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Extension of the "ring switch" approach to glutamate antagonists to δ-lactam urethanes

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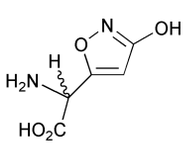
The versatile "ring switching" approach to antagonists of glutamate receptors has been extended to the use of δ-lactam urethanes. Three different types of δ-lactam urethane aldehydes **17**, **26** and **59** have been used successfully in this approach. Altering diastereoisomeric ratios in the synthesis by use of a hindered proton source has allowed homochiral products with two chiral centres to be obtained. Although the δ-lactam urethane system did not prove to be as versatile as the corresponding pyroglutamate or β-lactam urethanes, a variety of homologues of glutamate antagonists have been prepared.

The known activity of the natural product ibotenic acid **1**[1] gave impetus to the synthesis of analogous compounds consisting of a heterocyclic ring system fused to the α-carbon atom of a glycine moiety and of homologous compounds such as AMPA **2** with a heterocyclic ring fused to the β-carbon atom of L-alanine. These and other compounds were found to mimic



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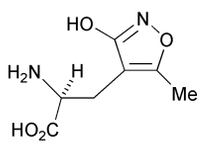

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glutamate, the fast excitatory receptor in the brain, but to have activity at specific and different ionotropic and metabotropic glutamate receptor sub-types.[2] The glutamate receptors have a variety of rôles in the central nervous system[3] and antagonists have been identified as potential drugs for variety of illnesses, including persistent pain,[4] Alzheimer's disease,[5] epilepsy[6] and ischaemia.[7]

We have discovered a versatile and economical synthesis for the preparation of a large variety of homochiral compounds in which a heterocyclic ring system is fused to the β-carbon atom of L-alanine.[8] This methodology has recently been extended to encompass the preparation of analogues of the lower homologue, ibotenic acid.[9] The synthesis, shown in Scheme 1, involves reaction of bisnucleophiles with an aldehyde of a pyroglutamic acid derivative **3** (n = 1) or an aldehyde of a β-lactam **3** (n = 0) or with their homologues **11**. It has the advantage of allowing a large variety of relevant, homochiral products to be obtained in a minimum number of steps. We have referred to this powerful synthetic tool as a "ring switching" reaction.[8a]

It was of interest to see whether the method might be applied to preparation of homologues with an additional carbon atom in the chain separating the heterocyclic and amino acid moieties by using the aldehydes **3** and **11** (n = 2) of 6-oxopiperidine-2-carboxylate in the synthesis. These compounds were expected to be less reactive than the corresponding β-lactam and pyroglutamate derivatives. We therefore prepared the methyl ester **14** using the method of Moloney,[10]§ and converted it into the urethane **15**[11] in 85% yield by reaction with di-*tert*-butyl dicarbonate and DMAP in acetonitrile as shown in Scheme 2. Reaction of the urethane **15** with four equivalents of *tert*-butoxybis(dimethylamino)methane in refluxing tetrahydrofuran gave the enaminone **16** in 48% yield (60% based on recovered starting material). Hydrolysis was achieved by maintaining the pH of a methanolic solution of the enaminone **16** at 4.0 by addition of 0.1 N aq. HCl and the reaction was judged to be complete after two days when λ_{max} 319 nm in the UV spectrum for the enaminone **16** had been entirely replaced by λ_{max} 261 for the enol of the aldehyde **17**. Hydrazine was added to the solution of the resultant aldehyde **17** *in situ* and the "ring switched" product, the pyrazole **18**, was obtained in 34% overall yield from the enaminone **16**. The product exhibited a singlet at δ 7.18 ppm for the proton H-3′ and an exchangeable doublet at δ 5.43 ppm for NHBoc. Other spectroscopic and analytical data were in agreement with the structural assignment. When methylhydrazine was used, then the pyrazole **19** was obtained in 32% overall yield from the enaminone **16**. Phenylhydrazine and *para*-nitrophenylhydrazine gave no useful products in this reaction.

It was later found that it was not necessary to hydrolyse the enaminone **16** to effect "ring switching" with hydrazine and methylhydrazine, since addition of one equivalent of acid to the enaminone **16**, followed immediately by addition of hydrazine or methylhydrazine gave the pyrazoles **18** or **19** in much the same yields as in the reaction where the enaminone had been hydrolysed. Presumably the electrophile in the ring switching reaction was the protonated enaminone **22**. The overall yield of the process could be enhanced by preparing the crude aldehyde **17** from the urethane **15** using LHMDS and methyl formate in THF and treating it with hydrazine or methylhydrazine in methanol. Overall yields for the two steps were 46% (**18**) and 40% (**19**) from the urethane **15** by this route, compared to 20% and 18% for the alternative three-step process. Reaction of the aldehyde **17** with 2-aminopyridine, which had given access to adducts useful in "ring switching" reactions when a pyro-

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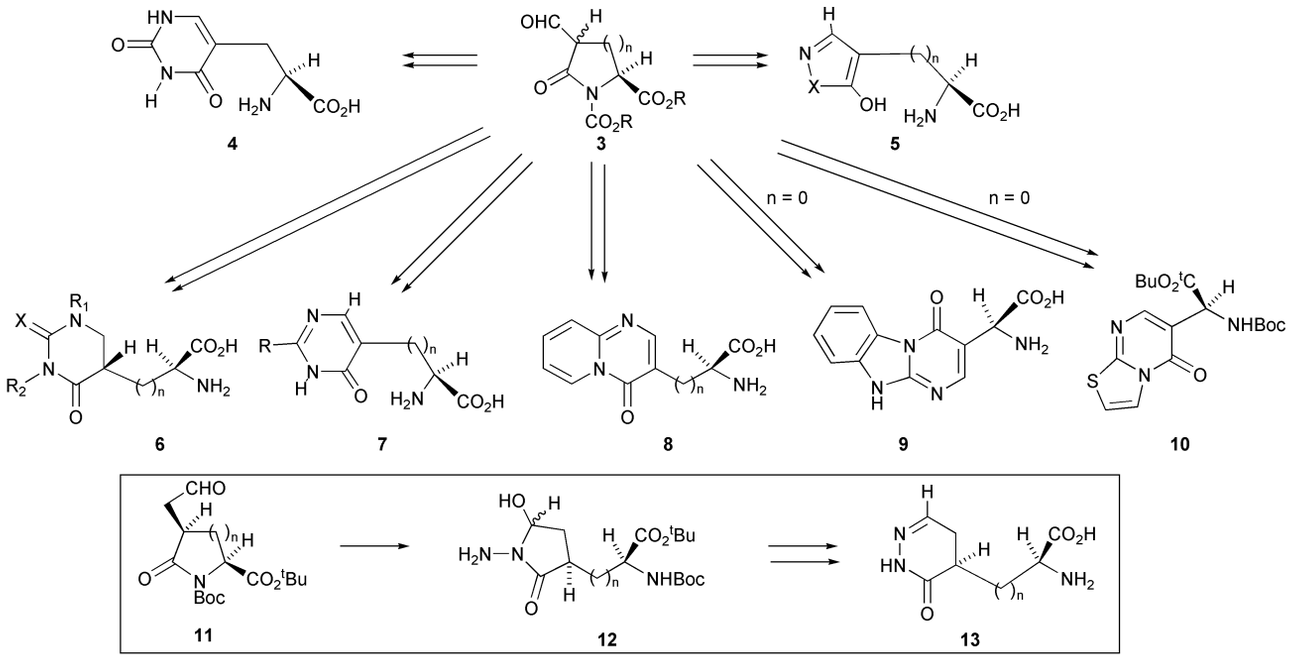
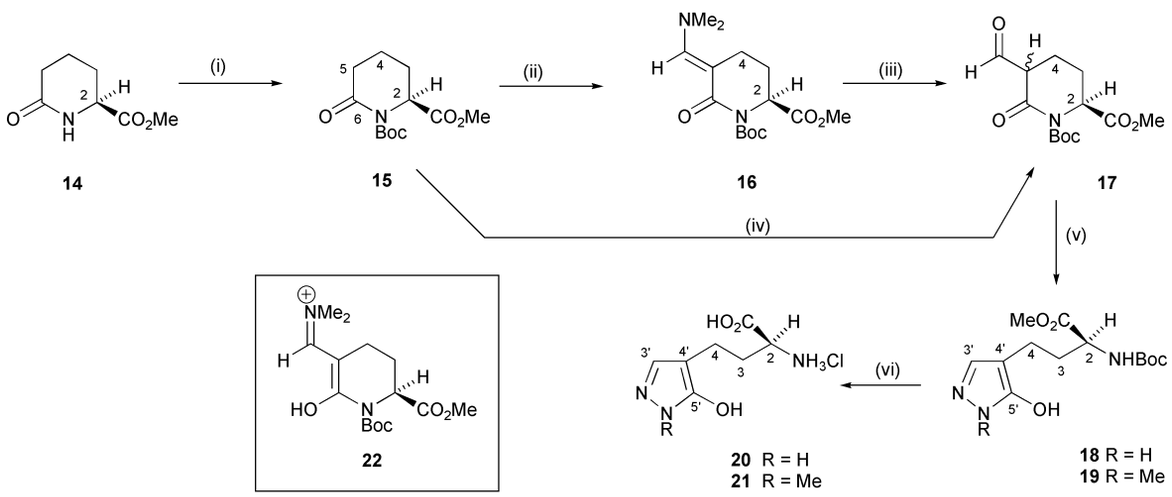


Scheme 1 $n = 0, 1$.

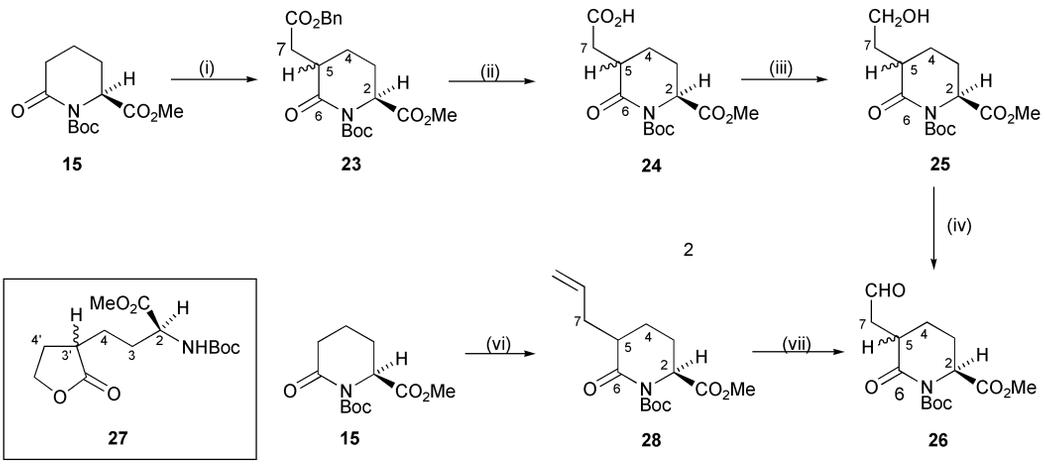


Scheme 2 (i) $(Boc)_2O$–DMAP–CH_3CN (85%); (ii) $tBuOCH(NMe_2)_2$ (48%); (iii) pH 4.0; (iv) LHMDS–THF–HCO_2Me; (v) $RNHNH_2$, [(iii) + (v) **18**, 34%; **19**, 32%], [(iv) + (v) **18**, 46%; **19**, 40%]; (vi) 6 N HCl–reflux (**20**, 57%; **21**, 40%).

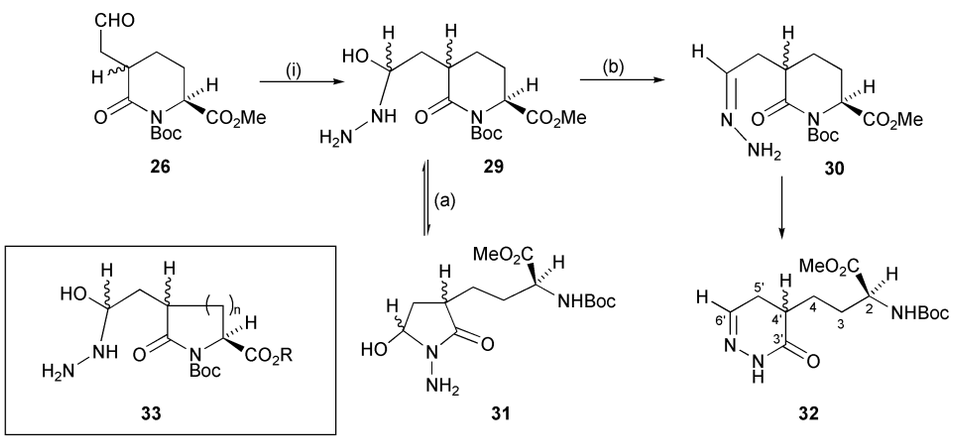
glutamate aldehyde had been used, gave no isolable products. The free amino acids **20** and **21** were obtained in 57% and 40% yields respectively from the urethane esters **18** and **19** by heating in 6 N aq. HCl at reflux.

Our next target as a substrate for "ring switching" reactions was the homologous aldehyde **26**. In our first attempt to synthesise this compound, we reacted the urethane **15** with LHMDS in THF followed by benzyl bromoacetate, as shown in Scheme 3. This reaction gave the diester **23**, which, on hydrogenolysis, afforded the monoacid **24**. Reduction to the alcohol **25** using $H_3B{\cdot}SMe_2$ gave a product in which the alcohol **25** was contaminated with the lactone **27**. The amount of lactone **27** increased with time and it was evidently produced by a spontaneous "ring switching" reaction of the alcohol **25**. Oxidation of the mixture of the alcohol and the lactone using oxalyl chloride and DMSO gave the aldehyde in only 20% yield.

