An alternative to the use of δ-lactam urethanes in the "ring switch" approach to higher homologues of AMPA-type glutamate antagonists

Peter B. Hitchcock, Shazia Rahman (née Masood) and Douglas W. Young *

*Sussex Centre for Biomolecular Design and Drug Development, CPES, University of Sussex, Falmer, Brighton, UK BN1 9QJ*

In an alternative strategy to the use of δ-lactam urethanes for the preparation of homologues of AMPA-type glutamate antagonists, we have used 5-exomethylene derivatives of pyroglutamate esters. The homochiral pyrazole amino acid derivatives **18** and **19** have been prepared in this way. Although this synthesis yields products with a glycine residue separated from a heterocyclic ring by two carbon atoms, the substitution of the heterocyclic ring is different from that in compounds prepared from δ-lactam urethanes. The branched chain compounds **32** and **33** have also been prepared in this way but the second chiral centre is epimerised during the synthesis. An interesting reaction, giving the pyridone **27** from the imino ether **24** and *tert*-butyl acetoacetate, is also reported.

Introduction

Glutamic acid is an excitatory neurotransmitter in the central nervous system and its receptors have been shown to be divided into a variety of sub-types which are addressed separately by various analogues of the neurotransmitter. Thus, compounds such as ibotenic acid **1**, consisting of a heterocyclic ring system fused to the α-carbon atom of a glycine moiety, and the homologous compounds such as AMPA **2** with a heterocyclic ring fused to the β-carbon atom of an L-alanine moiety are biologically active at specific and different ionotropic and metabotropic glutamate receptor sub-types.[1] This has led to great interest in the synthesis of such compounds. The glutamate receptors have a variety of rôles in the central nervous system[2] and antagonists have been identified as potential drugs for a variety of illnesses, including persistent pain,[3] Alzheimer's disease,[4] epilepsy[5] and ischaemia.[6]
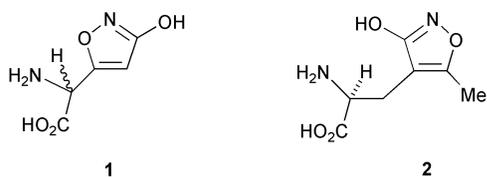

We have developed a versatile synthetic approach to homochiral compounds of this type, which is ideally suited to library synthesis.[7,8] In this method urethanes of aldehydes of activated

γ-lactams,[7a–f] β-lactams[7g,h] and δ-lactams[8] are used as starting materials and homochiral compounds with different numbers of atoms in the chain between the heterocyclic and amino acid moieties are obtained. Use of β-lactam urethanes gives the greatest variety of products in this approach.[7g,h] The approach has also been applied to the synthesis of potential antibacterial compounds.[9]

Reaction of δ-lactam urethane aldehydes **3** with bisnucleophiles yields a variety of homochiral compounds such as **4**, **5**, **6** and **7** where two carbon atoms separate the heterocyclic and amino acid moieties,[8] as shown in Scheme 1. It is known[10] that exocyclic enaminones of type **8** react with a variety of bisnucleophiles to yield substituted heterocyclic compounds such as **9**. This reaction involves 1,2-attack on the enaminone by the first nucleophilic group, followed by Michael attack by the second nucleophilic moiety as shown in Scheme 2. It therefore appeared that if this reaction could be applied to pyroglutamate derivatives such as compound **10**, then homochiral homologues of AMPA type compounds might be obtained. The method would not only be complementary to our "ring switching" reaction on δ-lactam urethanes[8] but it would give rise to compounds with heterocyclic moieties which were differently substituted from those prepared in our earlier synthesis.

Results and discussion

Our first task was to prepare a series of exocyclic enaminones of (2*S*)-pyroglutamate of type **10**. We therefore converted


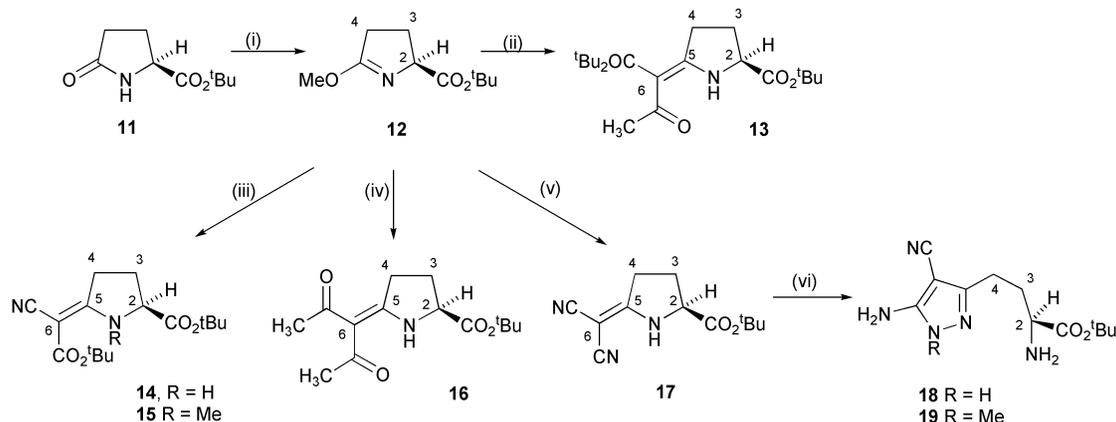Scheme 1

Fig. 1 NOE studies on compound **13**.
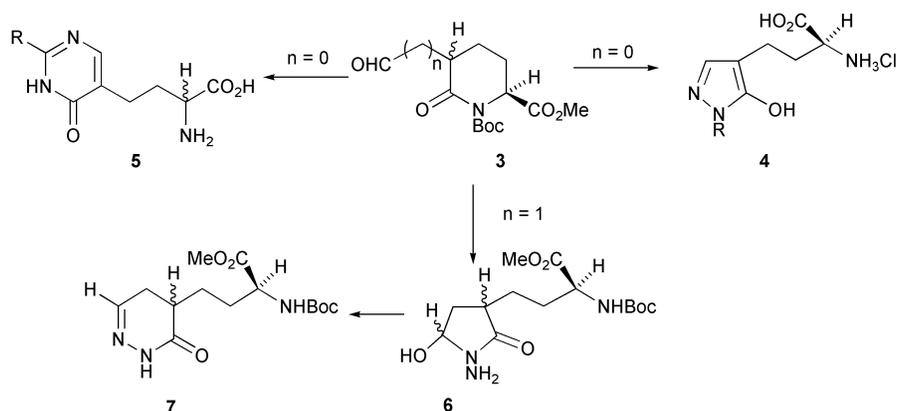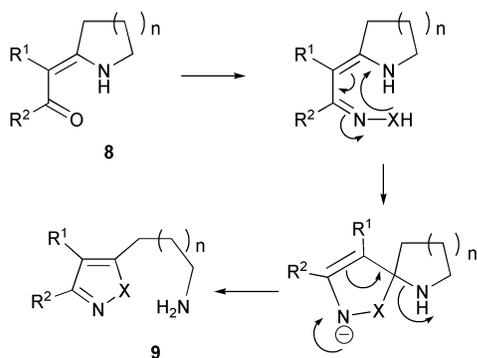
tert-butyl (2*S*)-pyroglutamate **11**[11] into the imino ether **12** using methyl trifluoromethanesulfonate as shown in Scheme 3. This was reacted with *tert*-butyl acetoacetate and triethylamine to yield the ketoester **13** in 36% yield. The ketoester **13** was shown to have *E*-stereochemistry on the basis of the NOE studies described in Fig. 1. Enhancements were seen in both signals for the protons, H-4, at δ 3.1 ppm and in the methyl proton singlet at δ 2.37 ppm when the *tert*-butyl singlet at δ 1.50 ppm was irradiated and enhancements were seen in the multiplet for H-2 at δ 4.35 ppm and in one of the multiplets for H-3 at δ 2.08 ppm when the *tert*-butyl signal at δ 1.45 ppm was irradiated. The nitrile ester **14** was also prepared in 52% yield from the imino ether **12** using *tert*-butyl cyanoacetate and triethylamine. The product **14** was accompanied by a 6% yield of the *N*-methyl derivative **15**, presumably due to alkylation of the product by the imino ether **12**. The structure of the compound **15** was confirmed by alkylation of the ester **14** using NaHMDS and methyl iodide when an identical compound was obtained. The diketone **16** and the dinitrile **17** were also prepared from the imino ether **12** in this way, and so a series of compounds was available for application to the "ring switching" reaction. In the event we were only able to obtain "ring switched" products from the dinitrile **17**. Reaction of this with hydrazine gave the pyrazole **18** in 50% yield, and reaction with methylhydrazine gave the *N*-methylpyrazole **19** in 87% yield.
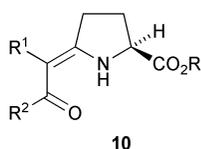
10

