Investigation of a route to ibotenic acid analogues *via* a reduced pyroglutamate template

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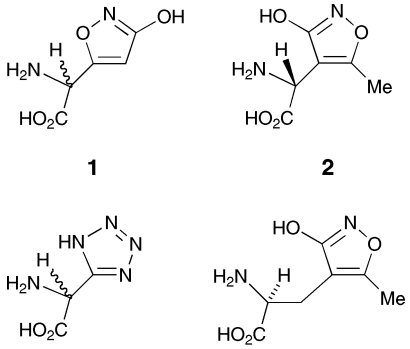
Two alternative "ring switch" based syntheses have been shown to give access to the reduced protected homochiral analogues, **27**, **28** and **36**, of the CNS active compound ibotenic acid.

Introduction

(2*S*)-Glutamic acid is an excitatory neurotransmitter which interacts with a variety of ionotropic (ion channel controlling) and metabotropic (G-protein linked) receptors.[1] Analogues of glutamic acid have been shown to be specific in their action by interacting with one or more of these receptors to give selective physiological effects. Thus, while 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,[1] analogues such as (*R*)-2-amino-2-(3-hydroxy-5-methylisoxazol-4-yl)-acetic acid [(*R*)-AMAA] **2** and DL-tetrazolylglycine **3** act specifically at the ionotropic *N*-methyl-D-aspartate (NMDA) receptor sub-type.[1] These compounds consist of a heterocyclic ring system fused to a glycine moiety. The homologue (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazoyl)-propionic acid (AMPA) **4** 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.[1] Glutamate receptors are involved in memory and learning processes and antagonists have been identified as potential drugs for variety of neurodegenerative diseases,[2] including Alzheimer's disease,[2] epilepsy[2,3] and ischaemia.[2,4]



1 **2** **3** **4**

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 individual receptors[5–9] and some have shown interesting CNS activity. The synthesis, shown in Scheme 1, involved reaction of aldehydes **5** of protected pyroglutamic acid ($n = 1$)[5–8] and of protected 6-oxopipecolic acid ($n = 2$),[9] with bisnucleophiles and involved a minimum of steps. We have christened this powerful synthetic tool a "ring switching" reaction[5] and recently extended it to the use of *β*-lactam aldehydes **12** from which a plethora of analogues of ibotenic acid could be obtained[10] (Scheme 2).

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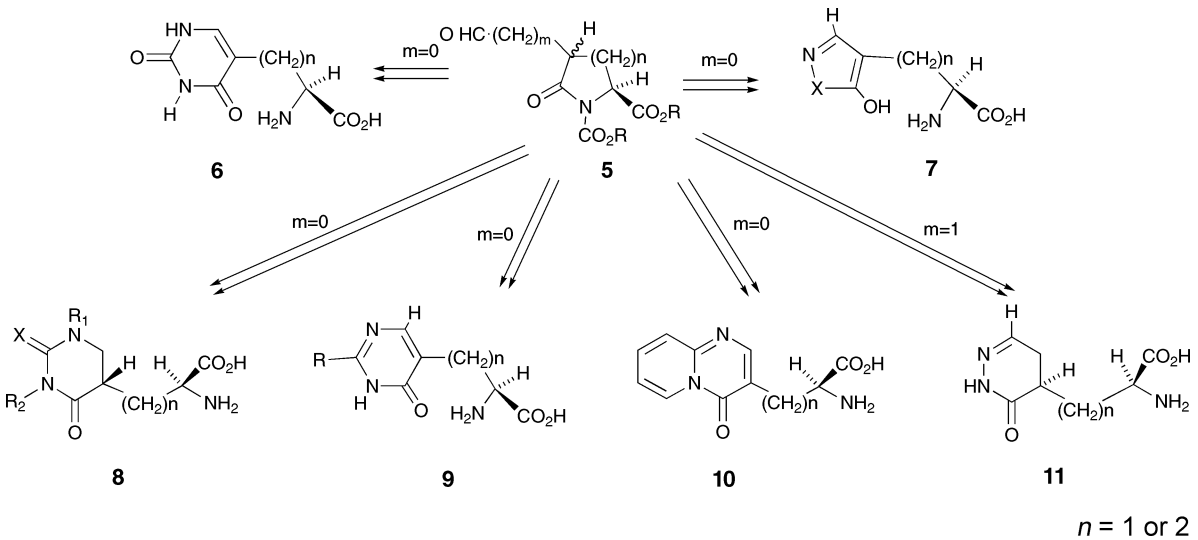
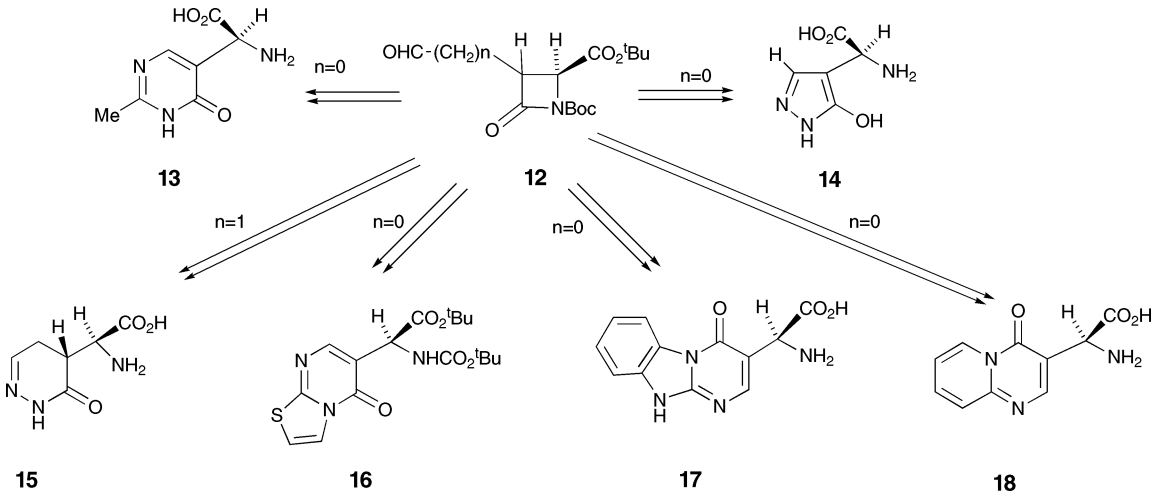


