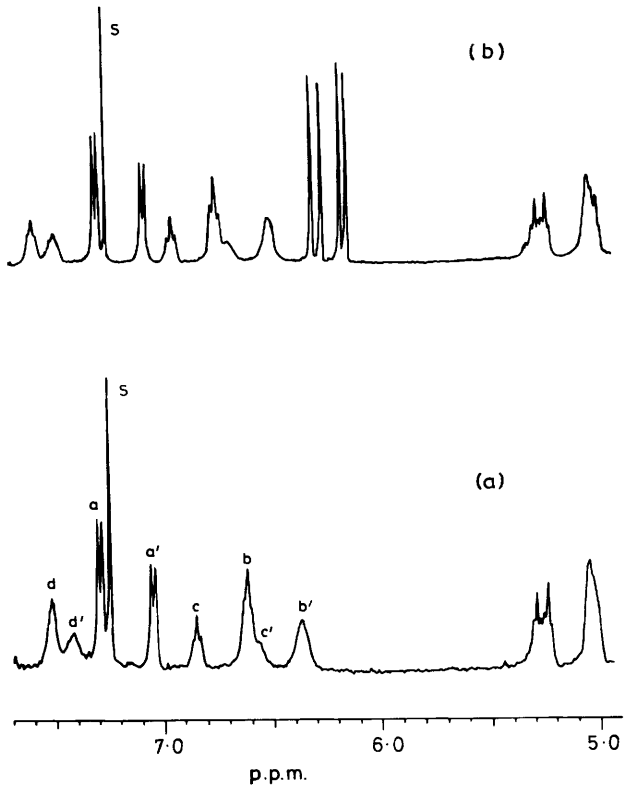


Figure 2. 400 MHz ^{1}H N.m.r. spectra of (−)-MPTA esters derived from (a), (*RS*)-model porphyrin (**22**); (b), dimethyl ester of (*RS*)-porphyrin *a* (**2**). Signal S is from solvent, $CDCl_3$, other assignments refer to positions marked in Scheme 5

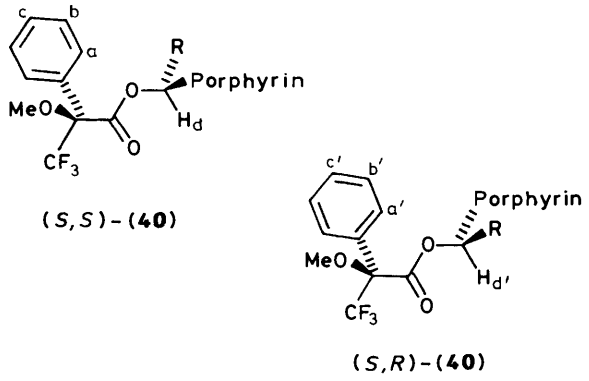
acetonitrile, and the 400 MHz ^{1}H n.m.r. spectrum of the mixture showed no extra resonances which could be attributed to non-equivalence of the two diasteroisomers. A chiral solvating agent[28] was tested next, but the 400 MHz ^{1}H n.m.r. spectrum of the racemic model porphyrin (**22**) failed to show significant non-equivalence for any resonance in the presence of up to 3 equivalents of the most commonly used agent, 1-(9-anthryl)-2,2,2-trifluoroethanol.

Esters of secondary alcohols with 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA) have been used by Mosher[29] for the assignment of stereochemistry. These esters have the advantage that the ^{19}F n.m.r. spectrum contains just a single resonance for each diasteroisomer, which can be very useful if the ^{1}H n.m.r. is crowded. The two diasteroisomers (**40**) were prepared from the separate enantiomers of the porphyrin alcohol (**22**) and (−)-(*S*)-MTPA chloride by the usual procedure; they were found to have ^{19}F n.m.r. signals almost 1 p.p.m. apart, the signal from the (*S*)-isomer being downfield of that from the (*R*) (Figure 1a—c). The same ester of synthetic, racemic porphyrin *a* dimethyl ester showed the same two signals in virtually identical positions (Figure 1d). There can be very little doubt that the downfield signal derives from the (*S*)-isomer in this case also.

In their ^{1}H n.m.r. spectra also considerable non-equivalence is observed for the two diastereoisomers (Figure 2a). Again the ^{1}H n.m.r. of the (−)-MTPA ester of racemic porphyrin *a* dimethyl ester shows all the same signals in very similar positions (Figure 2b; the signals at δ 6.1—6.3 are due to the vinyl group in porphyrin *a*). The signals belonging to the (*R*) and (*S*) isomers of the model porphyrin were again determined by comparing the spectra of the esters of the separate enantiomers. Thus, both the ^{19}F and ^{1}H n.m.r. spectra of the (−)-MTPA ester of porphyrin *a* dimethyl ester can be used to distinguish the two enantiomers and to correlate them with the now rigorously assigned stereochemistry of the porphyrin alcohol (**22**).

Mosher[29] has explained the chemical shifts of diastereoisomeric MTPA esters on the assumption that the important conformation is the one in which both the CF_3 group and the hydrogen atom of the secondary alcohol are *syn* to the carbonyl group (Scheme 5). Thus in this conformation of the (*S*)-MTPA derivatives, the phenyl and porphyrin groups are on opposite sides of the plane of the carbonyl for the (*S*)-porphyrin alcohol and on the same side for the (*R*)-alcohol. When these two groups are on the same side they would be expected to show a considerable shielding effect on each other in the ^{1}H n.m.r. This is indeed what is found; the chemical shifts of all the phenyl protons (Figure 2a) and of 5-H and 20-H on the porphyrin (not shown) are more upfield in the (*S,R*) diastereoisomer than in the (*S,S*) (see Scheme 5 for assignments).

The explanation[30] for the ^{19}F chemical shifts is that the fluorine nuclei experience the maximum deshielding effect of the carbonyl when the CF_3 group is coplanar with it. In the (*S,R*)-diastereoisomer the bulky phenyl and porphyrin groups are on the same side and the resultant steric compression can be eased by twisting about the bond adjacent to the carbonyl. This would cause the CF_3 group to be no longer coplanar with the carbonyl and therefore to be less deshielded. Again this is what is found.



Scheme 5.

The fact that the chemical shift differences of the two diastereoisomeric MTPA esters are as expected for the absolute configurations determined by degradation is heartening and it gives even more certainty to our view that the shift differences are the same in the porphyrin *a* derivatives as they are in the model. As a result we can be confident that when porphyrin *a* is isolated in optically active form, its configuration will readily be assigned simply by comparing the ^1H and ^{19}F n.m.r. spectra of its (−)-MTPA ester with those of our model porphyrin.

Experimental

M.p.s were determined on a Reichert Kofler hot-stage apparatus, and are uncorrected. U.v./visible spectra were recorded on a Pye Unicam SP8-100 spectrophotometer. I.r. spectra were recorded on Perkin-Elmer 983 and 297 instruments, as solutions in ethanol-free chloroform, unless stated otherwise. ^1H N.m.r. spectra were recorded on Varian EM360 (60 MHz), EM390 (90 MHz), and CFT20 (80 MHz) spectrometers, and on Bruker WM250 (250 MHz) and WH400 (400 MHz) spectrometers. The solvent used was deuteriochloroform unless stated otherwise. Chemical shifts are given on the δ scale with tetramethylsilane at δ = 0 p.p.m. ^{19}F N.m.r. spectra were recorded on a Bruker WM250 (^{19}F, 235 MHz), the solvent used was [$^2H_2$]dichloromethane and the chemical shifts are given on the δ scale with external trifluoroacetic acid at δ = 0 p.p.m. Mass spectra were recorded on A.E.I. MS30, MS902, and MS50 machines; only field desorption mass spectra were run on the latter. Fast atom bombardment (f.a.b.) mass spectra were run the MS902 instrument and electron impact spectra were recorded on the MS30 and MS902 instruments. High performance liquid chromatography (h.p.l.c.) was performed on two 300 × 3.9 mm C_{18} μ Bondapak Waters columns in series, eluting with 100% degassed acetonitrile at a flow rate of 2 ml/min. Circular dichroism (c.d.) spectra were recorded by Dr. P. M. Scopes (Westfield College, London). Optical rotations at the sodium D line were recorded on a Perkin-Elmer 241 polarimeter at ambient temperature. Gas chromatography (g.c.) was performed on a Carlo-Erba 4130 Gas Chromatograph with a SE54 capillary column, using hydrogen as carrier at a flow rate of 1.5 ml/min.

Analytical thin layer chromatography (t.l.c.) was performed on commercial Merck plates coated to a thickness of 0.25 mm with Kieselgel 60 F_{254} silica. Preparative t.l.c. (p.l.c.) was carried out using larger plates (200 × 200 mm) coated to a thickness of 0.25, 1.0, or 2.0 mm with Merck Kieselgel 60 F_{254}; the number of plates and coating thickness is reported (*e.g.* 8 × 1 mm). The 1.0 mm plates were prepared 'in house'. Porphyrins were purified on Merck plates, coated either to a thickness of 0.25 mm, or 2.0 mm with Kieselgel 60, without fluorescent indicator. Merck Kieselgel 60H, referred to as 'silica H,' was used for column chromatography.

Removal of solvents was carried out under reduced pressure at water pump pressure on a Büchi rotary evaporator, at 30 °C, unless otherwise stated. Ether is used to mean diethyl ether. All solvents were redistilled, dichloromethane, chloroform and ether being stored in the dark. Methyl acetate and, where used as reaction solvent, dichloromethane were distilled from anhydrous potassium carbonate. All aqueous solutions which were to come into contact with porphyrins were prepared from glass-distilled water and AnalaR grade reagents. Organic solutions which had been in contact with water were dried over anhydrous magnesium sulphate, or anhydrous AnalaR grade sodium sulphate (porphyrins) prior to solvent removal.

All manipulations involving the sensitive farnesyl substituted porphyrins were carried out under darkroom conditions.

Benzyl 5-Formyl-4-methoxycarbonyl-3-methyl-1H-pyrrole-2-carboxylate (**4**).—A solution of freshly distilled sulphuryl chloride (37.5 g, 267 mmol) in dichloromethane (200 ml) was added slowly to a solution of benzyl 4-methoxycarbonyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate[31] (**3**) (40 g, 133 mmol) stirred at room temperature. After 1 h the solution was washed with water (200 ml) and saturated aqueous sodium hydrogen carbonate (3 × 100 ml) and evaporated under reduced pressure. A solution of the residual oil in acetone (500 ml) and water (300 ml) was heated at 50 °C for 1 h, cooled to room temperature, and extracted with ether (3 × 100 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (100 ml) and evaporated. Recrystallisation of the residue from 95% ethanol gave the formylpyrrole (**4**) (34.2 g, 82%) as needles, m.p. 121—122 °C (lit.,[16] 122 °C); $\lambda_{max.}$ (95% EtOH) 311 and 271 nm; $\nu_{max.}$(CCl_4) 3 420, 1 700, and 1 660 cm^{-1}; δ (60 MHz) 2.58 (3 H, s, 3-CH_3), 3.83 (3 H, s, CO_2CH_3), 5.28 (2 H, s, CH_2), 7.30 (5 H, s, C_6H_5), 10.10 (1 H, s, CHO), and 10.1 (1 H, br s, NH); *m/z* 301 (M^+, 18%), 269 (10, M − MeOH), and 91 (100, $C_7H_7^+$).