The alternative "ring switching" reaction had therefore given homochiral products in which a heterocyclic ring was separated from a glycine moiety by a two carbon bridge.

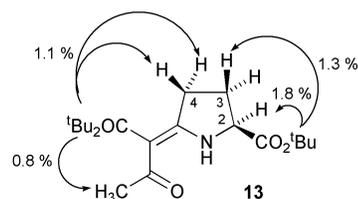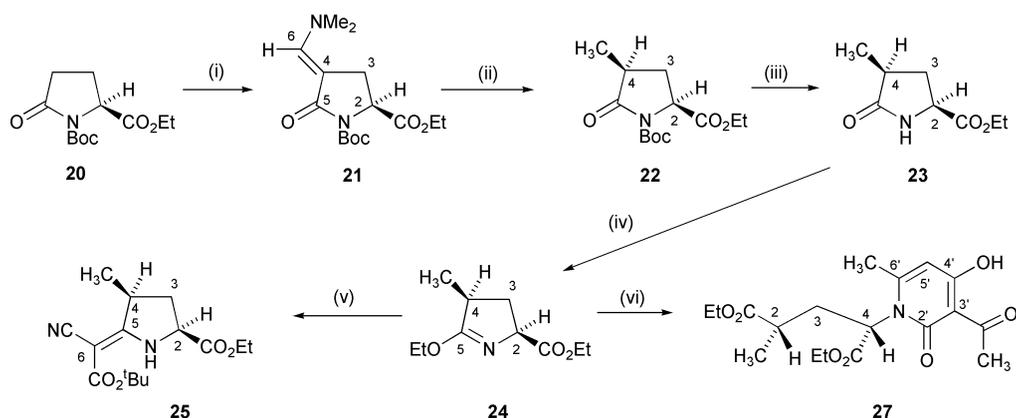We now investigated the possibility of using our synthesis to prepare compounds with a branch in the side chain and, in the first instance, we prepared the imino ether ethyl ester **24** as shown in Scheme 4. The urethane ester **20**[12] was converted into the enaminone **21** in 88% yield using Bredereck's reagent, *tert*-butoxybis(dimethylamino)methane, and was hydrogenated to yield compound **22** as a single diastereoisomer in 73% yield. Compound **22** was assumed to be the (2*S*,4*S*)-isomer by analogy to our work on the corresponding *tert*-butyl ester[13] and this was confirmed by using NOE experiments on the nitrile ester **25** as discussed below. Removal of the urethane to give the amide **23** in 93% yield was achieved using trifluoroacetic acid in dichloromethane, and the imino ether **24** was prepared from this in 86% yield using Meerwein's reagent, triethoxonium fluoroborate. The imino ether **24** could readily be converted to the nitrile ester **25** in 47% yield by heating with *tert*-butyl cyanoacetate and triethylamine. The (2*S*,4*S*)-stereochemistry of this compound was confirmed by the NOE experiments summarised in Fig. 2 where irradiation of the multiplet for H-2 at δ 4.44 ppm caused a 3.9% enhancement in the one proton multiplet for H-3 at δ 2.61 indicating it to be H-3*S*. Irradiation of the methyl doublet at δ 1.37 ppm caused an enhancement of 3.4% in the other one proton multiplet for H-3 (H-3*R*) at δ 2.0 ppm. The *E*-stereochemistry was proved by Secondary Isotope Multiplet NMR spectroscopy of Partially Labelled Entities (SIMPLE).[14] Addition of 0.3 molar equivalents of [²H₄]-methanol to a weighed sample in C²HCl₃ caused upfield shifts to signals in the ¹³C-NMR spectrum. This was due to the proximity of the relevant carbon atom in the molecule to the N–²H function in the compound as noted in Fig. 2. The carbonyl carbon of the *tert*-butyl ester showed a 64 ppb shift and the $C(CH_3)_3$ carbon showed a 14 ppb shift. This can only be due to the ester being on the same side of the double bond as the NH group in compound **25**.

Although the imino ether **12** had given the desired product **13** when reacted with *tert*-butyl acetoacetate and triethylamine, reaction of the imino ether **24** with ethyl acetoacetate and triethylamine in an attempt to prepare the corresponding methylated product **26** gave no reaction. Further, reaction with *tert*-butyl acetoacetate and Ni(acac)₂ monohydrate gave no product. Only when forcing conditions using Ni(acac)₂ monohydrate and triethylamine were used was any product obtained and this proved to be the pyridone **27** in 22% yield. The structure of this compound was confirmed by X-ray structure


Scheme 3 *Reagents and conditions* (i) CH₃OSO₂CF₃–Et₂O, −78 °C (71%); (ii) CH₃COCH₂CO₂ᵗBu–Et₃N (36%); (iii) NCCH₂CO₂ᵗBu–Et₃N (52% **14** + 6% **15**); (iv) CH₃COCH₂COCH₃–Et₃N (40%); (v) NCCH₂CN (76%); (vi) RNHNH₂ (**18** 50%; **19** 87%).

Scheme 4 *Reagents and conditions* (i) HC(NMe$_2$)$_2$O^{t}Bu (88%); (ii) H$_2$/10% Pd–C (73%); (iii) F$_3$CCO$_2$H–CH$_2$Cl$_2$ (93%); (iv) (EtO)$_3$·BF$_4$–CH$_2$Cl$_2$ (86%); (v) NCCH$_2$CO$_2^t$Bu–NEt$_3$ (47%); (vi) H$_3$CCOCH$_2$CO$_2^t$Bu–NEt$_3$–Ni(acac)$_2$ (22%).
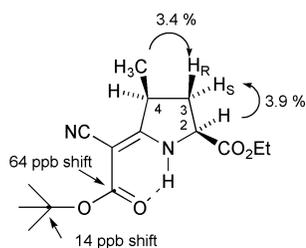
Fig. 2 NOE studies and upfield ^{13}C isotope shifts for N–^{2}H on compound **25**.

26
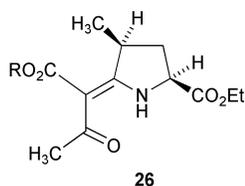
analysis (Fig. 3). Presumably this compound was formed by hydrolytic ring opening of the imino ether **24** to the corresponding ethyl ester, rather than the alternative hydrolysis to the lactam **23**. The amino ester would then react with two molecules of *tert*-butyl acetoacetate to yield the pyridone **27**. The 4-methyl group had evidently had a profound effect on preventing the "normal" reaction to give **26**.
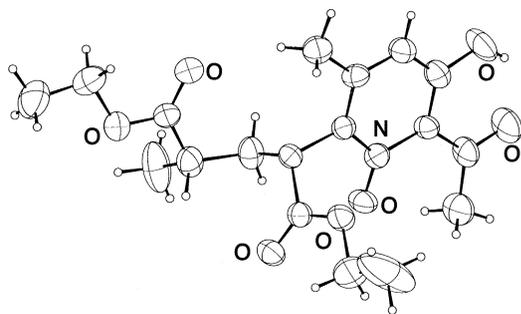
Fig. 3 X-Ray structure of the pyridone **27** from the reaction of the iminoether **24** with *tert*-butyl acetoacetate, triethylamine and Ni(acac)$_2$.

