Synthesis of fused 1,2,5-triazepine-1,5-diones and some N^2- and N^3-substituted derivatives: potential conformational mimetics for *cis*-peptidyl prolinamides[1]

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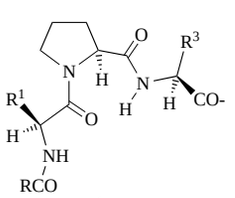
The synthesis of a new fused 1,2,5-triazepine-1,5-dione heterocycle, which is expected to mimic structural features of *cis*-peptidyl prolinamides, is described. The required parent heterocycle, corresponding to *cis*-glycyl-(2*S*)-prolinamide, has been prepared in good yield by the cyclisation of *N*-(2-bromoacetylprolyl)-hydrazine which is itself generated *in situ* from the bromoacetyl proline methyl ester. Analogues corresponding to *cis*-(2*R*)-alanyl- and *cis*-(2*S*)-alanyl-(2*S*)-prolinamide have been similarly prepared from the appropriate *N*-(2-bromopropionyl)proline methyl esters and hydrazine hydrate where the cyclisation step, involving the displacement of bromide, has been shown to occur with inversion of configuration at C-2 of the propionyl moiety. Acylation at the N-3 position of the triazepine is equivalent to N-terminal acylation of the residue preceding the proline residue in *cis*-aminoacyl prolinamides. This has been achieved without incident using standard peptide coupling procedures. Extension at the 'C-terminal' has been achieved by preparing elaborated hydrazine precursors which are reacted with suitably activated esters of *N*-α-halogenoacylprolines, prior to cyclisation, to give the required fused triazepine dione. Thus it is possible to prepare constrained *cis*-peptidyl prolyl peptide mimetics of defined stereochemistry based upon this new triazepine dione in which all of the non-proline residues can be varied.

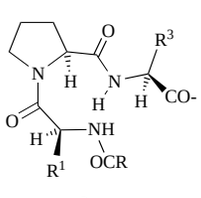
Introduction

Proline is unique amongst proteogenic amino acids in possessing a secondary amino group. Acyl prolines possess no amide hydrogen atoms and, therefore, the energies of the *cis*- and *trans*-isomeric forms are similar.[2] In nature, the Xaa–Pro peptide bond can exist in both stable conformations, structures **1** and **2**, and both forms occur in proteins, as in ribonuclease,[3] and in bioactive peptides, such as bradykinin.[4] The interconversions of the *cis*- and *trans*-forms of small peptides are quite slow in water[5] ($k = 10^{-1}$–10^{-3} s^{-1} at 30 °C) and peptidylprolyl *cis–trans*-isomerases (rotamases), for example cyclophilin[6] and FK506 binding protein,[7] exist to speed up the rates of isomerisation.[8] In recent years there has been immense interest in the enzyme activities and it is now believed that the slow uncatalysed isomerisation rate is important and may play a role in controlled proteolysis.



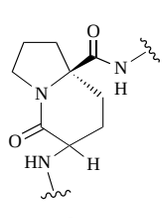
1

trans-Xaa-Pro-Yaa-



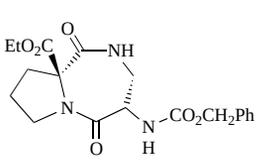
2

cis-Xaa-Pro-Yaa-



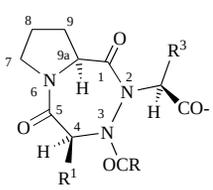
3

cis-Gly-Pro mimetic unit



4

cis-X-Pro dipeptide



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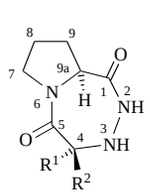


6 $R^1 = R^2 = H$

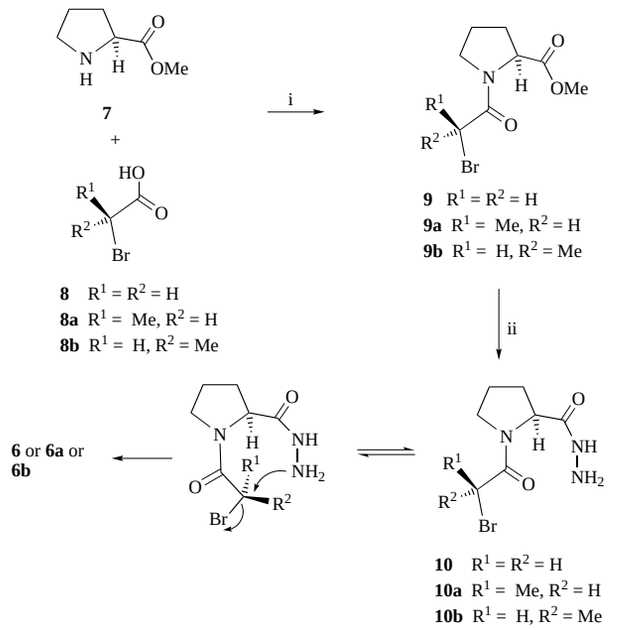
6a R^1 = Me, R^2 = H

6b R^1 = H, R^2 = Me

Given that some proline-containing bioactive peptides including angiotensin and thyroliberin might bind to their receptors with the Pro residue fixed in the *cis*-form[9] it has been of interest to synthesise constrained *cis*-peptidyl prolinamides which might serve as high affinity ligands. In all examples of previously reported constrained *cis*-peptidyl proline analogues, the constraining modification had caused a significant increase in the steric size of the system, for example, the C^{α}–C^{α} bridged type VI reverse-turn Gly-Pro mimetics recently described by Gramberg and Robinson (compound **3**)[10] and by McEnaney and Curran (compound **4**).[11] We wished to introduce the smallest modification possible in order to retain the maximum potential for biological activity in the finished peptides and/or structural motifs of proteins. Therefore, we opted to link the N^{α}-atom of the residue preceding Pro to the N^{α}-atom of the residue following Pro. Such a modification differs from the parent system **2** by just two H-atoms, but fixes the stereochemistry of the acyl proline amide bond in its *cis*- or (*E*)-configuration through the formation of a novel [*d*]-fused 1,2,5-triazepine-1,5-dione system **5**. This compound mimics a *cis*-peptidyl prolinamide, and as such might be used as a reverse-turn mimetic in the design of biologically active molecules that need to emulate features of the common β-turn motifs (*e.g.* type I, II, IV). β-Turns are not only important structural features in protein secondary structure but are implicated in the receptor bound conformations of many bioactive peptides.[4,12,13] Recently, work on the synthesis of systems designed to mimic the various types of β-turns include indole derivatives,[14] α-alkylated aspartic and glutamic acids,[15] azanorbornane derivatives[16] and acetylenes.[17,18]

Results and discussion

To synthesise the simplest [*d*]-fused 1,2,5-triazepine-1,5-dione **6**, (2*S*)-proline methyl ester **7** was treated with bromoacetic acid **8** activated as its mixed anhydride to give the required bromoacetamide **9**, Scheme 1. Treatment with hydrazine hydrate in ethanol was expected to give an equilibrium mixture of predominately the *trans*-α-bromoacetyl proline hydrazide **10** and



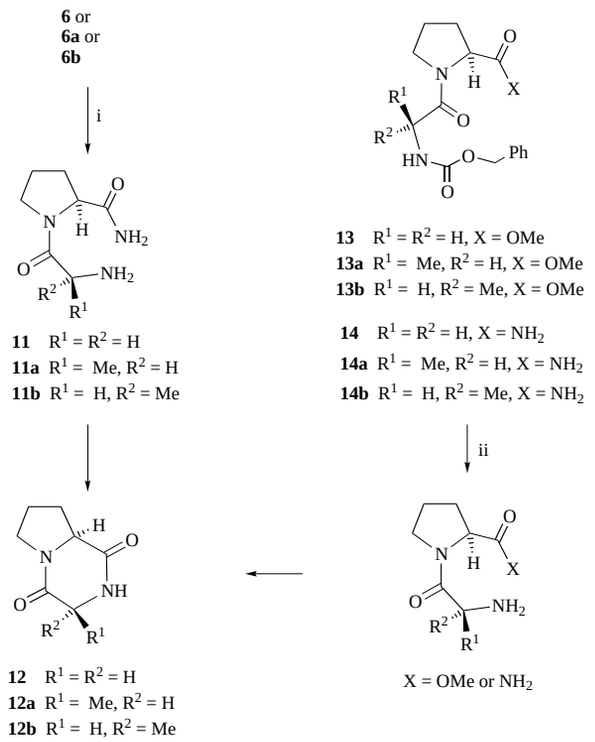
Scheme 1 *Reagents and conditions:* i, NMM, isobutyl chloroformate, THF–DMF, −40 °C; ii, $H_2NNH_2 \cdot H_2O$, EtOH, reflux

the *cis*-rotomer which would cyclise through the nucleophilic displacement of bromide ion in the *cis*-rotomer by the non-acylated hydrazine N-atom, to give the required *cis*-glycyl (2*S*)-prolinamide analogue **6**. In the event, after refluxing for 1.5 h a compound was isolated which gave the expected mass data and showed the existence of two major conformational isomers in its ^{1}H and ^{13}C NMR spectra in [$^2H_6$]DMSO. The compound failed to form a hydrazone adduct upon treatment with benzaldehyde and together these results indicated that the required 7-membered triazepine rather than a 6-membered piperazine ring had been formed.

Each of the diastereomeric (2*S*)- and (2*R*)-alanyl-(2*S*)-proline ester homologues, **9a** and **9b**, were prepared in a similar manner, starting from the appropriate chiral 2-bromopropionic acids, which were themselves prepared *via* the diazotisation–bromination of (2*S*)- and (2*R*)-alanine.[1] Each diastereomeric ester **9a** and **9b** was obtained as a crystalline solid in moderate yield but examination of the NMR spectra of the crude reaction mixtures for each of the coupling reactions indicated that some epimerisation had occurred. In subsequent reactions the epimerisation was largely prevented by lowering the temperature of both the acyl group activation and N-acylation reaction from −15 to −40 °C. For the compound **9b**, that derived from (2*R*)-2-bromopropionic acid, the absolute stereochemistry at C-2 of the 2-bromopropionyl moiety was verified by X-ray crystallography using the (2*S*)-configuration of the proline moiety as a stereochemical reference.[1]

Treatment of each of the individual esters **9a** and **9b** with hydrazine hydrate in refluxing ethanol gave a new product almost immediately, as judged by TLC and by NMR spectroscopy, but in each case, reaction to give a second new product was not complete until 16 h had elapsed, Scheme 1. Thus, it appeared that for each of the homologues **10a** and **10b** the cyclisation step was significantly slower than for the non-methylated derivative **10**. These observations are almost certainly explained by (i) the low equilibrium concentration of the *cis*-isomers of **10a** and **10b** which are required for the cyclisation, due to the steric effects of the extra methyl groups (compared to hydrazide **10**), and (ii) the fact that the cyclisation itself occurs *via* S_N2 attack on a secondary α-bromoacylamide instead of a primary α-bromoacylamide, as in the case for hydrazide **10**. Nevertheless, after prolonged reaction, 16 h in refluxing ethanol, each of the triazepines **6a** and **6b** were obtained in excellent yield (>90%) and each compound displayed the expected spectral and analytical properties.

In order to confirm the expectation that the cyclisations had proceeded with inversion of configuration at C-2 of the bromopropionyl moiety, the fused triazepines **6a** and **6b** were each subjected to dissolving metal reduction to cleave the N^2–N^3 bond and give the alanyl prolinamides **11a** and **11b**. Each of these compounds underwent an extremely rapid spontaneous cyclisation to give the fused dioxopiperazines **12a** and **12b** through the displacement of ammonia from the Pro carboxamide moiety, Scheme 2, which we now wished to compare



Scheme 2 *Reagents and conditions:* i, Na–$NH_{3(liq)}$, −68 °C; ii, H_2, Pd–C, MeOH, 22 °C

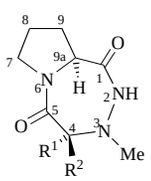
with authentic materials. Each of the diastereomeric dioxopiperazines **12a** and **12b** were therefore also prepared through the catalytic hydrogenolysis of the terminal benzyloxycarbonyl (Z) protecting group of samples of the *N*-Z-alanyl-(2*S*)-proline esters[19] **13a** and **13b**. The same compounds were also prepared from samples of the corresponding *N*-Z-alanyl-(2*S*)-prolinamides **14a** and **14b**, where in each case the amine product rapidly cyclised to the lactam, Scheme 2. The dipeptide esters and amides were prepared using standard solution phase coupling and protection strategies and displayed the expected spectral and analytical data. Comparison of the ^{1}H and ^{13}C NMR spectra of these dioxopiperazines indicated that the cyclisation of the hydrazides **10a** and **10b** to form the triazepines **6a** and **6b** (see Scheme 1) had occurred with inversion at the secondary carbon centre. Therefore, it was possible to synthesise *cis*-aminoacyl prolinamide mimetics of defined stereochemistry.

The reason that we had synthesised the protected dipeptide amides **14**, **14a** and **14b** was because the dissolving metal reduction of the triazepinediones **6**, **6a** and **6b** and their subsequent lactamisation reactions had been so facile. Essentially, no uncyclised material remained after work-up or after low temperature (−50 °C) NMR spectroscopic analysis of the reaction quenched with [$^2H_4$]methanol (after the blue colour due to solvated electrons had disappeared). Since cleavage of the hydrazine moiety under such conditions could generate highly nucleophilic metal amides or N-centred radicals derived from N-3, we wished to assess how rapidly the amines **11**, **11a** and **11b** derived from the protected dipeptide amides **14**, **14a** and **14b**

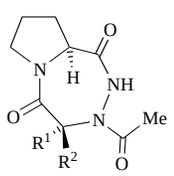
would cyclise. In the event, small quantities of uncyclised amine **11**, **11a** and **11b** could be detected as judged by ^{1}H NMR spectroscopy, after partial but rapid catalytic hydrogenolysis under neutral conditions at room temperature (20–25 °C). Thus, this finding appears to suggest that much more of the non-cyclised material **11**, **11a** and **11b** should have been detected in quenched dissolving metal reductions of compounds **6**, **6a** and **6b**, if the cyclisation involved the simple displacement of ammonia by a neutral amine nucleophile. A further allowance for the differences in the cyclisation rates must take into account the fact that at low temperature, all of the nascent amino amides derived from compounds **6**, **6a** and **6b** is in the *cis*-rotomer form and cannot isomerise to the *trans*-form. Thus, we are currently exploring less 'basic' conditions for generating the *cis*-forms of the amino amides **11**, **11a** and **11b** in order to evaluate each of the factors involved in determining the cyclisation rate.

The next objective in the synthesis of *cis*-peptidyl prolinamide mimetics was to extend both the N- and C-termini of the dipeptide mimetic, corresponding to N-2 and N-3 of the triazepine, to emulate longer and more elaborate polypeptides.

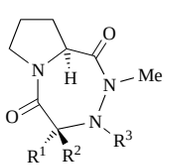
In order to achieve these ends, it was necessary to determine the regioselectivity for the reaction of unsymmetrical hydrazines with the two electrophilic centres present in the bromoacylprolinate esters **9**, **9a** and **9b**. Accordingly, each of the α-bromoacyl-(2*S*)-proline methyl esters **9**, **9a** and **9b** were treated with methylhydrazine. Unfortunately, but as expected, the ester methoxy group was displaced exclusively by the less hindered primary amino group and subsequent cyclisation occurred with inversion of configuration to give the N^3-methyl-1,2,5-triazepine diones **15**, **15a** and **15b**. Since these compounds



15 $R^1 = R^2 = H$
15a R^1 = Me, R^2 = H
15b R^1 = H, R^2 = Me



16 R^1 = Me, R^2 = H

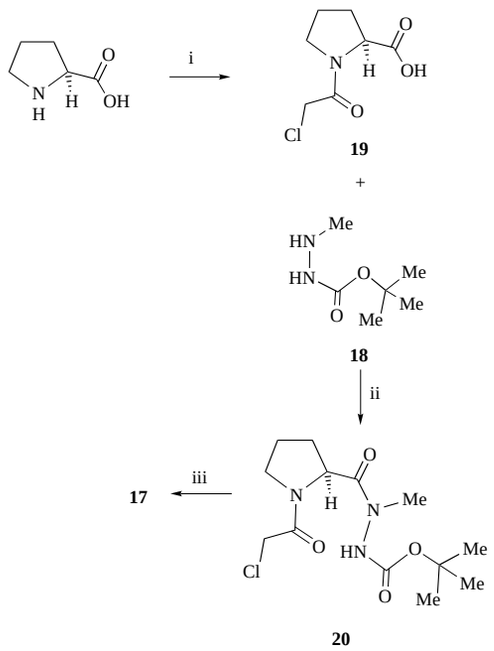


17 $R^1 = R^2 = R^3 = H$
17a R^1 = Me, $R^2 = R^3$ = H
17b R^1 = H, R^2 = Me, R^3 = H
17c R^1 = Me, R^2 = H, R^3 = ZPhe

were resistant to both dissolving metal and catalytic reduction, the structures of compounds **15** and **15a** were verified by X-ray crystallographic analysis using the known stereochemistry at C-2 of proline for reference.[1] The outcome of these reactions indicated that we would need to introduce alkyl groups at the N-2 position using a more elaborate approach, see below.

In order to assess the reactivity of the N-3 position of the triazepine which is equivalent to the N-terminal of a *cis*-dipeptide, compound **6a** was treated with acetic anhydride in pyridine. After 2 days the N^3-acetyl-1,2,5-triazepine-1,5-dione **16** was isolated in moderate yield. Similarly the reaction of compound **17a** (see below) with *N*-Z-(2*S*)-phenylalanine activated using isobutyl chloroformate and *N*-methylmorpholine gave the corresponding N^3-phenylalanyl derivative **17c**, indicating that extension at the N-terminal of the peptide mimetic was possible.