Methyl 5-(4-Ethyl-3,5-dimethyl-2H-pyrrol-2-ylidenemethyl)-3-methyl-1H-pyrrole-4-carboxylate Hydrobromide (**14**).—(With Dr. D. A. Lewton.) Aqueous 48% hydrobromic acid (11.0 ml, 200 mmol) was added to a solution of 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**10**)[10] (7.91 g, 47 mmol) and the α-free pyrrole (**7**) (7.91 g, 47 mmol) {prepared from (**4**) by the method of Kenner *et al.*[10]} in methanol (100 ml) stirred at 0 °C. After 1 h at 0 °C the solution was filtered to give the dipyrromethene (**14**) (13.8 g, 83%) as a red powder, m.p. 155—157 °C (crude) (lit.,[10] 163—165 °C); $\lambda_{max.}$ (95% EtOH) 482 and 417 nm; $\nu_{max.}$ 3 475, 3 410, 3 100, 3 055, 1 700, and 1 625 cm^{-1}; δ (60 MHz) 1.12 (3 H, t, *J* 8 Hz, CH_2CH_3), 2.33 and 2.38 (each 3 H, s, 2 × 3-CH_3), 2.49 (2 H, q, *J* 8 Hz, CH_2CH_3), 2.81 (3 H, s, 5-CH_3), 3.98 (3 H, s, CO_2CH_3), 7.33 (1 H, br d, *J* 4 Hz, 2-H), 8.52 (1 H, s, C*H*), and 13.5 and 13.9 (each 1 H, br s, 2 × NH); *m/z* (f.a.b.) 273 (M − Br, 80%), 241 (40), 213 (40), 213 (10), and 123 (100).

Benzyl 4-Ethyl-5-formyl-3-methyl-1H-pyrrole-2-carboxylate (**11**).—The formylpyrrole (**11**) (8.9 g, 84%) was prepared by the same method as for the formylpyrrole (**4**) from benzyl 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate[32] (**8**) (39 mmol) and obtained as needles, m.p. 86—87 °C (from ether–hexane) (lit.,[32] 86—87 °C); $\lambda_{max.}$ (95% EtOH) 305 nm; $\nu_{max.}$ 3 250, 1 700, and 1 665 cm^{-1}; δ (90 MHz) 1.20 (3 H, t, *J* 8 Hz, CH_2CH_3), 2.32 (3 H, s, 3-CH_3), 2.77 (2 H, q, *J* 8 Hz, CH_2CH_3), 5.39 (2 H, s, CH_2), 7.45 (5 H, s, C_6H_5), 9.5 (1 H, br s, NH), and 9.73 (1 H, s, CHO); *m/z* 271 (M^+, 24%), 180 (16, M − C_7H_7), and 91 (100, $C_7H_7^+$).

5-(4-Ethyl-3,5-dimethyl-2H-pyrrol-2-ylidenemethyl)-4-ethyl-3-methyl-1H-pyrrole-2-carboxylic Acid Hydrobromide (**13**).—

(With Dr. D. A. Lewton.) A solution of 60% hydrogen bromide in acetic acid (9.5 ml, 105 mmol) was added to a slurry of 4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylic acid (**12**) (6.32 g, 35 mmol) {prepared from (**11**) by the method of Kenner *et al.*[10]} and t-butyl 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**9**) (7.78 g, 35 mmol) in acetic anhydride (3.3 ml, 35 mmol). The mixture was stirred in the dark at room temperature for 2 h and then diluted with ether (300 ml). The precipitate was collected and washed well with ether to give the dipyrromethene (**13**) (11.15 g, 87%) as an orange-red powder, m.p. 141—142 °C (lit.,[33] 139 °C); $\lambda_{max.}$ (95% EtOH) 407 and 482 nm; $\nu_{max.}$ 3 500—2 600, 3 170, 3 100, 1 710, 1 620, 955, and 910 cm^{-1}; δ (90 MHz) 1.13 and 1.17 (each 3 H, t, *J* 7.5 Hz, 2 × CH_2CH_3), 2.33 and 2.39 (each 3 H, s, 2 × CH_3), 2.52 and 2.75 (each 2 H, q, *J* 7.5 Hz, 2 × CH_2CH_3), 2.77 (3 H, s, 5-CH_3), 7.33 (1 H, s, CH), 12.3 (1 H, br s, CO_2H), and 13—14 (2 H, br m, 2 × NH); *m/z* (f.a.b.) 287 (*M* − Br, 100%).

5-(5-*Bromomethyl*-4-*ethyl*-3-*methyl*-2H-*pyrrol*-2-*ylidene-methyl*)-2-*bromo*-4-*ethyl*-3-*methyl*-1H-*pyrrole Hydrobromide* (**15**).—(With Dr. D. A. Lewton.) A solution of bromine (23 ml, 450 mmol) in 1,2-dichloroethane (23 ml) was added to a solution of the foregoing dipyrromethene (**13**) (11.50 g, 31 mmol) in 1,2-dichloroethane (200 ml) and the mixture stirred in the dark at 80 °C for 1 h. The solution was cooled to room temperature, evaporated under reduced pressure and cyclohexene (50 ml) and 1,2-dichloroethane (50 ml) were added to the residue; the mixture was then re-evaporated under reduced pressure. The residue was recrystallised from chloroform–ether (1:1) to give the dipyrromethene (**15**) (9.69 g) as a powder. Concentration of the mother liquor and careful crystallisation afforded a second crop (3.28 g) as red needles, total yield (12.97 g, 86%), m.p. >300 °C (from chloroform–ether) (lit.,[34] >300 °C); $\lambda_{max.}$ (95% EtOH) 453 nm; $\nu_{max.}$ 3 415, 3 130, 3 030, 1 610, 1 495, 955, and 910 cm^{-1}; δ (90 MHz) 1.18 and 1.20 (each 3 H, t, *J* 7.5 Hz, 2 × CH_2CH_3), 2.08 and 2.33 (each 3 H, s, 2 × CH_3), 2.56 and 2.78 (each 2 H, q, *J* 7.5 Hz, 2 × CH_2CH_3), 4.91 (2 H, s, CH_2Br), 7.21 (1 H, s, CH), and 14.0 (2 H, br s, 2 × NH); *m/z* (f.a.b.) 483, 481, 479, and 477 [(M^+ − 1) 4, 7, 10, and 4%], and 319 (100).

Methyl 8,13,18-*Triethyl*-2,7,12,17-*tetramethyl*-21H,23H-*porphine*-3-*carboxylate* (**17**).—The porphyrin ester (**17**) made from dipyrromethenes (**14**) and (**15**) by the method of Kenner *et al.*[10] was obtained as purple needles, m.p. >300 °C (from chloroform–methanol) (lit.,[10] >300 °C); $\lambda_{max.}$ 405, 509, 547, 573, and 633 nm (115:4.8:7.1:4.0:1); $\nu_{max.}$ 3 415, 3 325, 1 690, 1 585, 1 540, and 1 080 cm^{-1}; δ (400 MHz) −3.71 (2 H, s, 2 × NH), 1.83, 1.86, and 1.86 (each 3 H, t, *J* 7.4 Hz, 8-, 13-, and 18-CH_2CH_3), 3.53, 3.64, 3.68, and 3.93 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 3.98, 4.12, and 4.12 (each 2 H, q, *J* 7.5 Hz, 8-, 13-, and 18-CH_2CH_3), 4.41 (3 H, s, CO_2CH_3), and 9.95, 9.96, 10.16, and 11.10 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* 508 (M^+, 100%).

(6E,10E)-*Methyl* 7,11,15-*Trimethyl*-3-*oxohexadeca*-6,10,14-*trienoate* (**25**).—A small portion (*ca.* 1 ml) of a solution of (5*E*,9*E*)-6,10,14-trimethyl-2-oxopentadeca-5,9,13-triene (**23**) (29.2 g, 0.11 mol) in dry tetrahydrofuran (90 ml) was added dropwise under argon to a suspension of sodium hydride [16 g, 0.33 mmol; from a 50% dispersion in oil, washed twice with tetrahydrofuran (20 ml)] and potassium hydride [0.9 g, 0.02 mol; washed twice with tetrahydrofuran (20 ml)] in tetrahydrofuran (75 ml) and dimethyl carbonate (27.0 ml, 0.32 mol) heated under argon at reflux. After 15 min the remaining solution was added dropwise. The mixture was then heated at reflux for a further 1.5 h, cooled to room temperature, and brought to pH 3 with hydrochloric acid (2M). The resulting solution was extracted with hexane (3 × 100 ml) and the combined organic layers were washed with water (100 ml) and saturated brine (50 ml). Evaporation provided the crude product (39.6 g) which was purified by chromatography (200 g; silica H) using gradient elution with ether–hexane (1→5:40). The β-*keto ester* (**25**) (35.26 g, 99%) was obtained as an oil, b.p. 187—194 °C, 0.03 mmHg (Found: C, 75.1; H, 10.3%; M^+, 320.2631. $C_{20}H_{32}O_3$ requires C, 74.95; H, 10.1%; *M*, 320.2621); $\nu_{max.}$ 1 755, 1 725, 1 660, and 1 630 cm^{-1}; δ (80 MHz) 1.58 and 1.66 (12 H, m, 7-, 11-, and 2 × 15-CH_3), 1.98 (8 H, s, 2 × CH_2CH_2), 2.30 (2 H, t, *J* 6.1 Hz, 4-CH_2), 2.50 (2 H, q, *J* 6.3 Hz, 5-CH_2), 3.41 (2 H, s, 2-CH_2), 3.71 (3 H, s, CO_2CH_3), and 5.07 (3 H, br m, 6-, 10-, and 14-H); *m/z* 320 (M^+, 12%), 183 (17, *M* − $C_{10}H_{17}$), 136 (98), and 109 (100).

(6E,10E)-*Methyl* 2,7,11,15-*Tetramethyl*-3-*oxohexadeca*-6,10,14-*trienoate* (**26**).—A suspension of potassium carbonate (0.5 g, 3.6 mmol), the foregoing β-keto ester (**25**) (0.261 g, 0.82 mmol), and iodomethane (0.25 g, 1.7 mmol), in acetone (20 ml) was heated at reflux for 2 h. The mixture was then cooled to room temperature, brought to pH 3 with hydrochloric acid (2M), and extracted with ether (2 × 50 ml). The combined extracts were washed with 5% aqueous brine (50 ml) and evaporated to give after purification by p.l.c. (4 × 1 mm), eluting with ether–hexane (1:4), the β-*keto ester* (**26**) (0.219 g, 80%) as an oil (Found: M^+, 334.2518. $C_{21}H_{34}O_3$ requires *M*, 334.2503); $\nu_{max.}$ 1 760 and 1 730 cm^{-1}; δ (60 MHz) 1.34 (3 H, d, *J* 7 Hz, 2-CH_3), 1.58 (12 H, s, 7-, 11-, and 2 × 15-CH_3), 1.96 (8 H, s, 2 × CH_2CH_2), 2.2—2.6 (4 H, br m, CH_2CH_2CO), 3.46 (1 H, q, *J* 7 Hz, 2-H), 3.65 (3 H, s, CO_2CH_3), and 4.95 (3 H, br m, 6-, 10-, and 14-H); *m/z* 334 (M^+, 12%), 197 (12, *M* − $C_{10}H_{17}$), 136 (80), 115 (54), and 109 (100).

(4E,8E)-*Methyl* 5,9,13-*Trimethyltetradeca*-4,8,12-*trienoate* (**27**).—*Method A.* The foregoing β-keto ester (**26**) (100 mg, 0.30 mmol) was added to a solution of sodium methoxide (20 mg, 0.36 mmol) in dry methanol (5 ml) and methyl nitrite[35] was bubbled slowly through until examination by analytical t.l.c., eluting with ether–hexane (1:20), showed no remaining β-keto ester (*ca.* 30 min). The solution was then brought to pH 3 with hydrochloric acid (2M) and extracted with hexane (3 × 10 ml). The combined organic extracts were washed with water (20 ml) and saturated brine (20 ml) and evaporated. The residue was purified by p.l.c. (2 × 1 mm), eluting with ether–hexane (1:40), to give the *methyl ester* (**27**) (42 mg, 51%) as an oil.