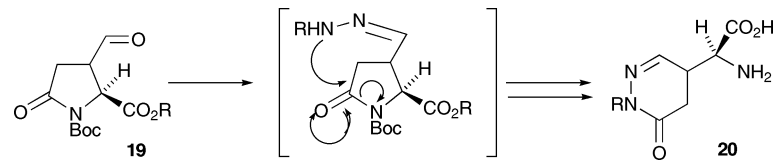
6 **5** **7** **8** **9** **10** **11**

Scheme 1

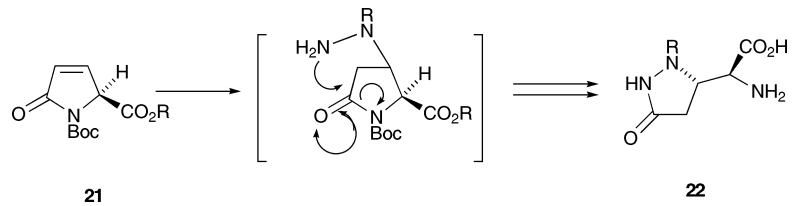


Scheme 2

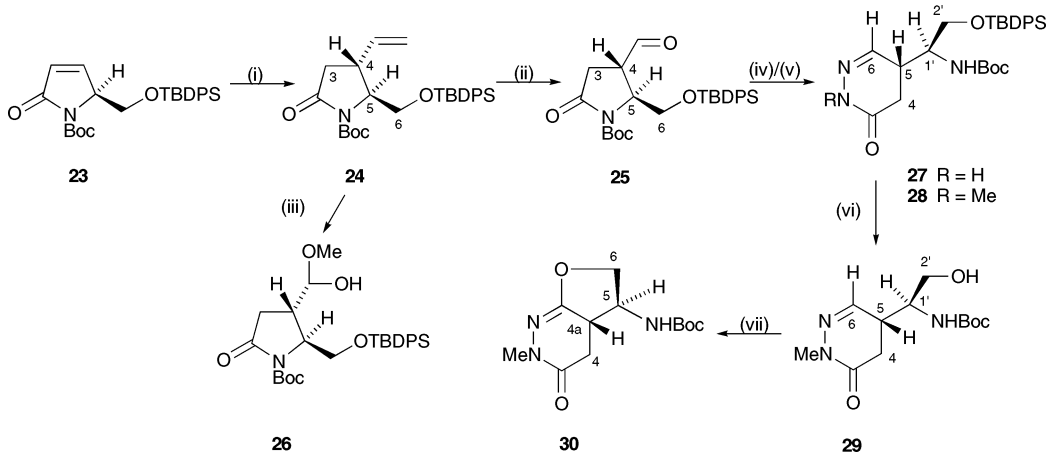
An alternative way of obtaining analogues of ibotenic acid might be to react the pyroglutamate-3-aldehyde **19** with bisnucleophiles and indeed reaction with a substituted hydrazine, as in Scheme 3, might yield isomers **20** of the ibotenate analogues **15**, obtained by the *β*-lactam route.[10] Further, reaction of an enone **21** with substituted hydrazines, as in Scheme 4, might yield the compounds **22**, reduced isomers of the ibotenate analogue **14**, which was obtained by the *β*-lactam route.[10] Unfortunately, synthesis of 3-substituted pyroglutamate derivatives such as the aldehydes **19** would best be approached *via* enones such as **21**, and we have



Scheme 3



Scheme 4



Scheme 5 Reagents and conditions: (i) ref. 13; (ii) (a) O_3, CH_2Cl_2, −78 °C, 15 min (b) Ph_3P, rt, 1 h (96%); (iii) (a) O_3, CH_2Cl_2, −78 °C, 15 min, (b) Zn, HOAc, rt, 1 h (18%); (iv) H_2NNH_2, MeOH, rt, 18 h (41% **27**); (v) $MeNHNH_2$, MeOH, rt, 18 h (65% **28**); (vi) TBAF, THF, 0 °C, then rt, 25 min (96%); (vii) $RuO_2{\cdot}H_2O$, $NaIO_4$, H_2O, CCl_4–CH_3CN, rt, 18 h (35%).

shown[11] that such compounds are extremely prone to racemisation and dimerisation under very mild conditions. We therefore decided to test the route using the reduced compounds **23** and **25**.

Results and discussion

The aldehyde **25** was prepared as shown in Scheme 5 by a similar route to one we have previously used.[12] The 4-vinyl substituted compound **24** was prepared from the enone **23** by the method of Herdeis and Hubmann.[13] Ozonolysis followed by a triphenylphosphine work-up then gave the aldehyde **25**. In an earlier ozonolysis reaction where zinc and acetic acid were used followed by methanol in the work-up, the hemiacetal **26** was obtained. The structure of this compound was assigned on the basis of the spectral data and confirmed by X-ray crystallography. The crystal structure is shown in Fig. 1, confirming the relative stereochemistry of two of the centres, the hydroxyl group being disordered over two locations in the crystal, indicating a mixture of epimers.

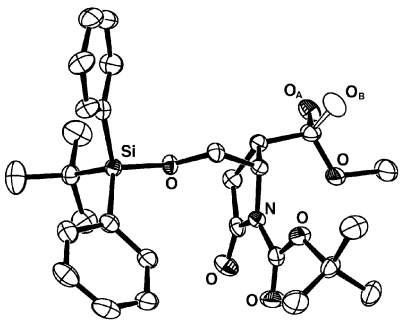


Fig. 1 X-Ray structure determination of (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-hydroxymethoxymethylpyrrolidin-2-one **26**.

Having prepared the desired aldehyde **25**, we were now in a position to attempt the "ring-switching" reaction. We therefore reacted the aldehyde separately with hydrazine and with methylhydrazine and obtained the "ring-switched" products **27** and **28** in 41 and 65% yields, respectively. The urethane–lactam band at *ca.* 1770 cm^{-1} was no longer present in the infra-red spectra of these compounds and the imine proton, H-6, appeared at δ 7.03 ppm in the ^{1}H NMR spectrum of product **27** and at δ 7.06 ppm in ^{1}H NMR spectrum of product **28**. A characteristic exchangeable NHBoc doublet was present at δ 4.86 ppm in the ^{1}H NMR spectrum of product **27** and at δ 4.74 ppm in the ^{1}H NMR spectrum of product **28**.