We had already prepared the *tert*-butyl ester **28**[13,15] and, using the method involving reduction of the corresponding enaminone,[13] we prepared a sample, mp 69–71 °C, [a]$_{22}^{D}$ −44.8 (*c* 1.12, CHCl$_3$).[16] The urethane was selectively removed in the presence of the *tert*-butyl ester using anhydrous 1 M HCl in ethyl acetate to give the amide **29** in 64% yield. This was converted to the imino ether **30** in 70% yield using methyl triflate in ether. Reaction with malononitrile then gave the dinitrile **31** as a single diastereoisomer in 90% yield. When the dinitrile **31** was heated in aqueous hydrazine until the ultra violet absorption,

λ_{max} 274 nm, due to the starting material had disappeared, the "ring switched" product **32** was obtained as a mixture of diastereoisomers in 28% yield. Thus we had obtained the desired branched chain "ring switched" product but epimerisation had occurred under the conditions of the reaction. Reaction of the dinitrile **31** with methylhydrazine gave the "ring switched" product **33** in 62% yield but again a mixture of diastereoisomers was obtained (Scheme 5).

We have therefore succeeded in developing an alternative "ring switching" reaction to prepare potential glutamate antagonists with a two carbon chain between an amino acid α-carbon atom and a heterocyclic moiety. Branched chain compounds were also prepared by the method but epimerisation was a problem and these compounds were prepared as mixtures of epimers.

Experimental

Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotation measurements were measured on a 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}. Infra-red spectra were recorded on a Perkin Elmer 1710 Fourier transform instrument and UV absorption spectra on an ATI Unicam UV2-100 Fourier transform scanning spectrophotometer. ε values are given in dm^3 mol^{-1} cm^{-1}. ^{1}H-NMR spectra were recorded on Bruker WM 360 (360 MHz), DPX 300 (300 MHz) and AMX 500 (500 MHz) Fourier transform instruments. *J* values are given in Hz. ^{13}C-NMR spectra were recorded on Bruker DPX 300 (75.5 MHz), AMX 500 (125.8) and AC–P 250 (62.9 MHz) Fourier transform instruments. INEPT and DEPT experiments were used to help assign ^{13}C-NMR resonances where necessary. Residual solvent peaks were used as internal references for all NMR spectra. Microanalyses were performed by Medac Ltd and also by Wellcome Research Laboratories, Beckenham and GlaxoSmithKline, Stevenage. Low resolution mass spectra and accurate mass measurements were recorded on Kratos MS80RF and Fisons Instruments VG Autospec double focusing spectrometers by Dr A. Abdul-Sada. Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh–Art. 9385) and Sorbsil C60 40/60 A. Unless otherwise stated all experiments were conducted under an inert atmosphere of argon. Petroleum ether refers to the fraction of hexanes of bp 60–80 °C.

tert-Butyl (2*S*)-5-Methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate (12)

Methyl trifluoromethanesulfonate (0.90 ml, 8.1 mmol) was added with care to a stirred solution of *tert*-butyl (2*S*)-pyroglutamate **11**[11] (1.0 g, 5.4 mmol) in anhydrous diethyl ether
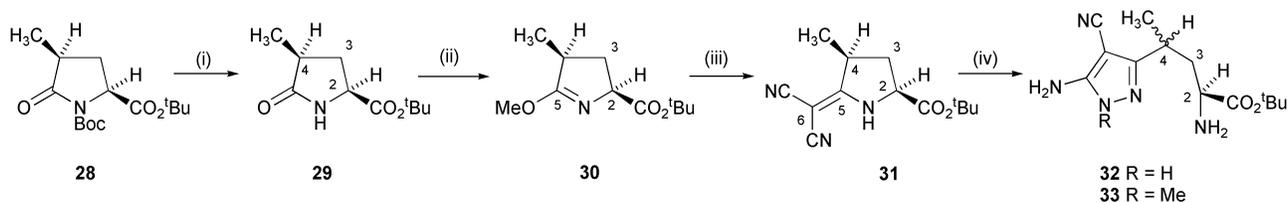
Scheme 5 *Reagents and conditions* (i) 1 M HCl–EtOAc (64%); (ii) H₃COSO₂CF₃–Et₂O (70%); (iii) NCCH₂CN (90%); (iv) RNHNH₂ (**32** 28%, **33** 62%).

(50 ml) at −78 °C. The reaction was stirred for 3 h at −78 °C and at room temperature for 18 h. Aqueous ammonium hydroxide (0.5M, 20 ml) was added and the mixture was stirred for 1 h to ensure that excess reagent was destroyed. The mixture was diluted with dichloromethane (20 ml) and the aqueous phase was extracted with dichloromethane (5 × 30 ml). The organic layers were combined and dried (MgSO₄). The solvent was removed *in vacuo* to yield *tert-butyl (2S)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate* **12** as a colourless oil (1.1 g, *ca.* 100%), which was used without further purification; *m/z* [+ve FAB (3-NBA)] 222 [M + Na]⁺ and 200 [M + H]⁺; ν_{max} (film)/cm⁻¹ 1737 (ester), 1681 (imine) and 1051 (ether); δ_H (300 MHz, C²HCl₃) 4.34 (1H, dd, $J_{2,3A}$ 7.9, $J_{2,3B}$ 5.3, H-2), 3.86 (3H, s, OCH₃), 2.00–2.55 (4H, m, H-4 and H-3) and 1.44 (9H, s, OC(CH₃)₃); δ_C (75.5 MHz, C²HCl₃) 174.7 (ester), 172.2 (C-5), 79.9 (OC(CH₃)₃), 67.7 (OCH₃), 55.0 (C-2), 29.8 (C-4), 27.0 (OC(CH₃)₃) and 26.9 (C-3).

tert-Butyl (2S)-5-(1-*tert*-butoxycarbonyl-2-oxopropylidene)-pyrrolidine-2-carboxylate (13)

tert-Butyl (2S)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate **12** (500 mg, 2.5 mmol), *tert*-butyl acetoacetate (0.72 ml, 5.0 mmol) and triethylamine (1.0 ml, 7.2 mmol) were heated at 100 °C for 120 h in a sealed tube. The solvent was removed *in vacuo* to give a brown oil. Purification by column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 5) as eluent gave a white solid, which was recrystallised from ethyl acetate and petroleum ether to yield *tert-butyl (2S)-5-(1-tert-butoxycarbonyl-2-oxopropylidene)pyrrolidine-2-carboxylate* **13** as a white solid (290 mg, 36%) mp 120–122 °C; $[a]_D^{25}$ +0.70 (*c* 1.0, MeOH) (Found: C, 63.0; H, 8.5; N, 4.3. C₁₇H₂₇NO₅ requires C, 62.75; H, 8.4; N, 4.3%); *m/z* [+ve FAB (3-NBA)] 326 [M + H]⁺; ν_{max} (film)/cm⁻¹ 1736 (ester) and 1690 (ketone); λ_{max} (MeOH)/nm 293 (ε 20700); δ_H (300 MHz, C²HCl₃) 11.53 (1H, br s, NH, slowly exchanges in ²H₂O), 4.35 (1H, dd, $J_{2,3A}$ 8.8, $J_{2,3B}$ 5.7, H-2), 3.10 (2H, m, H-4), 2.37 (3H, s, CH₃C=O), 2.34 (1H, m, H-3A), 2.08 (1H, m, H-3B), 1.50 (9H, s, OC(CH₃)₃) and 1.45 (9H, s, OC(CH₃)₃); δ_C (75.5 MHz, C²HCl₃) 198.2 (ketone), 173.4 (ester), 170.5 (ester), 168.3 (C-6), 126.2 (C-5), 83.0 (OC(CH₃)₃), 80.4 (OC(CH₃)₃), 62.4 (C-2), 34.5 (C-4), 31.3 (CH₃C=O), 28.9 (OC(CH₃)₃), 28.3 (OC(CH₃)₃) and 25.8 (C-3).

