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β-Lactams as versatile synthons for homochiral ibotenate analogues with potential for activity at glutamate receptors[1]

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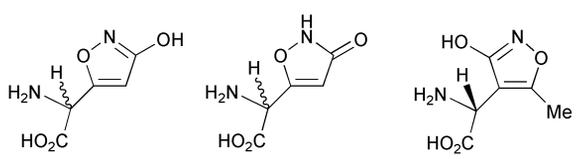
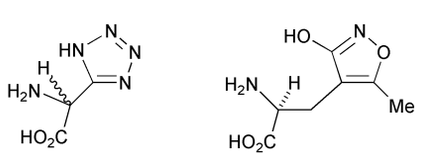
The activated β-lactam aldehydes **37**, **41** and **57** were synthesised. Aldehydes **37** and **57** proved to be more versatile substrates for our "ring switching" strategy to homochiral glutamate antagonists than the corresponding compounds in the pyroglutamate or 6-oxopipecolinate series had been. Substantial libraries of homochiral heteroaromatic glycine derivatives with potential for activity at specific glutamate receptor sub-types were prepared from these aldehydes. The aldehyde **41**, containing an additional anion stabilising group, underwent a retro-aldol process under "ring switching" conditions.

Introduction

The excitatory neurotransmitter glutamic acid is known to address a variety of both ionotropic (ion channel controlling) and metabotropic (G-protein linked) receptors. Various analogues of glutamic acid however are specific in their action and can address one or more of these receptors giving selective physiological effects. The natural product ibotenic acid **1**, an active constituent of the psychotropic fly agaric mushroom *Amanita muscaria*, acts at both ionotropic and metabotropic glutamate receptor sub-types.[2] It is racemic, presumably because of the acidity of the α-hydrogen in the amide tautomer **2**.[3] Analogues such as (*R*)-AMAA **3** and DL-tetrazolylglycine **4** act specifically at the ionotropic NMDA receptor sub-type.[2] These compounds consist of a heterocyclic ring system fused to a glycine moiety. The homologue AMPA **5** and many analogues which have a heterocyclic ring fused to the β-carbon of L-alanine are active at a different ionotropic glutamate receptor sub-type, the AMPA site.[2] The glutamate receptors are involved in memory and learning processes and antagonists have been identified as potential drugs for a variety of illness, including Alzheimer's disease,[4] epilepsy[5] and ischaemia.[6]



1 **2** **3**



4 **5**

We have discovered a versatile and economical synthesis for a large variety of homochiral compounds in which a heterocyclic ring system is fused to the β-carbon atom of L-alanine or the γ-carbon atom of ethylglycine. These compounds were designed to have potential for activity at the AMPA receptor[7–11] and some were tested and found to have biological activity at metabotropic receptors. The synthesis, shown in Scheme 1 and 2, involved reaction of aldehydes **6** or their homologues **12** of protected pyroglutamic acid ($n = 1$)[7–10] or 6-oxopipecolic acid ($n = 2$)[11] with bisnucleophiles and involved a minimum of steps. We have referred to this powerful synthetic tool as a "ring switching" reaction.[7]

The possibility of preparing a large variety of ibotenic acid **1** analogues by applying our "ring switching" reaction to a β-lactam template such as **15** using bisnucleophiles, as in Scheme 3, was appealing in spite of the fact that an attempt to prepare an analogue of the natural product TAN-950 by reacting an unactivated 3-acyl-β-lactam with hydroxylamine had been unsuccessful.[12]

Results and discussion

Our first task was to prepare a 3-acyl-β-lactam-4-carboxylate such as **15**. To this end we prepared the acid **19**[13] and converted it to the *tert*-butyl ester **20** using *O*-(*tert*-butyl)-trichloroacetamidate and $BF_3{\cdot}Et_2O$. Attempts to formylate either the acid **19** or the ester **20** directly were unsuccessful and, although we were able to prepare the acetyl derivative **21** in impure form, reaction of this with hydrazine in an attempt to initiate a "ring switching" reaction failed to give any recognisable products. We therefore opted for a more indirect route by preparing a 3-vinyl derivative and converting it to the corresponding aldehyde by ozonolysis.

The acid **19**[13] was first converted to the 3-trimethylsilyl-β-lactam **22**[14] in 95% yield, as outlined in Scheme 4, using 2.2 equivalents of LDA followed by TMSCl. This compound was subjected to a Peterson olefination reaction using LDA and acetaldehyde. The separate isomeric products **23** and **24** were isolated in 46% (*E*-isomer) and 29% (*Z*-isomer) overall yields respectively from the acid **19**. The geometry of the *E* isomer **23** was indicated by the fact that irradiating the methyl signal at δ 1.84 gave an NOE at the signal at δ 4.62 for H-4. In the *Z*-isomer **24**, when the signal at δ 4.48 for H-4 was irradiated, a NOE was induced in the olefinic signal at δ 5.84 for H-5.

Our plan was to rearrange the exocyclic double bond in the isomers **23** + **24** to obtain the isomer **25** since we reasoned that the conjugated compounds **23** + **24**, having an sp^2 hybridised olefinic atom in a β-lactam ring, would have more ring strain than the 3-vinyl derivative **25**. In the event, when we reacted the isomers **23** + **24** with 2.2 equivalents of LDA and quenched the dianion with 1 M aq. $KHSO_4$, very little rearrangement was observed. Reasoning that this might indicate that the unfavourable Coulombic interaction in **26b** might cause the balance of charge in the dianion **26** to reside on the distant carbon as in resonance form **26a**, we converted the mixture **23** + **24** into the *tert*-butyl esters **27** (51%) and **28** (32%) using *O*-(*tert*-butyl)-

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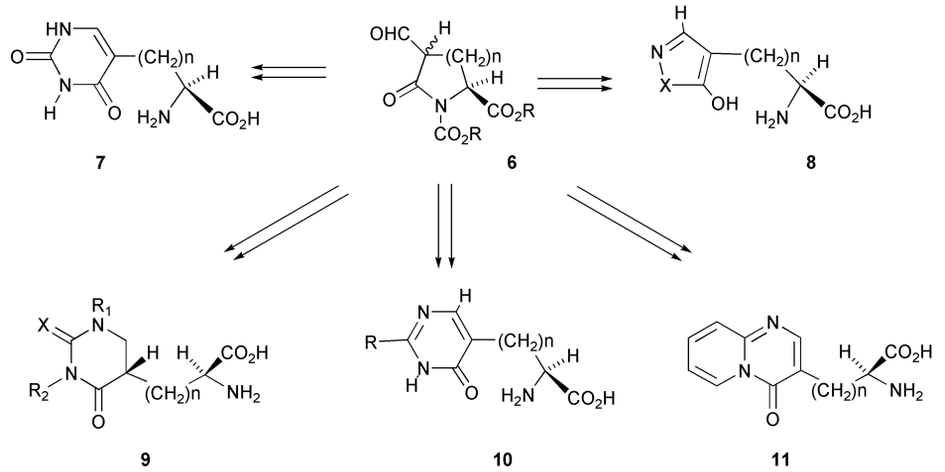
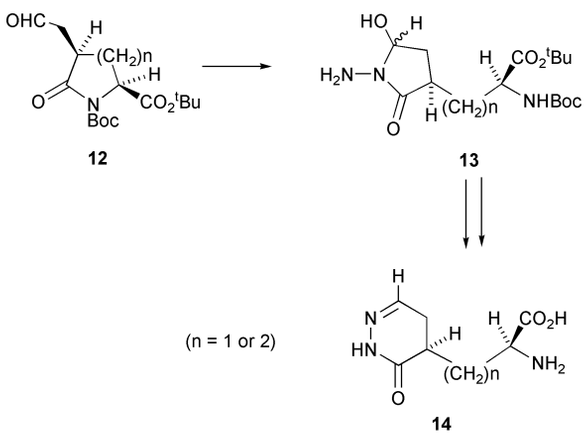
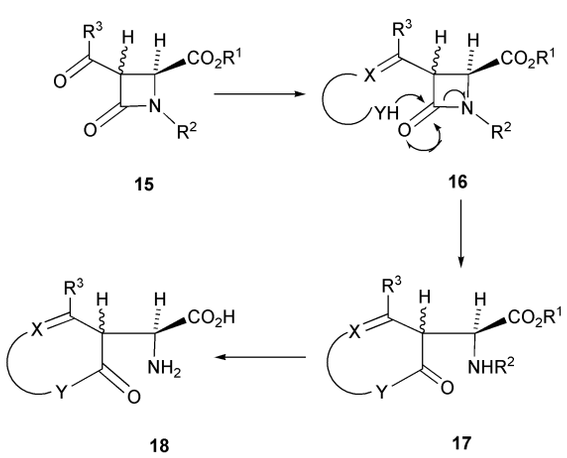


Scheme 1 (n = 1 or 2).

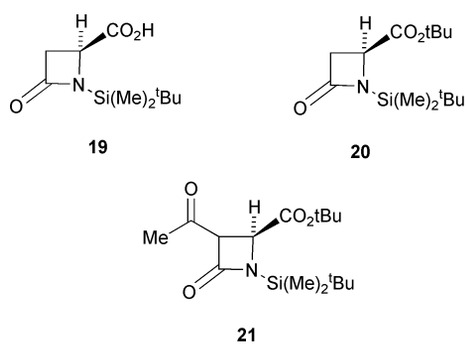


Scheme 2 (n = 1 or 2).



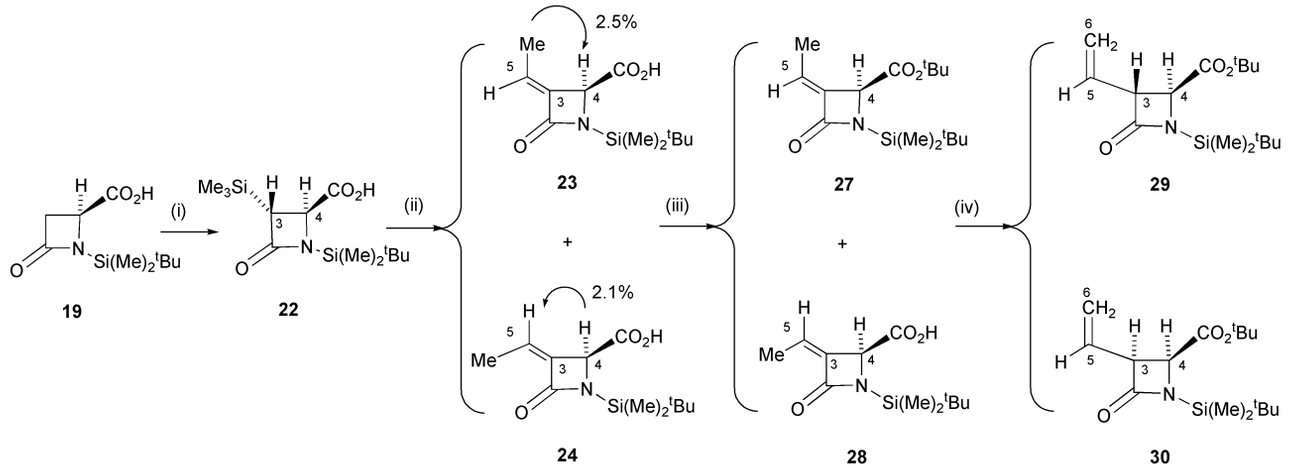
Scheme 3

trichloroacetimidate and $BF_3{\cdot}Et_2O$ in dichloromethane–cyclohexane. The geometry of the double bond in the esters was inferred from chemical shift similarities to the acids **23** and **24**. An initial attempt at deconjugation of the *Z*-isomer **28** using LDA gave the expected stereoisomers **29** and **30** in 5% yield together with the diisopropylamine adducts **31** (10%) and the dimeric product **32** (15%). It is of interest to note that, the adduct **31** is a mixture of the (5*RS*,3*R*,4*S*)-epimers since the coupling constant $J_{3,4}$ 2.3 Hz is clearly indicative of *trans* geometry between C-3 and C-4. The thermodynamically more stable isomers had therefore been formed. The coupling constant $J_{3,4}$ 6.7 Hz in compound **32**, however, would indicate that there is *cis* geometry between C-3 and C-4. We were eventually able to

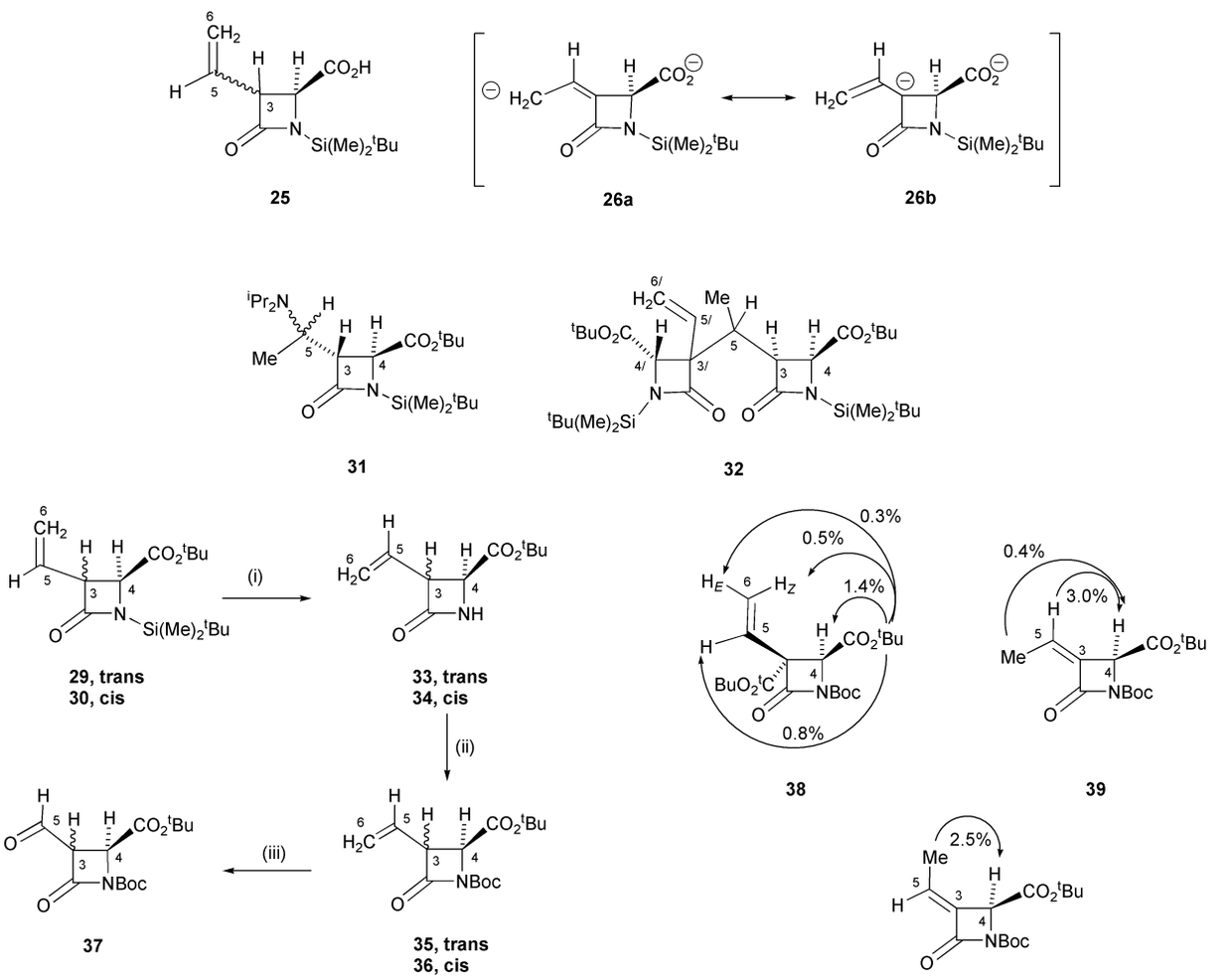


minimise the amounts of the Michael adducts **31** and **32** by adding a dilute solution of the conjugated β-lactams to a solution of LDA at −100 °C when a mixture of the *cis*- and *trans*-vinyl-β-lactams **29** + **30** was obtained in 65% yield as shown in Scheme 4.