It was evident that an alternative synthesis would be required to access the homologous aldehyde in good yield. The urethane **15** was, therefore, alkylated using LHMDS and allyl bromide to give the product **28** as a 1:1 mixture of diastereoisomers in 45% yield. These could not be separated by column chromatography. Ozonolysis of the product **28** in dichloromethane at −78 °C, followed by reduction of the ozonide with triphenylphosphine gave the aldehyde **26** in 72% yield. When the aldehyde **26** was reacted with hydrazine hydrate in methanol, a single product was obtained in 62% yield, as shown in Scheme 4. This compound had spectroscopic properties expected of the pyridazine **32**. This result was different from that found in the corresponding reaction in both the pyroglutamate series and β-lactam series, where carbinolamines corresponding to **31** were a major product. None of the carbinolamine **31** was obtained in this reaction. A possible explanation for this result is that the diminished electrophilicity of the ring carbonyl group in the six membered ring compared to that in the four and five membered rings, makes cyclisation to the carbinolamine **31** (Step [a] in Scheme 4) slower than dehydration of the intermediate carbinolamine **29** to the hydrazone **30**, (Step [b] in Scheme 4). Presumably the enhanced electrophilicity of the ring carbonyl group in the carbinolamine **33** in the β-lactam and pyroglutamate series allows for trapping of the carbinolamine by "ring switching", before dehydration can occur. The pyridazine **32** was converted into the free amino acid **34** in 33% yield by heating to reflux in 6 N aq. HCl. The corresponding *N*-methylpyridazine **35** was obtained in 40% yield by reacting the aldehyde **26** with methylhydrazine.



Scheme 3 (i) LHMDS–$BrCH_2CO_2Bn$ (56%); (ii) H_2–Pd-C (88%); (iii) $H_3B{\cdot}SMe_2$ (55%) (iv) ClCOCOCl–DMSO (20%); (vi) LHMDS–allylBr–THF (45%); (vii) O_3–Ph_3P (72%).

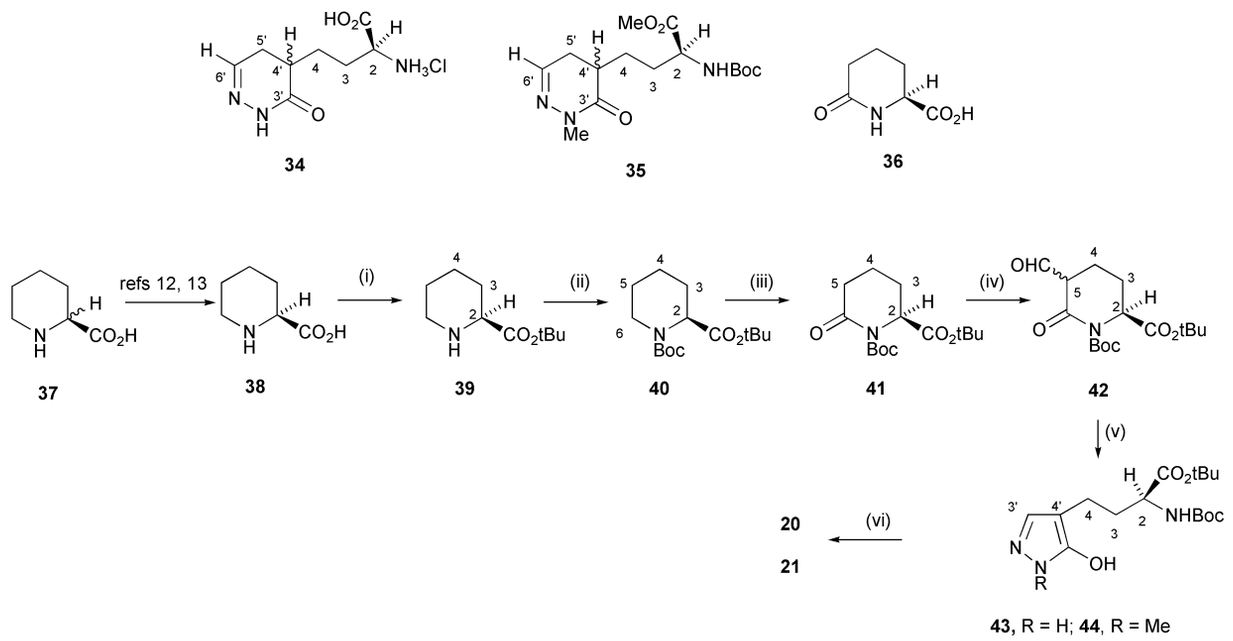


Scheme 4 (i) H_2NNH_2–MeOH (62% **32** from **26**).

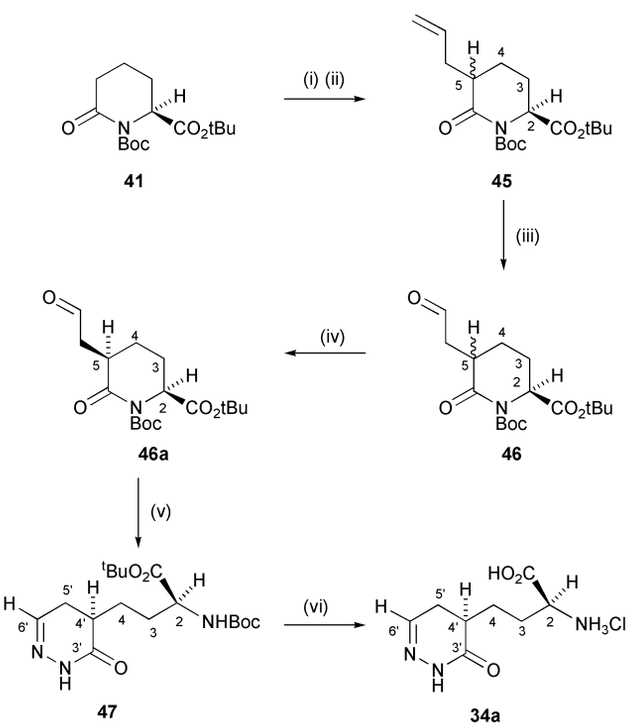
Because yields of amino acids were lower than we had come to expect in the pyroglutamic acid series where we had used *tert*-butyl esters, and because we wished to use a range of nucleophiles, some of which might react with the methyl ester, we decided that the hindered *tert*-butyl ester **41** might be a more useful substrate for our "ring switching" reactions. Attempts to hydrolyse the methyl ester **14** to (2*S*)-6-oxopiperidine-2-carboxylic acid **36** using acid gave low yields and use of LiOH was accompanied by racemisation, and so we opted for a more indirect approach. (2*S*)-Piperidine-2-carboxylic acid **38** was prepared in 28% yield from the racemate **37** by resolution *via* the salt with D-tartaric acid.[12,13] This was converted into the *tert*-butyl ester **39** in 54% yield, as shown in Scheme 5, using *tert*-butyl acetate and perchloric acid. The ester was converted into the urethane **40** in 85% yield using *tert*-butyl dicarbonate and triethylamine in methanol. Oxidation to the desired *δ*-lactam urethane **41** was finally achieved in 83% yield using ruthenium trichloride and sodium periodate. The product **41** was shown to be present in > 99% ee using chiral HPLC comparison with a racemic sample prepared from the racemate **37** by an identical route.

To compare the effect of using the *tert*-butyl ester **41** rather than the methyl ester **15** in the "ring switching"–deprotection sequence, we prepared the pyrazolones **43** and **44** by first reacting the ester **41** with LHMDS and methyl formate and then reacting the resultant aldehyde **42** *in situ* with either hydrazine or methylhydrazine. The pyrazolones **43** and **44** were obtained in 46% and 42% yields respectively and these could be deprotected by brief exposure to 6 N HCl at room temperature to give the amino acids **20** and **21** in 89% and 91% yields respectively. As before, no useful products were obtained when the aldehyde **42** was reacted with phenylhydrazine or *para*-nitrophenylhydrazine.

The homologous aldehydes **46** were obtained as in Scheme 6 *via* the allyl derivatives **45** in much the same way as the corresponding methyl esters **26** had been prepared. The allyl derivatives **45** were obtained in 59% yield as a 1:1 mixture of diastereoisomers and, when these were treated with LHMDS followed by the hindered proton source 2,6-di-*tert*-butylphenol, a 9:1 mixture of *cis*:*trans* isomers of **45** was obtained in 84% yield. Ozonolysis of the olefin in dichloromethane at −78 °C, followed by reduction of the ozonide using triphenylphosphine gave the diastereoisomeric *tert*-butyl esters **46**. The predominant (2*S*,5*R*)-diastereoisomer **46a** could be obtained in pure form by column chromatography. Although the stereochemistry of the predominant isomer was expected to be (2*S*,5*R*) due to protonation of the anion of the allyl derivative **45** from the less hindered face, this was confirmed by decoupling and NOE experiments on the product **46a**, shown in Fig. 1. Irradiation of the signal for H-2 at *δ* 4.57 ppm led to decoupling not only of the two signals for H-3 but also to the signal at *δ* 1.97 ppm. The latter was therefore assigned as H-4*R*, undergoing long range W-coupling with H-2, as shown in Fig. 1a. The NOE experiments, summarised in Figs. 1b and 1c and described in the experimental section, indicated that the proton H-3*S* which had the larger NOE to H-2 also showed enhancement when H-5 was irradiated. Further, H-4*R*, defined by the W-coupling experiment, showed enhancement when H-5 was irradiated. These data were all compatible with the (2*S*,5*R*)-stereochemistry shown in **46a**. The (2*S*,5*R*)-isomer **46a** was reacted with hydrazine hydrate in methanol to give the pyridazine **47** in 88% yield. Again none of the carbinolamine



Scheme 5 (i) tBuOAc–$HClO_4$ (54%); (ii) Boc_2O–$NaHCO_3$ (85%); (iii) (a) $RuCl_3 \cdot H_2O$ (b) $NaIO_4$–EtOAc–H_2O (83%), (ee >99%); (iv) LHMDS–HCO_2Me; (v) $RNHNH_2$–MeOH [**43** 46%, **44** 42% for (iv) + (v)]; (vi) 6 N aq. HCl (**20**, 89%, **21** 91%).



Scheme 6 (i) LHMDS–allylBr (59%, 1:1 *cis*:*trans*); (ii) (a) LHMDS, (b) 2, 6-di-*tert*-butylphenol (84% 9:1 *cis*:*trans*); (iii) (a) O_3–CH_2Cl_2 −78 °C, (b) PPh_3 (85%); (iv) separate; (v) H_2NNH_2–MeOH (88%); (vi) 6 N HCl (94%).

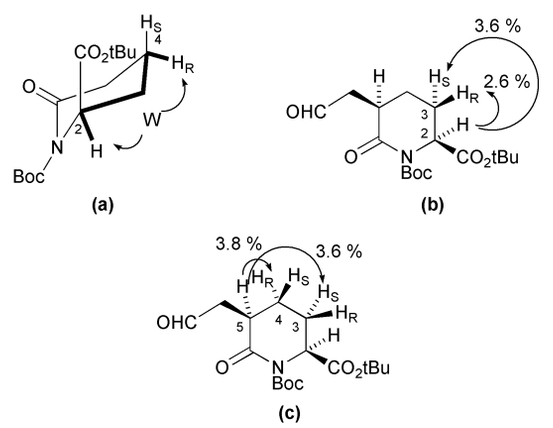
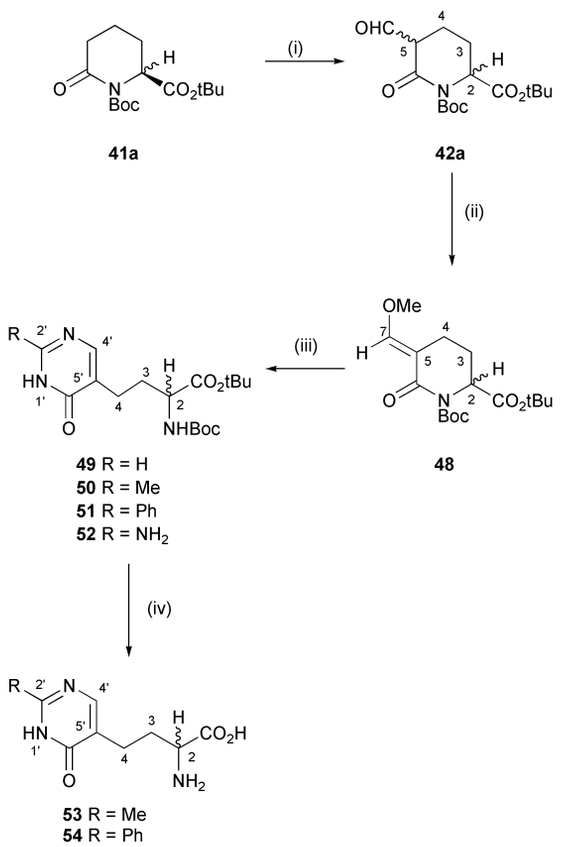


Fig. 1 Decoupling and NOE experiments on the diastereoisomer **46a**.

corresponding to **31** was present in the product. An attempt to achieve the corresponding reaction with methylhydrazine was unsuccessful. Hydrolysis of the pyridazine **47** with 6 N HCl at room temperature gave the amino acid hydrochloride **34a** in 94% yield.

Because the racemic compound **41a**, prepared in the same way as the (2*S*)-compound **41**, was more readily available, we used this to test the applicability of the "ring switching" method when bisnucleophiles other than substituted hydrazines were used. The *δ*-lactone urethane **41a** was therefore converted into the aldehyde **42a** as before and this was reacted with trimethylsilyldiazomethane in diethyl ether at 0 °C to afford the enol ether **48** in 52% overall yield from **41a** (Scheme 7). Heating an ethanolic solution of the enol ether **48** with formamidine acetate, acetamidine acetate, benzamidine hydrochloride or guanidine carbonate in the presence of potassium carbonate gave the pyrimidinones **49**, **50**, **51** and **52** in 43%, 83%, 59% and 19% yields respectively. These compounds had the expected analytical and spectroscopic properties and the pyrimidinones **50** and **51** were hydrolysed to the free amino acid hydrochlorides **53** and **54** in 97% and 98% yields respectively, using 6 N HCl at room temperature.

