ARTICLE

OBC
www.rsc.org/obc

Synthesis of 5/7-, 5/8- and 5/9-bicyclic lactam templates as constraints for external *β*-turns

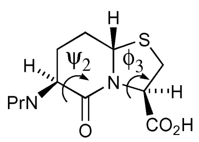
Heather M. E. Duggan, Peter B. Hitchcock and Douglas W. Young*
Department of Chemistry, University of Sussex, Falmer, Brighton, UK BN1 9QJ

Received 1st March 2005, Accepted 19th April 2005
First published as an Advance Article on the web 10th May 2005

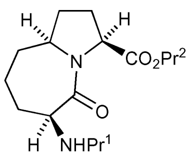
The 5/7-, 5/8- and 5/9-bicyclic lactams **3**, **17**, **5** and **6** have been synthesised as single diastereoisomers by a route involving ring closing olefin metathesis. The X-ray crystal structure of the amino acid hydrochloride **17** has been carried out and compared to that of the saturated external *β*-turn constraint **18**.

Introduction

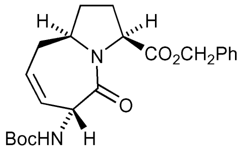
The reverse turn, a tetrapeptide motif, frequently occurs on the surface of large functional proteins and so it is an important motif for molecular recognition processes, which may be targeted for therapeutic intervention.[1,2] *β*-Turns have been classified[3] and, because synthetic analogues of the turn motif need not be part of a large protein to be constrained in appropriate stable conformations and they are less liable to proteolysis than natural turns, they have been increasingly investigated as potential drugs.[4] The first bicyclic dipeptide to be used in this way was the so-called "Bicyclic Turned Dipeptide" (BTD) **1**, prepared by Nagai and Sato.[5] This had a CD spectrum which was close to that of a known type II′ *β*-turn and, when incorporated into peptides in place of natural *β*-turns, showed useful biological activity.[6] In addition, BTD has also been used as an external constraint on which to synthesise a peptide which will adopt a *β*-turn conformation. Thus, a cyclo-BTD-tetrapeptide containing the LDV motif has been shown to inhibit the interaction between the integrin $\alpha_4\beta_1$ and vascular cell adhesion molecule-1 (VCAM-1).[7] Other bicyclic dipeptide mimetics have been investigated and the 5/7-bicyclic lactam **2** has been used both as a *β*-turn mimetic[8] and as an external restraint for a cyclic tetrapeptides containing either the RGD motif[9] or the LDV motif.[10] Both RGD and LDV occur in *β*-turns in extracellular matrix adhesive proteins recognised by integrins.



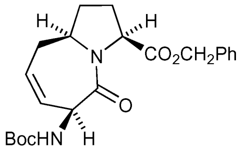
1, Pr = protecting group



2

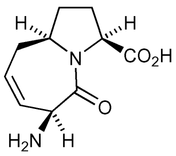


3a

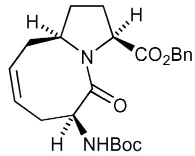


3b

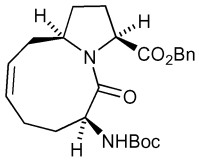
ratio 1 : 3



4



5



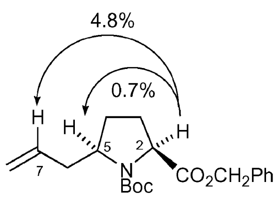
6

Following our work on the synthesis and use of the 5/7-bicyclic lactam **2** as an external constraint for a LDV containing *β*-turn,[10] we became interested in preparing a series of modified bicyclic lactams to which external tetrapeptides might be attached. We have therefore embarked on the synthesis of the 5/7-, 5/8- and 5/9-bicyclic lactams **3**, **4**, **5** and **6** by a common synthetic route.

Results and discussion

Our strategy is outlined in Scheme 1, where ring closing olefin metathesis of the compounds **8** (n = 0, 1 or 2) would lead to the corresponding bicyclic lactams **7** (n = 0, 1 or 2). The compounds **8** might be obtained by condensation of the allylpyrollidine **9** with an appropriate protected amino acid **10** (n = 0, 1 or 2). A ring closing olefin metathesis strategy has been developed by Moeller *et al*. to prepare 5/6- and 5/7-bicyclic lactams.[11]

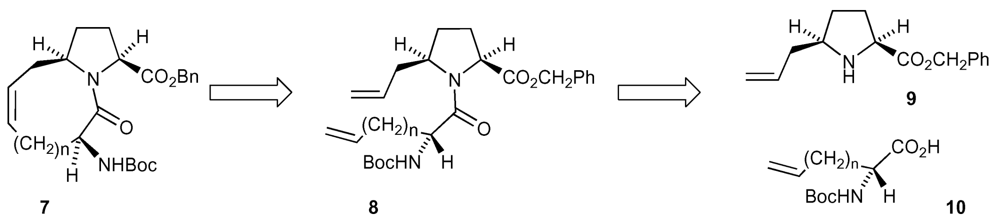
Since the synthon **9** is common for all of our target syntheses, its preparation was our first goal and we opted for a route which had been used by Scolastico *et al.*[12] to prepare the corresponding *tert*-butyl ester. We first converted benzyl-*N*-*tert*-butoxycarbonylpyroglutamate **11**[13] into the carbinolamine **12** by reduction with Super-Hydride® in THF at −78 °C, as shown in Scheme 2. The unstable carbinolamine **12** was stirred in methanol containing *para*-toluenesulfonic acid to yield the ether **13** and this was reacted with allyltributylstannane and $BF_3\cdot Et_2O$ in dichloromethane at −78 °C to give a 73% yield of the protected 5-allylpyrrolidine **14** as mixture of diastereoisomers. Although the ^1H NMR spectrum was complicated by rotational isomerism, some signals for the individual diastereoisomers in the mixture could be assigned by the NOE experiments summarised in Fig. 1. Irradiation at 3.9 ppm for H-2 caused a 0.7% enhancement to the signal for H-5*cis* at 4.27 ppm and no enhancement to the signal for H-5*trans* at 4.37 ppm. There was also a 4.7% enhancement in the combined multiplet for H-7 at 5.75 ppm. Integration suggested a *cis* : *trans* ratio of 2 : 1. This is in keeping with the findings of Scolastico *et al.*,[12] who obtained a *cis* : *trans* ratio of *ca.* 2 : 1 when the corresponding *tert*-butyl ester was prepared. It is interesting



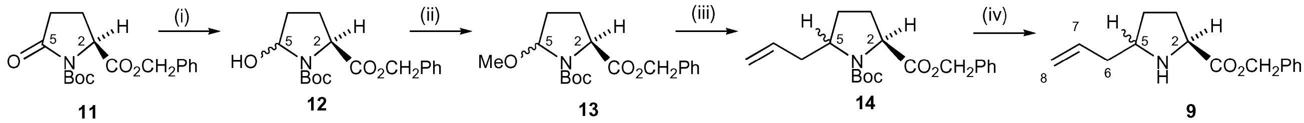
14a

Fig. 1 NOE experiments on the *cis*-component of the diastereoisomeric mixture **14**.

DOI: 10.1039/b503014e



Scheme 1



Scheme 2 *Reagents and conditions:* (i) $LiB(Et)_3H$, THF, −78 °C, 2 h (99%); (ii) MeOH, ptsa, rt, overnight (89%); (iii) $BF_3·Et_2O$, allylSn(Bu)$_3$, CH_2Cl_2, −78 °C, 3 h (73%); (iv) (a) TFA, CH_2Cl_2, rt, overnight (56%), (b) Et_3N, CH_2Cl_2, H_2O, 2 h.

that when Pedregal and coworkers[14] conducted the reaction using Grignard derived organocopper reagents in the ethyl ester series, a 94 : 6 *trans* : *cis* ratio was obtained. Deprotection using trifluoroacetic acid in dichloromethane gave the desired product as its trifluoroacetate **9a**. The free amine **9** was prepared as required, using triethylamine in dichloromethane–water.

To prepare the 5/7-bicyclic lactam **3**, the protected vinylglycine **10** (n = 0), was required. L-Vinylglycine was therefore prepared from L-methionine by the method of Rapaport and Afzali-Ardakani[15] and this was converted into the urethane **10** (n = 0) by the method of Gottlieb *et al.*[16] On reacting **10** (n = 0) with isobutyl chloroformate and condensing the resultant mixed anhydride with the amine **9**, the desired product **16** was obtained in 20% yield, together with a 23% yield of the urethane **15**, as shown in Scheme 3. The diene **16** was then heated at reflux in dichloromethane containing a catalytic quantity of Grubbs' catalyst to give two cyclised products, which could be separated by chromatography on silica gel. The first, obtained in 58% yield, was the (2*S*,5*R*,9*S*)-isomer **3a** and the second, obtained in 9% yield, was the (2*S*,5*R*,9*R*)-isomer **3b**. The stereochemistry of these compounds was deduced using NOE experiments, as shown in Fig. 2 and Fig. 3. When the signal due to H-5 at 3.40 ppm in compound **3a** was irradiated, a 1.8% enhancement at 4.53 ppm (H-2) and a 15% enhancement at 5.35 ppm (H-9) were observed, as shown in Fig. 2. This indicates a *cis*-relationship between H-2, H-5 and H-9 and defines the stereochemistry relative to H-2 as (2*S*,5*R*,9*S*). When the signal due to H-5 at 4.27 ppm in compound **3b** was irradiated, a 0.4% enhancement in the signal at 4.61 ppm (H-2) and a 4.1% enhancement in the signal at 4.97 ppm (NH) were observed, as shown in Fig. 3a. This suggests (2*S*,5*R*,9*R*)-stereochemistry which was confirmed by the additional NOE experiments summarised in Fig. 3b.

