Biosynthesis of porphyrins and related macrocycles. Part 45.[1,2] Determination by a novel X-ray method of the absolute configuration of the spiro lactam which inhibits uroporphyrinogen III synthase (cosynthetase)

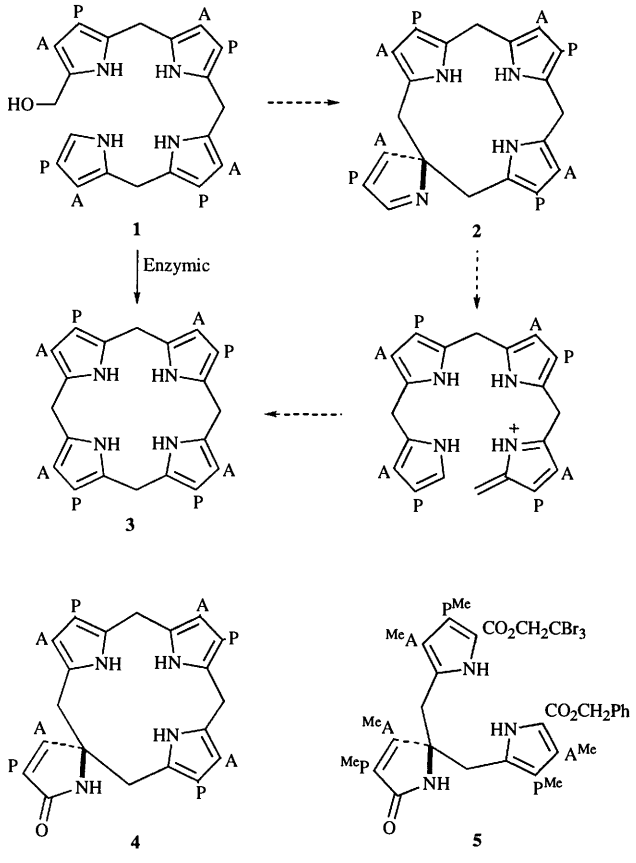
Alan C. Spivey,[a] Alfredo Capretta,[a] Christopher S. Frampton,[b] Finian J. Leeper[a] and Alan R. Battersby*,[a]

[a] *University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*
[b] *Roche Products Ltd., 40 Broadwater Road, Welwyn Garden City, Herts AL7 3AY, UK*

A novel approach, involving X-ray analysis of a specifically designed racemate, in combination with correlations by circular dichroism, allows the absolute configuration of the spiro lactam 4 to be determined. The outcome is that the enantiomer of this lactam which strongly inhibits uroporphyrinogen III synthase (cosynthetase) has the *R*-configuration and the implications of this finding are briefly discussed.

The enzyme cosynthetase (systematically uroporphyrinogen III synthase, E.C. 4.2.1.75) converts hydroxymethylbilane **1** into uroporphyrinogen III **3** (shortened to uro'gen III), a surprising process which involves intramolecular rearrangement of ring D.[3] Uro'gen III is the parent macrocycle for the biosynthesis of haem, chlorophyll and vitamin B_{12}. The preceding paper[1] outlined possible mechanisms for this rearrangement and one attractive idea is shown in Scheme 1. This involves the spiro pyrrolenine† **2** as a key intermediate *en route* to uro'gen III **3**. Support for this proposal came from the synthesis of the racemic‡ spiro lactam[4] **4** which acted as a strong competitive inhibitor of cosynthetase. Subsequently both enantiomers‡ of the spiro lactam **4** were synthesised separately[1,5] and one enantiomer inhibited cosynthetase much more strongly than the other. This result added further strength to the view that cosynthetase makes use of the spiro pyrrolenine **2** in its mechanism of action. One final piece of information, the absolute configuration of the inhibitory spiro lactam **4**, remained outstanding.

The enantiomeric spiro lactams **4** were synthesised[1] from the two enantiomers of the intermediate lactam **5**. It was the enantiomer showing a negative Cotton effect in its circular dichroism (CD) spectrum which afforded the strongly inhibiting enantiomer of the spiro lactam **4**. The problem thus becomes that of determining the absolute configuration of this enantiomer of the dipyrrolic lactam **5**. The present paper describes the solution of that problem by novel use of X-ray crystallography in combination with correlations by CD.



Scheme 1 A = CH_2CO_2H, P = $CH_2CH_2CO_2H$, A^{Me} = CH_2CO_2Me, P^{Me} = $CH_2CH_2CO_2Me$

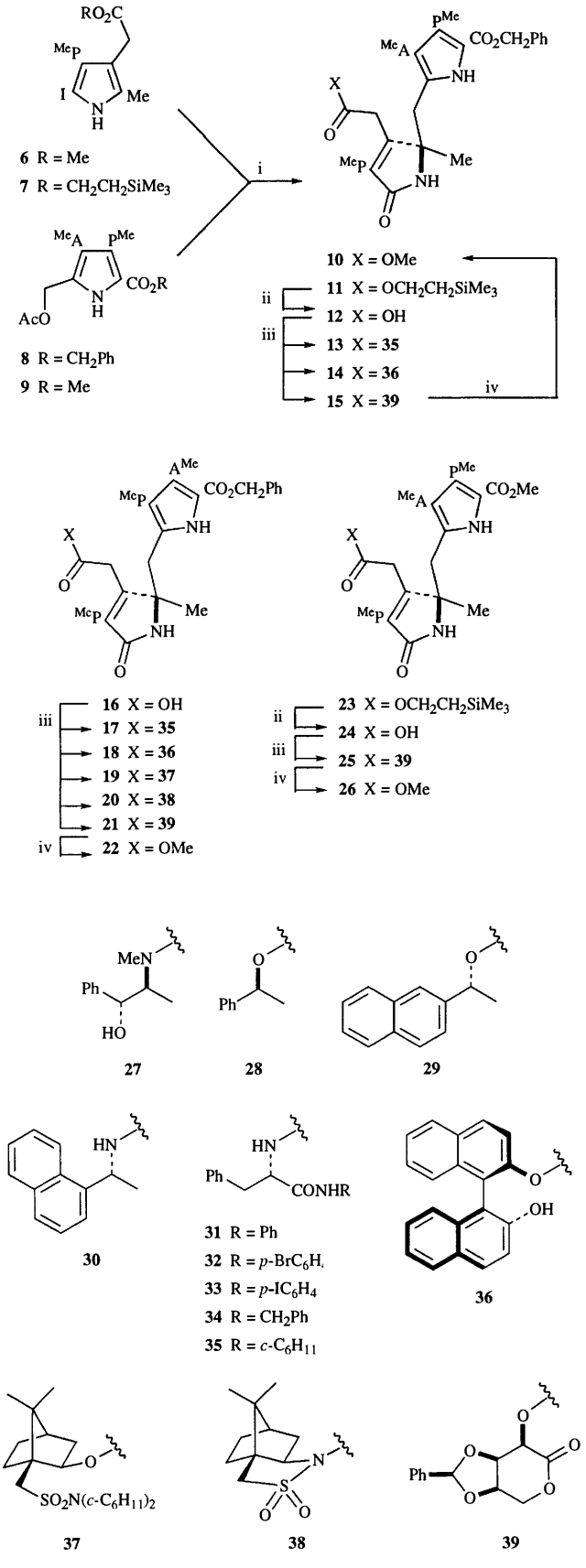
Results and discussion

Determination of the absolute configuration of lactam 10 by X-ray crystallography

The most direct route for solving the problem of the absolute configuration of lactam **5** would be to prepare a crystalline derivative carrying a chiral auxiliary of known configuration for standard X-ray analysis. Alternatively, a suitable partner could be attached to allow the Bijvoet method (anomalous dispersion) to be used. Some of these attempts were mentioned in the foregoing paper[1] and other substances prepared for exploration of these approaches will be recorded in the experimental section of a forthcoming paper on synthetic work.[6] Brevity is appropriate since none of these many experiments afforded crystalline materials. We became convinced we were working with a family of compounds which were inherently difficult to crystallise.

Attention therefore focused on monopyrrolic lactams such as **10**, especially since related work[7] yielded excellent crystals of a racemic member of this series. Both the racemic lactam[4] **10** and the racemic mono-acid[1] **16** (having the side-chains on the pyrrole reversed) had previously been synthesised (Scheme 2),

† IUPAC name: 2*H*-pyrrole.
‡ The structures throughout show only one of these two mixed (racemate) or separated enantiomers.



Scheme 2 *Reagents:* i, $SnCl_4$ then AgOAc, H_3O^+; ii, $Bu_4N^+F^-$; iii, $Me_2C{=}CClNMe_2$ then HX; iv, MeO^-, MeOH

the key reaction being the reaction of an α-iodopyrrole (*e.g.* **6** or **7**) with an α-acetoxymethylpyrrole (*e.g.* **8**, **9** or **8** with the A^{Me} and P^{Me} groups interchanged); an improved procedure and work-up for this reaction (see Experimental section) has now given much improved yields. Two closely related mono-acids **12** (from **7** and **8**) and **24** (from **7** and **9**) were similarly synthesised.

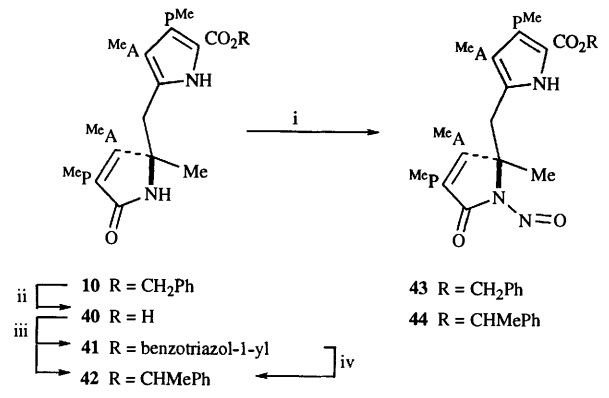
A free acetic acid residue had been built into lactams **12**, **16** and **24** so that a range of chiral auxiliaries could be attached through an ester or amide link. This generated two diastereoisomers and their separation by preparative thin layer chromatography (PLC) and high pressure liquid chromatography (HPLC) was then studied. The thirteen chiral auxiliaries **27**–**39** were all individually attached to monoacid **16**, ten (**28**–**31** and **34**–**39**) were attached to **12** and three (**28**, **29** and **39**) were attached to **24**. Out of these 26 pairs of diastereoisomers, successful separations were achieved in nine cases (compounds **13**–**15**, **17**–**21** and **25**) and in each case both diastereoisomers were fully characterised. However, only one of these 18 diastereoisomers could be induced to crystallise, amide **17**, derived from monoacid **16** and (*S*)-phenylalanine cyclohexyl amide. Unfortunately, its crystalline form (long thin needles) was unsuitable for X-ray analysis and this form persisted despite strenuous efforts to find conditions that would produce a different form. Also, modification of the structure, *e.g.* by changing its benzyl ester into the corresponding *p*-bromophenacyl ester, did not lead to suitable crystals.

We therefore concentrated on the three pairs of diastereoisomers prepared from 3,4-*O*-benzylidene-D-ribonic δ-lactone (**15**, **21** and **25**) which were separable on a preparative scale by PLC. That essentially complete separation (> 98% de) had been achieved in all three cases was demonstrated by ^1H NMR analysis. The chiral auxiliary could be smoothly cleaved by treatment of each of the diastereoisomers of **15**, **21** and **25** with methoxide in methanol to provide the pure enantiomers of the lactams **10**, **22** and **26**. However, none of these pure enantiomers was crystalline.

The next steps in our studies were guided by parallel work, directed to a different end, which had shown that the *N*-nitroso derivative **43** of racemic lactam **10** gave crystals suitable for a successful structure determination by X-ray analysis.[8] Accordingly, the pure enantiomers of **10** were *N*-nitrosated but the resultant enantiomers of **43** had totally different solubility properties compared to those of the racemic material and they remained amorphous. It appeared that some critical interaction between the packed molecules of opposite enantiomers led to lattice formation giving good crystals from the racemic lactam but that this interaction was lacking with the pure enantiomers. We therefore planned to cleave the benzyl ester from **10** and prepare a racemic diastereoisomeric derivative of the acid **40** using a chiral auxiliary of known configuration. We would know which resolved sample of **40** was combined with which enantiomer of the chiral auxiliary.

Cleavage of the benzyl esters from the pure enantiomers, **(+)-10** and **(−)-10** gave acids **40** (Scheme 3).§ The enantiomer derived from **(+)-10** was esterified with (*S*)-1-phenylethanol, of established absolute configuration,[9] to give lactam **(+)-42a**, whilst the other enantiomer, from **(−)-10**, was esterified with (*R*)-1-phenylethanol to give lactam **(−)-42a**, the opposite enantiomer of the *same* diastereoisomer. Each esterification was carried out by activation of the carboxy group using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), a process believed to proceed with retention of configuration for the amine component in peptide bond formation[10] and therefore expected also to proceed with retention of configuration of the alcohol component during ester formation. Independent evidence for retention of configuration in our esterification procedure was provided by isolation of an activated form of the carboxylic acid, benzotriazolyl ester[11] **(−)-41** derived from **(−)-10**. This benzotriazolyl ester reacted with (*R*)-1-phenylethanol to yield

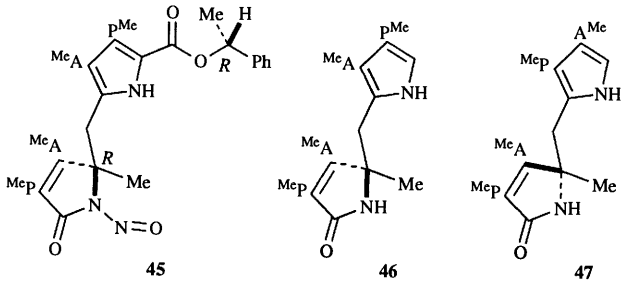
§ Enantiomers are distinguished by prefixes (+)- and (−)-, which refer to the sign of the Cotton effect at *ca.* 280 nm. Diastereoisomers are distinguished by suffixes **a** and **b**, here and in the Experimental section.