We had so far carried out our "ring switching" approach to glutamate antagonists *via* aldehydes prepared by α-substitution of β-, γ- and *δ*-lactam urethanes. We now decided to investigate the possibility of preparing these compounds *via* β-substituted lactam urethanes. We therefore prepared the α,β-unsaturated compound **56**, as shown in Scheme 8. The urethane ester **41** was treated with LHMDS at −30 °C followed by phenylselenyl chloride at −78 °C to give the monoselenide **55** as a 6:1 mixture of diastereoisomers in 64% yield. Oxidation using 30% aq. H_2O_2 gave the dehydro derivative **56** in 62% yield. Reaction with vinylmagnesium bromide and $CuBr \cdot SMe_2$ gave the diastereoisomeric products **57** in 43% yield and in a ratio of 2:1 as deduced from integration of the signals for H-2. Since it had been suggested[11] that *trans*-4-substituted-6-oxopiperidine-2-carboxylates have $J_{2,3}$ 2 and 4 Hz and the corresponding *cis*-isomers have $J_{2,3}$ 6 and 10 Hz, we assigned the major isomer ($J_{2,3}$ 2.7 and 5.8 Hz) as the *trans* (2*S*,4*R*)-isomer and the minor



Scheme 7 (i) LHMDS–HCO_2Me; (ii) $TMSCH_2N_2$ [52% for (i) + (ii)]; (iii) $RC(=NH)NH_2$–Na_2CO_3–EtOH [**49** 43%; **50** 83%; **51** 59%; **52** 19%; (iv) 6 N HCl (**53** 97%, **54** 98%).

isomer ($J_{2,3}$ 6.6 and 9.5 Hz) as the *cis* (2*S*,4*S*)-isomer.[14] Reaction of the dehydro derivative **56** with dimethylvinylmagnesium bromide and CuBr·SMe_2 gave a 5:1 mixture of diastereoisomers **58**. Neither of the diastereoisomeric mixtures **57** nor **58** could be separated. Ozonolysis of the olefins **57** and **58**, followed by reaction of the ozonides with triphenylphosphine gave the aldehyde **59** as an inseparable mixture of diastereoisomers. This was reacted immediately with hydrazine in methanol to give the pyridazine **60** in 80% overall yield from the starting olefin. We were unable to obtain useful products from this reaction using methylhydrazine. Deprotection of the pyridazine **60** was effected by 6 N aq. HCl at room temperature, giving the amino acid hydrochloride **61** in 79% yield.

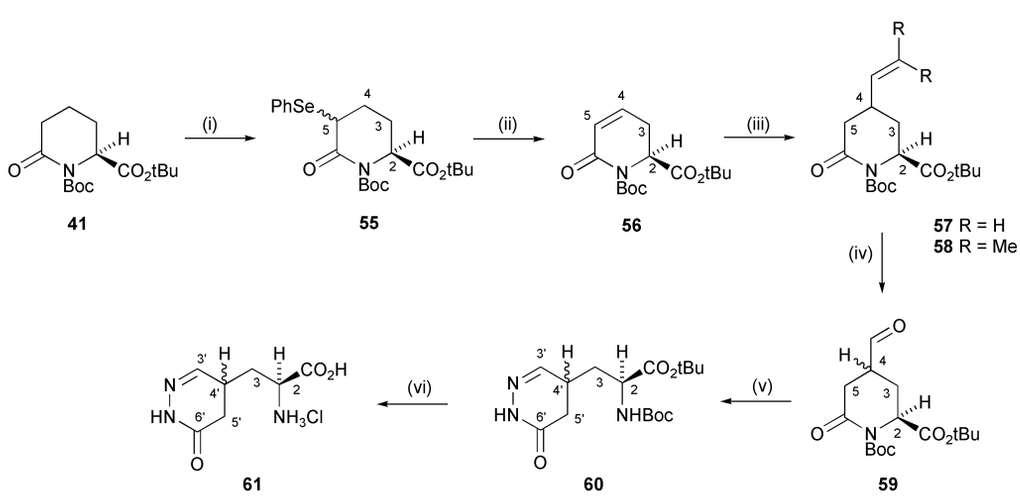
We have therefore successfully applied our "ring switching" strategy shown in Scheme 1 to the aldehydes **3** and **11** (n = 2) and also to the aldehyde **59**. Although not as versatile as the corresponding syntheses in the pyroglutamate (n = 1)[8] and β-lactam (n = 0)[11] series, useful homologues of glutamate antagonists have been prepared. Versatility in the synthesis seems to follow the order of the reactivity of the lactam carbonyl group in these reactions, with (n = 0) > (n = 1) > (n = 2).

Experimental

Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations (in units of 10^{-1} deg cm^2 g^{-1}) were measured on a Perkin–Elmer PE241 polarimeter using a 1 dm pathlength cell. IR spectra were recorded on a Perkin–Elmer 1720 Fourier-transform instrument. UV spectra were recorded on a ATI Unicam UV2–100 Fourier-transform scanning spectrometer. ^{1}H NMR spectra were recorded on Bruker DPX 300 (300 MHz) and Bruker DPX 400 (400 MHz) Fourier-transform instruments. *J* values are given in Hz. NOe spectra were recorded on a Bruker AMX 500 Fourier-transform instrument (500 MHz). ^{13}C NMR spectra were recorded on Bruker DPX 300 (75.48 MHz) and Bruker DPX 400 (100.61 MHz) Fourier transform instruments. DEPT experiments were used to assign ^{13}C resonances where necessary. Low resolution mass spectra were recorded by Dr A. Abdul Sada on a Kratos MS80RF and MS25 double focusing spectrometers. Accurate mass measurements were obtained from the EPSRC Central Mass spectrometry Service at Swansea and from GlaxoSmith-Kline, Stevenage. Microanalyses were carried out by Medac Ltd. Column chromatography was carried out using Fluka Kieselgel 60 (220–440 mesh). Petroleum ether refers to the fraction of alkanes of bp 60–80 °C.

Methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate (15)

Di-*tert*-butyl dicarbonate (903 mg, 4.14 mmol) was added to a mixture of methyl (2*S*)-6-oxopiperidine-2-carboxylate **14**[10] (500 mg, 3.18 mmol) and 4-dimethylaminopyridine (DMAP) (39 mg, 0.318 mmol) in acetonitrile (5 ml) under nitrogen at 0 °C. The mixture was allowed to warm to room temperature and was stirred for a further 3 h. The solvent was removed *in vacuo* to give a brown residue which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent to afford *methyl (2S)-N-tert-butoxycarbonyl-6-oxopiperidine-2-carboxylate* **15** as a yellow solid (696 mg, 85%); mp 52–54 °C; $[a]_D^{25}$ +9.4 (*c* 1.00, $CHCl_3$); Found: C, 56.25; H, 7.55; N, 5.4. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.4%; *m/z* [+ve FAB, 3-NBA] 258 [M + H]$^+$ and 280 [M + Na]$^+$; ν_{max} (KBr)/cm^{-1} 1766 and 1677 (C=O); δ_H (300



Scheme 8 (i) LHMDS–PhSeCl–THF −78°C (64%); (ii) H_2O_2–EtOAc (62%); (iii) R_2C=CHMgBr–CuBr.Me_2S (**57**, 43%; **58**, 38%); (iv) (a) O_3, (b) Ph_3P (80%); (v) H_2NNH_2–MeOH (80% for (iv) + (v)); (vi) 6 N HCl (79%).

MHz, C^2HCl_3) 4.58 (1H, *dd*, $J_{2,3A}$ 3.8, $J_{2,3B}$ 6.1, H-2), 3.70 (3H, *s*, OCH_3), 2.67–2.35 (2H, *m*, H-5), 2.22–1.93 (2H, *m*, H-3), 1.85–1.70 (2H, *m*, H-4) and 1.49 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.03 (C-6), 170.16 (ester), 152.21 (urethane), 83.59 [$OC(CH_3)_3$], 58.49 (C-2), 52.53 (OCH_3), 34.51 (C-5), 27.85 [$C(CH_3)_3$], 25.83 (C-3) and 18.24 (C-4).

Methyl (2*S*)-*N*-*tert*-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate (16)

A mixture of *tert*-butoxybis(dimethylamino)methane (1.60 ml, 7.77 mmol) and methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **15** (500 mg, 1.94 mmol) in tetrahydrofuran (5 ml) was heated under nitrogen at 70 °C for 18 h. The solvent was removed *in vacuo* to give a brown residue which was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (4:1) as eluent to afford *methyl (2S)-N-tert-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate* **16** as a yellow oil (289 mg, 48%); $[\alpha]_D^{25}$ +49.0 (*c* 1.0, $CHCl_3$); *m/z* [CI] Found 313.1759 $[M + H]^+$, $[C_{15}H_{24}N_2O_5 + H]^+$ requires 313.1763; *m/z* [+ve FAB, 3-NBA] 313 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1750, 1699 and 1678 (C=O); λ_{max} (MeOH)/nm 319 (log ε 4.24); δ_H (300 MHz, C^2HCl_3) 7.54 [1H, *s*, $=CHN(CH_3)_2$], 4.77 (1H, *t*, $J_{2,3}$ 4.7, H-2), 3.73 (3H, *s*, OCH_3), 3.02 [6H, *s*, $N(CH_3)_2$], 2.65 (1H, *m*, H-3), 2.46 (1H, *m*, H-3), 2.18 (1H, *m*, H-4A), 1.97 (1H, *m*, H-4B) and 1.49 [9H, *s*, $OC(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.23 (C-6), 167.00 (ester), 153.28 (urethane), 150.59 [$=CHN(CH_3)_2$], 94.99 (C-5), 82.27 [$OC(CH_3)_3$], 57.58 (C-2), 52.25 (OCH_3), 43.19 [$N(CH_3)_2$], 28.01 [$OC(CH_3)_3$], 25.58 (C-3) and 21.07 (C-4).

Methyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino(5-hydroxypyrazol-4-yl)butyrate (18)

Method A. Methyl (2*S*)-*N*-*tert*-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate **16** (120 mg, 0.384 mmol) was dissolved in methanol (10 ml) and 0.1 N aqueous hydrochloric acid was added dropwise to the solution with stirring, maintaining the pH of the solution at 4.0, until its UV spectrum showed reaction to be complete (*ca.* 0.461 mmol). Hydrazine hydrate (55% aq., 0.045 ml, 0.79 mmol) was added to the solution at room temperature and stirring was continued for a further 30 h. The solvent was removed *in vacuo* to give a yellow residue which was purified by column chromatography on silica gel using ethyl acetate as eluent to afford *methyl (2S)-2-N-tert-butoxycarbonylamino(5-hydroxypyrazol-4-yl)butyrate* **18** as a colourless oil (39 mg, 34%); $[\alpha]_D^{25}$ +6.5 (*c* 0.98, $CHCl_3$); *m/z* [+ve FAB, PEGH–NOBA] Found 299.1477 $[M]^+$, $C_{13}H_{21}N_3O_5$ requires 299.1481; *m/z* [+ve FAB, 3-NBA] 300 $[M + H]^+$; ν_{max} (film)/cm^{-1} 3300 (OH, NH), 1740 and 1691 (C=O); λ_{max} (MeOH)/nm 227 and 249 (log ε 3.66 and 3.45); λ_{max} (MeOH–HCl)/nm 232 (log ε 3.88); λ_{max} (MeOH–NaOH)/nm 241 (log ε 3.90); δ_H (300 MHz, C^2HCl_3) 9.49 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 7.18 (1H, *s*, H-3′), 5.43 (1H, *d*, *J* 8.3, NH, exchangeable with $^2H_3CO^2H$), 4.23 (1H, *m*, H-2), 3.67 (3H, *s*, OCH_3), 2.45–2.36 (2H, *m*, H-4), 2.05–1.79 (2H, *m*, H-3) and 1.41 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 173.49 (ester), 160.63 (C-4′), 155.69 (urethane), 129.46 (C-3′), 103.38 (C-5′), 79.92 [$OC(CH_3)_3$], 52.89 (C-2), 52.23 (OCH_3), 32.45 (C-4), 28.23 [$C(CH_3)_3$] and 18.25 (C-3).

Method B. 1 N aqueous hydrochloric acid (0.304 ml, 0.304 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate **16** (95 mg, 0.304 mmol) in methanol (10 ml) at room temperature followed by immediate addition of hydrazine hydrate (55% aq., 0.027 ml, 0.478 mmol). After stirring for 30 h, the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S)-2-N-tert-butoxycarbonylamino-(5-hydroxypyrazol-4-yl)butyrate* **18** as a colourless oil (31 mg, 34%). All spectra were identical to those of the product from Method A.

Method C. Lithium hexamethyldisilazide (1 M in THF, 7.0 ml, 7.0 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **15** (1.50 g, 5.83 mmol) in THF (15 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over a period of 30 min to ensure enolate formation and cooled to −78 °C. Methyl formate (0.719 ml, 12 mmol) was added and the solution was stirred for 5 min at −78 °C, warmed to 0 °C, and stirred for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at 0 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. The crude oil was dissolved in methanol (15 ml) and hydrazine hydrate (55% aq., 0.446 ml, 7.9 mmol) was added. The solution was stirred at room temperature for 30 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S)-2-N-tert-butoxycarbonylamino(5-hydroxypyrazol-4-yl)butyrate* **18** as a colourless oil (807 mg, 46%). All spectra were identical to those obtained by the previous methods.

Methyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino(1-methyl-5-hydroxypyrazol-4-yl)butyrate (19)

Method A. Methyl (2*S*)-*N*-*tert*-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate **16** (100 mg, 0.320 mmol) was dissolved in methanol (10 ml) and 0.1 N hydrochloric acid was added dropwise to the solution, maintaining the pH of the solution at 4.00, until its UV spectrum showed the reaction to be complete (*ca.* 0.384 mmol). Methylhydrazine (0.025 ml, 0.48 mmol) was added at room temperature and the solution was stirred for a further 30 h. The solvent was removed *in vacuo* to give a yellow residue which was purified by column chromatography on silica gel using ethyl acetate as eluent to afford *methyl (2S)-2-N-tert-butoxycarbonylamino(1-methyl-5-hydroxypyrazol-4-yl)butyrate* **19** as a colourless oil (32 mg, 32%); $[\alpha]_D^{25}$ +12.1 (*c* 0.9, $CHCl_3$); *m/z* [+ve FAB, PEGH–NOBA] Found 314.1697 $[M + H]^+$, $[C_{14}H_{23}N_3O_5 + H]^+$ requires 314.1716; *m/z* [+ve FAB, 3-NBA] 314 $[M + H]^+$; ν_{max} (film)/cm^{-1} 3400 (OH, NH), 1740 and 1689 (C=O); λ_{max} (MeOH)/nm 235 (log ε 3.86); λ_{max} (MeOH–HCl)/nm 239 (log ε 3.94); λ_{max} (MeOH–NaOH)/nm 256 (log ε 3.86); δ_H (300 MHz, C^2HCl_3) 8.37 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 6.99 (1H, *s*, H-3′), 5.16 (1H, *d*, *J* 8.3, NH, exchangeable with $^2H_3CO^2H$), 4.31 (1H, *m*, H-2), 3.71 (3H, *s*, NCH_3), 3.68 (3H, *s*, OCH_3), 2.48–2.32 (2H, *m*, H-4), 2.11–1.82 (2H, *m*, H-3) and 1.44 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 173.32 (ester), 159.94 (C-4′), 155.48 (urethane), 130.61 (C-3′), 103.12 (C-5′), 79.85 [$OC(CH_3)_3$], 52.78 (C-2), 52.19 (OCH_3), 38.06 (NCH_3), 32.71 (C-4), 28.27 [$C(CH_3)_3$] and 18.08 (C-3).

Method B. 1 M aqueous hydrochloric acid (0.320 ml, 0.320 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-5-dimethylaminomethylene-6-oxopiperidine-2-carboxylate **16** (100 mg, 0.320 mmol) in methanol (10 ml) at room temperature followed by immediate addition of methylhydrazine (0.025 ml, 0.480 mmol). After stirring for 30 h the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S)-2-N-tert-butoxycarbonylamino(1-methyl-5-hydroxypyrazol-4-yl)butyrate* **19** as a colourless oil (32 mg, 32%). All spectra were identical to the product from Method A.

Method C. Lithium hexamethyldisilazide (1 M in THF, 7.00 ml, 7.00 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **15** (1.50 g, 5.83 mmol) in THF (15 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over a period of 30 min to ensure enolate formation and was cooled to −78 °C. Methyl formate (0.719 ml, 12 mmol) was added and the solution was stirred for 5 min at −78 °C, warmed to 0 °C and stirred for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at 0 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. The crude oil was dissolved in methanol (15 ml) and methylhydrazine (0.419 ml, 7.9 mmol) was added. The solution was stirred at room temperature for 30 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S)-2-N-tert-butoxycarbonylamino(1-methyl-5-hydroxypyrazol-4-yl)butyrate* **19** as a colourless oil (731 mg, 40%). All spectra were identical to those of the product from Method A.

(2*S*)-2-Amino(5-hydroxypyrazol-4-yl)butyric acid hydrochloride (20)

A solution of methyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino-(5-hydroxypyrazol-4-yl)butyrate **18** (475 mg, 1.59 mmol) in 6 N aqueous hydrochloric acid (15 ml) was heated to reflux for 18 h. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S)-2-amino(5-hydroxypyrazol-4-yl)butyric acid hydrochloride* **20** as a glassy solid (200 mg, 57%); mp >250 °C; $[\alpha]_D^{25}$ +27.6 (*c* 1.03, H_2O); *m*/*z* [+ve es] Found 186.0875 $[M + H]^+$, $[C_7H_{11}N_3O_3 + H]^+$ requires 186.0878; ν_{max} (KBr)/cm^{-1} 3300 (OH, NH) and 1723 (C=O); λ_{max} (MeOH)/nm 232 and 252 (log ε 3.70 and 3.54); λ_{max} (MeOH–HCl)/nm 231 (log ε 3.87); λ_{max} (MeOH–NaOH)/nm 243 (log ε 3.83); δ_H (300 MHz,^2H_2O–^{2}HCl) 7.45 (1H, *s*, H-3′), 3.74 (1H, *t*, $J_{2,3}$ 6.5, H-2), 2.26 (2H, *m*, H-4) and 1.86 (2H, *m*, H-3); δ_C (75 MHz,^2H_2O–^{2}HCl) 171.60 (acid), 154.24 (C-4′), 134.22 (C-3′), 103.60 (C-5′), 52.11 (C-2), 29.38 (C-4) and 17.14 (C-3).

(2*S*)-2-Amino(1-methyl-5-hydroxypyrazol-4-yl)butyric acid hydrochloride (21)

A solution of methyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino(1-methyl-5-hydroxypyrazol-4-yl)butyrate **19** (365 mg, 1.16 mmol) in 6 N aqueous hydrochloric acid (15 ml) was heated to reflux for 18 h. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S)-2-amino-(1-methyl-5-hydroxypyrazol-4-yl)butyric acid hydrochloride* **21** as a colourless gum (110 mg, 40%); $[\alpha]_D^{25}$ +15.9 (*c* 1.6, H_2O); *m*/*z* [+ve es] Found 200.1039 $[M + H]^+$, $[C_8H_{13}N_3O_3 + H]^+$ requires 200.1035; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH) and 1716 (C=O); λ_{max} (MeOH)/nm 235 and 263 (sh) (log ε 3.77 and 3.17); λ_{max} (MeOH–HCl)/nm 239 (log ε 3.88); λ_{max} (MeOH–NaOH)/nm 257 (log ε 3.76); δ_H (300 MHz,^2H_2O–^{2}HCl) 7.35 (1H, *s*, H-3′), 3.72 (1H, *t*, $J_{2,3}$ 6.5, H-2), 3.46 (3H, *s*, NCH_3), 2.25 (2H, *m*, H-4) and 1.83 (2H, *m*, H-3); δ_C (75 MHz,^2H_2O–^{2}HCl) 171.65 (acid), 154.31 (C-4′), 136.83 (C-3′), 103.48 (C-5′), 52.11 (C-2), 37.24 (NCH_3), 29.50 (C-4) and 17.16 (C-3).

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-benzyloxycarbonyl-methyl-6-oxopiperidine-2-carboxylate (23)

Lithium hexamethyldisilazide (1 M in THF, 1.40 ml, 1.40 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **15** (300 mg, 1.17 mmol) in THF (5 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over a period of 30 min to ensure enolate formation and cooled to −78 °C. Benzyl bromoacetate (0.203 ml, 1.28 mmol) was added and stirring was continued for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at −78 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (1:1) as eluent afforded *methyl (2S,5RS)-N-tert-butoxycarbonyl-5-benzyloxycarbonylmethyl-6-oxopiperidine-2-carboxylate* **23** as a 1:1 mixture of diastereoisomers (266 mg, 56%); *m*/*z* [CI] Found 406.1862 $[M + H]^+$, $[C_{21}H_{27}NO_7 + H]^+$ requires 406.1866; *m*/*z* [+ve FAB, 3-NBA] 428 $[M + Na]^+$ and 406 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1778 and 1727 (C=O); δ_H (300 MHz, C^2HCl_3) 7.41–7.28 (5H, *m*, ArH), 5.15 and 5.13 (2H, 2 × *m*, OCH_2Ph), 4.77 (0.5H, *t*, *J* 6.4, H-2), 4.68 (0.5H, *m*, H-2), 3.76 (3H, *s*, OCH_3), 3.19–2.83 (2H, *m*, H-5 + H-7A), 2.57 and 2.39 (1H, 2 × *m*, H-7B), 2.27–1.91 (3H, *m*, H-3 + H-4A), 1.65 (1H, *m*, H-4B) and 1.50 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.03 and 171.88 (C-6), 171.78 and 171.75 (ester), 171.59 and 171.53 (ester), 152.01 (urethane), 136.70–128.15 (Ar), 83.78 and 83.61 [$OC(CH_3)_3$], 66.45 and 66.40 (OCH_2Ph), 58.82 and 58.10 (C-2), 52.60 (OCH_3), 41.20 and 39.80 (C-5), 35.94 and 35.83 (C-7), 27.82 [$C(CH_3)_3$], 25.48 and 24.70 (C-3), and 24.55 and 24.21 (C-4).

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-carboxymethyl-6-oxopiperidine-2-carboxylate (24)

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-benzyloxycarbonyl-methyl-6-oxopiperidine-2-carboxylate **23** (210 mg, 0.518 mmol) and 5% palladium on carbon catalyst (21 mg) were stirred in ethyl acetate (5 ml) in an atmosphere of hydrogen at room temperature for 3 h. The catalyst was removed by filtration through Celite® and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S,5RS)-N-tert-butoxycarbonyl-5-carboxymethyl-6-oxopiperidine-2-carboxylate* **24** as a colourless oil (143 mg, 88%); *m*/*z* [CI] Found 316.1394 $[M + H]^+$, $[C_{14}H_{21}NO_7 + H]^+$ requires 316.1396; *m*/*z* [+ve FAB, 3-NBA] 316 $[M + H]^+$ and 338 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1775 and 1724 (C=O); δ_H (300 MHz, C^2HCl_3) 8.05 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 4.78 (0.5H, *t*, $J_{2,3}$ 6.4, H-2), 4.68 (0.5H, *m*, H-2), 3.78 (3H, *s*, OCH_3), 3.13–2.81 (2H, *m*, H-5 + H-7A), 2.55 and 2.43 (1H, 2 × *m*, H-7B), 2.31–1.94 (3H, *m*, H-3 + H-4A), 1.65 (1H, *m*, H-4B) and 1.50–1.49 [9H, 2 × *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 177.24 and 176.98 (acid), 172.00 and 171.89 (C-6), 171.81 (ester), 152.48 and 151.94 (urethane), 84.00 and 83.84 [$OC(CH_3)_3$], 58.87 and 58.13 (C-2), 52.68 and 52.63 (OCH_3), 41.00 and 39.63 (C-5), 35.78 and 35.66 (C-7), 27.81 [$C(CH_3)_3$], 25.47 and 24.67 (C-3), and 24.25 and 21.03 (C-4).

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)-6-oxopiperidine-2-carboxylate (25)

Borane–dimethyl sulfide complex (1 M in THF, 0.380 ml, 0.761 mmol) was added to a stirred solution of methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-carboxymethyl-6-oxopiperidine-2-carboxylate **24** (200 mg, 0.634 mmol) in THF (6 ml) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 30 min. Methanol (2 ml) was added and, after stirring for 2 min, the solvents were removed *in vacuo* to yield a mixture of the alcohol **25** and the lactone **27** (106 mg, 55%); *m*/*z* [+ve es] Found 319.1871 $[M + NH_4]^+$, $[C_{14}H_{23}NO_6 + NH_4]^+$ requires 319.1869; *m*/*z* [+ve FAB, 3-NBA] 302 $[M + H]^+$

and 324 [M + Na]$^+$; ν_{max} (film)/cm^{-1} 1771, 1747 and 1721 (C=O). *Methyl (2S,5RS)-N-tert-butoxycarbonyl-5-(2-hydroxyethyl)-6-oxopipecolate* **25**; δ_H (300 MHz, C^2HCl_3 *recorded immediately*) 4.68 (1H, *m*, H-2), 3.74 (3H, *s*, OCH_3), 3.74 (2H, *m*, CH_2OH), 2.90 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 2.62 (1H, *m*, H-7A), 2.32–1.50 (6H, *m*, H-3, H-4, H-5 + H-7B) and 1.47 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 174.35 (C-6), 172.15 and 171.94 (ester), 152.20 (urethane), 83.70 and 83.61 [$OC(CH_3)_3$], 60.52 and 60.44 (CH_2OH), 58.78 and 58.33 (C-2), 52.56 (OCH_3), 41.97 and 40.76 (C-5), 34.66 and 34.33 (C-7), 28.18 [$C(CH_3)_3$], 25.29 and 24.85 (C-3), and 24.39 and 23.63 (C-4). *Methyl (2S,4RS)-2-tert-butoxycarbonylamino-4-(2-oxotetrahydrofuran-3-yl)butyrate* **27**; δ_H (300 MHz, C^2HCl_3, *recorded after 1 week in* C^2HCl_3) 5.17 (1H, *d*, *J* 7.9, NH, exchangeable with $^2H_3CO^2H$), 4.64 (1H, *m*, H-2), 4.38–4.03 (2H, *m*, CH_2O), 3.71 (3H, *s*, OCH_3), 2.53 (1H, *m*, H-4A), 2.39 (1H, *m*, H-4B), 2.31–1.50 (5H, *m*, H-3, H-3′+ H-4′) and 1.44 and 1.43 [9H, 2 × *s*, $C(CH_3)_3$]; The ^{13}C NMR spectrum was too complex to assign.

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate (26)

Method 1. Oxalyl chloride (0.014 ml, 0.16 mmol) was dissolved in dichloromethane (2 ml) and the stirred solution was cooled to −60 °C under nitrogen. Dimethyl sulfoxide (0.023 ml, 0.327 mmol) was added dropwise and the solution was stirred for 3 min. A solution of methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-hydroxyethyl-6-oxopiperidine-2-carboxylate **25** (45 mg, 0.149 mmol) in dichloromethane (1 ml) was added. Stirring was continued for a further 15 min and triethylamine (0.104 ml, 0.747 mmol) was added. Stirring at −60 °C was continued for 5 min and the solution was allowed to warm to room temperature. Water (2 × 5 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 5 ml). The combined organic layers were washed with brine (5 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *methyl (2S,5RS)-N-tert-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate* **26** (8 mg, 20%) as a 1:1 mixture of diastereoisomers; *m*/*z* [+ve FAB, 3-NBA] 300 [M + H]$^+$ and 322 [M + Na]$^+$; ν_{max} (film)/cm^{-1} 1775, 1747 and 1722 (C=O); δ_H (300 MHz, C^2HCl_3, *mixed diastereoisomers*) 9.80 (1H, *d*, *J* 8.5, CH=O), 4.78 and 4.68 (1H, 2 × *m*, H-2), 3.77 (3H, *s*, OCH_3), 3.17–2.93 (2H, *m*, H-5 + H-7A), 2.56 (1H, *m*, H-7B), 2.31–1.91 (3H, *m*, H-3 + H-4A), 1.73–1.50 (1H, *m*, H-4B) and 1.49 [9H *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 200.19 and 199.80 (CH=O), 171.94 and 171.91 (C-6), 171.75 (ester), 151.93 (urethane), 83.91 and 83.77 [$OC(CH_3)_3$], 58.76 and 58.05 (C-2), 52.64 and 52.60 (OCH_3), 44.98 (C-7), 39.45 and 38.22 (C-5), 27.78 [$C(CH_3)_3$], 25.44 and 24.93 (C-3), and 25.60 and 24.43 (C-4).