The *N*-TBDMS protecting group had now served its purpose, and an *N*-urethane was required to enhance the electrophilicity of the β-lactam carbonyl group for the "ring switching" reaction. The stereoisomers **29** and **30** were therefore deprotected by reaction with 1 M aqueous HCl in MeOH as shown in Scheme 5. The unstable products **33** and **34** were obtained in quantitative yield. The relative stereochemistry in these compounds was assigned from the coupling constants between H-3 and H-4 of the β-lactam rings (**33**, *trans* $J_{3,4}$ 2.6; **34**, *cis* $J_{3,4}$ 5.9). An attempt was now made to convert the amides **33** and **34** to the *tert*-butoxycarbonyl urethanes **35** and **36** by reacting them with 2.2 equivalents of Boc_2O in acetonitrile in the presence of a catalytic amount of DMAP. The product was the bisacylated compound **38**, obtained as a single diastereoisomer ($[\alpha]_D$ + 37.6) in 45% yield. C-Acylation at C-3 had evidently occurred from the opposite side of the molecule from the bulky ester group at C-4 as evidenced by the NOE experiments shown on the structure **38**, since irradiation of the two *tert*-butyl singlets at δ 1.47 and 1.43 caused enhancement of all olefinic protons, whereas irradiation of the third at δ 1.50 did not. When a minimal amount of Boc_2O was used in the urethanation reaction, conjugation accompanied the desired reaction giving 5% of the *Z*-ethylidene β-lactam **39** and 25% of the *E*-ethylidene β-lactam **40**. The geometry was assigned to the isomers based on the fact that compound **39** had an upfield shift in the ^{1}H-NMR spectrum for the vinylic proton, H-5, (δ 6.03 ppm) compared to that for the corresponding proton in the spectrum of compound **40** (δ 6.51). This was confirmed by the results of the NOE experiments shown on the structures **39** and **40**. Selective irradiation at the olefinic proton, H-5, in compound **39** gave a 3.0% enhancement to H-4 whereas irradiation at the olefinic methyl



Scheme 4 *Reagents and conditions* : (i) (a) 2.2 LDA–THF, 0 °C, (b) TMSCl (95%); (ii) (a) 1.1 LDA–THF, 0 °C, (b) CH_3CHO, (46% **23**, 29% **24**); (iii) $Cl_3C(NH)O^tBu$–$BF_3{\cdot}Et_2O$–CH_2Cl_2–C_6H_{12} (51% **27**, 32% **28**); (iv) LDA–THF, −100 °C (65%).



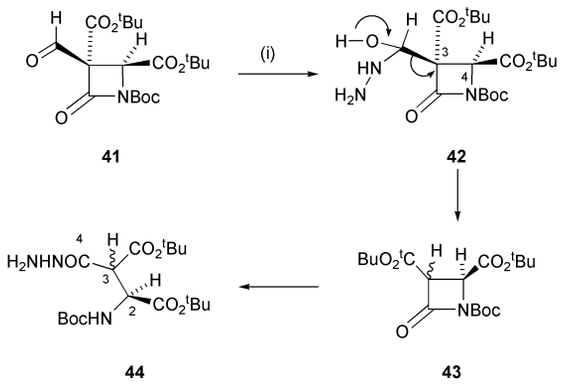
Scheme 5 *Reagents and conditions* : (i) 1 M aq HCl–MeOH (quant); (ii) Boc_2O–DMAP–^{t}BuOH–CH_3CN (45% **35**, 22% **36**); (iii) (a) O_3–CH_2Cl_2, −78 °C, (b) Me_2S.

protons in compound **40** gave a 2.5% enhancement to H-4. The desired vinyl-β-lactam urethanes **35** (45%, *trans* $J_{3,4}$ 3.2) and **36** (22%, *cis* $J_{3,4}$ 6.9) were eventually obtained by reacting the β-lactams **33** + **34** with excess Boc_2O in CH_3CN in the presence of the proton source ^{t}BuOH and a catalytic amount of DMAP as shown in Scheme 5.

We now had two possible compounds from which aldehyde templates for our "ring switching" reaction might be obtained, the required compounds **35** + **36** and the unexpected compound **38**. We decided to continue our studies using both of these. Ozonolysis of the mixed diastereoisomers **35** + **36** gave the aldehydes **37** in a *cis* : *trans* ratio of 1 : 9, irrespective of the *cis* : *trans* ratio of the olefinic starting material, as shown in Scheme 5. Ozonolysis of the vinylic compound **38** gave the aldehyde **41**. Both aldehydes were unstable and were used directly without further purification.

When aldehyde **41** was reacted with hydrazine hydrate, it was evident that none of the expected "ring switched" product was obtained. The ^{1}H NMR spectrum of the product, obtained in 49% overall yield from the vinylurethane **38**, was complicated by the presence of two diastereoisomers and the occurrence of rotamers due to restricted rotation. However, with the help of variable temperature and saturation transfer experiments, we

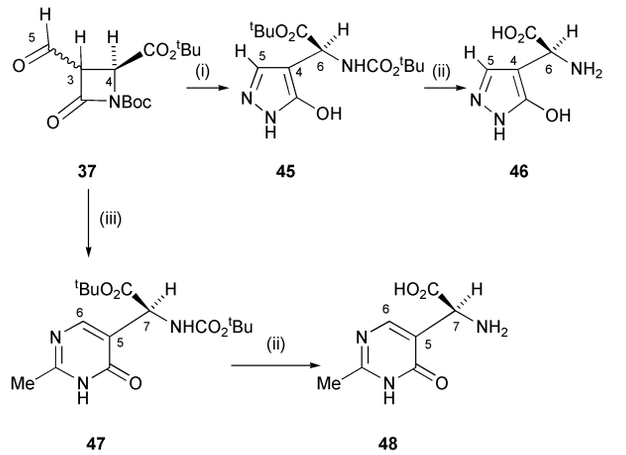
were able to identify this compound as the mixture of diastereoisomeric acylhydrazides **44**. We have rationalised the formation of these compounds as shown in Scheme 6. Initial attack of hydrazine on the aldehyde **41** would give the expected "ring switch" intermediate **42**. The presence of two carbonyl groups at C-3, however might now encourage the retro-aldol process shown in Scheme 6, to give the β-lactam **43** which would then undergo hydrazinolysis to the observed products **44**.



Scheme 6 *Reagents and conditions*: (i) H_2NNH_2.

When the aldehyde **37** was treated with hydrazine in MeOH at room temperature, as in Scheme 7, the product was obtained as a white solid in 75% yield. The characteristic β-lactam urethane absorption was no longer present in the infra red spectrum and a broad exchangeable doublet at δ 5.80 (N*H*Boc) and singlets at δ 9.20 (pyrazole N*H*) and δ 7.23 (H-5) in the ^{1}H NMR spectrum were consistent with the product **45** having been formed by a "ring switching" reaction. Hydrolysis to the hydrochloride of the amino acid **46** was achieved using 6 M aq. HCl at room temperature. Although ibotenic acid **1** had been shown to be racemic,[3] it is not possible for the compound **46** to convert to a tautomer analogous to **2** with potential for additional enolisation to the asymmetric centre. As expected, the specific rotation of this compound showed no change after leaving it as a solution in ^2H_2O for one month. The yield in the "ring switching" reaction was considerably better than had been obtained in the corresponding reaction in the pyroglutamic or 6-oxopipecolic acid series.[7–11] Reaction of the aldehyde **37** with hydroxylamine, however, gave no recognisable products.

Reaction of the aldehyde **37** with acetamidine hydrochloride in MeOH containing potassium carbonate at room temperature gave the pyrimidinone **47** in 61% yield as shown in Scheme 7. A broad exchangeable doublet at δ 5.82 (N*H*Boc) and a singlet at δ 8.01 (H-4) in the ^{1}H NMR spectrum and absorption in the UV spectrum at λ_{max} 223 and 276 nm were consistent with the

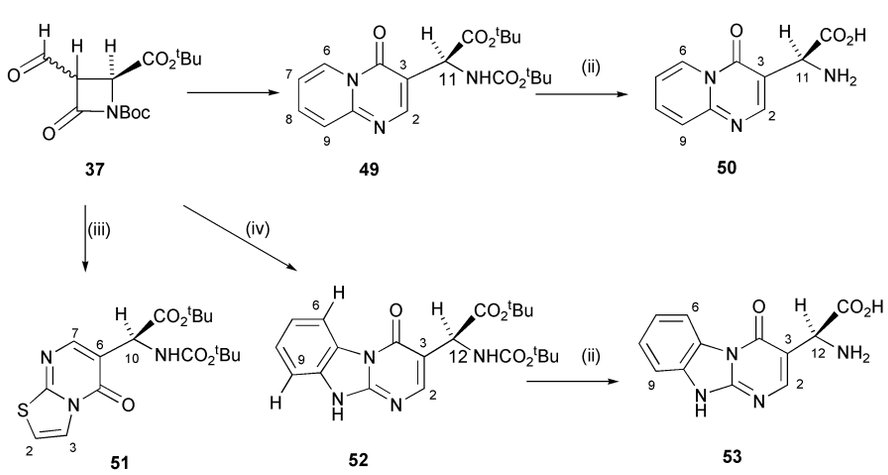


Scheme 7 *Reagents and conditions* : (i) H_2NNH_2–MeOH (75%); (ii) 6 M HCl (>94%); (iii) $CH_3C(=NH)NH_2$, HCl–K_2CO_3–MeOH (61%). Yields for steps (i) and (iii) are quoted for the two steps from the olefins **35**–**36**.

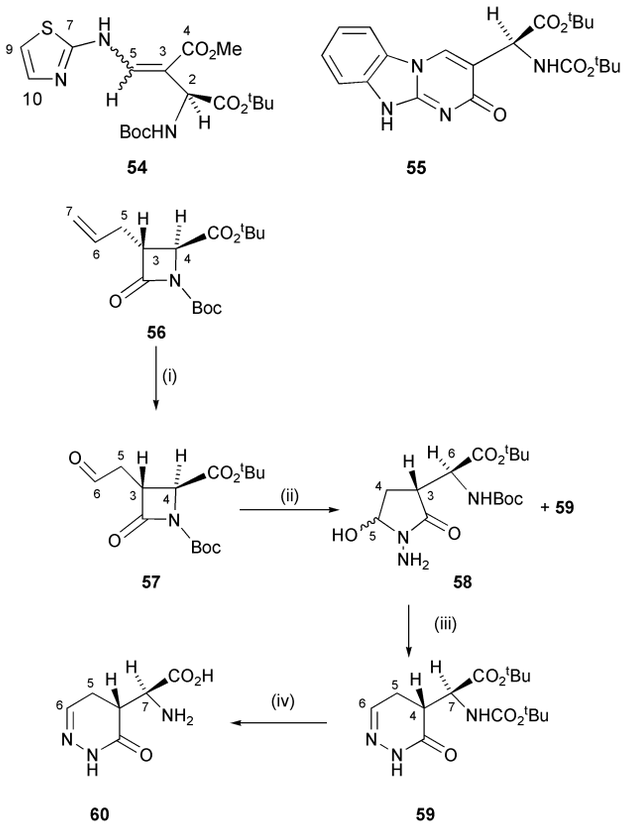
structure **47**. Hydrolysis in 6 M aq. HCl at room temperature gave the hydrochloride of the amino acid **48** in 97% yield and the specific rotation of this compound showed no change after leaving as a solution in ^2H_2O for one month.

When we used 2-aminoheteroaromatic compounds as bisnucleophiles in "ring switching" reactions with protected pyroglutamate aldehydes, we had obtained a very limited library of bicyclic AMPA analogues and a two-step process had been required to achieve this. Reaction of the aldehyde **37** with 2-aminopyridine in dioxane at room temperature, however was achieved in only one step, yielding the pyrido[1,2-*a*]-pyrimidinone **49** in 38% yield, as shown in Scheme 8. This was deprotected to the amino acid **50**. Initially when we reacted the aldehyde **37** with 2-aminothiazole in methanol the desired product **51** was obtained in only 16% yield together with 30% of a mixture of the *E*- and *Z*-alkylidene aspartates **54**. Changing the solvent to dioxane eliminated the by-products and gave the product **51** in 32% yield. Reaction of the aldehyde **37** with 2-aminobenzimidazole in dioxane at room temperature gave the benzimidazo[1,2-*a*]pyrimidinone **52** in 70% yield. The ^{1}H NMR spectrum had an exchangeable doublet at δ 6.39 for N*H*Boc and a singlet at δ 8.48 for H-2. The doublet for H-6 was at δ 8.09, deshielded by the carbonyl group, whereas H-9 was at δ 7.2. This is in keeping with the structure **52** rather than the alternative structure **55** where H-6 would not be expected to be especially deshielded. Hydrolysis in 6 M aq. HCl at room temperature gave the hydrochloride of the amino acid **53**.

