Cyclisation of *meta*-phenylene-bis-alanine derivatives

Andreas Ritzén and Torbjörn Frejd *

Organic Chemistry 1, Department of Chemistry, Lund University, PO Box 124, SE-221 00, Lund, Sweden

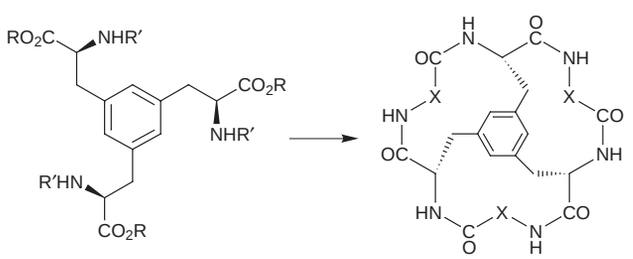
Received (in Cambridge) 9th July 1998, Accepted 20th August 1998

The cyclisation of a *meta*-phenylene-bis-alanine derivative with several different spacer moieties was investigated. A large difference in the ease of cyclisation was observed depending on which path of cyclisation was chosen. NMR studies indicate that the closed-loop molecules adopt folded conformations with the loop directly above the aromatic ring plane.

Introduction

Noncoded amino acid derivatives are attracting increasing interest for several reasons, one of which is the occurence of such structures in a number of antibiotics of the vancomycin and biphenomycin classes.[1–4] In addition, the possibility of making modified peptides using such derivatives is widely recognised.[5] Bis-armed amino acids of the phenylalanine type and their derivatives were synthesised in 1951 by Burckhalter *et al. via* alkyaltion of bis-benzylic bromides with ethyl acetamidocyanoacetate.[6] Since then several groups have developed alternative routes and a number of new structures have appeared in the literature including optically active derivatives.[7–13] For some time we have been working on synthetic methods for optically active aromatic bis-alanine derivatives carrying protecting groups useful for peptide synthesis.[14–21] In this report we wish to present aspects of the loop formation of *meta*-phenylene-bis-alanine derivatives.

We are currently investigating a tris-amino acid **1**, which we plan to use for the construction of synthetic host molecules for molecular recognition (Scheme 1). A concave host **2** can be

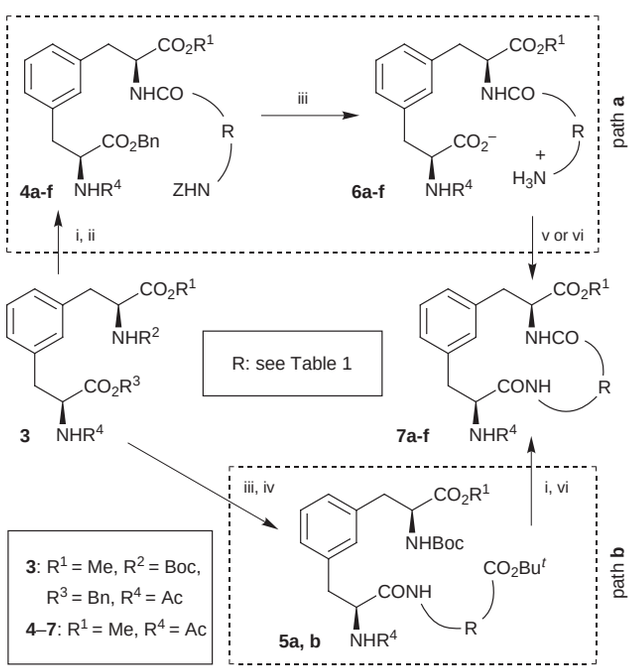


Scheme 1

envisaged where three loops are formed around the edges of **1** by linking the C- and N-terminals with various tethers. Since cyclisations leading to this type of system are not straightforward, we decided to investigate these cyclisations using a bis-amino acid model system, Scheme 2. In a recent publication by Travins and Etzkorn,[22] a very similar cyclised bis-amino acid system was constructed for use as a turn subunit in a helix–turn–helix motif for incorporation in a short synthetic peptide. This prompted us to communicate our hitherto obtained results.

Results and discussion

For maximum flexibility, we adopted a strategy where a common core derivative **3** is coupled to various protected amino



Scheme 2 *Reagents*: i, TFA; ii, ZHN–R–CO_2H, TEA, DCC, HOBt, THF; iii, 5% Pd/C, H_2 1 atm, EtOH; iv, HCl·H_2N–R–CO_2Bu^t, DIEA, DCC, HOBt, THF; v, DPPA, $NaHCO_3$, DMF; vi, HATU, DIEA, DMF.

acids to form **4** and **5**, Scheme 2, which are then cyclised. In principle, the cyclisation can occur in two ways: using an amine nucleophile either on the coupled amino acid, path **a**, or on the aromatic core, path **b**. It is not *a priori* evident that both directions will be equally successful. We reasoned that on steric grounds, the amino group of an amino acid without substituents α to nitrogen would be a better nucleophile than the amino group of the phenylalanine-like core. The difference would be expected to be small, and easily overridden by conformational effects, but we decided to try path **a** first.

To make the open-chain precursors, we needed a bis-armed phenylalanine derivative **3** with two blocking groups, R^1 and R^4, stable to all reaction conditions applied, and two orthogonal protecting groups, R^2 and R^3. This would ensure that the same core could be used for both directions of cyclisation. Furthermore, the blocking groups should not complicate the NMR spectra, so groups giving singlets in ^{1}H NMR would be preferred. Finally, it is well-known that N^{α}-carbamate protecting groups suppress racemisation of a C-terminal residue better than amides in most peptide couplings.[5] If R^4 is a carbamate,

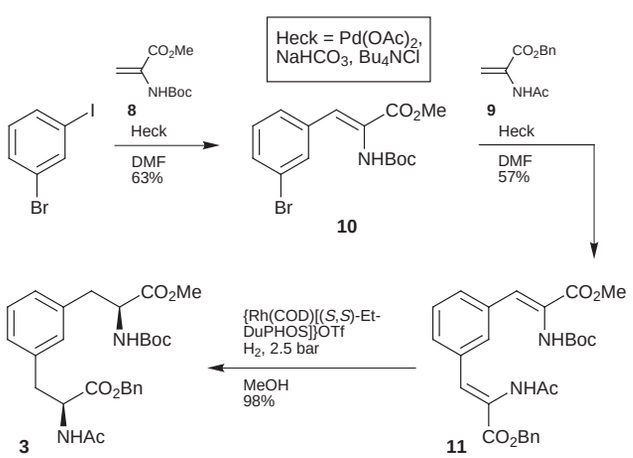
the proximal stereogenic centre would be less prone to racemisation during the cyclisation reaction following path **a**, than if R^4 is an amide. While this would be beneficial for this cyclisation reaction leading to **2**, Scheme 1, the corresponding amine would necessarily be part of an amide, and thus be more prone to racemisation. In conclusion, when path **a** is followed a carbamate at R^4 could mask racemisation in the model system that would later become a problem in the cyclisation leading to **2**. For this reason, the *N*-acetyl blocking group was chosen.