Scheme 3 *Reagents:* i, N_2O_4, NaOAc; ii, H_2, Pd/C; iii, benzotriazol-1-yl-O-P(NMe$_2$)$_3$$^+PF_6$$^-$, PhCHOHMe, Pr$^i_2$NEt; iv, PhCHOHMe, DMAP

the same diastereoisomer (−)-**42a** as had been produced by the foregoing 'one-pot' esterification method.

The two enantiomeric esters, (+)- and (−)-**42a**, were mixed in equimolar amounts to give racemic **42a** (one diastereoisomer) which was then *N*-nitrosated to give nitrosolactam **44a**. This product crystallised well in a form suitable for X-ray analysis, which showed it to have the configuration **45** (plus its



enantiomer).¶ This has the *N*-nitroso lactam having the *R*-configuration coupled to the 1-phenethyl residue of *R*-configuration. It was thus proved that the enantiomer (−)-**10**, which was the one esterified with (*R*)-1-phenylethanol after hydrogenolysis, has the *R*-configuration shown in Scheme 3. As far as we are aware, this represents a novel method for determination of an absolute configuration, by obtaining the crystal structure of a racemate in this way. It is very often true that a racemate is more crystalline than the pure enantiomers and so this should be a valuable approach in many cases.

For completeness, the alternative diastereoisomer **42b** was prepared by hydrogenolysis of enantiomer (+)-**10** followed by esterification with (*R*)-1-phenylethanol and hydrogenolysis of enantiomer (−)-**10** followed by esterification with (*S*)-1-phenylethanol. The two enantiomeric products, (+)- and (−)-**42b**, were then mixed to give the racemate. In contrast to the previous case, the *N*-nitroso derivative **44b** derived from this diastereoisomer of **42** failed to crystallise.

Correlation of the configurations of lactams 5 and 10 by circular dichroism

The rigorous determination of the absolute configuration of the monopyrrolic lactam **10** was the starting point for correlations by CD which then established the absolute configuration of the dipyrrolic lactam **5** as follows. The CD spectrum of the (*R*)-lactam **10** showed a negative Cotton-effect peak at 285 nm, essentially the mirror image of the CD curve from the (*S*)-

¶ The basic crystallographic data for this compound are recorded in ref. 2.

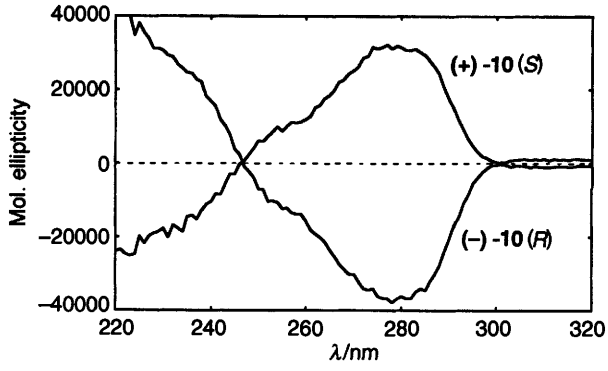


Fig. 1 Circular dichroism spectra of enantiomers (+)-**10** (*S*) and (−)-**10** (*R*)

enantiomer (Fig. 1).‖ These CD peaks appear at the wavelength at which pyrrole α-carboxylic esters absorb, whereas alkylated pyrroles lacking conjugation to a carbonyl group (ester, ketone, aldehyde) show no appreciable absorption above *ca.* 220 nm. Accordingly, the (*R*)-lactam **10** was converted by standard steps *via* acid **40** into the α-free pyrrole (*R*)-**46**, which, as expected, showed no peak in its CD spectrum above 220 nm.** The (*S*)-enantiomer of the isomer **22**, having the reversed substitution pattern on the pyrrole ring relative to **10**, was similarly converted into the decarboxylated system (*S*)-**47**. As for the previous case, the CD curve of this product ran along the baseline. These results prove that (i) the negative peak at 285 nm in CD spectrum of lactam **10** depends on the presence of the pyrrolic carboxylic ester residue; (ii) an α-free pyrrolylmethyl group attached to a chiral centre, as in **46** or **47**, is equivalent to a non-absorbing methyl group for CD measurements at *ca.* 285 nm.

The foregoing results allowed correlation of the monopyrrolic with the dipyrrolic series. It was the lactam **5x** (derived from peak **X** of the HPLC separation in ref. 1 and numbered **40a** there) which yielded the enantiomer of the spiro lactam **4** causing strong inhibition of cosynthetase. Either of the two pyrrolyl ester chromophores of this lactam **5x** can be eliminated from the CD analysis by deprotection of the appropriate carboxy group followed by decarboxylation. First, the benzyl group of **5x** was cleaved [13] to give the acid **48x**, which was decarboxylated yielding the α-free pyrrole **49x**; the tribromoethyl group was removed in a second experiment to afford the acid **50x** from which the α-free pyrrole **51x** was obtained by decarboxylation. As expected, the CD spectra of the two α-free pyrroles **49x** and **51x** resembled mirror images of each other (Fig. 2) because these substances are enantiomeric apart from the slightly differing substitution patterns on their pyrrolic rings. The pyrrolic lactam **49x** showed a negative CD peak at 285 nm whereas **51x** gave a positive peak.††

It was demonstrated above that the α-free lactam **49** is equivalent, for purposes of CD measurements, to the monopyrrolic lactam **10**. Since it was the illustrated *R*-enantiomer of **10** which showed the negative CD peak, it

‖ A simpler example of a monopyrrolic lactam similar to **10** which also shows a negative Cotton effect has recently been assigned the *R*-configuration by X-ray analysis (ref. 12).

** CD spectra of compounds **5x**, **5y**, (−)-**10**, (+)-**10**, **13b**, **13a**, **14b**, **14a**, **15b**, **15a**, **17b**, **17a**, **18b**, **18a**, **19b**, **19a**, **20b**, **20a**, **21b**, **21a**, (−)-**22**, (+)-**22**, **25b**, **25a**, (−)-**26**, (+)-**26**, (−)-**41**, (+)-**41**, (−)-**42b**, (+)-**42b**, (−)-**42a**, (+)-**42a**, (−)-**43**, (+)-**43**, (*R*)-**46**, (*S*)-**46**, (*S*)-**47**, **49x**, **49y**, **51x** and **51y** are available as supplementary data (Suppl. No. 57159) from the British Library. For details of the Supplementary Publications Scheme, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.

†† Starting with opposite enantiomer **5y** as the dipyrrolic lactam, the enantiomers **49y** and **51y** of the above products were prepared by the same steps. These substances **49y** and **51y** showed CD spectra which were the mirror images of those illustrated in Fig. 2.

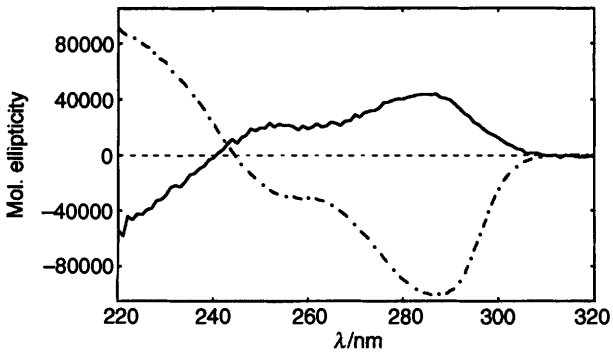
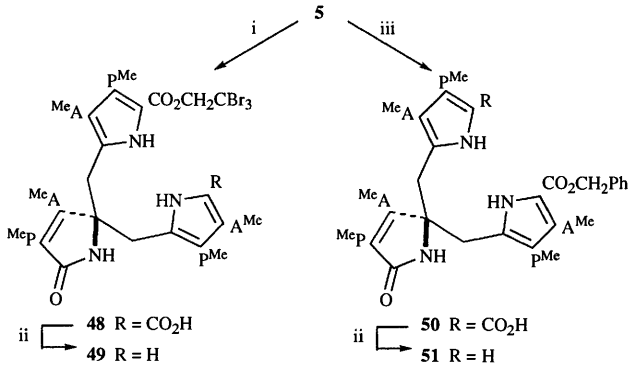


Fig. 2 Circular dichroism spectra of pyrrolylmethyl lactams **49x** (-·--·-) and **51x** (——) derived from the same enantiomer **5x**

follows that the dipyrrolic lactam **49x**, also giving a negative CD curve, has this same configuration with respect to the pyrrolic ester chromophore. The absolute configuration of this enantiomer **49x** is thus as illustrated in Scheme 4 and **5x** and



Scheme 4 *Reagents:* i, $AlCl_3$, PhOMe; ii, TFA; iii, Zn, AcOH

48x, which have been correlated with **49x**, also have the same configuration.

Finally, cosynthetase was strongly inhibited by that enantiomer of the spiro lactam which was synthesised from the illustrated *R*-enantiomer **5** of the dipyrrolic lactam and, therefore, the inhibiting spiro lactam has the configuration illustrated in structure **4**; this enantiomer has the *R*-configuration at the chiral centre.

The sum of all the evidence reported here and in earlier papers[1,5] strongly supports the spiro pyrrolenine **2** as an intermediate for the biosynthesis of uro'gen III **3** and indeed if **2** is formed, the evidence in this paper points to its absolute configuration being as shown in Scheme 1. This information will be of great interest when the structure of cosynthetase can be determined by X-ray analysis. This possibility has been brought nearer by the overproduction and purification[14] of cosynthetase from *Bacillus subtilis* and the finding that the enzyme from this source is substantially more stable than the previously studied rather fragile cosynthetases from other sources.

Experimental

General directions

General directions are as given in Parts 34[15] and 44[1] of this series. Additionally, (*R*)-(+)-1-phenylethanol, (*S*)-(−)-1-phenylethanol, (*R*)-(+)-1,1′-bi-2-naphthol, (−)-10-(*N*,*N*-dicyclohexylsulfamoyl)-D-isoborneol, (−)-3,4-*O*-benzylidene-D-ribonic δ-lactone, (2*S*)-(+)-10,2-camphorsultam and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate were purchased from Aldrich, Fluka or Sigma. CD spectra were recorded in MeCN with a Jobin-Yvon Dichrograph CD6 using 10 mm quartz cuvettes.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-3-(2-trimethylsilylethoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 11

A solution of 3-(2-methoxycarbonylethyl)-5-methyl-4-(2-trimethylsilylethoxycarbonylmethyl)pyrrole-2-carboxylic acid[1] (2.0 g, 5.42 mmol) in dichloromethane (30 cm^3) was stirred vigorously with a solution of sodium hydrogen carbonate (1.35 g, 16.07 mmol) in water (25 cm^3) under argon. An aqueous solution (60 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was then added over 5 min and after a further 2 min solid sodium metabisulfite was added to destroy the excess iodine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried and evaporated to yield the crude α-iodopyrrole **7** as an oil.

A stirred solution of this α-iodopyrrole and acetoxymethylpyrrole **8**[16] (2.28 g, 5.42 mmol) in anhydrous dichloromethane (50 cm^3) was cooled to −78 °C under argon, treated dropwise with stannic chloride (698 mm^3, 5.96 mmol) and then allowed to warm to 0 °C over 3 h. Saturated aqueous sodium hydrogen carbonate (5 cm^3) was added, the mixture was stirred for a further 10 min and then saturated aqueous EDTA disodium salt (50 cm^3) was added. The organic layer was separated and evaporated. A solution of the residual oil in tetrahydrofuran (100 cm^3) and water (100 cm^3) was stirred with toluene-*p*-sulfonic acid (1.5 g, 8.7 mmol) and silver acetate (250 mg, 1.5 mmol) under argon for 13 h, then treated with saturated aqueous EDTA disodium salt (400 cm^3) and extracted with ethyl acetate (4 × 150 cm^3). The combined extracts were dried and evaporated. Flash chromatography on silica, eluting with diethyl ether then diethyl ether–ethyl acetate (1:1), gave the *lactam* **11** as an oil (2.16 g, 57%) (Found: MH^+, 713.3108. $C_{36}H_{48}N_2O_{11}Si$ requires *M* + *H*, 713.3105); $\lambda_{max}(CH_2Cl_2)$/nm 280; $\delta_H(CDCl_3$, 400 MHz) 0.03 (9 H, s, $SiMe_3$), 1.02 (2 H, t, *J* 9, CH_2Si), 1.33 (3 H, s, 4-Me), 2.39–2.66 (6 H, m, CH_2CH_2 and CH_2CH_2), 2.75 (1 H, d, *J* 15, 5-CH_AH_B), 2.91–2.99 (3 H, m, CH_2CH_2 and 5-CH_AH_B), 3.28 and 3.61 (each 1 H, d, *J* 17, CH_2CO_2), 3.33 and 3.54 (each 1 H, d, *J* 16, CH_2CO_2), 3.58, 3.60 and 3.71 (each 3 H, s, OMe), 4.22 (2 H, t, *J* 9, CH_2CH_2Si), 5.19 and 5.29 (each 1 H, d, *J* 12, CH_2Ph), 7.02 (1 H, s, lactam-NH), 7.26–7.39 (5 H, m, Ph) and 10.15 (1 H, s, pyrrole-NH); $\delta_C(CDCl_3$, 100 MHz) −1.55 ($SiMe_3$), 17.29 (CH_2Si), 19.76 and 20.47 (2 × $CH_2CH_2CO_2$), 24.40 (4-Me), 29.64, 30.75, 31.27, 33.35 and 34.74 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5), 51.35, 51.45 and 52.39 (3 × OMe), 62.95 (CH_2CH_2Si), 64.52 and 65.62 (C-4 and $PhCH_2$), 115.26, 118.04, 127.91, 128.13 (2 C), 128.36 (2 C), 129.32, 129.79, 136.13, 136.25 and 150.45 (C=C), 160.35 (α-CO_2) and 171.03, 171.22, 173.45, 173.51 and 173.67 (4 × CO_2 and CONH); *m*/*z* (+FAB) 713 (MH^+, 75%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-3-carboxymethyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 12

A solution of the trimethylsilylethyl ester **11** (255 mg, 0.36 mmol) in tetrahydrofuran (5 cm^3) was stirred with tetrabutylammonium fluoride trihydrate (112 mg, 0.43 mmol) under argon at room temperature for 40 min, then diluted with water (10 cm^3), adjusted to a pH between 3.0 and 3.5 with dilute sulfuric acid and extracted with dichloromethane (2 × 20 cm^3). The combined organic extracts were dried and evaporated. The residual gum was crystallised from dichloromethane–diethyl ether–hexane to give the *acid* **12** (140 mg, 64%), mp 112–114 °C (Found: MH^+, 613.2362. $C_{31}H_{36}N_2O_{11}$ requires *M* + *H*, 613.2397); $\delta_H(CDCl_3$, 400 MHz) 1.31 (3 H, s, CMe), 2.39–2.60 (6 H, m, CH_2CH_2 and CH_2CH_2), 2.76 and 3.07 (each 1 H, d, *J* 15, 5-CH_2), 2.90 (2 H, t, *J* 8, CH_2CH_2), 3.34 and 3.47 (each 1 H, d, *J* 16, CH_2CO_2), 3.39 and 3.57 (each 1 H, d, *J* 17, CH_2CO_2), 3.57, 3.58, 3.65 (each 3 H, s, OMe), 5.23 (2 H, s, CH_2Ph), 7.26–

7.36 (5 H, m, Ph), 7.48 (1 H, br s, lactam-NH) and 10.48 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.74 and 20.74 (2 × $CH_2CH_2CO_2$), 23.32 (4-Me), 29.65, 30.92, 31.26, 33.44 and 34.83 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.45, 51.56 and 52.34 (OMe), 64.05 and 65.18 (C-4 and CH_2Ph), 115.70, 118.02, 128.14 (3 C), 128.55 (2 C), 129.87, 130.16, 135.22, 135.93 and 151.86 (C=C), 161.38 (α-CO_2) and 172.15, 173.29, 173.50, 173.57 and 173.64 (4 × CO_2 and CONH); *m/z* (+FAB) 613 (MH^+, 25%), 372 ($C_{20}H_{22}NO_6^+$, 30), 242 (70) and 154 (100).