tert-Butyl (2S)-5-(*tert*-Butoxycarbonylcyanomethylene)-pyrrolidine-2-carboxylate (14)

tert-Butyl (2S)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate **12** (8.50 g, 42.7 mmol), *tert*-butyl cyanoacetate (12.2 ml, 85.4 mmol) and triethylamine (1.0 ml, 7.17 mmol) were stirred at 60 °C for 48 h. The solvent was removed *in vacuo* to give a beige solid. Purification by column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 4) as eluent gave two products, *tert-butyl (2S)-5-(tert-butoxycarbonylcyano-methylene)-1-methylpyrrolidine-2-carboxylate* **15** as a colourless oil (0.83 g, 6%), identical in all respects with the compound prepared independently below, and *tert-butyl (2S)-5-(tert-butoxycarbonylcyanomethylene)pyrrolidine-2-carboxylate* **14** as a white crystalline solid (6.80 g, 52%), mp 144–146 °C; $[a]_D^{28}$ −2.8 (*c* 1.0, MeOH) (Found: C, 62.1; H, 8.05; N, 9.0.

C₁₆H₂₄N₂O₄ requires C, 62.3; H, 7.8; N, 9.1%.); *m/z* [+ve FAB (3-NBA)] 331 [M + Na]⁺ and 309 [M + H]⁺; ν_{max} (film)/cm⁻¹ 3335 (NH), 2208 (CN) and 1739 (ester); λ_{max} (MeOH)/nm 272 (ε 15100); δ_H (300 MHz, C²HCl₃) 9.10 (1H, br s, NH, slowly exchanges in ²H₂O), 4.34 (1H, dd, $J_{2,3A}$ 8.5, $J_{2,3B}$ 5.8, H-2), 2.87 (2H, m, H-4), 2.34 (1H, m, H-3A), 2.11 (1H, m, H-3B), 1.43 (9H, s, OC(CH₃)₃) and 1.41 (9H, s, OC(CH₃)₃); δ_C (75.5 MHz, C²HCl₃) 173.3 (C-5), 170.1 (ester), 167.4 (ester), 119.9 (CN), 83.5 (OC(CH₃)₃), 81.6 (OC(CH₃)₃), 70.6 (C-6), 63.1 (C-2), 32.8 (C-4), 28.7 (OC(CH₃)₃), 28.3 (OC(CH₃)₃) and 25.8 (C-3).

tert-Butyl (2S)-5-(*tert*-butoxycarbonylcyanomethylene)-1-methylpyrrolidine-2-carboxylate (15)

tert-Butyl (2S)-5-(*tert*-butoxycarbonylcyanomethylene)pyrrolidine-2-carboxylate **14** (100 mg, 0.33 mmol) was dissolved in anhydrous tetrahydrofuran (1 ml), cooled to −78 °C and stirred. Hexamethylphosphoramide (56 µl, 0.33 mmol) was added, followed by a solution of NaHMDS (1.0 M in THF) (0.32 ml, 0.33 mmol). The reaction was stirred at −78 °C for 1 h. Methyl iodide (44 µl, 0.72 mmol) was added and the mixture was stirred at −78 °C for 9 h and at room temperature for a further 16 h. Aqueous citric acid (5%, 1 ml) was added and the tetrahydrofuran was removed *in vacuo*. The mixture was diluted with water (2 ml) and extracted with ethyl acetate (5 × 1 ml). The organic layers were combined and dried (MgSO₄). The solvent was removed *in vacuo* to yield a yellow oil, which was purified by column chromatography on silica gel, using diethyl ether–dichloromethane–petroleum ether (5 : 20 : 30) as eluent to yield *tert-butyl (2S)-5-(tert-butoxycarbonylcyanomethyl-ene)-1-methylpyrrolidine-2-carboxylate* **15** as a colourless oil (30 mg, 29%); $[a]_D^{28}$ −74.5 (*c* 1.0, MeOH); (*m/z* (EI) Found 322.1894. C₁₇H₂₆N₂O₄ requires 322.1893); *m/z* [+ve FAB (3-NBA)] 345 [M + Na]⁺ and 323 [M + H]⁺; ν_{max} (film)/cm⁻¹ 2198 (CN) and 1723 (ester); λ_{max} (MeOH)/nm 285 (ε 16800); δ_H (300 MHz, C²HCl₃) 4.10 (1H, dd, $J_{2,3A}$ 9.1, $J_{2,3B}$ 4.2, H-2), 3.36 (3H, s, NCH₃), 3.14 (2H, m, H-4), 2.22 (1H, m, H-3A), 2.01 (1H, m, H-3B) and 1.47 (18H, s, 2 × OC(CH₃)₃); δ_C (75.5 MHz, C²HCl₃) 172.0 (C-5), 170.0 (ester), 166.1 (ester), 119.1 (CN), 83.6 (OC(CH₃)₃), 80.9 (OC(CH₃)₃), 70.9 (C-6), 70.3 (C-2), 36.5 (NCH₃), 34.5 (C-4), 28.7 (OC(CH₃)₃), 28.4 (OC(CH₃)₃) and 25.3 (C-3).

tert-Butyl (2S)-5-(1-acetyl-2-oxopropylidene)pyrrolidine-2-carboxylate (16)

tert-Butyl (2S)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate **12** (300 mg, 1.5 mmol), acetylacetone (0.34 ml, 3.4 mmol) and triethylamine (0.2 ml, 2.0 mmol) were heated at 100 °C for 120 h in a sealed tube. The solvent was removed *in vacuo* to give a brown oil. Purification by column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 5) as eluent gave *tert-butyl(2S)-5-(1-acetyl-2-oxopropylidene)pyrrolidine-2-carb-oxylate* **16** as a white crystalline solid (160 mg, 40%), mp 83–84 °C; $[a]_D^{29}$ +0.4 (*c* 1.0, MeOH) (Found: C, 62.95; H, 8.0; N, 5.2. C₁₄H₂₁NO₄ requires C, 62.9; H, 7.9; N, 5.2%); *m/z* [+ve FAB (3-NBA)] 290 [M + Na]⁺ and 268 [M + H]⁺; ν_{max} (film)/cm⁻¹ 3230 (NH), 1743 (ester) and 1697 (ketone); λ_{max} (MeOH)/nm 293 (ε 14200); δ_H (300 MHz, C²HCl₃) 11.53 (1H, br s, NH,

slowly exchanges in ^2H_2O), 4.40 (1H, dd, $J_{2,3A}$ 8.9, $J_{2,3B}$ 5.9, H-2), 3.08 (2H, m, H-4), 2.36 (6H, s, 2 × CH_3C=O), 2.31 (1H, m, H-3A), 2.12 (1H, m, H-3B) and 1.47 (9H, s, OC(CH$_3$)$_3$); δ_C (75.5 MHz, C^2HCl_3) 198.2 (2 × ketone), 172.7 (C-5), 170.3 (ester), 112.2 (C-6), 83.1 (OC(CH$_3$)$_3$), 62.3 (C-2), 34.2 (C-4), 31.8 (2 × CH$_3$C=O), 28.3 (OC(CH$_3$)$_3$) and 26.0 (C-3).