A very convenient route to optically active amino acids is *via* the corresponding didehydro derivatives, which are hydrogenated with a chiral, nonracemic Rh(I)–bisphosphine catalyst. The development of highly efficient ligands, such as DuPHOS† has led to ees of >98% for a large variety of substituted phenylalanines.[23]

For the synthesis of didehydrophenylalanine derivatives, we have earlier used the Heck–Jeffery reaction between aromatic halides and 2-amidoacrylates or 2-carbamatoacrylates.[14,16,18] This method tolerates a variety of protecting groups in the acrylate, which is readily available in multigram quantities in three steps from DL-serine, typically in 70% overall yield. The commercial availability of a number of aromatic halides enables the synthesis of many different substituted aromatic didehydroamino acids *via* this route.

An alternative method, the condensation of a phosphonylglycine derivative with an aromatic aldehyde in a Horner–Wadsworth–Emmons reaction, was developed by Schmidt *et al.*,[24,25] and has previously been used by us[19,20] and also by Travins and Etzkorn.[22] The Schmidt method generally gives somewhat higher yields in the coupling step, but at the cost of five–seven steps for the synthesis of most of the phosphonylglycines.

The synthesis of the core derivative **3** is based on the Heck–Jeffery method (Scheme 3). Starting with 3-bromoiodobenzene,



Scheme 3

two successive Heck–Jeffery reactions with olefins **8** and **9** gave the doubly unsaturated derivative **11**. Both couplings were highly *Z*-selective, as expected for this method,[14,18] and **11** was obtained as the single stereoisomer (*Z*,*Z*) after chromatography and recrystallisation. The stereochemistry of both **10** and **11** was confirmed by NOE measurements.[20] The stereochemistry may alternatively be determined by measuring the $^3J_{CH}$ coupling constant between the vinylic proton and the ester carbonyl carbon in a proton-coupled ^{13}C NMR experiment.[26] However, this coupling constant could not be determined for **10** and **11** due to line broadening of the carbonyl carbon peaks.

† List of abbreviations: DIEA = *N*,*N*-diisopropylethylamine, DPPA = diphenylphosphoryl azide, DuPHOS = 1,2-bis(2,5-dialkylphospholano)benzene, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole, TEA = triethylamine.

Table 1 Yield of cyclisation products **7a**–**f**

Chain R	Precursor	Product	Yield(%)
CH_2	**5a**, **6a**	**7a**	ND,[a] 82,[b] 16[c]
$(CH_2)_2$	**5b**, **6b**	**7b**	ND,[a] 36[b]
$(CH_2)_3$	**6c**	**7c**	24[a]
$(CH_2)_4$	**6d**	**7d**	29[a]
$(CH_2)_5$	**6e**	**7e**	50[c]
(*S*)-N^{α}(Boc)Lys[d]	**6f**	**7f**	50[c]

ND = not detected. [a] DPPA, path **a**. [b] HATU, path **b**. [c] HATU, path **a**. [d] Replaces CO–R–NHZ in **4**, CO–R–NH_3^+ in **6** and CO–R–NH in **7**.

The final hydrogenation worked well with (*S*,*S*)-Me-DuPHOS as a ligand giving **3** in 98% yield with a dr (diastereomeric ratio) of 95:5 as determined by ^1H NMR. Changing to (*S*,*S*)-Et-DuPHOS improved the dr to ≥99.5:0.5. The enantiomers of **3** could be separated using HPLC on a chiral (*R*,*R*)-Whelk-O1 column, but only one peak could be detected for the product from the Et-DuPHOS hydrogenation, thus establishing ≥98% ee. The absolute configuration was assigned as (*S*,*S*)-**3** based on the fact that the (*S*,*S*) enantiomer of the ligand in all examined cases gives the *S* amino acid.[23]

We initially synthesised several open-chain derivatives **6a**–**f** on which to try the cyclisation according to path **a**, Scheme 2. The results are summarized in Table 1. Compound **6e** was also synthesised as a racemic, 1:1 mixture of diastereomers for use as reference material in the dr estimation by NMR spectroscopy. The diastereomers of **6e** could be partially separated using flash chromatography.

We chose to try DPPA as cyclisation agent first, since it is known to suppress epimerisation,[5,27] and had been previously used by our group in a synthesis of a biphenomycin analogue.[17] Addition of a 0.1–0.2% solution of **6** in DMF to a suspension of DPPA and $NaHCO_3$ in DMF, using a syringe pump over 60 h, gave a moderate yield of the cyclised products **7c** and **7d**. Some epimerisation of the C-terminal residue, *ca.* 10%, was also observed. No cyclised product could be isolated in the short-chain cases **6a** and **6b**, but since the reactions were performed on a small scale, typically 20 mg, a <10% yield may have passed undetected.

We next tried HATU as cyclisation reagent, since it has been shown to be fast, versatile, and usually suppresses epimerisation of C-terminal residues in cyclisation reactions.[28] In a typical procedure, the deprotected amino acid (1 mM in DMF) was treated with HATU (1.1 equiv.) and DIEA (3 equiv.) for 1 h at room temp. For the cyclisations of **6e** and **6f**, cyclised products were formed in fair yields, but there was still *ca.* 10% epimerisation of the core C-terminal. We next attempted to cyclise **6a** with HATU, which gave a modest 16% yield of the cyclised product **7a**. Interestingly, no C-terminal epimerisation was evident from the ^1H NMR of **7a**. To try to improve the yields, we then changed the direction of cyclisation from path **a** to path **b**, Scheme 2. A high yield of the shortest-chain derivative **7a** and a moderate yield of the next shortest-chain one, **7b**, was obtained with HATU. These two derivatives, unlike the others, **7c**–**7f**, are insoluble or sparingly soluble in $CHCl_3$, and just by washing the crude product with water and $CHCl_3$ a fairly pure product was obtained.