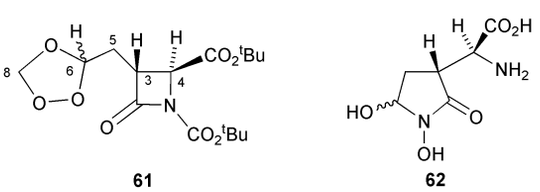
The homologous aldehyde **57** was synthesised as shown in Scheme 9, by preparing the ester-urethane **56** by modification of



Scheme 8 *Reagents and conditions*: (i) 2-aminopyridine–dioxane (38%); (ii) 6 M HCl (>94%); (iii) 2-aminothiazole–dioxane (32%); (iv) 2-amino-benzimidazole–dioxane (70%). Yields for steps (i), (iii) and (iv) are quoted for the two steps from the olefins **35/36**.



Scheme 9 *Reagents and conditions* : (i) (a) O_3–CH_2Cl_2, (b) Me_2S; (ii) H_2NNH_2–MeOH; (iii) Δ; (iv) F_3CCO_2H–CH_2Cl_2.



a literature route,[13] followed by ozonolysis and reduction using Me_2S. When insufficient Me_2S was used, the stable diastereoisomeric ozonides **61** were isolated, but use of 35 equivalents of Me_2S gave the crude aldehyde **57** which was reacted directly with hydrazine hydrate in MeOH at room temperature to give the epimeric hydroxypyrrolidinones **58** in 62% yield together with the pyridazine **59** in 17% yield. When the aldehyde **57** was heated to reflux in benzene with four equivalents of hydrazine hydrate, then the sole product was the pyridazine **59** in 65% overall yield from the olefin **57**. When a dry sample of the carbinolamines **58** was left at room temperature for more than two weeks, TLC and NMR spectroscopy indicated that the pyridazine **59** was gradually formed. The structure and stereochemistry of the pyridazine **59** was confirmed by single crystal X-ray crystallography as shown in Fig. 1. Hydrolysis of the protected pyridazine **59** with trifluoroacetic acid in dichloromethane gave the trifluoroacetate of the amino acid **60** in nearly quantitative yield. Although compound **58** is structurally similar to the natural product dealanylalahopcin **62**[15] we were unable to access this natural product *via* a "ring switching" reaction of the aldehyde **57** with hydroxylamine.

We have found that β-lactam 4-aldehydes are excellent electrophiles for our ring switching reactions and that a large number of homochiral compounds in which a glycine residue is directly attached to a heteroaromatic system can be prepared.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer PE 241 polarimeter using a 1 dm path length. Specific rotation values are in 10^{-1} deg cm^2 g^{-1} and concentrations, *c*, in g 100 ml^{-1}. UV spectra were recorded on a ATI Unicam UV2-100 Fourier transform spectrophotometer. ε values are given in dm^3 mol^{-1} cm^{-1}. IR spectra were recorded on a Perkin Elmer 1710 Fourier transform instrument. ^{1}H-NMR spectra were recorded using Bruker DPX 300 (300 MHz) and AMX 500 instruments (500 MHz). ^{13}C-NMR spectra (^{1}H decoupled) were recorded using Bruker DPX 300 (75.5 MHz) and AMX 500 (125.8 MHz) instruments with INEPT experiments to help assign the spectra. Chemical shifts are given in ppm using residual solvent peaks as internal references. Coupling constants (*J*) are in Hz. All NMR spectra were recorded at 25 °C unless otherwise stated. Microanalyses were performed by Medac Ltd. Low resolution mass spectra were recorded by Dr A. Abdul-Sada using a Kratos MS 80RF who also recorded one high resolution spectrum using a Bruker BioApex III 4.7 FT–ICR machine. All other high resolution mass measurements were obtained from the EPSRC Central Mass Spectrometry Service, Swansea. Flash column chromatography was performed using Fluka Silica Gel 60 (220–440 mesh). Petroleum ether refers to that fraction of hexanes of bp 60–80 °C.

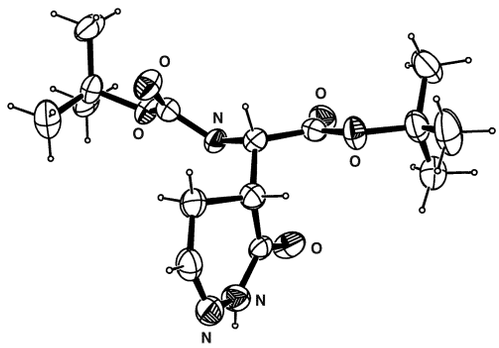


Fig. 1 X-Ray structure of the pyridazine **59** from the reaction of the aldehyde **57** with hydrazine.

tert-Butyl (4*S*)-*N*-*tert*-butyldimethylsilylazetidin-2-one-4-carboxylate (20)

(4*S*)-*N*-*tert*-Butyldimethylsilylazetidin-2-one-4-carboxylic acid **19**[13] (1 g, 4.367 mmol) was dissolved in tetrahydrofuran (4.4 ml) and cyclohexane (4.4 ml) under argon. Boron trifluoride diethyl etherate (0.175 ml, 1.38 mmol) and a solution of *O*-(*tert*-butyl)trichloroacetimidate (1.6 ml, 8.95 mmol) in cyclohexane (4.4 ml) were added simultaneously. The resulting suspension was stirred for 45 min at room temperature. Solid $KHCO_3$ (1.3 g) was added and the mixture was stirred for 5 min. The solvents were removed *in vacuo* to give a solid residue which was triturated with petroleum ether and filtered through Celite®. The residue was further washed with petroleum ether (3*x*) and solvents were removed from the combined filtrates to give an oil, which was purified by chromatography on silica gel, using a mixture of petroleum ether and diethyl ether (7 : 3) as eluent to afford *tert-butyl (4S)-N-tert-butyldimethylsilylazetidin-2-one-4-carboxylate* **20** as a colourless oil (647 mg, 52%); $[a]_D^{20}$ −78.0 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 286.1840 ([M + H]$^+$). [$C_{14}H_{27}NO_3Si$ + H] requires 286.1838; *m/z* [+ ve FAB (3-NBA)] 286 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1755 (β-lactam) and 1734 (ester); δ_H (300 MHz, C^2HCl_3) 3.89 (1H, dd, $J_{4,3R}$ 6.0, $J_{4,3S}$ 2.8, H-4), 3.28 (1H, dd, $J_{3R,3S}$ 15.1, $J_{3R,4}$ 6.0, H-3*R*), 2.94 (1H, dd, $J_{3S,3R}$ 15.1, $J_{3S,4}$ 2.8, H-3*S*), 1.45 (9H, s, $OC(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3$) and 0.27 and 0.10 (6H, 2 × s, 2 × $SiCH_3$); δ_C (75.5 MHz, C^2HCl_3) 171.4 and 171.1 (lactam and ester), 82.1 ($C(CH_3)_3$), 49.5 (C-4), 43.9 (C-3), 27.9 and 26.1 (2 × $C(CH_3)_3$), 18.5 ($SiC(CH_3)_3$) and −5.9 and −6.3 (2 × $SiCH_3$).

(3*R*,4*S*)-*N*-*tert*-Butyldimethylsilyl-3-trimethylsilylazetidin-2-one-4-carboxylic acid (22)[14]

n-Butyllithium (1.6 M solution in hexanes, 2.4 ml, 3.84 mmol) was added to a solution of diisopropylamine (0.54 ml, 3.843 mmol) in tetrahydrofuran (4.7 ml) at 0 °C under argon. The solution was stirred for 10 min and added to a solution of (4*S*)-*N*-*tert*-butyldimethylsilylazetidin-2-one-4-carboxylic acid **19**[13] (400 mg, 1.747 mmol) in tetrahydrofuran (6 ml) at 0 °C under argon and stirred for 10 min. Chlorotrimethylsilane (0.25 ml, 1.97 mmol) was added and, after stirring at 0 °C for 20 min, the reaction was quenched by transferring to a flask containing a mixture of 1 M aqueous $KHSO_4$ (20 ml) and ethyl acetate (20 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine (2×) and dried ($MgSO_4$). The solvents were removed *in vacuo* to give *(3R, 4S)-N-tert-butyldimethylsilyl-3-trimethylsilylazetidin-2-one-4-carboxylic acid* **22** as a light orange solid (526 mg, 95%) which was found to be sufficiently pure to be used in subsequent reactions. An analytical sample was obtained by chromatography on silica gel, using a mixture of chloroform–methanol–acetic acid (92 : 6 : 2) as eluent to give a white solid that was recrystallised from ethyl acetate and petroleum ether; mp 85–87 °C; $[\alpha]_D^{22}$ −98.5 (*c* 1.07, $CHCl_3$) (Found: C, 51.4; H, 9.1; N, 4.5; $C_{13}H_{27}NO_3Si_2$ requires C, 51.8; H, 9.0; N, 4.6%); *m/z* [+ ve FAB (3-NBA)] 302 ([M + H]$^+$); ν_{max} (KBr)/cm^{-1} 3468 (br, COOH), 1766 and 1700 (ester and lactam); δ_H (300 MHz, C^2HCl_3) 3.80 (1H, d, $J_{4,3}$ 3.0, H-4), 2.96 (1H, $J_{3,4}$ 3.0, H-3), 0.94 (9H, s, NSiC(CH_3)$_3$), 0.27 (3H, s, NSiCH_3), 0.15 (9H, s, 3-Si(CH_3)$_3$) and 0.11 (3H, s, NSiCH_3); δ_C (75.5 MHz, C^2HCl_3) 177.9 and 173.7 (lactam and acid), 50.04 (C-3 and C-4), 26.1 (NSiC(CH_3)$_3$), 18.3 (NSiC(CH$_3$)$_3$), −3.0 (3-Si(CH_3)$_3$) and −6.0 and −6.3 (2 × NSiCH_3).

(3*E*,4*S*)- and (3*Z*,4*S*)-*N*-*tert*-Butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylic acid (23) and (24)

n-Butyllithium (1.6 M solution in hexanes, 26.5 ml, 42.4 mmol) was added to a solution of diisopropylamine (5.9 ml, 42.4 mmol) in tetrahydrofuran (50 ml) at 0 °C, under argon. The solution was stirred for 10 min and added to a solution of (3*R*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-trimethylsilylazetidin-2-one-4-carboxylic acid **22** (5.81 g, 19.29 mmol) in tetrahydrofuran (64 ml) at 0 °C under argon. The mixture was stirred for 10 min, acetaldehyde (2.15 ml, 38.6 mmol) was added and, after stirring at 0 °C for 20 min, the reaction was quenched by transferring to a flask containing a mixture of 1 M aqueous $KHSO_4$ (250 ml) and ethyl acetate (250 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2×). The combined organic layers were washed with brine (2×) and dried ($MgSO_4$). The solvents were removed *in vacuo* to give an orange oil that was purified by chromatography on silica gel, using a gradient of chloroform–methanol–acetic acid (98 : 0 : 2 to 90 : 8 : 2) to afford *(3Z,4S)-N-tert-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylic acid* **24** as a colourless oil (1.43 g, 29%); $[\alpha]_D^{26}$ −10.5 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 256.1365 ([M + H]$^+$). [$C_{12}H_{21}NO_3Si$ + H] requires 256.1369; *m/z* [+ ve FAB (3-NBA)] 256 ([M + H]$^+$) and 512 ([2M + H]$^+$); ν_{max} (film)/cm^{-1} 3200 (br, COOH) and 1748 (br, β-lactam and acid); δ_H (500 MHz, C^2HCl_3) 7.10 (1H, br s, CO_2H), 5.84 (1H, qd, $J_{5,5\text{-Me}}$ 7.3, $J_{5,4}$ 1.4, H-5), 4.48 (1H, dq, $J_{4,5}$ 1.4, $J_{4,5\text{-Me}}$ 1.1, H-4), 2.04 (3H, dd, $J_{5\text{-Me},5}$ 7.3, $J_{5\text{-Me},4}$ 1.1, 5-Me), 0.98 (9H, s, SiC(CH_3)$_3$) and 0.34 and 0.18 (6H, 2 × s, 2 × SiCH_3); δ_C (75.5 MHz, C^2HCl_3) 176.2 (CO_2H), 167.7 (lactam), 138.1 (C-3), 127.6 (C-5), 57.4 (C-4), 26.2 (SiC(CH_3)$_3$), 18.7 (SiC(CH$_3$)$_3$), 14.6 (5-CH_3) and −5.8 and −6.0 (2 × SiCH_3). Selective irradiation of the proton at δ 4.48 (H-4) resulted in a 2.1% enhancement in the signal at δ 5.84 for H-5 and a negligible enhancement in the signal at δ 2.04 for 5-Me. Subsequent elution gave *(3E,4S)-N-tert-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylic acid* **23** as a white solid (2.26 g, 46%). An analytical sample was obtained by recrystallisation from ethyl acetate and petroleum ether; mp 83–85 °C; $[\alpha]_D^{20}$ −2.7 (*c* 1.08, $CHCl_3$) (Found: C, 56.1; H, 8.1; N, 5.8; $C_{12}H_{21}NO_3Si$ requires C, 56.4; H, 8.3; N, 5.5%); *m/z* (ES) Found: 256.1369 ([M + H]$^+$). [$C_{12}H_{21}NO_3Si$ + H] requires 256.1369; *m/z* [+ ve FAB (3-NBA)] 256 ([M + H]$^+$); ν_{max} (KBr)/cm^{-1} 3419 (br, COOH), 1748 (β-lactam) and 1712 (acid); δ_H (500 MHz, C^2HCl_3) 9.42 (1H, br s, CO_2H), 6.29 (1H, qd, $J_{5,5\text{-Me}}$ 7.3, $J_{5,4}$ 1.7, H-5), 4.62 (1H, dq, $J_{4,5}$ 1.7, $J_{4,5\text{-Me}}$ 0.8, H-4), 1.84 (3H, dd, $J_{5\text{-Me},5}$ 7.3, $J_{5\text{-Me},4}$ 0.8, 5-Me), 0.98 (9H, s, SiC(CH_3)$_3$) and 0.35 and 0.17 (6H, 2 × s, 2 × SiCH_3); δ_C (75.5 MHz, C^2HCl_3) 175.8 (CO_2H), 167.7 (lactam), 139.1 (C-3), 125.0 (C-5), 57.5 (C-4), 26.2 (SiC(CH_3)$_3$), 18.7 (SiC(CH$_3$)$_3$), 13.5 (5-CH_3) and −5.8 and −6.1 (2 × SiCH_3). Selective irradiation of the proton at δ 4.62 (H-4) resulted in a 0.5% enhancement in the signal at δ 1.84 for 5-Me and no enhancement in the signal at δ 6.29 for H-5. Selective irradiation of the protons at δ 1.84 (5-Me) resulted in a 2.5% enhancement in the signal for H-4 and an 8.8% enhancement for H-5.