Given the preferred regioselectivity for the reaction of methylhydrazine with compounds **9**, **9a** and **9b**, it was evident that extension at the proline carboxamide (substitution at the N^3-position of the triazepine-1,5-dione system) would require the synthesis of unsymmetrical alkylhydrazines protected on the primary amino group. Accordingly, N^2-*tert*-butoxycarbonyl-N^1-methylhydrazine **18** was prepared from methylhydrazine in three steps. Reaction of this with the mixed anhydride of chloroacetyl-(2*S*)-proline **19**, Scheme 3, gave the



19

18

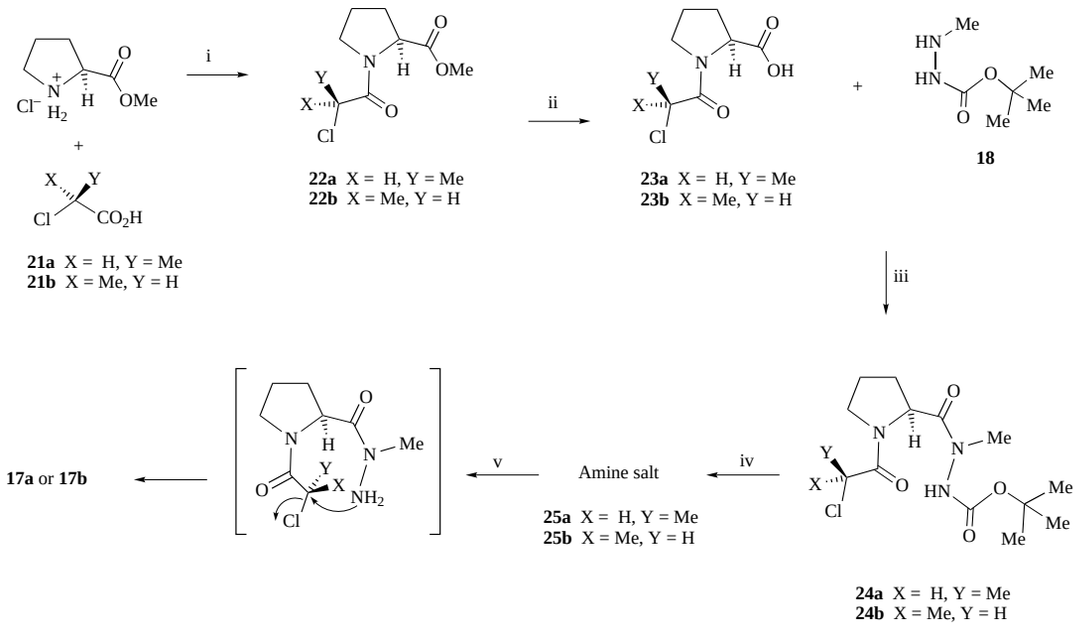
20

Scheme 3 *Reagents and conditions:* i, $ClCH_2COCl$, $NaHCO_3$, EtOAc, 78 °C, 50 min, 74%; ii, NMM, isobutyl chloroformate, THF, −10 °C, 12 h, 73%; iii, HCl, MeOH, 22 °C; 15 min; then NaOH, H_2O, 5 min, 79%

required proline hydrazide **20** in 73% yield. Our reasons for using the chloroacetyl rather than bromoacetyl derivatives are given below. Removal of the *tert*-butoxycarbonyl (Boc) protecting group with hydrogen chloride gave the amine salt which, upon treatment with sodium hydroxide, cyclised to give the desired N^2-methyl-1,2,5-triazepine-1,5-dione **17**.

The synthesis of the 4-methyl-N^2-methyl-1,2,5-triazepine-1,5-diones **17a** and **17b** proved to be more difficult due to unwanted reactions at the second chiral centre (C-2 of the propionyl moiety). The carboxylic acid precursors **23a** and **23b** were obtained through the saponification of the methyl esters **22a** and **22b** respectively, using 1 mol dm^{-3} aqueous sodium hydroxide, Scheme 4. It is worth noting that hydrolysis of the corresponding bromo dipeptide esters (see above) leads to products that contain two sets of signals in the ^{1}H and ^{13}C NMR spectra. These were later shown to be due to the presence of both diastereomers, and therefore it was reasoned that the C-2 brominated centre had undergone base-catalysed enolisation which had resulted in epimerisation. The 2-chloropropionyl analogues **22a** and **22b** were found to be much more stable and could be saponified without epimerisation, see below.

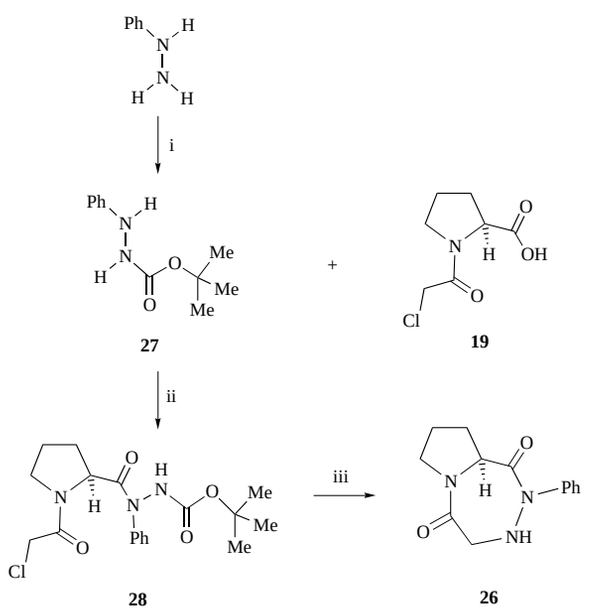
The (2*S*)- and (2*R*)-2-chloropropionic acids, **21a** and **21b** were prepared according to the method of Fu *et al.*[20] and were coupled with proline methyl ester using mixed anhydride methodology as for the bromide analogues. The methyl esters **22a** and **22b** were obtained in 71 and 83% yield respectively and base catalysed hydrolysis then gave the corresponding acids, **23a** and **23b**. The ^{1}H and ^{13}C NMR spectra showed only one set of signals for each compound, indicating that no epimerisation had taken place. Reaction of each of the free acids, **23a** and **23b**, activated as their respective mixed anhydrides, with the methylhydrazine derivative **18** (see Scheme 4) gave the prolyl hydrazides **24a** and **24b** in 69 and 74% yield respectively after



Scheme 4 *Reagents and conditions:* i, NMM, isobutyl chloroformate, THF, −15 °C, 3 h, 83%; ii, 1 mol dm^{-3} NaOH, MeOH–H_2O, room temp., 1 h, 84%; iii, NMM, isobutyl chloroformate, THF, −15 °C, 12 h, 74%; iv, HCl, MeOH, 22 °C; 20 min, 100%; v, NMM, 22 °C, 5 min, 64%

purification by column chromatography. Each compound showed the expected spectroscopic and analytical data. Removal of the Boc groups gave the hygroscopic salts, **25a** and **25b**, which were cyclised in the presence of 2 equiv. of *N*-methylmorpholine (NMM) to give the N^2-methyltriazepines **17a** and **17b**. These bicyclic compounds displayed appropriately different spectroscopic characteristics to the isomeric compounds **15a** and **15b** in accordance with the expected structures.

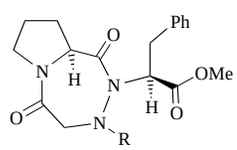
The N^2-phenyl derivative **26** was prepared in four steps in an overall yield of 23% in an analogous manner to that for compound **17** starting from (2*S*)-proline and phenylhydrazine, Scheme 5. The relatively difficult coupling reaction for



Scheme 5 *Reagents and conditions:* i, Boc_2O, Et_2O, 22 °C, 67 h, 86%; ii, $SOCl_2$, pyridine, DMAP, CH_2Cl_2, 22 °C, 2 days, 62%; iii, HCl, EtOAc, 22 °C; 30 min; then NaOH, H_2O, 30 min, 68%

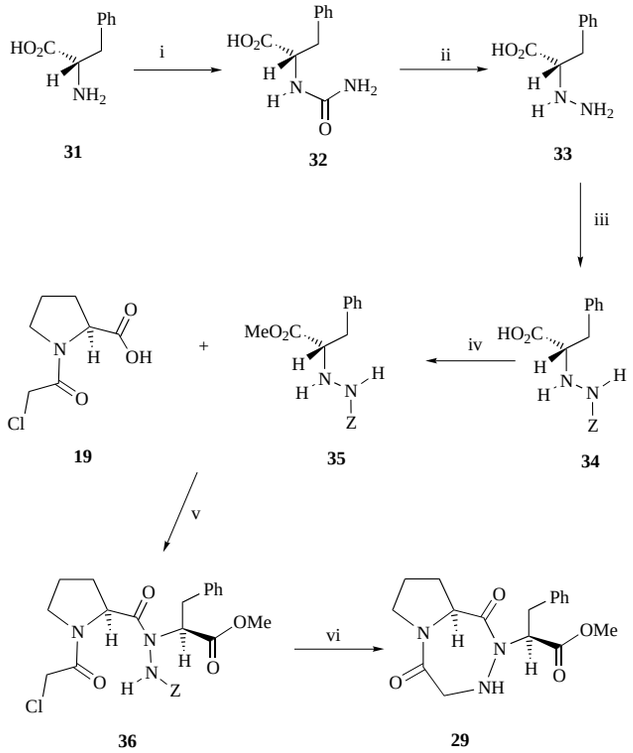
chloroacetyl-(2*S*)-proline **19** and hydrazide **27** was achieved by activation of the carboxylic acid as an acyl pyridinium salt. This intermediate was then used to acylate the phenylated N-atom of the hydrazide in good yield (62%), see Scheme 5. Removal of the Boc protecting group using hydrogen chloride followed by treatment with aqueous sodium hydroxide gave the required N^2-substituted bicycle **26**.

Thus, it was possible to prepare fused 1,2,5-triazepine diones with an alkyl or aryl group present at N-2. Since the ultimate objective was to introduce peptide extensions at the C-terminal end of the *cis*-peptidyl proline mimetic, we opted to prepare a structural analogue for a functional biological system, the *cis*-glycyl prolyl phenylalanine methyl ester mimetic **29**, which is



29 R = H
30 R = ZAla

part of the sequence of the self-cleaving polypeptide from the foot and mouth disease virus 2A region.[21,22] Accordingly (2*S*)-phenylalanine **31** was treated with aqueous potassium cyanate to give the hydantoic acid **32**, Scheme 6. Upon treatment with aqueous potassium hypochlorite this material underwent a Hofmann type rearrangement[23] to give (2*S*)-*N*-aminophenylalanine **33**. Benzyloxycarbonyl protection of the primary amino group, followed by esterification, using thionyl chloride and methanol, gave the methyl ester hydrazide **35** in 60% yield from the hydrazino amino acid. Reaction of the hindered secondary amino group of this hydrazide moiety with the activated ester of *N*-chloroacetyl-(2*S*)-proline **19** using a variety of coupling reagents including isobutyl chloroformate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), benzotriazole-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (pyBOP) and diphenylphosphoryl azide (DPPA) all met with failure. However, when the preformed acyl pyridinium salt of **19** (prepared using thionyl chloride in the presence of pyridine) was treated with the free base of hydrazide **35** the reaction proceeded to give the required substituted peptidic ester **36**. Under optimised conditions a yield of 53% was obtained and the compound displayed the expected properties. The removal of the benzyloxycarbonyl group from compound **36** was achieved using



Scheme 6 *Reagents and conditions:* i, KOCN, H_2O, 60 °C, 4 h; then HCl, H_2O, 86%; ii, KOCl, KOH, H_2O, 80 °C, 90 min; then HCl, H_2O, 36%; iii, benzyl chloroformate, NaOH, H_2O, 22 °C, 1 h, 79%; iv, $SOCl_2$, MeOH, 65 °C; 40 min, 74%; v, $SOCl_2$, pyridine, DMAP, CH_2Cl_2, 22 °C, 2–3 days, 53%; vi, HBr, AcOH, 22 °C, 2 h; then NaOH, H_2O, 90 min, 91%

strongly acidic conditions. Finally, neutralisation of the resulting salt with NaOH gave the free base which cyclised to give the N^2-(1-methoxycarbonyl-2-phenylethyl)triazepine **29** in 91% yield.

A preliminary attempt to prepare the N^2,N^3-disubstituted derivative **30**, by coupling the N^2-substituted triazepine **29** with Z-alanine using isobutyl chloroformate resulted in the required material, in low yield. Nevertheless, it is evident that both N-2 and N-3 of this new fused diazepinedione system can be elaborated to give constrained *cis*-peptidyl proline peptide mimetics of defined stereochemistry and sequence.

Experimental

Elemental microanalyses were performed in the departmental microanalytical laboratory. NMR spectra were recorded on a Bruker AM-300 (^{1}H, 300 MHz; ^{13}C, 74.76 MHz), a Varian Gemini 200 (^{1}H, 200 MHz; ^{13}C, 50.31 MHz), a Varian Gemini 300 (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) or by the SERC service at Warwick using a Bruker AM-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Chemical shifts are described in parts per million downfield from $SiMe_4$ and are reported consecutively as position (δ_H or δ_C), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, sep = septet, m = multiplet and br = broad), coupling constant (*J*/Hz) and assignment (numbering according to the IUPAC nomenclature for the compound). ^{1}H NMR spectra were referenced internally on ^{2}HOH (δ 4.68), $CHCl_3$ (δ 7.27) or $(C^2H_3)_2$SO (δ 2.47). ^{13}C NMR spectra were referenced on CH_3OH (δ 49.3), C^2HCl_3 (δ 77.5) or $(C^2H_3)_2SO$ (δ 39.7).

Pyrrolidine ring carbons and hydrogens are assigned in NMR spectra as α, β, γ and δ, going anticlockwise from the ring nitrogen, according to normal convention. Where more than one conformational isomer can be seen in the NMR spectrum due to the presence of a tertiary amide bond, these are assigned as *c* (*cis*) or *t* (*trans*), according to the isomeric state of the amide bond. Where two sets of peaks arise in NMR spectra due to different conformations of a constrained seven-membered ring, these are assigned as *A* and *B*, with *A* being the major isomer.

IR spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. The samples were prepared as Nujol mulls, solutions in chloroform or thin films between sodium chloride discs. The frequencies (*ν*) as absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard. Mass spectra and accurate mass measurements were recorded on a VG 70-250 SE, a Kratos MS-50 or by the SERC service at Swansea using a VG AZB-E. Fast atom bombardment spectra were recorded using glycerol as matrix. Major fragments are given as percentages of the base peak intensity (100%). UV spectra were recorded on Pye-Unicam SP8-500 or SP8-100 spectrophotometers.

Flash chromatography was performed according to the method of Still *et al.*[24] using Sorbsil C 60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography was carried out on 0.25 mm pre-coated silica gel plates (Macherey-Nagel SIL g/UV_{254}) and compounds were visualised using UV fluorescence, iodine vapour, ethanolic phosphomolybdic acid or ninhydrin.

Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured at 22 °C on an Optical Activity AA-1000 polarimeter using 10 or 20 cm path length cells and are given in units of 10^{-1} deg cm^2 g^{-1}.

The solvents used were either distilled or of analar quality and light petroleum refers to that portion boiling between 40–60 °C. Solvents were dried according to literature procedures. Ethanol and methanol were dried using magnesium turnings. DMF, propan-2-ol, 4-methylbutan-1-ol, toluene, CH_2Cl_2, acetonitrile, diisopropylamine, triethylamine and pyridine were distilled over CaH_2. THF and diethyl ether were dried over sodium–benzophenone and distilled under nitrogen. Thionyl chloride was distilled over sulfur and the initial fractions were always discarded. *N*-Methylmorpholine was distilled over ninhydrin.

(2*S*)-*N*-Bromoacetylproline methyl ester 9 ($R^1 = R^2 = H$)

To a solution of *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry THF (25 cm^3) was added bromoacetic acid **8** ($R^1 = R^2 = H$) (1.39 g, 10 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (1.36 cm^3, 10 mmol) was added with stirring and the resulting suspension was stirred at −15 °C for 2 min. A mixture of (2*S*)-proline methyl ester hydrochloride[25] **7** (1.66 g, 10 mmol) and *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry DMF (5 cm^3) was then added in one portion to the cold suspension. The reaction mixture was allowed to warm to room temperature and was then stirred overnight. The hydrochloride salts were filtered off and the solvents were removed under reduced pressure. The resulting brown oil was dissolved in CH_2Cl_2 (50 cm^3), washed with 0.5 mol dm^{-3} HCl (2 × 20 cm^3) and 5% aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the product as a pale yellow oil. Purification by silica column chromatography using ethyl acetate–light petroleum (1:1) as the eluent gave the pure product as a clear oil (2.07 g, 83%) (HRMS: found $[M + H]^+$, 250.0080. $C_8H_{13}{}^{79}BrNO_3$ requires 250.0079); $[\alpha]_D^{22}$ −96.7 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 1741 (ester CO), 1655 (amide CO) and 1448 (C–O); δ_H(200 MHz; C^2HCl_3) 1.81–2.28 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.48–3.73 (*t* and *c*, 2 H, m, δCH_2), 3.57 (*t*, 3 H, s, OCH_3), 3.62 (*c*, 3 H, s, OCH_3), 3.73 (*c*, 2 H, d, *J* 1.4, $COCH_2$), 3.96 (*t*, 2 H, d, *J* 1.4, $COCH_2$), 4.33 (*t*, 1 H, dd, J_1 4.0, J_2 8.2, αCH) and 4.45 (*c*, 1 H, dd, J_1 3.4, J_2 7.2, αCH); δ_C(50.31 MHz; C^2HCl_3) 22.63 (*c*, γCH_2), 25.24 (*t*, γCH_2), 29.47 (*t*, βCH_2), 31.55 (*c*, βCH_2), 42.38 (*t* and *c*, CH_2Br), 47.44 (*t* and *c*, δCH_2), 52.65 (*t*, OCH_3), 53.32 (*c*, OCH_3),

59.61 (*t* and *c*, αCH), 165.49 (*t*, NCO), 165.59 (*c*, NCO) and 172.56 (*t* and *c*, CO_2CH_3); *m*/*z* (EI) 252 and 250 (3%, M^+), 170 (40, $[M - Br]^+$), 156 (2, $[M - Br - CH_3 + H]^+$), 139 (14, $[M - Br - OCH_3]^+$) and 70 (100, $[C_4H_8N]^+$).

(9a*S*)-2,3,4,5,7,8,9,9a-Octahydro-1*H*-pyrrolo[2,1-*d*][1,2,5]-triazepine-1,5-dione 6 ($R^1 = R^2 = H$)

To a solution of hydrazine hydrate (1.5 g, 30 mmol) in ethanol (50 cm^3) was added (2*S*)-*N*-bromoacetylproline methyl ester **9** ($R^1 = R^2 = H$) (2.50 g, 10 mmol). The resulting solution was refluxed for 2 h and was then allowed to cool to room temperature whereupon colourless crystals of the product were formed (1.43 g, 57%), mp 265–266 °C (HRMS: found $[M + H]^+$, 170.0930. $C_7H_{12}N_3O_2$ requires 170.0930); $[\alpha]_D^{22}$ −74.4 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3403 (NH), 1664 (secondary amide CO) and 1637 (tertiary amide CO); δ_H(200 MHz; ^2H_2O) 1.83–2.25 (3 H, m, γCH_2 and ½βCH_2), 2.41 (1 H, m, ½βCH_2), 3.42–3.71 (2 H, m, δCH_2), 4.11 (1 H, d, *J* 16.5, ½$COCH_2$), 4.45–4.59 (1 H, m, αCH) and 4.59 (1 H, d, *J* 16.5, ½$COCH_2$); δ_H(200 MHz; $[^2H_6]$DMSO) 1.77–2.10 (*A* and *B*, 3 H, m, γCH_2 and ½βCH_2), 2.14–2.41 (*A* and *B*, 1 H, m, ½βCH_2), 3.34–3.62 (*A* and *B*, 2 H, m, δCH_2), 3.89 (*A*, 1 H, d, *J* 15.1, ½$COCH_2$), 4.11 (*B*, 1 H, d, *J* 16.0, ½$COCH_2$), 4.40 (*A*, 1 H, d, *J* 15.1, ½$COCH_2$), 4.42 (*A* and *B*, 1 H, m, αCH) and 4.61 (*B*, 1 H, d, *J* 16.0, ½$COCH_2$); δ_C(50.31 MHz; ^2H_2O) 24.71 (*A*, γCH_2), 24.85 (*B*, γCH_2), 30.56 (*B*, βCH_2), 30.72 (*A*, βCH_2), 48.39 (*A*, CO*C*H_2), 48.47 (*B*, CO*C*H_2), 54.51 (*A*, δCH_2), 54.90 (*B*, δCH_2), 61.44 (*A*, αCH), 61.59 (*B*, αCH), 166.61 (*A*, *C*OCH_2), 166.80 (*B*, *C*OCH_2), 170.47 (*B*, CONH) and 170.96 (*A*, CONH); δ_C(50.31 MHz; $[^2H_6]$DMSO) 25.99 (*A*, γCH_2), 26.11 (*B*, γCH_2), 31.89 (*B*, βCH_2), 32.12 (*A*, βCH_2), 48.75 (*A* and *B*, CO*C*H_2), 56.32 (*B*, δCH_2), 56.53 (*A*, δCH_2), 61.78 (*A*, αCH), 61.88 (*B*, αCH), 165.91 (*A*, *C*OCH_2), 166.17 (*B*, *C*OCH_2), 169.66 (*B*, CONH) and 170.44 (*A*, CONH); *m*/*z* (CI) 170 (100%, $[M + H]^+$), 155 (12, $[M - NH]^+$), 137 (7, $[M - 2NH_3]^+$) and 70 (5, $[C_4H_8N]^+$).