Methyl 5-acetoxymethyl-2-methoxycarbonyl-4-methoxycarbonylmethylpyrrole-3-propionate 9

A solution of 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylic acid [17] (1.00 g, 3.53 mmol) in methanol (8 cm^3) and dichloromethane (8 cm^3) was stirred with a solution of dicyclohexylcarbodiimide (909 mg, 4.41 mmol) in methanol (2 cm^3) at room temperature under an atmosphere of argon for 90 min, then filtered and evaporated. The residue was purified by chromatography on a short silica column, eluting with ethyl acetate–hexane (1 : 1), to give the methyl ester (786 mg, 75%), mp 90–92 °C (from diethyl ether) (Found: MH^+, 298.1262. $C_{14}H_{19}NO_6$ requires *M* + *H*, 298.1234); δ_H($CDCl_3$, 250 MHz) 2.20 (3 H, s, 5-Me), 2.53 and 2.98 (each 2 H, t, *J* 8, CH_2CH_2), 3.35 (2 H, s, CH_2CO_2), 3.63, 3.64 and 3.80 (each 3 H, s, OMe) and 9.15 (1 H, br s, NH); *m/z* (+FAB) 298 (MH^+, 100%) and 266 (85).

A solution of this pyrrole (1.25 g, 4.21 mmol) in dry dichloromethane (20 cm^3) at 0 °C was stirred with freshly distilled sulfuryl chloride (0.35 mg, 4.40 mmol) under argon for 1 h and then evaporated. A solution of the residue in glacial acetic acid (20 cm^3) was stirred with sodium acetate (1.00 g) at 70 °C for 1 h, then cooled, poured into water (500 cm^3) and extracted with dichloromethane (4 × 50 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3) followed by water (100 cm^3), dried and evaporated. Recrystallisation from dichloromethane–diethyl ether–hexane gave the acetoxymethylpyrrole **9** (1.195 g, 80%), mp 123–125 °C; δ_H($CDCl_3$, 250 MHz) 2.03 (3 H, s, Ac), 2.53 and 2.97 (each 2 H, t, *J* 8, CH_2CH_2), 3.52 (2 H, s, CH_2CO_2), 3.62, 3.64 and 3.81 (each 3 H, s, OMe), 5.03 (2 H, s, CH_2O) and 9.15 (1 H, br s, NH).

9-Methoxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-3-(2-trimethylsilylethoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 23

A solution of 3-(2-methoxycarbonylethyl)-5-methyl-4-(2-trimethylsilylethoxycarbonylmethyl)pyrrole-2-carboxylic acid [1] (340 mg, 0.92 mmol) in dichloromethane (5.4 cm^3) was stirred vigorously with a solution of sodium hydrogen carbonate (232 mg, 2.76 mmol) in water (4.1 cm^3) under argon and an aqueous solution (9.21 cm^3) of iodine (0.1 mol dm^{-3}) and potassium iodide (0.2 mol dm^{-3}) was added over 5 min. The mixture was stirred for a further 2 min then solid sodium metabisulfite was added to destroy the excess iodine. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were dried and evaporated. Flash chromatography on silica eluting with diethyl ether–hexane (1 : 1), gave the α-iodopyrrole **7** (294 mg, 0.65 mmol) as an oil.

A stirred solution of this α-iodopyrrole **7** and acetoxymethylpyrrole **9** (220 mg, 0.65 mmol) in anhydrous dichloromethane (20 cm^3) at 0 °C under argon was treated dropwise with stannic chloride (78 mm^3, 0.66 mmol) and then after 30 min with saturated aqueous sodium hydrogen carbonate (10 cm^3). After a further 10 min, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried and evaporated. A solution of the residual oil in tetrahydrofuran (8.4 cm^3) and water (840 μl) was stirred with toluene-*p*-sulfonic acid (172 mg, 0.9 mmol) and silver acetate (57 mg, 0.34 mmol) under argon for 13 h, then diluted with water (40 cm^3) and extracted with dichloromethane (4 × 40 cm^3). The combined extracts were dried and evaporated. The residue was filtered through a short column of silica eluting with ethyl acetate and then purified by preparative TLC, eluting with ethyl acetate, to give the *lactam* **23** as an oil (152 mg, 26%); δ_H($CDCl_3$, 250 MHz) 0.04 (9 H, s, Me_3Si), 1.04 (2 H, t, *J* 9, CH_2Si), 1.33 (3 H, s, 4-Me), 2.42–2.67 (6 H, m, CH_2CH_2 and CH_2CH_2), 2.75 and 2.96 (each 1 H, d, *J* 15, 5-H_2), 2.93–2.99 (2 H, m, CH_2CH_2), 3.29 and 3.59 (each 1 H, d, *J* 17, CH_2CO_2), 3.33 and 3.55 (each 1 H, d, *J* 16, CH_2CO_2), 3.62, 3.63, 3.71 and 3.76 (each 3 H, s, OMe), 4.26 (2 H, t, *J* 9, CH_2CH_2Si), 7.02 (1 H, s, lactam-NH) and 10.03 (1 H, s, pyrrole-NH); *m/z* (+FAB) 637 (MH^+, 40%) and 296 (100).

3-Carboxymethyl-9-methoxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 24

A solution of the trimethylsilylethyl ester **23** (100 mg, 0.157 mmol) in tetrahydrofuran (1 cm^3) was stirred with tetrabutylammonium fluoride trihydrate (130 mg, 0.50 mmol) under argon at room temperature for 40 min, then diluted with water (6 cm^3), adjusted to a pH of 3.0–3.5 with dilute sulfuric acid and extracted with dichloromethane (2 × 5 cm^3). The combined organic extracts were dried and evaporated and the residue was crystallised from dichloromethane–hexane to give the *acid* **24** (57 mg, 68%), mp 137–139 °C (Found: MH^+, 537.2083. $C_{25}H_{32}N_2O_{11}$ requires *M* + *H*, 537.2082); δ_H(CD_3OD, 400 MHz) 1.34 (3 H, s, 4-Me), 2.37–2.58 (6 H, m) and 2.90 (2 H, m, 2 × $CH_2CH_2CO_2$), 2.88 and 2.98 (each 1 H, d, *J* 15, 5-H_2), 3.30 (2 H, s, CH_2CO_2), 3.47 and 3.56 (each 1 H, d, *J* 16, CH_2CO_2) and 3.62, 3.62, 3.70 and 3.77 (each 3 H, s, OMe); δ_C(CD_3OD, 100 MHz) 20.6 and 20.7 ($CH_2CH_2CO_2$), 24.3 (4-Me), 30.1, 32.5, 33.6, 35.8 and 35.8 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.8, 52.0 (2 C) and 52.7 (OMe), 65.2 (C-4), 115.1, 116.7, 118.2, 131.2, 132.3 and 134.5 (C=C), 157.1 (α-CO_2) and 174.4, 175.1, 175.2 (2 C), 175.4 (4 × CO_2 and CONH); *m/z* (+FAB) 537 (MH^+, 4%), 460 (8), 307 (87) and 242 (100).

9-Benzyloxycarbonyl-3-{[(*S*)-1-(cyclohexylaminocarbonyl)-2-phenylethylamino]carbonylmethyl}-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 13a and 13b

A suspension of acid **12** (100 mg, 0.163 mmol) in dry dichloromethane (5 cm^3) was stirred with 1-chloro-1-dimethylamino-2-methylpropene [18] (60 mg, 0.48 mmol) under argon for 10 min. The resulting solution was then added dropwise to a solution of (*S*)-(−)-phenylalanine cyclohexylamide (200 mg, 0.813 mmol) in dichloromethane (5 cm^3). The solution was stirred for 6 h under argon and then evaporated. The residue was purified by preparative TLC, eluting with ethyl acetate, to give the following products.

(i) At higher R_f, *lactam* **13a** (36 mg, 27%) as an amorphous solid (Found: MH^+, 841.4085. $C_{46}H_{56}N_4O_{11}$ requires *M* + *H*, 841.4024); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (−8); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 0.95–1.88 (10 H, m, cyclohexyl), 1.39 (3 H, 4-Me), 2.49–2.73 (7 H, m, $CH_2CH_2CO_2$, $CH_2CH_2CO_2$ and 5-H_A), 2.96 (1 H, d, *J* 15, 5-H_B), 3.04–3.14 (4 H, m, $CH_2CH_2CO_2$ and $CHCH_2Ph$), 3.31 and 3.67 (each 1 H, d, *J* 16, CH_2CO_2), 3.41 and 3.65 (each 1 H, d, *J* 16, CH_2CO_2), 3.69 (6 H, s, 2 × OMe), 3.7 (1 H, m, NHC*H*), 3.82 (3 H, s, OMe), 4.68 (1 H, m, NHC*H*CO), 5.33 and 5.43 (each 1 H, d, *J* 13, CH_2Ph), 5.73 (1 H, br m, amide-NH), 7.14–7.53 (12 H, m, 2 × Ph and lactam- and amide-NH) and 10.75 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.19 and 19.65 ($CH_2CH_2CO_2$), 24.54 (4-Me), 24.63 (2 C), 25.28, 29.72, 31.38, 32.42, 32.53, 32.59, 33.25, 34.84 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5 and 5 × cyclohexyl-CH_2), 38.89 (CCH_2Ph),

48.56 (NHCH), 51.31, 51.48 and 52.38 (OMe), 55.14 ($CHCH_2Ph$), 63.05 and 65.38 (C-4 and OCH_2Ph), 115.02, 117.87, 126.67, 127.78, 127.94 (2 C), 128.35 (2 C), 128.47 (2 C), 129.21 (3 C), 129.56, 129.65, 135.70, 136.51 and 151.28 (C=C) and 160.53, 169.27, 171.27 (2 C), 173.58, 173.67 and 173.86 (4 × CO_2 and 3 × CONH); *m/z* (+FAB) 841 (MH^+, 90%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **13b** (32 mg, 24%) as an amorphous solid (Found: MH^+, 841.4083); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (+10); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 0.61–1.24 (10 H, m, cyclohexyl), 1.29 (3 H, 4-Me), 2.33–2.68 (6 H, m, $CH_2CH_2CO_2$ and $CH_2CH_2CO_2$), 2.73 and 2.91 (each 1 H, d, *J* 15, 5-H_2), 2.92–3.02 (4 H, m, $CH_2CH_2CO_2$ and $CHCH_2Ph$), 3.21 and 3.54 (each 1 H, d, *J* 16, CH_2CO_2), 3.29 and 3.51 (each 1 H, d, *J* 16, CH_2CO_2), 3.5 (1 H, m, NHC*H*), 3.57, 3.58 and 3.69 (each 3 H, s, OMe), 4.46 (1 H, m, NHC*H*CO), 5.18 and 5.33 (each 1 H, d, *J* 13, OCH_2Ph), 5.28 (1 H, br m, amide-NH); 7.10–7.40 (12 H, m, 2 × Ph and lactam- and amide-NH) and 10.69 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.68 and 20.51 ($CH_2CH_2CO_2$), 24.48 (2 × cyclohexyl-CH_2), 24.64 (4-Me), 25.22, 29.67, 31.41, 32.28, 32.37 (2 C), 33.25 and 34.80 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5 and 3 × cyclohexyl-CH_2), 38.49 ($CHCH_2Ph$), 48.29 (NHCH), 51.34, 51.50 and 52.38 (OMe), 55.39 ($CHCH_2Ph$), 63.06 and 65.33 (C-4 and OCH_2Ph), 115.06, 117.86, 127.10, 127.69, 126.15, 128.37 (2 C), 128.67 (2 C), 129.24 (3 C), 129.60, 129.76, 135.68, 136.36, 136.58 and 151.27 (C=C) and 160.39, 169.31, 169.40, 171.31, 173.53, 173.70 and 173.84 (4 × CO_2 and 3 × CONH); *m/z* (+FAB) 841 (MH^+, 95%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-3-{[(*S*)-1-(cyclohexylaminocarbonyl)-2-phenylethylamino]carbonylmethyl}-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 17a and 17b

Using the procedure described above, acid **16**[1] (100 mg, 0.163 mmol) was esterified with (*S*)-(−)-phenylalanine cyclohexylamide (200 mg, 0.813 mmol). Purification by preparative TLC, eluting with ethyl acetate, gave the following products.