The "ring switch" reactions had, therefore, succeeded but, to prepare the desired ibotenic acid analogues **20**, it was now necessary to deprotect the products to the corresponding alcohols and then oxidise these to the acids. The *N*-methylpyridazine **28** was therefore treated with tetrabutylammonium fluoride in tetrahydrofuran to afford the alcohol **29** in 96% yield. When this was oxidised using ruthenium oxide monohydrate and sodium periodate, no reaction was observed after 18 h at room temperature although, when 2.2 mol% of catalyst and 4.1 equivalents of sodium periodate were used, a new, less polar product was obtained in 34% yield. This was evidently not the desired acid and the spectroscopic data suggested that it might be the cyclic imino ether **30**. This, and the relative stereochemistry was confirmed by X-ray structure determination (Fig. 2). An attempt to oxidise the primary alcohol **29** using ruthenium trichloride and periodate which had proved successful in our hands[12] for oxidation of other protected amino alcohols was unsuccessful, as was the use of oxygen and a platinum catalyst.

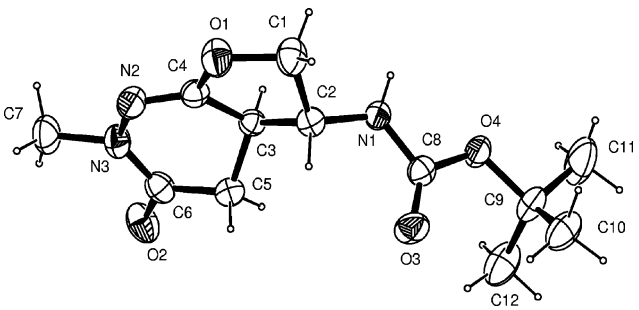
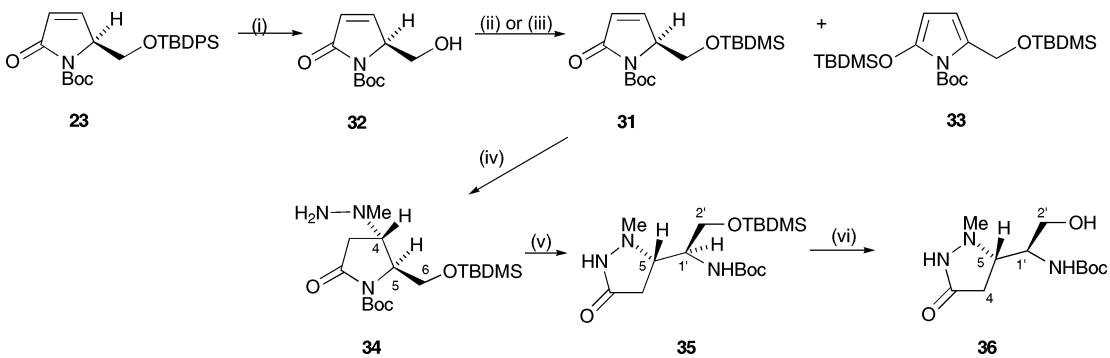


Fig. 2 X-Ray structure determination of (4a*S*,5*S*)-5-*tert*-butoxycarbonylamino-2-methyl-3-oxo-2,3,4,4*a*,5,6-hexahydrofuro[2,3-*c*]pyridazine **30**.

The alternative "ring switching" reaction method of Scheme 4 has already been carried out successfully on the reduced analogue **31**[14] but when we reacted the TBDPS derivative **23** with hydrazine hydrate or with methylhydrazine no reaction ensued. We therefore deprotected the TBDPS derivative **23** using tetrabutylammonium fluoride and acetic acid in tetrahydrofuran to obtain the alcohol **32** in quantitative yield as shown in Scheme 6. This was reacted with *tert*-butyldimethylsilyl triflate and lutidine in dichloromethane at



Scheme 6 Reagents and conditions: (i) TBAF, HOAc, THF, 0 °C then rt, 18 h (quant.); (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, then 0 °C, 30 min, then rt, 30 min (43% **31** + 43% **33**); (iii) TBDMSOTf, pyridine, CH_2Cl_2, −78 °C, 30 min, then −10 °C, 30 min then rt, 30 min (76% **31**); (iv) $MeNHNH_2$, MeOH, H_2O, rt, 18 h (80%); (v) aq. NaOH, MeOH, reflux, 18 h (48%); (vi) TBAF, HOAc, THF, 0 °C, then rt, 18 h (61%).

−78 °C to give the required TBDMS ether **31** in 43% yield. This was the only product in small scale reactions but the pyrrole **33** was obtained in yields of up to 46% in larger scale reactions. When pyridine was used as base in this reaction, the compound **31** was obtained in 76% yield. We were now able to react the enone **31** with methylhydrazine in water and methanol to obtain the product **34** in yields of up to 80%. The singlet *N*-methyl and the NH_2 signals in the ^{1}H NMR-spectrum confirmed the regiochemistry of nucleophilic attack. When the adduct **34** was heated at reflux for 18 h in aqueous methanolic sodium hydroxide the desired "ring switched" product **35** was obtained in 48% yield. The difference in reactivity between the TBDPS and TBDMS derivatives **23** and **31** respectively may be ascribed to steric considerations.

Treatment of the "ring switched" product with TBAF and acetic acid in tetrahydrofuran gave the alcohol **36** in 61% yield but, again, all attempts to oxidise this to the acid proved fruitless.