(2*S*,2′*S*)-*N*-(2′-Bromopropionyl)proline methyl ester 9a (R^1 = Me, R^2 = H)

To a stirred solution of (2*S*)-bromopropionic acid[26] **8a** (1.53 g, 10 mmol) in dry THF (20 cm^3) at −40 °C was added *N*-methylmorpholine (1.12 cm^3, 10 mmol). Isobutyl chloroformate (1.36 cm^3, 10 mmol) was immediately added and the suspension stirred at −40 °C for 2 min. A mixture of (2*S*)-proline methyl ester hydrochloride **5** (1.66 g, 10 mmol) and *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry DMF (5 cm^3) was then added. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The hydrochloride salts were filtered off and the solvents removed under reduced pressure. The resulting clear oil was dissolved in CH_2Cl_2 (25 cm^3) and washed with 0.5 mol dm^{-3} HCl (2 × 15 cm^3) and 5% aqueous sodium carbonate (2 × 15 cm^3). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a white solid. Recrystallisation from diethyl ether–light petroleum gave the product as colourless crystals (2.19 g, 83%), mp 116–118 °C (Found: C, 41.85; H, 5.4; N, 5.35. $C_9H_{14}BrNO_3$ requires C, 42.0; H, 5.35; N, 5.3%) (HRMS: found $[M + H]^+$, 264.0235. $C_9H_{15}{}^{79}BrNO_3$ requires 264.0235); $[\alpha]_D^{22}$ +127.3 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 1752 (ester CO), 1648 (amide CO) and 1197 (C–O); δ_H(400 MHz; C^2HCl_3) 1.76 (*t*, 3 H, d, *J* 6.6, CHCH_3), 1.77 (*c*, 3 H, d, *J* 6.7, CHCH_3), 1.80–2.28 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.45–3.64 (*t* and *c*, 1 H, m, ½δCH_2), 3.69 (*t*, 3 H, s, OCH_3), 3.73 (*c*, 3 H, s, OCH_3), 3.79–3.86 (*t* and *c*, 1 H, m, ½δCH_2), 4.18 (*t*, 1 H, q, *J* 6.6, C*H*CH_3), 4.40 (*c*, 1 H, q, *J* 6.6, C*H*CH_3), 4.45 (*t*, 1 H, dd, J_1 4.1, J_2 8.6, αCH) and 4.61 (*c*, 1 H, dd, J_1 4.1, J_2 8.6, αCH); δ_C(100 MHz; C^2HCl_3) 20.82 (*t*, CH*C*H_3), 20.97 (*c*, CH*C*H_3), 21.53 (*c*, γCH_2), 24.56 (*t*, γCH_2), 28.82 (*t*, βCH_2), 30.77 (*c*, βCH_2), 39.25 (*t*, *C*HCH_3), 39.97 (*c*, *C*HCH_3), 46.69 (*c*, δCH_2), 46.81 (*t*, δCH_2), 52.03 (*t*, OCH_3), 52.65 (*c*, OCH_3), 58.99 (*t*, αCH), 59.05 (*c*, αCH), 167.56 (*t*, *C*O$CHCH_3$), 167.99 (*c*, *C*O$CHCH_3$), 171.87 (*t*, CO_2CH_3) and 172.05 (*c*, CO_2CH_3); *m*/*z* (FAB) 264 and 266 (100%, M^+), 204 and 206 (38, $[M - HCOOCH_3]^+$), 184 (35, $[M - Br]^+$) and 128 (62, $[M - COCHCH_3Br]^+$).

(2*S*,2′*R*)-*N*-(2′-Bromopropionyl)proline methyl ester 9b (R^1 = H, R^2 = Me)

This compound was prepared in a manner identical with that for the (2*S*,2′*S*) methyl ester **9a**, using (2*R*)-bromopropionic acid **8b** (1.53 g, 10 mmol) to give the product as colourless crystals (2.09 g, 79%), mp 113–115 °C (Found: C, 41.95; H, 5.35; N, 5.3. $C_9H_{14}BrNO_3$ requires C, 42.0; H, 5.35; N, 5.3%) (HRMS: found $[M + H]^+$, 264.0232. $C_9H_{15}{}^{79}BrNO_3$ requires 264.0235); $[\alpha]_D^{22}$ +113.6 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 1752 (ester CO), 1646 (amide CO) and 1197 (C–O); δ_H(400 MHz; C^2HCl_3) 1.62 (*c*, 3 H, d, *J* 6.4, CHCH_3), 1.64 (*t*, 3 H, d, *J* 6.6, CHCH_3), 1.82–2.31 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.44–3.66 (*t* and *c*, 1 H, m, ½δCH_2), 3.71 (*t*, 3 H, s, OCH_3), 3.75 (*c*, 3 H, s, OCH_3), 3.82–3.94 (*t* and *c*, 1 H, m, ½δCH_2), 4.22 (*c*, 1 H, q, *J* 6.5, C*H*CH_3), 4.44 (*t*, 1 H, q, *J* 6.6, C*H*CH_3), 4.47 (*t*, 1 H, dd, J_1 4.3, J_2 8.6, αCH) and 4.69 (*c*, 1 H, dd, J_1 4.0, J_2 6.7, αCH); δ_C(100 MHz; C^2HCl_3) 20.21 (*t*, CH*C*H_3), 20.35 (*c*, CH*C*H_3), 22.21 (*c*, γCH_2), 24.67 (*t*, γCH_2), 28.82 (*t*, βCH_2), 30.89 (*c*, βCH_2), 39.27 (*t*, *C*HCH_3), 40.02 (*c*, *C*HCH_3), 46.70 (*c*, δCH_2), 46.75 (*t*, δCH_2), 50.69 (*t*, OCH_3), 50.81 (*c*, OCH_3), 58.87 (*c*, αCH), 59.04 (*t*, αCH), 167.44 (*t*, *C*O$CHCH_3$), 167.79 (*c*, *C*O$CHCH_3$), 171.92 (*t*, CO_2CH_3) and 172.24 (*c*, CO_2CH_3); *m*/*z* (FAB) 264 and 266 (95%, M^+), 204 and 206 (62, $[M - HCOOCH_3]^+$), 184 (41, $[M - Br]^+$) and 128 (100, $[M - COCHCH_3Br]^+$).

(4*R*,9a*S*)-4-Methyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 6a

To a solution of hydrazine hydrate (0.60 g, 12 mmol) in ethanol (20 cm^3) was added (2*S*,2′*S*)-*N*-(2′-bromopropionyl)proline methyl ester **9a** (2.64 g, 10 mmol). The resulting solution was refluxed for 16 h and was then allowed to cool slowly. The hydrazine hydrobromide precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to give the required product as a colourless oil (1.81 g, 98%) (HRMS: found $[M + H]^+$, 184.1083. $C_8H_{14}N_3O_2$ requires 184.1086); $[\alpha]_D^{22}$ +39.0 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 1665 (secondary amide CO) and 1639 (tertiary amide CO); δ_H(200 MHz; $[^2H_4]$methanol) 1.53 (3 H, d, *J* 7.0, CHCH_3), 1.86–2.15 (3 H, m, γCH_2 and ½βCH_2), 2.39 (1 H, m, ½βCH_2), 3.44–3.72 (2 H, m, δCH_2), 4.12 (1 H, q, *J* 7.0, C*H*CH_3) and 4.38 (1 H, dd, J_1 7.5, J_2 7.5, αCH); δ_C(50.31 MHz; $[^2H_4]$methanol) 17.01 (CH*C*H_3), 23.65 (γCH_2), 30.57 (βCH_2), 46.97 (δCH_2), 59.60 (αCH), 63.69 (*C*HCH_3), 167.85 (*C*O$CHCH_3$) and 168.49 (CONH); *m*/*z* (CI) 184 (100%, $[M + H]^+$), 169 (20, $[M - CH_3 + H]^+$), 154 (8, $[M - NHCH_3 + H]^+$), 138 (4, $[M - NHNH - CH_3]^+$), 126 (5, $[M - NHNHCHCH_3 + H]^+$) and 70 (10, $[C_4H_8N]^+$).

(4*S*,9a*S*)-4-Methyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 6b

This compound was prepared in a manner identical with that for the (4*R*,9a*S*) diastereomer **6a**, using (2*S*,2′*R*)-*N*-(2′-bromopropionyl)proline methyl ester **9b** (2.64 g, 10 mmol) to give the required material as a colourless oil (1.75 g, 96%) (HRMS: found $[M + H]^+$, 184.1082. $C_8H_{14}N_3O_2$ requires 184.1086); $[\alpha]_D^{22}$ +28.6 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 1658 (secondary amide CO) and 1645 (tertiary amide CO); δ_H(200 MHz; $[^2H_4]$methanol) 1.72 (3 H, d, *J* 6.8, CHCH_3),1.93–2.29 (3 H, m, γCH_2 and ½βCH_2), 2.52 (1 H, m, ½βCH), 3.54–3.86 (2 H, m, δCH_2), 4.35 (1 H, q, *J* 6.8, C*H*CH_3) and 4.38 (1 H, m, αCH); δ_C(50.31 MHz; $[^2H_4]$methanol) 18.36 (CH*C*H_3), 24.72 (γCH_2), 31.43 (βCH_2), 48.55 (δCH_2), 61.24 (αCH), 64.54 (*C*HCH_3), 167.49 (*C*O$CHCH_3$) and 170.68 (CONH); *m*/*z* (CI) 184 (100%, $[M + H]^+$), 169 (31, $[M - CH_3 + H]^+$), 154 (9, [M − NHNH-

$CH_3 + H]^+$), 130 (4, $[M - COCHCH_3 + 3H]^+$), 126 (6, $[M - NHNHCHCH_3 + H]^+$) and 70 (15, $[C_4H_8N]^+$).

(3*R*,8a*S*)-3-Methyl-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-*a*]-pyrazine-1,4-dione 12b

To a solution of (2*S*,2′*R*)-*N*-(*N*-benzyloxycarbonylalanyl)-prolinamide **14b** (0.64 g, 2 mmol) in methanol (30 cm^3) was added 10% palladium on activated charcoal (30 mg) and the vessel flushed with hydrogen gas. The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 12 h. The mixture was then filtered through a pre-washed Celite pad and the solvent removed under reduced pressure to give a white solid which was recrystallised from methanol to give the product as colourless crystals (0.32 g, 93%), mp 128–130 °C (lit.,[27] 127–129 °C) (Found: C, 57.4; H, 7.35; N, 16.65; M^+, 168.1902. Calc. for $C_8H_{12}N_2O_2$: C, 57.15; H, 7.2; N, 16.65%; M^+, 168.1899); $[\alpha]_D^{22}$ −175.2 (*c* 1.0 in EtOH) [lit.,[25] −182.3 (*c* 1.0 in EtOH)]; ν_{max}(Nujol)/cm^{-1} 3213 and 3162 (NH), 1687 (tertiary amide CO) and 1635 (secondary amide CO); δ_H(200 MHz; [$^2H_4$]methanol) 1.41 (3 H, d, *J* 7.0, CH_3), 1.84–2.13 (3 H, m, γCH_2 and $\frac{1}{2}\beta CH_2$), 2.63–2.84 (1 H, m, $\frac{1}{2}\beta CH_2$), 3.42–3.70 (2 H, m, δCH_2), 3.92 (1 H, q, *J* 7.1, C*H*CH_3) and 4.28 (1 H, dd, J_1 6.5, J_2 9.7, αCH); δ_C(74.76 MHz; [$^2H_4$]methanol) 20.19 (CH_3), 23.23 (γCH_2), 30.21 (βCH_2), 46.87 (δCH_2), 54.71 (*C*HCH_3), 59.46 (αCH), 169.34 (*C*OCHCH_3) and 171.39 (CONH); *m*/*z* (EI) 168 (71%, M^+), 140 (8, $[M - CHCH_3]^+$), 125 (28, $[M - NHCHCH_3]^+$), 112 (8, $[M - COCHCH_3]^+$), 97 (41, $[M - CONHCHCH_3]^+$) and 70 (100, $[C_4H_8N]^+$).

(3*S*,8a*S*)-3-Methyl-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-*a*]-pyrazine-1,4-dione 12a

This compound was prepared in a manner identical with that for the octahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **12b**, using (2*S*,2′*S*)-*N*-(*N*-benzyloxycarbonylalanyl)prolinamide **14a** (0.638 g, 2 mmol) to give a white solid which was recrystallised from methanol to give the product as colourless crystals (0.31 g, 91%), mp 152–156 °C (lit.,[27] 153–156 °C) (Found: C, 57.3; H, 7.25; N, 16.7; M^+, 168.1900. Calc. for $C_8H_{12}N_2O_2$: C, 57.15; H, 7.2; N, 16.65%; M^+, 168.1899); $[\alpha]_D^{22}$ −158.4 (*c* 1.0 in EtOH) [lit.,[25] −160.0 (*c* 1.0 in EtOH)]; ν_{max}(Nujol)/cm^{-1} 3287 (NH), 1687 (tertiary amide CO) and 1654 (secondary amide CO); δ_H(200 MHz; C^2HCl_3) 1.41 (3 H, d, *J* 6.6, CH_3), 1.68–2.39 (4 H, m, βCH_2 and γCH_2), 3.50 (2 H, m, δCH_2), 4.08 (2 H, m, αCH and C*H*CH_3) and 7.42 (1 H, s, NH); δ_C(74.76 MHz; [$^2H_4$]-methanol) 16.05 (CH_3), 23.89 (γCH_2), 29.43 (βCH_2), 46.48 (δCH_2), 52.33 (*C*HCH_3), 60.70 (αCH), 169.21 (*C*OCHCH_3) and 172.78 (CONH); *m*/*z* (EI) 168 (43%, M^+), 140 (18, $[M - NHCH_3 + 2H]^+$), 125 (35, $[M - NHCHCH_3]^+$), 97 (34, $[M - CONHCHCH_3]^+$) and 70 (100, $[C_4H_8N]^+$).

(2*S*)-*N*-(*N*-Benzyloxycarbonylglycyl)proline methyl ester 13

To a solution of *N*-benzyloxycarbonylglycine (2.09 g,10 mmol) in dry THF (20 cm^3) was added *N*-methylmorpholine (1.12 cm^3, 10 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (1.36 cm^3, 10 mmol) was added with stirring and the solution was stirred at −15 °C for 2 min. A solution of (2*S*)-proline methyl ester hydrochloride **7** (1.66 g, 10 mmol) and *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry DMF (5 cm^3) was then added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The hydrochloride salts were filtered off and the solvents removed under reduced pressure. The resulting oily residue was dissolved in CH_2Cl_2 (25 cm^3) and washed with 0.5 mol dm^{-3} HCl (2 × 15 cm^3) and 5% aqueous sodium carbonate (2 × 15 cm^3). The organic phase was then dried ($MgSO_4$) and the solvent removed under reduced pressure to give a pale yellow oil. The crude material was purified by silica column chromatography using ethyl acetate–light petroleum (1:1) as the eluent to give the product as a colourless oil (2.42 g, 76%) (HRMS: found $[M + H]^+$, 321.1453. $C_{16}H_{21}N_2O_5$ requires 321.1450); $[\alpha]_D^{22}$ −68.1 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 3336 (NH), 1732 (ester CO), 1711 (carbamate CO), 1652 (amide CO) and 736 and 699 (aromatic CH); δ_H(200 MHz; C^2HCl_3) 1.81–2.33 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.35–3.69 (*t* and *c*, 2 H, m, δCH_2), 3.73 (*t*, 3 H, s, OCH_3), 3.76 (*c*, 3 H, s, OCH_3), 4.02 (*t* and *c*, 2 H, d, *J* 2.6, $COCH_2$), 4.40 (*t*, 1 H, dd, J_1 4.0, J_2 6.6, αCH), 4.53 (*c*, 1 H, dd, J_1 3.8, J_2 7.0, αCH), 5.12 (*t* and *c*, 2 H, s, CH_2Ph), 5.74 (*t* and *c*, 1 H, t, *J* 2.6, N*H*CH_2) and 7.35 (*t* and *c*, 5 H, s, Ar−H); δ_C(50.31 MHz; C^2HCl_3) 22.52 (*c*, γCH_2), 24.97 (*t*, γCH_2), 29.33 (*t*, βCH_2), 31.66 (*c*, βCH_2), 43.52 (*c*, $COCH_2$), 43.66 (*t*, $COCH_2$), 46.20 (*t*, δCH_2), 47.00 (*c*, δCH_2), 52.68 (*t*, OCH_3), 53.15 (*c*, OCH_3), 58.80 (*c*, αCH), 59.20 (*t*, αCH), 128.28 (*t* and *c*, Ar−CH *para*), 128.37 (*t* and *c*, Ar−CH *ortho*), 128.81 (*t* and *c*, Ar−CH *meta*), 136.87 (*t* and *c*, Ar−C quaternary), 156.63 (*t* and *c*, *C*O_2CH_2Ph), 167.41 (*t*, *C*O_2CH_2), 167.69 (*c*, *C*O_2CH_2), 172.29 (*c*, *C*O_2CH_3) and 172.68 (*t*, *C*O_2CH_3); *m*/*z* (CI) 321 (100%, $[M + H]^+$), 230 (10, $[M - CH_2Ph + H]^+$), 213 (28, $[M - OCH_2Ph]^+$), 187 (36, $[M - CO_2CH_2Ph + 2H]^+$), 157 (63, $[M - CO_2CH_2Ph - OCH_2 + 3H]^+$) and 91 (41, $[CH_2Ph]^+$).