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate (28)

Lithium hexamethyldisilazide (1 M in THF, 11.66 ml, 12 mmol) was added to a stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopipecolate **15** (2.50 g, 9.72 mmol) in THF (25 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Allyl bromide (3.36 ml, 39 mmol) was added and stirring was continued for a further 90 min. Saturated aqueous ammonium chloride (15 ml) was added at −78 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (25 ml) and saturated aqueous ammonium chloride (20 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (1:1) as eluent afforded *methyl (2S,5RS)-N-tert-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate* **28** as a 1:1 mixture of diastereoisomers (1.30 g, 45%); *m*/*z* [CI] Found 298.1656 [M + H]$^+$, [$C_{15}H_{23}NO_5$ + H]$^+$ requires 298.1654; *m*/*z* [+ve FAB, 3-NBA] 298 [M + H]$^+$ and 320 [M + Na]$^+$; ν_{max} (film)/cm^{-1} 1777, 1749 and 1722 (C=O); δ_H (300 MHz, C^2HCl_3) 5.74 (1H, *m*, CH=), 5.05 (2H, *m*, $=CH_2$), 4.77 (1H, 2 × *m*, H-2), 3.75 (3H, *s*, OCH_3), 2.74–1.49 (7H, *m*, H-3, H-4, H-7 + H-5) and 1.48 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.84 and 172.40 (C-6), 172.11 and 172.04 (ester), 152.41 (urethane), 135.48 and 135.37 (CH=), 117.43 and 117.17 ($=CH_2$), 83.51 and 83.42 [$OC(CH_3)_3$], 58.79 and 58.26 (C-2), 52.52 and 52.45 (OCH_3), 43.60 and 42.73 (C-5), 35.85 and 35.47 (C-7), 27.83 [$C(CH_3)_3$], 23.70 and 23.34 (C-3), and 22.79 (C-4).

Methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate (26)

Method 2. A solution of methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate **28** (855 mg, 2.86 mmol) in dichloromethane (30 ml) was cooled to −78 °C and oxygen was passed through the solution for 5 min, followed by ozone for 15 min, during which time it turned blue. Triphenylphosphine (905 mg, 3.42 mmol) was added at −78 °C and the solution was allowed to warm slowly to room temperature. The solvent was removed *in vacuo* and the oil was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (1:1) as eluent to afford *methyl (2S,5RS)-N-tert-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate* **26** (622 mg, 72%) as a 1:1 mixture of diastereoisomers. The spectra were identical to those of the sample prepared by Method 1.

Methyl (2*S*,4*RS*)-2-*tert*-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate (32)

Hydrazine hydrate (55% aq., 0.052 ml, 0.919 mmol) was added to a stirred solution of methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate **26** (275 mg, 0.919 mmol) in methanol (6 ml) under nitrogen. The solution was stirred at room temperature for 2 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate–petroleum ether (4:1) as eluent afforded *methyl (2S,4RS)-2-tert-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate* **(32)** as a colourless oil (179 mg, 62%); *m*/*z* [CI] Found 314.1718 [M + H]$^+$, [$C_{14}H_{23}N_3O_5$ + H]$^+$ requires 314.1716; *m*/*z* [+ve FAB, 3-NBA] 314 [M + H]$^+$; ν_{max} (film)/cm^{-1} 1739, 1693 and 1634 (C=O); λ_{max} (MeOH)/nm 239 (log ε 3.60); δ_H (300 MHz, C^2HCl_3) 8.75 (1H, br *s*, NH, exchangeable with $^2H_3CO^2H$), 7.14 (1H, *t*, *J* 2.8, H-6′), 5.26 (1H, *d*, *J* 7.6, NH, exchangeable with $^2H_3CO^2H$), 4.20 (1H, *m*, H-2), 3.74 (3H, *s*, OCH_3), 2.62 (1H, *m*, H-5′A), 2.43 (1H, *m*, H-4′), 2.27 (1H, *m*, H-5′B), 1.98–1.69 (3H, *m*, H-3 + H-4A), 1.51 (1H, *m*, H-4B) and 1.43 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.88 (C-3′), 169.64 (ester), 155.40 (urethane), 144.39 (C-6′), 79.95 [$OC(CH_3)_3$], 53.03 (C-2), 52.39 (OCH_3), 34.94 (C-4′), 30.01 (C-5′), 28.25 [$C(CH_3)_3$], 27.81 (C-3) and 25.66 (C-4).

(2*S*,4*RS*)-2-Amino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)-butyrate hydrochloride (34)

A solution of methyl (2*S*,4*RS*)-2-*tert*-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate **32** (89 mg, 0.284 mmol) in 6 N aqueous hydrochloric acid (5 ml) was heated to reflux for 18 h. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S,4RS)-2-amino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)-butyrate hydrochloride* **34** as a foam (22 mg, 33%); *m*/*z* [+ve es] Found 200.1043 [M + H]$^+$, [$C_8H_{13}N_3O_3$ + H]$^+$ requires 200.1035; ν_{max} (KBr)/cm^{-1} 3400 (NH–OH), 1734 and 1653

(C=O); λ_{max} (MeOH)/nm 233 (log ε 2.35); δ_H (300 MHz, ^2H_2O–^2HCl) 6.76 (1H, *m*, H-6′), 3.52 (1H, *m*, H-2) and 2.67–0.97 (7H, *m*, H-3, H-4, H-4′ + H-5′); δ_C (75 MHz, ^2H_2O–^2HCl) 171.58 (C-3′), 165.88 (acid), 144.76 (C-6′), 52.55 (C-2), 33.41 (C-4′), 30.74 (C-5′), 28.88 (C-4) and 26.73 (C-3).

Methyl (2*S*,4*RS*)-2-*tert*-butoxycarbonylamino-4-(2-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate (35)

Methylhydrazine (0.049 ml, 0.92 mmol) was added to a stirred solution of methyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate **26** (275 mg, 0.919 mmol) in methanol (6 ml) under nitrogen. The solution was stirred at room temperature for 2 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate–petroleum ether (4:1) as eluent afforded *methyl (2S,4RS)-2-tert-butoxycarbonylamino-4-(2-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate* **34** as a colourless oil (120 mg, 40%); *m*/*z* [CI] Found 328.1872 $[M + H]^+$, $[C_{15}H_{25}N_3O_5 + H]^+$ requires 328.1872; *m*/*z* [+ve FAB, 3-NBA] 328 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1742, 1695 and 1657 (C=O); λ_{max} (MeOH)/nm 247 (log ε 3.60); δ_H (300 MHz, C^2HCl_3) 7.13 (1H, *t*, *J* 3.1, H-6′), 5.24 (1H, *d*, *J* 8.0, NH, exchangeable with $^2H_3CO^2H$), 4.26 (1H, *m*, H-2), 3.70 (3H, *s*, OCH_3), 3.30 (1H, *s*, NCH_3), 2.55 (1H, *m*, H-5′A), 2.37 (1H, *m*, H-4′), 2.23 (1H, *m*, H-5′B), 1.96–1.58 (4H, *m*, H-3 + H-4), and 1.40 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.81 (C-3′), 167.93 (ester), 155.32 (urethane), 144.12 (C-6′), 79.79 [O*C*$(CH_3)_3$], 53.01 (C-2), 52.27 (O*C*H_3), 36.32 (NCH_3), 35.20 (C-4′), 29.93 (C-5′), 28.17 [C(*C*$H_3)_3$], 28.05 (C-3) and 25.72 (C-4).

tert-Butyl (2*S*)-piperidine-2-carboxylate (39)

Perchloric acid (70%) was added dropwise to a vigorously stirred suspension of (2*S*)-piperidine-2-carboxylic acid **38**[12,13] (2.78 g, 22 mmol) in *tert*-butyl acetate (30 ml) until the suspension had completely dissolved. The solution was stirred for a further 10 min and the pH was adjusted to 9 using saturated aqueous sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 ml). Brine (50 ml) was added to the aqueous layer, which was further extracted with ethyl acetate (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford *tert-butyl (2S)-piperidine-2-carboxylate* **39** as a colourless oil (2.15 g, 54%); $[\alpha]_D^{25}$ −2.1 (*c* 1.5, $CHCl_3$); *m*/*z* [+ve es] Found 186.1492 $[M + H]^+$, $[C_{10}H_{19}NO_2 + H]^+$ requires 186.1494; ν_{max} (film)/cm^{-1} 3600 (OH, NH) and 1734 (C=O); δ_H (400 MHz, C^2HCl_3) 6.24 (1H, br *s*, NH, exchangeable with $^2H_3CO^2H$), 3.90 (1H, *m*, H-2), 3.64 (1H, *m*, H-6A), 3.20 (1H, *m*, H-6B), 2.26 (1H, *m*, H-3A), 1.99–1.80 (4H, *m*, H-3B, H-4A + H-5), 1.62 (1H, *m*, H-4B) and 1.51 [9H, *s*, $C(CH_3)_3$]; δ_C (100 MHz, C^2HCl_3) 167.49 (ester), 85.13 [2 × O*C*$(CH_3)_3$], 57.93 (C-2), 44.96 (C-6), 27.93 and 27.93 [2 × OC(*C*$H_3)_3$], 25.77 (C-3), 21.71 (C-5) and 21.62 (C-4).

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpiperidine-2-carboxylate (40)

Di-*tert*-butyl dicarbonate (2.74 g, 13 mmol) and triethylamine (1.75 ml, 13 mmol) were added to a solution of *tert*-butyl (2*S*)-piperidine-2-carboxylate **39** (1.55 g, 8.37 mmol) in methanol (650 ml) at room temperature under nitrogen. The solution was stirred for 12 h and the solvent was removed *in vacuo* to give a yellow residue. The residue was partitioned between ethyl acetate (20 ml) and water (10 ml). The organic layer was washed with water (2 × 5 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent afforded the product *tert-butyl (2S)-N-tert-butoxycarbonylpiperidine-2-carboxylate* **40** as a colourless oil (2.02 g, 85%); $[\alpha]_D^{25}$ −28.8 (*c* 1.45, $CHCl_3$); *m*/*z* [+ve es] Found 286.2020 $[M + H]^+$, $[C_{15}H_{27}NO_4 + H]^+$ requires 286.2018; *m*/*z* [+ve FAB, 3-NBA] 286 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1772, 1736 and 1698 (C=O); δ_H (400 MHz, C^2HCl_3, *rotamers present*) 4.80 and 4.62 (1H, 2 × *m*, H-2), 4.00 (1H, *m*, H-6A), 2.95 (1H, *m*, H-6B), 2.20 (1H, *m*, H-3A), 1.79–1.60 (4H, *m*, H-3B, H-4A + H-5), 1.48 [18H, 2 × *s*, 2 × $C(CH_3)_3$] and 1.26 (1H, *m*, H-4B); δ_C (100 MHz, C^2HCl_3) 170.96 (ester), 155.14 (urethane), 81.65 and 80.06 [2 × O*C*$(CH_3)_3$], 55.92 (C-2), 41.76 (C-6), 28.49 [2 × OC(*C*$H_3)_3$], 27.24 (C-5), 25.60 (C-3) and 21.60 (C-4).