Conclusions

We have shown that a further two alternative modes of "ring switching" reactions are viable. However for the first time it had proved necessary to use protected amino alcohols rather than protected amino acids in the synthesis. To obtain CNS active ibotenic acid analogues, however, subsequent oxidation was necessary. This did not prove possible using the heterocyclic products of the "ring switching" reactions and so it would appear that oxidation after addition to the double bond in **23** has removed the danger of dimerisation or racemisation would have to precede the "ring switching" process for the method to be completely successful. Oxidation of such pyroglutaminols has been achieved by a variety of methods.[15]

Experimental

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements (in units of 10^{-1} deg cm^2 g^{-1}) were obtained on a Perkin Elmer PE241 polarimeter using a 1 dm pathlength cell. IR spectra were recorded using a Perkin Elmer 1710 Fourier transform spectrometer. ^{1}H NMR spectra were recorded using a Bruker DPX 300 (300 MHz) Fourier transform instrument. ^{13}C NMR spectra (^{1}H decoupled) were recorded using a Bruker DPX 300 (75.5 MHz) Fourier transform instrument. DEPT, ^{1}H COSY and ^{1}H–^{13}C COSY experiments were used to help assign NMR spectra where necessary. Homonuclear decoupling and NOE experiments were used to help determine stereochemistry where necessary. δ are given in ppm and J in Hz. Residual undeuteriated solvent peaks and tetramethysilane (TMS) were used as internal references. All NMR spectra were recorded at 25 °C unless otherwise stated. Low-resolution mass spectra were recorded by Dr A. Abdul-Sada using Kratos MS 80RF (FAB), VG Autospec (EI) or Bruker BioApex III (ESI) double focusing spectrometers. High-resolution spectra were recorded by Dr A. Abdul-Sada using a 4.7 FT-ICR (Bruker BioApex III) spectrometer or obtained from the EPSRC Central Mass Spectrometry Service at Swansea. Microanalyses were performed by Medac Ltd., Egham, Surrey. Column chromatography was performed using Davisil® Silica 60A, 35–70 mesh silica gel. Petroleum ether refers to that fraction of hexanes of boiling point 60–80 °C.

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-formylpyrrolidin-2-one (25)

A solution of (4*R*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-vinylpyrrolidin-2-one (**24**)[13] (250 mg, 0.52 mmol) in dichloromethane (10 ml) was cooled to −78 °C under nitrogen. Nitrogen was displaced by bubbling oxygen through the solution for 15 min. Ozone was passed through the solution until a blue colouration was observed. Oxygen was passed for 5 min, followed by nitrogen for 5 min and triphenylphosphine (149 mg, 0.57 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for a further 1 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using petroleum ether–ethyl acetate (3 : 2) with 1% triethylamine as the mobile phase to give (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-formylpyrrolidin-2-one (**25**) as a clear colourless oil (240 mg, 96%); $[a]_D^{26}$ +1.3 (*c* 0.8, $CHCl_3$) (lit.[12] $[a]_D^{20}$ +1.5 (*c* 1.0, $CHCl_3$)); *m*/*z* [ES+ (NH_4)] Found 499.2628, [$C_{27}H_{35}NO_5Si$ + NH_4]$^+$ requires 499.2628; *m*/*z* [EI+] 424 ([M-^{t}Bu]$^+$); δ_H (300 MHz, C^2HCl_3) 9.70 (1H, s, CHO), 7.68–7.58 (4H, m, ArH), 7.46–7.37 (6H, m, ArH), 4.57 (1H, m, H-5), 3.98 (1H, dd, $J_{6A,6B}$ 10.5, $J_{6A,5}$ 3.9, H-6A), 3.81 (1H, dd, $J_{6B,6A}$ 10.5, $J_{6B,5}$ 2.6, H-6B), 3.19 (1H, m, H-3A), 2.97–2.90 (2H, m, H-3B, H-4), 1.43 (9H, s, $C(CH_3)_3$) and 1.05 (9H, s, $SiC(CH_3)_3$); δ_C (75.5 MHz, $C_6{}^2H_6$) 197.7 (C-7), 170.3 (lactam), 150.6 (urethane), 135.9, 133.2 and 130.2 (Ar), 82.6 ($OC(CH_3)_3$), 64.9 (C-6), 57.7 (C-5), 45.6 (C-4), 32.2 (C-3), 28.1 ($OC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$) and 19.3 ($SiC(CH_3)_3$).

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-hydroxymethoxymethylpyrrolidin-2-one (26)

A solution of (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-vinylpyrrolidin-2-one (**24**) (381 mg, 0.79 mmol) in dichloromethane (9 ml) was cooled to −78 °C under nitrogen with stirring. The nitrogen was displaced by bubbling oxygen through the solution for 15 min. Ozone was passed through the solution until a blue coloration was observed. Oxygen was passed for 5 min, followed by nitrogen for 5 min and acetic acid (0.45 ml, 7.9 mmol) and zinc dust (519 mg, 7.9 mmol) were added. The mixture was allowed to warm to room temperature and was stirred for a further 1 h. The mixture was filtered and the residue was rinsed with methanol. The solvent was removed from the filtrate *in vacuo* to give an oil which was purified by flash column chromatography on silica gel using petroleum ether–ethyl acetate (1 : 1) containing 1% triethylamine as the mobile phase. (4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-hydroxymethoxymethylpyrrolidin-2-one (**26**) was obtained as a white crystalline solid (74 mg, 18%); mp 112.4–113.8 °C; $[a]_D^{22}$ −36.5 (*c* 0.16, $CHCl_3$); (Found: C, 65.3; H, 7.7; N, 2.7. $C_{28}H_{39}NO_6Si$ requires C, 65.5; H, 7.65; N, 2.7%); *m*/*z* [+ve FAB (3-NBA)] 536 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 3479 (OH) and 1771 (urethane); δ_H (300 MHz, $C^2H_3O^2H$) 7.62–7.51 (4H, m, ArH), 7.38–7.31 (6H, m, ArH), 4.81 (3H, s, OCH_3), 4.45 (1H, d, $J_{7,4}$ 4.3, H-7), 4.13 (1H, m, H-5), 3.92 (1H, dd, $J_{6A,6B}$ 10.7, $J_{6A,5}$ 2.8, H-6A), 3.60 (1H, dd, $J_{6B,6A}$ 10.7, $J_{6B,5}$ 1.8, H-6B), 2.81 (1H, m, H-4), 2.48–2.32 (2H, m, H-3), 1.28 (9H, s, $C(CH_3)_3$) and 0.92 (9H, s, $SiC(CH_3)_3$); δ_C (75.5 MHz, $C^2H_3O^2H$) 177.7 (lactam), 151.4 (urethane), 137.0, 134.4, 134.2 and 129.4 (Ar), 100.4 (C-7), 84.5

(O*C*(CH_3)$_3$), 66.9 (C-6), 62.3 (C-5), 41.3 (C-4), 36.1 (C-3), 28.6 (OC(*C*H_3)$_3$), 27.7 (SiC(*C*H_3)$_3$), 20.4 (Si*C*(CH_3)$_3$) and 9.6 (OCH_3).