Method B. A suspension of potassium cyanide (15 g, 0.23 mol) and the β-keto ester (**25**) (34.82 g, 0.11 mmol) in dry tetrahydrofuran (600 ml) and dry methanol (100 ml) was stirred at 50 °C under argon for 300 h. The reaction was monitored by analytical t.l.c., eluting with ether–hexane (1:200). The reaction mixture was then cooled to room temperature, concentrated under reduced pressure (*ca.* 50 ml) and partitioned between 5% aqueous brine (200 ml) and ether (200 ml). The aqueous layer was back extracted with ether (2 × 100 ml) and the organic extracts were combined and evaporated under reduced pressure to give an oil. Sodium borohydride (0.7 g, 0.02 mol) was added slowly to a solution of this oil in methanol (100 ml) stirred at 0 °C. After 15 min the mixture was brought to pH 3 with hydrochloric acid (2M) and partitioned between ether (100 ml) and water (100 ml). The aqueous layer was back extracted with ether (100 ml) and the combined organic layers were washed with saturated brine (50 ml) and evaporated. The crude product was purified by chromatography (200 g; silica H), eluting with a gradient of ether–hexane (0→80:200) to give the *methyl ester* (**27**) (20.94 g, 69%) as an oil, b.p. 136—141 °C, 0.01 mmHg (Found: C, 77.7; H, 10.6%; M^+, 278.2248. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.9%; *M*, 278.2246); $\nu_{max.}$ 1 755 cm^{-1}; δ (60 MHz) 1.61 (12 H, s, 5-, 9-, and 2 × 13-CH_3), 2.00 (8 H, s, 2 × CH_2CH_2),

2.3 (4 H, m, CH_2CH_2CO), 3.60 (3 H, s, CO_2CH_3), and 5.05 (3 H, br m, 4-, 8-, and 12-H); *m/z* 278 (M^+, 5%), 136 (25), 81 (52), and 69 (100, $C_5H_9^+$).

(4E,8E)-*Methyl* 2-*Methoxycarbonyl*-5,9,13-*trimethyltetradeca*-4,8,12-*trienoate* (**28**).—A solution of the foregoing methyl ester (**27**) (0.3 g, 1.1 mmol) in dimethyl carbonate (2 ml) was added dropwise over 1 h to a suspension of sodium hydride [0.155 g, 3.3 mmol; from a 50% dispersion in oil washed twice with dry tetrahydrofuran (5 ml)] in dimethyl carbonate (5 ml) heated at reflux under nitrogen. After 2 h the suspension was cooled to room temperature, brought to pH 3 with hydrochloric acid (2M), and extracted with hexane (2 × 20 ml). The combined organic extracts were washed with saturated brine (10 ml) and evaporated. P.l.c. of the residue (4 × 1 mm), eluting with ether–hexane (1:20), gave the dimethyl malonate (**28**) (0.301 g, 83%) as an oil, g.c. retention time 6.8 min (Found: C, 71.3; H, 10.0%; M^+, 336.2293. $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%; *M*, 336.2300); $\nu_{max.}$ 1 760 and 1 750 cm^{-1}; δ (90 MHz) 1.55 (12 H, m, 5-, 9-, and 2 × 13-CH_3), 1.93 (8 H, s, 2 × CH_2CH_2), 2.55 (2 H, t, *J* 7.5 Hz, 3-CH_2), 3.33 (1 H, t, *J* 7.5 Hz, 2-H), 3.69 (6 H, s, 2 × CO_2CH_3), and 5.05 (3 H, br t, *J* 7 Hz, 4, 8, and 12-H); *m/z* 336 (M^+, 0.2%) and 136 (90).

(4E,8E)-2-*Methoxycarbonyl*-5,9,13-*trimethyltetradeca*-4,8,12-*trienoic Acid* (**29**).—A solution of butyl-lithium in hexane (1.58M) was added to a crystal of triphenylmethane in dry tetrahydrofuran (20 ml) at room temperature under argon until the solution just turned pink. *N*-2-Propylcyclohexylamine (1.48 ml, 8.7 mmol) was then added, followed by a solution of butyl-lithium in hexane (1.58M; 4.57 ml, 7.3 mmol; added over 5 min). The solution was stored under argon for 15 min, cooled to −78 °C and a solution of the methyl ester (**27**) (0.672 g, 2.4 mmol) in dry tetrahydrofuran (10 ml) added over 30 min. After a further 30 min at −78 °C, carbon dioxide was bubbled through the solution whilst allowing it to warm slowly to room temperature (*ca.* 30 min). The solution was brought to pH 3 with hydrochloric acid (2M) and extracted with hexane (2 × 30 ml). The combined organic extracts were washed with saturated brine (50 ml) and evaporated. The colourless oily residue was purified by p.l.c. (8 × 1 mm), eluting with ether–hexane (1:2) to give the *carboxylic acid* (**29**) (0.39 g, 50%; 86% based on unrecovered starting material) as an oil and starting material (0.28 g) (Found: M^+, 322.2149. $C_{19}H_{30}O_4$ requires *M*, 322.2144); $\nu_{max.}$ 3 300—2 600, 1 765, and 1 725 cm^{-1}; δ (60 MHz) 1.61 (12 H, s, 5-, 9-, and 2 × 13-CH_3), 2.00 (8 H, s, 2 × CH_2CH_2), 2.62 (2 H, t, *J* 7 Hz, 3-CH_2), 3.41 (1 H, t, *J* 7 Hz, 2-H), 3.68 (3 H, s, CO_2CH_3), 5.00 (3 H, br m, 4-, 8-, and 12-H), and 9.95 (1 H, br s, CO_2H); *m/z* 322 (M^+, 100%).

8,13,18-*Triethyl*-3-[(4E,8E)-2-*methoxycarbonyl*-5,9,13-*trimethyl*-1-*oxotetradeca*-4,8,12-*trienyl*]-2,7,12,17-*tetramethyl*-21H,23H-*porphine* (**20**).—(With Dr. D. A. Lewton.) Oxalyl chloride (5 ml, 57 mmol) was added rapidly to a solution of the porphyrin carboxylic acid (**18**) (0.415 g, 0.8 mmol) (made from the ester by the method of Kenner *et al.*[10]) in dichloromethane (50 ml) heated at reflux under argon in the dark. After 5 min the solution was cooled to room temperature and evaporated (20 °C, 0.01 mmHg, 2 h) to give the crude porphyrin carboxylic acid chloride (**19**).

A solution of propan-2-ylmagnesium chloride in dry tetrahydrofuran (1.4M; 31 ml, 43 mmol) was added dropwise to a solution of 2-methoxycarbonyl-5,9,13-trimethyltetradeca-4,8,12-trienoic acid (**29**) (6.7 g, 21 mmol) and 1,10-phenanthroline (1 mg) in dry tetrahydrofuran (10 ml) stirred at room temperature under argon, until the colour just turned wine-red. This solution of the magnesium chelate (**30**) was then added to the freshly prepared porphyrin acid chloride (**19**) and the mixture stirred at room temperature until clear. The solution was heated at reflux for 10 min under argon, cooled to room temperature, diluted with chloroform (40 ml), washed with hydrochloric acid (2M; 50 ml) and saturated brine (50 ml) and evaporated. The residual gum was purified by chromatography (50 g; silica H), eluting with chloroform. The eluate was purified by p.l.c. (8 × 1 mm), eluting with chloroform and then repurified, again by p.l.c. (8 × 1 mm), eluting with dichloromethane–hexane (1:1) to give the *porphyrin* β-*keto ester* (**20**) (0.446 g, 70%) as a waxy purple solid, m.p. 155—156 °C (from dichloromethane–hexane) (Found: C, 77.9; H, 8.1; N, 7.4. $C_{49}H_{62}N_4O_3$ requires C, 77.95; H, 8.3; N, 7.4%); $\lambda_{max.}$ 408 (178 000), 507 (12 200), 548 (17 200), 573 (12 500), and 625 nm (3 000); $\nu_{max.}$ 3 415, 3 325, 1 740, 1 665, 1 585, 1 535, 1 465, 1 450, and 885 cm^{-1}; δ (400 MHz) −3.63 (2 H, br s, 2 × NH), 1.44, 1.44, 1.56, and 1.65 (each 3 H, s, 5-, 9-, and 2 × 13-CH_3), 1.7—2.1 (17 H, m, 8-, 13-, and 18-CH_2CH_3 and 2 × CH_2CH_2), 3.08 and 3.13 (each 1 H, dt, *J* 14.6 and 7.3 Hz, 3-CH_2), 3.53, 3.53, 3.67, and 3.91 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 3.80 (3 H, s, CO_2CH_3), 3.98, 4.12, and 4.14 (each 2 H, q, *J* 7.6 Hz, 8-, 13-, and 18-CH_2CH_3), 4.85 and 4.91 (each 1 H, br t, *J* 6.7 Hz, 8- and 12-H), 5.16 (1 H, t, *J* 7.3 Hz, 2-H), 5.32 (1 H, br t, *J* 7.1 Hz, 4-H), and 9.99, 10.00, 10.18, and 10.55 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* (f.d.) 754 (M^+, 100%).

8,13,18-*Triethyl*-2,7,12,17-*tetramethyl*-3-[(4E,8E)-5,9,13-*trimethyl*-1-*oxotetradeca*-4,8,12-*trienyl*]-21H,23H-*porphine* (**21**).—(With Dr. D. A. Lewton.) A solution of the foregoing porphyrin β-ketone ester (**20**) (420 mg, 0.56 mmol), lithium iodide trihydrate (0.5 g, 2.7 mmol), and 12-crown-4 (40 mg, 0.23 mmol) in pyridine (100 ml) was heated at reflux under argon in the dark for 48 h. The reaction mixture was cooled to room temperature, evaporated, and the baseline material removed by chromatography (10 g; silica H), eluting with ether–dichloromethane–hexane (1:1:2). The eluate was evaporated under reduced pressure and purified by chromatography (50 g; silica H), eluting with a gradient of ether–hexane (1→5:100) to give starting material (22 mg) and the *porphyrin ketone* (**21**) (197 mg, 51%) as a waxy purple solid, m.p. 198—200 °C (from dichloromethane–hexane) (Found: C, 81.3; H, 8.9; N, 7.9. $C_{47}H_{60}N_4O$ requires C, 81.0; H, 8.7; N, 8.0%); $\lambda_{max.}$ 406.5 (181 000), 508 (10 000), 547 (13 600), 574 (8 700), and 630 nm (1 200); $\nu_{max.}$ 3 415, 3 325, 1 730, 1 660, 1 590, 1 540, 1 465, 1 450, and 885 cm^{-1}; δ (400 MHz) −3.68 (2 H, br s, 2 × NH), 1.54, 1.54, 1.62, and 1.69 (each 3 H, s, 5-, 9-, and 2 × 13-CH_3), 1.7—2.1 (17 H, m, 8-, 13-, and 18-CH_2CH_3 and 2 × CH_2CH_2), 2.87 (2 H, q, *J* 6.9 Hz, 3-CH_2), 3.54, 3.67, 3.67, and 3.88 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 3.67 (2 H, m, 2-CH_2), 3.99, 4.12, and 4.13 (each 2 H, q, *J* 7.5 Hz, 8-, 13-, and 18-CH_2CH_3), 5.04 and 5.11 (each 1 H, m, 8- and 12-H), 5.47 (1 H, br t, *J* 6.4 Hz, 4-H), and 10.00, 10.01, 10.17, and 10.67 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* (f.d.) 696 (M^+, 100%).