(2*S*,2′*S*)-*N*-(*N*-Benzyloxycarbonylalanyl)proline methyl ester 13a

This compound was prepared in a manner identical with that for the (2*S*)-*N*-(*N*-benzyloxycarbonylglycyl)proline methyl ester **13**, using (2*S*)-*N*-benzyloxycarbonylalanine (2.23 g, 10 mmol) instead of *N*-benzyloxycarbonylglycine to give a yellow oil which was purified by silica chromatography using ethyl acetate–light petroleum (1:1) as the eluent to give the product as a clear oil (2.89 g, 84%) (HRMS: found $[M + H]^+$, 335.1605. $C_{17}H_{23}N_2O_5$ requires 335.1606); $[\alpha]_D^{22}$ −86.5 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 2982 and 2953 (NH), 1746 (ester CO), 1716 (carbamate CO), 1654 (amide CO) and 669 and 666 (aromatic CH); δ_H(200 MHz; C^2HCl_3) 1.11 (*t* and *c*, 3 H, d, *J* 6.6, CHC*H*$_3$), 1.49–2.02 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.21–3.45 (*t* and *c*, 2 H, m, δCH_2), 3.40 (*t* and *c*, 3 H, s, OCH_3), 4.24 (*t* and *c*, 1 H, m, αCH), 4.26 (*t* and *c*, 1 H, q, *J* 6.6, C*H*CH_3), 4.82 (*t* and *c*, 2 H, s, CH_2Ph), 5.97 (*c*, 1 H, d, *J* 8.6, NH), 6.13 (*t*, 1 H, d, *J* 7.8, NH) and 7.06 (*t* and *c*, 5 H, s, Ar−H); δ_C(50.31 MHz; C^2HCl_3) 18.03 (*t*, CH*C*H_3), 19.06 (*c*, CH*C*H_3), 22.91 (*c*, γCH_2), 25.14 (*t*, γCH_2), 29.09 (*t*, βCH_2), 31.47 (*c*, βCH_2), 46.75 (*c*, δCH_2), 46.96 (*t*, δCH_2), 48.56 (*t*, *C*HCH_3), 48.77 (*c*, *C*HCH_3), 52.30 (*t*, OCH_3), 53.87 (*c*, OCH_3), 58.97 (*t*, αCH), 59.29 (*c*, αCH), 66.67 (*t*, CH_2Ph), 67.05 (*c*, CH_2Ph), 128.14 (*t* and *c*, Ar−CH *ortho*), 128.68 (*t* and *c*, Ar−CH *para*), 129.36 (*t* and *c*, Ar−CH *meta*), 137.05 (*t* and *c*, Ar−C quaternary), 155.73 (*c*, *C*O_2CH_2Ph), 156.13 (*t*, *C*O_2CH_2Ph), 171.65 (*t* and *c*, *C*OCHCH_3), 172.51 (*c*, *C*O_2CH_3) and 172.62 (*t*, *C*O_2CH_3); *m*/*z* (CI) 335 (100%, $[M + H]^+$), 319 (7, $[M - CH_3]^+$), 291 (13, $[M - COCH_3]^+$), 227 (12, $[M - OCH_2Ph]^+$) and 91 (8, $[PhCH_2]^+$).

Catalytic removal of the Z protecting group of this compound gave the diazepinedione **12a**, identical to the material prepared from compound **6a**.

(2*S*,2′*R*)-*N*-(*N*-Benzyloxycarbonylalanyl)proline methyl ester 13b

This compound was prepared in a manner identical with that for the methyl ester **13**, using (2*R*)-*N*-benzyloxycarbonylalanine (2.23 g, 10 mmol) instead of (2*S*)-*N*-benzyloxycarbonylalanine to give a yellow oil which was purified by silica column chromatography using ethyl acetate–light petroleum (1:1) as the eluent to give the product as a colourless oil (2.40 g, 72%) (HRMS: found $[M + H]^+$, 335.1614. $C_{17}H_{23}N_2O_5$ requires 335.1607); $[\alpha]_D^{22}$ −22.9 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 2982 and 2955 (NH), 1745 (ester CO), 1719 (carbamate CO), 1652 (amide CO) and 736 and 699 (aromatic CH); δ_H(200 MHz; C^2HCl_3) 1.27 (*c*, 3 H, d, *J* 7.0, CHC*H*$_3$), 1.33 (*t*, 3 H, d, *J* 6.6, CHC*H*$_3$), 1.79–2.33 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.38–3.62 (*t* and *c*, 2 H, m, δCH_2), 3.70 (*t*, 3 H, s, OCH_3), 3.74 (*c*, 3 H, s, OCH_3), 4.31 (*c*, 1 H, dq, J_1 7.0, J_2 8.0, C*H*CH_3), 4.42 (*t*, 1 H, dd, J_1 2.1, J_2 9.1,

αCH), 4.54 (*t*, 1 H, dq, J_1 6.6, J_2 7.6, C*H*CH_3), 4.91 (*c*, 1 H, dd, J_1 3.1, J_2 7.3, αCH), 5.08 (*t* and *c*, 2 H, s, CH_2Ph), 5.59 (*c*, 1 H, d, *J* 8.0, NH), 5.78 (*t*, 1 H, d, *J* 7.6, NH), 7.31 (*c*, 5 H, s, Ar–H) and 7.32 (*t*, 5 H, s, Ar–H); δ_C(50.31 MHz; C^2HCl_3) 17.89 (*c*, $CHCH_3$), 18.48 (*t*, $CHCH_3$), 22.67 (*c*, γCH_2), 24.92 (*t*, γCH_2), 29.22 (*t*, βCH_2), 31.31 (*c*, βCH_2), 46.81 (*c*, δCH_2), 47.00 (*t*, δCH_2), 48.42 (*c*, *C*HCH_3), 48.67 (*t*, *C*HCH_3), 52.25 (*t*, OCH_3), 52.72 (*c*, OCH_3), 59.32 (*t*, αCH), 60.46 (*c*, αCH), 66.63 (*t* and *c*, CH_2Ph), 128.13 (*t* and *c*, Ar–CH), 128.64 (*t* and *c*, Ar–CH), 136.93 (*c*, Ar–C quaternary), 137.03 (*t*, Ar–C quaternary), 155.77 (*t*, *C*O_2CH_2Ph), 156.37 (*c*, *C*O_2CH_2Ph), 171.05 (*t*, *C*OCHCH_3), 171.29 (*c*, *C*OCHCH_3), 172.53 (*t*, *C*O_2CH_3) and 172.98 (*t*, *C*O_2CH_3); *m*/*z* (CI) 335 (100%, $[M + H]^+$), 230 (5, $[M - CH_2Ph - CH_3 + 2H]^+$), 201 (3, $[M - CO_2CH_2Ph + 2H]^+$), 196 (4, $[M - OCH_2Ph - OCH_3]^+$) and 169 (6, $[M - CO_2CH_2Ph - OCH_3 + H]^+$).

(2*S*)-*N*-(*N*-Benzyloxycarbonylglycyl)prolinamide 14

To a saturated solution of ammonia in dry methanol (20 cm^3) was added (2*S*)-*N*-(*N*-benzyloxycarbonylglycyl)proline methyl ester **13** (1.60 g, 5 mmol). The solution was placed in a tightly stoppered vessel and left at room temperature. When the reaction was complete as judged by TLC (9 days), the stoppered vessel was cooled to 0 °C, opened and nitrogen gas bubbled through at room temperature for 5 min. The solvent was then removed under reduced pressure to give a white solid which was recrystallised from methanol–diethyl ether to give the product as a white solid (1.24 g, 81%), mp 148–149 °C (Found: C, 59.15; H, 6.4; N, 13.8. $C_{15}H_{19}N_3O_4$ requires C, 59.0; H, 6.3; N, 13.75%) (HRMS: found $[M + H]^+$, 306.1459. $C_{15}H_{20}N_3O_4$ requires 306.1454); $[a]_D^{22}$ −60.1 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3394 and 3213 (NH), 1687 (carbamate CO), 1671 (tertiary amide CO),1639 (primary amide CO) and 753 and 701 (aromatic CH); δ_H(200 MHz; $[^2H_6]$DMSO) 1.67–2.34 (*t* and *c*, 4 H, m, γCH_2 and βCH_2), 3.31–3.69 (*t* and *c*, 2 H, m, δCH_2), 3.79 (*c*, 2 H, d, *J* 5.8, $COCH_2$), 3.86 (*t*, 2 H, d, *J* 5.8, $COCH_2$), 4.21 (*t*, 1 H, dd, J_1 5.8, J_2 7.6, αCH), 4.35 (*c*, 1 H, dd, J_1 2.6, J_2 8.2, αCH), 5.01 (*t* and *c*, 2 H, s, CH_2Ph), 7.01 (*t*, 1 H, s, ½$CONH_2$), 7.28 (*c*, 1 H, s, ½$CONH_2$), 7.32 (*t*, 1 H, s, ½$CONH_2$), 7.38 (*t* and *c*, 5 H, s, Ar–H) and 7.61 (*c*, 1 H, s, ½$CONH_2$); δ_C(50.31 MHz; $[^2H_4]$methanol) 23.62 (*c*, γCH_2), 25.90 (*t*, γCH_2), 31.05 (*t*, βCH_2), 33.69 (*c*, βCH_2), 44.35 (*t*, $COCH_2$), 44.46 (*c*, $COCH_2$), 47.83 (*t*, δCH_2), 48.61 (*c*, δCH_2), 61.26 (*c*, αCH), 61.86 (*t*, αCH), 68.01 (*t* and *c*, CH_2Ph), 129.16 (*t* and *c*, Ar–CH *para*), 129.28 (*t* and *c*, Ar–CH *ortho*), 129.74 (*t* and *c*, Ar–CH *meta*), 138.43 (*t* and *c*, Ar–C quaternary), 159.30 (*t* and *c*, *C*O_2CH_2Ph), 170.58 (*t*, *C*OCH_2), 170.72 (*c*, *C*OCH_2), 177.49 (*c*, $CONH_2$) and 174.94 (*t*, $CONH_2$); *m*/*z* (CI) 306 (33%, $[M + H]^+$), 198 (100, $[M - OCH_2Ph]^+$), 172 (11, $[M - CO_2CH_2Ph + 2H]^+$), 155 (38, $[M - CO_2CH_2Ph - NH_2 + H]^+$), 139 (15, $[M - CO_2CH_2Ph - NH_2 - NH]^+$) and 91 (22, $[CH_2Ph]^+$).

Upon catalytic hydrogenolysis of the N-Z protection, this compound cyclised to give **12**, see below.

(8a*S*)-1,2,3,4,6,7,8,8a-Octahydropyrrolo[1,2-*a*]pyrazine-1,4-dione 12

Method 1. To liquid ammonia (40 cm^3) at −60 °C under an atmosphere of dry nitrogen was added a solution of the triazepinedione **6** (1.69 g, 10 mmol) in dry THF (10 cm^3). The resulting solution was stirred vigorously and sodium (approx. 0.8 g, 30 mmol) was added in small pieces until a homogenous dark blue colour was obtained. This blue colour was maintained for 15 min, after which time the solution cleared and ammonium chloride (1.60 g, 30 mmol) was added. The reaction mixture was allowed to warm to room temperature, methanol (20 cm^3) was added, and the mixture was left stirring for 1 h. The solvents were removed under reduced pressure and the resulting white solid was dissolved in water (25 cm^3) and extracted with ethyl acetate (3 × 25 cm^3). The combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a white solid which was recrystallised from methanol to give the required material as colourless crystals (1.23 g, 80%). All analytical and spectroscopic data were identical to those described for Method 2, see below.

Method 2. To a solution of (2*S*)-*N*-(*N*-benzyloxycarbonylglycyl)prolinamide **14** (0.610 g, 2 mmol) in methanol (50 cm^3) was added 10% palladium on activated charcoal (30 mg) and the vessel flushed with hydrogen. The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 12 h. The mixture was filtered through a Celite pad and the solvent removed under reduced pressure to give a white solid which was recrystallised from methanol to give the required material as colourless crystals (0.29 g, 93%), mp 205–208 °C (lit.,[19] 208–210 °C) (Found: C, 54.45; H, 6.8; N, 18.4; M^+, 154.0747. Calc. for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.65; N, 18.3%; M^+, 154.0742); $[a]_D^{22}$ −184.3 (*c* 0.5 in MeOH) [lit.,[19] −196.5 (*c* 0.5 in MeOH)]; ν_{max}(Nujol)/cm^{-1} 3162 and 3110 (NH), 1681 (tertiary amide CO) and 1652 (secondary amide CO); δ_H(300 MHz; $[^2H_4]$-methanol) 2.03–2.38 (3 H, m, γCH_2 and ½βCH_2), 2.45–2.64 (1 H, m, ½βCH_2), 3.73 (2 H, m, δCH_2), 3.93 (1 H, d, *J* 16.8, ½$COCH_2$), 4.30 (1 H, d, *J* 16.8, ½$COCH_2$) and 4.42 (1 H, dd, J_1 6.8, J_2 6.8, αCH); δ_C(74.76 MHz; $[^2H_4]$methanol) 23.60 (γCH_2), 29.68 (βCH_2), 46.60 ($COCH_2$), 47.29 (δCH_2), 60.15 (αCH), 166.74 (*C*OCH_2) and 172.27 (CONH); *m*/*z* (EI) 154 (70%, M^+), 126 (8, $[M - NHCH_2 + H]^+$), 111 (81, $[M - CONH]^+$), 98 (28, $[M - CONHCH_2 + 2H]^+$), 83 (100, $[M - CO_2 - NHCH_2 + 2H]^+$) and 70 (78, $[C_4H_8N]^+$).

(2*S*,2′*S*)-*N*-(*N*-Benzyloxycarbonylalanyl)prolinamide 14a

This compound was prepared in a manner identical with that for (2*S*)-*N*-(*N*-benzyloxycarbonylglycyl)prolinamide **14**, starting from the (2*S*,2′*S*)-*N*-(*N*-*tert*-butoxycarbonylalanyl)proline methyl ester **13a** (0.67 g, 2 mmol) to give an off-white solid which was recrystallised from methanol–diethyl ether to give the product as colourless crystals (0.51 g, 79%) mp 167–169 °C (Found: C, 60.5; H, 6.75; N, 13.3. $C_{16}H_{21}N_3O_4$ requires C, 60.2; H, 6.65; N, 13.2%) (HRMS: found $[M + H]^+$, 320.1612. $C_{16}H_{22}N_3O_4$ requires 320.1610); $[a]_D^{22}$ −81.3 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3402 and 3323 (NH), 1668 (carbamate CO), 1653 (tertiary amide CO), 1646 (primary amide CO) and 754 and 696 (aromatic CH); δ_H(200 MHz; $[^2H_6]$DMSO) 1.20 (3 H, d, *J* 7.6, CH_3), 1.62–2.18 (4 H, m, βCH_2 and γCH_2), 3.58 (2 H, m, δCH_2), 4.22 (1 H, dd, J_1 7.5, J_2 2.7, αCH), 4.32 (1 H, m, C*H*CH_3), 5.01 (2 H, s, CH_2Ph), 6.88 (1 H, s, ½$CONH_2$), 7.22 (1 H, s, ½$CONH_2$), 7.35 (5 H, s, Ar–H) and 7.51 (1 H, d, *J* 7.6, NH); δ_C(74.76 MHz; $[^2H_4]$methanol) 17.63 (*t*, CH_3), 18.28 (*c*, CH_3), 23.52 (*c*, γCH_2), 26.42 (*t*, γCH_2), 31.17 (*t*, βCH_2), 33.36 (*c*, βCH_2), 48.93 (*t* and *c*, δCH_2), 50.36 (*t*, *C*HCH_3), 50.72 (*c*, *C*HCH_3), 61.86 (*t*, αCH), 62.05 (*c*, αCH), 68.11 (*t*, CH_2Ph), 68.73 (*c*, CH_2Ph), 129.32 (*t* and *c*, Ar–CH *ortho*), 129.49 (*t* and *c*, Ar–CH *para*), 129.94 (*t* and *c*, Ar–CH *meta*), 138.66 (*t* and *c*, Ar–C quaternary), 158.66 (*t* and *c*, *C*O_2CH_2Ph), 174.45 (*t* and *c*, *C*OCHCH$_3$), 176.93 (*c*, $CONH_2$) and 177.54 (*t*, $CONH_2$); *m*/*z* (CI) 320 (100%, $[M + H]^+$), 303 (20, $[M - NH_2]^+$), 291 (21, $[M - CO]^+$), 276 (19, $[M - CONH_2 + H]^+$), 227 (34, $[M - PhCH_2 + H]^+$), 212 (38, $[M - PhCH_2O]^+$), 91 (40, $[PhCH_2]^+$) and 70 (23, $[C_4H_8N]^+$).

Under the conditions described for the preparation of compound **12**, Method 2, this compound **14a** spontaneously lactamised to give dioxopiperazine **12a**.

(2*S*,2′*R*)-*N*-(*N*-Benzyloxycarbonylalanyl)prolinamide 14b

This compound was prepared in a manner identical with that for the (2*S*,2′*S*)-*N*-(*N*-benzyloxycarbonylalanyl)prolinamide **14a**, using (2*S*,2′*R*)-*N*-(*N*-benzyloxycarbonylalanyl)proline methyl ester **13b** (1.60 g, 5 mmol) instead of (2*S*,2′*S*)-*N*-(*N*-benzyloxycarbonylalanyl)proline methyl ester **13a** to give the product as a clear oil (1.57 g, 98%) (HRMS: found $[M + H]^+$, 320.1606. $C_{16}H_{22}N_3O_4$ requires 320.1610); $[a]_D^{22}$ −19.8 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 1701 (carbamate CO), 1683 (ter-

tiary amide CO), 1642 (primary amide CO) and 743 and 699 (aromatic CH); δ_H(200 MHz; C^2HCl_3) 1.30 (3 H, d, *J* 6.8, CHC*H*$_3$), 1.70–2.43 (4 H, m, βCH$_2$ and γCH$_2$), 3.22–3.60 (1 H, m, ½δCH$_2$), 3.62–3.97 (1 H, m, ½δCH$_2$), 4.23–4.61 (2 H, m, αCH and C*H*CH$_3$), 5.04 (2 H, s, CH$_2$Ph), 5.79 (1 H, s, ½NH$_2$), 6.10 (1 H, d, *J* 6.6, N*H*CHCH$_3$), 6.86 (1 H, s, ½NH$_2$) and 7.32 (5 H, s, Ar–H); δ_C(50.31 MHz; [^{2}H$_4$]methanol) 17.44 (*t*, CH$_3$), 18.12 (*c*, CH$_3$), 23.96 (*c*, γCH$_2$), 25.89 (*t*, γCH$_2$), 31.08 (*t*, βCH$_2$), 33.77 (*c*, βCH$_2$), 48.42 (*c*, δCH$_2$), 48.75 (*t*, δCH$_2$), 50.04 (*t* and *c*, *C*HCH$_3$), 62.03 (*c*, αCH), 62.29 (*t*, αCH), 67.87 (*c*, CH$_2$Ph), 68.13 (*t*, CH$_2$Ph), 129.24 (*t* and *c*, Ar–CH *para*), 129.37 (*t* and *c*, Ar–CH *ortho*), 129.95 (*t* and *c*, Ar–CH *meta*), 138.46 (*t* and *c*, Ar–C quaternary), 158.56 (*c*, *C*O$_2$CH$_2$Ph), 158.68 (*t*, *C*O$_2$CH$_2$-Ph), 174.36 (*t*, *C*OCHCH$_3$), 175.02 (*c*, *C*OCHCH$_3$), 177.24 (*c*, CO$_2$NH$_2$) and 177.39 (*t*, CO$_2$NH$_2$); *m*/*z* (CI) 320 (100%, [M + H]$^+$), 303 (32, [M − NH$_2$]$^+$), 291 (15, [M − CO]$^+$), 276 (22, [M − CONH$_2$ + H]$^+$), 230 (31, [M − Ph − CH$_3$ + 3H]$^+$), 186 (36, [M − CO$_2$CH$_2$Ph + 2H]$^+$), 91 (52, [PhCH$_2$]$^+$) and 70 (18, [C$_4$H$_8$N]$^+$).