Crystal data for (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-hydroxymethoxymethylpyrrolidin-2-one (**26**),† $C_{28}H_{39}NO_6Si$, M = 513.69, monoclinic, space group $P2_1$ (No. 4), a = 7.6412(4), b = 11.8424(9), c = 15.8245(7) Å, β = 102.434(3)°, V = 1398.37(14) Å^3, Z = 2, D_{calc} 1.22 mg m^{-3}, μ(Mo Kα) = 0.13 mm^{-1}, T = 173(2) K, 3805 independent reflections (R_{int} = 0.044). The final R values were $R1$ = 0.042 (for 3372 reflections with $I > 2\sigma(I)$) and $wR2$ = 0.095 (for all reflections). The hydroxy group was disordered over two positions. Data collection was carried out using a Kappa CCD diffractometer, structure analysis using program package WinGX, and refinement using SHELXL-97. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

(5*S*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-*tert*-butyldiphenylsilanyloxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine (27)

A solution of (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-4-formylpyrrolidin-2-one (**25**) (207 mg, 0.43 mmol) in methanol (15 ml) was stirred at room temperature. Hydrazine monohydrate (31.4 μl, 0.6 mmol) was added and the reaction was stirred for 18 h at room temperature. The solvent was removed *in vacuo* and the crude pale yellow foam was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (3 : 2) containing triethylamine (1%) as eluent to afford (5*S*)-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldiphenylsilanyloxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine **27** as a white foam (87 mg, 41%); $[\alpha]_D^{23}$ +47.2 (*c* 0.6, $CHCl_3$); *m*/*z* [ES+] Found 496.2620, [$C_{27}H_{37}N_3O_4Si$ + H]$^+$ requires 496.2632; *m*/*z* [+ve FAB (3-NBA)] 518 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 3278 (NH) and 1694 (urethane, amide); δ_H (300 MHz, C^2HCl_3) 8.63 (1H, br s, exch. ^2H_2O, NH) 7.65–7.58 (4H, m, ArH), 7.45–7.37 (6H, m, ArH), 7.03 (1H, s, H-6), 4.86 (1H, br, d, $J_{NH,1'}$ 8.2, NH), 3.95 (1H, m, H-1′), 3.70 (2H, m, H-2′), 2.96 (1H, m, H-5), 2.54 (1H, dd, $J_{4A,4B}$ 17.1, $J_{4A,5}$ 7.3, H-4A), 2.28 (1H, dd, $J_{4B,4A}$ 17.1, $J_{4B,5}$ 12.0, H-4B), 1.45 (9H, s, C(CH_3)$_3$) and 1.08 (9H, s, SiC(CH_3)$_3$); δ_C (75.5 MHz, C^2HCl_3) 167.4 (amide), 155.7 (urethane), 146.5 (C-6), 135.9, 132.8, 130.5 and 128.4 (Ar), 80.5 (O*C*(CH_3)$_3$), 63.7 (C-2′), 52.0 (C-1′), 36.1 (C-5), 28.7 (OC(*C*H_3)$_3$), 28.3 (C-4), 27.3 (SiC(*C*H_3)$_3$) and 19.6 (Si*C*(CH_3)$_3$).

(5*S*)-2-Methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldiphenylsilanyloxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine (28)

A solution of (4*S*,5*S*) - *N* - *tert* - butoxycarbonyl - 5 - *tert* - butyl - diphenylsiloxymethyl-4-formylpyrrolidin-2-one (**25**) (436 mg, 0.906 mmol) in methanol (25 ml) was stirred at room temperature. Methylhydrazine (72.3 μl, 1.36 mmol) was added and the reaction was stirred for a further 18 h at room temperature. The solvent was removed *in vacuo* and the crude yellow foam was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (3 : 2) as eluent to afford (5*S*)-2-methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldiphenylsilanyloxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine **28** as a clear colourless oil (298 mg, 65%); $[\alpha]_D^{20}$ +91.38 (*c* 1.0, $CHCl_3$); *m*/*z* [ES+] Found 510.2799, [$C_{28}H_{39}N_3O_4Si$ + H]$^+$ requires 510.2788; *m*/*z* [+ve FAB (3-NBA)] 532 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 3326 (NH), 1712 (urethane) and 1662 (amide); δ_H (300 MHz, C^2HCl_3) 7.63–7.58 (4H, m, ArH), 7.48–7.36 (6H, m, ArH), 7.06 (1H, s, H-6), 4.74 (1H, br d, $J_{NH,1'}$ 8.8, NH), 3.95 (1H, m, H-1′), 3.70 (2H, m, H-2′), 3.30 (3H, s, NCH_3), 2.92 (1H, m, H-5), 2.50 (1H, dd, $J_{4A,4B}$ 16.7, $J_{4A,5}$ 7.5, H-4A), 2.26 (1H, dd, $J_{4B,4A}$ 16.7, $J_{4B,5}$ 12.6, H-4B), 1.43 (9H, s, C(CH_3)$_3$) and 1.06 (9H, s, SiC(CH_3)$_3$); δ_C (75.5 MHz, C^2HCl_3) 165.2 (amide), 155.3 (urethane), 146.0 (C-6), 135.5, 132.4, 130.1 and 127.9 (Ar), 80.0 (O*C*(CH_3)$_3$), 63.3 (C-2′), 51.6 (C-1′), 36.1 (NCH_3 and C-5), 28.5 (C-4), 28.2 (OC(*C*H_3)$_3$), 26.9 (SiC(*C*H_3)$_3$) and 19.2 (Si*C*(CH_3)$_3$).