8,13,18-*Triethyl*-3-[(4E,8E)-1-*hydroxy*-5,9,13-*trimethyltetradeca*-4,8,12-*trienyl*]-2,7,12,17-*tetramethyl*-21H,23H-*porphine* (**22**).—(With Dr. D. A. Lewton.) Sodium borohydride (0.1 g, 2.6 mmol) was added to a solution of the foregoing porphyrin ketone (**21**) (9.67 mg, 14 μmol) in dichloromethane (10 ml) and methanol (10 ml) stirred in the dark at room temperature. After 30 min hydrochloric acid (2M; 20 ml) was added and the organic layer separated and evaporated. The residue was purified by p.l.c. (1 × 2 mm; Merck), eluting with methanol–ether–hexane (1:2:20) to give the *model porphyrin* (**22**) (8.5 mg, 88%) as a waxy purple solid, m.p. 217—218 °C (from dichloromethane–hexane) (Found: M^+, 698.4919. $C_{47}H_{62}N_4O$ requires *M*, 698.4923); $\lambda_{max.}$ 399 (173 000), 497 (14 500), 531 (10 700), 567 (7 200), and 620 nm (1 200); $\nu_{max.}$ 3 790, 3 415, 3 320, 1 730, 1 485, 1 465, and 910 cm^{-1}; δ (400 MHz) −3.75 (2

H, br s, 2 × NH), 1.54, 1.54, 1.55, and 1.61 (each 3 H, s, 5-, 9-, and 2 × 13-CH_3), 1.86, 1.86, and 1.87 (each 3 H, t, *J* 7.5 Hz, 8-, 13-, and 18-CH_2CH_3), 2.1 (8 H, m, 2 × CH_2CH_2), 2.30 and 2.44 (each 1 H, dq, *J* 14.4 and 7.2 Hz, 3-CH_2), 2.65 and 2.81 (each 1 H, dq, *J* 14.5 and 7.1 Hz, 2-CH_2), 3.61, 3.64, 3.64, and 3.96 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 4.06, 4.11, and 4.12 (each 2 H, q, *J* 7.6 Hz, 8-, 13-, and 18-CH_2CH_3), 5.05 and 5.10 (each 1 H, br t, *J* 6.6 Hz, 8- and 12-H), 5.35 (1 H, br t, *J* 6.6 Hz, 4-H), 6.37 (1 H, t, *J* 7.0 Hz, 1-H), and 10.07, 10.08, 10.10, and 10.48 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* (f.d.) 698 (M^+, 100%) and 680 (18, $M - H_2O$).

Model Porphyrin Derivatives

3-[(4E,8E)-1-(−)-*Camphanyloxy*-5,9,13-*trimethyltetradeca*-4,8,12-*trienyl*]-8,13,18-*triethyl*-2,7,12,17-*tetramethyl*-21H,23H-*porphine* (**34**).—A solution of the racemic porphyrin alcohol (**22**) (27.9 mg, 40 μmol by u.v. assay, ε = 173 000), 4-dimethylaminopyridine (100 mg, 0.82 mmol), and (−)-camphanyl chloride (100 mg, 0.46 mmol) in dichloromethane (10 ml) was stirred in the dark at room temperature. After 30 min the solution was filtered through alumina (1 g, Woelm neutral, Brockmann activity III), eluting with ammonia-saturated dichloromethane until no red-fluorescent material remained on the alumina, to give the pair of porphyrin camphanate diastereoisomers (**34**). The diastereoisomers were separated by p.l.c. (8 × 0.25 mm), eluting first with dichloromethane to concentrate the band and then continuously with ether–hexane (initially 1:3) for 3 h. The chromatography tank contained a beaker of aqueous concentrated ammonia to ensure a saturated ammonia vapour throughout. The diastereoisomers appeared to be completely separate under visible light, but were slightly overlapping by fluorescence under long-wave u.v. light. The diastereoisomeric excess (d.e.) of each band was determined by h.p.l.c.

High R_F diastereoisomer (11.0 mg, 31% by u.v. assay, estimated ε 175 000) d.e. 93%; $\lambda_{max.}$ 399, 499, 536, 566, and 621 nm (52:3.8:3.0:2.0:1); δ (400 MHz; C_6D_6) −2.96 (2 H, br s, 2 × NH), 0.40, 0.40, and 0.58 (each 3 H, s, 3 × camphanate-CH_3), 0.90, 1.15, 1.25, and 1.95 (each 1 H, m, camphanate-CH_2CH_2), 1.49, 1.53, 1.56, and 1.60 (each 3 H, s, 5-, 9-, and 2 × 13-CH_3), 1.74, 1.74, and 1.82 (each 3 H, t, *J* 7.5 Hz, 8-, 13-, and 18-CH_2CH_3), 2.0—2.3 (8 H, m, 2 × CH_2CH_2), 2.29 and 2.52 (each 1 H, m, 3-CH_2), 2.91 and 3.20 (each 1 H, m, 2-CH_2), 3.35, 3.35, 3.70, and 3.81 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 3.91 (6 H, m, 8-, 13-, and 18-CH_2CH_3), 5.19 and 5.27 (each 1 H, br t, *J* 6.5 Hz, 8- and 12-H), 5.43 (1 H, br t, *J* 6.8 Hz, 4-H), 7.70 (1 H, t, *J* 7.3 Hz, 1-H), and 10.14, 10.14, 10.18, and 10.98 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* (f.d.) 878 (M^+, 100%).

Low R_F diastereoisomer (11.8 mg, 34% by u.v. assay), d.e. 57% (Found: M^+, 878.57094. $C_{57}H_{74}N_4O_4$ requires *M*, 878.57101); $\lambda_{max.}$ 399, 499, 536, 566, and 621 nm (52:3.8:3.0:2.0:1); δ (400 MHz, C_6D_6) −2.96 (2 H, br s, 2 × NH), 0.41, 0.415, and 0.70 (each 3 H, s, 3 × camphanate-CH_3), 0.8—1.4 (camphanate-CH_2CH_2, obscured by grease), 1.48, 1.51, 1.54, and 1.59 (each 3 H, s, 5-, 9-, and 2 × 13-CH_3), 1.73, 1.75, and 1.83 (each 3 H, t, *J* 7.5 Hz, 8-, 13-, and 18-CH_2CH_3), 2.0—2.3 (8 H, m, 2 × CH_2CH_2), 2.5 (2 H, m, 3-CH_2), 2.95 and 3.18 (each 1 H, m, 2-CH_2), 3.36, 3.36, 3.70, and 3.79 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 3.91, 3.91, and 3.93 (each 2 H, q, *J* 7.8 Hz, 8-, 13-, and 18-CH_2CH_3), 5.17 and 5.25 (each 1 H, br t, *J* 6.5 Hz, 8- and 12-H), 5.43 (1 H, br t, *J* 6.6 Hz, 4-H), 7.69 (1 H, t, *J* 7.4 Hz, 1-H), and 10.14, 10.14, 10.18, and 10.98 (each 1 H, s, 5-, 10-, 15-, and 20-H); *m/z* (f.d.) 878 (M^+, 100%).

Hydrolysis of the Camphanates (**34**).—A two-phase solution of potassium hydroxide (0.2 g, 3.6 mmol) and the porphyrin camphanate diastereoisomer (10.9 mg, 12 μmol by u.v. assay) in tetrahydrofuran (10 ml) and water (10 ml) was stirred vigorously in the dark at room temperature for 18 h. Dichloromethane (20 ml) was then added and the organic layer removed and evaporated. The residue was partitioned between dichloromethane (3 ml) and water (5 ml) and the organic layer removed and evaporated to give the porphyrin alcohol (**22**) (8.4 mg, 97% by u.v. assay, ε 173 00).

The diastereoisomeric excesses of the porphyrin alcohols were established by re-esterification to the porphyrin camphanates by the previous procedure; d.e. (high R_F) 91%; (low R_F) 58%.

8,13,18-*Triethyl*-2,7,12,17-*tetramethyl*-3-[(4E,8E)-1-(3,5-*dinitrobenzoyloxy*)-5,9,13-*trimethyltetradeca*-4,8,12-*trienyl*]-21H,23H-*porphine* (**35**).—A solution of the racemic porphyrin alcohol (**22**) (1.26 mg, 1.8 μmol by u.v. assay), 4-dimethylaminopyridine (10 mg, 80 μmol), and 3,5-dinitrobenzoyl chloride (10 mg, 44 μmol) in dichloromethane (1 ml) was stirred in the dark at room temperature for 30 min. The product was isolated by p.l.c. (1 × 0.25 mm; Merck), eluting with dichloromethane to give the *porphyrin* 3,5-*dinitrobenzoate* (**35**) (1.36 mg, 84% by u.v. assay) as a purple waxy solid; $\lambda_{max.}$ 399, 499, 536, 567, and 620 nm (49:3.8:3.1:2.0:1); δ (400 MHz) −3.79 (2 H, br s, 2 × NH), 1.50—1.60 (12 H, br m, 5-, 9-, and 2 × 13-CH_3), 1.87 (9 H, m, 8-, 13-, and 18-CH_2CH_3), 2.1 (8 H, m, 2 × CH_2CH_2), 2.30 and 2.45 (each 1 H, m, 3-CH_2), 3.05 and 3.20 (each 1 H, m, 2-CH_2), 3.58, 3.67, 3.75, and 3.81 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3), 4.03, 4.14, and 4.14 (each 3 H, q, *J* 7.7 Hz, 8-, 13-, and 18-CH_2CH_3), 5.10 (2 H, m, 8- and 12-H), 5.35 (1 H, m, 4-H), 7.64 (1 H, t, *J* 7.5 Hz, 1-H), 9.15 (1 H, t, *J* 2.0 Hz, 4-ArH), 9.37 (2 H, d, *J* 2.2 Hz, 2- and 6-ArH), and 10.07, 10.08, 10.15, and 10.45 (each 1 H, s, 5-, 10-, 15-, and 20-*H*); *m/z* (f.d.) 892 (M^+, 100%).

8,13,18-*Triethyl*-2,7,12,17-*tetramethyl*-3-[(4E,8E)-5,9,13-*trimethyl*-1-(2-*nitrobenzoyloxy*)*tetradeca*-4,8,12-*trienyl*]-21H,23H-*porphine* (**37**).—A solution of the racemic porphyrin alcohol (**22**) (0.56 mg, 0.8 μmol by u.v. assay), 4-dimethylaminopyridine (10 mg, 80 μmol), and 2-nitrobenzoyl chloride (10 mg, 50 μmol) in dichloromethane (1 ml) was stirred in the dark at room temperature for 15 min. The solution was washed with aqueous 5% sodium hydrogen carbonate (1 ml) and evaporated. The baseline material was then removed by rapid chromatography (0.1 g; 70—230 mesh, silica), eluting with ammonia-saturated dichloromethane to give the *porphyrin* 2-*nitrobenzoate* (**37**) (0.41 mg, 60% by u.v. assay) as a purple waxy solid; $\lambda_{max.}$ 399, 499, 535, 569, and 622 nm (43:3.3:2.7:1.8:1); *m/z* (f.d.) 847 (M^+, 100%).

8,13,18-*Triethyl*-2,7,12,17-*tetramethyl*-3-{(4E,8E)-5,9,13-*trimethyl*-1-[(−)-3,3,3-*trifluoro*-2-*methoxy*-2-*phenylpropanoyloxy*]*tetradeca*-4,8,12-*trienyl*}-21H,23H-*porphine* (**40**).—The pair of porphyrin ester diastereoisomers (**40**) (1.68 mg, 83% by u.v. assay) was prepared from the racemic porphyrin alcohol (**22**) (2.21 μmol) by the same method as for the racemic porphyrin 3,5-dinitrobenzoate and obtained as a waxy purple solid; δ (400 MHz) −3.80 and −3.77 (each 2 H, br s, 4 × NH), 1.4—1.6 [24 H, complex m partially obscured by H_2O, 2 × (5-, 9-, and 2 × 13-CH_3)], 1.8 [18 H, m, 2 × (8-, 13-, and 18-CH_2CH_3)], 2.0 (16 H, m, 4 × CH_2CH_2), 2.1—2.6 (4 H, complex m, 2 × 3-CH_2), 2.7 and 3.0 (each 1 H, complex m, 2-CH_2), 2.8 and 3.0 (each 1 H, complex m, 2-CH_2), 3.23, 3.40, 3.43, 3.56, 3.60, 3.64, 3.68, and 3.72 [30 H, 8 × s, 2 × (2-, 7-, 12-, and 17-CH_3 and OCH_3)], 4.03, 4.13, and 4.15 [each 4 H, q, *J*, 7.6 Hz, 2 × (8-, 13-, and 18-CH_2CH_3)], 5.0—5.1 [4 H, br m, 2 × (8- and 12-H)], 5.25 and 5.30 (each 1 H, br m, 2 × 4-H), 6.37 and 6.62 [each 2 H, br m, 2 × (3- and 5-ArH)], 6.55 and 6.85 (each 1 H, br m, 2 × 4-ArH), 7.05 and 7.30 [each 2 H, d, *J* 7.8 Hz, 2 × (2- and 6-ArH)],

7.35 and 7.51 (each 1 H, br m, 2 × 1-H), and 10.06, 10.07, 10.08, 10.11, 10.14, and 10.28 {8 H, 6 × s, 2 × (5-, 10-, 15-, and 20-H)}; δ (400 MHz; CD_2Cl_2, selected peaks only) 3.25, 3.42, 3.49, 3.63, 3.65, 3.71, and 3.76 [30 H, 7 × s, 2 × (2-, 7-, 12-, and 17-CH_3 and OCH_3)], 6.36 and 6.79 [each 2 H, br m, 2 × (3- and 5-ArH)], 6.60 and 6.99 (each 1 H, br m, 2 × 4-ArH), 7.04 and 7.36 [each 2 H, d, *J* 7.8 Hz, 2 × (2- and 6-ArH)], 7.44 and 7.53 (each 1 H, br m, 2 × 1-H), and 10.08, 10.15, 10.17, 10.22, and 10.32 [8 H, 5 × s, 2 × (5-, 10-, 15-, and 20-H)]; δ (^{19}F; 235 MHz; CD_2Cl_2) 5.40 and 6.36 (each 3 F, s, CF_3); *m/z* (f.d.) 914 (M^+, 100%).