In all cases, the monomeric formulation of the cyclised products **7a**–**f** was confirmed by MS. In no case could more than a few percent of cyclodimerised material be detected.

It is interesting at this point to compare our results with those obtained by Travins and Etzkorn.[22] In their work, path **b** was chosen in the cyclisation of a derivative very similar to our deprotected **5a**, and a high yield of cyclised product, 80%, was obtained after reaction with DPPA for 7 d. Although Travins and Etzkorn never tried path **a**, our results suggest that for **7a**, there is indeed a large difference in ease of cyclisation between these two paths. Computer modelling will be required to pin-

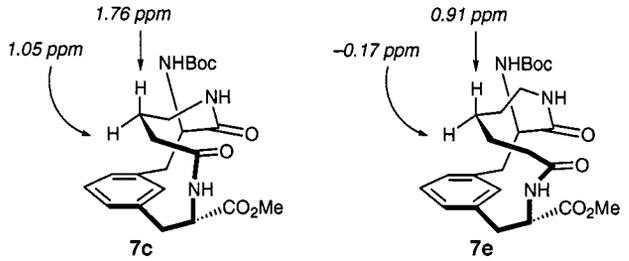


Fig. 1

point the exact cause for this.[29] In retrospect, the large difference between path **a** and **b** is perhaps not unexpected in view of results from cyclisation of tetra- to hexapeptides.[5,29]

A noteworthy feature of the ^{1}H NMR spectra of the cyclised derivatives with an odd number of methylene groups in the loop, is the large chemical shift difference of the protons of the central methylene group, see Fig. 1. These protons resonate at up to 1 ppm apart from each other, with one signal at very low shift. This is most readily explained by assuming that a folded conformation is adopted, where one of the protons is positioned closely above the aromatic ring.

With the successful construction and cyclisation of this model system at hand, we will try to extend it to also include the tris-armed receptor **2**. These results will be reported in due course.

Experimental

All reactions were carried out under an inert atmosphere of dry N_2. TLC was performed using Merck Silica Gel 60 coated glass plates with the same eluent as in the corresponding flash chromatography, unless otherwise noted. Me-DuPHOS and Et-DuPHOS were purchased from Strem Chemicals, and HATU was purchased from PerSeptive Biosystems. All commercial materials were used without further purification unless otherwise noted. The Rh hydrogenation catalysts were synthesised according to the published procedure.[23] Protected amino acids were either commercially available or synthesised *via* standard procedures.[30] Olefins **8**[14] and **9**[31] were synthesised according to the published procedures. NMR spectra were recorded on a Bruker DRX400 spectrometer operating at 400 MHz for proton and 75 MHz for carbon-13 experiments, and using $CDCl_3$ as solvent unless otherwise noted. *J* Values are given in Hz. $[\alpha]_D$ Values are given in units 10^{-1} deg cm^2 g^{-1}.

Methyl (*Z*)-3-(3-bromophenyl)-2-[(*tert*-butoxycarbonyl)amino]-prop-2-enoate 10

1-Bromo-3-iodobenzene (3.8 ml, 30 mmol), methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate **8** (7.0 ml, 36 mmol), $Pd(OAc)_2$ (0.34 g, 1.5 mmol), Bu_4NCl (8.3 g, 30 mmol), and $NaHCO_3$ (6.3 g, 75 mmol) were mixed in DMF (30 ml) in a screwcap vessel, and a few crystals of hydroquinone were added to prevent polymerisation of the olefin. The mixture was stirred at +60 °C for 18 h, and was then allowed to cool to room temp. It was diluted with EtOAc (200 ml) and washed with half-saturated brine (4 × 200 ml). The organic phase was dried over $MgSO_4$, the solvents were removed on a rotary evaporator, and the residue was purified by flash chromatography (heptane–EtOAc 4:1; TLC R_f 0.33 using heptane–EtOAc 3:1). The analytically pure product was obtained as white needles (6.78 g, 63%) by recrystallisation from EtOAc–heptane, mp 103–105 °C; δ_H 1.41 (9 H, s), 3.86 (3 H, s), 6.40 (1 H, br s), 7.17 (1 H, s), 7.22 (1 H, t, *J* 7.8), 7.41–7.43 (2 H, m) and 7.68 (1 H, t, *J* 1.8); δ_C(+40 °C) 28.31, 52.86, 81.44, 122.71, 125.61, 128.05, 128.47, 130.02, 132.03, 132.35, 136.68, 152.46 and 165.87; HRMS (FAB+): $C_{15}H_{19}BrNO_4$ (M + H); Found: *m*/*z*, 356.0490. Calc.: *m*/*z*, 356.0497.

1-{(*Z*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethenyl}-3-{(*Z*)-2-[(*tert*-butoxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-benzene 11

The reaction was carried out analogously to the one described for **10** above, using **10** (3.56 g, 10 mmol), methyl 2-(acetamido)acrylate **9** (2.63 g, 12 mmol), $Pd(OAc)_2$ (0.11 g, 0.50 mmol), Bu_4NCl (2.78 g, 10 mmol), and $NaHCO_3$ (2.10 g, 25 mmol) in DMF (15 ml). The reaction temperature was +85 °C, and the flash chromatography was performed using heptane–EtOAC 2:3 as eluent (TLC R_f 0.24). The analytically pure product was obtained as white needles (2.81 g, 57%) by dissolution in EtOAc (20 ml) followed by precipitation by slow addition of heptane (50 ml), mp 115–118 °C; δ_H(+55 °C) 1.38 (9 H, s), 2.08 (3 H, br s), 3.86 (3 H, s), 5.28 (2 H, s), 6.22 (1 H, br s), 7.07 (1 H, br s), 7.21 (1 H, s), 7.35–7.49 (9 H, m) and 7.64 (1 H, s); δ_C 23.55, 28.21, 52.90, 67.80, 81.41, 125.05, 125.23, 128.55, 128.61, 128.81, 129.29, 130.29, 130.70, 131.01, 131.50, 134.17, 134.63, 135.64, 152.91, 165.25, 166.07 and 169.16; HRMS (FAB+): $C_{27}H_{31}N_2O_7$ (M + H); Found: *m*/*z*, 495.2141. Calc.: *m*/*z*, 495.2131.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-(methoxycarbonyl)ethyl}-benzene 3