Under the conditions described for the preparation of compound **12**, Method 2, this compound **14b** spontaneously lactamised to give dioxopiperazine **12b**.

(9a*S*)-3-Methyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*]-[1,2,5]triazepine-1,5-dione 15

To a stirred solution of methylhydrazine (0.46 g, 10 mmol) in CH_2Cl_2 (15 cm^3) was added (2*S*)-*N*-bromoacetylproline methyl ester (1.25 g, 5 mmol). The mixture was refluxed for 30 min, allowed to cool to room temperature and extracted with water (2 × 20 cm^3). The organic phase was separated, the solvent removed under reduced pressure and the residue redissolved in ethanol (15 cm^3). Methylhydrazine (0.23 g, 5 mmol) was added and the resulting solution refluxed for 1 h. Removal of the solvent under reduced pressure gave a white solid which was recrystallised from methanol to give the product as colourless crystals (0.75 g, 82%), mp 236–238 °C (Found: C, 52.3; H, 7.3; N, 22.85. $C_8H_{13}N_3O_2$ requires C, 52.45; H, 7.2; N, 22.95%); $[\alpha]_D^{22}$ +118.1 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3101 (NH), 1699 (tertiary amide CO) and 1597 (secondary amide CO); δ_H(200 MHz; [^{2}H$_4$]methanol), 1.76–2.15 (3 H, m, ½βCH$_2$ and γCH$_2$), 2.33–2.58 (1 H, m, ½βCH$_2$), 2.69 (3 H, s, NCH$_3$), 3.41 (1 H, d, *J* 17.2, ½COCH$_2$), 3.55 (2 H, dd, $J_1 = J_2$ 6.6, δCH$_2$), 3.71 (1 H, d, *J* 17.2, ½COCH$_2$) and 5.19 (1 H, dd, $J_1 = J_2$ 7.1, αCH); δ_C(50.31 MHz; [^{2}H$_4$]methanol) 22.63 (γCH$_2$), 28.05 (βCH$_2$), 44.12 (NCH$_3$), 48.46 (δCH$_2$), 58.50 (CO*C*H$_2$), 63.55 (αCH), 169.77 (*C*OCH$_2$) and 173.36 (CONH); *m*/*z* (FAB) 184 (100%, [M + H]$^+$), 168 (7, [M − CH$_3$]$^+$), 154 (19, [M − NCH$_3$]$^+$), 112 (26, [M − CONHNCH$_3$ + H]$^+$) and 70 (63, [C$_4$H$_8$N]$^+$).

(4*R*,9a*S*)-3,4-Dimethyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 15a

This compound was prepared in a manner identical with that for the triazepine-1,5-dione **15**, using (2*S*,2′*S*)-*N*-(2′-chloropropionyl)proline methyl ester **25a** (1.10 g, 5 mmol) instead of (2*S*)-*N*-bromoacetylproline methyl ester to give the product as colourless crystals (0.83 g, 84%), mp 155–158 °C (Found: C, 54.6; H, 7.85; N, 21.4. $C_9H_{15}N_3O_2$ requires C, 54.8; H, 7.7; N, 21.3%) (HRMS: found [M + H]$^+$, 198.1244. $C_9H_{16}N_3O_2$ requires 198.1243); $[\alpha]_D^{22}$ +104.2 (*c* 0.1 in MeOH); ν_{max}(Nujol)/cm^{-1} 3184 and 3124 (NH), 1695 (tertiary amide CO) and 1600 (secondary amide CO); δ_H(300 MHz; C^2HCl_3) 1.38 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.67–2.02 (3 H, m, γCH$_2$ and ½βCH$_2$), 2.39–2.75 (1 H, m, ½βCH$_2$), 2.58 (3 H, s, NCH$_3$), 3.37 (1 H, q, *J* 6.6, C*H*CH$_3$), 3.35–3.66 (1 H, m, ½δCH$_2$), 3.80 (1 H, m, ½δCH$_2$), 5.10 (1 H, dd, J_1 5.5, J_2 7.6, αCH) and 7.69 (1 H, s, NH); δ_C(74.76 MHz; C^2HCl_3) 18.69 (CH*C*H$_3$), 22.91 (γCH$_2$), 27.01 (βCH$_2$), 41.80 (NCH$_3$), 48.76 (δCH$_2$), 57.04 (αCH), 68.64 (*C*HCH$_3$), 171.69 (*C*OCHCH$_3$) and 173.09 (CONH); *m*/*z* (FAB) 198 (100%, [M + H]$^+$), 182 (6, [M − CH$_3$]$^+$), 168 (24, [M − NCH$_3$]$^+$), 126 (19, [M − CONHCH$_3$ + H]$^+$) and 70 (85, [C$_4$H$_8$N]$^+$).

(4*S*,9a*S*)-3,4-Dimethyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 15b

This compound was prepared in a manner identical with that for the (4*R*,9a*S*) diastereomer **15a**, using (2*S*,2′*R*)-*N*-(2′-chloropropanoyl)proline methyl ester **25b** (1.10 g, 5 mmol) to give the product as colourless crystals (0.79 g, 80%), mp 146–150 °C (Found: C, 54.6; H, 7.9; N, 21.4. $C_9H_{15}N_3O_2$ requires C, 54.8; H, 7.7; N, 21.3%) (HRMS: found [M + H]$^+$, 198.1244. $C_9H_{16}N_3O_2$ requires 198.1243); $[\alpha]_D^{22}$ +18.2 (*c* 0.1 in MeOH); ν_{max}(Nujol)/cm^{-1} 2926 and 2854 (NH), 1696 (tertiary amide CO) and 1601 (secondary amide CO); δ_H(200 MHz; C^2HCl_3) 1.31 (3 H, d, *J* 7.0, CHC*H*$_3$), 1.71–2.12 (3 H, m, ½βCH$_2$ and γCH$_2$), 2.38–2.62 (1 H, m, ½βCH$_2$), 2.67 (3 H, s, NCH$_3$), 3.60 (2 H, m, δCH$_2$), 3.65 (1 H, q, *J* 7.0, C*H*CH$_3$), 5.00 (1 H, dd, $J_1 = J_2$ 7.6, αCH) and 7.24 (1 H, s, NH); δ_C(50.31 MHz; C^2HCl_3) 19.21 (CH*C*H$_3$), 22.70 (γCH$_2$), 27.69 (βCH$_2$), 41.88 (NCH$_3$), 48.57 (δCH$_2$), 58.10 (αCH), 65.08 (*C*HCH$_3$), 170.80 (*C*OCHCH$_3$) and 172.65 (CONH); *m*/*z* (FAB) 198 (100%, [M + H]$^+$), 182 (6, [M − CH$_3$]$^+$), 168 (24, [M − NCH$_3$]$^+$), 126 (19, [M − CONHCH$_3$ + H]$^+$) and 70 (85, [C$_4$H$_8$N]$^+$).

(4*R*,9a*S*)-3-Acetyl-4-methyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepine-1,5-dione 16

To a stirred solution of the triazepinedione **6a** (240 mg, 1.31 mmol) in acetic acid (5 cm^3, 88 mmol) was added acetic acid (140 mm^3, 1.4 mmol) and pyridine (130 mm^3, 1.6 mmol). After 45 h, 6 mol dm^{-3} aqueous sodium hydroxide (15 cm^3, 90 mmol) was added and the slurry was extracted with CH_2Cl_2 (2 × 15 cm^3) and diethyl ether (2 × 15 cm^3). The combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by silica chromatography using light petroleum and then CH_2Cl_2–ethanol (8:2) as the eluent to give the product as a colourless oil (140 mg, 48%) (HRMS: found M$^+$, 225.1104. $C_{10}H_{15}N_3O_3$ requires 225.1113); $[\alpha]_D^{22}$ −47.2 (*c* 1.1 in MeOH); ν_{max}(CCl_4)/cm^{-1} 3437 (NH), 1680 (CO) and 1641 (CO); δ_H(200 MHz; C^2HCl_3) 1.47 (3 H, d, *J* 7.2, CHC*H*$_3$), 1.85–2.09 (6 H, m, COCH$_3$, ½βCH$_2$ and γCH$_2$), 2.39 (1 H, m, ½βCH$_2$), 3.51–3.61 (2 H, m, δCH$_2$), 4.08–4.22 (2 H, m, C*H*CH$_3$ and αCH) and 8.81 (1 H, s, NH); δ_C(50.31 MHz; C^2HCl_3) 16.60 (CH*C*H$_3$), 20.71 (CO*C*H$_3$), 22.21 (γCH$_2$), 28.92 (βCH$_2$), 45.39 (δCH$_2$), 57.71 (αCH), 62.19 (*C*HCH$_3$), 165.74 (*C*OCHCH$_3$), 165.82 (CONH) and 169.23 (*C*OCH$_3$); *m*/*z* (EI) 225 (52%, M$^+$), 183 (80 [M + H − COCH$_3$]$^+$), 167 (49, [M − COCH$_3$ − CH$_3$]$^+$), 126 (78, [M + H − CH$_3$CONNHCO]$^+$) and 70 (100, [C$_4$H$_8$N]$^+$).

N-*tert*-Butoxycarbonyl-*N*′-benzyloxycarbonyl-*N*′-methylhydrazine

To a solution of *N*-benzyloxycarbonyl-*N*-methylhydrazine (3.60 g, 20 mmol) in propan-2-ol (25 cm^3) was added a solution of di-*tert*-butyl dicarbonate (4.80 g, 22 mmol) in CH_2Cl_2 (10 cm^3). The mixture was stirred for 4 h, and the solvent removed under reduced pressure to yield the product as a pale yellow oil. Purification by silica column chromatography using ethyl acetate–light petroleum (1:4) as the eluent gave the pure product as a clear oil (4.94 g, 88%) (HRMS: found [M + H]$^+$, 281.1504. $C_{14}H_{21}N_2O_4$ requires 281.1501); ν_{max}(thin film)/cm^{-1} 3307 (NH), 1733 (Z CO) and 1707 (Boc CO); δ_H(200 MHz; C^2HCl_3) 1.29 [9 H, s, C(CH$_3$)$_3$], 2.45 (3 H, s, NCH$_3$), 5.12 (2 H, s, CH$_2$Ph), 6.12 (1 H, s, NH) and 7.31 (5 H, s, Ar–H); δ_C(50.31 MHz; C^2HCl_3) 28.31 [C(*C*H$_3$)$_3$], 39.25 (NHCH$_3$), 63.98 (CH$_2$Ph), 80.74 [*C*(CH$_3$)$_3$], 128.15 (Ar–CH *ortho*), 128.33 (Ar–CH *meta*), 128.78 (Ar–CH *para*), 136.43 (Ar–C quaternary), 155.52 (*C*O$_2$CH$_2$Ph) and 157.11 (*C*O$_2$Bu^t); *m*/*z* (CI) 281 (54%, [M + H]$^+$), 265 (32, [M − CH$_3$]$^+$), 225 (71, [M − C(CH$_3$)$_3$ + 2H]$^+$), 191 {57, [M − CO$_2$C(CH$_3$)$_3$ + 2H]$^+$}, 91 (100, [PhCH$_2$]$^+$) and 57 {88, [C(CH$_3$)$_3$]$^+$}.

(2*S*)-*N*-Chloroacetylproline 19

To a stirred suspension of (2*S*)-proline (7.50 g, 65.1 mmol) in ethyl acetate (150 cm^3) was added chloroacetyl chloride (8.0 cm^3, 99.7 mmol). The suspension was refluxed for 50 min and cooled to yield the product as colourless crystals (7.93 g, 64%); mp 106–108 °C (lit.,[28] 112 °C) (Found: C, 43.8; H, 5.2; N, 7.2. $C_7H_{10}ClNO_3$ requires C, 43.9; H, 5.3; N, 7.3%); $[\alpha]_D^{22}$ −110.6 (*c* 0.9 in H_2O) [lit.,[28] −114 (*c* 2 in H_2O)]; ν_{max}(Nujol)/cm^{-1} 2900 (OH), 1722 (acid CO), 1620 (amide CO) and 690 (C–Cl); δ_H(200 MHz; [$^2H_4$]methanol) 1.90–2.13 (3 H, m, $\frac{1}{2}\beta CH_2$ and γCH_2), 2.18–2.35 (1 H, m, $\frac{1}{2}\beta CH_2$), 3.51–3.74 (2 H, m, δCH_2), 4.28 (2 H, d, *J* 2.8, CH_2Cl), 4.41–4.48 (*t*, 1 H, m, αCH) and 4.62–4.69 (*c*, 1 H, m, αCH); δ_C(74.76 MHz; [$^2H_4$]methanol) 23.49 (*c*, γCH_2), 25.99 (*t*, γCH_2), 30.51 (*t*, βCH_2), 32.37 (*c*, βCH_2), 43.12 (*c*, CH_2Cl), 43.23 (*t*, CH_2Cl), 48.46 (*t*, δCH_2), 48.73 (*c*, δCH_2), 60.98 (*t* and *c*, αCH), 167.76 (*t*, CON), 168.17 (*c*, CON), 174.87 (*c*, CO_2H) and 175.34 (*t*, CO_2H); *m*/*z* (EI) 191 (6%, M^+), 146 (52, $[M - CO_2H]^+$), 112 (36, $[M - Cl - CO_2H + H]^+$), 83 (23, $C_5H_7N^+$), 70 (100, $C_4H_8N^+$) and 41 (37, $COCH^+$).

***N*-*tert*-Butoxycarbonyl-*N*′-methylhydrazine 18**

To a solution of *N*-*tert*-butoxycarbonyl-*N*′-benzyloxycarbonyl-*N*′-methylhydrazine (1.40 g, 5 mmol) in methanol (30 cm^3) was added 10% palladium on activated charcoal (75 mg) and the vessel flushed with hydrogen gas. The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 12 h. The mixture was then filtered through a pre-washed Celite pad, and the solvent removed under reduced pressure to give a clear oil which solidified on standing to give colourless crystals of the product (0.68 g, 93%), mp 46–49 °C (Found: C, 49.25; H, 9.9; N, 19.2. $C_6H_{14}N_2O_2$ requires C, 49.3; H, 9.65; N, 19.15%); ν_{max}(Nujol)/cm^{-1} 3320 (amine NH), 3241 (amide NH) and 1700 (CO); δ_H(200 MHz; C^2HCl_3) 1.33 [9 H, s, $C(CH_3)_3$], 2.48 (3 H, s, $NHCH_3$), 3.76 (1 H, s, $NHCH_3$) and 6.00 (1 H, s, CONH); δ_C(50.31 MHz; C^2HCl_3) 28.88 [$C(CH_3)_3$], 39.69 ($NHCH_3$), 80.82 [$C(CH_3)_3$] and 157.27 (CO_2Bu^t); *m*/*z* (EI) 146 (15%, M^+), 131 (3, $[M - CH_3]^+$), 103 (51, $[M - NHNHCH_3 + 2H]^+$), 90 {33, $[M - C(CH_3)_3 + H]^+$}, 73 {27, $[OC(CH_3)_3]^+$} and 57 {100, $[C(CH_3)_3]^+$}.

***N*-*tert*-Butoxycarbonyl-*N*′-[(2*S*)-*N*-chloroacetylprolyl]-*N*′-methylhydrazine 20**

To a solution of (2*S*)-*N*-chloroacetylproline **19** (1.92 g, 10 mmol) in dry THF (25 cm^3) was added *N*-methylmorpholine (1.12 cm^3, 10 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (1.36 cm^3, 10 mmol) was added with stirring and the solution was stirred at −15 °C for 2 min. A solution of *N*-*tert*-butoxycarbonyl-*N*′-methylhydrazine **18** (1.46 g, 10 mmol) in dry THF (20 cm^3) was then added. The reaction mixture was allowed to warm to room temperature and then stirred for 6 h. The hydrochloride salts were filtered off and the solvents removed under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (25 cm^3) and washed with 0.5 mol dm^{-3} HCl (2 × 15 cm^3) and 5% aqueous sodium carbonate (2 × 15 cm^3). The organic phase was then dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil. The crude material was purified by silica column chromatography using ethyl acetate as the eluent to give the product as a white solid (2.17 g, 68%), mp 64–67 °C (HRMS: found $[M + H]^+$, 320.1373. $C_{13}H_{23}{}^{35}ClN_3O_4$ requires 320.1376); $[\alpha]_D^{22}$ −11.0 (*c* 0.5 in MeOH); ν_{max}(Nujol)/cm^{-1} 3227 (NH), 1730 (carbamate CO), 1695 (methylamide CO), 1678 (tertiary amide CO) and 771 (C–Cl); δ_H(200 MHz; C^2HCl_3) 1.48 [9 H, s, $C(CH_3)_3$], 1.74–2.45 (4 H, m, γCH_2 and βCH_2), 3.11 (3 H, s, NCH_3), 3.63 (2 H, m, δCH_2), 4.04 (1 H, d, *J* 13.0, $\frac{1}{2}COCH_2$), 4.13 (1 H, d, *J* 13.0, $\frac{1}{2}COCH_2$), 4.97 (1 H, dd, J_1 5.6, J_2 6.2, αCH) and 7.90 (1 H, s, NH); δ_C(50.31 MHz; C^2HCl_3) 25.15 (γCH_2), 28.47 [$C(CH_3)_3$], 28.55 (βCH_2), 35.54 (NCH_3), 42.48 ($COCH_2$), 47.59 (δCH_2), 57.32 (αCH), 81.49 [$C(CH_3)_3$], 154.96 (CONH), 165.31 ($CONCH_3$) and 173.73 ($COCH_2$); *m*/*z* (CI) 320 (3%, $[M + H]^+$), 284 (100, $[M - Cl]^+$), 240 {91, $[M - Cl - C(CH_3)_3 + H]^+$}, 225 {9, $[M - Cl - OC(CH_3)_3 + 2H^+$}, 170 {15, $[M - CH_2Cl - CO_2C(CH_3)_3 + H]^+$} and 155 {4, $[M - CH_2Cl - NHCO_2C(CH_3)_3 + H]^+$}.