tert-Butyl (2*S*)-5-dicyanomethylenepyrrolidine-2-carboxylate (17)

tert-Butyl (2*S*)-5-methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate 12 (1.6 g, 8.0 mmol) and malononitrile (600 mg, 9.1 mmol) were stirred together for 16 h at room temperature. The residual solid was washed with diethyl ether and recrystallised from absolute ethanol to yield *tert-butyl (2S)-5-dicyanomethylene-pyrrolidine-2-carboxylate* 17 as a beige solid (1.4 g, 75%); mp 130–131 °C; $[a]_D^{28}$ −52.3 (*c* 1.0, MeOH) (Found: C, 61.6; H, 6.5; N, 18.0. $C_{12}H_{15}N_3O_2$ requires C, 61.8; H, 6.5; N, 18.0%); *m/z* [+ve FAB (3-NBA)] 256 [M + Na]$^+$ and 234 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3227 (NH), 2212 (CN), 2195 (CN) and 1733 (ester); λ_{max} (MeOH)/nm 270 (ε 26200); δ_H (300 MHz, C^2HCl_3) 7.74 (1H, br s, NH, exchanges in ^2H_2O), 4.37 (1H, dd, $J_{2,3A}$ 8.6, $J_{2,3B}$ 5.9, H-2), 2.90 (2H, m, H-4), 2.42 (1H, m, H-3A), 2.21 (1H, m, H-3B) and 1.42 (9H, s, OC(CH$_3$)$_3$); δ_C (75.5 MHz, C^2HCl_3) 177.7 (ester), 171.0 (C-5), 126.2 (C-6), 116.6 (CN), 116.9 (CN), 85.4 (OC(CH$_3$)$_3$), 64.6 (C-2), 33.7 (C-4), 29.5 (OC(CH$_3$)$_3$) and 27.7 (C-3).

tert-Butyl (2*S*)-2-amino-4-(5-amino-4-cyano-1*H*-pyrazol-3-yl)-butyrate (18)

A suspension of *tert*-butyl (2*S*)-5-dicyanomethylenepyrrol-idine-2-carboxylate 17 (1.0 g, 4.3 mmol) in hydrazine mono-hydrate (0.95 ml, 21.5 mmol) and distilled water (0.4 ml) was heated at reflux for 15 min. After cooling, distilled water (8.6 ml) was added and the solution turned opaque. The solvent was removed *in vacuo* to yield *tert-butyl (2S)-2-amino-4-(5-amino-4-cyano-1H-pyrazol-3-yl)butyrate* 18 as a white solid (600 mg, 52%); mp 135–137 °C; $[a]_D^{28}$ +6.5 (*c* 1, DMSO) (Found: C, 54.3; H, 7.25; N, 26.5. $C_{12}H_{19}N_5O_2$ requires C, 54.3; H, 7.2; N, 26.4%); *m/z* [+ve FAB (3-NBA)], 288 [M + Na]$^+$ and 266 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3393 (NH, br), 2212 (CN) and 1727 (ester); δ_H (300 MHz, [$^2H_6$]-DMSO) 11.62 (1H, br s, NH, exchanges in ^2H_2O), 5.89 (4H, br s, 2 × NH$_2$, exchanges in ^2H_2O), 3.4 (1H, t, $J_{2,3}$ 6.0, H-2), 2.61 (2H, t, $J_{4,3}$ 7.7, H-4), 2.24 (1H, m, $J_{3A,3B}$ 13.6, $J_{3A,4}$ 7.7, $J_{3A,2}$ 6.0, H-3A), 1.91 (1H, m, $J_{3B,3A}$ 13.6, $J_{3B,4}$ 7.7, $J_{3B,2}$ 6.0, H-3B) and 1.30 (9H, s, OC(CH$_3$)$_3$); δ_C (75.5 MHz, ^2H_2O) 176.0 (ester), 155.4 (Ar), 152.5 (Ar), 126.3 (CN), 83.5 (OC(CH$_3$)$_3$), 72.1 (Ar), 54.0 (C-2), 32.3 (C-4), 27.4 (OC(CH$_3$)$_3$) and 22.4 (C-3).

tert-Butyl (2*S*)-2-amino-4-(5-amino-4-cyano-1-methyl-1*H*-pyrazol-3-yl)butyrate (19)

A suspension of *tert*-butyl (2*S*)-5-dicyanomethylenepyrrol-idine-2-carboxylate 17 (500 mg, 2.1 mmol) in methylhydrazine (0.6 ml, 10.7 mmol) and distilled water (0.2 ml) was heated at reflux for 20 min. After cooling, distilled water (0.2 ml) was added and the solution turned opaque. The solvent was removed *in vacuo* to yield *tert-butyl (2S)-2-amino-4-(5-amino-4-cyano-1-methyl-1H-pyrazol-3-yl)butyrate* 19 as an orange oil (500 mg, 87%); $[a]_D^{25}$ +5.0 (*c* 1.0, DMSO); (*m/z* (EI) Found: 279.1673. $C_{13}H_{21}N_5O_2$ requires 279.1695); *m/z* [+ve FAB (glycerol–water)] 280 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3343 (NH$_2$, br), 2209 (CN) and 1726 (ester); δ_H (300 MHz, $^2H_6$-DMSO) 6.55 (2H, br s, NH$_2$, exchanges in ^2H_2O), 3.51 (3H, s, NCH$_3$), 3.26 (1H, t, $J_{2,3}$ 5.8, H-2), 2.54 (2H, t, $J_{4,3}$ 7.7, H-4), 1.92 (1H, m, H-3A), 1.78 (1H, m, H-3B) and 1.48 (9H, s, OC(CH$_3$)$_3$); δ_C (75.5 MHz, ^2H_2O) 176.0 (ester), 153.7 (Ar), 152.3 (Ar), 115.8 (CN), 83.3 (Ar), 73.4 (OC(CH$_3$)$_3$), 54.1 (C-2), 34.2 (NCH$_3$), 32.7 (C-4), 27.5 (OC(CH$_3$)$_3$) and 23.3 (C-3).

Ethyl (2*S*)-*N-tert*-butoxycarbonyl-4-dimethylaminomethylene-pyroglutamate (21)

Ethyl (2*S*)-*N-tert*-butoxycarbonylpyroglutamate 20[12] (6.0 g, 23.3 mmol) was dissolved in anhydrous dimethoxyethane (65 ml) and the solution was stirred at room temperature under nitrogen. *tert*-Butoxybis(dimethylamino)methane (Bredereck's reagent) (7.22 ml, 35.0 mmol) was added and the mixture was heated at 80 °C for 15 h. The solvent was removed *in vacuo* to give a solid, which was recrystallised using ethyl acetate–petroleum ether to yield *ethyl (2S)-N-tert-butoxycarbonyl-4-dimethylaminomethyl-enepyroglutamate* 21 as an off-white crystalline solid (6.39 g, 88%), mp 79–81 °C, $[a]_D^{18}$ −50.3 (*c* 1.31, CHCl$_3$) (Found: C, 57.5; H, 7.6; N, 9.0. $C_{15}H_{24}N_2O_5$ requires C, 57.7; H, 7.7; N, 9.0%); *m/z* [+ve FAB (3-NBA)] 313 [M + H]$^+$; ν_{max} (film)/cm^{-1} 1745, (br, imide / urethane / ester); λ_{max} (MeOH)/nm 313 (ε 31700); δ_H (360 MHz, C^2HCl_3) 7.10 (1H, t, $J_{6,3}$ 1.6 Hz, H-6), 4.50 (1H, dd, $J_{2,3A}$ 10.8, $J_{2,3B}$ 3.2, H-2), 4.18 (2H, m, OCH_2CH$_3$), 3.21 (1H, m, $J_{3A,2}$ 10 8, $J_{3A,3B}$ 14.5, H-3A), 2.98 (6H, s, N(CH$_3$)$_2$), 2.85 (1H, m, $J_{3B,2}$ 3.2, $J_{3B,3A}$ 14.5, H-3B), 1.47 (9H, s, OC(CH$_3$)$_3$) and 1.25 (3H, t, J 7.12, CH$_2$CH_3); δ_C (62.9 MHz, C^2HCl_3) 172.1 (amide), 169.4 (ester), 150.5 (urethane), 146.3 (C-6), 90.9 (C-4), 82.1 (OC(CH$_3$)$_3$), 61.3 (OCH$_2$CH$_3$), 56.9 (C-2), 41.9 (N(CH$_3$)$_2$), 28.0 (OC(CH$_3$)$_3$), 26.2 (C-3), and 14.1 (OCH$_2$$CH_3$).