(i) At higher R_f, *lactam* **17a** (36 mg, 27%) as fine needles, mp 129–131 °C (from toluene–dichloromethane) (Found: MH^+, 841.4099. $C_{46}H_{56}N_4O_{11}$ requires *M* + *H*, 841.4024); CD λ_{max}/nm (Mol.Ellip./10^4) 284 (−10); λ_{max}(MeCN)/nm 283; δ_H($CDCl_3$, 400 MHz) 0.83–1.27 (10 H, m, cyclohexyl), 1.29 (3 H, s, 4-Me), 2.34–2.72 (9 H, m, 2 × $CH_2CH_2CO_2$ and 5-H_A), 2.90–3.04 (3 H, m, $CHCH_2Ph$ and 5-H_B), 3.24 and 3.49 (each 1 H, d, *J* 16, CH_2CO_2), 3.53, 3.59 and 3.66 (each 3 H, s, OMe), 3.6 (1 H, m, NHC*H*), 3.61 and 3.90 (each 1 H, d, *J* 16, CH_2CO_2), 4.56 (1 H, m, NHC*H*CO), 5.21 and 5.31 (each 1 H, d, *J* 13, OCH_2Ph), 5.61 (1 H, br m, amide-NH), 6.74 (1 H, s, lactam-NH), 7.13–7.51 (11 H, m, 2 × Ph and amide-NH) and 10.53 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.24 and 19.67 ($CH_2CH_2CO_2$), 24.39 (4-Me), 24.68 (2 C) and 25.35 (3 × cyclohexyl-CH_2), 29.71, 30.97, 31.35, 32.60, 32.66, 33.23 and 34.66 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5 and 2 × cyclohexyl-CH_2), 38.93 ($CHCH_2Ph$), 48.46 (NHCH), 51.59, 51.76 and 51.91 (OMe), 55.21 ($CHCH_2Ph$), 63.17 and 65.41 (C-4 and OCH_2Ph), 118.93, 121.87, 125.31, 126.99, 127.87, 128.04 (2 C), 128.24, 128.38 (2 C), 128.57 (2 C), 129.05 (2 C), 129.27, 135.32, 136.59 and 151.93 (C=C) and 160.73, 168.97, 169.38, 171.50, 172.15, 173.94 and 174.42 (4 × CO_2 and 3 × CONH); *m/z* (+FAB) 841 (MH^+, 80%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **17b** (31 mg, 24%) as an amorphous solid (Found: MH^+, 841.4077. $C_{46}H_{56}N_4O_{11}$ requires *M* + *H*, 841.4024); CD λ_{max}/nm (Mol.Ellip./10^4) 283 (+7); λ_{max}(MeCN)/nm 283; δ_H($CDCl_3$, 400 MHz), 0.74–1.61 (10 H, m, cyclohexyl), 1.30 (3 H, 4-Me), 2.34–2.69 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.72 and 3.03 (each 1 H, d, *J* 15, 5-H_2), 2.90–3.04 (2 H, m, $CHCH_2Ph$), 3.27 and 3.64 (each 1 H, d, *J* 16, CH_2CO_2), 3.53, 3.59 and 3.64 (each 3 H, s, OMe), 3.6 (1 H, m, NHC*H*), 3.58 and 3.86 (each 1 H, d, *J* 17, CH_2CO_2), 4.47 (1 H, m, NHC*H*CO), 5.17 and 5.29 (each 1 H, d, *J* 13, OCH_2Ph), 5.45 (1 H, br d, *J* 8, amide-NH), 6.87 (1 H, s, lactam-NH), 7.14–7.49 (11 H, m, 2 × Ph and amide-NH) and 10.58 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.21 and 19.63 ($CH_2CH_2CO_2$), 24.44 (4-Me), 24.52 (2 C) and 25.28 (3 × cyclohexyl-CH_2), 30.38, 31.38, 32.45 (2 C), 32.59, 33.19 and 34.71 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5 and 2 × cyclohexyl-CH_2), 38.51 ($CHCH_2Ph$), 48.33 (NHCH), 51.59, 51.77 and 51.88 (OMe), 55.40 ($CHCH_2Ph$), 63.19 and 65.38 (C-4 and OCH_2Ph), 118.88, 121.88, 122.31, 127.06, 127.92, 128.15 (2 C), 128.37 (3 C), 128.66 (2 C), 129.29 (2 C), 135.38, 136.52, 136.57 and 152.02 (C=C) and 160.61, 169.10, 169.42, 171.54, 172.13, 173.88 and 174.31 (4 × CO_2 and 3 × CONH); *m/z* (+FAB) 841 (MH^+, 95%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-3-{[(*R*)-1-(2-hydroxy-1-naphthyl)-2-naphthyl]oxycarbonylmethyl}-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1-(10*H*)-one 14a and 14b

Acid **12** (100 mg, 0.163 mmol) was suspended in dry dichloromethane (5 cm^3) and treated with 1-chloro-1-dimethylamino-2-methylpropene[18] (50 mg, 0.376 mmol). The resulting solution was stirred under argon for 10 min and then treated with (*R*)-(+)-1,1′-bi-2-naphthol (115 mg, 0.4 mmol). After 6 h the mixture was evaporated and the residue was purified using preparative TLC, eluting with diethyl ether, to give the following products.

(i) At higher R_f, *lactam* **14a** (62 mg, 37%) as an amorphous solid (Found: MH^+, 881.3369, $C_{51}H_{48}N_2O_{12}$ requires *M* + *H*, 881.3285); CD λ_{max}/nm (Mol.Ellip./10^4) 233 (−60); λ_{max}(MeCN)/nm 279; δ_H($CDCl_3$, 400 MHz) 0.93 (3 H, s, 4-Me), 1.97 (1 H, d, *J* 15, 5-H_A), 2.17–2.56 (7 H, m, $CH_2CH_2CO_2$, $CH_2CH_2CO_2$ and 5-H_B), 2.91–3.02 (3 H, m, $CH_2CH_2CO_2$ and $CH_AH_BCO_2$), 3.31 and 3.44 (each 1 H, d, *J* 16, CH_2CO_2), 3.46 (1 H, d, *J* 17, $CH_AH_BCO_2$), 3.55, 3.58 and 3.66 (each 3 H, s, OMe), 5.08 and 5.23 (each 1 H, d, *J* 12, CH_2Ph), 5.76 (1 H, br s, lactam-NH), 6.96–8.06 (17 H, m, Ar-H) and 9.61 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.50 and 20.61 ($CH_2CH_2CO_2$), 23.28 (4-Me), 29.69, 30.06, 31.26, 33.19 and 34.80 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.45, 51.55 and 52.38 (OMe), 62.81 and 65.73 (C-4 and CH_2Ph), 113.65, 115.35, 118.12 (2 C), 121.26, 123.52, 123.58, 124.47, 125.88, 126.45, 126.89, 127.19, 127.47, 127.94, 127.99 (2 C), 128.30 (2 C), 128.33 (2 C), 128.79, 129.50, 129.89, 130.21, 130.67, 132.38, 133.27, 133.35, 135.96, 136.09, 147.39, 149.95 and 151.93 (C=C) and 160.48, 169.25, 171.20, 173.36 and 173.76 (2 C) (C=O); *m/z* (+FAB) 881 (MH^+, 90%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **14b** (63 mg, 38%) as an amorphous solid (Found: MH^+, 881.3308); CD λ_{max}/nm (Mol.Ellip./10^4) 233 (−80); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 0.97 (3 H, s, 4-Me), 1.93 (1 H, d, *J* 15, 5-H_A), 2.09–2.53 (7 H, m, $CH_2CH_2CO_2$, $CH_2CH_2CO_2$ and 5-H_B), 2.90–2.96 (2 H, m, $CH_2CH_2CO_2$), 3.12 and 3.41 (each 1 H, d, *J* 18, CH_2CO_2), 3.24 and 3.41 (each 1 H, d, *J* 17, CH_2CO_2), 3.53, 3.58 and 3.65 (each 3 H, s, OMe), 5.05 and 5.23 (each 1 H, d, *J* 12, CH_2Ph), 6.47 (1 H, br s, lactam-NH), 6.90–8.05 (17 H, m, Ar-H) and 9.77 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.57 and 20.54 ($CH_2CH_2CO_2$), 23.62 (4-Me), 29.63, 30.03, 31.25, 32.83 and 34.76 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2, C-5), 51.43, 51.60 and 52.39 (OMe), 62.76 and 65.67 (C-4 and CH_2Ph), 113.62, 115.19, 117.79, 118.01, 121.24, 121.35, 123.36, 123.57, 124.46, 125.88, 126.11, 126.34, 126.89, 127.14, 127.32, 127.48, 127.86 (2 C), 128.06 (2 C), 128.28, 129.65, 130.38, 132.33, 133.54, 133.63, 136.05, 136.17, 147.28, 149.73, 151.94 and 152.85 (C=C) and 160.51, 169.46, 171.11, 173.70, 173.76 and 174.00 (C=O); *m/z* (+FAB) 881 (MH^+, 90%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-3-{[(*R*)-1-(2-hydroxy-1-naphthyl)-2-naphthyl]oxycarbonylmethyl}-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 18a and 18b

Using the procedure described above, acid **16**[1] (100 mg, 0.163 mmol) was esterified with (*R*)-(+)-1,1′-bi-2-naphthol (115 mg, 0.4 mmol). Purification by preparative TLC, eluting with diethyl ether, gave the following products.

(i) At higher R_f, *lactam* **18a** (60 mg, 36%) as an amorphous solid (Found: MH^+, 881.3343. $C_{51}H_{48}N_2O_{12}$ requires $M + H$, 881.3285); CD λ_{max}/nm (Mol.Ellip./10^4) 233 (−60); λ_{max}(MeCN)/nm 281; δ_H($CDCl_3$, 400 MHz) 0.94 (3 H, s, 4-Me), 1.84 (1 H, d, *J* 15, 5-H_A), 2.10–2.69 (9 H, m, 2 × $CH_2CH_2CO_2$ and 5-H_B), 2.94 and 3.46 (each 1 H, d, *J* 17, CH_2CO_2), 3.55, 3.56 and 3.61 (each 3 H, s, OMe), 3.63 and 3.88 (each 1 H, d, *J* 17, CH_2CO_2), 5.07 and 5.16 (each 1 H, d, *J* 12, CH_2Ph), 5.90 (1 H, br s, OH), 6.63 (1 H, br s, lactam-NH), 6.93–8.04 (17 H, m, Ar-H) and 9.46 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.12 and 19.56 (*C*$H_2CH_2CO_2$), 23.43 (4-Me), 30.15, 30.73, 31.21, 32.66 and 34.63 (2 × CH_2*C*H_2CO_2, 2 × *C*H_2CO_2, C-5), 51.55, 51.88 and 51.91 (OMe), 62.72 and 65.62 (C-4 and *C*H_2Ph), 113.54, 118.28, 119.23, 121.31, 121.65, 122.21, 123.46, 123.82, 124.50, 126.06, 126.34, 126.80, 127.32, 127.93 (2 C), 128.10, 128.22 (2 C), 128.29 (2 C), 128.58, 128.73, 130.04, 130.40, 132.33, 133.34, 133.41, 135.68, 136.16, 147.18, 150.50, 152.11 (C=C) and 160.46, 168.72, 171.32, 172.42, 173.68 and 174.12 (C=O); *m*/*z* (+FAB) 881 (MH^+, 60%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **18b** (63 mg, 38%) as an amorphous solid (Found: MH^+, 881.3304); CD λ_{max}/nm (Mol.Ellip./10^4) 233 (−100); λ_{max}(MeCN)/nm 281; δ_H($CDCl_3$, 400 MHz) 1.00 (3 H, s, 4-Me), 2.12–2.69 (9 H, m, 2 × $CH_2CH_2CO_2$ and 5-H_A), 2.75 (1 H, d, *J* 15, 5-H_B), 3.20 and 3.30 (each 1 H, d, *J* 17, CH_2CO_2), 3.54 (6 H, s, 2 × OMe), 3.63 (3 H, s, OMe), 3.62 and 3.88 (each 1 H, d, *J* 17, CH_2CO_2), 5.06 and 5.23 (each 1 H, d, *J* 12, CH_2Ph), 6.14 (1 H, br s, OH), 6.72 (1 H, br s, lactam-NH), 6.95–8.10 (17 H, m, Ar-H) and 9.73 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.18 and 19.54 (*C*$H_2CH_2CO_2$), 23.51 (4-Me), 30.25, 30.83, 31.16, 32.86 and 34.55 (2 × CH_2*C*H_2CO_2, 2 × *C*H_2CO_2, C-5), 51.59, 51.79 and 51.87 (OMe), 62.85 and 65.64 (C-4 and *C*H_2Ph), 113.65, 117.99, 118.95, 121.38, 121.79, 122.53, 123.56, 123.75, 124.58, 126.06, 126.36, 126.81, 127.36, 127.81, 127.88, 128.09 (2 C), 128.30 (2 C), 128.57 (3 C), 128.79, 130.43, 132.34, 133.52, 133.58, 135.82, 136.08, 147.34, 150.26 and 151.94 (C=C) and 160.58, 169.06, 171.26, 171.95, 173.99 and 174.14 (C=O); *m*/*z* (+FAB) 881 (MH^+, 70%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-3-({(1*S*,2*R*)-1-(*N*,*N*-dicyclohexylsulfamoylmethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl}oxycarbonylmethyl)-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 19a and 19b

A solution of acid **16** (100 mg, 0.163 mmol) in dry dichloromethane (5 cm^3) was stirred with 1-chloro-1-dimethylamino-2-methylpropene[18] (50 mg, 0.376 mmol) under argon at room temperature for 10 min and then evaporated. A solution of the residue in toluene (1 cm^3) was added dropwise to a solution of (−)-10-(*N*,*N*-dicyclohexylsulfamoyl)-D-isoborneol (300 mg, 0.752 mmol) in toluene (5 cm^3). Silver cyanide (50 mg, 0.373 mmol) was added and the solution was stirred at 100 °C under argon for 6 h, then filtered through Celite and evaporated. The residue was purified by preparative TLC, eluting with diethyl ether, to give the following products.