(9a*S*)-2-Methyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*]-[1,2,5]triazepine-1,5-dione 17

Hydrogen chloride gas was bubbled through a solution of *N*-*tert*-butoxycarbonyl-*N*′-[(2*S*)-*N*-chloroacetylprolyl]-*N*′-methylhydrazine **20** (1.60 g, 5 mmol) in ethyl acetate (30 cm^3) for 20 min at 0 °C. The solvent was then removed under reduced pressure and the resultant hygroscopic white solid was dissolved in water (25 cm^3) and NaOH solution (1 mol dm^{-3}) added until the solution reached pH 9. The solution was then extracted with ethyl acetate (3 × 20 cm^3), the combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the product as a white solid (0.59 g, 64%), mp 75–79 °C (HRMS: found M^+, 183.1001. $C_8H_{13}N_3O_2$ requires 183.1007); $[\alpha]_D^{22}$ −40.2 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3440 (NH), 1652 (methylamide CO) and 1637 (tertiary amide CO); δ_H(200 MHz; C^2HCl_3) 1.82–2.38 (*A* and *B*, 4 H, m, γCH_2 and βCH_2), 3.18 (*A*, 3 H, s, NCH_3), 3.22 (*B*, 3 H, s, NCH_3), 3.69 (*A* and *B*, 2 H, m, δCH_2), 3.91 (*A* and *B*, 1 H, s, NH), 4.03 (*A* and *B*, 1 H, d, *J* 12.4, $\frac{1}{2}COCH_2$), 4.13 (*A* and *B*, 1 H, d, *J* 12.4, $\frac{1}{2}COCH_2$), 5.39 (*B*, 1 H, dd, J_1 3.2, J_2 8.6, αCH) and 5.47 (*A*, 1 H, dd, J_1 3.9, J_2 7.9, αCH); δ_C(50.31 MHz; C^2HCl_3) 22.22 (*B*, γCH_2), 24.52 (*A*, γCH_2), 29.07 (*A*, βCH_2), 31.67 (*B*, βCH_2), 38.26 (*A*, NCH_3), 38.43 (*B*, NCH_3), 42.41 (*A* and *B*, $COCH_2$), 47.44 (*A*, δCH_2), 47.65 (*B*, δCH_2), 57.46 (*A*, αCH), 57.88 (*B*, αCH), 164.51 (*A*, $CONCH_3$), 165.13 (*B*, $CONCH_3$) and 172.97 (*A* and *B*, $COCH_2$); *m*/*z* (EI) 183 (45%, M^+), 155 (15, $[M - NCH_3 + H]^+$), 139 (65, $[M - NHNCH_3]^+$), 125 (20, $[M - CH_2NHNCH_3]^+$), 111 (40, $[M - CONCH_3NH]^+$) and 70 (100, $[C_4H_8N]^+$).

(2*S*,2′*S*)-*N*-(2′-Chloropropionyl)proline methyl ester 22a

To a solution of *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry THF (20 cm^3) was added (2*S*)-2-chloropropionic acid **21a**,[29] (1.09 g, 10 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (1.36 cm^3, 10 mmol) was added with stirring and the resultant suspension was stirred at −15 °C for 2 min. A mixture of (2*S*)-proline methyl ester hydrochloride (1.66 g, 10 mmol) and *N*-methylmorpholine (1.12 cm^3, 10 mmol) in dry DMF (5 cm^3) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 3 h. The hydrochloride salts were filtered off and the solvents removed under reduced pressure. The resulting clear oil was dissolved in CH_2Cl_2 (25 cm^3) and washed with 0.5 mol dm^{-3} HCl (2 × 15 cm^3) and 5% aqueous sodium carbonate (2 × 15 cm^3). The organic phase was then dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a yellow oil which was purified by silica chromatography using ethyl acetate–light petroleum (1:1) as the eluent to give the product as a clear oil (1.56 g, 71%) (HRMS: found $[M + H]^+$, 220.0747. $C_9H_{15}{}^{35}ClNO_3$ requires 220.0742); $[\alpha]_D^{22}$ −70.8 (*c* 1.0 in MeOH); ν_{max}(thin film)/cm^{-1} 1746 (ester CO), 1659 (amide CO) and 1433 (C–O); δ_H(200 MHz; C^2HCl_3) 1.62 (3 H, d, *J* 6.8, $CHCH_3$), 1.85–2.32 (4 H, m, γCH_2 and βCH_2), 3.51–3.92 (2 H, m, δCH_2), 3.69 (3 H, s, OCH_3), 4.47 (1 H, dd, J_1 3.4, J_2 6.6, αCH) and 4.49 (1 H, q, *J* 6.8, $CHCH_3$); δ_C(50.31 MHz; C^2HCl_3) 20.50 (*t*, $CHCH_3$), 21.32 (*c*, $CHCH_3$), 21.99 (*c*, γCH_2), 24.79 (*t*, γCH_2), 29.05 (*t*, βCH_2), 31.35 (*c*, βCH_2), 46.91 (*t* and *c*, δCH_2), 51.17 (*t* and *c*, $CHCH_3$), 52.13 (*t*, OCH_3), 52.48 (*c*, OCH_3), 59.18 (*t*, αCH), 59.28 (*c*, αCH), 167.52 (*t* and *c*, $COCHCH_3$), 172.07 (*c*, CO_2CH_3) and 172.23 (*t*, CO_2CH_3); *m*/*z* (EI) 220 (7%, $[M + H]^+$), 184 (5, $[M - Cl]^+$), 170 (54, $[M - Cl - CH_3 + H]^+$), 160 (84, $[M - CO_2CH_3]^+$), 128 (58, $[M - Cl - CO_2CH_3 + 3H]^+$) and 70 (100, $[C_4H_8N]^+$).

(2*S*,2′*R*)-*N*-(2′-Chloropropionyl)proline methyl ester 22b

This compound was prepared in a manner identical with that for the (2*S*,2′*S*) diastereomer **22a**, using (2*R*)-2-chloropropionic acid **21b**,[29] (1.09 g, 10 mmol) to give the product as colourless crystals (1.82 g, 83%), mp 118–120 °C (Found: C, 49.2; H, 6.4; N, 6.4. $C_9H_{14}ClNO_3$ requires C, 49.05; H, 6.6; N, 6.4%); $[\alpha]_D^{22}$ −113.9 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 1751 (ester CO), 1656 (amide CO) and 1454 (C–O); δ_H(200 MHz; C^2HCl_3) 1.64 (*c*, 3 H, d, *J* 6.4, CHCH_3), 1.66 (*t*, 3 H, d, *J* 6.6, CHCH_3), 1.80–2.33 (*t* and *c*, 4 H, m, γCH_2 and βCH_2), 3.46–3.70 (*t*, 2 H, m, δCH_2), 3.74 (*t*, 3 H, s, OCH_3), 3.77 (*c*, 3 H, s, OCH_3), 3.82–3.98 (*c*, 2 H, m, δCH_2), 4.24 (*c*, 1 H, q, *J* 6.4, C*H*CH$_3$), 4.46 (*t*, 1 H, dd, J_1 3.2, J_2 8.4, αCH) and 4.71 (*c*, 1 H, dd, J_1 5.0, J_2 5.6, αCH); δ_C(74.76 MHz; C^2HCl_3) 20.82 (*t*, CH*C*H$_3$), 20.94 (*c*, CH*C*H$_3$), 22.78 (*c*, γCH_2), 25.24 (*t*, γCH_2), 29.41 (*t*, βCH_2), 31.44 (*c*, βCH_2), 47.26 (*c*, δCH_2), 47.35 (*t*, δCH_2), 51.29 (*t*, *C*HCH$_3$), 51.39 (*c*, *C*HCH$_3$), 52.62 (*t*, OCH_3), 53.27 (*c*, OCH_3), 59.47 (*c*, αCH), 59.62 (*t*, αCH), 167.99 (*t*, *C*OCHCH$_3$), 168.35 (*c*, *C*OCHCH$_3$), 172.48 (*t*, *C*O$_2$CH$_3$) and 172.78 (*c*, *C*O$_2$CH$_3$); *m*/*z* (EI) 220 (3%, $[M + H]^+$), 184 (4, $[M - Cl]^+$), 170 (5, $[M - Cl - CH_3 + H]^+$), 160 (63, $[M - CO_2CH_3]^+$), 127 (58, $[M - Cl - CO_2CH_3 + 2H]^+$) and 70 (100, $[C_4H_8N]^+$).

(2*S*,2′*S*)-*N*-(2′-Chloropropionyl)proline 23a

To a solution of (2*S*,2′*S*)-*N*-(2′-chloropropionyl)proline methyl ester **22a** (2.20 g, 10 mmol) in methanol (20 cm^3) was added 1 mol dm^{-3} aqueous sodium hydroxide (22 cm^3). The solution was stirred at room temperature for 1 h and then 1 mol dm^{-3} aqueous HCl (10 cm^3) was added. Methanol was removed under reduced pressure and a second portion of 1 mol dm^{-3} aqueous HCl (10 cm^3) was added. The precipitated white solid was filtered and recrystallised from methanol to give the product as colourless crystals (1.77 g, 84%), mp 164–165 °C (Found: C, 46.95; H, 5.95; N, 6.75. $C_8H_{12}ClNO_3$ requires C, 46.75; H, 5.9; N, 6.8%); $[\alpha]_D^{22}$ −62.1 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3045 (OH), 1739 (acid CO) and 1624 (amide CO); δ_H(200 MHz; C^2HCl_3) 1.68 (3 H, d, *J* 6.6, CH_3), 1.92–2.33 (4 H, m, βCH_2 and γCH_2), 3.64 (1 H, m, $\frac{1}{2}$δCH_2), 3.78 (1 H, m, $\frac{1}{2}$δCH_2), 4.53 (1 H, q, *J* 6.6, C*H*CH$_3$), 4.57 (1 H, dd, $J_1 = J_2$ 5.8, αCH) and 9.19 (1 H, s, CO_2H); δ_C(50.31 MHz; C^2HCl_3) 20.99 (CH_3), 25.34 (γCH_2), 29.39 (βCH_2), 47.79 (δCH_2), 51.67 (*C*HCH_3), 60.11 (αCH), 169.23 (NCO) and 175.57 (CO_2H); *m*/*z* (EI) 205 (14%, M^+), 172 (46, $[M - Cl + 2H]^+$), 144 (66, $[M - CHClCH_3 + 2H]^+$), 116 (59, $[M - COCHClCH_3 + 2H]^+$), 97 (87, $[C_4H_8NCO]^+$) and 70 (100, $[C_4H_8N]^+$).

(2*S*,2′*R*)-*N*-(2′-Chloropropionyl)proline 23b

This was prepared in a manner identical with that for the (2*S*,2′*S*) diastereomer using (2*S*,2′*R*)-*N*-(2′-chloropropionyl)-proline methyl ester **22b**, except that after the addition of the second portion of 1 mol dm^{-3} aqueous HCl (10 cm^3), the solution was extracted with ethyl acetate (3 × 50 cm^3). The combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the product as a white solid (1.54 g, 79%), mp 102–106 °C (HRMS: found $[M + H]^+$, 206.0589. $C_8H_{13}{}^{35}ClNO_3$ requires 206.0584); $[\alpha]_D^{22}$ −110.2 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3344 (OH), 1750 (acid CO) and 1616 (amide CO); δ_H(200 MHz; C^2HCl_3) 1.64 (*c*, 3 H, d, *J* 6.4, CH_3), 1.65 (*t*, 3 H, d, *J* 6.6, CH_3), 1.85–2.43 (*t* and *c*, 4 H, m, βCH_2 and γCH_2), 3.58 (*t* and *c*, 1 H, m, $\frac{1}{2}$δCH_2), 3.89 (*t* and *c*, 1 H, m, $\frac{1}{2}$δCH_2), 4.32 (*c*, 1 H, q, *J* 6.4, C*H*CH$_3$), 4.48 (*t*, 1 H, q, *J* 6.6, C*H*CH$_3$), 4.52 (*t*, 1 H, dd, J_1 4.3, J_2 6.7, αCH), 4.72 (*c*, 1 H, dd, J_1 4.3, J_2 6.7, αCH) and 10.25 (*t* and *c*, 1 H, s, CO_2H); δ_C(50.31 MHz; C^2HCl_3) 20.45 (*t* and *c*, CH_3), 22.37 (*c*, γCH_2), 24.70 (*t*, γCH_2), 28.88 (*t*, βCH_2), 30.99 (*c*, βCH_2), 47.21 (*c*, δCH_2), 47.26 (*t*, δCH_2), 51.07 (*t* and *c*, *C*HCH$_3$), 59.36 (*t* and *c*, αCH), 168.53 (*t*, NCO), 168.81 (*c*, NCO), 173.92 (*c*, CO_2H) and 174.73 (*t*, CO_2H); *m*/*z* (CI) 206 (58%, $[M + H]^+$), 170 (100, $[M - Cl]^+$), 156 (23, $[M - Cl - CH_3 + H]^+$), 142 (6, $[M - Cl - CHCH_3]^+$), 113 (12, $[M - CHCl - CO_2]^+$) and 97 (3, $[C_4H_8NCO]^+$).

***N-tert*-Butoxycarbonyl-*N*′-[(2*S*,2′*S*)-*N*-(2′-chloropropionyl)-prolyl]-*N*′-methylhydrazine 24a**

To a solution of (2*S*,2′*S*)-*N*-(2′-chloropropionyl)proline **23a** (2.06 g, 10 mmol) in dry THF (40 cm^3) was added *N*-methylmorpholine (1.12 cm^3, 10 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (1.36 cm^3, 10 mmol) was added with stirring and the resulting suspension stirred at −15 °C for 2 min. A solution of *N*-*tert*-butoxycarbonyl-*N*′-methylhydrazine **18** (1.46 g, 10 mmol) in dry THF (10 cm^3) was added and the reaction mixture was allowed to warm to room temperature and left to stir for 12 h. The hydrochloride salts were filtered off and the solvent removed under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (25 cm^3) and washed with 0.5 mol dm^{-3} HCl (2 × 15 cm^3) and 5% aqueous sodium carbonate (2 × 15 cm^3). The organic phase was then dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a yellow oil which was purified by silica chromatography using ethyl acetate–light petroleum (1:1) as the eluent to give the product as a white solid (2.31 g, 69%), mp 81–83 °C (Found: C, 50.6; H, 7.25; N, 12.5. $C_{14}H_{24}ClN_3O_4$ requires C, 50.4; H, 7.25; N, 12.6%) (HRMS: found $[M + H]^+$, 334.1538. $C_{14}H_{25}{}^{35}ClN_3O_4$ requires 334.1536); $[\alpha]_D^{22}$ −16.7 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3327 (NH), 1735 (carbamate CO), 1685 (methylamide CO) and 1646 (tertiary amide CO); δ_H(200 MHz; C^2HCl_3) 1.48 [9 H, s, C(CH_3)$_3$], 1.64 (3 H, d, *J* 6.6, CHCH_3), 1.82–2.31 (4 H, m, βCH_2 and γCH_2), 3.12 (3 H, s, NCH_3), 3.52–3.89 (2 H, m, δCH_2), 4.53 (1 H, q, *J* 6.6, C*H*CH$_3$), 4.98 (1 H, dd, $J_1 = J_2$ 6.3, αCH) and 7.87 (1 H, s, NH); δ_C(50.31 MHz; C^2HCl_3) 21.10 (CH*C*H$_3$), 25.20 (γCH_2), 28.64 [C(*C*H$_3$)$_3$], 28.78 (βCH_2), 35.55 (NCH_3), 47.77 (δCH_2), 51.68 (*C*HCH$_3$), 57.77 (αCH), 81.78 [*C*(CH$_3$)$_3$], 155.11 (*C*O$_2$Bu^t), 168.09 (*C*ONCH$_3$) and 173.86 (*C*OCHCH$_3$); *m*/*z* (CI) 334 (33%, $[M + H]^+$), 300 (15, $[M - Cl + 2H]^+$), 278 {100, $[M - C(CH_3)_3 + 2H]^+$}, 244 {28, $[M - Cl - C(CH_3)_3 + 3H]^+$}, 234 {12, $[M - CO_2C(CH_3)_3 + 2H]^+$} and 200 {13, $[M - Cl - CO_2C(CH_3)_3 + 3H]^+$}.

***N-tert*-Butoxycarbonyl-*N*′-[(2*S*,2′*R*)-*N*-(2′-chloropropionyl)-prolyl]-*N*′-methylhydrazine 24b**

This compound was prepared in a manner identical with that for the (2*S*,2′*S*) diastereomer **24a**, using (2*S*,2′*R*)-*N*-(2′-chloropropionyl)proline **23b** (2.06 g, 10 mmol) to give the product as a white solid (2.47 g, 74%), mp 132–135 °C (Found: C, 50.6; H, 7.3; N, 12.5. $C_{14}H_{24}ClN_3O_4$ requires C, 50.4; H, 7.25; N, 12.6%) (HRMS: found $[M + H]^+$, 334.1539. $C_{14}H_{25}{}^{35}ClN_3O_4$ requires 334.1536); $[\alpha]_D^{22}$ −20.3 (*c* 0.2 in MeOH); ν_{max}(Nujol)/cm^{-1} 3209 (NH),1728 (carbamate CO), 1687 (methylamide CO) and 1652 (tertiary amide CO); δ_H(200 MHz; C^2HCl_3) 1.47 [*t*, 9 H, s, C(CH_3)$_3$], 1.51 [*c*, 9 H, s, C(CH_3)$_3$], 1.60 (*c*, 3 H, d, *J* 6.6, CHCH_3), 1.65–2.48 (*t* and *c*, 4 H, m, γCH_2 and βCH_2), 1.65 (*t*, 3 H, d, *J* 6.6, CHCH_3), 3.11 (*t*, 3 H, s, NCH_3), 3.13 (*c*, 3 H, s, NCH_3), 3.57 (*t* and *c*, 1 H, m, $\frac{1}{2}$δCH_2), 3.89 (*t* and *c*, 1 H, m, $\frac{1}{2}$δCH_2), 4.49 (*t* and *c*, 1 H, q, *J* 6.8, C*H*CH$_3$), 4.96 (*t* and *c*, 1 H, dd, J_1 4.2, J_2 7.8, αCH) and 7.92 (*t* and *c*, 1 H, s, NH); δ_C(50.31 MHz; C^2HCl_3) 20.75 (*c*, CH*C*H$_3$), 21.05 (*t*, CH*C*H$_3$), 22.37 (*c*, γCH_2), 24.71 (*t*, γCH_2), 28.03 [*c*, C(*C*H$_3$)$_3$], 28.39 [*t*, C(*C*H$_3$)$_3$], 31.37 (*c*, βCH_2), 35.17 (*t*, NCH_3), 36.05 (*c*, NCH_3), 47.37 (*c*, δCH_2), 47.50 (*t*, δCH_2), 51.15 (*t*, *C*HCH$_3$), 53.86 (*c*, *C*HCH$_3$), 57.25 (*t*, αCH), 58.02 (*c*, αCH), 81.38 [*t* and *c*, *C*(CH$_3$)$_3$], 155.17 (*t* and *c*, *C*O$_2$Bu^t), 167.95 (*t* and *c*, *C*ONCH$_3$) and 173.86 (*t* and *c*, *C*OCHCH$_3$); *m*/*z* (CI) 334 (41%, $[M + H]^+$), 300 (11, $[M - Cl + 2H]^+$), 278 {100, $[M - C(CH_3)_3 + 2H]^+$}, 234 {12, $[M - CO_2C(CH_3)_3 + 2H]^+$}, 219 {11, $[M - NHCO_2C(CH_3)_3 + 2H]^+$} and 185 {8, $[M - Cl - CH_3 - CO_2C(CH_3)_3 + 3H]^+$}.