***tert*-Butyl (3*E*,4*S*)- and (3*Z*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate (27) and (28)**

A mixture of (3*E*,4*S*)- and (3*Z*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylic acid **23** and **24** (4.67 g, 18.3 mmol) was dissolved in dichloromethane (20 ml) and cyclohexane (20 ml) under argon. Boron trifluoride diethyl etherate (0.73 ml, 5.76 mmol) and a solution of *O*-(*tert*-butyl)-trichloroacetimidate (7.2 ml, 40.3 mmol) in cyclohexane (20 ml) were added simultaneously. The resulting suspension was stirred for 30 min at room temperature and solid $KHCO_3$ (5.5 g) was added. The mixture was stirred for a further 5 min, and removal of the solvents *in vacuo* gave a solid which was added to petroleum ether and filtered through Celite®. The solid residue was further washed with petroleum ether (3×) and the solvent was removed from the combined filtrates to give an oil that was purified by chromatography on silica gel, using a mixture of petroleum ether and diethyl ether (4 : 1) as eluent to afford *tert-butyl (3Z,4S)-N-tert-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate* **28** as a colourless oil (1.82 g, 32%); $[\alpha]_D^{23}$ −46.7 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 312.1992 ([M + H]$^+$). [$C_{16}H_{29}NO_3Si$ + H] requires 312.1995; *m/z* [+ ve FAB (3-NBA)] 312 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1746 (br, β-lactam and ester); δ_H (300 MHz, C^2HCl_3) 5.68 (1H, qd, $J_{5,5\text{-Me}}$ 7.3, $J_{5,\ 4}$ 1.2, H-5), 4.27 (1H, dq, $J_{4,5}$ 1.2, $J_{4,5\text{-Me}}$ 1.0, H-4), 1.98 (3H, dd, $J_{5\text{-Me},5}$ 7.3, $J_{5\text{-Me},4}$ 1.0, 5-Me), 1.43 (9H, s, OC(CH_3)$_3$), 0.94 (9H, s, SiC(CH_3)$_3$) and 0.30 and 0.10 (6H, 2 × s, 2 × SiCH_3); δ_C (75.5 MHz, C^2HCl_3) 169.7 and 168.0 (ester and lactam), 139.3 (C-3), 125.8 (C-5), 82.0 (OC(CH$_3$)$_3$), 58.5 (C-4), 28.1 (OC(CH_3)$_3$), 26.2 (SiC(CH_3)$_3$), 18.6 (SiC(CH$_3$)$_3$), 14.5 (5-CH_3) and −5.7 and −6.1 (2 × SiCH_3). *tert-Butyl (3E,4S)-N-tert-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate* **27** eluted next as a colourless oil (2.9 g, 51%); $[\alpha]_D^{23}$ + 1.1 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 312.1991 ([M + H]$^+$). [$C_{16}H_{29}NO_3Si$ + H] requires 312.1995; *m/z* [+ ve FAB (3-NBA)] 312 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1755 (br, β-lactam and ester C=O); λ_{max} (MeOH)/nm 213 (ε 12100); δ_H (300 MHz, C^2HCl_3) 6.17 (1H, q, $J_{5,5\text{-Me}}$ 7.3, H-5), 4.44 (1H, s, H-4), 1.77 (3H, d, $J_{5\text{-Me},5}$ 7.3, 5-Me), 1.46 (9H, s, OC(CH_3)$_3$), 0.94 (9H, s, SiC(CH_3)$_3$) and 0.32 and 0.11 (6H, 2 × s, 2 × SiCH_3); δ_C (75.5 MHz) 169.9 and 168.1 (ester and lactam), 140.3 (C-3), 123.2 (C-5), 82.2 (C(CH$_3$)$_3$), 58.8 (C-4), 27.9 (C(CH$_3$)$_3$), 26.2 (SiC(CH_3)$_3$), 18.7 (SiC(CH$_3$)$_3$), 13.4 (5-CH_3) and −5.6 and −6.1 (2 × SiCH_3).

***tert*-Butyl (3*R*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-[(1*RS*)-1-*N*,*N*-diisopropylaminoethyl]azetidin-2-one-4-carboxylate (31) and *tert*-butyl (3*R*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-[(1*RS*)-1-((3*RS*,4*S*)-4-*tert*-butoxycarbonyl-1-*tert*-butyldimethylsilyl-3-vinylazetidin-2-on-3-yl)ethyl]azetidin-2-one-4-carboxylate (32)**

n-Butyllithium (1.6 M solution in hexanes, 0.18 ml, 0.285

mmol) was added to a solution of diisopropylamine (40 μl, 0.285 mmol) in tetrahydrofuran (0.5 ml) at 0 °C, under argon. The solution was stirred for 10 min, cooled to −78 °C, and a solution of *tert*-butyl (3*Z*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate **28** (81 mg, 0.259 mmol) in tetrahydrofuran (1 ml) was added slowly. The resulting bright orange solution was stirred at −78 °C for 30 min and quenched by addition of saturated aqueous NH_4Cl. The solution was allowed to warm to room temperature, the two phases were separated and the aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (9 : 1 to 6 : 4) to afford *tert-butyl (3R,4S)-N-tert-butyldimethylsilyl-3-[(1RS)-1-N,N-diisopropylaminoethyl]-azetidin-2-one-4-carboxylate* **31** as an orange oil (10 mg, 10%); *m*/*z* (ES) Found 357.2567 ([M + H-C_4H_8]$^+$, McClafferty). $C_{18}H_{37}N_2O_3Si$ requires 357.2573; *m*/*z* [+ ve FAB (3-NBA)] 413 ([M + H]$^+$) and 435 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 1751 (C=O); δ_H (300 MHz, C^2HCl_3) 3.65 (1H, d, $J_{4,3}$ 2.3, H-4), 3.15 (1H, dd, $J_{3,5}$ 10.2, $J_{3,4}$ 2.3, H-3), 3.00–3.15 (3H, m, H-5 and 2 × C*H*(CH_3)$_2$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.19 (3H, d, $J_{5\text{-Me},5}$ 6.2, 5-Me), 1.01 and 0.99 (2 × 6H, 2 × d, *J* 4.1, 2 × CH(C*H*$_3$)$_2$), 0.94 (9H, s, SiC(C*H*$_3$)$_3$) and 0.28 and 0.08 (6H, 2 × s, 2 × $SiCH_3$); δ_C (75.5 MHz, C^2HCl_3) 174.7 and 171.8 (ester and lactam), 81.6 (O*C*(CH_3)$_3$), 62.8 (C-3), 55.8 (C-4), 50.1 (C-5), 44.4 (N*C*H(CH_3)$_2$), 27.9 (OC(*C*H$_3$)$_3$), 26.2 (SiC(*C*H$_3$)$_3$), 23.8 and 22.1 (NCH(*C*H$_3$)$_2$)), 19.0 (5-Me), 18.4 (Si*C*(CH_3)$_3$), and −5.8 and −6.3 (2 × Si*C*H$_3$). *tert-Butyl (3S,4S)-N-tert-butyldimethylsilyl-3-((1RS)-1-((3RS,4S)-4-tert-butoxycarbonyl-1-tert-butyldimethylsilyl-3-vinylazetidin-2-on-3-yl)ethyl)azetidin-2-one-4-carboxylate* **32** was eluted as a white solid (25 mg, 15%); mp 102–103 °C; *m*/*z* (ES) Found: 623.3906 ([M + H]$^+$). [$C_{32}H_{58}N_2O_6Si_2$ + H] requires 623.3911; *m*/*z* [+ ve FAB (3-NBA)] 623 ([M + H]$^+$); ν_{max} (KBr)/cm^{-1} 1744 (C=O); δ_H (300 MHz, C^2HCl_3) 5.88 (1H, dd, $J_{5',6'Z}$, 17.3, $J_{5',6'E}$ 10.6, H-5′), 5.43 (1H, dd, $J_{6'Z,5'}$ 17.3, $J_{6'Z,6'E}$ 1.4, H-6′*Z*), 5.29 (1H, dd, $J_{6'E,5'}$ 10.6, $J_{6'E,6'Z}$ 1.4, H-6′*E*), 4.17 (1H, s, H-4′), 4.04, (1H, d, $J_{4,3}$ 6.7, H-4), 3.86 (1H, dd, $J_{3,4}$ 6.7, $J_{3,5}$ 2.2, H-3), 2.27 (1H, qd, $J_{5,5\text{-Me}}$ 7.0, $J_{5,3}$ 2.2, H-5), 1.46 and 1.41 (18H, 2 × s, 2 × OC(C*H*$_3$)$_3$), 1.13 (3H, d, $J_{5,5\text{-Me}}$ 7.0, 5-Me), 0.96 and 0.93 (18H, 2 × s, 2 × SiC(C*H*$_3$)$_3$) and 0.30, 0.29, 0.095 and 0.089 (12H, 4 × s, 2 × $SiCH_3$); δ_C (75.5 MHz, C^2HCl_3) 173.7, 171.7, 169.8 and 169.1 (ester and lactam), 130.8 (C-5′), 120.1 (C-6′), 82.5 and 82.1 (2 × O*C*(CH_3)$_3$), 70.4 (C-3′), 60.2 (C-4′), 56.9 (C-3), 54.0 (C-4), 35.5 (C-5), 28.1 (2 × OC(*C*H$_3$)$_3$), 26.5 and 26.3 (2 × SiC(*C*H$_3$)$_3$), 18.7 and 18.5 (2 × Si*C*(CH_3)$_3$), 12.3 (5-Me) and −5.8, −6.0 and −6.2 (4 × Si*C*H$_3$). *(3R,4S)-* and *(3S,4S)-tert-butyl N-tert-butyldimethylsilyl-3-vinylazetidin-2-one-4-carboxylate* **29** and **30** were also eluted as an inseparable mixture (4 mg, 5%) spectroscopically identical to the mixture prepared in the following experiment. A number of other fractions were eluted from the column as complex mixtures that could not be characterised.

tert-Butyl (3*R*,4*S*)- and (3*S*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-vinylazetidin-2-one-4-carboxylate (29) and (30)

n-Butyllithium (1.6 M solution in hexanes, 3.3 ml, 5.3 mmol) was added to a solution of diisopropylamine (0.74 ml, 5.3 mmol) in tetrahydrofuran (7 ml) at 0 °C, under argon. The solution was stirred for 10 min at 0 °C, cooled to −100 °C and a solution of *tert*-butyl (3*Z*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate **28** (1.5 g, 4.83 mmol) in tetrahydrofuran (50 ml) was added over a period of 15 min. The resulting bright orange solution was stirred at −100 °C for 15 min and quenched by addition of saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and the aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (90 : 10 to 85 : 15) as eluent, to afford an inseparable mixture of *tert-butyl (3R,4S)-* and *(3S,4S)-N-tert-butyldimethylsilyl-3-vinylazetidin-2-one-4-carboxylate* **29** and **30** as an oil (975 mg, 65%). We were able to isolate an analytical sample of *tert-butyl (3R,4S)-N-tert-butyldimethylsilyl-3-vinylazetidin-2-one-4-carboxylate* **29** by means of a second chromatographic separation of a fraction enriched in this isomer. In no case could we isolate a pure sample of the other isomer; colourless oil; $[a]_D^{27}$ + 11.2 (*c* 1, $CHCl_3$); *m*/*z* (ES) Found: 312.1996 ([M + H]$^+$). [$C_{16}H_{29}NO_3Si$ + H] requires 312.1995); *m*/*z* [+ ve FAB (3-NBA)] 312 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1759 (br, β-lactam and ester); δ_H (300 MHz, $C_6^2H_6$) 5.75 (1H, ddd, $J_{5,6Z}$ 17.1, $J_{5,6E}$ 10.3, $J_{5,3}$ 6.8, H-5), 5.23 (1H, dt, $J_{6Z,5}$ 17.1, $J_{6Z,6E} = J_{6Z,3}$ 1.4, H-6*Z*), 4.98 (1H, ddd, $J_{6E,5}$ 10.3, $J_{6E,6Z} = J_{6E,3}$ 1.4, H-6*E*), 3.78 (1H, ddt, $J_{3,5}$ 6.8, $J_{3,4}$ 2.9, $J_{3,6Z} = J_{3,6E}$ 1.4, H-3), 3.74, (1H, d, $J_{4,3}$ 2.9, H-4), 1.27 (9H, s, OC(C*H*$_3$)$_3$), 1.00 (9H, s, SiC(C*H*$_3$)$_3$) and 0.37 and 0.09 (6H, 2 × s, 2 × $SiCH_3$); δ_C (75.5 MHz, C^2HCl_3) 171.8 and 170.8 (ester and lactam), 130.9 (C-5), 119.0 (C-6), 82.2 (O*C*(CH_3)$_3$), 60.7 (C-4), 56.3 (C-3), 27.9 (OC(*C*H$_3$)$_3$), 26.2 (SiC(*C*H$_3$)$_3$), 18.5 (Si*C*(CH_3)$_3$), and −5.8 and −6.4 (2 × Si*C*H$_3$). Finally, starting material *tert-butyl (3Z,4S)-N-tert-butyldimethylsilyl-3-ethylideneazetidin-2-one-4-carboxylate* **28** was eluted as an oil (225 mg, 15%).