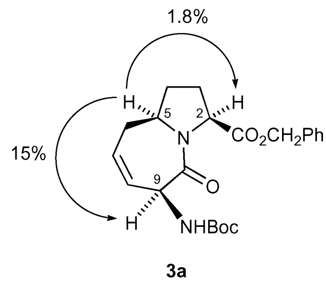


Fig. 2 NOE experiments on the 5/7-bicyclic lactam **3a**.

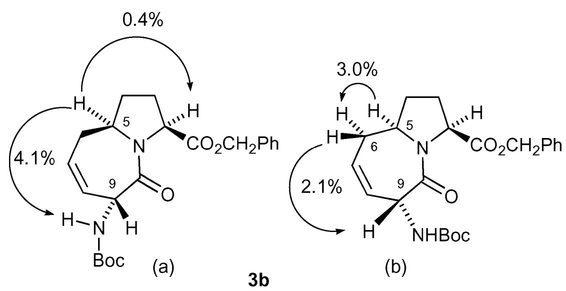
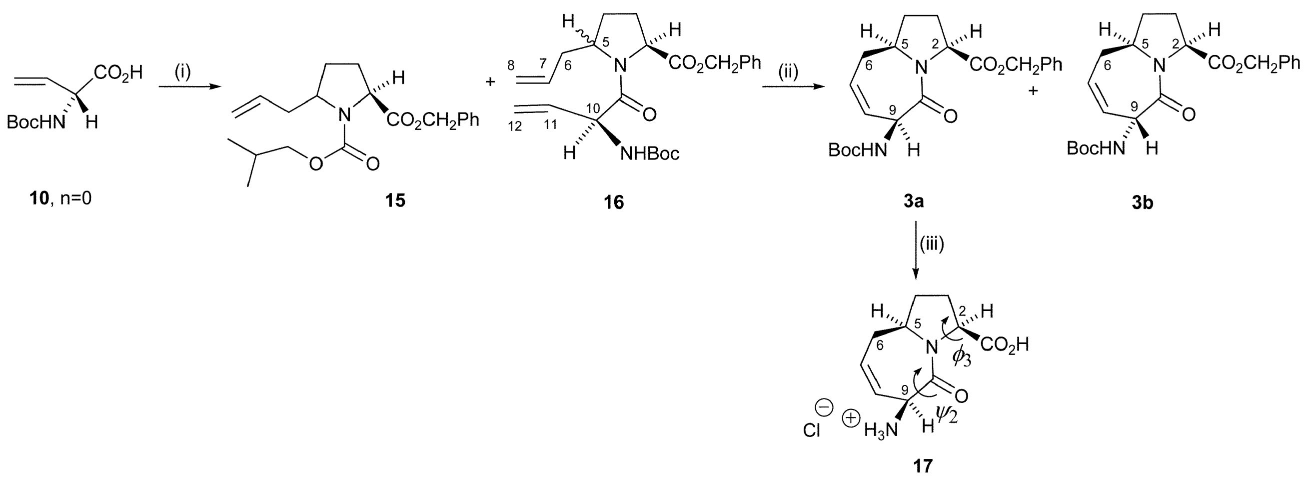


Fig. 3 NOE experiments on the 5/7-bicyclic lactam **3b**.



Scheme 3 *Reagents and conditions:* (i) (a) $ClCO_2{}^iBu$, pyridine, THF, 0 °C, 15 min, (b) **9**, THF, rt, 3 h (23% **15**, 20% **16**); (ii) ([c-C_6H_{10})$_3$]P)$_2Cl_2Ru$=H_2Cl_2, reflux, 24 h (58% **3a**, 9% **3b**); (iii) 6 N HCl, 60 °C, overnight (quant.).

Irradiation at H-5 showed a 4.0% enhancement in the signal at 2.55 ppm for H-6α and irradiation at 2.28 ppm (H-6β) resulted in a 2.1% enhancement in the signal at 4.74 ppm for H-9.

Although the starting material **16** was a 2 : 1 mixture of C-5 epimers, the products **3** both had *cis*-stereochemistry between H-2 and H-5 but were epimeric at C-9. This may reflect loss of stereochemistry in the final steps of the synthesis of vinylglycine, where our use of the stronger base of Gottlieb *et al*.[16] for the Schotten–Baumann urethenylation of vinylglycine may have caused some racemisation. The major bicyclic lactam stereoisomer **3a** was hydrolysed to the amino acid hydrochloride **17** in quantitative yield using 6 N aq. hydrochloric acid at 60 °C. An X-ray structure determination (Fig. 4) confirmed our stereochemical assignments.

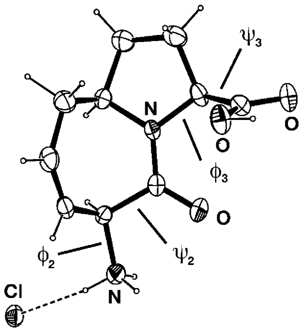


Fig. 4 X-Ray structure of the amino acid hydrochloride **17**.

The dihedral angles ψ_2 and ϕ_3 from the X-ray structure are shown in Table 1 where they are compared with these angles from the X-ray structures of the saturated compound **18**[17] and the turn BTD **1**.[18] The double bond in the seven membered ring has a evidently made a difference to the conformation of the 5/7-system in the solid state.

Our next target, the 5/8-bicyclic lactam **5**, required the protected allylglycine **10** (n = 1). The corresponding *tert*-butyl ester has been reported in a note,[19] and we have prepared it by *in situ* Wittig reaction from the known protected aspartic semialdehyde **19**.[20] The required protected allylglycine **10** (n = 1) was prepared from this by hydrolysis using 6 N aq. hydrochloric acid in THF and treatment of the resultant amino acid with Boc_2O under Schotten–Baumann conditions. This was now reacted with isobutyl chloroformate to give the mixed anhydride, which was condensed *in situ* with the allylproline ester **9** to give the desired diene **21** in 13% yield together with the unwanted urethane **15**. Ring closing olefin metathesis using Grubbs' catalyst now gave the 5/8-bicyclic lactam **5** as a single diastereoisomer in 65% yield (Scheme 4). NOE studies, shown in Fig. 5, indicated that H-2, H-5 and H-10 were *cis* to one another, since irradiation at 4.86 ppm for H-10 caused a 6.7% enhancement at 4.14 ppm for H-5 and irradiation at 4.55 ppm for H-2 caused a 0.7% enhancement at H-5.

Table 1 Torsion angles for compopunds **1**, **17** and **18**

Torsion angle	Compound **1**	Compound **17**	Compound **18**
ψ_2	−161	+169	+175
ϕ_3	−69.4	−86.5	−58

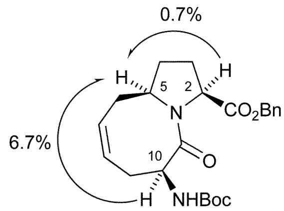
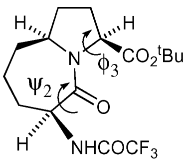
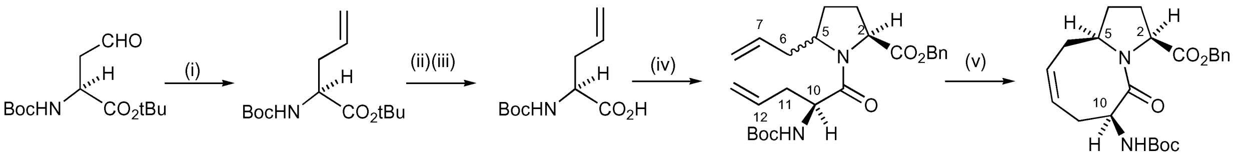


Fig. 5 NOE experiments on the 5/8-bicyclic lactam **5**.

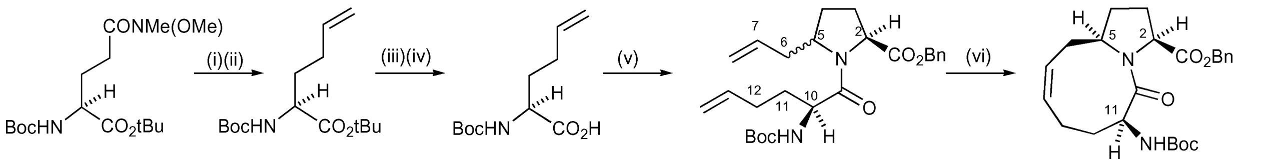
For our final target, the 5/9-bicyclic lactam **6**, we required **10** (n = 2), the ester **23** of which had been reported in preliminary form by Martinez *et al*.[19] We accessed this ester by reducing the known Weinreb amide **22**[21] to the corresponding aldehyde using lithium tri-*tert*-butoxyaluminium hydride, followed by Wittig reaction. Hydrolysis using 6 N aq. HCl in THF gave the corresponding amino acid, which was protected using Boc_2O under Schotten–Baumann conditions to give the desired acid **10** (n = 2). Conversion into the mixed anhydride and reaction with the allylproline ester **9** as before gave the diene **24** in 27% yield together with the ubiquitous urethane **15**. Overlap in the ^1H NMR spectrum did not allow assessment of the relative stereochemistry by NOE experiments. Ring closing olefin metathesis using Grubbs' catalyst gave the 5/9-bicyclic lactam **6** as a single diastereoisomer in 84% yield (Scheme 5). NOE studies, shown in Fig. 6, suggested that H-2, H-5 and H-11 were *cis* to one another, since irradiation at 3.98 ppm for H-5 caused a 1% enhancement in the signal at 4.37 ppm for H-2 and a 15% enhancement at 4.30 ppm for H-11.