Ethyl (2*S*,4*S*)-*N-tert*-butoxycarbonyl-4-methylpyroglutamate (22)

Ethyl (2*S*)-*N-tert*-butoxycarbonyl-4-dimethylaminomethylene-pyroglutamate 21 (4.1 g, 13 mmol) was dissolved in ethyl acet-ate (80 ml) and the solution was stirred under nitrogen at room temperature. 10% Palladium on activated carbon (4.1 g, 100% w/w) was carefully added. The solution was vigorously stirred for 115 h under an atmosphere of hydrogen at room temper-ature. The mixture was filtered through Celite® and the solvent was removed *in vacuo* to yield *ethyl (2S,4S)-N-tert-butoxy-carbonyl-4-methylpyroglutamate* 22 as a colourless oil (2.6 g, 73%), $[a]_D^{28}$ −46.9 (*c* 1.0, MeOH) (Found C, 57.6; H, 7.9; N, 5.4. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.8; N, 5.2%); *m/z* [EI] 271 [M]$^+$; ν_{max} (film)/cm^{-1} 1792, 1749 and 1719 (imide/urethane/ ester), δ_H (360 MHz, C^2HCl_3) 4.46 (1H, t, $J_{2,3}$ 8.2, H-2), 4.20 (2H, q, J 7.2, OCH_2CH$_3$), 2.56 (2H, m, H-4 and H-3A), 1.58 (1H, m, H-3B), 1.47 (9H, s, OC(CH$_3$)$_3$) and 1.27 (6H, 2 × t, OCH$_2$CH_3 and CH$_3$); δ_C (62.9 MHz, C^2HCl_3) 178.3 (amide), 174.1 (ester), 152.1 (urethane), 86.2 (OC(CH$_3$)$_3$), 64.2 (OCH$_2$-CH$_3$), 60.1 (C-2), 40.1 (C-4), 32.3 (C-3), 30.4 (OC(CH$_3$)$_3$), 18.8 (C–CH$_3$) and 16.7 (OCH$_2$$CH_3$).

Ethyl (2*S*,4*S*)-4-methylpyroglutamate (23)

Trifluoroacetic acid (15 ml) was added to a stirred solution of ethyl (2*S*,4*S*)-*N-tert*-butoxycarbonyl-4-methylpyroglutamate 22 (2.6 g, 9.59 mmol) in anhydrous dichloromethane (30 ml) at room temperature. The reaction was stirred for 18 h at room temper-ature. The solvent was azeotropically removed *in vacuo* with di-ethyl ether to give a colourless oil. Purification by flash column chromatography on silica gel using ethyl acetate as eluent gave *ethyl (2S,4S)-4-methylpyroglutamate* 23 as a white crystalline solid (1.52 g, 93%), mp 63–66 °C; $[a]_D^{21}$ −27.2 (*c* 1.0, MeOH); *m/z* [+ve FAB (3-NBA)] 194 [M + Na]$^+$ and 172 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3276 (br, NH) and 1739 (ester); δ_H (360 MHz, C^2HCl_3) 6.12 (1H, br s, NH, exchanges in ^2H_2O), 4.17 (3H, m, H-2 and OCH_2CH$_3$), 2.66 (1H, m, H-3A), 2.48 (1H, m, H-4), 1.75 (1H, m, H-3B), 1.26 (3H, t, J 7.1, OCH$_2$CH_3) and 1.18 (3H, d, $J_{Me,4}$ 7.1, CH$_3$); δ_C (62.9 MHz, C^2HCl_3) 180.3 (amide), 172.0 (ester), 61.5 (OCH$_2$CH$_3$), 53.7 (C-2), 35.9 (C-4), 33.3 (C-3), 15.8 (OCH$_2$$CH_3$) and 13.94 (C–$CH_3$).

Ethyl (2*S*,4*S*)-5-ethoxy-3,4-dihydro-4-methyl-2*H*-pyrrole-2-carboxylate (24)

A solution of triethyloxonium tetrafluoroborate (1.67 g, 8.8 mmol) in dichloromethane (10 ml) was added to a solution

of ethyl (2S,4S)-4-methylpyroglutamate **23** (1.5 g, 8.8 mmol) in anhydrous dichloromethane (20 ml) with stirring at room temperature. The reaction was stirred at room temperature for 48 h. Saturated aqueous potassium hydrogen carbonate (30 ml) was carefully added. When effervescence had ceased, the mixture was filtered through Celite® and the organic layer was separated. The aqueous layer was extracted with dichloromethane (5 × 30 ml). The organic layers were combined and dried (MgSO$_4$). The solvent was removed *in vacuo* to yield *ethyl (2S,4S)-5-ethoxy-3,4-dihydro-4-methyl-2H-pyrrole-2-carboxylate* **24** as a colourless oil (1.50 g, 86%), which was used without further purification, [a]$_D^{28}$ +4.1 (*c* 0.68, CHCl$_3$); (*m/z* (EI) Found: 199.1214. C$_{10}$H$_{17}$NO$_3$ requires 199.1208); ν_{max} (film)/cm^{-1} 1741 (ester); δ_H (300 MHz, C^{2}HCl$_3$) 4.36–4.15 (5H, m, H-2 and 2 × OCH_2CH$_3$), 2.70 (1H, m, H-3A), 2.56 (1H, m, H-4), 1.68 (1H, m, H-3B), 1.24 (6H, m, 2 × OCH$_2$CH_3) and 1.18 (3H, d, $J_{Me,4}$ 7.1, CH$_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 176.9 (ester), 174.1 (C-5), 66.0 (C-2), 64.4 (OCH$_2$CH$_3$), 60.9 (OCH$_2$CH$_3$), 38.7 (C-4), 35.3 (C-3), 17.1 (C–CH$_3$), 14.28 (OCH$_2$CH$_3$) and 13.94 (OCH$_2$CH$_3$).