(i) At higher R_f, *lactam* **19a** (36 mg, 19%) as an amorphous solid (Found: MH^+, 993.5048. $C_{52}{}^{13}CH_{73}N_3O_{13}S$ requires $M + H$, 993.4975); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (+6); λ_{max}(MeCN)/nm 282; δ_H($CDCl_3$, 400 MHz) 0.87 and 0.99 (each 3 H, s, CMe_2) 1.00–1.35 (7 H, m) and 1.60–1.88 (20 H, m, isobornyl and cyclohexyl), 1.37 (3 H, s, 4-Me), 2.45–2.71 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.49 and 3.25 (each 1 H, d, *J* 14, CH_2SO_2), 2.69 and 3.04 (each 1 H, d, *J* 15, 5-H_2), 3.26 (2 H, m, 2 × NCH), 3.28 and 3.56 (each 1 H, d, *J* 17, CH_2CO_2), 3.56, 3.57 and 3.65 (each 3 H, s, OMe), 3.62 and 3.96 (each 1 H, d, *J* 17, CH_2CO_2), 4.94 (1 H, m, OCH), 5.16 and 5.34 (each 1 H, d, *J* 12.5, CH_2Ph), 6.71 (1 H, br s, lactam-NH), 7.12–7.41 (5 H, m, Ph) and 10.11 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.3 and 19.7 (*C*$H_2CH_2CO_2$), 20.1 and 20.3 (*CMe*$_2$), 24.4 (4-Me), 25.3 (2 C), 26.4, 26.5 (2 C), 26.6 (2 C), 26.9, 30.7, 30.8, 30.9, 31.4, 32.8 (2 C), 32.9 (2 C), 33.3, 34.6 and 39.5 (CH_2), 44.5 (isobornyl-CH), 49.3 and 49.7 (isobornyl-C), 51.4 (OMe), 51.8 (2 × OMe), 54.2 (CH_2SO_2), 57.7 (2 × NCH), 63.0 (C-4), 65.6 (*C*H_2Ph), 80.2 (OCH), 119.2, 121.7, 122.4, 128.4, 136.0, 136.3 and 150.9 (C=C), 128.2, 128.3 and 128.4 (C=*C*H) and 160.5, 169.1, 171.5, 172.1, 173.2 and 174.2 (C=O); *m*/*z* (+FAB) 993 (MH^+, 100%) and 372 ($C_{20}H_{22}NO_6^+$, 70).

(ii) At lower R_f, *lactam* **19b** (38 mg, 20%) as an amorphous solid (Found: M^+, 993.4978); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (−4); λ_{max}(MeCN)/nm 282; δ_H($CDCl_3$, 400 MHz) 0.86 and 1.02 (each 3 H, s, CMe_2) 1.03–1.39 (7 H, m) and 1.62–1.83 (20 H, m, cyclohexyl and isobornyl), 1.36 (3 H, s, 4-Me), 2.33–2.74 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.68 and 3.25 (each 1 H, d, *J* 13.5, CH_2SO_2), 2.90 and 3.05 (each 1 H, d, *J* 15, 5-H_2), 3.26 (2 H, m, 2 × NCH), 3.32 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.56, 3.58 and 3.66 (each 3 H, s, OMe), 3.62 and 3.94 (each 1 H, d, *J* 17, CH_2CO_2), 4.93 (1 H, m, OCH), 5.14 and 5.35 (each 1 H, d, *J* 12.5, CH_2Ph), 6.58 (1 H, br s, lactam-NH), 7.11–7.39 (5 H, m, Ph) and 10.34 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.2 and 19.9 (*C*$H_2CH_2CO_2$), 20.1 and 20.3 (*CMe*$_2$), 24.5 (4-Me), 25.3 (2 C), 26.6 (2 C), 26.6 (2 C), 26.9, 30.7, 30.8, 30.9, 31.1, 32.8 (2 C), 32.9 (2 C), 34.5 and 39.2 (CH_2), 44.5 (isobornyl-CH), 49.4 and 49.7 (isobornyl-C), 51.5, 51.8 and 51.9 (OMe), 54.5 (CH_2SO_2), 57.7 (2 × NCH), 62.9 (C-4), 65.2 (*C*H_2Ph), 80.3 (O-CH), 118.8, 121.6, 122.5, 128.4, 135.8, 136.7 and 151.1 (C=C), 127.8, 127.9 and 128.1 (C=*C*H) and 160.4, 170.2, 171.3, 172.0, 173.5 and 174.6 (C=O); *m*/*z* (+FAB) 993 (MH^+, 90%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

9-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-4-methyl-3-{(3a*S*,7a*R*)-8,8-dimethyl-*S*,*S*-dioxy-3a,6-methanoperhydrobenzo[*c*]isothiazol-1-yl}carbonylmethyl-4,5-dihydrodipyrrin-1(10*H*)-one 20a and 20b

A suspension of sodium hydride (60% dispersion in mineral oil; 15 mg) in toluene (1 cm^3) was treated with (2*S*)-(+)-10,2-camphorsultam (70 mg, 0.327 mmol) and stirred under argon for 15 min. Meanwhile, a solution of acid **16** (100 mg, 0.163 mmol) in dichloromethane (2 cm^3) was stirred with 1-chloro-1-dimethylamino-2-methylpropene[18] (50 mg, 0.376 mmol) under argon for 15 min and then added dropwise to the sultam solution. The resultant mixture was stirred under argon for 8 h and then evaporated. A solution of the residue on dichloromethane (5 cm^3) was washed successively with dilute hydrochloric acid (1 mol dm^{-3}; 5 cm^3), 10% aqueous sodium carbonate (5 cm^3) and water (5 cm^3), dried and evaporated. The residue was purified by preparative TLC, eluting with diethyl ether, to give the following products.

(i) At higher R_f, *lactam* **20a** (30 mg, 23%) as an amorphous solid (Found: MH^+, 810.3316. $C_{41}H_{51}N_3O_{12}S$ requires $M + H$, 810.3271); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (+3); λ_{max}(MeCN)/nm 283; δ_H($CDCl_3$, 400 MHz) 0.98 and 1.18 (each 3 H, s, CMe_2), 1.39 (3 H, s, 4-Me), 1.33 (1 H, m), 1.47 (1 H, m) and 1.80–2.05 (5 H, m, sultam), 2.38–2.73 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.71 and 3.08 (each 1 H, d, *J* 15, 5-H_2), 3.48 and 3.56 (each 1 H, d, *J* 14, SO_2CH_2), 3.58, 3.60 and 3.66 (each 3 H, s, OMe and obscured C$H_AH_BCO_2$), 3.76 and 3.93 (each 1 H, d, *J* 17.5, CH_2CO_2), 3.86 (1 H, m, NCH), 4.00 (1 H, d, *J* 17, $CH_AH_BCO_2$), 5.13 and 5.35 (each 1 H, d, *J* 12.5, CH_2Ph), 6.48 (1 H, br s, lactam-NH), 7.25–7.37 (5 H, m, Ph) and 10.04 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.0 and 20.2 (*C*$H_2CH_2CO_2$), 19.8 and 20.6 (*CMe*$_2$), 24.7 (4-Me), 26.3, 30.7, 31.3, 31.5, 32.8, 32.8, 34.5 and 38.0 (CH_2), 44.6 (CH), 49.7 and

48.6 (sultam-C), 51.5, 51.8 and 51.9 (OMe), 53.0 (CH_2SO_2), 62.7 (C-4), 65.3 (CH_2Ph), 65.6 (CHN), 116.8, 121.6, 122.6, 128.6, 136.5, 136.5 and 150.7 (C=C), 127.8, 128.0 and 128.3 (C=CH) and 160.3, 166.6, 171.0, 172.1, 173.3 and 174.4 (C=O); *m/z* (+FAB) 810 (MH^+, 95%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **20b** (27 mg, 21%) as an amorphous solid (Found: MH^+, 810.3296); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (−3); λ_{max}(MeCN)/nm 281; δ_H($CDCl_3$, 400 MHz) 0.96 and 1.11 (each 3 H, s, CMe_2), 1.36 (3 H, s, 4-Me), 1.25 (1 H, m), 1.38 (1 H, m) and 1.79–1.99 (5 H, m, sultam), 2.45–2.71 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.62 and 3.07 (each 1 H, d, *J* 15, 5-H_2), 3.49 and 3.55 (each 1 H, d, *J* 14, SO_2CH_2), 3.57, 3.60 and 3.66 (each 3 H, s, OMe), 3.60 and 3.69 (each 1 H, d, *J* 17.5, CH_2CO_2), 3.79 (1 H, m, NCH), 3.97 and 3.99 (each 1 H, d, *J* 17.5, CH_2O_2), 5.15 and 5.31 (each 1 H, d, *J* 12.5, CH_2Ph), 6.57 (1 H, br s, lactam-NH), 7.24–7.39 (5 H, m, Ph) and 10.04 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.1 and 20.0 ($CH_2CH_2CO_2$), 19.8 and 20.9 (CMe_2), 24.6 (4-Me), 26.2, 30.7, 31.4, 31.5, 32.8, 33.0, 34.5 and 38.2 (CH_2), 44.7 (CH), 47.8 and 48.6 (sultam-C), 51.5, 51.6 and 51.7 (OMe), 52.9 (CH_2SO_2), 62.8 (C-4), 65.5 (CH_2Ph), 65.6 (CHN), 117.0, 121.8, 122.4, 128.4, 136.4, 136.5 and 150.4 (C=C), 127.9, 128.3 and 128.3 (C=CH) and 160.4, 166.1, 171.2, 172.1, 173.3 and 174.3 (C=O); *m/z* (+FAB) 810 (MH^+, 80%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

3-{(3*R*,4*R*,5*R*)-4,5-[(*R*)-Benzylidenedioxy]-2-oxotetrahydropyran-3-yloxycarbonylmethyl}-9-benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 15a and 15b

A suspension of acid **12** (140 mg, 0.23 mmol) in anhydrous dichloromethane (10 cm^3) was stirred with 1-chloro-1-dimethylamino-2-methylpropene[18] (92 mg, 0.68 mmol) under argon for 10 min. (−)-3,4-*O*-Benzylidene-D-ribonic δ-lactone (270 mg, 1.10 mmol) was added and the solution was stirred for a further 4 h and then evaporated. The residue was purified on preparative TLC plates, developed three times with ethyl acetate–diethyl ether (9:1), to give the following products.

(i) At higher R_f, *lactam* **15a** (75 mg, 39%) as an amorphous solid (Found: MH^+, 831.2964. $C_{43}H_{46}N_2O_{15}$ requires *M* + *H*, 831.2976); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+1); λ_{max}(MeCN)/nm 279; δ_H($CDCl_3$, 400 MHz) 1.28 (3 H, s, 4-Me), 2.44–2.63 (6 H, m) and 2.90–2.98 (2 H, m, 2 × $CH_2CH_2CO_2$), 2.66 and 2.96 (each 1 H, d, *J* 15, 5-H_2), 3.29 and 3.41 (each 1 H, d, *J* 16, CH_2CO_2), 3.55 and 3.79 (each 1 H, d, *J* 17, CH_2CO_2), 3.59 (6 H, s) and 3.69 (3 H, s, OMe), 4.27 and 4.31 (each 1 H, d, *J* 13, OCHCH_2O), 4.64 (1 H, d, *J* 8, OC*H*CH$_2$O), 4.83 (1 H, dd, *J* 8 and 3, CHC*H*CH), 5.21 and 5.28 (each 1 H, d, *J* 12, CH_2Ph), 5.51 (1 H, d, *J* 3, OCHC=O), 5.75 (1 H, s, CHPh), 6.93 (1 H, br s, lactam-NH), 7.29–7.51 (10 H, m, Ph) and 9.64 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.79 and 20.61 ($CH_2CH_2CO_2$), 23.67 (4-Me), 29.60, 30.26, 31.35, 33.77 and 34.71 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.44, 51.55 and 52.41 (OMe), 63.15 and 65.89 (C-4 and CH_2Ph), 68.44, 69.62, 73.10 and 74.12 (4 × ribonic lactone), 104.97 (CHPh), 115.79, 118.24, 127.25 (2 C), 128.16, 128.35 (2 C), 128.52 (2 C), 128.58 (2 C), 129.52, 130.10, 130.28, 130.42, 136.12, 136.22 and 150.20 (C=C) and 160.51, 165.05, 169.62, 171.14, 173.32, 173.42 and 173.60 (C=O); *m/z* (+FAB) 831 (MH^+, 95%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **15b** (77 mg, 41%) as an amorphous solid (Found: MH^+, 831.3004); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−2); λ_{max}(MeCN)/nm 278; δ_H(CD_3CN, 400 MHz) 1.31 (3 H, s, 4-Me), 2.39–2.66 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.71 and 3.02 (each 1 H, d, *J* 15, 5-H_2), 3.53 and 3.72 (each 1 H, d, *J* 17, CH_2CO_2), 3.51, 3.56 and 3.60 (each s, 3 H, OMe), 3.62 and 3.81 (each 1 H, d, *J* 17, CH_2CO_2), 4.30 and 4.50 (each 1 H, d, *J* 13, OCHCH_2O), 4.60 (1 H, d, *J* 8, OC*H*CH$_2$O), 4.78 (1 H, dd, *J* 8 and 3, CHC*H*CH), 5.13 and 5.19 (each 1 H, d, *J* 12, CH_2Ph), 5.50 (1 H, d, *J* 3, OCHC=O), 5.74 (1 H, s, CHPh), 7.08 (1 H, br s, lactam-NH), 7.42–7.52 (10 H, m, Ph) and 9.95 (1 H, br s, pyrrole-NH); δ_C(CD_3CN, 100 MHz) 20.36 and 21.26 ($CH_2CH_2CO_2$), 23.56 (4-Me), 29.99, 30.78, 32.13, 33.76 and 35.17 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.80, 51.94 and 52.59 (OMe), 64.06 and 66.20 (C-4 and CH_2Ph), 68.05, 69.26, 74.35 and 74.45 (4 × ribonic lactone), 104.72 (CHPh), 116.75, 118.44, 127.88 (2 C), 128.82, 128.90 (2 C), 129.27 (2 C), 129.30 (2 C), 130.75, 130.93, 131.19, 136.09, 136.53, 137.61 and 151.88 (C=C) and 161.09, 167.22, 170.45, 171.83, 173.91, 173.99 and 174.04 (C=O); *m/z* (+FAB) 831 (MH^+, 90%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

3-{(3*R*,4*R*,5*R*)-4,5-[(*R*)-Benzylidenedioxy]-2-oxotetrahydropyran-3-yloxycarbonylmethyl}-9-benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 21a and 21b

Using the procedure described above, acid **16**[1] (268 mg, 0.438 mmol) was esterified with (−)-3,4-*O*-benzylidene-D-ribonic δ-lactone (500 mg, 2.328 mmol). Preparative TLC, developing four times with ethyl acetate, gave the following products.