tert-Butyl (3*R*,4*S*)- and (3*S*,4*S*)-3-vinylazetidin-2-one-4-carboxylate (33) and (34)

tert-Butyl (3*RS*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-vinylazetidin-2-one-4-carboxylate **29** + **30** (1.38 g, 4.437 mmol) was dissolved in methanol (40 ml) and 1 M aqueous HCl (22.2 ml, 22.2 mmol) and cooled to 0 °C. The resulting mixture was stirred at 0 °C for 3 h and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate and water and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2×) and the combined organic layers were washed with water and brine and dried ($MgSO_4$). Removal of solvents *in vacuo* gave a white solid (890 mg). This crude compound was found to be clean (^{1}H-NMR) but was unstable and extensively decomposed on silica gel. It was therefore used immediately in the next step. Attempted column chromatography on silica gel gave clean samples of the two isomers although significant decomposition occurred: *tert-butyl (3R,4S)-3-vinylazetidin-2-one-4-carboxylate* **33** as a white solid; δ_H (300 MHz, C^2HCl_3) 6.38 (1H, br s, exch. with ^2H_2O, NH), 5.92 (1H, ddd, $J_{5,6Z}$ 17.3, $J_{5,6E}$ 10.4, $J_{5,3}$ 7.2, H-5), 5.35 (1H, dt, $J_{6Z,5}$ 17.3, $J_{6Z,6E} = J_{6Z,3}$ 1.2, H-6*Z*), 5.27 (1H, dt, $J_{6E,5}$ 10.4, $J_{6E,6Z} = J_{6E,3}$ 1.2, H-6*E*), 3.90 (1H, d, $J_{4,3}$ 2.6, H-4), 3.79 (1H, ddt, $J_{3,5}$ 7.2, $J_{3,4}$ 2.6, $J_{3,6Z} = J_{3,6E}$ 1.2, H-3) and 1.45 (9H, s, C(C*H*$_3$)$_3$); δ_C (75.5 MHz, C^2HCl_3) 169.7 and 167.4 (ester and lactam), 130.1 (C-5), 119.8 (C-6), 82.7 (O*C*(CH_3)$_3$), 60.2 (C-4), 54.5 (C-3) and 27.9 (OC(*C*H$_3$)$_3$); and *tert-butyl (3S,4S)-3-vinylazetidin-2-one-4-carboxylate* **34** as a white solid; δ_H (300 MHz, C^2HCl_3) 6.35 (1H, br s, exch. with ^2H_2O, NH), 5.71 (1H, ddd, $J_{5,6Z}$ 17.2, $J_{5,6E}$ 10.2, $J_{5,3}$ 8.2, H-5), 5.38 (1H, dt, $J_{6Z,5}$ 17.2 and $J_{6Z,6E} = J_{6Z,3}$ 1.2, H-6*Z*), 5.28 (1H, dt, $J_{6E,5}$ 10.2 and $J_{6E,6Z} = J_{6E,3}$ 1.2, H-6*E*), 4.21 (1H, d, $J_{4,3}$ 5.9, H-4), 4.11 (1H, ddt, $J_{3,5}$ 8.2, $J_{3,4}$ 5.9, $J_{3,6Z} = J_{3,6E}$ 1.2, H-3) and 1.43 (9H, s, C(C*H*$_3$)$_3$); δ_C (75.5 MHz, C^2HCl_3) 168.8 and 167.5 (ester and lactam), 128.0 (C-5), 121.7 (C-6), 82.8 (O*C*(CH_3)$_3$), 58.4 (C-3), 53.2 (C-4) and 28.1 (OC(*C*H$_3$)$_3$).

tert-Butyl (3*R*,4*S*)-1,3-di-*tert*-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate (38)

A mixture of *tert*-butyl (3*R*,4*S*)- and (3*S*,4*S*)-3-vinylazetidin-2-one-4-carboxylate **33** + **34** (512 mg, 2.60 mmol), di-*tert*-butyl dicarbonate (1.25 g, 5.71 mmol) and DMAP (82 mg, 0.675 mmol) were dissolved in acetonitrile (37 ml) and stirred for 16 h at room temperature. The reaction mixture was poured into a

mixture of ethyl acetate and 1 M aqueous $KHSO_4$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to give an orange oil that was purified by column chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (85 : 15 to 80 : 20) to afford *tert-butyl (3R,4S)-1,3-di-tert-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate* **38** as a colourless oil (452 mg, 45%); $[\alpha]_D^{21}$ +37.6 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 415.2441 ($[M + NH_4]^+$). [$C_{20}H_{31}NO_7 + NH_4$] requires 415.2444; *m/z* [+ ve FAB (3-NBA)] 398 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1825 (β-lactam) and 1733 (ester); δ_H (300 MHz, C^2HCl_3) 5.78 (1H, dd, $J_{5,6Z}$ 17.5, $J_{5,6E}$ 10.6, H-5), 5.56 (1H, dd, $J_{6Z,5}$ 17.5, $J_{6Z,6E}$ 0.6, H-6*Z*), 5.39 (1H, dd, $J_{6E,5}$ 10.6, $J_{6E,6Z}$ 0.6, H-6*E*), 4.63 (1H, s, H-4), 1.50 (9H, s, $NCO_2C(CH_3)_3$), 1.47 (9H, s, 4-$CO_2C(CH_3)_3$) and 1.43 (9H, s, 3-$CO_2C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 165.25, 165.15 and 160.0 (ester and lactam), 146.8 (urethane), 126.4 (C-5), 121.6 (C-6), 84.05, 83.98 and 83.2 (3 × $OC(CH_3)_3$), 69.0 (C-3), 59.7 (C-4) and 28.0, 27.9 and 27.8 (3 × $OC(CH_3)_3$). Irradiation of the *tert*-butyl signal at δ 1.50 gave a 0.9% enhancement in H-4 at δ 4.63 and irradiation of the *tert*-butyl signal at δ 1.47 gave a 1.4% enhancement in H-4, a 0.3% enhancement in H-6E at δ5.39, a 0.5% enhancement in H-6Z at δ5.56 and a 0.8% enhancement in H-5 at δ5.78. Irradiation of the *tert*-butyl signal at δ1.43 gave a 1.3% enhancement in H-4, a 1.2% enhancement in H-6E, a 0.6% enhancement in H-6Z and a 2.9% enhancement in H-5. These results allowed us to assign chemical shifts to the three different $CO_2{}^t$Bu groups as described above and also confirmed the *trans* relationship between the 3- and 4-$CO_2{}^t$Bu groups as this is the only possible conformation that can account for the NOE enhancements observed for all three vinylic protons when 4-$CO_2{}^t$Bu protons (δ1.47) are irradiated.

tert-Butyl (3*Z*,4*S*)- and (3*E*,4*S*)-*N*-*tert*-butoxycarbonyl-3-ethylideneazetidin-2-one-4-carboxylate (39) and (40)

A mixture of *tert*-butyl (3*R*,4*S*)- and (3*S*,4*S*)-3-vinylazetidin-2-one-4-carboxylate **33** and **34** (489 mg, 2.48 mmol), di-*tert*-butyl dicarbonate (437 mg, 2.0 mmol) and DMAP (30 mg, 0.248 mmol) were dissolved in acetonitrile (6 ml) and stirred for 20 h at room temperature. Removal of the solvent *in vacuo* gave a dark orange residue, which was purified by chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (8 : 2 to 7 : 3) as eluent to afford *tert-butyl (3Z,4S)-N-tert-butoxycarbonyl-3-ethylideneazetidin-2-one-4-carboxylate* **39** as a white solid (37 mg, 5%). An analytical sample was prepared by recrystallisation from petroleum ether and diethyl ether; mp 89 °C (decomp.); $[\alpha]_D^{23}$ −39.5 (*c* 1, $CHCl_3$) (Found: C, 60.6; H, 7.8; 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 ($[M + H]^+$), 320 ($[M + Na]^+$) and 617 ($[2M + Na]^+$); ν_{max} (KBr)/cm^{-1} 1789 (β-lactam), 1745 (ester) and 1722 (urethane); δ_H (300 MHz, C^2HCl_3) 6.03 (1H, qd, $J_{5,5\text{-Me}}$ 7.3, $J_{5,4}$ 1.3, H-5), 4.59 (1H, dq, $J_{4,5}$ 1.3, $J_{4,5\text{-Me}}$ 1.2, H-4), 2.06 (3H, dd, $J_{5\text{-Me},5}$ 7.3, $J_{5\text{-Me},4}$ 1.2, 5-Me) and 1.49 and 1.44 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 166.6 and 158.9 (lactam), 147.0 (urethane), 135.0 (C-3), 132.6 (C-5), 83.2 and 82.7 (2 × $OC(CH_3)_3$), 58.8 (C-4), 28.0 and 27.9 (2 × $OC(CH_3)_3$) and 15.3 (5-CH_3). Selective irradiation of the proton at δ 6.03 (H-5) resulted in enhancements in the signals at δ 4.59 (H-4, 3.0%) and δ 2.06 (5-Me, 1.7%). Selective irradiation of the signal at δ 2.06 (5-Me) resulted in enhancements in the signals at δ 6.03 (H-5, 2.6%) and δ 4.59 (H-4, 0.4%). *tert-Butyl (3E,4S)-N-tert-butoxycarbonyl-3-ethylideneazetidin-2-one-4-carboxylate* **40** was eluted next as a white solid (183 mg, 25%). An analytical sample was prepared by recrystallisation from petroleum ether and diethyl ether; mp 62–65 °C; $[\alpha]_D^{24}$ −18.0 (*c* 1, $CHCl_3$) (Found: C, 60.7; 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 ($[M + H]^+$), 320 ($[M + Na]^+$) and 617 ($[2M + Na]^+$); ν_{max} (KBr)/cm^{-1} 1811 (β-lactam), 1740 (ester) and 1728 (urethane); δ_H (300 MHz, C^2HCl_3) 6.51 (1H, qd, $J_{5,5\text{-Me}}$ 7.3, $J_{5,4}$ 1.8, H-5), 4.73 (1H, d, $J_{4,5}$ 1.8, H-4), 1.86 (3H, d, $J_{5\text{-Me},5}$ 7.3, 5-Me) and 1.49 and 1.46 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 167.0 (lactam and ester), 136.0 (C-3), 130.1 (C-5), 83.3 and 82.9 (2 × $OC(CH_3)_3$), 59.1 (C-4), 27.95 and 27.85 (2 × $OC(CH_3)_3$) and 14.1 (5-CH_3). Selective irradiation of the signal at δ 6.51 (H-5) resulted in a 1.4% enhancement in the signal at δ 1.86 for 5-Me and no enhancement at δ 4.73 for H-4. Selective irradiation of the signal at δ 1.86 (5-Me) resulted in a 2.5% enhancement in the signal at δ 4.73 (H-4). *tert-butyl (3S,4S)-1, 3-di-tert-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate* **35** also eluted as an oil (48 mg, 5%) with identical spectroscopic properties to the compound prepared above.

tert-Butyl (3*R*,4*S*)- and (3*S*,4*S*)-*N*-*tert*-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate (35) and (36)

A mixture of *tert*-butyl (3*R*,4*S*)- and (3*S*,4*S*)-3-vinylazetidin-2-one-4-carboxylate **33** and **34** (657 mg, 3.34 mmol), di-*tert*-butyl dicarbonate (985 mg, 4.51 mmol) and DMAP (81 mg, 0.66 mmol) was dissolved in acetonitrile (33 ml) and *tert*-butanol (6.4 ml) and stirred for 15 min at room temperature. The reaction mixture was immediately poured into a mixture of ethyl acetate and 1 M aqueous $KHSO_4$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to give a light orange oil that was purified by column chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (85 : 15 to 80 : 20) to afford *tert-butyl (3R,4S)-N-tert-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate* **35** as a colourless oil (446 mg, 45%); $[\alpha]_D^{26}$ + 8.8 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 315.1922 ($[M + NH_4]^+$). [$C_{15}H_{23}NO_5 + NH_4$] requires 315.1920; *m/z* [+ ve FAB (3-NBA)] 298 ($[M + H]^+$), 320 ($[M + Na]^+$), 595 ($[2M + H]^+$) and 617 ($[2M + Na]^+$); ν_{max} (film)/cm^{-1} 1821 (β-lactam) and 1733 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 5.87 (1H, ddd, $J_{5,6Z}$ 17.1, $J_{5,6E}$ 10.3, $J_{5,3}$ 7.0, H-5), 5.39 (1H, ddd, $J_{6Z,5}$ 17.1, $J_{6Z,3}$ 1.5, $J_{6Z,6E}$ 0.9, H-6*Z*), 5.33 (1H, ddd, $J_{6E,5}$ 10.3, $J_{6E,3}$ 1.4, $J_{6E,6Z}$ 0.9, H-6*E*), 4.09 (1H, d, $J_{4,3}$ 3.2, H-4), 3.73 (1H, dddd, $J_{3,5}$ 7.0, $J_{3,4}$ 3.2, $J_{3,6Z}$ 1.5, $J_{3,6E}$ 1.4, H-3) and 1.49 and 1.47 (2 × 9H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 167.7 and 163.5 (ester and lactam), 146.9 (urethane), 128.6 (C-5), 120.7 (C-6), 83.9 and 82.9 (2 × $C(CH_3)_3$), 57.7 (C-3), 56.7 (C-4) and 28.0 and 27.9 ($C(CH_3)_3$). *tert-Butyl (3S,4S)-N-tert-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate* **36** eluted next from the column as a white solid (218 mg, 22%). An analytical sample was prepared by recrystallisation from petroleum ether and diethyl ether; mp 97–99 °C; $[\alpha]_D^{23}$ −35.8 (*c* 1, $CHCl_3$) (Found: C, 60.6; H, 8.0; 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} (KBr)/cm^{-1} 1812 (β-lactam), 1744 (ester) and 1730 (urethane); δ_H (300 MHz, C^2HCl_3) 5.69 (1H, ddd, $J_{5,6Z}$ 17.1, $J_{5,6E}$ 10.3, $J_{5,3}$ 7.2, H-5), 5.43 (1H, dt, $J_{6Z,5}$ 17.1, $J_{6Z,3}$ = $J_{6Z,6E}$ 1.2, H-6*Z*), 5.33 (1H, dt, $J_{6E,5}$ 10.3, $J_{6E,3}$ = $J_{6E,6Z}$ 1.2, H-6*E*), 4.41 (1H, d, $J_{4,3}$ 7.1, H-4), 4.06 (1H, tt, $J_{3,5}$ = $J_{3,4}$ 7.1, $J_{3,6Z}$ = $J_{3,6E}$ 1.2, H-3) and 1.49 and 1.44 (2 × 9H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 166.3 and 164.1 (ester and lactam), 146.9 (urethane), 126.1 (C-5), 122.8 (C-6), 83.7 and 83.0 (2 × $C(CH_3)_3$), 55.6 (C-3 and C-4) and 28.1 and 27.9 ($OC(CH_3)_3$).

tert-Butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate (37)

A mixture of *tert*-butyl (3*R*,4*S*)- and (3*S*,4*S*)-*N*-*tert*-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate **35** + **36** (275 mg, 0.926 mmol) was dissolved in dichloromethane (5 ml) and cooled to −78 °C. Argon was passed through the solution for 10 min followed by ozone. After approximately 20 min, the solution had turned pale blue and ozone was replaced by argon.