(5*S*)-2-Methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-hydroxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine (29)

A solution of (5*S*)-2-methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldiphenylsilanyloxy]-3-oxo-2,3,4,5-tetrahydropyridazine (**28**) (100 mg, 0.19 mmol) in tetrahydrofuran (5 ml) was cooled to 0 °C with stirring. Tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF containing 5%wt water, 0.235 ml, 0.235 mmol) was slowly added and the mixture was allowed to warm to room temperature with stirring over a further 25 min. Ethyl acetate (10 ml) was added and the solution was washed with saturated aqueous ammonium chloride (2 × 10 ml). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to give a pale yellow clear oil. The crude product was purified by column chromatography on silica gel initially using ethyl acetate (100%) and then ethyl acetate–methanol (96 : 4) as eluent to afford (5*S*)-2-methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-hydroxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine (**29**) as a clear colourless oil (51 mg, 96%); $[\alpha]_D^{27}$ +133.8 (*c* 0.25, $CHCl_3$); *m*/*z* [ES+] Found 272.1606, [$C_{12}H_{22}N_3O_4$ + H]$^+$ requires 272.1610; *m*/*z* [+ve FAB (3-NBA)] 294 ([M + Na]$^+$) and 272 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3400 (OH, NH), 1690 (urethane) and 1649 (amide); δ_H (300 MHz, C^2HCl_3) 7.20 (1H, s, H-6), 5.35 (1H, br d, $J_{NH,1'}$ 8.1, NH), 3.92 (1H, m, H-1′), 3.71 (2H, br, H-2′), 3.34 (3H, s, NCH_3), 2.97 (1H, m, H-5), 2.61 (1H, dd, $J_{4A,4B}$ 16.8, $J_{4A,5}$ 6.9, H-4A), 2.41 (1H, dd, $J_{4B,4A}$ 16.8, $J_{4B,5}$ 11.3, H-4B) and 1.45 (9H, s, C(CH_3)$_3$); δ_C (75.5 MHz, C^2HCl_3) 165.3 (amide), 155.3 (urethane), 146.2 (C-6), 80.3 (O*C*(CH_3)$_3$), 62.9 (C-2′), 51.6 (C-1′), 36.2 and 36.0 (NCH_3 and C-5), 28.7 (C-4) and 28.2 (OC(*C*H_3)$_3$)

(4*aS*,5*S*)-5-*tert*-Butoxycarbonylamino-2-methyl-3-oxo-2,3,4,4*a*,5,6-hexahydrofuro[2,3-*c*]pyridazine (30)

Sodium periodate (160 mg, 0.75 mmol) was added to a flask of vigorously stirred water (0.6 ml) at room temperature. Ruthenium oxide monohydrate (0.5 mg, 0.00376 mmol) was added and stirring was continued for 10 min as the solution turned orange. A solution of (5*S*)-2-methyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-hydroxyethyl]-3-oxo-2,3,4,5-tetrahydropyridazine (**29**) (50 mg, 0.18 mmol) in carbon tetrachloride (0.35 ml) and acetonitrile (0.35 ml) was added and a black colouration was instantly observed in both phases. Vigorous stirring was continued for 18 h

† CCDC reference number 294595. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b600195e

at room temperature and isopropyl alcohol (4 drops) was added. The mixture was stirred for 30 min and filtered through a pad of Celite®. The aqueous layer was extracted with ethyl acetate (3 × 1 ml). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a clear colourless oil. Purification by column chromatography on silica gel using ethyl acetate as eluent gave (4*aS*,5*S*)-5-*tert*-butoxycarbonylamino-2-methyl-3-oxo-2,3,4,4*a*,5,6-hexahydrofuro[2,3-*c*]pyridazine **30** as a clear colourless residue which crystallised on standing to give a white solid (17 mg, 35%); *m/z* [+ve FAB (3-NBA)] 270 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3303 (NH), 1712 (urethane) and 1644 (amide); δ_H (300 MHz, C^{2}HCl$_3$) 4.89 (1H, br d, $J_{NH,5}$ 7.5, NH), 4.59 (1H, t, $J_{6A,5}$ 7.9, H-6A), 4.20 (1H, m, H-5), 3.90 (1H, t, $J_{6B,5}$ 9.0, H-6B), 3.15 (3H, s, NCH_3), 2.95–2.84 (2H, m, H-4a, H-4A), 2.41 (1H, br, H-4B) and 1.37 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 162.4 and 162.0 (amide, C-8), 154.0 (urethane), 79.8 ($OC(CH_3)_3$), 72.2 (C-6), 54.5 (C-5), 37.8 (C-4a), 35.2 (NCH_3), 31.8 (C-4) and 27.2 ($OC(CH_3)_3$). A second compound (146 mg, 28%) was also isolated as a clear colourless oil with spectroscopic data identical to those of the starting material **29**.

Crystal data for (4*aS*,5*S*)-5-*tert*-butoxycarbonylamino-2-methyl-3-oxo-2,3,4,4*a*,5,6-hexahydrofuro[2,3-*c*]pyridazine (**30**)‡, $C_{12}H_{19}N_3O_4$, M = 269.30, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 5.6733(2), b = 11.5380(9), c = 21.3149(16) Å, V = 1395.24(16) Å^3, Z = 4, D_{calc} 1.28 mg m^{-3}, μ(Mo Kα) = 0.10 mm^{-1}, T = 173(2) K, 1449 independent reflections (R_{int} = 0.056). The final R values were $R1$ = 0.045 (for 1208 reflections with $I > 2\sigma(I)$) and $wR2$ = 0.107 (for all reflections). Data collection was carried out using a Kappa CCD diffractometer, structure analysis using program package WinGX, and refinement using SHELXL-97. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

(5*S*)-*N*-*tert*-Butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (32)

Acetic acid (1.14 ml, 19.94 mmol) was added to a solution of (5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**23**) (4.50 g, 9.97 mmol) in tetrahydrofuran (60 ml) and the mixture was cooled to 0 °C. Tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF containing 5wt% water, 11.9 ml, 11.9 mmol) was slowly added and the mixture was allowed to warm to room temperature. After stirring for 18 h at room temperature, the solvent was removed *in vacuo* and the pale brown solid residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (3 : 2) as eluent to afford (5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**32**) as a clear pale yellow oil (2.121 g, quant.); *m/z* [ES+] Found 236.0881, [$C_{10}H_{15}NO_4$ + Na]$^+$ requires 236.0893; *m/z* [+ve FAB (3-NBA)] 449 ([2M + Na]$^+$), 236 ([M + Na]$^+$) and 214 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3425 (OH), 1765 (urethane) and 1716 (lactam); δ_H (300 MHz, C^{2}HCl$_3$) 7.25 (1H, dd, $J_{4,3}$ 1.7, $J_{4,5}$ 3.7, H-4), 6.13 (1H, d, $J_{3,4}$ 1.7, H-3), 4.73–4.68 (1H, m, H-5), 4.02–3.95 (2H, m, H-6), 3.38 (1H, br, s, OH) and 1.55 (9H, s, $OC(CH_3)_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 170.1 (lactam), 150.4 (urethane), 149.4 (C-3), 127.7 (C-3), 83.9 ($OC(CH_3)_3$), 65.0 (C-5), 62.5 (C-6) and 28.4 ($OC(CH_3)_3$).