(i) At higher R_f, *lactam* **21a** (116 mg, 32%) as an amorphous solid (Found: MH^+, 831.3022. $C_{43}H_{46}N_2O_{15}$ requires *M* + *H*, 831.2976); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+3); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 1.31 (3 H, s, 4-Me), 2.39–2.66 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.71 and 3.02 (each 1 H, d, *J* 15, 5-H_2), 3.51, 3.56 and 3.60 (each 3 H, s, OMe), 3.53 and 3.72 (each 1 H, d, *J* 17, CH_2CO_2), 3.62 and 3.81 (each 1 H, d, *J* 17, CH_2CO_2), 4.30 and 4.50 (each 1 H, d, *J* 13, OCHCH_2O), 4.60 (1 H, d, *J* 8, OC*H*CH$_2$O), 4.78 (1 H, dd, *J* 8 and 3, CHC*H*CH), 5.13 and 5.19 (each 1 H, d, *J* 12, CH_2Ph), 5.50 (1 H, d, *J* 3, OCHC=O), 5.74 (1 H, s, CHPh), 7.08 (1 H, br s, lactam-NH), 7.42–7.52 (10 H, m, Ph) and 9.95 (1 H, br s, pyrrole-NH); δ_H($CDCl_3$, 100 MHz) 19.22 and 19.73 ($CH_2CH_2CO_2$), 23.55 (4-Me), 30.29, 30.80, 31.38, 33.31 and 34.78 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.52 and 51.76 (2 C, OMe), 63.47, 65.80 (C-4 and CH_2Ph), 67.51, 69.66, 73.39 and 74.22 (4 × ribonic lactone), 104.83 (CHPh), 119.16, 122.06, 122.37, 127.28 (2 C), 128.11, 128.27 (2 C), 128.45 (2 C), 128.58 (2 C), 128.97, 130.37, 134.56, 135.76, 136.16 and 150.87 (C=C) and 160.80, 165.32, 169.27, 171.61, 172.10, 173.38 and 173.78 (C=O); *m/z* (+FAB) 831 (MH^+, 70%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **21b** (110 mg, 30%) as an amorphous solid (Found: MH^+, 831.3045); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−2); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 1.36 (3 H, s, 4-Me), 2.40–2.67 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.80 and 3.05 (each 1 H, d, *J* 15, 5-H_2), 3.55, 3.57 and 3.61 (each 3 H, s, OMe), 3.55 and 3.80 (each 1 H, d, *J* 17, CH_2CO_2), 3.63 and 3.77 (each 1 H, d, *J* 17, CH_2CO_2), 4.31 and 4.52 (each 1 H, d, *J* 13, OCHCH_2O), 4.61 (1 H, d, *J* 8, OC*H*CH$_2$O), 4.79 (1 H, dd, *J* 8 and 3, CHC*H*CH), 5.17 and 5.21 (each 1 H, d, *J* 12, CH_2Ph), 5.52 (1 H, d, 3, OCHC=O), 5.77 (1 H, s, CHPh), 7.03 (1 H, br s, lactam-NH), 7.25–7.44 (10 H, m, Ph) and 9.91 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.21 and 19.80 ($CH_2CH_2CO_2$), 23.73 (4-Me), 30.36, 30.90, 31.32, 33.19 and 34.67 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.56 and 51.80 (2 C, OMe), 63.58 and 65.73 (C-4 and CH_2Ph), 67.61, 69.79, 73.38 and 74.20 (4 × ribonic lactone), 104.87 (CHPh), 119.00, 122.23, 122.35, 127.31 (2 C), 128.03, 128.11 (2 C), 128.25 (2 C), 128.31 (2 C), 128.91, 130.37, 134.57, 135.91, 136.28 and 150.76 (C=C) and 160.84, 165.41, 169.80, 171.55, 172.08, 173.53 and 174.07 (C=O); *m/z* (+FAB) 831 (MH^+, 65%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

3-{(3*R*,4*R*,5*R*)-4,5-[(*R*)-Benzylidenedioxy]-2-oxotetrahydropyran-3-yloxycarbonylmethyl}-9-methoxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 25a and 25b

Using the procedure described above, acid **24** (50 mg, 0.095 mmol) was esterified with (−)-3,4-*O*-benzylidene-D-ribonic

δ-lactone (70 mg, 0.3 mmol). Preparative TLC, developed three times with ethyl acetate, gave the following products.

(i) At higher R_f, *lactam* **25a** (20 mg, 29%) as an amorphous solid (Found: MH^+, 755.2699. $C_{37}H_{42}N_2O_{15}$ requires $M + H$, 755.2663); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+1); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 250 MHz) 1.33 (3 H, s, 4-Me), 2.28–2.66 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.73 and 3.05 (each 1 H, d, *J* 15, 5-H_2), 3.52–3.74 (3 H, m, CH_2CO_2 and $CH_AH_BCO_2$), 3.56, 3.59, 3.62 and 3.68 (each 3 H, s, OMe), 3.78 (1 H, d, *J* 13, $CH_AH_BCO_2$), 4.37 and 4.57 (each 1 H, d, *J* 13, $OCHCH_2O$), 4.67 (1 H, d, *J* 8, $OCHCH_2O$), 4.84 (1 H, dd, *J* 8 and 3, CHCHCH), 5.55 (1 H, d, *J* 3, OCHC=O), 5.77 (1 H, s, CHPh), 6.98 (1 H, br s, lactam-NH), 7.31–7.45 (5 H, m, Ph) and 9.71 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.36 and 19.88 ($CH_2CH_2CO_2$), 23.77 (4-Me), 30.48, 30.86, 31.50, 33.52 and 34.85 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.27, 51.70, 51.92 and 52.07 (OMe), 63.58 (C-4), 67.66, 69.76, 73.52 and 74.36 (4 × ribonic lactone), 105.09 (CHPh), 119.37, 122.07, 122.49, 127.42 (2 C), 128.63, 128.73 (2 C), 130.55, 134.58, 135.97 and 151.03 (C=C) and 161.50, 165.28, 169.29, 171.72, 172.32, 173.54 and 173.94 (C=O); *m/z* (+FAB) 755 (MH^+, 40%) and 296 ($C_{14}H_{18}NO_6^+$, 100).

(ii) At lower R_f, *lactam* **25b** (19 mg, 27%) as an amorphous solid (Found: MH^+, 755.2717); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−1); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 250 MHz) 1.35 (3 H, s, 4-Me), 2.44–2.72 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.81 and 3.07 (each 1 H, d, *J* 15, 5-H_2), 3.54–3.75 (3 H, m, CH_2CO_2 and $CH_AH_BCO_2$), 3.58, 3.62, 3.65 and 3.72 (each 3 H, s, OMe), 3.85 (1 H, d, 17, $CH_AH_BCO_2$), 4.38 and 4.57 (each 1 H, d, *J* 13, $OCHCH_2O$), 4.68 (1 H, d, *J* 8, $OCHCH_2O$), 4.86 (1 H, dd, *J* 8 and 3, CHCHCH), 5.59 (1 H, d, *J* 3, OCHC=O), 5.80 (1 H, s, CHPh), 6.77 (1 H, br s, lactam-NH), 7.32–7.47 (5 H, m, Ph) and 9.73 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.34 and 19.97 ($CH_2CH_2CO_2$), 24.19 (4-Me), 30.50, 30.99, 31.47, 33.25 and 34.67 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.22, 51.70, 51.99 and 52.06 (OMe), 63.44 (C-4), 67.75, 69.90, 73.52 and 74.35 (4 × ribonic lactone), 105.11 (CHPh), 119.18, 122.06, 122.36, 127.46 (2 C), 128.73 (3 C), 130.55, 134.61, 136.29 and 150.61 (C=C) and 161.15, 165.39, 170.01, 171.40, 172.27, 173.70 and 174.31 (C=O); *m/z* (+FAB) 755 (MH^+, 70%) and 296 ($C_{14}H_{18}NO_6^+$, 100).

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1-(10*H*)-one (+)-10 and (−)-10

A solution of the resolved lactam **15a** (20 mg, 24 μmol) in methanol (4 cm^3) and tetrahydrofuran (1 cm^3) was stirred with a solution of sodium methoxide in methanol (55 mmol dm^{-3}; 438 mm^3, 24 μmol) under argon at room temperature for 25 min. Water (5 cm^3) was added, the pH was adjusted to *ca.* 4 with glacial acetic acid, and the solution was extracted with dichloromethane (4 × 5 cm^3). The combined organic extracts were washed with water (3 cm^3), dried and evaporated. The residue was purified by preparative TLC, eluting with ethyl acetate, to give the *methyl ester* (+)-**10** (14 mg, 93%) as a glass (Found: MH^+, 627.2497. $C_{32}H_{38}N_2O_{11}$ requires $M + H$, 627.2554); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+3.5). Similarly lactam **26b** (20 mg, 24 μmol) gave *methyl ester* (−)-**10** (13 mg, 86%) as a glass (Found: MH^+, 627.2543); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−3.5). The other physical characteristics of both enantiomers were identical to those reported for the racemic material.[4]

Lactams **14a** and **14b** (6.0 mg, 7 μmol) were each methanolysed for 16 h using an analogous procedure to that described above. Lactam **14a** gave methyl ester (−)-**10** (4.2 mg, *ca.* 100%) and lactam **14b** gave methyl ester (+)-**10** (4.2 mg, *ca.* 100%). The lactams **13a** and **13b** derived from (*S*)-(−)-phenylalanine cyclohexylamide were resistant to methanolysis.

9-Benzyloxycarbonyl-2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one (+)-22 and (−)-22

Lactam **21a** (20 mg, 24 μmol) was methanolysed using the procedure described above. Preparative TLC, eluting with ethyl acetate, gave the *methyl ester* (+)-**22** (14 mg, 93%) as a glass (Found: MH^+, 627.2593. $C_{32}H_{38}N_2O_{11}$ requires $M + H$, 627.2554); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (+3); λ_{max}(MeCN)/nm 280; δ_H(CD_3CN, 400 MHz) 1.29 (3 H, s, 4-Me), 2.39 (6 H, m) and 2.66 (2 H, m, 2 × $CH_2CH_2CO_2$), 2.83 and 3.01 (each 1 H, d, *J* 15, 5-H_2), 3.47 and 3.53 (each 1 H, d, *J* 17, CH_2CO_2), 3.52, 3.59, 3.61 and 3.70 (each 3 H, s, OMe), 3.69 and 3.77 (each 1 H, d, *J* 17, CH_2CO_2), 5.17 and 5.25 (each 1 H, d, *J* 12, CH_2Ph), 7.06 (1 H, br s, lactam-NH), 7.31–7.44 (5 H, m, Ph) and 10.14 (1 H, br s, pyrrole-NH); δ_C(CD_3CN, 100 MHz) 19.67 and 20.32 ($CH_2CH_2CO_2$), 23.76 (4-Me), 31.17 (2 C), 32.09, 33.68 and 35.53 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.96 (2 C), 52.11 and 53.12 (OMe), 64.24 and 66.13 (C-4 and CH_2Ph), 119.23, 123.33, 123.59, 127.90, 128.81, 128.91 (2 C), 129.26 (2 C), 130.15, 137.59 and 152.85 (C=C) and 161.23, 171.88 (2 C), 172.78, 173.89 and 174.26 (C=O); *m/z* (+FAB) 627 (MH^+, 70%) and 372 ($C_{20}H_{22}NO_6^+$, 100).

Similarly lactam **21b** (20 mg, 24 μmol) gave *methyl ester* (−)-**22** (13 mg, 86%) as a glass (Found: MH^+, 627.2571); CD λ_{max}/nm (Mol.Ellip./10^4) 282 (−3); the other physical characteristics were identical to those reported above for (+)-**22**.

The following lactams underwent methanolysis using an analogous procedure to that described above: lactam **18a** (3.0 mg, 3 μmol) after 17 h gave methyl ester (−)-**22** (2.1 mg, *ca.* 100%) and lactam **18b** (2.0 mg, 2 μmol) gave methyl ester (+)-**22** (1.4 mg, *ca.* 100%); lactam **19b** (4.0 mg, 4 μmol) after 17 h at reflux gave methyl ester (−)-**22** (0.7 mg, 28%); lactam **20a** (5.0 mg, 6 μmol) after 27 h gave methyl ester (+)-**22** (0.6 mg, 15%) and lactam **20b** (6.0 mg, 7 μmol) gave methyl ester (−)-**22** (0.5 mg, 11%). The lactams **17a** and **17b** derived from (*S*)-(−)-phenylalanine cyclohexylamide and lactam **19a** derived from (−)-10-(*N*,*N*-dicyclohexylsulfamoyl)-D-isoborneol were resistant to methanolysis even under refluxing conditions.