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate (41)

A solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonylpiperidine-2-carboxylate **40** (2.02 g, 7.07 mmol) in ethyl acetate (60 ml) was added at room temperature to a vigorously stirred solution of ruthenium(III) chloride hydrate (368 mg, 1.8 mmol) and sodium periodate (6.05 g, 28 mmol) in water (60 ml). The solution was stirred for 18 h. The aqueous layer was extracted with ethyl acetate (4 × 25ml), the organic layers were combined and the excess ruthenium tetroxide was destroyed by stirring for 2 h with isopropyl alcohol (1.5 ml). The precipitate was removed by filtration through Celite®. The filtrate was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give an orange residue. Column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent afforded *tert-butyl (2S)-N-tert-butoxycarbonyl-6-oxopiperidine-2-carboxylate* **41** as a white solid (1.76 g, 83%); mp 80–82 °C; $[\alpha]_D^{25}$ 0.00 (*c* 1.5, $CHCl_3$); *m*/*z* [+ve es] Found 300.1819 $[M + H]^+$, $[C_{15}H_{25}NO_5 + H]^+$ requires 300.1811; *m*/*z* [+ve FAB, 3-NBA] 300 $[M + H]^+$ and 322 $[M + Na]^+$; ν_{max} (KBr)/cm^{-1} 1777 and 1723 (C=O); δ_H (400 MHz, C^2HCl_3) 4.58 (1H, *dd*, $J_{2,3}$ 3.6 and 6.2, H-2), 2.62–2.42 (2H, *m*, H-5), 2.17 (1H, *m*, H-3A), 1.99 (1H, *m*, H-3B), 1.85–1.66 (2H, *m*, H-4), 1.51 [9H, *s*, $C(CH_3)_3$] and 1.47 [9H, *s*, $C(CH_3)_3$]; δ_C (100 MHz, C^2HCl_3) 170.52 (C-6), 170.48 (ester), 152.19 (urethane), 83.22 and 82.13 [2 × O*C*$(CH_3)_3$], 58.98 (C-2), 34.48 (C-5), 27.89 [2 × C(*C*$H_3)_3$], 25.82 (C-3) and 18.17 (C-4); HPLC on a Chiracel OD-H chiral column using 2% EtOH in heptane, flow rate 1.0 ml min^{-1} at room temperature gave a single peak, Rt 9.14 min whereas a racemic sample prepared from (2*RS*)-piperidine-2-carboxylic acid showed two peaks, Rt 7.14 and 9.4 min under these conditions.

tert-Butyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino(5-hydroxypyrazol-4-yl)butyrate (43)

Lithium hexamethyldisilazide (1 M in THF, 5.51 ml, 5.51 mmol) was added to a stirred solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **41** (1.50 g, 5.01 mmol) in THF (15 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Methyl formate (0.618 ml, 10 mmol) was added. The solution was stirred for 5 min at −78 °C, warmed to 0 °C and stirred for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at 0 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. The crude oil was dissolved in methanol (15 ml) and hydrazine hydrate (55% aq., 0.446 ml, 15 mmol) was added. The solution was stirred at room temperature for 30 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate afforded *tert-butyl (2S)-2-N-tert-butoxycarbonylamino(5-hydroxypyrazol-4-yl)butyrate* **43** as a colourless oil (786 mg, 46%); $[\alpha]_D^{25}$ +6.0 (*c* 0.2, $CHCl_3$); *m*/*z* [CI] Found 342.2029 $[M + H]^+$, $[C_{16}H_{27}N_3O_5 + H]^+$ requires 342.2029; *m*/*z* [+ve FAB, 3-NBA] 342 $[M + H]^+$ and 364 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1713 and 1695 (C=O); λ_{max}

(MeOH)/nm 226 and 252 (log ε 3.55 and 3.26); λ_{max} (MeOH–HCl)/nm 230 (log ε 3.70); λ_{max} (MeOH–NaOH)/nm 241 (log ε 3.64); δ_H (300 MHz, C^2HCl_3) 9.95 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 7.18 (1H, *s*, H-3′), 5.30 (1H, *d*, *J* 8.3, NH, exchangeable with $^2H_3CO^2H$), 4.17 (1H, *m*, H-2), 2.44 (2H, *t*, *J* 7.2, H-4), 2.05–1.77 (2H, *m*, H-3) and 1.43 [18H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 172.11 (ester), 160.77 (C-4′), 155.66 (urethane), 129.14 (C-3′), 103.76 (C-5′), 81.84 and 79.69 [2 × $OC(CH_3)_3$], 53.58 (C-2), 32.93 (C-4), 28.27 and 27.91 [2 × $C(CH_3)_3$] and 18.19 (C-3).

tert-Butyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino(5-hydroxy-1-methylpyrazol-4-yl)butyrate (44)

Lithium hexamethyldisilazide (1 M in THF, 5.51 ml, 5.51 mmol) was added to a stirred solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **41** (1.50 g, 5.01 mmol) in THF (15 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Methyl formate (0.618 ml, 10 mmol) was added. The solution was stirred for 5 min at −78 °C, warmed to 0 °C, and stirred for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at 0 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. The crude oil was dissolved in methanol (15 ml) and methylhydrazine (0.359 ml, 6.7 mmol) was added. The solution was stirred at room temperature for 30 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent gave *tert-butyl (2S)-2-N-tert-butoxycarbonylamino(5-hydroxy-1-methylpyrazol-4-yl)butyrate* **44** as a colourless oil (748 mg, 42%); $[\alpha]_D^{25}$ +2.3 (*c* 1.0, $CHCl_3$); *m*/*z* [+ve es] Found 356.2187 $[M + H]^+$, $[C_{17}H_{29}N_3O_5 + H]^+$ requires 356.2185; ν_{max} (film)/cm^{-1} 1713 and 1640 (sh) (C=O); λ_{max} (MeOH)/nm 233 (log ε 3.62); λ_{max} (MeOH–HCl)/nm 240 (log ε 3.64); λ_{max} (MeOH–NaOH)/nm 254 (log ε 3.55); δ_H (300 MHz, C^2HCl_3) 8.62 (1H, br *s*, OH, exchangeable with $^2H_3CO^2H$), 6.88 (1H, *s*, H-3′), 5.10 (1H, *d*, *J* 8.1, NH, exchangeable with $^2H_3CO^2H$), 4.15 (1H, *m*, H-2), 3.58 (3H, *s*, NCH_3), 2.34 (2H, *t*, *J* 6.9, H-4), 2.05–1.77 (2H, *m*, H-3) and 1.45 [18H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 171.97 (ester), 160.19 (C-4′), 155.46 (urethane), 130.22 (C-3′), 103.36 (C-5′), 81.71 and 79.53 [2 × $OC(CH_3)_3$], 53.48 (C-2), 38.02 (NCH_3), 33.03 (C-4), 28.21 and 27.91 [2 × $C(CH_3)_3$] and 17.97 (C-3).

(2*S*)-2-Amino(5-hydroxypyrazol-4-yl)butyric acid hydrochloride (20)

A suspension of *tert*-butyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino-(5-hydroxypyrazol-4-yl)butyrate **(43)** (135 mg, 0.395 mmol) in 6 N aqueous hydrochloric acid (3 ml) was stirred for 90 min at room temperature. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S)-2-amino(5-hydroxypyrazol-4-yl)butyric acid hydrochloride* **20** as a glassy solid (78 mg, 89%). The spectra were identical with those of the sample prepared from the corresponding methyl ester **18**.

(2*S*)-2-Amino(5-hydroxy-1-methylpyrazol-4-yl)butyric acid hydrochloride (21)

A suspension of *tert*-butyl (2*S*)-2-*N*-*tert*-butoxycarbonylamino-(5-hydroxy-1-methylpyrazol-4-yl)butyrate **44** (156 mg, 0.439 mmol) in 6 N aqueous hydrochloric acid (3 ml) was stirred for 90 min at room temperature. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S)-2-amino(5-hydroxy-1-methylpyrazol-4-yl)butyric acid hydrochloride* **(21)** as a glassy solid (94 mg, 91%). The spectra were identical with those of the sample prepared from the corresponding methyl ester **19**.

tert-Butyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate (45)

Lithium hexamethyldisilazide (1 M in THF, 12.03 ml, 12 mmol) was added to a stirred solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **41** (3.00 g, 10 mmol) in THF (30 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Allyl bromide (3.47 ml, 40 mmol) was added and stirring was continued for a further 90 min. Saturated aqueous ammonium chloride (15 ml) was added at −78 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (25 ml) and saturated aqueous ammonium chloride (20 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent afforded *tert-butyl (2S,5RS)-N-tert-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate* **45** as a 1:1 mixture of *cis*/*trans* diastereoisomers (2.01 g, 59%); *m*/*z* [CI] Found 340.2127 $[M + H]^+$, $[C_{18}H_{29}NO_5 + H]^+$ requires 340.2124; *m*/*z* [+ve FAB, 3-NBA] 340 $[M + H]^+$ and 362 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1776, 1740 and 1722 (C=O); δ_H (400 MHz, C^2HCl_3) 5.76 (1H, *m*, CH=), 5.06 (2H, *m*, $=CH_2$), 4.59 (0.5H, *t*, *J* 5.6, H-2), 4.52 (0.5H, *m*, H-2), 2.65 (1H, *m*, H-7A), 2.54–1.77 (5H, *m*, H-3, H-4A, H-5 + H-7B), 1.60 (1H, *m*, H-4B), 1.50 [9H, *s*, $C(CH_3)_3$] and 1.46 [9H, *s*, $C(CH_3)_3$]; δ_C (100 MHz, C^2HCl_3) 173.10 and 172.60 (C-6), 170.68 and 170.59 (ester), 152.77 and 152.55 (urethane), 135.65 and 135.56 (CH=), 117.30 and 117.09 ($=CH_2$), 83.18, 83.08 and 82.09 [2 × $OC(CH_3)_3$], 59.52 and 58.83 (C-2), 43.63 and 42.70 (C-5), 35.93 and 35.59 (C-7), 27.89 and 27.86 [2 × $C(CH_3)_3$], 25.54 and 23.83 (C-3), and 23.53 and 22.75 (C-4).

Altering the ratio of diastereoisomers in (45) by quenching with 2,6-di-*tert*-butylphenol

Lithium hexamethyldisilazide (1 M in THF, 1.41 ml, 1.41 mmol) was added to a stirred solution of *tert*-butyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate **45** (300 mg, 0.884 mmol) as a 1:1 *cis*/*trans* mixture in THF (5 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. 2,6-Di-*tert*-butylphenol (365 mg, 1.77 mmol) was added and stirring was continued at −78 °C for a further 90 min. Saturated aqueous ammonium chloride (5 ml) was added at −78 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (10 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using petroleum ether–ethyl acetate (6:1) as eluent afforded *tert-butyl (2S,5RS)-N-tert-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate* **45** (252 mg, 84%) as a 9:1 mixture of *cis*/*trans* diastereoisomers as judged by the integration of H-2, δ_H (300 MHz, C^2HCl_3) 4.58 (0.1H, *t*, *J* 5.6, H-2A), 4.52 (0.9H, *dd*, $J_{2,3}$ 2.1 and 5.1, H-2B),

tert-Butyl (2*S*,5*R*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate (46a)

A solution of *tert*-butyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allyl-6-oxopiperidine-2-carboxylate **45** (560 mg, 1.65 mmol) in

dichloromethane (15 ml) was cooled to −78 °C and oxygen was passed through the solution for 5 min followed by ozone for 15 min, during which time it turned blue. Triphenylphosphine (519 mg, 1.98 mmol) was added at −78 °C and the solution was allowed to warm slowly to room temperature. The solvent was removed *in vacuo* to give a yellow oil. Partial separation of the two stereoisomers was achieved by column chromatography on silica gel using petroleum ether–ethyl acetate (6:1) as eluent. The *cis*-product, *tert*-butyl (2*S*,5*R*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate **46a** (148 mg, 26%), was obtained together with a mixture of the *cis*- and *trans*-products (331 mg, 59%). *tert-Butyl (2S,5R)-N-tert-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate* **46a** was an oil, $[\alpha]_D^{25}$ + 24.8 (*c* 0.5, $CHCl_3$); *m/z* [+ve es] Found 342.1922 $[M + H]^+$, $[C_{17}H_{27}NO_6 + H]^+$ requires 342.1917; ν_{max} (film)/cm^{-1} 1773 and 1723 (C=O); δ_H (500 MHz, C^2HCl_3) 9.84 (1H, *t*, *J* 1.3, C*H*=O), 4.57 (1H, *ddd*, $J_{2,4S}$ 1.2, $J_{2,3R}$ 2.4, $J_{2,3S}$ 5.7, H-2), 3.11 (1H, *ddd*, $J_{7A,8}$ 1.3, $J_{7A,5}$ 5.6, $J_{7A,7B}$ 17.5, H-7A), 3.02 (1H, *m*, H-5), 2.52 (1H, *ddd*, $J_{7B,8}$ 1.3, $J_{7B,5}$ 5.6, $J_{7B,7A}$ 17.5, H-7), 2.23 (1H, *m*, H-3*R*), 2.11 (1H, *m*, H-3*S*), 1.97 (1H, *m*, H-4*R*), 1.57 (1H, *m*, H-4*S*), 1.51 [9H, *s*, $C(CH_3)_3$] and 1.48 [9H, *s*, $C(CH_3)_3$]; irradiation of H-2 at δ 4.57 ppm gave enhancement to H-3*R* at δ 2.23 ppm (2.6%) and H-3*S* at δ 2.11 ppm (3.6%); irradiation of H-5 at δ 3.02 ppm gave enhancement to H-7B at δ 2.52 ppm (2.7%), H-3*S* at δ 2.11 ppm (3%) and H-4*R* at δ 1.97 ppm (3.0%); irradiation of H-7B at δ 2.52 ppm gave enhancement to H-7A at δ 3.11(21%) and H-5 at δ 3.02 ppm (3%); δ_C (75 MHz, C^2HCl_3) 200.37 (CH=O), 172.17 (C-6), 170.61 (ester), 152.53 (urethane), 83.49 and 82.37 [2 × O*C*$(CH_3)_3$], 59.54 (C-2), 45.15 (C-7), 39.58 (C-5), 27.90 [2 × C(*C*$H_3)_3$], 25.62 (C-3) and 25.10 (C-4).

tert-Butyl (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate (47)

Hydrazine hydrate (55% aq., 0.008 ml, 0.14 mmol) was added to a stirred solution of *tert*-butyl (2*S*,5*R*)-*N*-*tert*-butoxycarbonyl-5-(2-oxoethyl)-6-oxopiperidine-2-carboxylate **53a** (50 mg, 0.146 mmol) in methanol (10 ml) under nitrogen. The solution was stirred at room temperature for 2 h, and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate–petroleum ether (2:1) as eluent afforded *tert-butyl (2S,5R)-2-tert-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate* **47** as a colourless oil (46 mg, 88%); $[\alpha]_D^{25}$ +46.8 (*c* 1.0, $CHCl_3$); *m/z* [CI] Found 356.2181 $[M + H]^+$, $[C_{17}H_{29}N_3O_5 + H]^+$ requires 356.2185; *m/z* [+ve FAB, 3-NBA] 356 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1696 and 1680 (C=O); λ_{max} (MeOH)/nm 241 (log ε 3.67); δ_H (300 MHz, C^2HCl_3) 8.5 (1H, br, NH), 7.12 (1H, *m*, H-6′), 5.27 (1H, *d*, *J* 7.7, NH, exchangeable with $^2H_3CO^2H$), 4.15 (1H, *m*, H-2), 2.56 (1H, *m*, H-5′A), 2.40 (1H, *m*, H-4′), 2.24 (1H, *m*, H-5′B), 1.99–1.60 (3H, *m*, H-3A + H-4), 1.51 (1H, *m*, H-3B), 1.43 [9H, *s*, $C(CH_3)_3$] and 1.41 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 171.39 (C-6), 169.63 (ester), 155.30 (urethane), 144.21 (C-6′), 81.93 and 79.60 [2 × O*C*$(CH_3)_3$], 53.62 (C-2), 34.94 (C-4′), 29.38 (C-5), 28.21 and 27.88 [2 × C(*C*$H_3)_3$], 27.32 (C-4) and 24.96 (C-3).