Compound **11** (1.00 g, 2.02 mmol) and {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+$OTf$^-$ (5 mg, 7 μmol) were dissolved in MeOH (10 ml) which had been deoxygenated by N_2 bubbling for 30 min. The solution was hydrogenated at 40 psi for 6 h at room temp. after which the solvent was removed on a rotary evaporator. The residue was passed through a plug of silica using EtOAc as eluent to remove the catalyst. After evaporation of the solvent, the analytically pure product was obtained as an oil that crystallised on standing. To get a more easily handled product, crystallisation from EtOAc–heptane was performed, which gave the product as white, fluffy needles (0.99 g, 98%), mp 90–93 °C; $[\alpha]_D^{22}$ +34 (*c* 1.6, $CHCl_3$); ee ≥98% by HPLC (Merck (*R*,*R*)-Whelk-O1 4.6 × 250 mm; *n*-hexane–propan-2-ol 80:20 +0.25% HOAc at 1.0 ml min^{-1}; t_R 18.5 (*S*,*S*)-**3**, 20.1 (*R*,*R*)-**3** min; dr ≥99.5:0.5 by ^{1}H NMR; δ_H 1.42 (9 H, s), 2.01 (3 H, s), 2.97–3.11 (4 H, m), 3.71 (3 H, s), 4.53–4.57 (1 H, m), 4.90–4.97 (2 H, m), 5.14 (1 H, d, *J* 12), 5.20 (1 H, d *J* 12), 5.97 (1 H, br d, *J* 7.6), 6.81 (1 H, s), 6.87 (1 H, d, *J* 7.7), 6.99 (1 H, d, *J* 7.7), 7.13 (1 H, t, *J* 7.7) and 7.32–7.40 (5 H, m); δ_C 23.50, 28.70, 38.06, 38.71, 52.67, 53.46, 54.85, 67.67, 80.44, 128.44, 128.52, 129.00, 129.08, 129.19, 130.75, 135.55, 136.44, 136.74, 155.46, 170.21, 171.86 and 172.71; HRMS (FAB+): $C_{27}H_{35}N_2O_7$ (M + H); Found: *m*/*z*, 499.2438. Calc.: *m*/*z*, 499.2444.

The (*R*,*R*) isomer was prepared analogously using (*R*,*R*)-Me-DuPHOS as ligand, and a racemic sample was prepared as a 1:1 mixture of diastereomers by hydrogenation using DPPE as ligand. The methyl ester resonance at δ_H 3.7 was used to measure the dr, since two baseline-separated singlets, one corresponding to each diastereomer, were seen in the spectrum of a 1:1 diastereomeric mixture of **3**.

Deprotection and general coupling, path a

Compound **3** (0.20 g, 0.40 mmol) was dissolved in TFA (5 ml) and kept for 15 min at room temp. after which the TFA was removed on a rotary evaporator. The residue was washed with ether to remove the last traces of TFA, and vacuum-dried. The resulting white solid was dissolved in dry THF (3 ml) and the Z-protected amino acid (0.40 mmol), TEA (0.14 ml, 1.0 mmol), and HOBt (61 mg, 0.40 mmol, monohydrate) were added. The resulting solution was cooled on an ice-bath under N_2 and DCC (87 mg, 0.42 mmol) was added. After stirring for 1 h at 0 °C followed by 16 h at room temp. the reaction mixture was filtered to remove the separated dicyclohexylurea. The filtrate was evaporated to dryness, dissolved in EtOAc (5 ml) and the solu-