The separate diastereoisomers (**40**) were each prepared from the corresponding enantiomer of the porphyrin alcohol (**22**) by the same procedure.

From the (*R*)-alcohol; δ (400 MHz, CD_2Cl_2, selected peaks only) 2.8 and 3.0 (each 1 H, complex m, 2-CH_2), 3.42, 3.63, 3.65, and 3.71 (15 H, 4 × s, 2-, 7-, 12-, and 17-CH_3 and OCH_3), 6.36 (2 H, br m, 3-and 5-ArH), 6.60 (1 H, br m, 4-ArH), 7.04 (2 H, d, *J* 7.8 Hz, 2- and 6-ArH), and 10.08, 10.15, and 10.17 (4 H, 3 × s, 5-, 10-, 15-, and 20-H); δ (^{19}F; 235 MHz; CD_2Cl_2) 5.40 (3 F, s, CF_3).

From the (*S*)-alcohol; δ (400 MHz, selected peaks only) 2.7 and 3.0 (each 1 H, complex m, 2-CH_2), 3.23, 3.43, 3.60, 3.68, and 3.72 (each 3 H, s, 2-, 7-, 12-, and 17-CH_3 and OCH_3), 6.62 (2 H, br m, 3- and 5-ArH), 6.85 (1 H, br m, 4-ArH), 7.30 (2 H, d, *J* 7.8 Hz, 2- and 6-ArH), and 10.07, 10.14, and 10.28 (4 H, 3 × s, 5-, 10-, 15-, and 20-H); δ (^{19}F; 235 MHz; CD_2Cl_2) 6.36 (3 F, s, CF_3).

Dimethyl 17-Formyl-2,7,12-trimethyl-3-{(4E,8E)-5,9,13-trimethyl-1-[(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]tetradeca-4,8,12-trienyl}-8-vinyl-21H,23H-porphyrin-13,18-dipropionate (*Porphyrin a Ester*, MTPA *Ester*).—The pair of porphyrin ester diastereoisomers (1.75 mg, 84% by u.v. assay) was prepared, by the same method as for the model porphyrin, from synthetic porphyrin *a* (**2**) dimethyl ester[3] (2 μmol) and obtained as a waxy greenish purple solid (Found: M^+, 1 042.5033. $C_{61}H_{69}F_3N_4O_8$ requires *M*, 1 042.5067); $\lambda_{max.}$ 418, 520, 559, 581, 652 nm (48:2.5:5.0:3.7:1); δ (400 MHz) −3.38 and −3.35 (each 2 H, br s, 4 × NH), 1.4—1.7 [24 H, complex m partially obscured by H_2O, 2 × (5-, 9-, and 2 × 13-CH_3)], 1.9—2.1 (16 H, m, 4 × CH_2CH_2), 2.2—2.5 (4 H, complex m, 2 × 3-CH_2), 2.7—3.1 (4 H, complex m, 2 × 2-CH_2), 3.30 and 3.40 (each 4 H, t, *J* 7.5 Hz, 4 × CH_2CH_2CO), 3.25, 3.41, 3.43, 3.56, 3.61, 3.62, 3.63, 3.66, 3.71, and 3.80 [36 H, 10 × s, 2 × (2-, 7-, and 12-CH_3, 2 × CO_2CH_3, and OCH_3)], 4.46 and 4.76 (each 4 H, t, *J* 7.5 Hz, 4 × CH_2CH_2CO), 5.0—5.1 [4 H, br m, 2 × (8- and 12-H)], 5.25 and 5.30 (each 1 H, br m, 2 × 4-*H*), 6.17 (2 H, dd, *J* 11.5 and 1.3 Hz, CH=CH_aH$_b$), 6.29 (2 H, dd, *J* 17.7 and 1.3 Hz, CH=CH$_a$CH_b), 6.51 (2 H, br m, 3- and 5-ArH), 6.70 (1 H, br m, 4-ArH), 7.08 (2 H, d, *J* 7.7 Hz, 2- and 6-ArH), 6.75 (2 H, t, *J* 7.6 Hz, 3- and 5-ArH), 6.95 (1 H, t, *J* 7.5 Hz, 4-ArH), 7.29 (2 H, d, *J* 7.8 Hz, 2- and 6-ArH), 7.49 and 7.59 (each 1 H, br m, 2 × 1-H), 8.18 (2 H, dd, *J* 17.6 and 11.4 Hz, C*H*=CH$_2$), 10.06, 10.11, 10.115, 10.25, 10.29, 10.295, 11.00, and 11.04 [each 1 H, s, 2 × (5-, 10-, 15-, and 20-*H*)], and 11.58 (2 H, s, 2 × CHO); δ (^{19}F; 235 MHz; CD_2Cl_2) 5.53 and 6.35 (each 3 F, s, CF_3).

Cyclopentenyl Derivatives

Cyclopent-2-enyl Dimethyl-t-butylsilyl Ether (**42**).—A solution of dimethyl-t-butylsilyltrifluoromethanesulphonate (2.90 ml, 12.6 mmol) in dry toluene (10 ml) was added dropwise under argon to a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (2.50 ml, 16.7 mmol) and cyclopentene oxide (1.10 ml, 12.6 mmol) in dry toluene (40 ml) heated with vigorous stirring under argon at 60 °C. After a further 20 h at 60 °C the mixture was cooled to room temperature, pentane (150 ml) added, and the upper layer decanted. The lower layer was back extracted with pentane (50 ml), the extracts combined, washed rapidly with methanol (50 ml), and evaporated carefully (15 °C/20 mmHg). Bulb-to-bulb distillation (40 °C/10 mmHg) gave an oil which was purified by chromatography (10 g; silica H), eluting with ether to give the silyl ether (**42**) (1.46 g, 58%) as an oil, b.p. 40—45 °C, 10 mmHg (lit.,[20] 36—38 °C, 1 mmHg); δ (90 MHz; CD_2Cl_2) 0.1 [6 H, s, $Si(CH_3)_2$], 0.9 [9 H, s, $SiC(CH_3)_3$], 1.4—2.6 (4 H, m, CH_2CH_2), 4.9 (1 H, m, 1-H), 5.7 (1 H, m, 2-H), and 5.9 (1 H, m, 3-H); *m/z* 199 (M^+ + 1, 57%) and 67 (100, $C_5H_7^+$).

Cyclopent-2-enyl 3,5-Dinitrobenzoate (**43**).—A solution of tetrabutylammonium fluoride in dry tetrahydrofuran (1M; 3 ml, 3 mmol) was added dropwise to a stirred mixture of the foregoing silyl ether (**42**) (0.5 g, 2.5 mmol) and 4 Å molecular sieves (1 g) at room temperature under argon. After 30 min, a solution of 3,5-dinitrobenzoyl chloride (0.6 g, 2.6 mmol) and 4-dimethylaminopyridine (0.8 g, 6.5 mmol) in dichloromethane (20 ml) was added and the mixture stirred at room temperature under argon for a further 10 min. The mixture was then filtered, evaporated, and purified by chromatography (10 g; silica H), eluting with dichloromethane. Recrystallisation gave the 3,5-dinitrobenzoate (**43**) (0.48 g, 68%) as needles, m.p. 123—123.5 °C (from dichloromethane–hexane) (lit.,[36] 118—121 °C) (Found: C, 51.6; H, 3.6; N, 9.9. Calc. for $C_{12}H_{10}N_2O_6$: C, 51.8; H, 3.6; N, 10.1%); $\nu_{max.}$ 3 100, 3 045, 1 725, 1 625, 1 600, 1 545, 1 460, and 1 345 cm^{-1}; δ (400 MHz; CD_2Cl_2) 1.4—1.6 (4 H, complex m, CH_2CH_2), 5.95, 6.02, and 6.26 (each 1 H, m, 1-, 2-, and 3-H), 9.12 (2 H, d, *J* 2.1 Hz, 2- and 6-ArH), and 9.19 (1 H, t, *J* 2.1 Hz, 4-ArH); *m/z* (f.d.) 278 (M^+, 100%).

Cyclopent-2-enyl Benzoate (**45**).—The *benzoate* (**45**) (0.12 g, 74%) was obtained by the preceding method as an oil from the silyl ether (**42**) (0.86 mmol) (Found: M^+, 188.0841. $C_{12}H_{12}O_2$ requires *M*, 188.0837); $\nu_{max.}$(CH_2Cl_2) 1 710, 1 600, and 1 580 cm^{-1}; δ (90 MHz) 1.6—2.7 (4 H, m, CH_2CH_2), 6.0 and 6.2 (3 H, m, 1-, 2- and 3-H), 7.5 (3 H, m, 3-, 4-, and 5-ArH), and 8.1 (2 H, dd, *J* 8 and 2 Hz, 2- and 6-ArH); *m/z* 188 (M^+, 16%), 105 (100, $C_7H_5O^+$), 83 (40, $C_5H_7O^+$), 77 (49, $C_6H_5^+$), and 67 (74, $C_5H_7^+$).

Cyclopent-2-enyl 4-Bromobenzoate (**46**).—The 4-*bromobenzoate* (**46**) (70 mg, 52%) was obtained by the preceding method as an oil from the silyl ether (**42**) (0.5 mmol) (Found: M^+, 267.9917 and 265.9945. $C_{12}H_{11}BrO_2$ requires *M*, 267.9923 and 265.9943); $\nu_{max.}$(CH_2Cl_2) 1 710, 1 590, and 1 480 cm^{-1}; δ (90 MHz), 1.6—2.7 (4 H, m, CH_2CH_2), 5.9 and 6.2 (3 H, m, 1-, 2-, and 3-H), 7.65 (2 H, d, *J* 8 Hz, 3- and 5-ArH), and 7.95 (2 H, d, *J* 8 Hz, 2- and 6-ArH); *m/z* 268 and 266 (M^+, 11 and 9%), 202 and 200 (5 and 5, $C_7H_5BrO_2^+$), 187 (18, *M* − Br), 185 and 183 (51 and 53, $C_7H_4BrO^+$), 157 and 155 (18 and 19, $C_6H_4Br^+$), 83 (46, $C_5H_7O^+$), and 67 (100, $C_5H_7^+$).

Cyclopent-2-enyl 2-Nitrobenzoate (**48**).—The 2-*nitrobenzoate* (**48**) (0.43 g, 73%) was obtained by the preceding method as an oil from the silyl ether (**42**) (2.5 mmol) (Found: C, 61.7; H, 4.85; N, 5.9. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.8; N, 6.0%); $\nu_{max.}$ 3 055, 1 725, 1 610, 1 580, 1 535, and 1 350 cm^{-1}; δ (90 MHz) 1.6—2.7 (4 H, m, CH_2CH_2), 5.9 and 6.2 (3 H, m, 1-, 2-, and 3-H), and 7.5—8.0 (4 H, m, 4 × ArH); *m/z* (f.d.) 233 (M^+, 100%).