(2*S*,5*R*)-2-amino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)-butyric acid hydrochloride (34a)

A suspension of *tert*-butyl (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)butyrate **47** (220 mg, 0.619 mmol) was stirred in 6 N aqueous hydrochloric acid (3 ml) at room temperature for 90 min. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S,5R)-2-amino-4-(3-oxo-2,3,4,5-tetrahydropyridazin-4-yl)-butyric acid hydrochloride* **34a** as a white foam (137 mg, 94%); $[\alpha]_D^{25}$ +9.9 (*c* 0.94, H_2O); *m/z* [+ve es] Found 200.1043 $[M + H]^+$, $[C_8H_{13}N_3O_3 + H]^+$ requires 200.1035; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1734 and 1655 (C=O); λ_{max} (MeOH)/nm 233 (log ε 2.35); δ_H (300 MHz, ^2H_2O) 6.76 (1H, *m*, H-6′), 3.54 (1H, *m*, H-2) and 2.73–0.95 (7H, *m*, H-3, H-4, H-4′ + H-5′).

tert-Butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate (48)

Lithium hexamethyldisilazide (1 M in THF, 12.03 ml, 12 mmol) was added to a stirred solution of *tert*-butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **41a** (3.00 g, 10 mmol) in THF (30 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Ethyl formate (1.62 ml, 20 mmol) was added. The solution was stirred for 5 min at −78 °C, warmed to 0 °C and stirred for a further 90 min. Saturated aqueous ammonium chloride (15 ml) was added at 0 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (20 ml) and saturated aqueous ammonium chloride (10 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. The crude oil was dissolved in diethyl ether (30 ml) and trimethylsilyldiazomethane (2 M in hexanes, 5.01 ml, 10 mmol) was added. The reaction was allowed to stand overnight. The solvent was removed with a stream of nitrogen to give a brown oil. Column chromatography on silica gel using ethyl acetate as eluent afforded the product *tert-butyl (2RS)-N-tert-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate* **48** as a pale yellow oil (1.78 g, 52%); *m/z* (+ve es) 342 $[M + H]^+$; δ_H (300 MHz, C^2HCl_3) 7.44 (1H, *s*, CH=), 4.69 (1H, *t*, $J_{2,3}$ 4.6 and 10.2, H-2), 3.85 (3H, *s*, OCH_3), 2.52 (1H, *m*, H-4A), 2.22 (1H, *m*, H-4B), 2.13 (1H, *m*, H-3A), 1.95 (1H, *m*, H-3B), 1.52 [9H, *s*, $OC(CH_3)_3$] and 1.47 [9H, *s*, $OC(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 170.04 (C-6), 165.16 (ester), 158.60 (C-7), 152.24 (urethane), 107.97 (C-5), 82.72 and 81.83 [2 × O*C*$(CH_3)_3$], 61.46 (O*C*H_3), 58.13 (C-2), 27.80 [2 × OC(*C*$H_3)_3$], 24.22 (C-3) and 18.27 (C-4).

tert-Butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(6-oxopyrimidin-5-yl)butyrate (49)

tert-Butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate **48** (100 mg, 0.293 mmol), formamidine acetate (122 mg, 1.17 mmol) and potassium carbonate (162 mg, 1.17 mmol) were heated in absolute ethanol (10 ml) at reflux for 18 h. The solvent was removed *in vacuo* to give a yellow residue which was partitioned between 5% aqueous citric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was separated and extracted with dichloromethane (2 × 5 ml). The combined organic phases were washed with brine (10 ml), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a pale yellow residue. Column chromatography on silica gel using methanol–ethyl acetate (5:95) as eluent afforded *tert-butyl (2RS)-2-tert-butoxycarbonylamino-4-(6-oxopyrimidin-5-yl)-butyrate* (**49**) as a pale white foam (42 mg, 43%); *m/z* [+ve es] Found 354.2040 $[M + H]^+$, $[C_{17}H_{27}N_3O_5 + H]^+$ requires 354.2029; ν_{max} (film)/cm^{-1} 3400 (OH–NH), 1737 (sh) and 1651 (C=O); λ_{max} (MeOH)/nm 228 and 271 (log ε 3.83 and 3.70); λ_{max} (MeOH–HCl)/nm 231 and 261 (log ε 3.89 and 3.62); λ_{max} (MeOH–NaOH)/nm 234 and 272 (log ε 3.97 and 3.70); δ_H (300 MHz, C^2HCl_3) 12.91 (1H, br *s*, NH, exchangeable with $^2H_3CO^2H$), 8.11 (1H, *s*, H-2′), 7.92 (1H, *s*, H-4′), 5.35 (1H, *d*, *J* 8.2, NH, exchangeable with $^2H_3CO^2H$), 4.21 (1H, *m*, H-2), 2.55 (2H, *t*, *J* 7.6, H-4), 2.14–1.84 (2H, 2 × *m*, H-3), 1.46 [9H, *s*, $OC(CH_3)_3$] and 1.44 [9H, *s*, $OC(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 171.64 (C-6′), 163.93 (ester), 155.46 (urethane), 152.46 (C-2′), 147.12 (C-4′), 128.31 (C-5′), 82.02 and 79.70 [2 × O*C*$(CH_3)_3$], 53.64 (C-2), 30.99 (C-4), 28.29 and 27.94 [2 × C(*C*$H_3)_3$] and 23.65 (C-3).

tert-Butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(2-methyl-6-oxopyrimidin-5-yl)butyrate (50)

tert-Butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate **48** (100 mg, 0.293 mmol), acetamidine acetate (111 mg, 1.17 mmol) and potassium carbonate (162 mg, 1.17 mmol) were heated in absolute ethanol (10 ml) at reflux for 18 h. The solvent was removed *in vacuo* to give a yellow residue which was partitioned between 5% aqueous citric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was separated and extracted with dichloromethane (2 × 5 ml). The combined organic phases were washed with brine (10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow residue. Column chromatography on silica gel using methanol–ethyl acetate (5:95) as eluent afforded *tert-butyl (2RS)-2-tert-butoxycarbonylamino-4-(2-methyl-6-oxopyrimidin-5-yl)butyrate* **50** as a pale white solid (89 mg, 83%); mp 175–177 °C; *m*/*z* [+ve es] Found 368.2190 [*M* + H]$^+$, [$C_{18}H_{29}N_3O_5$ + H]$^+$ requires 368.2185; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1737 (sh) and 1645 (C=O); λ_{max} (MeOH)/nm 226 and 275 (log ε 3.54 and 3.47); λ_{max} (MeOH–HCl)/nm 230 and 260 (log ε 3.59 and 3.39); λ_{max} (MeOH–NaOH)/nm 232 and 272 (log ε 3.63 and 3.43); δ_H (300 MHz, C^2HCl_3) 13.19 (1H, *s*, NH, exchangeable with $^2H_3CO^2H$), 7.83 (1H, *s*, H-4′), 5.36 (1H, *d*, *J* 8.2, NH, exchangeable with $^2H_3CO^2H$), 4.21 (1H, *m*, H-2), 2.59–2.46 (2H, *t*, *J* 7.6, H-4), 2.46 (3H, *s*, CH_3), 2.12–1.82 (2H, 2 × *m*, H-3), 1.46 [9H, *s*, $OC(CH_3)_3$] and 1.44 [9H, *s*, $OC(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3)), 171.71 (C-6′), 164.99 (ester), 157.41 (C-2′), 155.43 (urethane), 152.88 (C-4′), 124.42 (C-5′), 81.86 and 79.62 [2 × O*C*$(CH_3)_3$], 53.65 (C-2), 31.28 (C-4), 28.30 and 27.96 [2 × C(*C*$H_3)_3$], 23.20 (C-3) and 21.41 (CH_3).

tert-Butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(6-oxo-2-phenylpyrimidin-5-yl)butyrate (51)

tert-Butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate **48** (100 mg, 0.293 mmol), benzamidine hydrochloride (183 mg, 1.17 mmol), and potassium carbonate (162 mg, 1.17 mmol) were heated in absolute ethanol (10 ml) at reflux for 18 h. The solvent was removed *in vacuo* to give a yellow residue which was partitioned between 5% aqueous citric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was separated and extracted with dichloromethane (2 × 5 ml). The combined organic phases were washed with brine (10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow residue. Column chromatography on silica gel using methanol–ethyl acetate (5:95) as eluent afforded *tert-butyl (2RS)-2-tert-butoxycarbonylamino-4-(6-oxo-2-phenylpyrimidin-5-yl)-butyrate* **51** as a pale white solid (74 mg, 59%); mp 186–188 °C; *m*/*z* [+ve es] Found 430.2347 [*M* + H]$^+$, [$C_{23}H_{31}N_3O_5$ + H]$^+$ requires 430.2342; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1733 (sh) and 1651 (C=O); λ_{max} (MeOH)/nm 239 and 297 (log ε 4.16 and 4.05); λ_{max} (MeOH–HCl)/nm 241 and 280 (log ε 4.15 and 4.11); λ_{max} (MeOH–NaOH)/nm 233, 252 and 285 (log ε 4.29, 4.00 and 3.92); δ_H (300 MHz, C^2HCl_3) 13.04 (1H, *s*, NH, exchangeable with $^2H_3CO^2H$), 8.17–8.24 (2H, *m*, ArH), 8.04 (1H, *s*, H-4′), 7.63–7.52 (3H, *m*, ArH), 5.25 (1H, *d*, *J* 8.4, NH, exchangeable with $^2H_3CO^2H$), 4.28 (1H, *m*, H-2), 2.60 (2H, *m*, H-4), 2.18–1.99 (2H, *m*, H-3) and 1.44 [18H, s, 2 × $OC(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 171.78 (C-6′), 164.73 (ester), 155.75 (C-2′), 155.52 (urethane), 152.90 (C-4′), 125.38 (C-5′), 127.31–131.81 (Ar), 81.97 and 79.69 [2 × O*C*$(CH_3)_3$], 53.83 (C-2), 31.31 (C-4), 28.29 and 27.96 [2 × C(*C*$H_3)_3$] and 24.06 (C-3).

tert-Butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(2-amino-6-oxopyrimidin-5-yl)butyrate (52)

tert-Butyl (2*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxymethylene-6-oxopiperidine-2-carboxylate **48** (100 mg, 0.293 mmol), guanidine carbonate (158 mg, 0.87 mmol), and potassium carbonate (162 mg, 1.17 mmol) were heated in absolute ethanol (10 ml) at reflux for 18 h. The solvent was removed *in vacuo* to give a yellow residue which was partitioned between 5% aqueous citric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was separated and extracted with dichloromethane (2 × 5 ml). The combined organic phases were washed with brine (10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow residue. Column chromatography on silica gel using methanol–dichloromethane (1:9) as eluent afforded *tert-butyl (2RS)-2-tert-butoxycarbonylamino-4-(2-amino-6-oxopyrimidin-5-yl)butyrate* **52** as a pale white foam (20 mg, 19%) *m*/*z* [+ve es] 369 [*M* + H]$^+$; ν_{max} (film)/cm^{-1} 3400 (OH–NH), 1744 (sh) and 1645 (C=O); λ_{max} (MeOH)/nm 226 and 291 (log ε 4.13 and 3.90); λ_{max} (MeOH–HCl)/nm 220 and 260 (log ε 4.09 and 3.88); λ_{max} (MeOH–NaOH)/nm 232 and 280 (log ε 4.09 and 3.85); δ_H (400 MHz, C^2HCl_3) 7.39 (1H, *s*, H-4′), 5.60 (1H, *d*, *J* 8.4, NH, exchangeable with $^2H_3CO^2H$), 4.13 (1H, *m*, H-2), 2.37 (2H, *m*, H-4), 2.04–1.80 (2H, *m*, H-3), 1.46 [9H, *s*, $OC(CH_3)_3$] and 1.44 [9H, *s*, $OC(CH_3)_3$.

(2*RS*)-2-amino-4-(2-methyl-6-oxopyrimidin-5-yl)butyrate hydrochloride (53)

A suspension of *tert*-butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(2-methyl-6-oxopyrimidin-5-yl)butyrate **50** (52 mg, 0.142 mmol) in 6 N aqueous hydrochloric acid (1 ml) was stirred at room temperature for 90 min. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2RS)-2-amino-4-(2-methyl-6-oxopyrimidin-5-yl)butyrate hydrochloride* **53** as a glassy solid (34 mg, 97%); mp softens at 199 °C; *m*/*z* [+ve es] Found 212.1032 [*M* + H]$^+$, [$C_9H_{13}N_3O_3$ + H]$^+$ requires 212.1035; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1739 and 1687 (C=O); λ_{max} (MeOH)/nm 226 and 273 (log ε 3.39 and 3.32); λ_{max} (MeOH–HCl)/nm 230 and 260 (log ε 3.47 and 3.26); λ_{max} (MeOH–NaOH)/nm 233 and 272 (log ε 3.48 and 3.30); δ_H (300 MHz, ^2H_2O) 7.29 (1H, *s*, H-4′), 3.51 (1H, *t*, *J* 6.4, H-2), 2.31–1.92 (5H, *s* + *m*, CH_3 + H-4) and 1.56 (2H, *m*, H-3); δ_C (75 MHz, ^2H_2O) 171.30 (acid), 161.89 (C-2′), 161.37 (C-6′), 138.57 (C-4′), 126.16 (C-5′), 52.12 (C-2), 27.51 (C-4), 22.61 (C-3) and 17.60 (CH_3).