9-Methoxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one (+)-26 and (−)-26

Lactam **25a** (8.0 mg, 10 μmol) was methanolysed using the procedure described above. Preparative TLC, eluting with ethyl acetate, gave *methyl ester* (+)-**26** (5.6 mg, *ca.* 100%) as an oil (Found: MH^+, 551.2283. $C_{26}H_{34}N_2O_{11}$ requires $M + H$, 551.2241); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+3); λ_{max}(MeCN)/nm 280; δ_H($CDCl_3$, 400 MHz) 1.37 (3 H, s, 4-Me), 2.49–2.74 (8 H, 2 × $CH_2CH_2CO_2$), 2.71 and 3.10 (each 1 H, d, *J* 15, 5-H_2), 3.36 and 3.59 (each 1 H, d, *J* 17, CH_2CO_2), 3.61 and 3.93 (each 1 H, d, *J* 17, CH_2CO_2), 3.64, 3.67, 3.67, 3.76 and 3.78 (each 3 H, s, OMe), 6.48 (1 H, br s, lactam-NH) and 9.70 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.1 and 19.8 ($CH_2CH_2CO_2$), 24.4 (4-Me), 30.6, 30.8, 31.2, 33.1 and 34.4 (2 × $CH_2CH_2CO_2$, 2 × CH_2CO_2 and C-5), 51.1, 51.6, 51.9, 51.9 and 52.9 (OMe), 62.9 (C-4), 119.2, 121.7, 122.2, 128.1, 122.2, 128.1, 135.8 and 151.0 (C=C) and 161.0, 170.9, 171.2, 172.1, 173.5 and 174.3 (C=O); *m/z* (+FAB) 551 (MH^+, 30%), 307 (70) and 154 (100).

Similarly lactam **25b** (3.5 mg, 4.6 μmol) gave *methyl ester* (−)-**26** as an oil (2.1 mg, 82%) (Found: MH^+, 551.2232); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−3); the other physical characteristics were identical to those reported above for (+)-**26**.

9-Benzyloxycarbonyl-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-10-nitroso-4,5-dihydrodipyrrin-1(10*H*)-one (+)-43 and (−)-43

Fused sodium acetate (7.5 mg, 92 μmol) was stirred with a solution of lactam (+)-**10** (28.8 mg, 46 μmol) in anhydrous dichloromethane (4 cm^3) at 0 °C under argon and a solution of dinitrogen tetroxide in dichloromethane (0.77 mol dm^{-3}; 72

mm^3, 55 μmol) was added dropwise. After 2 h the solution was evaporated and the residue was purified by preparative TLC, eluting with ethyl acetate–hexane (7:3), to give the N-*nitroso lactam* (+)-**43** (27.5 mg, 91%) as a yellow oil (Found: MH$^+$, 656.2459. $C_{32}H_{37}N_3O_{12}$ requires *M* + *H*, 656.2455); CD λ_{max}/nm (Mol.Ellip./10^4) 279 (+9). Similarly lactam (−)-**10** (53 mg, 84 μmol) gave N-*nitroso lactam* (−)-**43** (43.8 mg, 79%) as a yellow oil (Found: MH$^+$, 656.2406); CD λ_{max}/nm (Mol.Ellip./10^4) 279 (−9); the other physical characteristics of both enantiomers were identical to those reported for the racemic material.[8]

2,8-Bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-9-(1-phenylethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one (+)-42a and (−)-42a

A solution of the benzyl ester (+)-**10** (42 mg, 67 μmol) in tetrahydrofuran (4 cm^3) was stirred with 10% palladium-on-charcoal (10 mg) under hydrogen at room temperature and atmospheric pressure for 2 h and then filtered through Celite and evaporated. The residual acid **40** was dissolved in anhydrous dichloromethane and treated with *N*,*N*-diisopropylethylamine (14 mm^3, 80 μmol), (*S*)-(−)-1-phenylethanol (87 mg, 700 μmol) and a solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (33 mg, 70 μmol) in dichloromethane (500 μl). The solution was stirred for 13 h and then evaporated. The residue was purified by preparative TLC, eluting with ethyl acetate, to give *lactam* (+)-**42a** (33.1 mg, 77%) as an oil (Found: MH$^+$, 641.2683. $C_{33}H_{40}N_2O_{11}$ requires *M* + *H*, 641.2710); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (+5); λ_{max}(MeCN)/nm 278; δ_H($CDCl_3$, 400 MHz) 1.34 (3 H, s, 4-Me), 1.54 (3 H, d, *J* 6.5, CH*Me*), 2.42–2.66 (6 H, m) and 2.91–2.98 (2 H, m, 2 × $CH_2CH_2CO_2$), 2.73 and 2.94 (each 1 H, d, *J* 15, 5-H_2), 3.30 and 3.51 (each 1 H, d, *J* 15.5, CH_2CO_2), 3.31 and 3.67 (1 H, d, *J* 17, CH_2CO_2), 3.59, 3.61, 3.71 and 3.77 (each 3 H, s, OMe), 6.03 (1 H, q, *J* 6.5, C*H*Me), 7.03 (1 H, br s, lactam-NH), 7.21–7.44 (5 H, m, Ph) and 10.15 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.8 and 20.5 (*C*$H_2CH_2CO_2$), 22.4 and 24.5 (C*Me*), 29.6, 30.2, 31.2, 33.2 and 34.8 (4 × *C*H_2CO_2 and C-5), 51.4, 51.5, 52.5 and 53.0 (OMe), 62.9 (C-4), 71.9 (*C*HMe), 115.2, 118.3, 129.0, 129.6, 136.2, 141.9 and 150.2 (C=C), 126.2, 127.7 and 128.4 (aromatic CH), 159.8 (9-CO_2) and 171.1, 171.6, 173.5, 173.6 and 173.7 (4 × *C*O_2Me and CONH); *m*/*z* (+FAB) 641 (MH$^+$, 100%).

Similarly, hydrogenolysis of benzyl ester (−)-**10** (40 mg, 64 μmol) and esterification with (*R*)-(+)-1-phenylethanol gave *lactam* (−)-**42a** (28.2 mg, 59%) as an oil (Found: MH$^+$, 641.2702); CD λ_{max}/nm (Mol.Ellip./10^4) 280 (−5); the other physical characteristics were identical to those reported above for (+)-**42a**.

2,8-Bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-9-(1-phenylethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one (+)-42b and (−)-42b

Using the procedure described above, hydrogenolysis of benzyl ester (+)-**10** (24.3 mg, 39 μmol) and esterification with (*R*)-(+)-1-phenylethanol afforded, after purification by preparative TLC eluting with ethyl acetate, the *lactam* (+)-**42b** (16.7 mg, 67%) as an oil (Found: MH$^+$, 641.2741. $C_{33}H_{40}N_2O_{11}$ requires *M* + *H*, 641.2710); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (+1); λ_{max}(MeCN)/nm 278; δ_H($CDCl_3$, 400 MHz) 1.33 (3 H, s, 4-Me), 1.59 (3 H, d, *J* 6.5, CH*Me*), 2.40–2.65 (6 H, m) and 2.92–3.01 (2 H, m, 2 × $CH_2CH_2CO_2$), 2.75 and 2.94 (each 1 H, d, *J* 15, 5-H_2), 3.31 and 3.69 (each 1 H, d, *J* 17, CH_2CO_2), 3.32 and 3.53 (each 1 H, d, *J* 15.5, CH_2CO_2), 3.60, 3.62, 3.72 and 3.79 (each 3 H, s, OMe), 6.00 (1 H, q, *J* 6.5, C*H*Me), 6.97 (1 H, br s, lactam-NH), 7.24–7.37 (5 H, m, Ph) and 10.08 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.8 and 20.6 (*C*$H_2CH_2CO_2$), 22.4 and 24.5 (C*Me*), 29.7, 30.3, 31.2, 33.3 and 34.9 (4 × *C*H_2CO_2 and C-5), 51.4, 51.5, 52.5 and 53.0 (OMe), 62.9 (C-4), 72.3 (*C*HMe), 115.2, 116.5, 129.1, 129.2, 136.2, 141.7 and 150.2 (C=C), 127.7, 128.4 and 129.1 (aromatic CH), 160.1 (9-CO_2) and 171.1, 171.6, 173.6, 173.6 and 173.7 (4 × *C*O_2Me and CONH); *m*/*z* (+FAB) 641 (MH$^+$, 25%) and 460 (100).

Similarly, hydrogenolysis of benzyl ester (−)-**10** (10 mg, 16 μmol) and esterification with (*S*)-(−)-1-phenylethanol gave the enantiomeric *lactam* (−)-**42b** (8.5 mg, 83%) as an oil (Found: MH$^+$, 641.2675); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (−1); the other physical characteristics were identical to those reported above for (+)-**42b**.

9-(Benzotriazol-1-yloxycarbonyl)-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one (−)-41

The benzyl ester (−)-**10** (48.3 mg, 7.7 μmol) was hydrogenolysed as described above and esterified with (*R*)-(+)-1-phenylethanol, allowing a reaction time of only 4 h, to give lactam (−)-**42a** (17.7 mg, 36%) and, at lower R_f *benzotriazol-1-yl ester* (−)-**41** (17.3 mg, 34%) as an oil (Found: MH$^+$, 654.2439. $C_{31}H_{35}N_5O_{11}$ requires *M* + *H*, 654.2411); CD λ_{max}/nm (Mol.Ellip./10^4) 292 (−2); λ_{max}(MeCN)/nm 293 and 261; δ_H($CDCl_3$, 400 MHz) 1.42 (3 H, s, 4-Me), 2.43–2.68 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.89 and 3.08 (each 1 H, d, *J* 15.5, 5-H_2), 3.05 and 3.31 (each 1 H, d, *J* 17.5, CH_2CO_2), 3.39 and 3.71 (each 1 H, d, *J* 16, CH_2CO_2), 3.36, 3.59, 3.76 and 3.77 (each 3 H, s, OMe), 7.10 (1 H, br s, lactam-NH), 7.40 (2 H, m), 7.51 (1 H, d, *J* 4) and 8.04 (1 H, d, *J* 8.5, Ar) and 10.92 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.7 and 20.5 (*C*$H_2CH_2CO_2$), 25.0 (4-Me), 29.5, 30.2, 31.1, 33.1 and 34.2 (4 × *C*H_2CO_2 and C-5), 51.4, 51.6, 52.7 and 53.3 (OMe), 62.6 (C-4), 106.7, 120.2, 124.6 and 126.5 (C=*C*H), 112.1, 117.1, 129.1, 133.6, 135.3, 137.1, 143.4 and 149.6 (C=C) and 155.4, 166.2, 171.0, 172.4, 173.3 and 173.4 (C=O); *m*/*z* (+FAB) 654 (MH$^+$, 35%), 519 (90) and 307 (100).

A solution of benzotriazolyl ester (−)-**41** (15.4 mg, 23 μmol), (*R*)-(+)-1-phenylethanol (29 mg, 0.23 mmol) and 4-dimethylaminopyridine (29 mg, 0.23 mmol) in dichloromethane (2 cm^3) was stirred under argon for 43 h and then evaporated. Purification of the residue by preparative TLC, eluting with ethyl acetate, gave lactam (−)-**42a** (8.1 mg, 54%).

10-Nitroso-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-9-(1-phenylethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one 44a

Fused sodium acetate (20 mg, 0.175 mmol) was suspended in a solution of lactams (+)-**42a** (26 mg, 41 μmol) and (−)-**42a** (26 mg, 41 μmol) in anhydrous dichloromethane (3 cm^3). The mixture was cooled to 0 °C under argon and a solution of dinitrogen tetroxide in dichloromethane (0.77 mol dm^{-3}; 210 mm^3, 0.131 mmol) was added dropwise. After 1 h the solution was evaporated and the residue was purified by preparative TLC, eluting with ethyl acetate–hexane (7:3), to give the N-*nitroso lactam* **44a** (41.3 mg, 76%; 95% based on unrecovered starting material) as yellow rods, mp 132–133.5 °C (from ethyl acetate–toluene–hexane) (Found: M$^+$, 669.2524. $C_{33}H_{39}N_3O_{12}$ requires *M*, 669.2534); λ_{max}(CD_3CN)/nm 272 and 251; δ_H($CDCl_3$, 500 MHz) 1.50 (3 H, s, 4-Me), 1.59 (3 H, d, *J* 6.5, CH*Me*), 2.41–2.48 (2 H, m), 2.63–2.67 (3 H, m), 2.79–2.86 (2 H, m) and 2.91–2.94 (1 H, m, 2 × $CH_2CH_2CO_2$), 2.81 and 3.49 (each 1 H, d, *J* 15.5, 5-H_2), 3.22 and 3.30 (each 1 H, d, *J* 16.5, CH_2CO_2), 3.40 and 3.87 (each 1 H, d, *J* 17.5, CH_2CO_2), 3.61, 3.64, 3.65 and 3.84 (each 3 H, s, OMe), 6.06 (1 H, q, *J* 6.5, C*H*Me), 7.24–7.43 (5 H, m, Ph) and 9.96 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 20.0 and 20.5 (*C*$H_2CH_2CO_2$), 20.7 and 22.4 (C*Me*), 26.9, 29.9, 30.3, 30.4 and 34.6 (4 × *C*H_2CO_2 and C-5), 51.4, 51.7, 51.9 and 53.6 (OMe), 67.7 (C-4), 71.8 (CHMe), 116.4, 119.0, 126.4, 129.7, 134.5, 141.6 and 154.0 (C=C), 126.1, 127.7 and 128.3 (C=*C*H), 159.6, 166.5, 170.7, 172.4, 173.2 and 173.6 (C=O); *m*/*z* (+FAB) 669 (M$^+$, 100%).