Cyclopent-2-enyl (−)-Camphanate (**44**).—A solution of cyclopent-2-enol (18 mg, 0.21 mmol), (−)-camphanyl chloride (50 mg, 0.23 mmol), and 4-dimethylaminopyridine (90 mg, 0.74 mmol) in dichloromethane (5 ml) was stirred at room temperature for 10 min. The solution was then washed with hydrochloric acid (2M; 20 ml) and evaporated. P.l.c. (2 × 0.25 mm), eluting with ether gave the crude product which was recrystallised to give the pair of *camphanate diastereoisomers* (**44**) (10.5 mg, 19%) as colourless needles, m.p. 85—92 °C (from pentane) (Found: C, 67.9; H, 7.8. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%); $\nu_{max.}$ 3 015, 1 785, 1 740, 1 720, and 1 615 cm^{-1}; δ (400

MHz) 0.92, 0.93, 1.03, and 1.11 (18 H, 4 × s, 6 × CH_3), 1.70, 1.94, 2.01, 2.35, and 2.50 (16 H, m, 4 × CH_2CH_2) and 5.80, 5.82, and 6.14 (each 2 H, m, 1-, 2-, and 3-H); *m/z* 264 (M^+, 0.2%), 182 (0.1, $C_{10}H_{13}O_3^+$), 83 (20, $C_5H_7O^+$), and 67 (100, $C_5H_7^+$).

Cyclopent-2-enyl 2,6-Dinitrobenzoate (**47**).—A solution of cyclopent-2-enol (0.5 g, 6 mmol), 2.6-dinitrobenzoyl chloride (1.9 g, 8.2 mmol), and 4-dimethylaminopyridine (2.60 g, 21.3 mmol) in dichloromethane (20 ml) was stirred at reflux for 18 h. The solution was then cooled to room temperature, washed with hydrochloric acid (2M; 20 ml), 10% aqueous sodium hydrogen carbonate (2 × 20 ml), and evaporated. Chromatography of the residue (6 g; silica H), eluting with dichloromethane gave the crude product which was purified by p.l.c. (8 × 1 mm), eluting with dichloromethane. Recrystallisation gave the 2,6-*dinitrobenzoate* (**47**) (1.13 g, 68%) as needles, m.p. 95—101 °C (decomp.) (from ether–hexane) (Found: C, 51.7; H, 3.5; N, 10.0. $C_{12}H_{10}N_2O_6$ requires C, 51.8; H, 3.6; N, 10.1%); $\nu_{max.}$(CH_2Cl_2) 1 750, 1 580, 1 550, and 1 350 cm^{-1}; δ (400 MHz; CD_2Cl_2) 2.10 and 2.55 (each 1 H, m, 5-CH_2), 2.40 (2 H, m, 4-CH_2), 5.95, 6.10, and 6.20 (each 1 H, m, 1-, 2-, and 3-H), 7.80 (1 H, t, *J* 8 Hz, 4-ArH), and 8.45 (2 H, d, *J* 8 Hz, 3- and 5-ArH); *m/z* (f.d.) 278 (M^+, 100%).

Pentanedioate Derivatives

(R,S)-*Dimethyl 2-Hydroxypentanedioate* (**50**).—Sodium borohydride (0.1 g, 2.6 mmol) was added slowly to a solution of dimethyl 2-oxopentanedioate (0.28 g, 1.6 mmol) in dichloromethane (10 ml) and methanol (10 ml) stirred at room temperature. After 30 min the solution was concentrated (*ca.* 1 ml) under reduced pressure, 10% aqueous ammonium chloride (40 ml) added, and the mixture extracted with ether (2 × 20 ml). The combined extracts were washed with saturated brine (20 ml) and evaporated to give the (*R,S*)-alcohol (**50**) (0.21 g, 74%) as an oil, b.p. 130—140 °C/0.3 mmHg (lit.,[23] 115—118 °C, 0.1 mmHg); $\nu_{max.}$ 3 535, 3 600—3 300, 1 730, 1 440, 1 370 cm^{-1}; δ (250 MHz) 1.93 (1 H, dtd, *J* 14.3, 7.9, and 6.4 Hz, 3-C$H_a$$H_b$), 2.17 (1 H, dtd, *J* 14.1, 7.6, and 4.1 Hz, 3-C$H_a$$H_b$), 2.43 (1 H, ddd, *J* 16.4, 7.7, and 6.4 Hz, 4-C$H_a$$H_b$), 2.50 (1 H, dt, *J* 16.4 and 7.8 Hz, 4-C$H_a$$H_b$), 2.85 (1 H, br s, OH), 3.67 and 3.79 (each 3 H, s, 2 × CO_2CH_3), and 4.23 (1 H, dd, *J* 7.9 and 4.1 Hz, 2-H); *m/z* 175 (M^+ − 1, 2%), 159 (100), and 145 (2, *M* − MeO).

(S)-*Dimethyl 2-Hydroxypentanedioate* (**50**).—A solution of (*S*)-2-hydroxypentanedioic acid, disodium salt (0.5 g, 2.6 mmol) in water (25 ml) was added to a solution of silver nitrate (1 g, 5.9 mmol) in water (5 ml) and the mixture shaken vigorously; after centrifugation the supernatant was decanted. The precipitate was washed at the centrifuge sequentially with water (30 ml), 95% ethanol (30 ml), and ether (30 ml) to give the disilver salt which was ground into a fine powder.

A suspension of the disilver salt in iodomethane (30 ml) was heated at reflux. After 3 h the mixture was cooled to room temperature, filtered through a bed of Celite and evaporated to give the (*S*)-alcohol (**50**) (0.35 g, 76%) as an oil, $[\alpha]_D^{16}$ −2.48° (neat) (lit.,[23] −2.5°).

The (*R*)-alcohol (**50**) (0.38 g, 83%), was prepared by the foregoing procedure from (*R*)-2-hydroxypentanedioic acid, disodium salt (2.6 mmol) as an oil, $[\alpha]_D^{20}$ +2.58° (neat) (lit.,[23] +2.53°).

(R,S)-*Dimethyl 2-(Dimethyl-t-butylsilyloxy)pentanedioate*.—A solution of the foregoing (*R,S*)-alcohol (**50**) (102 mg, 0.56 mmol) imidazole (50 mg, 0.73 mmol), and dimethyl-t-butylsilyl chloride (100 mg, 0.66 mmol) in dimethylformamide (5 ml) was kept at room temperature overnight. The solution was evaporated (30 °C/0.1 mmHg, 5 h), and the product isolated by p.l.c. (1 × 1 mm), eluting with ether–hexane (1:3). Bulb-to-bulb distillation gave the (R,S)-*silyl ether* (147 mg, 87%) as an oil, b.p. 130 °C/0.3 mmHg (Found: C, 54.1; H, 8.7. $C_{13}H_{26}SiO_5$ requires C, 53.8; H, 9.0%); $\nu_{max.}$ 1 730, 1 460, 1 435, and 1 360 cm^{-1}; δ (90 MHz) 0.05 and 0.08 (each 3 H, s, 2 × $SiCH_3$), 0.92 [9 H, s, $C(CH_3)_3$], 1.85—2.20 (2 H, m, 3-CH_2), 2.35—2.60 (2 H, m, 4-CH_2), 3.72 and 3.77 (each 3 H, s, 2 × CO_2CH_3), and 4.33 (1 H, t, *J* 6 Hz, 2-*H*); *m/z* (f.a.b.) 293 (M^+ + 3, 20%), 291 (15, M^+ + 1), 235 (100), 232 (40), 175 (90), and 173 (20).

(R,S)-*Dimethyl 2-(3,5-Dinitrobenzoyloxy)pentanedioate* (**51**).—A solution of the foregoing (*R,S*)-alcohol (**50**) (0.25 g, 1.4 mmol), 4-dimethylaminopyridine (0.61 g, 5 mmol), and 3,5-dinitrobenzoyl chloride (0.5 g, 2.2 mmol) in dichloromethane (5 ml) was stirred at room temperature for 30 min. Baseline material was removed by p.l.c. (4 × 1 mm), eluting with dichloromethane to give the (R,S)-3,5-*dinitrobenzoate* (**51**) (0.32 g, 61%) as needles, m.p. 72.5—73.5 °C (from dichloromethane–ether) (Found: C, 45.6; H, 3.9; N, 7.35%; M^+, 370.0653. $C_{14}H_{14}N_2O_{10}$ requires C, 45.4; H, 3.8; N, 7.6%; *M*, 370.0648); $\nu_{max.}$(CH_2Cl_2) 1 740, 1 620, 1 600, 1 550, and 1 350 cm^{-1}; δ (400 MHz) 2.37 (1 H, dq, *J* 14.7 and 7.5 Hz, 3-C$H_a$$H_b$), 2.45 (1 H, dtd, *J* 14.7, 7.5, and 4.8 Hz, 3-C$H_a$$H_b$), 2.54 (1 H, dt, *J* 16.7 and 6.0 Hz, 4-C$H_a$$H_b$), 2.57 (1 H, dt, *J* 16.7 and 8.4 Hz, 4-C$H_a$$H_b$), 3.70 and 3.705 (each 3 H, s, 2 × CO_2CH_3), 5.41 (1 H, dd, *J* 7.8 and 4.8 Hz, 2-*H*), 9.15 (2 H, d, *J* 2.1 Hz, 2- and 6-Ar*H*), and 9.24 (1 H, t, *J* 2.2 Hz, 4-Ar*H*); *m/z* 370 (M^+, 0.1%) and 195 (100, $C_7H_3N_2O_5^+$).

The (R)-3,5-*dinitrobenzoate* (0.23 g, 63%), and the (S)-3,5-*dinitrobenzoate* (0.59 g, 80%) were prepared by the same method as for the racemate, from the (*R*)-alcohol (1 mmol) and the (*S*)-alcohol (2 mmol) and obtained as needles, m.p. 89.0—89.5 °C (from methyl acetate–hexane) [Found: (*R*); C, 45.3; H, 3.7; N, 7.6%; (*S*); C, 45.4; H, 3.7; N, 7.5%. $C_{14}H_{14}N_2O_{10}$ requires C, 45.4; H, 3.8; N, 7.6], $[\alpha]_D^{16}$ (*R*), −19.9°; (*S*), +19.4° (*c* 1.0 in CH_2Cl_2).

(R,S)-*Dimethyl 2-(Benzoyloxy)pentanedioate* (**53**).—The (R,S)-*benzoate* (**53**) (0.15 g, 72%) was obtained by the preceding method from the (*R,S*)-alcohol (**50**) (0.74 mmol) as an oil (Found: M^+, 280.0943. $C_{14}H_{16}O_6$ requires *M*, 280.0947); $\nu_{max.}$(CH_2Cl_2) 1 740, 1 600, and 1 580 cm^{-1}; δ (90 MHz) 2.3—2.7 (4 H, complex m, CH_2CH_2), 3.71 and 3.79 (each 3 H, s, 2 × CO_2CH_3), 5.35 (1 H, t, *J* 6 Hz, 2-H), 7.5 (3 H, m, 3-, 4-, and 5-ArH), and 8.15 (2 H, dd, *J* 8 and 2 Hz, 2- and 6-ArH); *m/z* 280 (M^+, 0.1%), 249 (0.2, *M* − MeO), 248 (0.1, *M* − MeOH), 221 (0.1, *M* − CO_2Me), 105 (100, $C_7H_5O^+$), and 77 (23, $C_6H_5^+$).

(R,S)-*Dimethyl 2-(4-Bromobenzoyloxy)pentanedioate* (**54**).—The (R,S)-4-*bromobenzoate* (**54**) (0.18 g, 62%) was obtained by the preceding method from the (*R,S*)-alcohol (**50**) (0.81 mmol) as an oil (Found: M^+, 360.0046 and 358.0080. $C_{14}H_{15}O_6$ requires *M*, 360.0033 and 358.0052); $\nu_{max.}$ 3 050, 1 730, 1 605, and 1 590 cm^{-1}; δ (90 MHz) 2.3—2.7 (4 H, complex m, CH_2CH_2), 3.71 and 3.79 (each 3 H, s, 2 × CO_2CH_3), 5.35 (1 H, t, *J* 6 Hz, 2-H), 7.6 (2 H, d, *J* 8 Hz, 2- and 6-ArH), and 8.0 (2 H, d, *J* 8 Hz, 3- and 5-ArH); *m/z* 360 and 358 (M^+, 2 and 2%), 329 and 327 (1 and 1, *M* − MeO), 328 and 326 (2 and 2, *M* − MeOH), 301 and 299 (10 and 10, *M* − CO_2Me), 185 and 183 (100 and 100, $C_7H_4BrO^+$), 157 and 155 (20 and 20, $C_6H_4Br^+$), and 104 (15, $C_7H_4O^+$).