tion washed with saturated aqueous $NaHCO_3$ (3 ml). After brief drying over Na_2SO_4 the solution was chromatographed using heptane–EtOAc–acetone 2:7:1 as eluent (TLC R_f 0.2–0.3) after which the pure product **4a**–**f** was obtained as a white solid.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(2-{[(benzyloxy)carbonyl]amino}acetyl)amino]-2-(methoxycarbonyl)ethyl} benzene 4a. Yield 67%; mp 38–41 °C; $[\alpha]_D^{22}$ +30 (*c* 1.5, $CHCl_3$); δ_H 1.93 (1 H, s), 2.95–3.12 (4 H, m), 3.71 (3 H, s), 3.74–3.91 (2 H, m), 4.80–4.84 (1 H, m), 4.90–4.94 (1 H, m), 5.08–5.18 (4 H, m), 5.88 (1 H, br t, *J* 7), 6.32 (1 H, br d, *J* 7.6), 6.61 (1 H, br d, *J* 7.2), 6.82 (1 H, s), 6.89 (1 H, d, *J* 7.6), 6.94 (1 H, d, *J* 7.2), 7.12 (1 H, t, *J* 7.6) and 7.28–7.37 (10 H, m); δ_C 23.04, 37.55, 38.02, 44.56, 52.61, 53.12, 53.34, 67.21, 67.44, 128.08, 128.15, 128.32, 128.61, 128.66, 128.71, 128.80, 128.88, 130.29, 135.22, 136.10, 136.35, 136.49, 156.82, 169.16, 170.22 and 171.86; HRMS (FAB+): $C_{32}H_{36}N_3O_8$ (M + H); Found: *m*/*z*, 590.2500. Calc.: *m*/*z*, 590.2502.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(3-{[(benzyloxy)carbonyl]amino}propanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 4b. Yield 60%; mp 99–101 °C; $[\alpha]_D^{22}$ +31 (*c* 1.6, $CHCl_3$); δ_H 1.95 (3 H, s), 2.36–2.40 (2 H, m), 2.93–3.11 (4 H, m), 3.37–3.43 (2 H, m), 3.70 (3 H, s), 4.78–4.84 (1 H, m), 4.88–4.94 (1 H, m), 5.06 (2 H, s), 5.10–5.18 (2 H, m), 5.50 (1 H, br t, *J* 7), 6.21–6.27 (2 H, m), 6.83 (1 H, s), 6.87 (1 H, d, *J* 7.5), 6.94 (1 H, d, *J* 7.6), 7.12 (1 H, t, *J* 7.6) and 7.28–7.37 (10 H, m); δ_C 23.05, 35.88, 37.21, 37.75, 37.96, 52.54, 53.17, 53.24, 66.70, 67.38, 128.09, 128.17, 128.34, 128.58, 128.60, 128.69, 128.78, 128.84, 130.13, 135.24, 136.29, 136.43, 136.71, 156.58, 170.04, 171.27, 171.72 and 172.15; HRMS (FAB+): $C_{33}H_{38}N_3O_8$ (M + H); Found: *m*/*z*, 604.2657. Calc.: *m*/*z*, 604.2659.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(4-{[(benzyloxy)carbonyl]amino}butanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 4c. Yield 61%; mp 135–137 °C; $[\alpha]_D^{23}$ +26 (*c* 1.6, $CHCl_3$); δ_H 1.72–1.79 (2 H, m), 1.95 (3 H, s), 2.16–2.21 (2 H, m), 2.97–3.10 (4 H, m), 3.12–3.18 (2 H, m), 3.70 (3 H, s), 4.80–4.92 (2 H, m), 5.07 (2 H, s), 5.09–5.16 (2 H, m), 5.24 (1 H, br t, *J* 7), 6.13 (1 H, br d, *J* 7.8), 6.31 (1 H, br d, *J* 7.6), 6.84–6.88 (2 H, m), 6.94 (1 H, d, *J* 7.6), 7.12 (1 H, t, *J* 7.6) and 7.28–7.37 (10 H, m); δ_C 23.15, 26.07, 33.42, 37.77, 38.09, 40.35, 52.56, 53.17, 53.39, 66.80, 67.45, 128.25, 128.30, 128.67, 128.76, 128.84, 128.91, 130.26, 135.26, 136.36, 136.49, 136.79, 156.95, 170.13, 171.73, 172.33 and 172.46; HRMS (FAB+): $C_{34}H_{40}N_3O_8$ (M + H); Found: *m*/*z*, 618.2793. Calc.: *m*/*z*, 618.2815.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 4d. Yield 50%; mp 91–94 °C; $[\alpha]_D^{23}$ +34 (*c* 1.6, $CHCl_3$); δ_H 1.22–1.28 (2 H, m), 1.42–1.49 (2 H, m), 1.96 (3 H, s), 2.11–2.21 (2 H, m), 2.95–3.18 (6 H, m), 3.70 (3 H, s), 4.81–4.92 (2 H, m), 5.07 (2 H, s), 5.09–5.16 (2 H, m), 5.21 (1 H, br t, *J* 7), 6.11 (1 H, br d, *J* 7.7), 6.23 (1 H, br d, *J* 7.7), 6.83 (1 H, s), 6.87 (1 H, d, *J* 7.4), 6.94 (1 H, d, *J* 7.6), 7.13 (1 H, t, *J* 7.6) and 7.28–7.36 (10 H, m); δ_C 22.61, 23.06, 29.34, 35.67, 37.81, 37.92, 40.51, 52.48, 53.04, 53.33, 66.63, 67.34, 128.12, 128.15, 128.23, 128.60, 128.68, 128.77, 128.84, 130.30, 135.22, 136.31, 136.39, 136.82, 156.70, 170.08, 171.68, 172.27 and 172.59; HRMS (FAB+): $C_{35}H_{42}N_3O_8$ (M + H); Found: *m*/*z*, 632.2992. Calc.: *m*/*z*, 632.2972.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(6-{[(benzyloxy)carbonyl]amino}hexanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 4e. Yield 49%; mp 95–97 °C; $[\alpha]_D^{22}$ +35 (*c* 1.5, $CHCl_3$); δ_H 1.25–1.32 (2 H, m), 1.43–1.49 (2 H, m), 1.53–1.61 (2 H, m), 1.97 (3 H, s), 2.12–2.16 (2 H, m), 2.96–3.08 (4 H, m), 3.13–3.18 (2 H, m), 3.70 (3 H, s), 4.82–4.93 (2 H, m), 5.03 (1 H, br t, *J* 7), 5.08 (2 H, s), 5.09–5.15 (2 H, m), 5.98 (1 H, d, *J* 8.0), 6.16 (1 H, d, *J* 7.8), 6.82 (1 H, s), 6.88 (1 H, d, *J* 7.6), 6.94 (1 H, d, *J* 7.7), 7.14 (1 H, t, *J* 7.6) and 7.28–7.37 (10 H, m); δ_C 23.14, 25.16, 26.28, 29.66, 36.18, 37.89, 37.99, 40.92, 52.54, 52.97, 53.32, 66.67, 67.37, 128.21, 128.24, 128.27, 128.64, 128.73, 128.80, 128.88, 130.29, 135.21, 136.28, 136.37, 136.82, 156.60, 170.06, 171.69, 172.35 and 172.65; HRMS (FAB+): $C_{36}H_{44}N_3O_8$ (M + H); Found: *m*/*z*, 646.3134. Calc.: *m*/*z*, 646.3128.

1-{(2*S*)-2-(Acetylamino)-2-[(benzyloxy)carbonyl]ethyl}-3-{(2*S*)-2-[(6-{[(benzyloxy)carbonyl]amino}-2-(2*S*)-{[*tert*-butoxycarbonyl]amino}hexanoyl)amino]-2-(methoxycarbonyl)ethyl}-benzene 4f. Yield 50%; mp 133–135 °C; $[\alpha]_D^{22}$ +19 (*c* 0.26, $CHCl_3$); δ_H(+55 °C) 1.33–1.63 (14 H, m), 1.75–1.85 (1 H, m), 1.97 (3 H, s), 3.00–3.20 (6 H, m), 3.70 (3 H, s), 4.02–4.09 (1 H, m), 4.78–4.84 (1 H, m), 4.88–4.96 (2 H, m), 5.10 (2 H, s), 5.12–5.22 (2 H, m), 5.23–5.28 (1 H, m), 6.21 (1 H, br s), 6.43 (1 H, br s), 6.85 (1 H, br s), 6.91–6.96 (2 H, m), 7.14 (1 H, t, *J* 7.6) and 7.29–7.39 (10 H, m); δ_C 22.77, 23.06, 28.53, 29.70, 32.14, 37.88, 38.20, 40.87, 52.45, 53.15, 53.60, 54.92, 66.85, 67.51, 80.35, 128.24, 128.50, 128.68, 128.85, 128.97, 130.51, 135.55, 136.29, 136.73, 137.07, 155.84, 156.76, 170.09, 171.89 and 172.06; HRMS (FAB+): $C_{41}H_{53}N_4O_{10}$ (M + H); Found: *m*/*z*, 761.3769. Calc.: *m*/*z*, 761.3762.