18



Scheme 4 *Reagents and conditions:* (i) $MePPh_3{\cdot}Br$, KHMDS, THF, rt, 1 h (40%); (ii) 6 N HCl, THF, rt, overnight (67%); (iii) NaOH, H_2O, ^tBuOH, Boc_2O, rt, overnight (94%); (iv) (a) $ClCO_2{}^iBu$, pyridine, THF, −78 °C, 15 min, (b) **9**, CH_2Cl_2, rt, 3 h (33% **15**, 15% **21**); (v) ([c-$C_6H_{10})_3$]P)$_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 24 h (65%).



22 **23** **10**, n=2 **24** **6**

Scheme 5 *Reagents and conditions:* (i) (a) $LiAlH(O^tBu)_3$, THF, rt, 3 h, (b) $MePPh_3{\cdot}Br$, KHMDS, THF, rt, 1 h (14%); (iii) 6 N HCl, THF, rt, overnight (81%); (iv) NaOH, H_2O, ^tBuOH, Boc_2O, rt, overnight (59%); (v) $ClCO_2{}^iBu$, pyridine, THF, −78 °C, 15 min, (b) **9**, CH_2Cl_2, rt, 3 h (36% **15**, 27% **24**); (vi) $([c\text{-}C_6H_{10})_3]P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 24 h (84%).

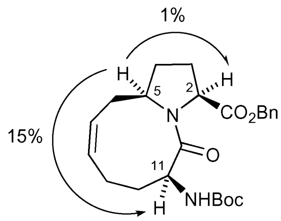


Fig. 6 NOE experiments on the 5/9-bicyclic lactam **6**.

Conclusions

We have therefore prepared the 5/7-, 5/8- and 5/9-bicyclic lactams **3**, **17**, **5** and **6** as single enantiomers by a common route involving metathesis. These are available as potential external *β*-turn constraints. The X-ray crystal structure of the amino acid hydrochloride **17** has been carried out, showing significant differences from the saturated compound **18** and so should act as a different external turn template.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations (given in units of 10^{-1}deg cm^2 g^{-1}) were measured on a Perkin Elmer PE241 polarimeter using a 1 dm path length cell. IR spectra were recorded on a Perkin Elmer Spectrum 1710 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker DPX300 (300 MHz) and AMX500 (500 MHz) Fourier transform instruments and COSY and NOE experiments were carried out to aid assignment of signals. *J* values are given in Hertz. ^{13}C NMR spectra (^{1}H decoupled) were recorded on Bruker DPX300 (75.5 MHz) and AMX500 (125.8 MHz) Fourier transform instruments. DEPT experiments were used to help assign ^{13}C resonances where necessary. Low resolution mass spectra were recorded by Dr A. Al Sada on Kratos MS-80RF and MS25 double focusing spectrometers. High resolution mass measurements were performed by the EPSRC Central Mass Spectrometry Service at Swansea, or by Dr A. Abdul Sada at Sussex using a Bruker BioApex III 4.7 FT-IRC spectrometer. Microanalyses were carried out by Medac Ltd. Column chromatography was performed using Fluka silica gel 60 (230–400 mesh). Petroleum ether refers to that fraction of hexanes of bp 60–80 °C.

Benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-hydroxypyrrolidine-2-carboxylate (12)

A solution of benzyl (2*S*)-*N*-*tert*-butoxycarbonypyroglutamate **11**[13] (1.0 g, 3.13 mmol) in tetrahydrofuran (20 ml) was stirred at −78 °C under nitrogen. Lithium triethylborohydride (Super-Hydride®) (1 M in tetrahydrofuran, 4.69 ml, 4.69 mmol) was added slowly and the mixture was stirred for 2 h at −78 °C. Saturated aq. sodium hydrogen carbonate (3 ml) was added and the mixture was allowed to warm to 0 °C. Hydrogen peroxide (27.5 wt%, in H_2O, 39 drops) was added and the reaction was stirred at 0 °C for a further 20 min. The organic solvent was removed *in vacuo* and the aqueous residue was extracted with dichloromethane (3 × 10 ml). The organic extracts were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-hydroxypyrrolidine-2-carboxylate **12** as a clear oil (995 mg, 99%) which was not further purified; *m*/*z* [ES+] (found 339.1921; $[C_{17}H_{23}NO_5 + NH_4]^+$ requires 339.1920); *m*/*z* [+ve FAB (3-NBA)] 344 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 3428 (br, OH), 1746 (ester) and 1694 (urethane); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers and rotamers, ratio 62 : 38 at 26 °C) 7.28 (5H, *br*, ArH), 5.50 (1H, br m, H-5), 5.08 (2H, m, OCH_2Ar), 4.28 (1H, m, H-2), 2.58–1.74 (4H, br m, H-4 and H-3), 1.41 (9H, *s*, $C(CH_3)_3$ minor) and 1.26 (9H, *s*, $C(CH_3)_3$ major); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers and rotamers at 26 °C) 173.4, 173.1, 172.7 and 172.5 (ester), 154.4, 154.2 and 153.6 (urethane), 135.9 and 129.0–127.3 (Ar), 82.7, 82.4, 82.1 and 81.6 (C-5), 77.9, 77.4 and 77.0 ($OC(CH_3)_3$), 67.3, 37.2 and 67.1 (OCH_2Ar), 59.81 and 59.6 (C-2), 32.6 and 31.4 (C-4), 28.7 and 28.5 ($C(CH_3)_3$), 28.2 and 27.5 (C-3).

Benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxypyrrolidine-2-carboxylate (13)

A solution of benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-hydroxypyrrolidine-2-carboxylate **12** (896 mg, 2.79 mmol) in methanol (13 ml) was stirred at rt under nitrogen. *para*-Toluenesulfonic acid monohydrate (53 mg, 0.279 mmol) was added and stirring was continued overnight. Saturated aq. sodium hydrogen carbonate (6 ml) was added and the methanol was removed *in vacuo*. The aqueous layer was extracted with ether (3 × 50 ml). The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxypyrrolidine-2-carboxylate **13** as a clear oil (836 mg, 89%); *m*/*z* [ES+] (found 336.1813; $[C_{18}H_{25}NO_5 + H]^+$ requires 336.1811); *m*/*z* [+ve FAB (3-NBA)] 358 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1748 (ester) and 1708 (urethane); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers and/or rotamers, ratio 55 : 45 at 26 °C) 7.27 (5H, br, ArH), 5.20 (1H, m, H-5), 5.05 (2H, br m, OCH_2Ar), 4.30 (1H, m, H-2), 3.29 (3H, 4 × s, OCH_3), 2.40–1.61 (4H, br m, H-4 and H-3), 1.40 (9H, s, $C(CH_3)_3$ minor) and 1.26 (9H, s, $C(CH_3)_3$ major); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers and rotamers) 172.9 and 172.7 (ester), 154.6, 154.4 and 154.2 (urethane), 136.1, 136.0 and 135.8 and 129.0–127.3 (Ar), 89.67, 89.62, 88.8 and 88.7 (OCH_3), 81.2, 81.0 and 80.9 ($OC(CH_3)_3$), 67.17, 67.11 and 67.0 (OCH_2Ar), 60.0, 59.7, 59.4 and 59.3 (C-5), 56.6, 56.3, 55.7 and 55.3 (C-2), 33.3, 32.6, 31.4 and 30.4 (C-4), 28.6 and 28.4 ($C(CH_3)_3$), 27.4 and 27.3 (C-3).

Benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allylpyrrolidine-2-carboxylate (14)

A solution of 2-benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-methoxypyrrolidine-2-carboxylate **13** (500 mg, 1.49 mmol) in dichloromethane (50 ml) was stirred under nitrogen at −78 °C. Boron trifluoride diethyl etherate (0.183 ml, 1.49 mmol) was added dropwise and the solution was stirred for 20 min at

−78 °C. Allyltributylstannane (0.55 ml, 1.78 mmol) was added slowly and the reaction was stirred at −78 °C for 3 h. Deionised water (120 ml) was added and the solution was allowed to warm to rt. The aqueous layer was extracted with dichloromethane (3 × 40 ml). The organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a white solid. Purification by flash column chromatography on silica gel using ethyl acetate–petroleum ether (15 : 85) as eluent gave benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allylpyrrolidine-2-carboxylate **14** as a clear oil (376 mg, 73%); ν_{max} (film)/cm^{-1} 1749 (ester) and 1699 (urethane); δ_H (500 MHz, C^2HCl_3, 10 °C, 2 : 1 mixture of diastereoisomers and/or rotamers at 26 °C) 7.32 (5H, br, ArH), 5.75 (1H, m, H-7), 5.75 (2H, m, H-8), 5.17 (1H, AB, J_{AB} 12.5, OCH_AAr), 5.15 (1H, AB, J_{BA} 12.5, OCH_BAr), 4.37 and 4.27 (1H, 2 × m, H-5*trans* and H-5*cis*), 3.90 (1H, m, H-2), 2.25–1.69 (6H, br m, H-4, H-3 and H-6), 1.46, 1.32 and 1.31 (9H, 3 × s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers) 172.1, and 171.9 (ester), 152.5 (urethane), 134.6, 134.3, 134.08 and 134.0 (C-7), 127.5, 127.4, 127.3, 127.2 and 126.9 (Ar), 116.2 and 115.8 (C-8), 78.9 ($OC(CH_3)_3$), 65.6 (OCH_2Ar), 59.2, 58.9 and 58.6 (C-5), 56.9 and 56.5 (C-2), 38.0, 37.9, 37.2 and 37.0 (C-6), 29.9 (C-4), 27.4–26.8 ($C(CH_3)_3$), 16.4 (C-3).

Benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate trifluoroacetate (9a)

2-Benzyl (2*S*,5*RS*)-*N*-*tert*-butoxycarbonyl-5-allylpyrrolidine-2-carboxylate **14** (70 mg, 0.202 mmol) was dissolved in dichloromethane (1.4 ml) and stirred at rt under nitrogen. Trifluoroacetic acid (0.70 ml) was added and the reaction was stirred at rt overnight. The solvents were removed *in vacuo* to give a brown oil which was recrystallised from cold diethyl ether and petroleum ether to give benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate trifluoroacetate **9a** as a yellow solid (41 mg, 56%), mp 54.0–55.9 °C; (found C, 56.8; H, 5.6; N, 3.8%; $C_{17}H_{20}NO_4F_3$ requires C, 56.8; H, 5.6; N, 3.9%); *m*/*z* [+ve FAB (3-NBA)] 246 ([$M_{free\ amine}$ + H]$^+$); ν_{max} (KBr)/cm^{-1} 3418 (NH), 1754 (ester), 1694 and 1667 (salt); δ_H (300 MHz, $C^2H_3O^2H$, mixture of diastereoisomers) 7.15 (5H, m, ArH), 5.59 (1H, m, H-7), 5.12–4.86 (4H, m, H-8 and OCH_2Ar), 4.28 (1H, m, H-5), 3.48 (1H, m, H-2) and 2.24–1.42 (6H, m, H-4, H-6 and H-3); δ_C (75.5 MHz, $C^2H_3O^2H$, mixture of diastereoisomers) 170.3 (ester), 134.4 (Ar), 132.0 (C-7), 129.4, 129.2, 129.1 and 128.9 (Ar), 120.9 and 119.3 (C-8), 69.2 and 68.6 (OCH_2Ar), 62.0 and 60.0 (C-5), 59.2 and 59.5 (C-2), 36.8 (C-4), 29.6 and 28.9 (C-3).

Benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate (9)

A solution of benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate trifluoroacetate **9a** (50.3 mg, 0.14 mmol) in dichloromethane–water (2 : 1, 8 ml) was stirred vigorously and triethylamine (0.070 ml, 0.5 mmol) was added. Stirring was continued at rt for 2 h. The phases were separated and the aqueous phase was extracted with dichloromethane. The organic extracts were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate **9** as a clear oil which was used without further purification; ν_{max} (film)/cm^{-1} 3416 (NH) and 1747 (ester); δ_H (300 MHz, $C^2H_3COC^2H_3$, mixture of diastereoisomers) 7.34–7.19 (5H, m, ArH), 5.69 (1H, m, H-7), 5.13–4.86 (4H, m, H-8 and OCH_2Ar), 4.39 (1H, m, H-5), 3.52 (1H, m, H-2), 3.0 (2H, m, H-6), 2.56 (1H, m, H-3A), 2.15 (1H, m, H-4) and 1.50–1.40 (1H, m, H-3B).

2-Benzyl (2*S*,5*RS*)-*N*-iso-butoxycarbonyl-5-allylpyrrolidine-2-carboxylate (15) and benzyl (2*S*,5*RS*)-5-allyl-1-(2-*tert*-butoxycarbonylaminobut-3-enoyl)-pyrrolidine-2-carboxylate (16)

A solution of 2-*tert*-butoxycarbonylaminobut-3-enoic acid (**10**, n = 0)[15,16] (28 mg, 0.139 mmol) in anhydrous THF (1 ml) was stirred under nitrogen at 0 °C. Pyridine (112 µml) was added and the mixture was stirred for 15 min. Isobutyl chloroformate (182 µml, 0.139 mmol) was added and stirring was continued for 15 min at 0 °C. Benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate **9** (34 mg, 0.139 mmol) in THF (1.5 ml) was added followed by further THF (0.5 ml). The mixture was allowed to warm to rt over 3 h. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (17 ml). The organic phase was washed with 5% aq. sodium hydrogen carbonate, 5% aq. HCl and brine, then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 4) as eluent. 2-Benzyl 1-isobutyl (2*S*,5*RS*)-5-allylpyrrolidine-1,2-dicarboxylate **15** eluted as a clear colourless oil (11 mg, 23%); *m*/*z* [ES+] (found 346.2015; [$C_{20}H_{27}NO_4$+H]$^+$ requires 346.2018); *m*/*z* [+ve FAB (3-NBA)] 368 ([M + Na]$^+$) and 346 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1750 (ester) and 1705 (urethane); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers and rotamers at 26 °C) 7.31 (5H, br, ArH), 5.72 (1H, m, H-7), 5.14–4.96 (4H, m, OCH_2Ar and H-8), 4.31 (1H, m, H-2), 3.96–3.73 (3H, m, H-5 and $OCH_2CH(CH_3)_2$), 2.65 (1H, m, $CH_2CH(CH_3)_2$), 2.10 (2H, m, H-6), 1.97–1.58 (4H, m, H-4 and H-3), 0.91 (3H, *m*, $CHCH_3$) and 0.80 (3H, d, J_{AB} 6.3, $CHCH_3$); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers and rotamers at 26 °C) 173.2 and 173.1 (ester), 155.6 and 154.9 (urethane), 135.9, 135.5, 135.4 and 133.9 (C-7), 129.1–128.4 (Ar), 118.9, 118.0 and 117.4 (C-8), 71.9 and 71.7 (OCH_2Ar), 68.0, 67.6 and 67.1 (C-6), 61.0, 60.9 and 60.6 (C-5), 58.8 and 58.4 (C-2), 39.3, 38.6 and 37.7 (C-4), 30.5, 29.8 and 29.6 (C-3 and $CH_2CH(CH_3)_2$), 28.2 ($OCH_2CH(CH_3)_2$), 19.5 and 19.3 ($CH(CH_3)_2$). Benzyl (2*S*,5*RS*)-5-allyl-1-(2-*tert*-butoxycarbonylaminobut-3-enoyl)-pyrrolidine-2-carboxylate **16** eluted as a clear colourless oil (12 mg, 20%); *m*/*z* [ES+] (found 429.2392; [$C_{24}H_{32}N_2O_5$+H]$^+$ requires 429.2389); *m*/*z* [+ve FAB (3-NBA)] 429 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3323 (NH), 1747 (ester), 1712 (urethane) and 1650 (lactam); δ_H (500 MHz, C^2HCl_3, mainly *cis* isomer, rotamers at 26 °C) 7.35 (5H, m, ArH), 5.85 (1H, ddd, $J_{11,9}$ 5.4, $J_{11,12A}$ 10.3, $J_{11,12B}$ 17.2, H-11), 5.73 (1H, dddd, $J_{7,6A}$ 2.1, $J_{7,6B}$ 6.8, $J_{7,8A}$ 9.3, $J_{7,8B}$ 19.5, H-7), 5.49 (1H, d, $J_{NH,10}$ 8.9, NH), 5.43–5.05 (6H, m, OCH_2Ar, H-8 and H-12), 4.58 (1H, m, H-10), 4.52 (1H, m, H-2), 4.35 (1H, m, H-5), 2.33–1.91 (6H, m, H-6, H-4 and H-3), 1.44, 1.43 and 1.41 (9H, 3 × s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.3 and 172.2 (ester), 155.5 (ketone), 135.9–133.8 (C-7 and C-11), 129.0–128.4 (Ar), 119.5–117.6 (C-8, C-12 and OCH_2Ar), 80.3 and 80.0 ($OC(CH_3)_3$), 68.1 and 67.2 (C-6), 60.2, 60.1 and 59.8 (C-5), 59.2, 58.9 and 58.2 (C-10), 55.6, 55.2 and 54.1 (C-2), 39.1 and 38.2 (C-4), 30.7, 29.7 and 27.1 (C-3) and 28.7 ($C(CH_3)_3$).