(R,S)-*Dimethyl 2-(2-Nitrobenzoyloxy)pentanedioate* (**56**).—The (R,S)-2-*nitrobenzoate* (**56**) (0.43 g, 83%) was obtained by the preceding method from the (*R,S*)-alcohol (**50**) (1.59 mmol) as an oil (Found: C, 51.3; H, 4.7; N, 4.2. $C_{14}H_{15}NO_8$ requires C, 51.7; H, 4.65; N, 4.3%); $\nu_{max.}$ 1 740, 1 535, and 1 350 cm^{-1}; δ (400

MHz) 2.20 (1 H, dtd, *J* 14.5, 8.2, and 6.3 Hz, 3-CH_aH_b), 2.33 (1 H, dtd, *J* 14.5, 7.4, and 4.5 Hz, 3-CH_aH_b), 2.46 (1 H, ddd, *J* 16.3, 7.4, and 6.4, 4-CH_aH_b), 2.50 (1 H, dt, *J* 16.3 and 7.8 Hz, 4-CH_aH_b), 3.66 and 3.79 (each 3 H, s, 2 × CO_2CH_3), 5.33 (1 H, dd, *J* 8.2 and 4.4 2-H), 7.65 (1 H, td, *J* 7.8 and 1.4 Hz, 4-ArH), 7.70 (1 H, td, *J* 7.5 and 1.4 Hz, 5-ArH), 7.81 (1 H, dd, *J* 7.3 and 1.4 Hz, 6-ArH), and 7.94 (1 H, dd, *J* 7.9 and 1.4 Hz, 3-ArH); *m/z* (f.d.) 326 (M^+, 100%) and 266 (40).

The (R)-2-*nitrobenzoate* (0.61 g, 95%) and the (S)-2-*nitrobenzoate* (0.31 g, 94%) were prepared by the same method as for the racemate, from the (*R*)-alcohol (2 mmol) and the (*S*)-alcohol (1 mmol) and obtained as oils [Found: (*R*); C, 51.4; H, 4.8; N, 4.3; (*S*); C, 51.9; H, 4.9; N, 4.2. $C_{14}H_{15}NO_8$ requires C, 51.7; H, 4.65; N, 4.3%]; $[\alpha]_D^{20}$ (*R*), −22.0°; (*S*), +22.0° (*c* 0.9 in CH_2Cl_2).

(R,S)-*Dimethyl* 2-(−)-*Camphanyloxypentanedioate*.—The pair of *camphanate diastereoisomers* (0.18 g, 83%) was obtained by the preceding method from the (*R,S*)-alcohol (**50**) (0.61 mmol) as an oil (Found: M^+, 356.1474. $C_{17}H_{24}O_8$ requires *M*, 356.1471); $\nu_{max.}$ 1 785, 1 740, and 1 435 cm^{-1}; δ (250 MHz) 1.00, 1.04, 1.06, and 1.125 (each 3 H, s, 4 × CH_3), 1.12 (6 H, s, 2 × CH_3), 1.55—2.55 (16 H, complex m, 4 × CH_2CH_2), 3.68 (6 H, s, 2 × CO_2CH_3), 3.75 and 3.76 (each 3 H, s, 2 × CO_2CH_3), and 5.18 (2 H, dd, *J* 7.6 and 4.8 Hz, 2-H); *m/z* (f.d.) 357 (M^+ + 1, 100%).

(R,S)-*Dimethyl* 2-(2,6-*Dinitrobenzoyloxy*)*pentanedioate* (**55**).—A solution of (*R,S*)-dimethyl 2-hydroxypentanedioate (**50**) (51 mg, 0.29 mmol), 2,6-dinitrobenzoyl chloride (0.19 g, 0.82 mmol), and 4-dimethylaminopyridine (0.30 g, 2.46 mmol) in dichloromethane (10 ml) was stirred at reflux under argon for 48 h. The solution was then cooled to room temperature and the baseline material removed by chromatography (10 g; silica H), eluting with dichloromethane. The eluate was purified by p.l.c. (1 × 1 mm), eluting with ether–hexane (1:10), and the product finally recrystallised to give the 2,6-*dinitrobenzoate* (**55**) (81 mg, 76%) as needles, m.p. 101—102 °C (from dichloromethane–hexane) (Found: C, 45.2; H, 3.6; N, 7.6%; M^+, 370.0640. $C_{14}H_{14}N_2O_{10}$ requires C, 45.4; H, 3.8; N, 7.6%; *M*, 370.0648); $\nu_{max.}$(CH_2Cl_2) 1 750, 1 550, and 1 350 cm^{-1}; δ (90 MHz) 2.2—2.5 (4 H, complex m, CH_2CH_2), 3.60 and 3.79 (each 3 H, s, 2 × CO_2CH_3), 5.35 (1 H, t, *J* 5 Hz, 2-H), 7.75 (1 H, t, *J* 8 Hz, 4-ArH), and 8.35 (2 H, d, *J* 8 Hz, 3- and 5-ArH); *m/z* 371 (M^+ + 1, 0.2%), 370 (0.1, M^+), 339 (31), 311 (78), 195 (100, $C_7H_3N_2O_5^+$), and 175 (65, *M* − $C_7H_3N_2O_5$).

The (R)-2,6-*dinitrobenzoate* (0.33 g, 73%) and the (S)-2,6-*dinitrobenzoate* (0.43 g, 68%) were prepared by the same method as for the racemate from the (*R*)-alcohol (1.2 mmol) and the (*S*)-alcohol (1.7 mmol) as oils [Found: (*R*); C, 45.3; H, 3.8; N, 7.3; (*S*); C, 45.3; H, 3.9; N, 7.1. $C_{14}H_{14}N_2O_{10}$ requires C, 45.4; H, 3.8; N, 7.6%]; $[\alpha]_D^{18}$ (*R*), −12.2°; (*S*), +12.7° (*c* 7.4 in CH_2Cl_2).

(S)-*Bis*(4-*bromophenyl*) 2-(2,6-*Dinitrobenzoyloxy*)*pentanedioate* (**58**).—A two-phase solution of aqueous sodium hydroxide (0.1M; 3 ml) and (*S*)-dimethyl 2-(2,6-dinitrobenzoyloxy)pentanedioate (**55**) (38.6 mg, 104 μmol), in tetrahydrofuran (1 ml) was stirred vigorously at room temperature for 5 h. Ethyl acetate (5 ml) was added, followed by sodium chloride (1 g), after which the organic layer was separated and evaporated. A solution of the residue, dicyclohexylcarbodi-imide (0.12 g, 582 μmol), 4-dimethylaminopyridine (3 mg, 25 μmol), and 4-bromophenol (40 mg, 231 μmol) in dry tetrahydrofuran (5 ml) was stirred at room temperature under argon overnight. The solvent was evaporated and the residue extracted with acetone (5 ml). The acetone extract was purified firstly by p.l.c. (1 × 1 mm), eluting with ether and then by p.l.c. (1 × 1 mm), eluting with ether–hexane (1:3). Recrystallisation gave the (S)-4-*bromophenyl ester* (**58**) (30 mg, 44%) as needles, m.p. 136—138 °C (from tetrachloromethane) (Found: C, 44.1; H, 2.4; N, 4.3. $C_{24}H_{16}Br_2N_2O_{10}$ requires C, 44.2; H, 2.5; N, 4.3%); $\nu_{max.}$(CCl_4) 1 760, 1 600, 1 580, 1 550, 1 480, and 1 350 cm^{-1}; δ (250 MHz) 2.4—2.9 (4 H, complex m, CH_2CH_2), 5.80 (1 H, dd, *J* 6.6 and 5.4 Hz, 2-H), 6.95 (2 H, d, *J* 8.8 Hz, 2- and 6-ArH), 7.09 (2 H, d, *J* 8.9 Hz, 2- and 6-ArH), 7.45 (2 H, d, *J* 8.8 Hz, 3- and 5-ArH), 7.51 (2 H, d, *J* 8.9 Hz, 3- and 5-ArH), 7.86 (1 H, dd, *J* 8.7 and 7.7 Hz, 4-ArH), and 8.535 and 8.54 (each 1 H, d, *J* 8 Hz, 3- and 5-ArH); *m/z* (f.d.) 655, 653, and 651 (M^+ + 1, 10, 20, and 12%) and 654, 652, and 650 (80, 90, and 100, M^+); $[\alpha]_D^{20}$ +18° (*c* 0.4 in CH_2Cl_2).

(R,S)-5-*Oxotetrahydrofuran*-2-*carboxylic Acid* (**59**).—Sodium borohydride (0.4 g, 11 mmol) was added slowly to a solution of 2-oxopentanedioic acid (1 g, 6.8 mmol) in aqueous sodium hydroxide (25 ml, 25 mmol; 1M) stirred at room temperature. After 1 h the solution was brought to pH 2 with hydrochloric acid (2M) and evaporated. Bulb-to-bulb distillation (200 °C/ 0.3 mmHg) of the residue gave the (*R,S*)-lactone (**59**) (0.47 g, 53%) as an oil, b.p. 180—190 °C/0.3 mmHg (lit.,[37] 168—170 °C/1.5 mmHg); $\nu_{max.}$ 3 300—2 700, 1 790, 1 730, and 1 460 cm^{-1}; δ [90 MHz; $CDCl_3$–CD_3OD (10:1)] 2.1—2.8 (4 H, complex m, CH_2CH_2). 4.65 (1 H. br s, OH), and 5.0 (1 H, m, 2-H); *m/z* (f.d.) 131 (M^+ + 1, 90%), 130 (34, M^+), 102 (100, *M* − CO), and 85 (85, *M* − CO_2H).

(R,S)-4-*Bromophenyl* 5-*Oxotetrahydrofuran*-2-*carboxylate* (**61**).—A solution of the foregoing (*R,S*)-lactone (**59**) (100.2 mg, 0.77 mmol) and oxalyl chloride (5 ml) in dichloromethane (5 ml) was heated at reflux for 3 h. The solution was then cooled to room temperature and evaporated. After bulb-to-bulb distillation (100 °C/0.3 mmHg) the acid chloride was added to a solution of 4-dimethylaminopyridine (280 mg, 2.3 mmol) and 4-bromophenol (140 mg, 0.81 mmol) in dichloromethane (10 ml) stirred at room temperature. After 30 min the product was isolated by p.l.c. (1 × 1 mm), eluting with ether and recrystallised to give the (R,S)-*ester* (**61**) (167 mg, 76%) as needles, m.p. 112—113 °C (from methyl acetate–hexane) (Found: C, 46.1; H, 3.4%; M^+, 285.9668 and 283.9695. $C_{11}H_9BrO_4$ requires C, 46.3; H, 3.2%; *M*, 285.9665 and 283.9684); $\nu_{max.}$ 1 790, 1 740, 1 590, and 1 490 cm^{-1}; δ (250 MHz; CD_2Cl_2) 2.4—2.8 (4 H, complex m, CH_2CH_2), 5.18 (1 H, dd, *J* 7.5 and 6.3 Hz, 2-H), 7.17 (2 H, d, *J* 8.5 Hz, 2- and 6-ArH), and 7.56 (2 H, d, *J* 8.5 Hz, 3- and 5-ArH); *m/z* 286 and 284 (M^+, 3 and 3%), 174 and 172 (4 and 4, $C_6H_5BrO^+$), and 85 (100, $C_4H_5O_2^+$).