10-Nitroso-2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-9-(1-phenylethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one 44b

Using the procedure described above, a mixture of lactams (+)-**42b** (8.5 mg, 1.3 μmol) and (−)-**42b** (8.5 mg, 1.3 μmol) was *N*-nitrosated to give the N-*nitroso lactam* **44b** (9.1 mg, 51%; 78% based on unrecovered starting material) as a yellow oil (Found: MH^+, 670.2615. $C_{33}H_{39}N_3O_{12}$ requires $M + H$, 670.2612); λ_{max}($CDCl_3$)/nm 272 and 251; δ_H($CDCl_3$, 400 MHz) 1.48 (3 H, s, 4-Me), 1.60 (3 H, d, *J* 6.5, CH*Me*), 2.40–2.62 (5 H, m), 2.74–2.83 (2 H, m) and 2.92–2.97 (1 H, m, 2 × $CH_2CH_2CO_2$), 2.78 and 3.48 (each 1 H, d, *J* 15.5, 5-H_2), 3.22 and 3.29 (each 1 H, d, *J* 16.5, CH_2CO_2), 3.38 and 3.88 (each 1 H, d, *J* 17.5, CH_2CO_2), 3.61, 3.61, 3.64 and 3.84 (each 3 H, s, OMe), 6.02 (1 H, q, *J* 6.5, C*H*Me), 7.23–7.42 (5 H, m, Ph) and 9.94 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.9 and 20.6 (*C*$H_2CH_2CO_2$), 20.7 and 22.2 (C*Me*), 29.0, 30.0, 30.3, 30.5 and 34.7 (4 × *C*H_2CO_2 and C-5), 51.4, 51.7, 51.9 and 53.5 (OMe), 67.7 (C-4), 72.2 (*C*HMe), 116.4, 119.2, 126.6, 129.6, 134.6, 141.7 and 154.1 (C=*C*), 126.3, 127.7 and 128.4 (C=*C*H), 159.6, 166.5, 170.6, 172.3, 173.3 and 173.6 (C=O); *m*/*z* (+FAB) 670 (MH^+, 100%).

2,8-Bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 46

A solution of benzyl ester (+)-**10** (4 mg, 6 μmol) in tetrahydrofuran (2 cm^3) was stirred with 10% palladium-on-charcoal (5 mg) under hydrogen at room temperature and atmospheric pressure for 2 h, then filtered through Celite and evaporated. The resulting acid **40** was dissolved in trifluoroacetic acid (2 cm^3) and stirred under argon for 3 h. The solvent was evaporated and the residue was purified by preparative TLC, eluting with ethyl acetate, to give (S)-*lactam* **46** (2.9 mg, 92%) as an oil (Found: MH^+, 493.2190. $C_{24}H_{32}N_2O_9$ requires $M + H$, 493.2186); CD λ_{max}/nm (Mol.Ellip./10^4) no peak above 200; λ_{max}(MeCN)/nm no peak above 200; δ_H($CDCl_3$, 400 MHz) 1.31 (3 H, s, 4-Me), 2.47–2.75 (8 H, m, 2 × $CH_2CH_2CO_2$), 2.73 and 2.91 (each 1 H, d, *J* 15, 5-H_2), 3.32 and 3.42 (each 1 H, d, *J* 15, CH_2CO_2), 3.40 and 3.58 (each 1 H, d, *J* 17, CH_2CO_2), 3.65, 3.65, 3.71 and 3.76 (each 3 H, s, OMe), 6.36 (1 H, d, *J* 2, 9-H), 6.91 (1 H, br s, lactam-NH) and 8.86 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.8 and 20.7 (*C*$H_2CH_2CO_2$), 24.3 (4-Me), 30.1, 30.5, 31.1, 33.5 and 34.7 (4 × *C*H_2CO_2 and C-5), 51.5, 51.6, 52.2 and 52.7 (OMe), 63.5 (C-4), 112.0, 121.0, 124.1, 135.4 and 151.0 (C=C), 114.2 (C-9) and 171.3, 171.4, 173.7, 173.8 and 173.9 (C=O); *m*/*z* (+FAB) 493 (MH^+, 6%), 307 (50) and 154 (100).

2,7-Bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-4,5-dihydrodipyrrin-1(10*H*)-one 47

Using the procedure described above, benzyl ester (+)-**22** (10 mg, 16 μmol) was hydrogenolysed and decarboxylated to give (S)-*lactam* **47** (4 mg, 51%) as an oil (Found: MH^+, 493.2190. $C_{24}H_{32}N_2O_9$ requires $M + H$, 493.2186); CD λ_{max}/nm (Mol.Ellip./10^4) no peak above 200; λ_{max}(MeCN)/nm no peak above 200; δ_H($CDCl_3$, 400 MHz) 1.13 (3 H, s, 4-Me), 2.50–2.74 (9 H, m, 2 × $CH_2CH_2CO_2$ and 5-H_A), 3.02 (1 H, d, *J* 15, 5-H_B), 3.40 (2 H, s, CH_2CO_2), 3.42 and 3.51 (each 1 H, d, *J* 17, CH_2CO_2), 3.64, 3.66, 3.67, 3.74 (each 3 H, s, OMe), 6.51 (1 H, d, *J* 3, 9-H), 6.72 (1 H, br s, lactam-NH) and 8.78 (1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.5 and 19.8 (*C*$H_2CH_2CO_2$), 24.0 (4-Me), 30.7, 31.2, 31.5, 33.3 and 34.8 (4 × *C*H_2CO_2 and C-5), 51.6, 51.8, 51.8 and 52.7 (OMe), 63.6 (C-4), 113.8 (C-9), 116.4, 118.4, 122.9, 134.9 and 152.0 (C=C) and 170.7, 171.7, 172.83, 173.8 and 174.5 (C=O); *m*/*z* (+FAB) 493 (MH^+, 50%), 307 (70) and 238 (100).

4-[3-(2-Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-pyrrol-2-ylmethyl]-2,8-bis(2-methoxycarbonylethyl)-3,7-bis-(methoxycarbonylmethyl)-9-(2,2,2-tribromoethoxycarbonyl)-4,5-dihydrodipyrrin-1(10*H*)-one 49x and 49y

A solution of *lactam* **5x** (lactam **40a** in the preceding paper [1]) (18 mg, 15 μmol) in dichloromethane (1 cm^3) and anisole (1 cm^3) was stirred with aluminium trichloride (21 mg, 150 μmol) for 2 h under argon and then evaporated. A solution of the residue in ethyl acetate (5 cm^3) was washed with water (3 × 5 cm^3), dried and evaporated to afford the crude acid **48x** as an oil. A solution of this oil in trifluoroacetic acid (2.5 cm^3) was stirred under argon for 2 h and then evaporated. The residue was purified by preparative TLC, eluting with ethyl acetate, to give α-*free pyrrole* **49x** (13.3 mg, 84%) as an oil (Found: MH^+, 1022.0509. $C_{38}H_{46}Br_3N_3O_{15}$ requires $M + H$, 1022.0559); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (−10); λ_{max}(MeCN)/nm 282; δ_H($CDCl_3$, 400 MHz) 2.43–2.56 and 2.67–2.73 (12 H, m, 6 × CH_2CH_2), 2.83 (1 H, d, *J* 15), 2.97–3.08 (2 H, m) and 3.14 (1 H, d, *J* 16, CH_2CCH_2), 3.40 and 3.51 (each 1 H, d, *J* 17, CH_2CO_2), 3.40 (2 H, s, CH_2CO_2), 3.44 and 3.48 (2 H, m, CH_2CO_2), 3.60, 3.61, 3.64, 3.66, 3.68, 3.77 (each 3 H, s, OMe), 5.04 and 5.09 (each 1 H, d, *J* 12, CH_2CBr_3), 6.48 (1 H, d, *J* 2, α-H), 7.63 (1 H, br s, lactam-NH) and 8.42 and 10.36 (each 1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.58, 19.87, 20.40 (3 × *C*$H_2CH_2CO_2$), 29.03, 30.29, 30.42, 31.31 (2 C), 32.99, 34.98, 35.09 and 35.98 (3 × $CH_2CH_2CO_2$, 3 × *C*H_2CO_2, CH_2CCH_2 and *C*Br_3), 51.48, 51.57, 51.97, 52.60, 53.17 and 53.42 (6 × OMe), 68.37 (C-4), 76.76 (*C*H_2CBr_3), 113.94, 115.85, 116.49, 116.74, 116.87, 118.59, 122.33, 130.48, 137.88 and 149.59 (C=C), 159.67 (α-CO_2) and 171.93, 172.28, 172.83, 173.49 (2 C), 173.60 and 173.92 (6 × CO_2 and CONH); *m*/*z* (+FAB) 1022, 1024, 1026 and 1028 (1:3:3:1, MH^+, 100%).

Similarly lactam **5y** (lactam **40b** in the preceding paper [1]) (12 mg, 10 μmol) gave α-*free pyrrole* **49y** as an oil (4.5 mg, 44%) (Found: MH^+, 1022.0543); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (+10).

4-[5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)pyrrol-2-ylmethyl]-2,8-bis-(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4,5-dihydrodipyrrin-1(10*H*)-one 51x and 51y

A solution of *lactam* **5x** [1] (11.6 mg, 10 μmol) in acetic acid (1 cm^3) was stirred with zinc powder (50 mg) for 30 min and then filtered through Celite. The filtrate was diluted with water (10 cm^3) and extracted with dichloromethane (4 × 5 cm^3). The combined extracts were washed with water, dried and evaporated to afford the crude acid **50x** as an oil. A solution of the oil in redistilled trifluoroacetic acid (1 cm^3) was stirred at room temperature for 3 h under argon and then evaporated. A solution of the residue in dichloromethane (5 cm^3) was washed with saturated aqueous sodium hydrogen carbonate (2 × 2 cm^3), dried and evaporated. The residue was purified by preparative TLC, eluting with diethyl ether–methanol (19:1), to give α-*free pyrrole* **51x** (5.8 mg, 68%) as an oil (Found: MH^+, 850.3421. $C_{43}H_{51}N_3O_{15}$ requires $M + H$, 850.3398); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (+4); λ_{max}(MeCN)/nm 281; δ_H($CDCl_3$, 400 MHz) 2.37–2.50 and 2.64–2.67 (12 H, m, 3 × CH_2CH_2), 2.77 and 3.00 (each 1 H, d, *J* 15, CH_2CCH_2), 2.79 and 3.08 (each 1 H, d, *J* 15, CH_2CCH_2), 3.22 and 3.38 (each 1 H, d, *J* 16, CH_2CO_2), 3.49 and 3.57 (each 1 H, d, *J* 15, CH_2CO_2), 3.54, 3.59, 3.59, 3.62, 3.63 and 3.75 (each 3 H, s, OMe), 3.72 and 3.79 (each 1 H, d, *J* 17, CH_2CO_2), 5.14 and 5.23 (each 1 H, d, *J* 12, CH_2Ph), 6.33 (1 H, d, *J* 2, α-H), 7.25–7.35 (5 H, m, Ph), 7.48 (1 H, br s, lactam-NH) and 8.99 and 9.72 (each 1 H, br s, pyrrole-NH); δ_C($CDCl_3$, 100 MHz) 19.18, 19.70 and 20.65 (3 × *C*$H_2CH_2CO_2$), 29.81, 30.45, 30.62, 30.77, 31.63, 31.81 and 34.73 (2 C) (3 × CH_2CH_2CO, 3 × *C*H_2CO_2, *C*H_2CCH_2), 51.48, 51.58, 51.72, 51.77, 52.09 and 53.00 (OMe), 65.71 and 66.54 (CH_2Ph and C-4), 112.26, 114.42, 114.76, 119.05, 120.92, 121.91, 122.35, 123.30, 128.03, 128.26 (2 C), 128.39 (2 C), 136.07, 137.36 and 149.76 (C=C), 160.43 (α-CO_2) and 171.48, 171.90, 172.37, 173.38, 173.58, 173.70 and 173.80 (6 × CO_2 and CONH); *m*/*z* (+FAB) 850 (MH^+, 90%), 609 (45) and 238 (100).

Similarly *lactam* **5y** [1] (11.5 mg) gave α-*free pyrrole* **51y** (5.6

mg, 66%) as an oil (Found: MH^+, 850.3421); CD λ_{max}/nm (Mol.Ellip./10^4) 285 (−4).

Acknowledgements

Grateful acknowledgement is made to the EPSRC, Zeneca, Roche Products and F. Hoffmann-La Roche for financial support, to the Natural Sciences and Engineering Research Council of Canada for the award of a postdoctoral fellowship (to A. C.) and Dr D. Obrecht (F. Hoffmann-La Roche, Basel) for a gift of (*S*)-(−)-phenylalanine cyclohexylamide.

References

1 Part 44, M. A. Cassidy, N. Crockett, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2079.
2 Preliminary account of part of this work: A. C. Spivey, A. Capretta, C. S. Frampton, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1995, 1789.
3 F. J. Leeper and A. R. Battersby, *Chem. Rev.*, 1990, **90**, 1261; F. J. Leeper, *Nat. Prod. Rep.*, 1989, **6**, 171.
4 W. M. Stark, C. J. Hawker, G. J. Hart, A. Philippides, P. M. Petersen, J. D. Lewis, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2875.
5 M. A. Cassidy, N. Crockett, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1991, 384.
6 C. J. Hawker, P. M. Petersen, A. C. Spivey, F. J. Leeper and A. R. Battersby, unpublished results.
7 C. J. Hawker, PhD Thesis, Cambridge, 1988.
8 A. C. Spivey, A. R. Battersby and C. S. Frampton, *J. Chem Soc., Perkin Trans. 1*, 1996, 2103.
9 K. Mislow, *J. Am. Chem. Soc.*, 1951, **73**, 3954.
10 E. Frerot, J. Coste, A. Pantaloni, M.-N. Dufour and P. Jouin, *Tetrahedron*, 1991, **47**, 259.
11 J. Coste and J.-M. Campagne, *Tetrahedron Lett.*, 1995, **36**, 4253.
12 L. Floch, F. Nydegger, A. Gossauer and C. Kratky, *Helv. Chim. Acta*, 1994, **77**, 445.
13 T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitana, S. Hirai, T. Maeda and W. Nagota, *Tetrahedron Lett.*, 1979, 2793.
14 N. P. J. Stamford, A. Capretta and A. R. Battersby, *Eur. J. Biochem.*, 1995, **231**, 236; see also M. Hansson, L. Rutberg, I. Schröder and L. Hederstedt, *J. Bacteriol.*, 1991, **173**, 2590.
15 A. D. Miller, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1943.
16 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2413.
17 A. R. Battersby, S. Kishimoto, E. McDonald, F. Satoh and H. K. W. Wurziger, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1927.
18 B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye and L. Ghosez, *Org. Synth.*, 1979, **59**, 26.

Paper 6/01623E
Received 7th March 1996
Accepted 7th June 1996