Deprotection and general coupling, path b

Compound **3** (0.50 g, 1 mmol) was dissolved in 99.5% ethanol (10 ml) and 5% Pd on carbon (50 mg) was added. After stirring for 3 h at room temp. under hydrogen at atmospheric pressure, the catalyst was removed by filtration through Celite. The solvent was removed on a rotary evaporator, and EtOAc was added and evaporated to remove residual ethanol. After storage in vacuum overnight, the free acid 1-[(2*S*)-2-(acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-(methoxycarbonyl)ethyl}benzene was obtained as a white powder (0.42 g, >100%) that retained a small amount of EtOAc, but was otherwise pure. The NMRs had to be recorded at elevated temperature in DMSO, since at ordinary temperatures the different rotamers around the carbamate interconvert slowly on the NMR time scale, thus complicating the spectra. It is known [32] that the occurence of free carboxylic acids stabilises the minor rotamer of the carbamate. Data for the free acid: mp 60–63 °C; δ_H(DMSO-d_6, +70 °C) 1.34 (9 H, s), 1.80 (3 H, s), 2.82–3.06 (4 H, m), 3.61 (3 H, s), 4.15–4.26 (1 H, m), 4.41–4.50 (1 H, m), 6.85 (1 H, br s), 7.04–7.12 (3 H, m), 7.18 (1 H, t, *J* 7.8) and 7.84 (1 H, d, *J* 8.0); δ_C 21.98, 27.81, 36.50, 36.63, 51.26, 53.10, 54.97, 78.13, 126.82, 127.66, 129.49, 137.00, 137.35, 154.82, 168.86, 172.05 and 172.54; HRMS (FAB+): $C_{20}H_{29}N_2O_7$ (M + H); Found: *m*/*z*, 409.1978. Calc.: *m*/*z*, 409.1975.

This material (204 mg, 0.50 mmol) was used directly in the coupling reaction. After dissolution in dry THF (3 ml), the amino acid ester hydrochloride (0.50 mmol), DIEA (0.22 ml, 1.3 mmol), and HOBt (77 mg, 0.50 mmol, monohydrate) were added. The resulting solution was cooled on an ice-bath under N_2 and DCC (109 mg, 0.53 mmol) was added. The reaction conditions and work-up were as for the general coupling following path **a** above.

1-{(2*S*)-2-(Acetylamino)-2-[({2-[(*tert*-butoxycarbonyl)]-methyl}amino)carbonyl]ethyl}-3-{(2*S*)-2-[(*tert*-butoxycarbonyl)-amino]-2-(methoxycarbonyl)ethyl}benzene 5a. Yield 64%; mp 61–64 °C; $[\alpha]_D^{22}$ +20 (*c* 1.5, $CHCl_3$); δ_H(+50 °C) 1.39 (9 H, s), 1.44 (9 H, s), 1.96 (3 H, s), 2.94–3.11 (4 H, m), 3.70 (3 H, s), 3.84 (2 H, br s), 4.49 (1 H, br s), 4.65–4.71 (1 H, m), 5.12 (1 H, br d, *J* 7.6), 6.32 (1 H, br d, *J* 7.6), 6.46 (1 H, br s), 6.99 (1 H, d, *J* 7.5), 7.03 (1 H, s), 7.08 (1 H, d, *J* 7.7) and 7.19 (1 H, t, *J* 7.6); δ_C 23.24, 28.15, 28.44, 38.39, 42.09, 52.42, 54.47, 54.76,

80.02, 82.36, 128.03, 128.19, 128.89, 130.43, 136.67, 136.99, 155.29, 168.68, 170.34, 171.28 and 172.47; HRMS (FAB+): $C_{26}H_{40}N_3O_8$ (M + H); Found: *m*/*z*, 522.2798. Calc.: *m*/*z*, 522.2815.

1-{(2*S*)-2-(Acetylamino)-2-[({3-[(*tert*-butoxycarbonyl)]ethyl}-amino)carbonyl]ethyl}-3-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-(methoxycarbonyl)ethyl}benzene 5b. Yield 74%; mp 55–58 °C; $[\alpha]_D^{22}$ +26 (*c* 1.5, $CHCl_3$); δ_H 1.40 (9 H, s), 1.42 (9 H, s), 1.99 (3 H, s), 2.26–2.37 (2 H, m), 2.89–3.01 (2 H, m), 3.06–3.11 (2 H, m), 3.35–3.41 (2 H, m), 3.74 (3 H, s), 4.53–4.59 (2 H, m), 5.09 (1 H, br d, *J* 8.3), 6.23–6.26 (2 H, m), 6.98–7.07 (3 H, m), 7.21 (1 H, t, *J* 7.5); δ_C 23.36, 28.25, 28.47, 35.02, 35.17, 38.65, 38.78, 52.53, 54.85, 80.14, 81.30, 128.17, 129.01, 130.35, 136.79, 137.06, 155.22, 170.04, 170.76, 171.61 and 172.41; HRMS (FAB+): $C_{27}H_{42}N_3O_8$ (M + H); Found: *m*/*z*, 536.2974. Calc.: *m*/*z*, 536.2972.

Second deprotection, path a

Compound **4** (100 mg) was dissolved in ethanol and 5% Pd on carbon (50 mg) was carefully added. The mixture was stirred under 1 atm of H_2 for 16 h. Sometimes the free amino acid precipitated, and was in those cases dissolved by addition of a small amount of water. The catalyst was removed by filtration through Celite, the filtrate was evaporated, and the residue was recrystallised by dissolution in ethanol or methanol followed by precipitation by the addition of ether. After centrifugation and drying, compound **6** was obtained as a white powder that retained some solvents. It was used immediately in the ring-closing experiments.

1-[(2*S*)-2-(Acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(2-amino-acetyl)amino]-2-(methoxycarbonyl)ethyl}benzene 6a. Yield 73%; mp 193–196 °C; δ_H(D_2O, +40 °C) 1.95 (3 H, s), 2.94 (1 H, dd, *J* 8.2 and 13.7), 3.04 (1 H, dd, *J* 8.9 and 14.1), 3.14 (1 H, dd, *J* 5.5 and 13.8), 3.24 (1 H, dd, *J* 5.4 and 14.1), 3.77 (3 H, s), 3.77–3.85 (2 H, m), 4.44 (1 H, dd, *J* 5.5 and 8.0), 4.80 (1 H, dd, *J* 5.4 and 8.8), 7.12 (1 H, s), 7.15 (1 H, d, *J* 7.6), 7.19 (1 H, d, *J* 7.8) and 7.33 (1 H, t, *J* 7.6); δ_C 22.44, 37.04, 38.08, 40.86, 53.60, 54.71, 56.91, 127.95, 128.66, 129.33, 130.43, 137.04, 138.74, 167.36, 173.81, 173.83 and 178.20; HRMS (FAB+): $C_{17}H_{24}N_3O_6$ (M + H); Found: *m*/*z*, 366.1664. Calc.: *m*/*z*, 366.1665.