(4*R*,9a*S*)-2,4-Dimethyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 17a

Hydrogen chloride gas was bubbled through a solution of *N*-*tert*-butoxycarbonyl-*N*′-[(2*S*,2′*S*)-*N*-(2′-chloropropionyl)-

prolyl]-*N′*-methylhydrazine **24a** (1.35 g, 5 mmol) in ethyl acetate (30 cm^3) for 20 min at 0 °C. The solvent was then removed under reduced pressure and the resulting hygroscopic white solid dissolved in methanol (25 cm^3) and *N*-methylmorpholine (1.12 cm^3, 10 mmol) was added. The solvent was then removed under reduced pressure and the remaining residue dissolved in water and extracted with ethyl acetate (3 × 30 cm^3). The combined organic fractions were then dried ($MgSO_4$) and the solvent removed under reduced pressure to yield an off-white solid which was purified by silica chromatography using ethyl acetate–methanol (95:5) as the eluent to give the product as a white solid (0.61 g, 62%), mp 108–110 °C (HRMS: found M^+, 197.1159. $C_9H_{15}N_3O_2$ requires 197.1163); $[\alpha]_D^{22}$ −82.6 (*c* 0.5 in MeOH); ν_{max}(Nujol)/cm^{-1} 3336 and 3215 (NH), 1655 (tertiary amide CO) and 1641 (secondary amide CO); δ_H(200 MHz; C^2HCl_3) 1.66 (3 H, d, *J* 6.6, CHCH_3), 1.83–2.36 (4 H, m, γCH_2 and βCH_2), 3.18 (3 H, s, NCH_3), 3.76 (2 H, m, δCH_2), 4.54 (1 H, q, *J* 6.6, C*H*CH_3) and 5.48 (1 H, dd, J_1 4.6, J_2 8.0, αCH); δ_C(50.31 MHz; C^2HCl_3) 21.14 (CH*C*H_3), 25.28 (γCH_2), 29.69 (βCH_2), 39.25 (NCH_3), 47.89 (δCH_2), 51.97 (*C*HCH_3), 57.54 (αCH), 167.80 (*C*ONCH_3) and 174.08 (*C*OCHCH_3); *m*/*z* (EI) 197 (15%, M^+), 182 (9, $[M - CH_3]^+$), 153 (17, $[M - CH_3 - NCH_3]^+$), 139 (5, $[M - NHNCH_3 - CH_3 + H]^+$), 127 (15, $[M - CHCH_3NHNCH_3 + 2H]^+$) and 70 (100, $[C_4H_8N]^+$).

(4*S*,9a*S*)-2,4-Dimethyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo-[2,1-*d*][1,2,5]triazepine-1,5-dione 17b

This compound was prepared in a manner identical with that for the (4*R*,9a*S*) diastereomer **17a**, starting from *N*-*tert*-butoxycarbonyl-*N′*-[(2*S*,2′*R*)-*N*-(2′-chloropropionyl)prolyl]-*N′*-methylhydrazine **24b** (1.35 g, 5 mmol) instead of *N*-*tert*-butoxycarbonyl-*N′*-[(2*S*,2′*S*)-*N*-(2′-chloropropionyl)prolyl]-*N′*-methylhydrazine **24a** to give the product as a white solid (0.63 g, 64%), mp 112–115 °C (HRMS: found M^+, 197.1159. $C_9H_{15}N_3O_2$ requires 197.1163); $[\alpha]_D^{22}$ −119.4 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3299 and 3210 (NH), 1652 (tertiary amide CO) and 1634 (secondary amide CO); δ_H(200 MHz; C^2HCl_3) 1.57 (*B*, 3 H, d, *J* 6.6, CHCH_3), 1.62 (*A*, 3 H, d, *J* 6.8, CHCH_3), 1.78–2.34 (*A* and *B*, 4 H, m, γCH_2 and βCH_2), 3.14 (*A*, 3 H, s, NCH_3), 3.18 (*B*, 3 H, s, NCH_3), 3.59 (*A* and *B*, 1 H, m, ½δCH_2), 3.92 (*A* and *B*, 1 H, m, ½δCH_2), 4.48 (*A* and *B*, 1 H, *J* 6.7, C*H*CH_3), 5.40 (*A*, 1 H, dd, J_1 4.4, J_2 7.8, αCH) and 5.42 (*B*, 1 H, dd, J_1 4.4, J_2 8.6, αCH); δ_C(50.31 MHz; C^2HCl_3) 21.03 (*A*, CH*C*H_3), 21.14 (*B*, CH*C*H_3), 22.69 (*B*, γCH_2), 25.03 (*A*, γCH_2), 29.42 (*A*, βCH_2), 32.09 (*B*, βCH_2), 38.69 (*A*, NCH_3), 39.21 (*B*, NCH_3), 47.84 (*A* and *B*, δCH_2), 51.62 (*A*, *C*HCH_3), 51.71 (*B*, *C*HCH_3), 57.40 (*A*, αCH), 58.40 (*B*, αCH), 167.49 (*A*, *C*OCHCH$_3$), 168.33 (*B*, *C*OCHCH$_3$), 173.45 (*A*, *C*ONCH_3) and 173.92 (*B*, *C*ONCH_3); *m*/*z* (EI) 197 (5%, M^+), 182 (19, $[M - CH_3]^+$), 153 (7, $[M - CH_3 - NCH_3]^+$), 139 (6, $[M - NHNCH_3 - CH_3 + H]^+$), 127 (23, $[M - CHCH_3NHNCH_3 + 2H]^+$), 97 (37, $[C_4H_8NCO]^+$) and 70 (100, $[C_4H_8N]^+$).

(4*R*,9a*S*)-2,4-Dimethyl-3-[(2*S*)-*N*-benzyloxycarbonylphenylalanyl]-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepine-1,5-dione 17c

This compound was prepared in a manner identical with that for *N*-*tert*-butoxycarbonyl-*N′*-[(2*S*)-*N*-chloroacetylprolyl]-*N′*-methylhydrazine **20**, using (2*S*)-*N*-benzyloxycarbonylphenylalanine (1.50 g, 5 mmol) instead of (2*S*)-*N*-chloroacetylproline **19** and (4*R*,9a*S*)-2,4-dimethyl-1,2,5-triazepine-1,5-dione **17a** (1.99 g, 5 mmol) instead of *N*-*tert*-butoxycarbonyl-*N′*-methylhydrazine **18**. The crude material was purified by silica column chromatography using ethyl acetate–light petroleum (7:3) as the eluent to give the product as a white solid (1.96 g, 82%), mp 82–85 °C (HRMS: found $[M + H]^+$, 479.2282. $C_{26}H_{31}N_4O_5$ requires 479.2294); $[\alpha]_D^{22}$ +0.8 (*c* 1.0 in MeOH); ν_{max}(Nujol)/cm^{-1} 3270 (NH), 1717 (carbamate CO), 1695 (methylamide CO), 1659 (secondary amide CO) and 1645 (tertiary amide CO); δ_H(200 MHz; C^2HCl_3) 1.59 (3 H, d, *J* 6.6, CHCH_3), 1.68–2.35 (4 H, m, γCH_2 and βCH_2), 2.89 (3 H, s, NCH_3), 3.09 (2 H, d, *J* 7.6, ½CHCH_2Ph), 3.14 (2 H, d, *J* 7.0, ½CHCH_2Ph), 3.56 (2 H, m, δCH_2), 4.44 (1 H, dd, J_1 7.4, J_2 8.8, αCH), 4.47 (1 H, q, *J* 6.6, C*H*CH_3), 4.70 (1 H, m, C*H*NH), 5.08 (2 H, d, *J* 2.2, OCH_2Ph), 5.51 (1 H, d, *J* 7.2, NH), 7.22 (5 H, m, Ar–H, CHCH_2Ph) and 7.32 (5 H, s, Ar–H, OCH_2Ph); δ_C(50.31 MHz; C^2HCl_3) 21.15 (CH*C*H_3), 25.37 (γCH_2), 29.21 (βCH_2), 35.66 (CH*C*H_2Ph), 38.66 (NCH_3), 47.90 (δCH_2), 51.99 (*C*HCH_3), 55.46 (CHNH), 57.13 (αCH), 67.60 (O*C*H_2Ph), 127.75 (Ar–CH *para*), 128.51 (Ar–CH *ortho*), 128.72 (Ar–CH *para*), 129.07 (Ar–CH *ortho*), 129.30 (Ar–CH *meta*), 129.96 (Ar–CH *ortho*), 136.37 (Ar–C quaternary), 136.72 (Ar–C quaternary), 156.53 (CONH), 168.26 (*C*ONCH_3), 170.90 (*C*OCHCH_3) and 173.65 (*C*OCHCH_2Ph); *m*/*z* (CI) 513 (100%, $[M + 2NH_3 + H]^+$), 479 (19, $[M + H]^+$), 403 (3, $[M - Ph + H]^+$), 345 (3, $[M - CO_2CH_2Ph + 2H]^+$), 295 (4, $[M - OCH_2Ph - Ph + H]^+$), 254 (5, $[M - NHCO_2CH_2Ph - Ph + 3H]^+$) and 181 (32, $[M - COCHCH_2Ph - NHCO_2CH_2Ph - CH_3]^+$).

N-*tert*-Butoxycarbonyl-*N′*-phenylhydrazine 27

To a solution of phenylhydrazine (5.0 cm^3, 30.8 mmol) in diethyl ether (125 cm^3) was added di-*tert*-butyl dicarbonate (11.08 g, 50.8 mmol), and the mixture was stirred at room temperature for 3 days. The solvent was then removed under reduced pressure to yield a yellow solid which was washed with light petroleum (25 cm^3), 0.5 mol dm^{-3} hydrochloric acid (25 cm^3) and water (25 cm^3). The resulting *N*-protected *N′*-phenylhydrazine **27** was dried under reduced pressure and then recrystallised from ethyl acetate–light petroleum to give colourless needles (9.14 g, 86%), mp 88–90 °C (found: C, 63.5; H, 7.8; N, 13.65. $C_{11}H_{16}N_2O_2$ requires C, 63.4; H, 7.7; N, 13.45%); ν_{max}(thin film)/cm^{-1} 3354 (amine NH), 3278 (amide NH) and 1700 (CO); δ_H(200 MHz; C^2HCl_3) 1.48 [9 H, s, C(CH_3)$_3$], 5.90 (1 H, s, N*H*Ph), 6.64 (1 H, s, N*H*Boc), 6.80 (2 H, d, *J* 8.4, Ar–H *ortho*), 6.89 (1 H, t, *J* 7.5, Ar–H *para*) and 7.23 (2 H, t, *J* 8.0, Ar–H *meta*); δ_C(74.76 MHz; C^2HCl_3) 28.15 [C(*C*H$_3$)$_3$], 81.03 [*C*(CH$_3$)$_3$], 112.88 (Ar–CH *ortho*), 120.56 (Ar–CH *para*), 129.00 (Ar–CH *meta*), 148.33 (Ar–C quaternary) and 156.25 (*C*O$_2$Bu^t); *m*/*z* (EI) 208 (9%, M^+), 152 (81, $[M - C_4H_9 + H]^+$), 108 (57, $[M - CO_2C_4H_9 + H]^+$), 92 (44, $C_6H_5NH^+$), 77 (52, $C_6H_5^+$), 65 (31, $C_5H_5^+$) and 57 (100, $C_4H_9^+$).

N-(*tert*-Butoxycarbonyl)-*N′*-[(2*S*)-*N*-chloroacetylprolyl]-*N′*-phenylhydrazine 28

To a stirred solution of (2*S*)-*N*-chloroacetylproline **19** (0.33 g, 1.7 mmol) and pyridine (0.19 cm^3, 2.4 mmol) in dichloromethane (10 cm^3) was added, dropwise, thionyl chloride (0.15 cm^3, 2.0 mmol). After 10 min, a solution of hydrazide **27** (0.30 g, 1.4 mmol) and DMAP (0.39 g, 32 mmol) in dichloromethane (10 cm^3) was added in one portion. After 3–4 days, the orange solution was washed with 0.1 mol dm^{-3} hydrochloric acid (2 × 20 cm^3), 5% aqueous sodium hydrogen carbonate (2 × 20 cm^3) and brine (20 cm^3). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a brown oil which was purified by silica chromatography using light petroleum–ethyl acetate (3:2) as eluent to give the desired compound as a pale brown oil (0.34 g, 62%) (HRMS: found $[M - OC_4H_9]^+$, 308.0808. $C_{14}H_{15}ClN_3O_3$ requires 308.0802); $[\alpha]_D^{22}$ −21.5 (*c* 0.4 in MeOH); ν_{max}(thin film)/cm^{-1} 1733 (ester CO), 1694 (secondary amide CO), 1654 (tertiary amide CO) and 1162 (ester C–O); δ_H(200 MHz; C^2HCl_3), 1.38 [9 H, s, C(CH_3)$_3$], 1.76–2.12 (4 H, m, βCH_2 and γCH_2), 3.38–3.63 (2 H, m, δCH_2), 4.00–4.09 (2 H, m, CH_2Cl), 4.40 (*c*, 1 H, m, αCH), 5.15 (*t*, 1 H, m, αCH), 7.06–7.52 (5 H, m, Ar–H), 9.05 (*c*, 1 H, br s, NH) and 9.35 (*t*, 1 H, br s, NH); δ_C(74.76 MHz; C^2HCl_3) 25.28 (*c*, γCH_2), 25.42 (*t*, γCH_2), 28.60 [CO(*C*H$_3$)$_3$], 28.95 (*t*, βCH_2), 29.20 (*c*, βCH_2), 42.50 (CH_2Cl), 47.86 (δCH_2), 58.17 (*t*, αCH), 58.39 (*c*, αCH), 81.86 [*C*(CH$_3$)$_3$], 125.15, 126.95 (Ar–CH *ortho*), 128.37, 128.87 (Ar–CH *para*), 129.11, 129.95 (Ar–CH

meta), 141.56, 142.14 (Ar–C quaternary), 154.97 (*t*, CO_2Bu^t), 155.96 (*c*, CO_2Bu^t), 165.39 (*t*, $COCH_2Cl$), 165.83 (*c*, $COCH_2Cl$) and 173.47 (*C*ONPh); *m*/*z* (EI) 382 (2%, M^+), 308 (6, $[M - OC_4H_9]^+$), 281 (14, $[M - CO_2C_4H_9]^+$), 174 (55, $[C_7H_9NO_2Cl + H]^+$), 146 (100, $C_6H_9NOCl^+$), 70 (77, $[C_4H_8N + H]^+$) and 57 (57, $C_4H_9^+$).

(9a*S*)-2-Phenyl-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*]-[1,2,5]triazepine-1,5-dione 26

Dry hydrogen chloride gas was bubbled through a solution of the dipeptide **28** (0.84 g, 2.2 mmol) in ethyl acetate (25 cm^3) for 40 min. The solvent was removed under reduced pressure and the resulting yellow solid was redissolved in hydrochloric acid (0.5 mol dm^{-3}, 25 cm^3). The solution was washed with diethyl ether (30 cm^3), and basified with aqueous sodium hydroxide (1 mol dm^{-3}, 35 cm^3). The solution was allowed to stand for 30 min and then extracted with ethyl acetate (3 × 50 cm^3). The organic phase was washed with water (50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the compound **26** as an orange–brown oil (0.36 g, 68%) (HRMS: found M^+, 245.1170. $C_{13}H_{15}N_3O_2$ requires 245.1164); ν_{max}(thin film)/cm^{-1} 3336 (NH) and 1650 (br, CO); δ_H(300 MHz; C^2HCl_3), 1.84–1.97 (3 H, m, $\frac{1}{2}\beta CH_2$ and γCH_2), 2.08–2.17 (1 H, m, $\frac{1}{2}\beta CH_2$), 3.51–3.67 (2 H, m, δCH_2), 3.95–4.06 (2 H, m, CH_2NH), 4.41 (1 H, m, αCH), 4.81 (1 H, br s, NH) and 7.20–7.50 (5 H, m, Ar–H); δ_C(74.76 MHz; C^2HCl_3) 25.55 (γCH_2), 29.84 (βCH_2), 42.65 (CH_2NH), 48.04 (δCH_2), 58.17 (αCH), 127.99 (Ar–CH *ortho*), 128.93 (Ar–CH *para*), 130.08 (Ar–CH *meta*), 142.35 (Ar–C quaternary), 165.28 ($COCH_2N$) and 171.15 (*C*ONPh); *m*/*z* (EI) 245 (15%, M^+), 217 (33, $[M - CO]^+$), 110 (40, $C_6H_8NO^+$), 93 (57, $C_6H_5NH_2^+$), 77 (42, $C_6H_5^+$) and 70 (100, $C_4H_8N^+$).

(2*S*)-2-Benzylhydantoic acid 32

To a stirred suspension of (2*S*)-phenylalanine **31** (5.00 g, 30.3 mmol) in water (80 cm^3) was added potassium cyanate (22.9 g, 0.28 mol), and the resulting mixture was heated at 60 °C for 4 h. The clear solution was ice-cooled and carefully acidified with concentrated hydrochloric acid (37%, 50 cm^3). The precipitate thus formed was filtered off, washed with cold water and dried under vacuum to yield (2*S*)-2-benzylhydantoic acid (5.40 g, 86%), mp 189–190 °C (lit.,[23] 189 °C); $[\alpha]_D^{22}$ +38.5 (*c* 1.0 in MeOH) [lit.,[23] 45.0 (*c* 1.0 in EtOH)]; ν_{max}(Nujol)/cm^{-1} 3450 (N–H), 3297 (N–H), 2926 (OH), 1693 (acid CO) and 1559 (amide CO); δ_H(200 MHz; $[^2H_6]$DMSO) 2.82–3.08 (2 H, m, CH_2), 4.35 (1 H, m, αCH), 5.70 (2 H, s, NH_2), 6.23 (1 H, d, *J* 8.0, NH) and 7.19–7.45 (5 H, m, Ar–H); δ_C(50.31 MHz; $[^2H_6]$DMSO) 37.79 (CH_2), 53.92 (αCH), 126.65 (Ar–CH *para*), 128.41 (Ar–CH *ortho*), 129.47 (Ar–CH *meta*), 137.70 (Ar–C quaternary), 158.53 ($CONH_2$) and 174.17 (CO_2H); *m*/*z* (EI) 208 (6%, M^+), 148 (86, $[M - NHCONH_2 + H]^+$), 120 (41, $C_6H_5CH_2CHNH^+$), 91 (100, $C_7H_7^+$), 74 (61, $NHCHCO_2H^+$) and 65 (28, $C_5H_5^+$).