After passing argon through the solution for 10 min, dimethyl sulfide (1.4 ml, 19.1 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 3 h. Solvents were removed *in vacuo* to afford *tert-butyl (3RS,4S)-N-tert-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate* **37** as a colourless oil (280 mg). This crude product was used in the next step without further purification due to its instability; δ_H (300 MHz, C^2HCl_3) 9.66 (1H, d, $J_{CHO,3}$ 0.9, CHO), 4.61 (1H, d, $J_{4,3}$ 3.0, H-4), 4.15 (1H, dd, $J_{3,4}$ 3.0, $J_{3,CHO}$ 0.9, H-3) and 1.42 and 1.40 (18H, 2 × s, 2 × $CO_2C(CH_3)_3$).

tert-Butyl (3*S*,4*S*)-1,3-di-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate (41)

tert-Butyl (3*R*,4*S*)-1,3-di-*tert*-butoxycarbonyl-3-vinylazetidin-2-one-4-carboxylate **38** (77 mg, 0.194 mmol) was dissolved in dichloromethane (2 ml) and cooled to −78 °C. Argon was passed through the solution for 10 min followed by ozone. After approximately 20 min the solution had turned pale blue and ozone was replaced by argon. After passing argon through the solution for 10 min, dimethyl sulfide (0.14 ml, 1.94 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 3 h. Solvents were removed *in vacuo* to afford *tert-butyl (3S,4S)-1,3-di-tert-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate* **41** as a colourless oil (80 mg). This crude product was used without further purification due to its instability; δ_H (300 MHz, C^2HCl_3) 9.65 (1H, s, CHO), 4.72 (1H, s, H-4) and 1.51, 1.49 and 1.48 (27H, 3 × s, 3 × $C(CH_3)_3$).

Di-*tert*-butyl (2*S*,3*RS*)-*N*-*tert*-butoxycarbonyl-3-hydrazinocarbonylaspartate (44)

Hydrazine monohydrate (13 µl, 0.27 mmol) was added to a solution of *tert*-butyl (3*S*,4*S*)-1,3-di-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **41** (70 mg, 0.175 mmol) in methanol (2 ml) and the reaction was stirred for 16 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (1 : 1) to afford *di-tert-butyl (2S,3RS)-N-tert-butoxycarbonyl-3-hydrazinocarbonylaspartate* **44** as a colourless oil (35 mg, 49%); *m/z* (ES) Found: 404.2393 ([M + H]$^+$). [$C_{18}H_{33}N_3O_7$ + H] requires 404.2397; *m/z* [+ ve FAB (3-NBA)] 404 ([M + H]$^+$) and 426 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 3336 (br, NH) and 1723 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3, 2 epimers with 2 rotamers each) 8.31 (0.4H, s, 4-N*H*NH_2, exch. with ^2H_2O, *first epimer*), 7.96 (0.6H, s, 4-N*H*NH_2, exch. with ^2H_2O, *second epimer*), 5.79 (0.3H, d, $J_{NH,2}$ 9.5, 2-NH, exch. with ^2H_2O, *first epimer, A-rotamer*), 5.68 (0.45H, d, $J_{NH,2}$ 9.8, 2-NH, exch. with ^2H_2O, *second epimer, A-rotamer*), 5.47 (0.15H, br s, 2-NH, exch. with ^2H_2O, *second epimer*, *B-rotamer*), 5.43 (0.1H, br s, 2-NH, exch. with ^2H_2O, *first epimer*, *B-rotamer*), 4.90 (0.6H, dd, $J_{2,NH}$ 9.8, $J_{2,3}$ 4.2, H-2, *second epimer*), 4.88 (0.4H, dd, $J_{2,NH}$ 9.5, $J_{2,3}$ 3.4, H-2, *first epimer*), 4.66 (0.1H, d, $J_{3,2}$ 4.3, H-3, *first epimer, B rotamer*), 3.95 (2H, br s, exch. with ^2H_2O, NHNH_2), 3.92 (0.6H, d, $J_{3,2}$ 4.2, H-3, *second epimer, both rotamers*), 3.67 (0.3H, d, $J_{3,2}$ 3.4, H-3, *first epimer, A rotamer*) and 1.48, 1.47, 1.45, 1.44 and 1.42 (27H, 5 × s, 3 × $C(CH_3)_3$, *both epimers*); δ_C (75.5 MHz, C^2HCl_3, 2 epimers) 169.4, 169.1, 167.9, 167.8 and 167.6 (ester and hydrazide C=O, *2 epimers*), 155.7 and 155.6 (urethane, *2 epimers*), 83.5, 82.8, 82.5, 80.1 and 79.7 (3 × $C(CH_3)_3$, *2 epimers*), 53.7 (C-2, *major epimer*), 53.6 (C-2, *minor epimer*), 53.1 (C-3, *minor epimer*), 52.7 (C-3, *major epimer*) and 28.2, 27.87, 27.84, 27.79 and 27.76 (3 × $C(CH_3)_3$, *2 epimers*). Selective irradiation at δ 3.67 (H-3, minor epimer, major rotamer) gave no saturation transfer to the proton at δ 3.92 (H-3, major epimer) either at 25 °C and 50 °C. Selective irradiation of the proton at δ 4.66 (H-3, minor epimer, minor rotamer) resulted in saturation transfer to the proton at δ 3.67 (H-3, minor epimer, major rotamer). Selective irradiation of the proton at δ 5.79 (2-NH, minor epimer, major rotamer) resulted in saturation transfer to the proton at δ 5.43 (2-NH, minor epimer, minor rotamer) and selective irradiation of the proton at δ 5.68 (2-NH, major epimer, major rotamer) resulted in saturation transfer to the proton at δ 5.47 (2-NH, major epimer, minor rotamer). When the ^{1}H-NMR spectrum was recorded at 50 °C we observed broadening of all the peaks corresponding to NH protons and also broadening of the peaks at δ 4.66 and δ 3.92 as a result of faster proton exchange between rotamers.

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(3-hydroxy-2*H*-pyrazol-4-yl)-glycinate (45)

Hydrazine monohydrate (39 µl, 0.803 mmol) was added to a solution of freshly made *tert*-butyl (3*RS*, 4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (200 mg, 0.669 mmol) in methanol (6 ml) and the reaction was stirred for 11 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using ethyl acetate as eluent to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(3-hydroxy-2H-pyrazol-4-yl)-glycinate* **45** as a white solid (157 mg, 75%). An analytical sample was prepared by recrystallisation from ethyl acetate and petroleum ether; mp 181 °C (decomp.); $[\alpha]_D^{23}$ + 44.2 (*c* 1, MeOH); (Found: C, 53.7; H, 7.4; N, 13.3; $C_{14}H_{23}N_3O_5$ requires C, 53.7; H, 7.4; N, 13.4%); *m/z* [+ ve FAB (3-NBA)] 314 ([M + H]$^+$); ν_{max} (KBr)/cm^{-1} 3436 (br, NH), 1744 (ester) and 1697 (urethane); λ_{max} (MeOH)/nm 222 (ε 5600); λ_{max} (MeOH–HCl)/nm 227 (ε 6500); λ_{max} (MeOH–NaOH)/nm 236 (ε 6800) (reversible); δ_H (300 MHz, C^2HCl_3) 9.20 (1H, br s, 2-NH), 7.23 (1H, s, H-5), 5.80 (1H, d, $J_{NH,6}$ 7.6, 6-NH), 5.07 (1H, d, $J_{6,NH}$ 7.6, H-6) and 1.40 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 170.1 (ester), 159.4 (C-3), 156.1 (urethane), 129.2 (C-5), 101.8 (C-4), 82.7 and 80.9 ($C(CH_3)_3$), 48.9 (C-6) and 28.3 and 27.9 ($C(CH_3)_3$).

Hydrochloride of (2*S*)-2-(3-hydroxy-2*H*-pyrazol-4-yl)glycine (46)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(3-hydroxy-2*H*-pyrazol-4-yl)glycinate **45** (25 mg, 0.08 mmol) was stirred in 6 M aqueous HCl (1 ml) for 45 min at room temperature. The solvents were removed by heating gently *in vacuo* to give a glassy solid that was recrystallised from methanol and diethyl ether to afford the hydrochloride of *(2S)-2-(3-hydroxy-2H-pyrazol-4-yl)glycine* **46** as a white solid (15 mg, 97%); mp > 250 °C; $[\alpha]_D^{26}$ + 56.3 (*c* 0.71, H_2O); *m/z* [+ ve FAB (3-NBA)] 158 ([MH]$^+$); ν_{max} (KBr)/cm^{-1} 3423 (br, NH), 2700 (br, COOH), 1739 (C=O); λ_{max} (MeOH)/nm 245 (ε 2700); δ_H (300 MHz, ^2H_2O) 7.57 (1H, s, H-5) and 4.88 (1H, s, H-6); δ_C (75.5 MHz, ^2H_2O) 170.8 (carboxylic acid), 159.9 (C-3), 134.0 (C-5), 97.0 (C-4) and 47.3 (C-6).

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(2-methylpyrimidin-4-one-5-yl)glycinate (47)

Acetamidine hydrochloride (84 mg, 0.89 mmol) and potassium carbonate (123 mg, 0.89 mmol) were added to a solution of freshly made *tert*-butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (66 mg, 0.22 mmol) in methanol (2 ml) and the mixture was stirred for 24 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using ethyl acetate as eluent to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(2-methylpyrimidin-4-one-5-yl)glycinate* **47** as a white solid (46 mg, 61%). An analytical sample was prepared by recrystallisation from petroleum ether and ethyl acetate; mp 178 °C (decomp.); $[\alpha]_D^{23}$ + 138.7 (*c* 0.6, $CHCl_3$) (Found: C, 56.0; H, 7.4; N, 12.0; $C_{16}H_{25}N_3O_5$ requires C, 56.6; H, 7.4; N, 12.4%); *m/z* (ES) Found: 340.1872 ([M + H]$^+$). [$C_{16}H_{25}N_3O_5$ + H] requires 340.1872; *m/z* [+ ve FAB (3-NBA)] 340 ([M + H]$^+$), 362 ([M + Na]$^+$) and 679 ([2M + H]$^+$); ν_{max} (KBr)/cm^{-1} 3437 (br, NH), 1748 and 1736 (ester), and 1704 (urethane);

λ_{max} (MeOH)/nm 223 and 276 (ε 3000 and 2600); λ_{max} (MeOH–HCl)/nm 228 and 263 (ε 3300 and 2300); λ_{max} (MeOH–NaOH)/nm 233 and 276 (ε 3700 and 2300) (reversible); δ_H (300 MHz, C^2HCl_3) 13.10 (1H, br s, exch. ^2H_2O, 3-NH), 8.01 (1H, s, H-6), 5.82 (1H, d, $J_{NH,7}$ 8.1, 7-NH), 5.06 (1H, d, $J_{7,NH}$ 8.1, H-7), 2.43 (3H, s, 2-Me) and 1.41 and 1.40 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 168.8 (ester), 164.0 (C-4), 158.9 (C-2), 155.1 (urethane), 154.6 (C-6), 122.3 (C-5), 82.5 and 80.0 ($C(CH_3)_3$), 52.8 (C-7), 28.3 and 27.8 ($C(CH_3)_3$) and 21.5 (2-Me).

Hydrochloride of (2*S*)-2-(2-methylpyrimidin-4-on-5-yl)glycine (48)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(2-methylpyrimidin-4-on-5-yl)glycinate **47** (16 mg, 0.047 mmol) was stirred in 6 M aqueous HCl (1 ml) for 45 min at room temperature. The solvents were removed by heating gently *in vacuo* to give a glassy solid that was recrystallised from methanol and diethyl ether to afford the hydrochloride of *(2S)-2-(2-methylpyrimidin-4-on-5-yl)glycine* **48** as a white solid (10 mg, 97%); mp > 250 °C; $[\alpha]_D^{32}$ + 42.2 (*c* 0.45, H_2O); *m/z* (ES) Found: 184.0720 ($[MH]^+$). [$C_7H_9N_3O_3$ + H] requires 184.0722; *m/z* [+ ve FAB (3-NBA)] 184 ($[MH]^+$) and 367 ($[2M + H]^+$); ν_{max} (KBr)/cm^{-1} 3413 (br, NH), 2722 (COOH), 1701 and 1659 (C=O); λ_{max} (MeOH)/nm 222 and 278 (ε 6500 and 5400); λ_{max} (MeOH–HCl)/nm 223 and 269 (ε 6900 and 4500); λ_{max} (MeOH–NaOH)/nm 234 and 274 (ε 8300 and 5300) (reversible); δ_H (300 MHz, ^2H_2O) 8.16 (1H, s, H-6), 4.97 (1H, s, H-7) and 2.59 (3H, s, 2-Me); δ_C (75.5 MHz, ^2H_2O) 169.3 (CO_2H), 164.6 (C-4), 161.6 (C-2), 145.8 (C-6), 118.7 (C-5), 51.4 (C-7) and 29.9 (2-Me).