Ethyl (2S,4S)-5-(*tert*-butoxycarbonylcyanomethylene)-4-methylpyrrolidine-2-carboxylate (25)

(2S,4S)-5-Ethoxy-2-ethoxycarbonyl-4-methyl-1-pyrroline **24** (310 mg, 1.6 mmol), *tert*-butyl cyanoacetate (0.45 ml, 3.2 mmol) and triethylamine (0.22 ml, 1.6 mmol) were stirred at 70 °C for 48 h. The solvent was removed *in vacuo* to give a brown oil, which was purified by column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 3) as eluent to yield *ethyl (2S,4S)-5-(tert-butoxycarbonylcyanomethylene)-4-methylpyrrolidine-2-carboxylate* **25** as a white crystalline solid (210 mg, 47%), mp 124–127 °C; [a]$_D^{28}$ +55.6 (*c* 0.9, MeOH) (Found: C, 61.2; H, 7.6; N, 9.4. C$_{15}$H$_{22}$N$_2$O$_4$ requires C, 61.2; H, 7.5; N, 9.5%); *m/z* [+ve FAB (3-NBA)] 317 [M + Na]$^+$ and 295 [M + H]$^+$; ν_{max} (film) / cm^{-1} 3337 (NH), 2203 (CN), 1747 (ester) and 1672 (C=C); λ_{max} (MeOH)/nm 280 (ε 16800); δ_H (500 MHz, C^{2}HCl$_3$) 9.25 (1H, s br, N*H*, slowly exchanges in ^{2}H$_2$O), 4.44 (1H, ddd, $J_{2,3A}$ 5.8, $J_{2,3B}$ 2.9, $J_{2,NH}$ 1.3, H-2), 4.25 (2H, ABX$_3$, OCH_2CH$_3$), 3.23 (1H, m, H-4), 2.61 (1H, m, H-3*S*), 2.01 (1H, m, H-3*R*), 1.50 (9H, s, OC(CH$_3$)$_3$), 1.37 (3H, d, $J_{Me,4}$ 7.3, CH$_3$), 1.33 (3H, t, *J* 7.1, OCH$_2$CH_3); δ_C (125.8 MHz, C^{2}HCl$_3$) 177.1 (C-5), 171.1 (ester), 167.5 (ester), 118.2 (CN), 81.2 (OC(CH$_3$)$_3$), 69.9 (C-6), 62.0 (OCH$_2$CH$_3$), 60.1 (C-2), 39.3 (C-4), 33.2 (C-3), 28.3 (OC(CH$_3$)$_3$), 19.1 (C–CH$_3$), and 14.1 (OCH$_2$CH$_3$).

Diethyl (2S,4S)-2-(3-acetyl-4-hydroxy-6-methyl-2-oxo-2H-pyridin-1-yl)-4-methylpentanedioate (27)

Ethyl (2S,4S)-5-ethoxy-3,4-dihydro-4-methyl-2H-pyrrole-2-carboxylate **24** (160 mg, 0.80 mmol), *tert*-butyl acetoacetate (0.26 ml, 1.6 mmol), nickel acetylacetonate monohydrate (3 mg, 1 μmol) and triethylamine (1 ml, 7.2 mmol) were stirred at 80 °C for 20 h, followed by further addition of nickel acetylacetonate monohydrate (3 mg, 1 μmol). The reaction was stirred for a further 24 h and the solvent was removed *in vacuo* to give a brown oil. Purification by column chromatography on silica gel, using ethyl acetate and petroleum ether (1 : 6) as eluent gave diethyl *(2S,4S)-2-(3-acetyl-4-hydroxy-6-methyl-2-oxo-2H-pyridin-1-yl)-4-methylpentanedioate* **27** as a white crystalline solid (60 mg, 22%), mp 124–127 °C, [a]$_D^{28}$ −35.8 (*c* 0.6, MeOH); *m/z* [+ve FAB (3-NBA)] 390 [M + Na]$^+$ and 368 [M + H]$^+$; ν_{max} (film)/cm^{-1} 2983 (br, OH) and 1744 (ester); λ_{max} (MeOH)/nm 330 (ε 87100); δ_H (500 MHz, C^{2}HCl$_3$, −30 °C) 15.54 (1H, s, OH, exchanges in ^{2}H$_2$O), 5.85 (1H, s, ArH), 4.32 (1H, m, H-2), 4.24 and 4.10 (4H, m, 2 × OCH_2CH$_3$), 2.97 (1H, m, H-4), 2.72 (4H, m, H-3A and CH$_3$C=O), 2.42 (3H, s, ArCH$_3$), 2.05 (1H, m, H-3B) and 1.24 (9H, m, CH$_3$ and 2 × OCH$_2$CH_3); δ_C (75.5 MHz, C^{2}HCl$_3$) 205.6 (ketone), 176.5 (C-2′), 175.4 (C-4′), 169.4 (ester), 162.5 (ester), 153.4 (C-6′), 105.7 (C-3′), 101.7 (C-5′), 61.4 (OCH$_2$CH$_3$), 60.7 (OCH$_2$CH$_3$), 57.2 (C-2), 36.9 (C-4), 33.8

(C-3), 31.3 (CH$_3$C=O), 21.2 (Ar–CH$_3$), 18.7 (OCH$_2$CH$_3$) and 14.1 (OCH$_2$CH$_3$).

Crystal data– compound 27†

C$_{18}$H$_{25}$NO$_7$, *M* = 367.4, hexagonal, space group *P*6$_1$ (No169), *a* = 8.994(2), *b* = 8.994(2), *c* = 43.134(6) Å, α = 90°, β = 90°, γ = 120°, *V* = 3021.7(10) Å^3, *Z* = 6, D_{calc}= 1.211 mg m^{-3}, *F*(000) = 1170, μ(Mo-Kα) = 0.09 mm^{-1}, *T* = 293(2) K, 2787 total reflections measured; 1259 independent reflections collected on Enruf-Nonius CAD4 diffractometer (R_{int}= 0.0837) using Mo-Kα radiation (λ = 0.71073 Å) for 2 < θ < 22°. Structure solution by direct methods (SHELXS) and refinement on *F*^{2} using SHELXL-93 with non-H atoms anisotropic and H atoms in riding mode. Final residuals were *R*1 = 0.045 and *wR*2 = 0.108 (for 1031 reflections with *I* > 2σ(*I*)), *R*1 = 0.062, *wR*2 = 0.120 for all reflections.

tert-Butyl (2S,4S)-4-methylpyroglutamate (29)

tert-Butyl (2S,4S)-*N*-tert-butoxycarbonyl-4-methylpyroglutamate **28**[13] (5.9 g, 19.7 mmol) was dissolved in anhydrous 1 M HCl in ethyl acetate (850 ml) and stirred at room temperature for 3 h. The solvent was removed *in vacuo* to give a pale yellow solid, which was recrystallised from diethyl ether–petroleum ether to yield *tert-butyl (2S,4S)-4-methylpyroglutamate* **29** as a white solid (2.52 g, 64%); mp 54–60 °C; [a]$_D^{22}$ −19.72 (*c* 1.0, MeOH); *m/z* [+ve FAB (3-NBA)] 222 [M + Na]$^+$ and 200 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3269 (br, NH), 1739 (ester) and 1708 (lactam); δ_H (360 MHz, C^{2}HCl$_3$) 6.55 (1H, br s, NH, exchanges in ^{2}H$_2$O), 4.03 (1H, t, $J_{2,3}$ 7.9, H-2), 2.57 (1H, m, H-3A), 2.44 (1H, m, H-4), 1.67 (1H, m, H-3B), 1.42 (9H, s, OC(CH$_3$)$_3$) and 1.16 (3H, d, $J_{Me,4}$ 7, CH$_3$); δ_C (62.9 MHz, C^{2}HCl$_3$) 182.8 (amide), 173.3 (ester), 83.1 (OC(CH$_3$)$_3$), 55.9 (C-2), 37.3 (C-4), 34.5 (C-3), 28.2 (OC(CH$_3$)$_3$) and 16.6 (C–CH$_3$).

tert-Butyl (2S,4S)-5-methoxy-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate (30)