(5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (31) and *N*-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsiloxy-5-*tert*-butyldimethylsiloxymethylpyrrole (33)

Method A: Using 2,6-lutidine as the hindered base. *tert*-Butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf, 3.17 ml, 13.8 mmol) was added dropwise to a solution of (5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**32**) (1.960 g, 9.2 mmol) and 2,6-lutidine (2.14 ml, 18.4 mmol) in dichloromethane (110 ml) at −78 °C under nitrogen. The solution was allowed to warm to 0 °C for 30 min and to room temperature for a further 30 min. Saturated aqueous sodium hydrogen carbonate (80 ml) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 60 ml), the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude pungent oil was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (10 : 1) as eluent to afford (5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**31**) as a clear colourless oil which crystallised on standing to give a white solid (1.288 g, 43%); mp 57.3–58.4 °C; $[\alpha]_D^{26}$ −174.2 (*c* 0.5, CH_2Cl_2) (lit[16] mp 64–65 °C, $[\alpha]_D^{25}$ −176 (*c* 1.0, $CHCl_3$)); *m/z* [ES+] Found 677.3613, [2 × $C_{16}H_{29}NO_4Si$ + Na]$^+$ requires 677.3623; ν_{max} (film)/cm^{-1} 1782 (urethane), 1745 and 1713 (lactam); δ_H (300 MHz, C^{2}HCl$_3$) 7.24 (1H, dd, $J_{4,3}$ 1.8, $J_{4,5}$ 6.0, H-4), 6.06 (1H, d, $J_{3,4}$ 1.8, H-3), 4.55 (1H, br, $J_{5,6A}$ 3.7, $J_{5,6B}$ 3.0, H-5), 4.10 (1H, dd, $J_{6A,6B}$ 9.6, $J_{6A,5}$ 3.7, H-6A), 3.66 (1H, dd, $J_{6B,6A}$ 9.6, $J_{6B,5}$ 3.0, H-6B), 1.53 (9H, s, $OC(CH_3)_3$), 0.84 (9H, s, $SiC(CH_3)_3$) and 0.03 (6H, s, $Si(CH_3)_2$); δ_C (75.5 MHz, C^{2}HCl$_3$) 169.7 (lactam), 150.1 (C-4), 149.8 (urethane), 127.4 (C-3), 83.3 ($OC(CH_3)_3$), 63.9 (C-5), 62.8 (C-6), 28.5 ($OC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$) and −5.1 ($SiCH_3$).

The above procedure was followed using (5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**32**) (705 mg, 3.31 mmol) and 2,6-lutidine (0.77 ml, 6.62 mmol) in dichloromethane (40 ml). After work up, the crude oil was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (15 : 1) as eluent to afford *N*-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsiloxy-5-*tert*-butyldimethylsiloxymethylpyrrole (**33**) as a clear colourless oil (371 mg, 25%); *m/z* [ES+] Found 442.2780, [$C_{22}H_{43}NO_4Si_2$ + H]$^+$ requires 442.2803; ν_{max} (film)/cm^{-1} 1756 (urethane); δ_H (300 MHz, C^{2}HCl$_3$) 5.82 (1H, d, $J_{4,3}$ 3.4, H-4), 5.13 (1H, d, $J_{3,4}$ 3.4, H-3), 4.67 (2H, s, H-6), 1.55 (9H, s, $OC(CH_3)_3$), 0.96 (9H, s, $SiC(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.22 (6H, s, $Si(CH_3)_2$) and 0.00 (6H, s, $Si(CH_3)_2$); δ_C (75.5 MHz, C^{2}HCl$_3$) 147.6 (urethane), 142.9 (C-2), 124.4 (C-5), 89.2 (C-3), 81.9 ($OC(CH_3)_3$), 59.0 (C-6), 26.8 ($OC(CH_3)_3$), 24.9 ($SiC(CH_3)_3$), 24.7 ($SiC(CH_3)_3$), 17.7 ($SiC(CH_3)_3$) and −4.1 ($SiCH_3$). (5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**31**) (325 mg, 30%) was also eluted with spectroscopic data identical to those of the sample of **31** prepared above.

Method B: Using pyridine as the base. *tert*-Butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf, 161.7 μl, 0.704 mmol) was slowly added to a solution of (5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**32**) (100 mg,

‡ CCDC reference number 294596. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b600195e

0.469 mmol) and pyridine (163.0 µl, 2.01 mmol) in dichloromethane (4 ml) at −78 °C under nitrogen. After 30 min the solution was allowed to warm to −10 °C for 30 min and to room temperature for a further 30 min. Saturated aqueous sodium hydrogen carbonate (3 ml) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 4 ml), the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* using a vacuum pump with heating. The viscous, pale brown crude oil was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (13 : 1) as eluent to afford (5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**31**) as a clear colourless oil which crystallised on standing to give a white solid (117 mg, 76%) with identical spectra to those of the sample prepared by method A.

The above procedure was followed using (5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**32**) (1.844 g, 8.657 mmol) and pyridine (3.0 ml, 37.1 mmol) in dichloromethane (45 ml). After work up the crude oil was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (12 : 1) as eluent to afford *N*-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsiloxy-5-*tert*-butyldimethylsiloxymethylpyrrole (**33**) (690 mg, 18%) with spectroscopic data identical to those of the sample prepared using method A.