1-[(2*S*)-2-(Acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(3-aminopropanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 6b. Yield 48%; mp 181–183 °C; δ_H(D_2O) 1.91 (3 H, s), 2.59–2.68 (2 H, m), 2.88 (1 H, dd, *J* 8.7 and 13.9), 2.98 (1 H, dd, *J* 9.3 and 13.9), 3.11–3.16 (3 H, m), 3.21 (1 H, dd, *J* 5.3 and 13.9), 3.73 (3 H, s), 4.39 (1 H, *J* 5.0 and 8.7), 4.72 (1 H, dd, *J* 5.4 and 9.2), 7.11–7.17 (3 H, m) and 7.29 (1 H, t, *J* 7.7); δ_C 22.16, 31.90, 35.75, 36.76, 37.89, 53.30, 54.39, 56.85, 127.68, 128.36, 129.08, 130.23, 136.94, 138.57, 172.29, 173.56, 173.98 and 178.50; HRMS (FAB+): $C_{18}H_{26}N_3O_6$ (M + H); Found: *m*/*z*, 380.1821. Calc.: *m*/*z*, 380.1822.

1-[(2*S*)-2-(Acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(4-aminobutanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 6c. Yield 45%; mp 112–114 °C; δ_H(D_2O) 1.77–1.86 (2 H, m), 1.92 (3 H, s), 2.26–2.36 (2 H, m), 2.79–3.00 (4 H, m), 3.14–3.26 (2 H, m), 3.73 (3 H, s), 4.45–4.49 (1 H, m), 4.68–4.72 (1 H, m), 7.12–7.19 (3 H, m) and 7.30 (1 H, t, *J* 7.7); δ_C(+50 °C) 22.51, 23.44, 32.74, 37.10, 37.90, 39.44, 53.63, 54.72, 56.34, 128.17, 128.60, 129.44, 130.55, 137.46, 138.60, 174.10, 174.38, 175.30 and 177.39; HRMS (FAB+): $C_{19}H_{28}N_3O_6$ (M + H); Found: *m*/*z*, 394.1976. Calc.: *m*/*z*, 394.1978.

1-[(2*S*)-2-(Acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(5-aminopentanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 6d. Yield 75%; mp 136–140 °C; δ_H(D_2O) 1.44–1.54 (4 H, m), 1.91 (3 H, s), 2.21–2.25 (2 H, m), 2.88–2.99 (4 H, m), 3.17–3.25 (2 H, m), 3.73 (3 H, s), 4.49–4.53 (1 H, m), 4.65–4.69 (1 H, m), 7.12–7.19 (3 H, m) and 7.30 (1 H, t, *J* 7.6); δ_C(+40 °C) 22.44, 22.52, 26.52, 35.06, 36.97, 38.02, 39.63, 53.50, 54.59, 56.85, 127.98, 128.41, 129.30, 130.48, 137.31, 138.73, 173.83, 174.33, 176.44 and 178.09; HRMS (FAB+): $C_{20}H_{30}N_3O_6$ (M + H); Found: *m*/*z*, 408.2135. Calc.: *m*/*z*, 408.2135.

1-[(2*S*)-2-(acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-[(6-aminohexanoyl)amino]-2-(methoxycarbonyl)ethyl}benzene 6e. Yield 92%; mp 170–173 °C; δ_H(D_2O, +40 °C) 1.10–1.19 (2 H, m), 1.43–1.61 (4 H, m), 1.92 (3 H, s), 2.21 (2 H, t, *J* 7.3), 2.85–3.00 (4 H, m), 3.15–3.27 (2 H, m), 3.76 (3 H, s), 4.39–4.43 (1 H, m), 4.68–4.73 (1 H, m), 7.12–7.19 (3 H, m) and 7.31 (1 H, t, *J* 7.5); δ_C 22.48, 25.15, 25.36, 26.93, 35.59, 36.95, 38.19, 39.84, 53.51, 54.48, 57.06, 127.90, 128.31, 129.29, 130.54, 137.32, 138.90, 173.73, 174.38, 177.02 and 178.67; HRMS (FAB+): $C_{21}H_{32}N_3O_6$ (M + H); Found: *m*/*z*, 422.2290. Calc.: *m*/*z*, 422.2291.

1-[(2*S*)-2-(acetylamino)-2-carboxyethyl]-3-{(2*S*)-2-{6-amino-2-(2*S*)-[(*tert*-butoxycarbonyl)amino]hexanoyl}amino]-2-(methoxycarbonyl)ethyl}benzene 6f. Yield 82%; mp 118–121 °C; δ_H(D_2O, +40 °C) 1.24–1.69 (15 H, m), 1.95 (3 H, s), 2.94–3.08 (4 H, m), 3.18–3.26 (2 H, m), 3.75 (3 H, s), 3.94 (1 H, br s), 4.54–4.59 (1 H, m), 4.73–4.77 (1 H, m), 7.14–7.21 (3 H, m) and 7.33 (1 H, t, *J* 7.5); δ_C 22.31, 22.56, 26.83, 28.14, 31.26, 37.01, 37.50, 39.77, 53.50, 54.29, 55.29, 55.58, 82.16, 128.29, 128.39, 129.45, 130.49, 137.15, 138.08, 157.63, 173.86, 174.19, 175.18 and 176.63; HRMS (FAB+): $C_{26}H_{41}N_4O_8$ (M + H); Found: *m*/*z*, 537.2920. Calc.: *m*/*z*, 537.2924.

Cyclisation with DPPA, path a

Using a syringe pump, a solution of **6** (20–30 mg) in DMF (10–20 ml) was added to a stirred suspension of DPPA (0.10 ml) and $NaHCO_3$ (0.10 g) in DMF (20 ml) over a period of 60 h at room temp. After this time, the reaction mixture was evaporated to dryness and the residue was partitioned between water and $CHCl_3$ (1+1 ml). The organic layer was dried over $MgSO_4$ and purified by flash chromatography or HPLC (SiO_2, $CHCl_3$–MeOH 20 : 1) to yield the cyclised product **7** as a white solid.