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(pyrido[1,2-*a*]-pyrimidin-4-on-3-yl)glycinate (49)

2-Aminopyridine (132 mg, 1.40 mmol) was added to a solution of freshly made *tert*-butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (100 mg, 0.334 mmol) in dioxane (2.5 ml) and the reaction was stirred for 20 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (3 : 2) as eluent to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(pyrido[1, 2-a]pyrimidin-4-on-3-yl)glycinate* **49** as a white solid (50 mg, 38%); mp 185–187 °C; $[\alpha]_D^{23}$ + 140.7 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 376.1867 ($[M + H]^+$). [$C_{19}H_{25}N_3O_5$ + H] requires 376.1872; *m/z* [+ ve FAB (3-NBA)] 376 ($[M + H]^+$), 398 ($[M + Na]^+$), 751 ($[2M + H]^+$) and 773 ($[2M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3415 (br, NH), 1742 and 1690 (C=O); λ_{max} (MeOH)/nm 242 and 346 (ε11200 and 12600); δ_H (300 MHz, C^2HCl_3) 9.00 (1H, ddd, $J_{6,7}$ 7.2, $J_{6,8}$ 1.5, $J_{6,9}$ 0.8, H-6), 8.39 (1H, s, H-2), 7.71 (1H, ddd, $J_{8,9}$ 9.0, $J_{8,7}$ 6.6, $J_{8,6}$ 1.5, H-8), 7.67 (1H, ddd, $J_{9,8}$ 9.0, $J_{9,7}$ 1.7, $J_{9,6}$ 0.8, H-9), 7.15 (1H, ddd, $J_{7,6}$ 7.2, $J_{7,8}$ 6.6, $J_{7,9}$ 1.7, H-7), 6.04 (1H, d, $J_{NH,11}$ 8.5, NH), 5.23 (1H, d, $J_{11,NH}$ 8.5, H-11) and 1.39 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 169.1 (ester), 156.8, 155.3 and 151.0 (urethane, C-10 and C-4), 154.0 (C-2), 136.0 (C-8), 127.1 (C-6), 126.5 (C-9), 115.8 (C-7), 114.9 (C-3), 82.5 and 79.8 (2 × $C(CH_3)_3$), 54.0 (C-11) and 28.3 and 27.9 (2 × $C(CH_3)_3$).

Hydrochloride of (2*S*)-2-(pyrido[1,2-*a*]pyrimidin-4-on-3-yl)-glycine (50)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(pyrido[1,2-*a*]pyrimidin-4-on-3-yl)glycinate **49** (18 mg, 0.048 mmol) was stirred in 6 M aqueous HCl (1.2 ml) for 35 min at room temperature. The solvents were removed by heating gently *in vacuo* to give a solid that was recrystallised from methanol and diethyl ether to afford the hydrochloride of *(2S)-2-(pyrido[1,2-a]pyrimidin-4-one-3-yl)glycine* **50** as a white solid (12 mg, 98%); mp > 250 °C; $[\alpha]_D^{29}$ + 16.3 (*c* 1, H_2O); *m/z* (ES) Found: 220.0714 ($[M - Cl]^+$). [$C_{10}H_9N_3O_3$ + H] requires 220.0722; *m/z* [+ ve FAB (3-NBA)] 220 ($[MH]^+$) and 242 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3418 (br, NH), 2800 (br, COOH), 1728 and 1641 (C=O); λ_{max} (MeOH)/nm 241 and 347 (ε 4100 and 5230); δ_H (300 MHz, ^2H_2O) 9.27 (1H, d, $J_{6,7}$ 6.9, H-6), 8.66 (1H, s, H-2), 8.55 (1H, t, $J_{8,9}$ = $J_{8,7}$ 8.8, H-8), 8.09 (1H, d, $J_{9,8}$ 8.8, H-9), 7.87 (1H, t, $J_{7,6}$ = $J_{7,8}$ 6.9, H-7) and 5.26 (1H, s, H-11); δ_C (75.5 MHz, ^2H_2O) 170.0 (CO_2H), 156.6 and 148.2 (C-10 and C-4), 146.8 (C-2), 146.1 (C-8), 130.0 (C-6), 121.6 (C-9), 120.1 (C-7), 109.0 (C-3) and 52.6 (C-11).

1-*tert*-Butyl 4-methyl (2*S*,3*EZ*)-*N*-*tert*-butoxycarbonyl-3-(thiazol-2-ylaminomethylene)aspartate (54)

2-Aminothiazole (67 mg, 0.67 mmol) was added to a solution of freshly made *tert*-butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (50 mg, 0.168 mmol) in methanol (1 ml) and the reaction was stirred for 24 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a gradient of petroleum ether and ethyl acetate (4 : 1 to 3 : 2) as eluent to afford a mixture of *(2S,3EZ)-1-tert-butyl 4-methyl N-tert-butoxycarbonyl-3-(thiazol-2-yl-aminomethylene)aspartate* **54** as an oil (21 mg, 30%); *m/z* (ES) Found: 414.1697 ($[M + H]^+$). [$C_{18}H_{27}N_3O_6S$ + H] requires 414.1699; *m/z* [+ ve FAB (3-NBA)] 414 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3437 (br, NH), 1710 (br, C=O). By examining the ^{1}H-NMR spectra of two different fractions, each one enriched in one of the two geometric isomers, eluted from the column, we were able to assign the ^{1}H-NMR spectrum for each isomer; the geometry of the double bond was assigned by the chemical shift of H-5, which was deshielded by the electron withdrawing 3-CO_2Me group; δ_H (300 MHz, C^2HCl_3) *(E)-isomer*; 10.10 (1H, d, $J_{NH,5}$ 10.2, exch. ^2H_2O, 5-NH), 8.11 (1H, d, $J_{5,NH}$ 10.2, H-5), 7.29 and 6.74 (2H, 2 × d, $J_{9,10}$ 3.4, H-9 and H-10), 5.83 (1H, d, $J_{NH,2}$ 7.5, 2-NH), 4.96 (1H, d, $J_{2,NH}$ 7.5, H-2), 3.69 (3H, s, CO_2CH_3) and 1.43 and 1.42 (18H, 2 × s, 2 × $C(CH_3)_3$); *(Z)-isomer*; 10.49 (1H, d, $J_{NH,5}$ 11.7, exch. ^2H_2O, 5-NH), 7.70 (1H, d, $J_{5,NH}$ 11.7, H-5), 7.29 and 6.76 (2H, 2 × d, $J_{9,10}$ 3.8, H-9 and H-10), 5.49 (1H, d, $J_{NH,2}$ 8.3, 2-NH), 4.79 (1H, d, $J_{2,NH}$ 8.3, H-2), 3.73 (3H, s, CO_2CH_3) and 1.42 and 1.40 (18H, 2 × s, 2 × $C(CH_3)_3$); *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(thiazolo-[3,2-a]pyrimidin-5-on-6-yl)glycinate* **51** eluted next as a white solid (11 mg, 16%). This compound had identical spectroscopic properties to the sample obtained below.

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(thiazolo[3,2-*a*]-pyrimidin-5-on-6-yl)glycinate (51)

2-Aminothiazole (84 mg, 0.84 mmol) was added to a solution of freshly made *tert*-butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (50 mg, 0.167 mmol) in dioxane (2 ml) and the reaction was stirred for 48 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (3 : 2) as eluent to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(thiazolo[3,2-a]pyrimidin-5-on-6-yl)glycinate* **51** as a white solid (20 mg, 32%); mp 191–194 °C; $[\alpha]_D^{26}$ + 92.4 (*c* 1, $CHCl_3$); *m/z* (ES) Found: 382.1426 ($[M + H]^+$). [$C_{17}H_{23}N_3O_5S$ + H] requires 382.1436; *m/z* [+ ve FAB (3-NBA)] 382 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 3425 (NH), 1734 (ester), 1710 (urethane) and 1656 (conjugated lactam); λ_{max} (MeOH)/nm 226, 255, 263, 324 and 336 (ε7500, 5800, 6000, 15800 and 14200); δ_H (300 MHz, C^2HCl_3) 8.11 (1H, s, H-7), 7.96 (1H, d, $J_{3,2}$ 4.9, H-3), 7.03 (1H, d, $J_{2,3}$ 4.9, H-2), 5.96 (1H, d, $J_{NH,7}$ 8.7, NH), 5.17 (1H, d, $J_{7,NH}$ 8.7, H-7) and 1.41 and 1.40 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 169.0 (C=O), 155.2 (urethane), 152.6 (C-7), 121.8 (C-3), 116.2 (C-6), 112.2 (C-2), 82.7 and 79.9 (2 × $C(CH_3)_3$), 53.4 (C-10) and 28.3 and 27.9 (2 × $C(CH_3)_3$). The signal for C-9 was not strong enough to be observed.

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(benzo[4,5]imidazo-[1,2-*a*]pyrimidin-4-on-3-yl)glycinate (52)

2-Aminobenzimidazole (160 mg, 1.20 mmol) was added to a solution of freshly made *tert*-butyl (3*RS*,4*S*)-*N*-*tert*-butoxycarbonyl-3-formylazetidin-2-one-4-carboxylate **37** (90 mg, 0.30 mmol) in dioxane (3 ml) and the reaction was stirred for 3 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (3 : 2) as eluent to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-(benzo[4,5]imidazo[1,2-a]pyrimidin-4-on-3-yl)glycinate* **52** as a white solid (87 mg, 70%). An analytical sample was prepared by recrystallisation from petroleum ether and diethyl ether; mp > 250 °C; $[a]_D^{20}$ + 155.3 (*c* 1, $CHCl_3$); *m*/*z* (ES) Found: 415.1973 ($[M + H]^+$). [$C_{21}H_{26}N_4O_5$ + H] requires 415.1981; *m*/*z* [+ ve FAB (3-NBA)] 415 ($[M + H]^+$) and 437 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3431 (NH), 1734 (ester), 1698 (urethane) and 1651 (conjugated lactam); λ_{max} (MeOH)/nm 234, 324 and 335 (ε 42000, 28000 and 3000); λ_{max} (MeOH–NaOH)/nm 242 and 345 (ε 45000 and 38000) (reversible); δ_H (300 MHz, C^2HCl_3) 8.48 (1H, s, H-2), 8.09 (1H, d, $J_{6,7}$ 7.6, H-6), 7.42 (1H, t, $J_{8,7} = J_{8,9}$ 7.6, H-8), 7.15–7.27 (2H, m, H-9 and H-7), 6.39 (1H, d, $J_{NH,14}$ 7.6, 14-NH), 5.49 (1H, d, $J_{14,NH}$ 7.6, H-14) and 1.46 and 1.40 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 169.4 (ester), 158.3 (C-4), 155.5 (urethane), 148.9 (C-2), 147.6 (C-13), 132.4 and 126.0 (C-11 and C-12), 126.7 (C-8), 122.6 (C-7), 116.2 (C-6), 112.5 (C-9), 111.9 (C-3), 82.4 and 79.9 ($C(CH_3)_3$), 53.5 (C-14), and 28.5 and 27.8 ($C(CH_3)_3$).

Hydrochloride of (2*S*)-2-(benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-on-3-yl)glycine (53)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonyl-2-(benzo[4,5]imidazo-[1,2-*a*]pyrimidin-4-on-3-yl)glycinate **52** (39 mg, 0.094 mmol) was stirred in 6 M aqueous HCl (1.5 ml) for 40 min at room temperature. The solvents were removed by heating gently *in vacuo* to give a solid that was crystallised from methanol and diethyl ether to afford the hydrochloride of *(2S)-2-(benzo-[4,5]imidazo[1,2-a]pyrimidin-4-on-3-yl)glycine* **53** as a white solid (26 mg, 94%); mp > 250 °C; $[a]_D^{28}$ + 79.2 (*c* 1, H_2O); *m*/*z* (ES) Found: 259.0834 ($[MH]^+$); [$C_{12}H_{10}N_4O_3$ + H] requires 259.0826; *m*/*z* [+ ve FAB (3-NBA)] 259 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 3112 (br, NH), 2822 (br, COOH), 1768, 1701 and 1654 (C=O); λ_{max} (MeOH)/nm 234, 263, 324 and 335 (ε 20100, 27400, 11600 and 11900); λ_{max} (MeOH–NaOH)/nm 246, 266 and 348 (ε 30700, 32400 and 9200) (reversible); δ_H (500 MHz, ^2H_2O) 8.24 (1H, s, H-2), 7.85 (1H, d, $J_{6,7}$ 8.2, H-6), 7.27 (1H, t, $J_{8,7} = J_{8,9}$ 8.4, H-8), 7.21 (1H, d, $J_{9,8}$ 8.4, H-9), 7.11 (1H, t, $J_{7,8} = J_{7,6}$ 8.2, H-7) and 5.27 (1H, s, H-14); δ_C (125.8 MHz, ^2H_2O) 171.0 (carboxylic acid), 159.6 (C-4), 154.0 (C-2), 148.5 (C-13), 130.2 (C-12), 127.7 (C-8), 125.0 (C-11), 123.8 (C-7), 115.8 (C-6), 112.1 (C-9), 106.7 (C-3) and 52.3 (C-14); Tertiary carbons were assigned by means of a ^{13}C–^1H correlation *via* multiple bonds experiment.

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-3-allylazetidin-2-one-4-carboxylate (56)

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butyldimethylsilyl-3-allylazetidin-2-one-4-carboxylate[13] (2.9 g, 8.923 mmol), di-*tert*-butyl dicarbonate (4.28 g, 19.63 mmol) and DMAP (283 mg, 2.32 mmol) were dissolved in acetonitrile (127 ml) and the solution was stirred for 24 h at room temperature. Removal of the solvent *in vacuo* gave a dark orange residue, which was purified by chromatography on silica gel, using a gradient of petroleum ether and diethyl ether (8 : 2 to 7 : 3) as eluent to afford *tert-butyl (3R,4S)-N-tert-butoxycarbonyl-3-allylazetidin-2-one-4-carboxylate* **56** as a white solid (2.64 g, 95%); $[a]_D^{20}$ −51.2 (*c* 1, $CHCl_3$) [lit.[13] $[a]_D^{20}$ −49.8 (*c* 0.5, $CHCl_3$)]; *m*/*z* [+ ve FAB (3-NBA)] 312 ($[M + H]^+$); δ_H (300 MHz, C^2HCl_3) 5.77 (1H, ddt, $J_{6,7Z}$ 17.0, $J_{6,7E}$ 10.2, $J_{6,5}$ 6.7, H-6), 5.17 (1H, ddd, $J_{7Z,6}$ 17.0, $J_{7E,7Z}$ 2.9, $J_{7Z,5}$ 1.4, H-7*Z*), 5.15 (1H, ddd, $J_{7E,6}$ 10.2, $J_{7Z,7E}$ 2.9, $J_{7E,5}$ 1.5, H-7*E*), 3.97 (1H, d, $J_{4,3}$ 3.0, H-4), 3.19 (1H, ddd, $J_{3,5A}$ 8.7, $J_{3,5B}$ 5.5, $J_{3,4}$ 3.0, H-3), 2.40–2.62 (1H, m, H-5) and 1.48 and 1.46 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 168.0 and 165.3 (lactam and ester), 147.0 (urethane), 132.6 (C-6), 118.5 (C-7), 83.7 and 82.7 ($C(CH_3)_3$), 56.0 (C-4), 54.2 (C-3), 31.8 (C-5) and 27.91 and 27.89 ($C(CH_3)_3$).