(R,S)-N-(4-*Bromophenyl*) 5-*Oxotetrahydrofuran*-2-*carboxamide* (**60**).—The (R,S)-*anilide* (**60**) (1.0 g, 46%) was obtained by the preceding method, from the (*R,S*)-lactone (**59**) (7.6 mmol), m.p. 146—147 °C (from dichloromethane–hexane) (Found: C, 46.7; H, 3.7; N, 5.0%; M^+, 284.9829 and 282.9853. $C_{11}H_{10}BrNO_3$ requires C, 46.5; H, 3.55; N, 4.9%; *M*, 284.9825 and 282.9844); $\nu_{max.}$ 3 405, 1 795, 1 695, 1 590, 1 525, and 1 485 cm^{-1}; δ (400 MHz) 2.45 and 2.70 (each 1 H, complex m, 3-CH_2), 2.62 (2 H, m, 4-CH_2), 4.96 (1 H, t, *J* 7.6 Hz, 2-H), 7.44 and 7.46 (each 2 H, d, *J* 9.1 Hz, 4 × ArH), and 8.18 (1 H, br s, NH); *m/z* 285 and 283 (M^+, 15 and 15%), 173 and 171 (9 and 9, $C_6H_5BrN^+$), and 85 (100, $C_4H_5O_2^+$).

(S)-4-*Bromophenyl* 5-*Oxotetrahydrofuran*-2-*carboxylate* (**61**).—*Method A*. The (S)-*ester* (**61**) (66 mg, 78%) was prepared by the same method as for the racemate from the (*S*)-lactone (**59**)[22] (0.3 mmol).

Method B. A solution of (*S*)-dimethyl 2-(2-nitrobenzoyloxy)pentanedioate (**56**) (103 mg, 0.36 mmol) in tetrahydrofuran (10 ml) and aqueous sodium hydroxide (1M; 10 ml) was stirred

vigorously at room temperature. After 70 h, hydrochloric acid (1M; 10 ml) was added and the solution evaporated. Bulb-to-bulb distillation (200 °C/0.3 mmHg) of the residue gave the lactone carboxylic acid (**59**). A solution of the lactone, 4-bromophenol (125 mg, 0.72 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol), and 1-cyclohexyl-3-(2-morpholinoethyl)-carbodi-imide methyl toluene-*p*-sulphonate (300 mg, 0.72 mmol) in dichloromethane (10 ml) was stirred overnight at room temperature. The product was isolated by p.l.c. (1 × 1 mm), eluting with ether and then recrystallised to give the (S)-*ester* (**61**) (26 mg, 29%) as needles, m.p. 117—119 °C (from methyl acetate–hexane) (Found: C, 46.4; H, 3.5%; M^+, 285.9674 and 283.9675. $C_{11}H_9BrO_4$ requires C, 46.3; H, 3.2%; *M*, 285.9664 and 283.9684); $[\alpha]_D^{20}$ +9.2° (*c* 0.9 in CH_2Cl_2).

The (R)-*ester* (**61**) (196 mg, 58%) was prepared by method B from (*R*)-dimethyl 2-(2-nitrobenzoyloxy)pentanedioate (**61**) (1.18 mmol) as needles, m.p. 118—119 °C (from methyl acetate–hexane) (Found: C, 46.3; H, 3.2%; M^+, 285.9664 and 283.9661. $C_{11}H_9BrO_4$ requires C, 46.3; H, 3.2% *M*, 285.9664 and 283.9684); $[\alpha]_D^{20}$ −10.0° (*c* 0.8 in CH_2Cl_2).

(S)-N-(4-*Bromophenyl*) 5-*Oxotetrahydrofuran*-2-*carboxamide* (**60**).—*Method A*. A solution of the (*S*)-lactone (**59**) (27 mg, 0.21 mmol), 4-bromoaniline (36 mg, 0.21 mmol), 4-dimethylaminopyridine (4 mg, 33 μmol), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodi-imide methyl toluene-*p*-sulphonate (100 mg, 0.24 mmol) in dichloromethane (20 ml) was stirred at room temperature. After 30 min the solution was washed with hydrochloric acid (2M; 3 × 50 ml) and evaporated. The residue was recrystallised from dichloromethane–hexane to give the (S)-*anilide* (**60**) (42 mg, 70%) as needles.

Method B. The (S)-*anilide* (**60**) (12 mg, 22%) was prepared from (*S*)-dimethyl 2-(2-nitrobenzoyloxy)pentanedioate (**56**) (0.19 mmol) by the same procedure as for the (*S*)-ester (**61**) (method B), m.p. 158—160 °C (from dichloromethane–hexane) (Found: C, 46.8; H, 3.8; Br, 27.65; N, 5.0%; M^+, 284.9808 and 282.9868. $C_{11}H_{10}BrNO_3$ requires C, 46.5; H, 3.55; Br, 28.1; N, 4.9%; *M*, 284.9824 and 282.9844); $[\alpha]_D^{20}$ −24.4° (*c* 4.1 in CH_2Cl_2).

Degradation of Protoporphyrin IX, *Dimethyl Ester* (**62**).—*Method A*. A solution of protoporphyrin IX, dimethyl ester (0.2 g, 0.34 mmol) in dichloromethane (20 ml) was cooled to −78 °C (solid CO_2–acetone bath) under nitrogen. Ozone (Wallace and Tiermann ozoniser, 30—35 l h^{-1} of oxygen at 210 V) was passed through the solution for 10 min, by which time the colour of the solution had changed from deep purple to pale green-brown. Nitrogen was then passed through whilst the solution was allowed to warm to room temperature. The solvent was evaporated, aqueous 100 vol. hydrogen peroxide (10 ml) and methanol (10 ml) were added and the mixture heated at reflux for 15 min. The solution was then cooled to room temperature, evaporated and a solution of diazomethane in ether added until the pale yellow colour persisted. Excess of diazomethane was destroyed with acetic acid (*ca.* 5 drops) and the solution evaporated. Bulb-to-bulb distillation (60 °C/0.1 mmHg) of the residue gave dimethyl succinate (42.7 mg, 43%) as an oil.

Method B. Method A was followed except that formic acid (10 ml) replaced the methanol and the time of reflux was reduced to 5 min. Dimethyl succinate (25.5 mg, 26%) was obtained.

Tritiated Compounds

N-(4-*Bromophenyl*)-5-*oxotetrahydro*[2-^{3}H]*furan*-2-*carboxamide* (**60**).—Sodium borohydride (1 μg, 0.02 μmol) was added to a solution of dimethyl 2-oxopentanedioate (0.1 mg, 0.6 μmol) in methanol (1 ml) and dichloromethane (1 ml) stirred at room temperature. After 5 min tritiated sodium borohydride (0.1 mg, 0.55 mCi, 209 mCi/mmol) was added and the solution was left at room temperature for 30 min. Sodium borohydride (1 mg, 0.026 mmol) was then added and the solution extracted with saturated aqueous sodium hydrogen carbonate (2 ml). The aqueous extract was back extracted with dichloromethane (1 ml) and the combined organic extracts evaporated.

A solution of the residue in tetrahydrofuran (10 ml) and aqueous sodium hydroxide (1M; 10 ml) was stirred vigorously at room temperature. After 3 h hydrochloric acid (1M; 10 ml) was added and the solution evaporated. Bulb-to-bulb distillation (200 °C/0.5 mmHg) of the residue gave the lactone carboxylic acid (**59**).

A solution of the lactone carboxylic acid, 4-dimethylaminopyridine (1 mg, 8.2 μmol), 4-bromoaniline (5 mg, 29 μmol), and *N*-methyl 1-cyclohexyl-3-(2-morpholinoethyl)carbodi-imidium toluene-*p*-sulphonate (30 mg, 70 μmol) in dichloromethane (20 ml) was stirred at room temperature for 1 h. The product was isolated by p.l.c. (1 × 0.25 mm), eluting with dichloromethane and further purified by p.l.c. (1 × 0.25 mm), eluting with ether to give the *tritiated anilide* (**60**) (60 μg, 38%; 0.31 μCi, 1.47 mCi/mmol) as an amorphous solid.

A portion of this product was diluted with unlabelled anilide (**60**) (27.9 mg). After four recrystallisations the activity was constant at 54% of the original activity.

8,13,18-*Triethyl*-3-{(4E,8E)-1-*hydroxy*-5,9,13-*trimethyl*-[1-^{3}H]*tetradecatrienyl*}-2,7,12,17-*tetramethyl*-21H,23H-*porphine* (**22**).—Sodium borohydride (4 μg, 0.1 μmol) was added to a solution of the porphyrin ketone (**21**) (0.67 mg, 0.97 μmol by u.v. assay, ε 181 000) in propan-2-ol (0.5 ml) and dichloromethane (0.5 ml) stirred in the dark at room temperature. After 10 min the solution was added to tritiated sodium borohydride (0.56 mg, 15 μmol, 100 mCi), stirred for 5 min, and then set aside in the dark at room temperature for 62 h before evaporation under reduced pressure. The residue was partitioned between dichloromethane (10 ml) and hydrochloric acid (2M; 10 ml), after which the organic layer was removed and evaporated. The product was purified by p.l.c. (1 × 1 mm), eluting with dichloromethane. Dichloromethane (10 ml) and methanol (10 ml) were added and the solution evaporated to remove exchangeable tritium and give the tritiated porphyrin alcohol (**22**) (0.55 mg, 82% by u.v. assay, ε 173 000; 190 μCi), which was resolved in the usual way as the camphanate.

The tritiated porphyrin alcohol (**22**) from the high R_F camphanate (0.26 mg, by u.v. assay; 66.3 μCi, 224 mCi/mmol) was derivatised without further purification by the procedure used for the unlabelled racemic porphyrin alcohol and the tritiated porphyrin 2-nitrobenzoate (**37**) (65.9 μCi) was degraded by method B. The product from the esterification with diazomethane was divided into two portions for the dilution analysis.

The first portion was diluted with unlabelled (*R*)-2-nitrobenzoate (**56**) (91.04 mg) and the mixture purified by p.l.c. (1 × 1 mm), eluting with dichloromethane and then p.l.c. (1 × 1 mm), eluting with ether (6.72 μCi). The *N*-(4-bromophenyl)-5-oxotetrahydrofuran-2-carboxamide was prepared from the dimethyl ester by the same procedure as for unlabelled material. Purification by p.l.c. (1 × 1 mm), eluting with dichloromethane and then p.l.c. (1 × 1 mm), eluting with ether gave the *anilide* (**60**) (34.92 mg, 44%; 3.10 μCi, 25.3 mCi/mmol).

The other portion was diluted with the (*S*)-2-nitrobenzoate (**56**) (90.91 mg) and purified by p.l.c. (7.60 μCi). This was converted into the anilide (**60**) (34.42 mg, 43%; 3.09 μCi, 25.5 mCi/mmol).

The tritiated porphyrin alcohol (**22**) from the low R_F camphanate (0.26 mg by u.v. assay, estimated ε 175 000; 65.7 μCi, 222 mCi/mmol) gave the tritiated porphyrin 2-nitrobenzoate (**37**) (64.3 μCi), which was degraded by method B. The

product from the esterification with diazomethane was divided into two portions for the dilution analysis.

The first portion was diluted with unlabelled (*R*)-2-nitrobenzoate (**56**) (74.45 mg) and purified by p.l.c. (1.26 μCi). This was converted into the anilide (**60**) (12.97 mg, 20%; 0.261 μCi, 5.71 mCi/mmol).

The other portion was diluted with unlabelled (*S*)-2-nitrobenzoate (**56**) (87.41 mg) and purified by p.l.c. (1.25 μCi). This was converted into the anilide (**60**) (18.21 mg, 24%; 0.296 μCi, 4.62 mCi/mmol).

All four samples of tritiated anilide were recrystallised to constant activity from dichloromethane–hexane (see Table 2).

Acknowledgements

We thank F. Hoffmann-La Roche, Switzerland for the gift of (*E,E*)-farnesylacetone. Dr. D. A. Lewton for the early work on the indicated experiments, and the S.E.R.C. for a studentship (to K. S. C.) and for financial support.

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Received 16*th September* 1985; *Paper* 5/1589