(2*S*)-*N*-Aminophenylalanine 33

To an ice-cooled solution of (2*S*)-2-benzylhydantoic acid **32** (1.00 g, 4.8 mmol) in aqueous potassium hydroxide (2.5 mol dm^{-3}; 7 cm^3) was added aqueous potassium hypochlorite (1.37 mol dm^{-3}, 4.4 cm^3). After 5 min at 0 °C, the solution was heated at 80 °C for 1.5 h, after which toluene (20 cm^3), hydrazine hydrate (0.3 cm^3) and concentrated hydrochloric acid (35%, 4 cm^3) were added consecutively.

Heating was continued for a further 30 min, the mixture was cooled to room temperature, the phases separated, and the solvent removed from the aqueous phase under reduced pressure to yield a mixture of salts. The salts were extracted with hot ethanol (3 × 10 cm^3) and the extracts brought to pH 6.2 with diethylamine. The white solid thus formed was filtered off, washed with ethanol and dried under vacuum to yield (2*S*)-*N*-aminophenylalanine **33** (0.31 g, 36%), mp 199–201 °C (HRMS: found M^+, 180.0904. Calc. for $C_9H_{12}N_2O_2$: 180.0899); $[\alpha]_D^{22}$ −8.0 (*c* 1.0 in 5 mol dm^{-3} aq. HCl) [lit.,[23] −15.8 (*c* 0.5 in 6 mol dm^{-3} aq. HCl)]; ν_{max}(Nujol)/cm^{-1} 2900 (OH), 1735 (CO), 1377 (C–O) and 1075 (C–N); δ_H(200 MHz; ^2H_2O) 2.96–3.16 (2 H, m, CH_2), 3.77 (1 H, t, *J* 6.2, αCH) and 7.16–7.42 (5 H, m, ArH); δ_C(74.76 MHz; ^2H_2O) 33.49 (CH_2), 63.46 (αCH), 125.54 (Ar–CH *para*), 127.03 (Ar–CH *ortho*), 127.36 (Ar–CH *meta*), 133.67 (Ar–C quaternary) and 172.76 (CO_2H); *m*/*z* (EI) 180 (5%, M^+), 91 (100, $C_7H_7^+$), 89 (100, $[M - C_7H_7]^+$), 77 (23, $C_6H_5^+$), 71 (91, $[COCH(CH_2)NH + H]^+$), 65 (35, $C_5H_5^+$) and 43 (46, $[CH_2CHNH + H]^+$).

(2*S*)-*N*-(Benzyloxycarbonylamino)phenylalanine 34

To an ice–cooled solution of (2*S*)-*N*-aminophenylalanine **33** (1.50 g, 8.3 mmol) in aqueous sodium hydroxide (0.2 mol dm^{-3}, 40 cm^3) was added benzyl chloroformate (1.42 g, 8.4 mmol) and the mixture was allowed to reach room temperature whilst stirring vigorously over 1 h. Additional aqueous sodium hydroxide (1 mol dm^{-3}; 10 cm^3) was then added to redissolve the white precipitate. The solution was washed with diethyl ether (2 × 30 cm^3) and the aqueous phase acidified with dilute hydrochloric acid (0.5 mol dm^{-3}) to pH 3. The resulting precipitate was filtered off, washed with cold water and dried under reduced pressure to give the hydrazide **34** as a white solid (2.06 g, 79%), mp 163–165 °C (Found: C, 64.7; H, 5.8; N, 8.9. $C_{17}H_{18}N_2O_4$ requires C, 65.0; H, 5.8; N, 8.9%); $[\alpha]_D^{22}$ −3.9 (*c* 0.5 in MeOH); ν_{max}(Nujol)/cm^{-1} 3365 (NH), 3287 (NH), 2900 (OH), 1749 (acid CO), 1710 (amide CO) and 1273 (C–O); δ_H(200 MHz; $[^2H_4]$methanol) 2.96–3.01 (2 H, m, CH_2Ph), 3.85 (1 H, m, αCH), 5.10 (2 H, s, OCH_2Ph) and 7.21–7.34 (10 H, m, Ar–H); δ_C(74.76 MHz; $[^2H_4]$methanol) 38.07 ($CH_2C_6H_5$), 65.92 (αCH), 68.12 ($OCH_2C_6H_5$), 127.99, 129.23, 129.40, 129.78, 130.67 (Ar–CH), 138.26, 138.71 (Ar–C quaternary), 159.51 (CO_2CH_2Ph) and 176.13 (CO_2H); *m*/*z* (EI) 314 (13%, M^+), 223 (42, $[M - CH_2C_6H_5]^+$), 179 (22, $[M - CO_2CH_2C_6H_5]^+$), 91 (100, $C_7H_7^+$), 77 (22, $C_6H_5^+$) and 65 (34, $C_5H_5^+$).

Methyl (2*S*)-*N*-(benzyloxycarbonylamino)phenylalaninate 35

To ice-cooled methanol (5 cm^3) was added, dropwise, thionyl chloride (0.14 cm^3, 1.9 mmol), followed by hydrazide **34** (0.50 g, 1.6 mmol). The resulting solution was refluxed for 40 min, and allowed to cool to room temperature. The solvent and excess thionyl chloride were removed under reduced pressure and the resulting pale yellow oil was redissolved in ethyl acetate (40 cm^3). The solution was washed with 5% aqueous sodium hydrogen carbonate (2 × 20 cm^3), water (2 × 10 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give a pale yellow solid which was recrystallised from ethyl acetate–light petroleum to give colourless crystals (0.39 g, 74%), mp 62–64 °C (Found: C, 65.5; H, 6.0; N, 8.5. $C_{18}H_{20}N_2O_4$ requires C, 65.8; H, 6.1; N, 8.5%) (HRMS: found M^+, 328.1414. $C_{18}H_{20}N_2O_4$ requires 328.1423); $[\alpha]_D^{22}$ +10.9 (*c* 0.2 in MeOH); ν_{max}(Nujol)/cm^{-1} 1735 (CO) and 1406 (ester C–O); δ_H(200 MHz; C^2HCl_3) 2.93–3.16 (2 H, m, CH_2Ph), 3.70 (3 H, s, CO_2CH_3), 4.00 (1 H, t, *J* 6.3, αCH), 4.20 (1 H, br s, NH), 5.09 (2 H, s, OCH_2Ph), 6.52 (1 H, br s, NH) and 7.22–7.31 (10 H, m, Ar–H); δ_C(50.31 MHz; C^2HCl_3), 37.74 (CH_2Ph), 52.48 (CO_2CH_3), 64.43 (αCH), 67.50 ($OCH_2C_6H_5$), 127.45, 128.66, 128.71, 128.99, 129.06, 129.61 (Ar–CH), 136.55, 136.83 (Ar–C quaternary), 157.42 ($CO_2CH_2C_6H_5$) and 173.57 (CO_2CH_3); *m*/*z* (EI) 328 (5%, M^+), 237 (57, $[M - CH_2C_6H_5]^+$), 193 (35, $[M - CO_2CH_2C_6H_5]^+$), 162 (26, $H_3CO_2CCCH_2C_6H_5^+$), 105 (17, $[CHCH_2C_6H_5 + H]^+$), 91 (100, $C_7H_7^+$) and 65 (22, $C_5H_5^+$).

Methyl (2*S*)-*N*-(benzyloxycarbonylamino)-*N*-[(2*S*)-*N*-chloroacetylprolyl]phenylalaninate 36

To a stirred solution of (2*S*)-*N*-chloroacetylproline **19** (0.53 g, 2.8 mmol) and pyridine (0.31 cm^3, 3.9 mmol) in CH_2Cl_2 (10 cm^3) was added, dropwise, thionyl chloride (0.26 cm^3, 3.6 mmol). After 10 min, a solution of the hydrazide **35** (0.60 g, 1.8 mmol) and DMAP (0.49 g, 4.0 mmol) in CH_2Cl_2 (10 cm^3) were added

in one portion. After 3–4 days, the dark brown solution was washed with 0.5 mol dm^{-3} hydrochloric acid (2 × 20 cm^3), 5% aqueous sodium hydrogen carbonate (2 × 20 cm^3) and brine (30 cm^3). The organic phase was dried ($MgSO_4$), and the solvent removed under reduced pressure to give a brown oil which was purified by silica chromatography using light petroleum–ethyl acetate (3:2) as the eluent to give the desired product **36** as a light oil (0.49 g, 53%) (HRMS: found M^+, 501.1675. $C_{25}H_{28}ClN_3O_6$ requires 501.1667); $[\alpha]_D^{22}$ −66.8 (*c* 1.1 in MeOH); ν_{max}(thin film)/cm^{-1} 3241 (NH), 1744 (ester CO), 1690 (secondary amide CO) and 1645 (tertiary amide CO); δ_H(200 MHz; C^2HCl_3) 1.92–2.06 (3 H, m, $\frac{1}{2}\beta CH_2$ and γCH_2), 2.11–2.18 (1 H, m, $\frac{1}{2}\beta CH_2$), 3.00–3.21 (2 H, m, $CH_2C_6H_5$), 3.55–3.65 (2 H, m, δCH_2), 3.70 (3 H, s, CO_2CH_3), 3.93–4.08 (2 H, dd, J_1 13.2, J_2 4.0, CH_2Cl), 4.61 [*t*, 1 H, m, αCH(Pro)], 4.73 [*c*, 1 H, m, αCH(Pro)], 5.10–5.25 [3 H, m; *c*, αCH(Phe); and CO_2CH_2Ph], 5.50 [*t*, 1 H, m, αCH(Phe)], 7.25–7.39 (5 H, m, Ar–H) and 8.10 (1 H, br s, NH); δ_C(74.76 MHz; C^2HCl_3) 22.40 (*c*, γCH_2), 25.38 (*t*, γCH_2), 29.11 (*t*, βCH_2), 31.00 (*c*, βCH_2), 34.79 ($CH_2C_6H_5$), 42.09 (*c*, CH_2Cl), 42.16 (*t*, CH_2Cl), 47.74 (δCH_2), 52.51 (*c*, CO_2CH_3), 53.02 (*t*, CO_2CH_3), 60.42 (αCH), 68.21 (*c*, OCH_2Ph), 68.80 (*t*, OCH_2Ph), 127.10–129.63 (Ar–CH), 136.15, 137.09 (Ar–C quaternary), 155.94 (CO_2CH_2Ph), 165.62 ($COCH_2Cl$), 169.93 (CON) and 174.37 (CO_2CH_3); *m*/*z* (EI) 502 (9%, M^+), 328 (31, [M − $ClCH_2CONC_4H_7CO$ + H]$^+$), 237 (21, [M − $ClCH_2CONC_4H_7$-CO − C_7H_7 + H]$^+$), 174 (57, $ClCH_2CONC_4H_7CO^+$), 146 (100, $ClCH_2CONC_4H_7^+$), 91 (71, $C_7H_7^+$) and 70 (74, [C_4H_7N + H]$^+$).

(9a*S*)-2-[(1*S*)-1-Methoxycarbonyl-2-phenylethyl]-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepine-1,5-dione 29

To the dipeptide **36** (100 mg, 0.2 mmol) was added a solution of hydrogen bromide in acetic acid (30%; 6 cm^3). The solution was stirred at room temperature for 2 h and then poured into diethyl ether (100 cm^3), resulting in the formation of a flocculent white precipitate (this decomposed to a brown oil if exposed to air). The solvents were carefully decanted, the suspension diluted with diethyl ether (50 cm^3), shaken, and the solvent again decanted. The remaining solvents were removed under reduced pressure and the residue redissolved in aqueous sodium hydroxide (0.01 mol dm^{-3}; 20 cm^3) to give neutral pH. The solution was allowed to stand for 90 min, and extracted with ethyl acetate (3 × 20 cm^3). The organic phase was washed with water (50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a clear oil which crystallised from ethyl acetate–light petroleum to give pale yellow crystals (60 mg, 91%), mp 114–116 °C (Found: C, 49.5; H, 5.5; N, 10.0. $C_{17}H_{21}N_3O_4$·HBr requires C, 49.5; H, 5.4; N, 10.2%) (HRMS: found M^+, 331.1523. $C_{17}H_{21}N_3O_4$ requires 331.1532); $[\alpha]_D^{22}$ −78.3 (*c* 0.8 in MeOH); ν_{max}(thin film)/cm^{-1} 3353 (NH), 1740 (ester CO), 1672 (amide CO, br), 1170 (C–O) and 1093 (C–N); δ_H(300 MHz; C^2HCl_3) 1.75–2.15 (3 H, m, $\frac{1}{2}\beta CH_2$ and γCH_2), 2.18 (*A*, 1 H, m, $\frac{1}{2}\beta CH_2$), 2.32 (*B*, 1 H, m, $\frac{1}{2}\beta CH_2$), 2.61 (1 H, d, *J* 11.3, $\frac{1}{2}COCH_2N$), 2.99–3.50 (2 H, m, $CH_2C_6H_5$), 3.09 (1 H, d, *J* 11.3, $\frac{1}{2}COCH_2N$), 3.50–3.82 (2 H, m, δCH_2), 3.67 (*A* or *B*, 3 H, s, CO_2CH_3), 3.76 (*A* or *B*, 3 H, s, CO_2CH_3), 5.12 [*B*, 1 H, dd, J_1 8.9, J_2 3.0, αCH(Pro)], 5.29 [*A*, 1 H, dd, J_1 8.9, J_2 3.0, αCH(Pro)], 5.45 [*A* or *B*, 1 H, dd, J_1 9.2, J_2 6.3, αCH(Phe)], 5.65 [*A* or *B*, 1 H, dd J_1 12.3, J_2 4.8, αCH(Phe)] and 7.19–7.33 (5 H, m, Ar–H); δ_C(74.56 MHz; C^2HCl_3) 22.36, 24.66 (γCH_2), 27.29, 27.42 ($COCH_2N$), 29.00, 31.52 (βCH_2), 33.59, 34.10 ($CH_2C_6H_5$), 47.80, 48.12 (δCH_2), 52.41, 52.77 (CO_2CH_3), 57.57, 58.13 [αCH(Pro)], 57.96, 58.69 [αCH(Phe)], 127.27, 127.81 (Ar–CH *para*), 128.39, 128.82 (Ar–CH *ortho*), 129.05, 129.36 (Ar–CH *meta*), 135.90, 136.42 (Ar–C quaternary), 165.14, 165.25 ($COCH_2N$), 171.42, 172.05 (CON) and 174.71 (CO_2CH_3); *m*/*z* (EI) 331 (M^+, 53%), 212 (63, [M − CO-$CH_2C_6H_5$]$^+$), 168 (38, [M − $C_6H_5CH_2CHCO_2CH_3$]$^+$), 125 (39, $NC_4H_7CONCH^+$), 112 (51, $NC_4H_9CON^+$), 91 (48, $C_7H_7^+$) and 70 (100, $C_4H_8^+$).

(9a*S*)-2-[(1*S*)-1-Methoxycarbonyl-2-phenylethyl]-3-[(2*S*)-*N*-benzyloxycarbonylalanyl]-2,3,4,5,7,8,9,9a-octahydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepine-1,5-dione 30

To a solution of *N*-methylmorpholine (40 mm^3, 0.36 mmol) in dry THF (3 cm^3) was added (2*S*)-*N*-benzyloxycarbonylalanine (76 mg, 0.34 mmol) and the solution cooled to −15 °C. Isobutyl chloroformate (50 mm^3, 0.32 mmol) was added with stirring and the resulting suspension was stirred at −15 °C for 2 min. A mixture of triazepine-1,5-dione **29** (100 mg, 0.30 mmol) and *N*-methylmorpholine (40 mm^3, 0.36 mmol) in dry DMF (1 cm^3) was then added in one portion to the cold suspension. The reaction mixture was allowed to warm to room temperature and stirred for a further 5 h. The hydrochloride salts were filtered off and the solvents were removed under reduced pressure. The resulting oil was dissolved in ethyl acetate (10 cm^3) washed with 0.5 mol dm^{-3} aqueous HCl (2 × 5 cm^3), 5% aqueous sodium hydrogen carbonate (2 × 5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the product as a pale yellow oil. Purification by silica column chromatography using ethyl acetate as the eluent gave the pure product as a clear oil (6 mg, 4%) (HRMS: found M^+, 536.2283. $C_{28}H_{32}N_4O_7$ requires 536.2271); ν_{max}(thin film)/cm^{-1} 1742 (ester CO), 1725 (urethane CO), 1680 (secondary amide CO), 1650 (tertiary amide CO) and 1180 (C–O); δ_H(300 MHz; C^2HCl_3) 1.42 (3 H, d, *J* 7.1, $CHCH_3$), 1.79–2.27 (4 H, m, γCH_2 and βCH_2), 3.18–3.49 (2 H, m, CH_2Ph), 3.62–3.87 (2 H, m, δCH_2), 3.71 (*A*, 3 H, s, OCH_3), 3.76 (*B*, 3 H, s, OCH_3), 4.00–4.08 (2 H, m, CH_2N), 4.36 [1 H, m, αCH (Ala)], 5.11 (2 H, s, OCH_2Ph), 5.21–5.42 [2 H, αCH (Pro and Phe)], 6.64 (*A* or *B*, 1 H, m, NH), 6.80 (*A* or *B*, 1 H, m, NH) and 7.07–7.36 (10 H, m, Ar–H); δ_C(74.76 MHz; C^2HCl_3) 18.65 (CH_3), 22.27, 24.99 (γCH_2), 29.03, 31.61 (βCH_2), 33.39, 34.33 ($CH_2C_6H_5$), 41.79, 42.01 (CH_2N), 47.67, 47.97 (δCH_2), 49.70 [αCH(Ala)], 52.68, 52.97 (CO_2CH_3), 58.43, 58.69 [αCH(Pro)], 64.10, 64.33 [αCH(Phe)], 67.05 (OCH_2Ph), 127.04, 127.48, 128.24, 128.36, 128.70, 128.75, 128.89, 129.16 and 129.39 (Ar–CH), 136.65 and 137.76 (Ar–CH_2 quaternary), 141.71 and 143.09 (Ar–CH_2O quaternary), 155.83 (CO_2CH_2Ph), 164.95, 169.79 and 172.33 (CO); *m*/*z* (EI) 536 (M^+, 8%), 190 [27, $OCNCH(CO_2)$-$CH_2C_6H_5^+$], 174 [30, $OCNCH(CO)CH_2C_6H_5^+$], 146 (66, $OCNCHCH_2C_6H_5^+$), 140 (29, $CH_3CONC_4H_7CO^+$), 112 (45, $NC_4H_8CON^+$), 91 (100, $C_7H_7^+$) and 70 (96, $C_4H_8N^+$).

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References

1 Please note that in the preliminary communication on this work (M. M. Lenman, S. L. Ingham and D. Gani, *Chem. Commun*., 1996, 85), we referred to the fused system **6** as a 1,2,5-triazepine-3,6-dione and **12** as a 2,5-diketopiperazine. The numbering of the diones was based upon the unfused compounds, we apologise for any confusion this may have caused.

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