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-3-*N*-methylhydrazinopyrrolidin-2-one (34). Methylhydrazine (0.29 ml, 5.413 mmol) was slowly added to a solution of (5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**31**) (1.180 g, 3.609 mmol) in methanol (40 ml) and water (1 ml) at room temperature. The solution was stirred for 18 h at room temperature and the solvent was removed *in vacuo*. The residual oil was purified by gradient column chromatography on silica gel using petroleum ether–ethyl acetate (4 : 1) followed by ethyl acetate (100%) as eluent to afford (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-3-*N*-methylhydrazinopyrrolidin-2-one (**34**) as a clear colourless oil (1.081 g, 80%); $[\alpha]_D^{22}$ −39.5 (*c* 2.0, MeOH) (lit[14] $[\alpha]_D^{20}$ − 37.3 (*c* 2.2, MeOH)); *m*/*z* [ES+] Found 374.2457, $[C_{17}H_{35}N_3O_4Si + H]^+$ requires 374.2469; ν_{max} (film)/cm^{-1} 3344 (NH), 1784 (urethane) and 1712 (lactam); δ_H (300 MHz, C^2HCl_3) 4.24 (1H, m, H-5), 3.88 (1H, dd, $J_{6A,6B}$ 10.4, $J_{6A,5}$ 3.7, H-6A), 3.68 (1H, dd, $J_{6B,6A}$ 10.4, $J_{6B,5}$ 2.2, H-6B), 3.05 (1H, m, H-4), 2.86 (2H, br s, exch. $C^2H_3O^2H$, NH_2), 2.70 (1H, dd, $J_{3A,3B}$ 18.0, $J_{3A,4}$ 8.1, H-3A), 2.53 (1H, dd, $J_{3B,3A}$ 18.0, $J_{3B,4}$ 1.1, H-3B), 2.47 (3H, s, NCH_3), 1.51 (9H, s, $OC(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.03 (3H, s, $SiCH_3$) and 0.01 (3H, s, $SiCH_3$); δ_C (75.5 MHz, C^2HCl_3) 174.1 (lactam), 150.4 (urethane), 83.1 ($OC(CH_3)_3$), 63.9 (C-6), 62.1 and 61.9 (C-4 and C-5), 47.5 (NCH_3), 36.4 (C-3), 28.5 ($OC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), −5.1 ($SiCH_3$) and −5.2 ($SiCH_3$).

(5*S*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-*tert*-butyldimethylsiloxyethyl]-1-methylpyrazolidin-3-one (35)

0.25 M Aqueous sodium hydroxide (2.0 ml, 0.5 mmol) was added to a solution of (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-3-*N*-methylhydrazinopyrrolidin-2-one (**34**) (1.08 g, 2.895 mmol) in methanol (20 ml). The mixture was heated at reflux for 18 h, cooled and the solvent was removed *in vacuo*. The pale brown crude oil was purified by gradient column chromatography on silica gel using petroleum ether–ethyl acetate (3 : 2, 1 : 1 and 2 : 3) as eluent to afford (5*S*)-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldimethylsiloxyethyl]-1-methylpyrazolidin-3-one (**35**) as a pale yellow oil which crystallised on standing (512 mg, 48%); mp 131–132.5 °C; $[\alpha]_D^{20}$ +14.0 (*c* 2.0, MeOH) [lit[14] $[\alpha]_D^{20}$ +12.2 (*c* 1.7, MeOH)]; *m*/*z* [ES+] Found 769.4735 [2M + Na]$^+$, $[C_{34}H_{70}N_6O_8Si_2 + Na]^+$ requires 769.4685; ν_{max} (film)/cm^{-1} 3275 (NH) and 1693 (amide); δ_H (300 MHz, $C^2H_3O^2H$) 3.73 (1H, dd, $J_{2'A,2'B}$ 10.1, $J_{2'A,1'}$ 4.5, H-2′A), 3.62 (1H, dd, $J_{2'B,2'A}$ 10.1, $J_{2'B,1'}$ 3.3, H-2′B), 3.44 (1H, m, H-1′), 3.12 (1H, m, H-5), 2.81 (1H, dd, $J_{4A,4B}$ 17.3, $J_{4A,5}$ 8.8, H-4A), 2.50 (3H, s, NCH_3), 2.18 (1H, dd, $J_{4B,4A}$ 17.3, $J_{4B,5}$ 3.3, H-4B), 1.35 (9H, s, $OC(CH_3)_3$), 0.85 (9H, s, $SiC(CH_3)_3$) and 0.03 (6H, s, $Si(CH_3)_2$); δ_C (75.5 MHz, C^2HCl_3) 174.4 (C-3), 156.0 (urethane), 80.0 ($OC(CH_3)_3$), 64.7 (C-5), 62.3 (C-2′), 53.5 (C-1′), 48.0 (NCH_3), 31.6 (C-4), 28.7 ($OC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 18.6 ($SiC(CH_3)_3$) and −5.1 (2 × $SiCH_3$).

(5*S*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-hydroxyethyl]-1-methylpyrazolidin-3-one (36)

Acetic acid (23.5 µl, 0.410 mmol) was added to a solution of (5*S*)-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butyldimethylsiloxyethyl]-1-methylpyrazolidin-3-one (**35**) (139 mg, 0.373 mmol) in tetrahydrofuran (5 ml) at 0 °C. Tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, containing 5% wt. water, 0.485 ml, 0.485 mmol) was slowly added and the solution was allowed to warm to room temperature. After stirring at room temperature for 3 h, further TBAF (1.0 M solution in THF, containing 5wt% water, 0.186 ml, 0.186 mmol) was added and the mixture was stirred for 15 h at room temperature. The solvent was removed *in vacuo* and the pale brown oil was purified by column chromatography on silica gel using chloroform–methanol (95 : 5) as eluent to afford (5*S*)-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-hydroxyethyl]-1-methylpyrazolidin-3-one (**36**) as a clear colourless oil which crystallised on standing to give a white solid (59 mg, 61%); mp 189.5–190.5 °C; $[\alpha]_D^{21}$ +27.2 (*c* 1.5, MeOH); *m*/*z* [ES+] Found 260.1611, $[C_{11}H_{21}N_3O_4 + H]^+$ requires 260.1604; ν_{max} (film)/cm^{-1} 3278 (NH, OH) and 1686 (br, lactam, urethane); δ_H (300 MHz, $C^2H_3O^2H$) 3.76–3.54 (3H, m, H-1′ and H-2′), 3.24 (1H, m, H-5), 2.93 (1H, dd, $J_{4A,4B}$ 17.3, $J_{4A,5}$ 8.8, H-4A), 2.63 (3H, s, NCH_3), 2.27 (1H, dd, $J_{4B,4A}$ 17.3, $J_{4B,5}$ 3.3, H-4B) and 1.46 (9H, s, $OC(CH_3)_3$); δ_C (75.5 MHz, $C^2H_3O^2H$) 176.9 (amide), 158.8 (urethane), 80.7 ($OC(CH_3)_3$), 66.3 (C-5), 62.9 (C-2′), 55.4 (C-1′), 47.7 (NCH_3), 32.8 (C-4) and 29.1 ($OC(CH_3)_3$).

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