Methyl trifluoromethanesulfonate (0.45 ml, 4.0 mmol) was added with care to a stirred solution of *tert*-butyl (2S,4S)-4-methylpyroglutamate **29** (400 mg, 2.0 mmol) in anhydrous diethyl ether (40 ml) at −78 °C. The reaction was stirred at −78 °C for 3 h and at room temperature for 18 h. 0.5 M Aqueous ammonium hydroxide (20 ml) was added, the mixture was stirred for 1 h, dichloromethane (20 ml) was added and the aqueous phase was extracted with dichloromethane (4 × 40 ml). The organic layers were combined and dried (MgSO$_4$). The solvent was removed *in vacuo* to yield *tert-butyl (2S,4S)-5-methoxy-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate* **30** as a colourless oil (300 mg, 70%), which was used without further purification, [a]$_D^{25}$ −21.8 (*c* 1.0, MeOH); *m/z* [+ve FAB (3-NBA)] 236 [M + Na]$^+$ and 214 [M + H]$^+$; ν_{max} (film)/cm^{-1} 1737 (ester); δ_H (300 MHz, C^{2}HCl$_3$) 4.36 (1H, t, $J_{2,3}$ 7.5, H-2), 3.86 (3H, s, OCH$_3$), 2.76 (1H, m, H-3A), 2.58 (1H, m, H-4), 2.25 (1H, m, H-3B), 1.47 (9H, s, OC(CH$_3$)$_3$) and 1.18 (3H, d, $J_{Me,4}$ 7.1, CH$_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 177.7 (ester), 173.8 (C-5), 81.2 (OC(CH$_3$)$_3$), 66.7 (OCH$_3$), 56.3 (C-2), 38.9 (C-4), 36.8 (C-3), 28.4 (OC(CH$_3$)$_3$) and 17.5 (C–CH$_3$).

tert-Butyl (2S,4S)-5-dicyanomethylene-4-methylpyrrolidine-2-carboxylate (31)

tert-Butyl (2S,4S)-5-methoxy-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate **30** (0.43 g, 2.0 mmol) and malononitrile (0.13 g, 2.0 mmol) were stirred together for 16 h at room temperature to give a red oil. Purification by column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 3) as eluent gave *tert-butyl (2S,4S)-5-dicyanomethylene-4-methyl-*

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† CCDC reference numbers 209172. See http://www.rsc.org/suppdata/ob/b3/b304609p/ for crystallographic data in .cif or other electronic format.

pyrrolidine-2-carboxylate **31** as an off-white crystalline solid (450 mg, 90%) mp 104–106 °C; $[a]_D^{28}$ +36.4 (*c* 1.0, CHCl$_3$) (Found: C, 62.8; H, 6.9; N, 16.9. C$_{13}$H$_{17}$N$_3$O$_2$ requires C, 63.1; H, 6.9; N, 17.0%.); *m/z* [+ve FAB (3-NBA)] 270 [M + Na]$^+$ and 248 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3255 (br, NH), 2217 (CN), 2199 (CN) and 1733 (ester); λ_{max} (MeOH)/nm 274 (ε 2800); δ_H (300 MHz, C^{2}HCl$_3$) 7.41 (1H, br s, NH, exchanges in ^{2}H$_2$O), 4.26 (1H, dd, $J_{2,3A}$ 9.8, $J_{2,3B}$ 6.9, H-2), 3.13 (1H, m, H-3A), 2.60 (1H, m, H-4), 1.96 (1H, m, H-3B), 1.43 (9H, s, OC(CH$_3$)$_3$) and 1.29 (3H, d, $J_{Me,4}$ 7.3, CH$_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 180.5 (C-5), 170.3 (ester), 115.5 (CN), 115.4 (CN), 84.1 (O*C*(CH$_3$)$_3$), 61.9 (C-2), 55.1 (C-6), 39.5 (C-4), 34.7 (C-3), 28.4 (OC(*C*H$_3$)$_3$) and 19.3 (C–*C*H$_3$).

tert-Butyl (2*S*,4*RS*)-2-amino-4-(5-amino-4-cyano-1*H*-pyrazol-3yl)pentanoate (32)

A suspension of *tert*-butyl (2*S*,4*S*)-5-dicyanomethylene-4-methylpyrrolidine-2-carboxylate **31** (100 mg, 0.4 mmol) in hydrazine monohydrate (98 μl, 2.0 mmol) and distilled water (35 μl,) was heated at reflux for 15 min. After cooling, the solvent was removed *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel using ammonia–ethanol–dichloromethane (1 : 18 : 89) as eluent gave *tert-butyl (2S,4RS)-2-amino-4-(5-amino-4-cyano-1H-pyrazol-3yl)penta-noate* **32** as an inseparable mixture of two diastereoisomers in the form of an oil (30 mg, 28%); *m/z* [+ve FAB (3-NBA)] 280 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3393 (br, NH), 2212 (CN) and 1727 (ester); δ_H (300 MHz, ^{2}H$_2$O) 3.80 (1H, m, H-2), 2.90 (1H, m, H-4), 2.10 (2H, m, H-3), 1.24 (9H, s, OC(CH$_3$)$_3$) and 1.12 (3H, 2 × d, $J_{Me,4}$ 7, CH$_3$); δ_C (75.5 MHz, ^{2}H$_2$O) 178.2 (ester), 168.8 (Ar), 156.8 (Ar), 126.3 (CN), 116.0 (Ar), 86.1 (O*C*(CH$_3$)$_3$), 52.2 and 51.8 (C-2, both isomers), 35.4 (C-3), 29.3 (C-4), 27.2 and 21.4 (OC(*C*H$_3$)$_3$) and 20.0 and 19.2 (C–*C*H$_3$, both isomers).

tert-Butyl (2*S*,4*RS*)-2-amino-4-(5-amino-4-cyano-1-methyl-1*H*-pyrazol-3yl)pentanoate (33)

A suspension of *tert*-butyl (2*S*,4*S*)-5-dicyanomethylene-4-methylpyrrolidine-2-carboxylate **31** (60 mg, 0.28 mmol) in methylhydrazine (120 μl, 2.0 mmol) and distilled water (22 μl, 1 mmol) was heated at reflux for 20 min. After cooling, distilled water (22 μl) was added and the solution turned opaque. The solvent was removed *in vacuo* to give an orange oil, which was purified by column chromatography using trifluoroacetic acid, water, methanol and dichloromethane (3 : 6 : 30 : 70) as eluent to yield *tert-butyl (2S,4RS)-2-amino-4-(5-amino-4-cyano-1-methyl-1H-pyrazol-3yl)pentanoate* **33** as an inseparable mixture of two diastereoisomers as an orange oil (51 mg, 62%); $[a]_D^{25}$ −98.5 (*c* 1.0, H$_2$O); (*m/z* (EI) Found 293.1851. C$_{14}$H$_{23}$N$_5$O$_2$ requires 293.1851.); *m/z* [+ve FAB (glycerol)] 294 [M + H]$^+$; ν_{max} (film)/cm^{-1} 3343 (br, NH), 2212 (CN) and 1736 (ester);

δ_H (300 MHz, [^{2}H$_6$]-DMSO) 6.39 (2H, br s, NH$_2$, exchanges in ^{2}H$_2$O), 3.70 (1H, m, H-2 both isomers), 3.32 (3H, 2 × s, NCH$_3$, both isomers), 2.83 (1H, m, H-4), 2.02 (2H, m, H-3), 1.79 (9H, 2 × s, OC(CH$_3$)$_3$, both isomers) and 1.08 (3H, 2 × d, $J_{Me,4}$ 7.0, CH$_3$, both isomers); δ_C (75.5 MHz, ^{2}H$_2$O) 179.1 (ester), 169.4 (Ar), 157.2 (Ar), 153.1 (CN), 116.4 (Ar), 86.4 (O*C*(CH$_3$)$_3$), 52.2 (C-2), 35.9 (C-3), 34.5 (NCH$_3$), 30.1 (C-4), 27.7 and 22.2 ((OC(*C*H$_3$)$_3$, both isomers) and 20.8 and 19.9 (C–*C*H$_3$, both isomers).

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