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-3-((3*RS*)-1,2,4-trioxolan-3-ylmethyl)azetidin-2-one-4-carboxylate (61)

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-3-allylazetidin-2-one-4-carboxylate **56** (180 mg, 0.58 mmol) was dissolved in dichloromethane (6 ml) and cooled at −78 °C. Argon was bubbled through the solution for 10 min followed by ozone. After approximately 20 min the solution had turned pale blue and ozone was replaced by argon. After bubbling argon for 10 min, dimethyl sulfide (47 μl, 0.64 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. Solvents were removed *in vacuo* to give an oily residue that was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (4 : 1) as eluent to afford *tert-butyl (3R,4S)-N-tert-butoxycarbonyl-3-((3RS)-1,2,4-trioxolan-3-ylmethyl)azetidin-2-one-4-carboxylate* **61** as a colourless oil (19 mg, 9%); *m*/*z* [+ ve FAB (3-NBA)] 382 ($[M + Na]^+$); ν_{max} (thin film)/cm^{-1} 1820 (β-lactam) and 1733 (urethane); δ_H (500 MHz, C^2HCl_3, 2 epimers) 5.42 (0.5H, t, $J_{6,5}$ 3.8, H-6, *first epimer*), 5.38 (0.5H, t, $J_{6,5}$ 4.2, H-6, *second epimer*), 5.20 (0.5H, d, $J_{7,6}$ 0.4, H-8A, *first epimer*), 5.14 (0.5H, s, H-8A, *second epimer*), 5.11 (0.5H, s, H-8B, *second epimer*), 5.06 (0.5H, s, H-8B, *first epimer*), 4.15 (0.5H, d, $J_{4,3}$ 3.0, H-4, *first epimer*), 4.08 (0.5H, d, $J_{4,3}$ 3.0, H-4, *second epimer*), 3.31–3.37 (1H, m, H-3), 2.28–2.37 (1H, m, H-5A) 2.08–2.17 (1H, m, H-5B), 1.51 (9H, s, $C(CH_3)_3$) and 1.50 and 1.49 (9H, 2 × s, $C(CH_3)_3$, *both epimers*); δ_C (75.5 MHz, C^2HCl_3) 168.2, 168.1 and 165.0 (lactam and ester, *both epimers*), 147.0 (urethane), 101.2 (C-6), 94.7 and 94.5 (C-8, *both epimers*), 84.4 and 83.3 ($C(CH_3)_3$), 57.7 (C-4), 50.0 (C-3), 30.8 and 30.4 (C-5, *both epimers*) and 28.34 and 28.29 ($C(CH_3)_3$). Selective irradiation of the proton at δ 5.06 (H-8B) resulted in a 16.1% enhancement in the signal for H-8A at δ 5.06 and a 1.0% enhancement in the signal for H-6 at δ 5.42. No enhancement was observed for the signals at δ 5.38, 5.14 and 5.11 and so these were assigned to belong to the other epimer. This assumption was further supported by appropriate decoupling experiments.

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-3-oxoethylazetidin-2-one-4-carboxylate (57)

tert-Butyl (3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-3-allylazetidin-2-one-4-carboxylate **56** (750 mg, 2.427 mmol) was dissolved in dichloromethane (25 ml) and cooled at −78 °C. Argon was bubbled into the solution for 10 min followed by ozone. After approximately 20 min the solution had turned pale blue and ozone was replaced by argon. After bubbling argon through the solution for 10 min, dimethyl sulfide (5.3 ml, 72.8 mmol) was added and the reaction was allowed to warm to room temperature and stirred for 3 days. Solvents were removed *in vacuo* to afford *tert-butyl (3R,4S)-N-tert-butoxycarbonyl-3-oxoethylazetidin-2-one-4-carboxylate* **57** as a colourless oil (801 mg). This crude product was used without further purification; *m*/*z* [+ ve FAB (3-NBA)] 314 ($[M + H]^+$) and 336 ($[M + Na]^+$); δ_H (300 MHz, C^2HCl_3) 9.76 (1H, s, C*H*O), 3.96 (1H, d, $J_{4,3}$ 2.9, H-4), 3.48–3.54 (1H, m, H-3), 3.07 (1H, dd, $J_{5A,5B}$ 19.2, $J_{5A,3}$ 4.2, H-5A), 2.89 (1H, dd, $J_{5B,5A}$ 19.2, $J_{5B,3}$ 9.2, H-5B) and 1.49 and 1.48 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 197.2 (*C*HO), 167.7 and 165.0 (lactam and ester), 147.4 (urethane), 83.9 and 82.9 ($OC(CH_3)_3$), 56.8 (C-4), 48.3 (C-3), 40.9 (C-5) and 27.9 and 27.8 ($C(CH_3)_3$).

tert-Butyl (2*S*)-*N*-_tert_-butoxycarbonyl-2-((4*R*)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycinate (59) and _tert_-butyl (2*S*)-*N*-_tert_-butoxycarbonyl-2-((3*R*,5*RS*)-1-amino-5-hydroxypyrrolidine-2-on-3-yl)glycinate (58)

Method A. Hydrazine monohydrate (62 μl, 1.278 mmol) was added to a solution of _tert_-butyl (3*R*,4*S*)-*N*-_tert_-butoxycarbonyl-3-oxoethylazetidin-2-one-4-carboxylate **57** (200 mg, 0.639 mmol) in methanol (3 ml) and the reaction was stirred for 24 h at room temperature. The solvents were removed *in vacuo* and the resulting oily residue was purified by chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate (4 : 1) followed by ethyl acetate as eluents, to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-((4R)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycinate* **59** as a white solid (35 mg, 17%). An analytical sample was prepared by recrystallisation from petroleum ether and ethyl acetate; mp 93–94 °C (α-form) and 126–128 °C (β-form); $[\alpha]_D^{20}$ −96.6 (*c* 0.61, $CHCl_3$) (Found: C, 55.3; H, 7.7; N, 12.6; $C_{15}H_{25}N_3O_5$ requires C, 55.0; H, 7.7; N, 12.8%); *m/z* [+ ve FAB (3-NBA)] 328 $([M + H])^+$ and 350 $([M + Na]^+)$; ν_{max} (KBr)/cm^{-1} 3304 (br, NH), 1747 (ester), 1711 (urethane) and 1671 and 1686 (secondary amide); λ_{max} (MeOH)/nm 242 (ε 5900); δ_H (300 MHz, C^2HCl_3) 8.47 (1H, s, 2-NH), 7.18 (1H, s, H-6), 5.37 (1H, d, $J_{7\text{-NH},7}$ 8.2, 7-NH), 4.30 (1H, dd, $J_{7,NH}$ 8.2, $J_{7,4}$ 2.4, H-7), 3.31 (1H, ddd, $J_{4,5B}$ 7.5, $J_{4,7}$ 2.4, H-4), 2.45–2.64 (2H, m, H-5A and H-5B) and 1.45 and 1.42 (18H, 2 × s, 2 × $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 169.3 and 167.4 (CO_2H and C-3), 156.7 (urethane), 145.5 (C-6), 82.5 and 80.1 ($C(CH_3)_3$), 53.1 (C-7), 38.9 (C-4), 28.2 and 27.8 (-$C(CH_3)_3$) and 26.8 (C-5). Recrystallisation from ethyl acetate and petroleum ether gave crystals of *tert-butyl (2S)-N-tert-butoxycarbonyl-2-((4R)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycinate* **59** that were suitable for single crystal X-ray structure determination.

Crystal data †. $C_{15}H_{25}N_3O_5$, M = 327.38, orthorhombic, a = 10.2189(3) Å, b = 15.3206(5) Å, c = 27.7208(6) Å, U = 4340.0(2) Å^3, T = 173 K, space group $P2_12_12_1$ (No. 19), Z = 8, D_{calc} 1.002, μ = 0.075 mm^{-1}, 5957 independent reflections (R_{int} = 0.051). The final R values were $R1$ = 0.066 (for 5028 reflections with $I > 2\sigma(I)$) and $wR2$ = 0.199 (for all reflections).

tert-Butyl (2S)-N-tert-butoxycarbonyl-2-((3R,5RS)-1-amino-5-hydroxypyrrolidine-2-on-3-yl)glycinate **58** eluted next from the column as a colourless oil (125 mg, 57%); *m/z* (ES) Found: 368.1795 $([M + Na]^+)$. $[C_{15}H_{27}N_3O_6 + Na]$ requires 368.1798; *m/z* [+ ve FAB (3-NBA)] 346 $([M + H]^+)$; ν_{max} (film)/cm^{-1} 3325 (br, NH and OH) and 1705 (br, C=O); δ_H (300 MHz, C^2HCl_3, 2 epimers) 5.54 (0.4H, br s, exch. with ^2H_2O, 6-NH, *first epimer*), 5.35 (0.6H, d, $J_{NH,6}$ 8.0, exch. with ^2H_2O, 6-NH, *second epimer*, 60%), 5.15 (0.6H, dd, $J_{5,4A}$ 5.0, $J_{5,4B}$ 2.5, H-5, *second epimer*), 5.10 (0.4H, dd, $J_{5,4A}$ 6.8, $J_{5,4B}$ 4.1, H-5, *first epimer*), 4.36 (1H, br d, $J_{6,NH}$ 8.0, H-6, *both epimers*), 3.80–4.30 (2H, br s, exch. with ^2H_2O, NNH_2, *both epimers*), 3.39 (0.6H, td, $J_{3,4A} = J_{3,4B}$ 8.8, $J_{3,6}$ 5.8, H-3, *second epimer*), 3.09 (0.4H, ddd, $J_{3,4A}$ 10.4, $J_{3,4B}$ 7.2, $J_{3,6}$ 3.8, H-3, *first epimer*), 2.50 (0.4H, ddd, $J_{4A,4B}$ 16.5, $J_{3,4A}$ 10.4, $J_{4A,5}$ 6.8, H-4A, *first epimer*), 2.04–2.12 (1H, m, H-4A and H-4B, *both epimers*), 1.78 (0.4H, ddd, $J_{4B.4A}$ 16.5, $J_{4B,3}$ 7.2, $J_{4B,5}$ 4.1, H-4B, *first epimer*), 1.46, 1.45 and 1.40 (18H, 3 × s, 2 × $C(CH_3)_3$, *both epimers*); δ_C (75.5 MHz, $(C^2H_3)_2SO$, 2 epimers) 170.4, 169.6 and 169.1 (ester and lactam, *both epimers*), 155.9 and 155.8 (urethane, *both epimers*), 82.4 and 81.6 (C-5, *both epimers*), 81.32, 81.26, 81.18 and 78.7 (2 × $C(CH_3)_3$, *both epimers*), 54.3 (C-6, *both epimers*), 41.7 and 41.1 (C-3, *both epimers*), 29.8 and 29.6 (C-4, *both epimers*), and 28.5, 27.97 and 27.92 (2 × $C(CH_3)_3$, *both epimers*).

Method B. A solution of _tert_-butyl (3*R*,4*S*)-*N*-_tert_-butoxycarbonyl-3-oxoethylazetidin-2-one-4-carboxylate **57** (300 mg, 0.958 mmol) in benzene was heated to reflux and hydrazine monohydrate (186 μl, 3.83 mmol) was added. After heating at reflux for 24 h the solvents were removed *in vacuo* and the resulting solid residue was purified by chromatography on silica gel, using a gradient of petroleum ether and ethyl acetate (4 : 1 to 3 : 2) to afford *tert-butyl (2S)-N-tert-butoxycarbonyl-2-((4R)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycinate* **59** as a white solid (203 mg, 65%) with identical properties to the sample obtained by Method A.

Trifluoroacetate of (2*S*)-2-((4*R*)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycine (60)

tert-Butyl (2*S*)-*N*-_tert_-butoxycarbonyl-2-((4*R*)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycinate **59** (41 mg, 0.125 mmol) was stirred in dichloromethane (1.2 ml) and trifluoroacetic acid (1.2 ml) at room temperature for 24 h. The solvents were removed *in vacuo* to give a glassy solid that was crystallised from methanol and diethyl ether to afford the trifluoroacetate of *(2S)-2-((4R)-2,3,4,5-tetrahydropyridazin-3-on-4-yl)glycine* **60** as a white solid (35 mg, 98%); mp > 250 °C; $[\alpha]_D^{20}$ −60.0 (*c* 0.57, H_2O); *m/z* (ES) Found: 172.0722 $([MH]^+)$. $[C_6H_9N_3O_3 + H]$ requires 172.0722; *m/z* [+ ve FAB (3-NBA)] 172 $([M + H])^+$ and 194 $([M + Na])^+$; ν_{max} (KBr)/cm^{-1} 3421 (br, NH and OH) and 1677 (br, C=O); λ_{max} (MeOH)/nm 241 (ε 5000); δ_H (300 MHz, $C^2H_3O^2H$) 7.25 (1H, dd, $J_{6,5A}$ 4.5, $J_{6,5B}$ 1.8, H-6), 4.33 (1H, d, $J_{7,4}$ 4.9, H-7), 3.28 (1H, ddd, $J_{4,5A}$ 7.4, $J_{4,7}$ 4.9, H-4), 2.77 (1H, ddd, $J_{5A,5B}$ 17.3, $J_{5A,4}$ 7.4, $J_{5A,6}$ 4.5, H-5A) and 2.55 (1H, ddd, $J_{5B,5A}$ 17.3, $J_{5B,6}$ 1.8, H-5B); δ_C (75.5 MHz, $C^2H_3O^2H$) 169.9 and 167.8 (CO_2H and C-3), 145.9 (C-6), 53.2 (C-7), 37.0 (C-4) and 25.6 (C-5).

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