Benzyl (2*S*,5*R*,9*S*)-9-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (3a) and benzyl (2*S*,5*R*,9*R*)-6-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (3b)

Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (Grubbs catalyst) (147 mg, 0.179 mmol) was added to a solution of benzyl (2*S*,5*RS*)-5-allyl-1-(2-*tert*-butoxycarbonylaminobut-3-enoyl)-pyrrolidine-2-carboxylate **16** (385 mg, 0.898 mmol) in dichloromethane (100 ml) and the solution was heated at reflux for 24 h. The mixture was cooled to 20 °C, lead tetraacetate (0.119 mg, 0.269 mmol) was added and stirring was continued for 12 h. The solvent was removed *in vacuo* to give a black oil which was flash chromatographed on silica gel using petroleum ether–diethyl ether (1 : 2) as eluent. Benzyl (2*S*,5*R*,9*S*)-9-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo [1,2-*a*]azepine-3-carboxylate **3a** was obtained as an oil (208 mg, 58%); *m*/*z* [ES+] (found 401.2076;

$[C_{22}H_{28}N_2O_5 + H]^+$ requires 401.2076); *m/z* [+ve FAB (3-NBA)] 423 ([M + Na]$^+$) and 401 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3409 (NH), 1741 (ester), 1714 (urethane) and 1661 (lactam); δ_H (500 MHz, $C_6{}^2H_6$) 7.10 (5H, br, ArH), 6.14 (1H, d, $J_{NH,9}$ 4.6, NH), 5.42 (1H, m, $J_{8,7}$ 10, $J_{8,9}$ 4, $J_{8,6}$ 2, H-8), 5.35 (1H, m, H-9), 5.21 (1H, m, H-7), 4.98 (1H, AB, J_{AB} 11, OCH_AAr), 4.96 (1H, BA, J_{AB} 11, OCH_BAr), 4.53 (1H, dd, $J_{2,3A}$ 6.0, $J_{2,3B}$ 3.5, H-2), 3.40 (1H, m, H-5), 2.05 (1H, m, H-6A), 1.55 (2H, m, H-3B and H-6B), 1.50 (9H, s, $C(CH_3)_3$), 1.38 (1H, m, H-3A), 1.24 (1H, m, H-4A) and 0.80 (1H, m, H-4B); δ_C (75.5 MHz, C^2HCl_3) 172.2 (ester), 169.6 (lactam), 156.1 (urethane), 135.8 and 128.9–128.1 (Ar, C-7 and C-8), 80.1 ($OC(CH_3)_3$), 60.5 (C-2), 55.9 (C-5), 52.1 (C-9), 35.2 (C-6), 31.9 (C-4), 28.7 ($C(CH_3)_3$), and 28.3 (C-3). Benzyl (2*S*,5*R*,9*R*)-6-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo [1,2-*a*]azepine-3-carboxylate **3b** was obtained as an oil (33 mg, 9%); *m/z* [ES+] (found 401.2082, $[C_{22}H_{28}N_2O_5 + H]^+$ requires 401.2076); *m/z* [+ve FAB (3-NBA)] 423 ([M + Na]$^+$) and 401 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3314 (br, NH), 1738 (ester), 1698 (urethane) and 1645 (lactam); δ_H (500 MHz, C^2HCl_3, 45 °C) 7.33 (5H, m, ArH), 5.86 (1H, ddd, $J_{7,8}$ 11.0, $J_{7,6A}$ 3.0, $J_{7,6B}$ 5.9, H-7), 5.81 (1H, ddt, $J_{8,7}$ 11.0, $J_{8,9}$ 7.2, $J_{8,6A}$, 2.4, $J_{8,6B}$ 0.7, H-8), 5.17 (1H, AB, J_{AB} 11, OCH_AAr), 5.15 (1H, BA, J_{BA} 11, OCH_BAr), 4.97 (1H, br s, NH), 4.74 (1H, br, H-9), 4.61 (1H, dd, $J_{2,3A}$ 8.6, $J_{2,3B}$ 3.5, H-2), 4.27 (1H, br, H-5), 2.55 (1H, m, H-6α), 2.28 (1H, m, $J_{6B,6A}$ 17.6, $J_{6B,7}$ 5.9, $J_{6B,5}$ 2.3, H-6β), 2.22 (1H, m, H-4B), 2.10 (1H, m, H-3B), 2.00 (1H, m, H-3A), 1.76 (1H, m, H-4A), 1.45 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.4 (ester), 168.7 (lactam), 155.1 (urethane), 136.0 and 128.9–128.4 (Ar, C-7 and C-8), 80.7 ($OC(CH_3)_3$), 67.2 (OCH_2Ar), 61.2 (C-2), 55.3 (C-5), 35.1 (C-6), 32.5 (C-4), 30.7 (C-9), 28.7 ($C(CH_3)_3$) and 27.7 (C-3).

(2*S*,5*R*,9*S*)-6-Amino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate hydrochloride (17)

Benzyl (2*S*,5*R*,9*S*)-9-*tert*-butoxycarbonylamino-5-oxo-2,3,5,-6,9,9*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **3a** (25 mg, 0.0625 mmol) was suspended in 6 N aq. HCl (2 ml) and warmed to 60 °C under nitrogen. The mixture was left stirring at 60 °C overnight. The aqueous layer was lypholised to give a yellow oil which was dissolved in a minimum of methanol and addition of cold diethyl ether gave (2*S*,5*R*,9*S*)-6-amino-5-oxo-2,3,5,6,9,9*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate hydrochloride **17** as an off-white solid (16 mg, quant.); $[\alpha]_D^{25}$ −51.75 (*c* 0.4, MeOH); (found C, 47.2; H, 6.2; N, 10.7%. $C_{10}H_{15}N_2O_3Cl$. 0.5 H_2O requires C, 47.0; H, 6.3; N, 11.0%.); *m/z* [EI] (found 210.1000; $[C_{10}H_{14}N_2O_3]^+$ requires 210.1004); *m/z* [+ve FAB (3-NBA)] 211 ([$M_{free\ amine}$ + H]$^+$); ν_{max} (film)/cm^{-1} 3440 (br, NH), 1704 (acid) and 1670 (lactam); δ_H (500 MHz, $C^2H_3O^2H$) 5.89 (1H, ddt, $J_{8,7}$ 11.4, $J_{8,9}$ 3.2, $J_{8,6A}$ 4.7, $J_{8,6B}$ 4.0, H-8), 5.38 (1H, ddd, $J_{7,8}$ 11.4, $J_{7,6A}$ 4.4, $J_{7,6B}$ 2.4, H-7), 5.23 (1H, t, $J_{9,8}$ 3.2, H-9), 4.52 (1H, dd, $J_{2,3A}$ 8.2, $J_{2,3B}$ 5.8, H-2), 4.47 (1H, m, H-5), 2.49 (1H, m, H-6B), 2.40 (1H, m, H-6A), 2.33 (1H, m, H-4A), 2.28 (1H, m, H-3A), 2.12 (1H, m, H-3B), 1.81 (1H, m, H-4B); δ_C (125.8 MHz, $C^2H_3O^2H$) 175.3 (acid), 168.3 (urethane), 133.5 (C-8), 121.1 (C-7), 62.2, 57.2 and 53.1 (C-2, C-5 and C-9), 36.3, 32.8 and 29.6 (C-6, C-4 and C-3).

Crystal Data. Compound **17**, $C_{10}H_{15}ClN_2O_3$, M = 246.69, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.4839(4), b = 12.5501(10), c = 13.7734(7) Å, V = 1120.8(1) Å^3, Z = 4, D_{calc} = 1.46 mg/m^3, μ (*Mo*–*Kα*) 0.34 mm^{-1}, T = 173(2) K, 1971 independent reflections, final residuals were R1 = 0.036 for 1735 reflections with $I>2\sigma(I)$, $wR2$ = 0.080 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 (deposition number)†.

tert-Butyl (2*S*)-2-*tert*-butoxycarbonylaminopent-4-enoate (20)

Potassium hexamethyldisilazide (1 M in THF, 2.63 ml, 1.317 mmol) was added slowly to a suspension of methyltriphenylphosphonium bromide (522 mg, 1.45 mmol) in THF (5 ml) at rt. The solution was stirred for 30 min at rt and a solution of freshly prepared aldehyde **19**[20] (175 mg, 0.64 mmol) in THF (2 ml) was added. The solution was stirred for 1 h and saturated aq. ammonium chloride (10 ml) was added. The aqueous layer was extracted with diethyl ether (2 × 20 ml), the organic extracts were washed with water (2 × 10 ml) and brine, (2 × 10 ml) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 9) to give *tert*-butyl (2*S*)-2-*tert*-butoxycarbonylaminopent-4-enoate **20** as a clear oil (68 mg, 40%); $[\alpha]_D^{31}$ −31.45 (*c* 1.03, MeOH); *m/z* [+ve FAB (3-NBA)] 295 ([M + Na]$^+$), 272 ([M + H]$^+$); ν_{max} (nujol)/cm^{-1} 3440 and 3365 (NH), 1717 (ester), 1642 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotamers, ratio 95 : 5 at 10 °C) 5.66 (1H, dd t, $J_{4,5cis}$ 11.5, $J_{4,5A}$ 4.6, $J_{4,5trans}$ 18.8, $J_{4,3B}$ 2.5, H-4), 5.10 (3H, m, H-5 and NH major), 4.80 (1H, d, $J_{NH,2}$ 7.6, NH minor), 4.25 (1H, m, H-2 major), 4.04 (1H, m, H-2 minor), 2.45 (2H, m, H-3), 1.42 (9H, s, $C(CH_3)_3$) and 1.41 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 171.5 (ester), 155.5 (urethane), 132.8 (C-4), 119.1 (C-5), 82.2 and 79.9 (2 × $OC(CH_3)_3$), 53.6 (C-2), 37.4 (C-3), 28.6 and 28.3 (2 × $C(CH_3)_3$).