(2*RS*)-2-amino-4-(6-oxo-2-phenylpyrimidin-5-yl)butyrate hydrochloride (54)

A suspension of *tert*-butyl (2*RS*)-2-*tert*-butoxycarbonylamino-4-(6-oxo-2-phenylpyrimidin-5-yl)butyrate **51** (44 mg, 0.102 mmol) in 6 N aqueous hydrochloric acid (1 ml) was stirred at room temperature for 90 min. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to give *(2RS)-2-amino-4-(6-oxo-2-phenylpyrimidin-5-yl)butyrate hydrochloride* **54** as a glassy solid (31 mg, 98%); mp >250 °C, *m*/*z* [+ve es] Found 274.1185 [*M* + H]$^+$, [$C_{14}H_{15}N_3O_3$ + H]$^+$ requires 274.1192; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1737 (sh) and 1700 (C=O); λ_{max} (MeOH)/nm 245 and 280 (log ε 3.68 and 3.72); λ_{max} (MeOH–HCl)/nm 242 (sh), 252 (sh) and 276 (log ε 3.67, 3.70 and 3.78); λ_{max} (MeOH–NaOH)/nm 234, 260 and 277 (log ε 3.76, 3.67 and 3.67); δ_H (300 MHz, ^2H_2O) 7.73 (1H, *s*, H-4′), 7.57–7.29 (5H, *m*, ArH), 3.95 (1H, *t*, *J* 7.1, H-2), 2.41 (2H, *m*, H-4) and 1.93 (2H, *m*, H-3); δ_C (75 MHz, ^2H_2O) 171.28 (acid), 161.77 (C-2′), 159.54 (C-6′), 139.02 (C-4′), 135.53 (C-5′), 129.91–124.30 (Ar), 52.15 (C-2), 27.54 (C-4) and 22.77 (C-3).

tert-Butyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-6-oxo-5-phenylselenylpiperidine-2-carboxylate (55)

Lithium hexamethyldisilazide (1 M in THF, 13.36 ml, 13 mmol) was added to a stirred solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxopiperidine-2-carboxylate **41** (2.00 g, 6.68

mmol) in THF (20 ml) at −78 °C under nitrogen. The solution was allowed to warm to −30 °C over 30 min to ensure enolate formation and cooled to −78 °C. Phenylselenyl chloride (1.41 g, 7.35 mmol) was added and stirring was continued for 90 min. Saturated aqueous ammonium chloride (5 ml) was added at −78 °C and the solvent was removed *in vacuo* to give an orange residue. The residue was partitioned between ethyl acetate (5 ml) and saturated aqueous ammonium chloride (5 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–diethyl ether (2:1) as eluent afforded *tert-butyl (2S,5RS)-N-tert-butoxycarbonyl-6-oxo-5-phenylselenylpiperidine-2-carboxylate* **55** as a 6:1 mixture of *trans*/*cis* diastereoisomers (1.94 g, 64%); *m*/*z* [CI] Found 456.1250, $[C_{21}H_{29}NO_5Se + H]^+$ requires 456.1289; *m*/*z* [+ve FAB, 3-NBA] 455 $[M]^+$ and 478 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1774, 1740 (sh) and 1723 (C=O); δ_H (300 MHz, C^2HCl_3) 7.70–7.60 (2H, *m*, ArH), 7.37–7.22 (3H, *m*, ArH), 4.50 (1H, *m*, H-5), 4.00 (1H, *m*, H-2), 2.18 (1H, *m*, H-3A), 2.10–1.80 (3H, *m*, H-3B, H-4), 1.51 [9H, *s*, $C(CH_3)_3$] and 1.47 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 169.97 (C-6), 169.67 (ester), 152.51 (urethane), 135.75–128.01 (Ar), 83.43 and 82.30 [2 × O*C*$(CH_3)_3$], 59.26 (C-2), 44.11 (C-5), 27.85 and 27.80 [2 × C(*C*$H_3)_3$], 26.97 (C-3) and 25.66 (C-4).

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-3,6-dihydro-6-oxopyridine-2-carboxylate (56)

Hydrogen peroxide (30%, 3.30 ml, 29 mmol) was added to a stirred solution of *tert*-butyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-phenylselenyl-6-oxopipecolate **55** (494 mg, 1.09 mmol) in ethyl acetate (10 ml) at 0 °C. The solution was allowed to warm to room temperature and stirred for 3 h. The aqueous layer was separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (3 × 15 ml). The combined organic layers were washed with brine (2 × 10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent afforded *tert-butyl (2S)-N-tert-butoxycarbonyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate* **56** as a white solid (200 mg, 62%); mp 47–49 °C; $[\alpha]_D^{25}$ +14.1 (*c* 1.0, $CHCl_3$); Found: C, 60.4; H, 7.9; N, 4.7. $C_{15}H_{23}NO_5$ requires C, 60.6; H, 7.8; N; 4.7%; *m*/*z* [+ve FAB, 3-NBA] 298 $[M + H]^+$ and 320 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1771, 1717 (sh) 1696 and 1640 (C=O); δ_H (300 MHz, C^2HCl_3) 6.60 (1H, *m*, H-4), 5.97 (1H, *dd*, $J_{5,3}$ 2.4, $J_{5,4}$ 9.8, H-5), 4.90 (1H, *dd*, $J_{2,3}$ 1.9 and 6.5, H-2), 2.92–2.68 (2H, *m*, H-3), 1.55 [9H, *s*, $C(CH_3)_3$] and 1.43 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 169.62 (C-6), 162.59 (ester), 152.17 (urethane), 139.76 (C-5), 126.59 (C-4), 83.26 and 82.65 [2 × O*C*$(CH_3)_3$], 56.22 (C-2), 27.97 and 27.78 [2 × C(*C*$H_3)_3$] and 27.25 (C-3).

tert-Butyl (2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-vinyl-6-oxopiperidine-2-carboxylate (57)

Vinyl magnesium bromide (1 M in THF, 4.17 ml, 4.17 mmol) was added slowly to a suspension of copper bromide–dimethyl sulfide complex (429 mg, 2.09 mmol) at −25 °C under nitrogen. The mixture was stirred for 15 min at −25 °C and cooled to −78 °C. A solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate **56** (124 mg, 0.417 mmol) and trimethylsilyl chloride (0.106 ml, 0.834 mmol) in THF (5 ml) was added. The mixture was stirred for a further 90 min at −78 °C. Saturated aqueous ammonium chloride (5 ml) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with saturated aqueous ammonium chloride (3 × 10 ml) and brine (2 × 10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (3:1) as eluent afforded *tert-butyl (2S,4RS)-N-tert-butoxycarbonyl-4-vinyl-6-oxopipecolate* **57** as a 2:1 mixture of *trans*/*cis* diastereoisomers (58 mg, 43%); *m*/*z* [CI] Found 326.1966 $[M + H]^+$, $[C_{17}H_{27}NO_5 + H]^+$ requires 326.1967; *m*/*z* [+ve FAB, 3-NBA] 348 $[M + Na]^+$; ν_{max} (film)/cm^{-1} 1779, 1737 (sh) and 1723 (C=O); δ_H (300 MHz, C^2HCl_3) 5.67 (1H, *m*, CH=), 5.04 (2H, *m*, $=CH_2$), 4.58 (0.66H, *dd*, $J_{2,3}$ 2.7 and 5.8, H-2), 4.46 (0.33H, *dd*, $J_{2,3}$ 6.6 and 9.5, H-2), 2.70–2.42 (2H, *m*, H-5), 2.36–2.17 (2H, *m*, H-3), 1.82 (1H, *m*, H-4), 1.48 [9H, *s*, $C(CH_3)_3$] and 1.45 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 170.40 (C-6), 169.52 (ester), 151.98 (urethane), 139.27 and 138.92 (CH=), 115.00 and 114.84 ($=CH_2$), 83.47, 83.26, 82.23 and 82.08 [2 × O*C*$(CH_3)_3$], 58.55 and 58.36 (C-2), 39.93 (C-5), 34.80 and 33.67 (C-4), 31.72 and 31.39 (C-3), and 27.81 and 27.76 [$C(CH_3)_3$].

tert-Butyl (2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-(2-methyl-1-propenyl)-6-oxopiperidine-2-carboxylate (58)

2-Methyl-1-propenylmagnesium bromide (0.5 M in THF, 26.91 ml, 13 mmol) was added slowly to a suspension of copper bromide–dimethyl sulfide complex (1.39 g, 6.72 mmol) at −25 °C under nitrogen. The mixture was stirred for 15 min at −25 °C and cooled to −78 °C. A solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate **56** (400 mg, 1.35 mmol) and trimethylsilyl chloride (0.342 ml, 2.69 mmol) in THF (5 ml) was added. The mixture was stirred for a further 90 min at −78 °C and saturated aqueous ammonium chloride (15 ml) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with saturated aqueous ammonium chloride (3 × 20 ml) and brine (2 × 20 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (6:1) as eluent afforded *tert-butyl (2S,4RS)-N-tert-butoxycarbonyl-4-(2-methyl-1-propenyl)-6-oxopipecolate* **58** as a 5:1 mixture of *trans*/*cis* diastereoisomers (181 mg, 38%); *m*/*z* [CI] Found 354.2284 $[M + H]^+$, $[C_{19}H_{31}NO_5 + H]^+$ requires 354.2280; *m*/*z* [+ve FAB, 3-NBA] 354 $[M + H]^+$; ν_{max} (KBr)/cm^{-1} 1778, 1737 (sh) and 1723 (C=O); δ_H (300 MHz, C^2HCl_3) 4.88 (1H, *d*, *J* 8.7, CH=), 4.57 (0.83H, *dd*, $J_{2,3}$ 2.5 and 5.8, H-2), 4.46 (0.17H, *dd*, $J_{2,3}$ 6.7 and 9.6, H-2), 2.79–2.45 (2H, *m*, H-5), 2.28–2.01 (2H, *m*, H-3), 1.89–1.65 (4H, *m* + *s*, CH_3 + H-4), 1.50 (3H, *s*, CH_3), 1.49 [9H, *s*, $C(CH_3)_3$] and 1.47 [9H, *s*, $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 170.62 (C-6), 170.08 (ester), 152.14 (urethane), 133.56 (C=), 126.12 (CH=), 83.23 and 82.12 [2 × O*C*$(CH_3)_3$], 58.69 (C-2), 41.10 (C-5), 32.22 (C-3), 29.28 (C-4), 27.88 and 27.84 [2 × C(*C*$H_3)_3$], and 25.57 and 17.80 (CH_3).

tert-Butyl (2*S*,4′*RS*)-2-*tert*-butoxycarbonylamino-3-(6-oxo-1,4,5,6-tetrahydropyridazin-4-yl)propionate (60)

A solution of *tert*-butyl (2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-(2-methyl-1-propenyl)-6-oxopiperidine-2-carboxylate **58** (112 mg, 0.317 mmol) in dichloromethane (15 ml) was cooled to −78 °C and oxygen was passed through the solution for 5 min. Ozone was passed through the solution for 15 min during which time it turned blue. Triphenylphosphine (100 mg, 0.38 mmol) was added at −78 °C and the solution was allowed to warm slowly to room temperature. The solvent was removed *in vacuo* to give a yellow oil. Column chromatography on silica gel using petroleum ether–ethyl acetate (1:1) as eluent afforded the aldehyde **59** as a 5:1 mixture of *trans*/*cis* products. The aldehyde was dissolved in methanol (5 ml) and hydrazine hydrate (55% aq., 0.024 ml, 0.42 mmol) was added. The solution was stirred for 2 h and the solvent was removed *in vacuo* to give a yellow residue. Column chromatography on silica gel using ethyl acetate as eluent afforded *tert-butyl (2S,4′RS)-2-tert-butoxycarbonylamino-3-(6-oxo-1,4,5,6-tetrahydropyridazin-4-yl)propionate* **60**

as a colourless oil (87 mg, 80%); *m*/*z* [+ve es] Found 342.2034 $[M + H]^+$, $[C_{16}H_{27}N_3O_5 + H]^+$ requires 342.2029; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1735 (sh), 1685 and 1654 (C=O); λ_{max} (MeOH)/nm 228 (log ε 3.35); δ_H (300 MHz, C^2HCl_3) 8.77 (1H, br *s*, NH, exchangeable with $^2H_3CO^2H$), 7.11 (1H, *d*, *J* 2.3, H-3′), 5.25 (1H, *d*, *J* 8.1, NH, exchangeable with $^2H_3CO^2H$), 4.32 (1H, *m*, H-2), 2.86–2.42 (2H, *m*, H-4′+ H-5′A), 2.41–2.16 (1H, *m*, H-5′B), 2.05–1.73 (2H, *m*, H-3) and 1.60 and 1.45 [18H, 2 × *s*, 2 × $C(CH_3)_3$]; δ_C (75 MHz, C^2HCl_3) 171.02 (C-6′), 166.88 (ester), 156.26 (urethane), 147.60 (C-3′), 82.86 and 80.23 [$OC(CH_3)_3$], 51.73 (C-2), 35.95 (C-4′), 31.76 (C-3), 30.61 (C-5′), and 28.23 and 27.92 [$C(CH_3)_3$].

(2*S*,4′*RS*)-2-Amino-3-(6-oxo-1,4,5,6-tetrahydropyridazin-4-yl)-propionic acid hydrochloride (61)

A suspension of *tert*-butyl (2*S*,4′*RS*)-2-*tert*-butoxyamino-3-(6-oxo-1,4,5,6-tetrahydropyridazine-4-yl)propionate **60** (60 mg, 0.169 mmol) was stirred in 6 N aqueous hydrochloric acid (2 ml) at room temperature for 90 min. After 30 min the suspension had dissolved. The solvent was removed *in vacuo* and residual water was removed using a freeze dryer to afford *(2S,4′RS)-2-amino-3-(6-oxo-1,4,5,6-tetrahydropyridazin-4-yl)-propionic acid hydrochloride* **61** as a colourless oil (30 mg, 79%); *m*/*z* [+ve FAB, glycerol] 185 $[M]^+$; ν_{max} (KBr)/cm^{-1} 3400 (OH–NH), 1724 and 1636 (C=O); λ_{max} (MeOH)/nm 217 (log ε 3.13); δ_H (300 MHz,^2H_2O–^{2}HCl) 6.94 (1H, *d*, *J* 2.1, H-3′), 3.75 (1H, *m*, H-2) and 2.82–1.37 (5H, *m*, H-4′, H-5′ + H-3).

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