(2*S*)-2-Aminopent-4-enoate hydrochloride

A solution of *tert*-butyl (2*S*)-2-*tert*-butoxycarbonylaminopent-4-enoate **20** (105 mg, 0.39 mmol) in THF (6 ml) was stirred at rt under nitrogen. 6 N Aq. hydrochloric acid (6 ml) was added and the reaction was stirred overnight. The solvents were removed *in vacuo* to give an off-white solid which was recrystallised from methanol and diethyl ether to give (2*S*)-2-aminopent-4-enoate hydrochloride as a pure white solid (40 mg, 67%); mp 154–156 °C (decomposed); $[\alpha]_D^{33}$ +196.6 (*c* 0.5, MeOH); *m/z* [ES+] (found 231.1341; [2 × $C_5H_9NO_2$ + H]$^+$ requires 231.1339); *m/z* [+ve FAB (3-NBA)] 231 ([2$M_{free\ amine}$ + H]$^+$) and 116 ([$M_{free\ amine}$ + H]$^+$); ν_{max} (KBr)/cm^{-1} 3431 (br, NH) and 1730 (acid); δ_H (300 MHz, $C^2H_3O^2H$) 5.81 (1H, m, H-4), 5.35 (1H, br, H-5A), 5.29 (1H, d, $J_{5B,4}$ 9.4, H-5B), 4.09 (1H, t, $J_{2,3}$ 6.0, H-2), 2.70 (2H, m, H-3); δ_C (75.5 MHz, $C^2H_3O^2H$) 171.6 (acid), 132.2 (C-4), 121.9 (C-5), 53.7 (C-2) and 36.1 (C-3).

(2*S*)-2-*tert*-Butoxycarbonylaminopent-4-enoate (10, n = 1)

(2*S*)-2-Aminopent-4-enoate hydrochloride (32 mg, 0.211 mmol) was dissolved in *tert*-butanol–water (2 : 1) (2 ml). 1 N Aq. sodium hydroxide (0.192 ml, 0.192 mmol) and di-*tert*-butyl dicarbonate (55 mg, 0.252 mmol) were added and the reaction was stirred overnight at rt. The reaction was diluted with deionised water, washed with hexane (3 × 3 ml) and acidified to pH 2 by dropwise addition of aq. 1 N potassium hydrogen sulfate. The acidic aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give (2*S*)-2-*tert*-butoxycarbonylaminopent-*4*-enoate **10** (n = 1) as a clear oil (43 mg, 94%); $[\alpha]_D^{27}$ +2.8 (*c* 0.5, $CHCl_3$); *m/z* [+ve FAB (3-NBA)] 238 ([M + Na]$^+$) and 216 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3326 (NH) and 1719 (br, acid); δ_H (300 MHz $C^2H_3COC^2H_3$ 2 rotamers, ratio 87 : 13 at 26 °C) 5.91 (1H, br s, NH), 5.71 (1H, m,

† CCDC reference number 265180. See http://www.rsc.org/suppdata/ob/b5/b503014e/ for crystallographic data in CIF or other electronic format.

H-4), 5.01 (1H, d, $J_{5trans,4}$ 17.1, H-5*trans*), 4.94 (1H, d, $J_{5cis,4}$ 9.9, H-5*cis*), 4.09 (1H, t, $J_{2,3}$ 5.0, H-2 major), 3.26 (1H, t, $J_{2,NH}$ 6.9, H-2 minor), 2.48–2.32 (2H, m, H-3), 1.27 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, $C^2H_3COC^2H_3$) 173.9 (acid), 156.6 (urethane), 135.0 (C-4), 118.6 (C-5), 79.6 ($OC(CH_3)_3$), 54.2 (C-2), 37.1 (C-3) and 28.9 ($C(CH_3)_3$).

Benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylamino-5-pent-4-enoyl)-pyrrolidine-2-carboxylate (21)

Pyridine (10% w/v in THF, 0.23 ml, 0.29 mmol) was added to a solution of (2*S*)-2-*tert*-butoxycarbonylaminopent-4-enoate **10** (n = 1) (66 mg, 0.307 mmol) in THF (8 ml) with stirring at −78 °C under nitrogen. Isobutyl chloroformate (10% w/v solution in THF, 0.39 ml 0.285 mmol) was added and the solution was stirred at −78 °C for 15 min. Benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate **9** (75 mg, 0.307 mmol) in THF (2 ml) was added slowly followed by further THF (1 ml). The solution was allowed to warm to rt over 3 h, the organic solvent was removed *in vacuo* and the residue was dissolved in dichloromethane. The organic layer was extracted with 5% aq. sodium hydrogen carbonate (5 ml), 5% aq. hydrochloric acid (5 ml) and brine (5 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a brown oil which was purified by flash column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 4) as eluent to give 2-benzyl 1-iso-butyl (2*S*,5*RS*)-5-allylpyrrolidine-1,2-dicarboxylate **15** as a clear oil (34 mg, 33%) with spectra identical to those of the sample prepared above and benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylamino-5-pent-4-enoyl)-pyrrolidine-2-carboxylate **21** as a clear oil (20 mg, 15%); $[\alpha]_D^{27}$ −4.72 (*c* 2, MeOH); *m*/*z* [ES+] (found 443.2543; $[C_{25}H_{34}N_2O_5 + H]^+$ requires 443.2540); *m*/*z* [ES+] 465 ($[M + Na]^+$) and 443 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3291 (NH), 1745 (ester), 1701 (urethane) and 1638 (lactam); δ_H (300 MHz, C^2HCl_3) 7.27 (5H, *br s*, ArH), 5.70 (2H, m, H-7 and H-12), 5.21–4.87 (7H, m, H-13, H-8, CH_2Ar and NH), 4.49–4.33 (3H, br m, H-2, H-5 and H-10), 2.44–1.82 (8H, m, H-3, H-4, H-6 and H-11) and 1.34 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.3 and 171.8 (ester and lactam), 155.7 (urethane), 136.0 (Ar), 134.3 and 133.5 (C-7 and C-12), 128.9, 128.6 and 128.5 (Ar), 118.7 (C-8 and C-13), 80.1 ($OC(CH_3)_3$), 67.2 (OCH_2Ar), 59.2 (C-2), 58.6 (C-10), 51.3 (C-5), 39.8 (C-6), 38.2 (C-11), 29.9 (C-4), 28.6 ($C(CH_3)_3$) and 27.2 (C-3).

Benzyl 12-*tert*-butoxycarbonylamino-(2*S*,5*R*,12*S*)-5-oxo-1,2,3,5,6,7,10,10*a*-octahydro-1*H*-pyrrolo[1,2*a*]azocine-3-carboxylate (5)

Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (Grubbs' catalyst) (12.9 mg, 0.015 mmol) was added to a solution of benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylamino-5-pent-4-enoyl-pyrrolidine-2-carboxylate **21** (33 mg, 0.075 mmol) in dichloromethane (10 ml) and the mixture was heated at reflux for 24 h under nitrogen. The reaction was allowed to cool to rt and the solvent was removed *in vacuo* to give a brown oil which was purified by flash column chromatography on silica gel using petroleum ether–diethyl ether (1 : 2) as eluent to give benzyl 12-*tert*-butoxycarbonylamino-(2*S* 5*R*,12*S*)-5-oxo-1,2,3,5,6,7,10,10*a*-octahydro-1*H*-pyrrolo[1,2*a*]azocine-3-carboxylate **5** as a white foam (20.1 mg, 65%), $[\alpha]_D^{28}$ −7.51 (*c* 2.01, MeOH); *m*/*z* [ES+] (found 437.2022; $[C_{23}H_{30}N_2O_5+Na]^+$ requires 437.2046); ν_{max} (film)/cm^{-1} 3421 (NH), 1745 (ester), 1707 (urethane) and 1641 (lactam); δ_H (500 MHz, C^2HCl_3, 25 °C) 7.34 (5H, br, ArH), 5.61 (3H, m, H-7, H-8 and NH), 5.19 (1H, AB, J_{AB} 12, OCH_AAr), 5.06 (1H, BA, J_{BA} 12, OCH_BAr), 4.86 (1H, ddd, $J_{10,9A}$ 10.1, $J_{10,NH}$ 7.7, $J_{10,9B}$ 5.9, H-10), 4.55 (1H, dd, $J_{2,3A}$ 9.1, $J_{2,3B}$ 3.2, H-2), 4.14 (1H, m, H-5), 2.78 (2H, m, H-6A and H-9A), 2.38 (1H, m, H-9B), 2.24 (1H, m, H-6B), 2.14 (1H, m, H-4A), 2.05 (1H, m, H-3A), 1.97 (1H, m, H-4B), 1.89 (1H, m, H-3B) and 1.43 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.0 (ester), 171.4 (ketone), 155.5 (urethane), 136.0 (Ar), 129.6 (C-7), 128.8 and 128.6 (Ar), 125.9 (C-8), 79.9 ($OC(CH_3)_3$), 67.1 (OCH_2Ar), 60.7 (C-2), 59.0 (C-10), 52.1 (C-5), 35.6 (C-6), 33.2 (C-9), 33.1 (C-4), 28.7 ($C(CH_3)_3$) and 27.5 (C-3).

1-*tert*-Butyl (2*S*)-2-*tert*-butoxycarbonylaminohex-5-enoate (23)

A solution of 1-*tert*-butyl (2*S*)-2-*tert*-butoxycarbonylamino-pentan-1,5-dioate γ-*N*-methoxy-*N*-methylamide **22**[21] (300 mg, 0.865 mmol) in THF (10 ml) was stirred under nitrogen at rt. Lithium tri-*tert*-butoxyaluminium hydride (1 M in THF, 2.59 ml, 2.59 mmol) was added slowly and stirring was continued for 3 h. 5% Aq. potassium hydrogen sulfate (5 ml) and diethyl ether (50 ml) were added. The aqueous phase was separated and extracted with diethyl ether (3 × 50 ml). The organic extracts were combined and washed with 3 N aq. HCl (3 × 10 ml), saturated aq. sodium hydrogen carbonate (3 × 10 ml) and brine (3 × 10 ml). The organic phases were combined and dried ($MgSO_4$) and the solvent was removed *in vacuo* to give aldehyde (197 mg) as a clear colourless oil which was used immediately without further purification. Potassium hexamethyldisilazide (0.5 M in THF, 3.11 ml, 1.55 mmol) was added slowly to a stirred suspension of methyltriphenylphosphonium bromide (618 mg, 1.72 mmol) in THF (5 ml) and stirring was continued for 30 min at rt. A solution of the aldehyde (197 mg) in THF (5 ml) was added slowly to the yellow ylide and the reaction was stirred for 1 h. Saturated aq. ammonium chloride (10 ml) was added and the aqueous layer was extracted with diethyl ether (2 × 20 ml). The organic extracts were washed with deionised water (2 × 10 ml), brine (2 × 10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow oil which was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 9) as eluent, to give 1-*tert*-butyl (2*S*)-2-*tert*-butoxycarbonylaminohex-5-enoate **23** as a clear oil (35 mg, 14%); $[\alpha]_D^{26}$ −17.9 (*c* 1.18, MeOH), (lit.[19] $[\alpha]_D^{20}$ −19.0 (*c* 1, MeOH)); *m*/*z* [+ve FAB (3-NBA)] 308 ($[M + Na]^+$) and 286 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3378 (NH), 1698 (br, ester) and 1642 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotamers, ratio 84 : 16, at 10 °C) 5.78 (1H, dd t, $J_{5,6cis}$ 9.5, $J_{5,6trans}$ 17.0, $J_{5,4}$ 5.7, H-5), 5.11 (1H, d, $J_{NH,2}$ 8.5, NH major), 4.80 (1H, d, $J_{NH,2}$ 4.7, NH minor), 5.02 (1H, ddd, $J_{6trans,5}$ 17.0, $J_{6trans,4}$ 1.6, $J_{6B,6A}$ 3.9, H-6*trans*), 4.96 (1H, ddd, $J_{6cis,5}$ 9.5, $J_{6A,4B}$ 6.7, $J_{6A,4A}$ 3.9, H-6*cis*), 4.19 (1H, ddd, $J_{2,NH}$ 8.5, $J_{2,3A}$ 7.7, $J_{2,3B}$ 4.9, H-2 major), 3.99 (1H, ddd, $J_{2,NH}$ 4.7, $J_{2,3A}$ 12.8, $J_{2,3B}$ 7.8, H-2 minor), 2.08 (2H, m, H-4), 1.84 (1H, m, H-3A), 1.64 (1H, m, H-3B), 1.44 (9H, s, ($C(CH_3)_3$) and 1.41 (9H, s, ($C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.3 (ester), 155.7 (urethane), 137.7 (C-5), 115.7 (C-6), 82.1 and 79.9 (2 × $OC(CH_3)_3$), 53.9 (C-2), 32.6 (C-4), 29.8 (C-3), 28.7 and 28.3 (2 × $C(CH_3)_3$).

(2*S*)-2-Aminohex-5-enoate hydrochloride

1-*tert*-Butyl (2*S*)-2-*tert*-butoxycarbonylaminohex-5-enoate **23** (125 mg, 0.439 mmol) was dissolved in THF (10 ml) and 6 N aq. HCl (10 ml) and stirred at rt overnight. The aqueous layer was lyophilised to give a white solid which was purified by recrystallisation from methanol and diethyl ether to give (2*S*)-2-aminohex-5-enoate hydrochloride as a white solid (59 mg, 81%); mp 165–167 °C; $[\alpha]_D^{30}$ +30.0 (*c* 0.97, MeOH); (found C, 39.8: H, 7.2: N, 7.9%. $C_6H_{12}NO_2Cl.H_2O$ requires C, 39.2; H, 7.6: N, 7.6%.); *m*/*z* [EI] (found 130.0866; $C_6H_{11}NO_2$ requires 130.0868); ν_{max} (film)/cm^{-1} 3414 (NH) and 1738 (acid); δ_H (300 MHz, $C^2H_3O^2H$) 5.87 (1H, dd t, $J_{5,6cis}$ 10.2, $J_{5,6trans}$ 17.1, $J_{5,4}$ 6.3, H-5), 5.16 (1H, dd, $J_{6B,6A}$ 1.6, $J_{6trans,5}$ 17.1, H-6*trans*), 5.11 (1H, dd, $J_{6A,6B}$ 1.6, $J_{6cis,5}$ 10.2, H-6*cis*), 3.99 (1H, t, $J_{2,3}$ 6.3, H-2), 2.30 (2H, m, H-4) and 2.0 (2H, m, H-3); δ_C (75.5 MHz, $C^2H_3O^2H$) 172.1

(acid), 137.7 (C-5), 117.2 (C-6), 53.7 (C-2), 31.3 and 30.4 (C-4 and C-3).

(2*S*)-2-*tert*-Butoxycarbonylaminohex-5-enoate (10, n = 2)

(2*S*)-2-Aminohex-5-enoate hydrochloride (61 mg, 0.368 mmol) was dissolved in *tert*-butanol–water (2 : 1) (v/v) (5 ml) and 1 N aq. sodium hydroxide (0.735 ml, 0.736 mmol) and di-*tert*-butyl dicarbonate (104 mg, 0.478 mmol) were added. The solution was stirred under nitrogen at rt overnight, diluted with deionised water and washed with hexane (3 × 3 ml). The aqueous phase was acidified to pH 2 with 1 N aq. potassium hydrogen sulfate and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give (2*S*)-2-*tert*-butoxycarbonylaminohex-5-enoate **10** (n = 2) as a clear oil (50 mg, 59%); $[a]_D^{27}$ +37.24 (*c* 0.5, $CHCl_3$); *m/z* [ES+] (found 252.1218; $[C_{11}H_{19}NO_4 + Na]^+$ requires 252.1206); *m/z* [+ve FAB (3-NBA)] 252 ($[M + Na]^+$) and 230 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3329 (NH) and 1717 (br, acid); δ_H (500 MHz, $C^2H_3COC^2H_3$, rotamers at 253 K, ratio 8 : 2) 6.54 (1H, d, $J_{NH,2}$ 8.5, NH major), 6.42 (1H, d, $J_{NH,2}$ 7.3, NH minor), 5.82 (1H, dd t, $J_{5,6cis}$ 10.3, $J_{5,6trans}$ 17.0, $J_{5,4}$ 6.5, H-5), 5.06 (1H, ddd, $J_{6trans,5}$ 17.2, $J_{6B,4}$ 3.6, $J_{6B,6A}$ 1.5, H-6*trans*), 4.98 (1H, m, H-6*cis*), 4.12 (1H, m, H-2), 2.15 (2H, m, H-4), 1.90 (1H, m, H-3A), 1.75 (1H, m, H-3B), 1.38 (9H, *s*, OC(CH_3)$_3$ minor) and 1.37 (9H, s, C(CH_3)$_3$ major); δ_C (75.5 MHz, $C^2H_3COC^2H_3$) 174.7 (acid), 156.9 (urethane), 138.8 (C-5), 116.1 (C-6), 79.5 (O*C*(CH_3)$_3$), 54.1 (C-2), 32.3 (C-4), 31.9 (C-3) and 28.9 (C(CH_3)$_3$).

Benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylaminohex-5-enoyl)-pyrrolidine-2-carboxylate (24)

Pyridine (10% w/v solution in THF, 0.155 ml, 0.192 mmol) was added to a solution of (2*S*)-2-*tert*-butoxycarbonylaminohex-5-enoate **10** (n = 2) (44.2 mg, 0.192 mmol) in THF (6 ml) and the mixture was stirred at −78 °C under nitrogen for 15 min. Isobutyl chloroformate (10% w/v solution in THF, 0.25 ml, 0.183 mmol) was added and the solution was stirred for a further 15 min. A solution of benzyl (2*S*,5*RS*)-5-allylpyrrolidine-2-carboxylate **9** (47.2 mg, 0.192 mmol) in THF (2 ml) was slowly added to the cooled mixture and further THF (1 ml) was added. The mixture was allowed to warm to rt over 3 h. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (5 ml). The organic phase was extracted with 5% aq. sodium hydrogen carbonate (5 ml), 5% aq. hydrochloric acid (5 ml) and brine (5 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a brown oil. Purification by flash column chromatography on silica gel using ethyl acetate–petroleum ether as eluent to give 2-benzyl 1-iso-butyl (2*S*,5*RS*)-5-allylpyrrolidine-1,2-dicarboxylate **15** (24.4 mg, 36%), with identical spectra to the sample isolated above, and benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylaminohex-5-enoyl)-pyrrolidine-2-carboxylate **24** (24.6 mg, 27%); $[a]_D^{26}$ −3.91 (*c* 2.4, MeOH); (*m/z* [ES+] found 457.2701; $[C_{26}H_{36}N_2O_5+H]^+$ requires 457.2702); ν_{max} (film)/cm^{-1} 3293 (NH), 1748 (ester), 1702 (lactam) and 1640 (urethane); δ_H (500 MHz C^2HCl_3, 2 rotamers, ratio 86 : 14 at 3 °C) 7.30 (5H, s, ArH), 5.72 (2H, m, H-7 and H-13), 5.54 (1H, d, $J_{NH,10}$ 9.2, NH major), 5.44 (1H, d, $J_{NH,10}$ 9.3, NH minor), 5.18 (1H, AB, J_{AB} 12, OCH_AAr), 5.14 (1H, AB, J_{AB} 12, OCH_BAr), 5.0 (4H, m, H-8 and H-14), 4.44 (1H, m, H-2), 4.36 (2H, m, H-5 and H-10), 2.34 (1H, m, H-6A), 2.25 (3H, m, H-6B, H-3B and H-4B), 1.65 (2H, q, *J* 7.3, H-11), 1.38 (9H, s, C(CH_3)$_3$ minor) and 1.37 (9H, s, C(CH_3)$_3$ major); δ_C (75.5 MHz C^2HCl_3 + $C^2H_3O^2H$) 172.7 and 172.3 (ester and lactam), 156.0 (urethane), 137.4 (C-7), 135.8 (Ar), 134.1 (C-13), 128.8, 128.6 and 128.4 (Ar), 118.7 (C-8), 116.0 (C-14), 80.1 (O*C*(CH_3)$_3$), 67.2 (OCH_2Ar), 59.9 (C-2), 58.6 (C-5), 50.9 (C-10), 39.5, 32.7, 29.9, 29.7 and 27.1 (C-12, C-11, C-6, C-4 and C-3) and 28.6 (C(CH_3)$_3$).

Benzyl (2*S*,5*R*,11*S*)-11-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,7,8,11,11*a*-octahydro-1*H*-pyrrolo[1,2*a*]azonine-3-carboxylate (6)

Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (Grubbs' catalyst) (8.8 mg, 0.010 mmol) was added to a solution of benzyl (2*S*,5*R*)-5-allyl-1-(2-*tert*-butoxycarbonylaminohex-5-enoyl)-pyrrolidine-2-carboxylate **24** (24.6 mg, 0.054 mmol) in dichloromethane (8 ml). The solution was heated at reflux for 24 h under nitrogen and allowed to cool to rt. The solvent was removed *in vacuo* to give a brown oil which was purified by flash column chromatography on silica gel using petroleum ether–diethyl ether (1 : 2) as eluent to give benzyl (2*S*,5*R*,11*S*)-11-*tert*-butoxycarbonylamino-5-oxo-2,3,5,6,7,8,11,11*a*-octahydro-1*H*-pyrrolo[1,2*a*]azonine-3-carboxylate **6** as a white foam (19.5 mg, 84%), $[a]_D^{35}$ −58.4 (*c* 1.95, MeOH); *m/z* [ES+] (found 429.2362; $[C_{24}H_{32}N_2O_5+H]^+$ requires 429.2384); ν_{max} (film)/cm^{-1} 3446 (NH), 1743 (ester), 1697 (urethane) and 1633 (lactam); δ_H (500 MHz, C^2HCl_3 + $C^2H_3O^2H$, 25 °C) 7.18 (5H, br, ArH), 5.67 (1H, m, H-7), 5.48 (1H, m, H-8), 5.08 (1H, AB, J_{AB} 12, OCH_AAr), 4.97 (1H, AB, J_{BA} 12, OCH_BAr), 4.37 (1H, dd, $J_{2,3A}$ 10.0, $J_{2,3B}$ 7.6, H-2), 4.30 (1H, br dd, $J_{11,10A}$ 11.3, $J_{11,10B}$ 3.5, H-11), 3.98 (1H, t, $J_{5,6A}$ 7.5, H-5), 2.75 (1H, m, H-6A), 2.22 (2H, m, H-9A and H-3A), 2.02 (1H, m, H-4A), 1.80 (3H, m, H-4B, H-6B and H-3B), 1.69 (2H, m, H-10A and H-9B), 1.50 (1H, m, H-10B) and 1.33 (9H, s, C(CH_3)$_3$); δ_C (75.5 MHz, C^2HCl_3 + $C^2H_3O^2H$) 177.4 and 176.6 (ester and lactam), 160.0 (urethane), 139.6 (Ar), 136.5 (C-7), 132.8, 132.6 and 132.5 (Ar), 132.1 (C-8), 84.0 (O*C*(CH_3)$_3$), 71.3 (OCH_2Ar), 64.7 (C-2), 64.2 (C-11), 54.2 (C-5), 39.6 (C-6), 38.6 and 38.4 (C-9 and C-10), 32.4 (C(CH_3)$_3$), 31.5 (C-4) and 27.7 (C-3).

Acknowledgements

We thank Dr A. G. Avent for NMR spectroscopic experiments and Dr Ali Al Sada and the EPSRC Central Mass Spectrometry Service at Swansea for mass spectra.

References

1 G. D. Rose, L. M. Gierasch and J. A. Smith, *Adv. Protein Chem.*, 1985, **37**, 1–109.
2 J. A. Smith and L. G. Pease, *CRC Crit. Rev. Biochem.*, 1980, **8**, 315–399.
3 J. B. Ball, R. A. Hughes, P. F. Alewood and P. R. Andrews, *Tetrahedron*, 1993, **49**, 3467–3478 and references cited therein.
4 S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789–12854.
5 U. Nagai and K. Sato, *Tetrahedron Lett.*, 1985, **26**, 647–650.
6 For example; (*a*) antibacterial activity–K. Sato and U. Nagai, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1231–1234; (*b*) growth homone releasing factor; K. Sato, M. Hotta, M.-H. Dong, H.-Y. Hu, J. P. Taulene, M. Goodman, U. Nagai and N. Ling, *Int. J. Pept. Protein Res.*, 1991, **38**, 340–345; (*c*) luteinising hormone release factor activity; U. Nagai, K. Sato, R. Nakamura and R. Kato, *Tetrahedron*, 1993, **49**, 3577–3592.
7 P. M. Doyle, C. J. Harris, C. M. Moody, P. J. Sadler, M. Sims, J. M. Thornton, J. Uppenbrink and J. H. Viles, *Int. J. Pept. Protein Res.*, 1996, **47**, 427–436.
8 J. A. Robl, C.-Q. Sun, J. Stevenson, D. E. Ryono, L. M. Simpkins, M. P. Cimarusti, T. Dejneka, W. A. Slusarchyk, S. Chao, L. Stratton, R. N. Misra, M. S. Bednarz, M. M. Asaad, H. S. Cheung, B. E. Abboa-Offei, P. L. Smith, P. D. Mathers, M. Fox, T. R. Schaeffer, A. A. Seymour and N. C. Trippodo, *J. Med. Chem.*, 1997, **40**, 1570–1577.
9 L. Belvisi, A. Bernardi, A. Checchia, L. Manzoni, D. Potenza, C. Scolastico, M. Castorina, A. Cupelli, G. Giannini, P. Carminati and C. Pisano, *Org. Lett.*, 2001, **3**, 1001–1004.
10 D. E. Davies, P. M. Doyle, R. D. Hill and D. W. Young, *Tetrahedron*, 2005, **61**, 301–312.
11 L. M. Beal, B. Liu, W. Chu and K. D. Moeller, *Tetrahedron*, 2000, **56**, 10113–10125.

12 M. V. Chiesa, L. Manzoni and C. Scolastico, *Synlett*, 1996, 441–443.
13 R. A. August, J. A. Khan, C. M. Moody and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1996, 507–514.
14 I. Collado, J. Ezquerra and C. Pedregal, *J. Org. Chem.*, 1995, **60**, 5011–5015.
15 A. Afzali-Ardakani and H. Rapoport, *J. Org. Chem.*, 1980, **45**, 4817–4820.
16 D. Marcovici-Mizrahi, H. E. Gottlieb, V. Marks and A. Nudelman, *J. Org. Chem.*, 1996, **61**, 8402–8406.
17 D. E. Davies, P. M. Doyle, R. D. Farrant, R. D. Hill, P. B. Hitchcock, P. N. Sanderson and D. W. Young, *Tetrahedron Lett.*, 2003, **44**, 8887–8891.
18 Y. T. Osano, U. Nagai and T. Matsuzaki, *Anal. Sci.*, 1969, **5**, 625–626.
19 C. Douat, A. Heitz, J. Martinez and J.-A. Fehrentz, *Tetrahedron Lett.*, 2001, **42**, 3319–3321.
20 D. Wernic, J. DiMaio and J. Adams, *J. Org. Chem.*, 1989, **54**, 4224–4228.
21 R. M. Adlington, J. E. Baldwin, D. Catterick and G. J. Pritchard, *J. Chem. Soc., Perkin Trans. 1*, 1999, 855–866.