Second deprotection, path b, and cyclisation with HATU, path a and b

In the case of path **b**, protected amino acid **5** (0.10 mmol) was first dissolved in TFA (1 ml) and the solution was stored under N_2 at room temp. for 2 h. After this time, the solution was evaporated to dryness and the residue was washed with ether to remove traces of TFA. After brief vacuum drying, the deprotected amino acid was obtained as a white powder, which was immediately used in the cyclisation reaction.

The deprotected amino acid so prepared (path **b**), or separately prepared as **6** (path **a**), was dissolved in DMF (100 ml) to make a solution 1 mM in amino acid. HATU (42 mg, 0.11 mmol) and DIEA (52 µl, 0.30 mmol) were added which caused the solution to turn yellow. After 1 h at room temp. the reaction mixture was evaporated to dryness and worked up as described for DPPA above, except in the cases of **7a** and **7b** which are insoluble in $CHCl_3$. For these two derivatives, a simple filtration of the added $CHCl_3$–water mixture was sufficient to isolate the compounds in fairly pure states. Recrystallisation from DMF–ether did not significantly improve purity.

Methyl (3*S*,9*S*)-9-(acetylamino)-5,8-dioxo-4,7-diazabicyclo-[9.3.1]pentadeca-1(15),11,13-triene-3-carboxylate 7a. Yield 16% (path **a**) and 82% (path **b**) respectively; mp >350 °C (decomp.); δ_H(DMSO-d_6) 1.85 (3 H, s), 2.72–2.91 (3 H, m), 3.02–3.09 (2 H, m), 3.67 (3 H, s), 4.07–4.13 (1 H, m), 4.22–4.28 (1 H, m), 4.35–4.41 (1 H, m), 6.80 (1 H, s), 7.04–7.09 (2 H, m), 7.16–7.19 (1 H,

m), 7.64 (1 H, d, *J* 8.7), 7.99 (1 H, d, *J* 7.4) and 8.08–8.11 (1 H, m); δ_C 22.54, 36.14, 38.61, 42.97, 52.07, 52.11, 54.70, 127.03, 127.63, 128.58, 132.08, 135.70, 136.49, 168.30, 168.82, 170.80 and 171.26; HRMS (FAB+): $C_{17}H_{22}N_3O_5$ (M + H); Found: *m*/*z*, 348.1571. Calc.: *m*/*z*, 348.1559.

Methyl (3*S*,10*S*)-10-(acetylamino)-5,9-dioxo-4,8-diazabicyclo[10.3.1]hexadeca-1(16),12,14-triene-3-carboxylate 7b. Yield 36%; mp >350 °C (decomp.); δ_H(DMSO-d_6) 1.84 (3 H, s), 2.01–2.08 (1 H, m), 2.61–2.85 (5 H, m), 3.00–3.06 (1 H, m), 3.25–3.30 (1 H, m), 3.68 (3 H, s), 4.11–4.16 (1 H, m), 4.42–4.48 (1 H, m), 6.90 (1 H, s), 7.07–7.11 (2 H, m), 7.23 (1 H, t, *J* 7.6), 7.55–7.59 (1 H, m), 8.02 (1 H, d, *J* 7.5) and 8.27 (1 H, d, *J* 9.5); δ_C 23.36, 34.56, 36.59, 37.69, 40.43, 52.94, 54.02, 56.51, 128.01, 128.38, 129.49, 131.62, 137.60, 138.33, 169.43, 170.45, 171.49 and 172.73; HRMS (FAB+): $C_{18}H_{24}N_3O_5$ (M + H); Found: *m*/*z*, 362.1717. Calc.: *m*/*z*, 362.1716.

Methyl (3*S*,11*S*)-11-(acetylamino)-5,10-dioxo-4,9-diazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-3-carboxylate 7c. Yield 24%; dr 87 : 13; mp >280 °C (decomp.); δ_H 1.00–1.10 (1 H, m), 1.75–1.83 (2 H, m), 2.03 (3 H, s), 1.23–1.30 (1 H, m), 2.60–2.70 (2 H, m), 2.95–3.03 (2 H, m), 3.25–3.32 (1 H, m), 3.44–3.50 (1 H, m), 3.83 (3 H, s), 4.48–4.55 (1 H, m), 5.25–5.32 (1 H, m), 5.80 (1 H, d, *J* 9), 6.33 (1 H, d, *J* 8), 6.93 (1 H, d, *J* 8), 7.03 (1 H, d, *J* 8), 7.17 (1 H, t, *J* 8) and 7.25 (1 H, s); δ_C 22.86, 23.58, 35.15, 39.15, 40.08, 40.37, 51.63, 52.94, 55.68, 128.69, 128.87, 129.26, 129.34, 136.31, 137.67, 169.45, 169.99, 172.56 and 174.03; HRMS (FAB+): $C_{19}H_{26}N_3O_5$ (M + H); Found: *m*/*z*, 376.1871. Calc.: *m*/*z*, 376.1872.

Methyl (3*S*,12*S*)-12-(acetylamino)-5,11-dioxo-4,10-diazabicyclo[12.3.1]octadeca-1(18),14,16-triene-3-carboxylate 7d. Yield 29%; mp 240–260 °C (decomp.); δ_H 0.80–0.93 (1 H, m), 1.23–1.33 (1 H, m), 1.36–1.53 (2 H, m), 2.03 (3 H, s), 2.12–2.20 (2 H, m), 2.68–2.77 (1 H, m), 2.80–2.88 (1 H, m), 3.13–3.18 (1 H, m), 3.30–3.36 (1 H, m), 3.83 (3 H, s), 4.56–4.65 (1 H, m), 5.13–5.22 (1 H, m), 6.23 (1 H, br d, *J* 7), 6.55 (1 H, d, *J* 10), 6.61 (1 H, d, *J* 8), 7.04–7.08 (2 H, m) and 7.16–7.24 (2 H, m); δ_C 21.82, 23.43, 27.37, 34.98, 38.45, 39.04, 39.42, 52.63, 52.83, 55.29, 127.97, 128.17, 128.73, 131.43, 136.68, 136.86, 169.94, 170.82, 172.93 and 173.03; HRMS (FAB+): $C_{20}H_{28}N_3O_5$ (M + H); Found: *m*/*z*, 390.2033. Calc.: *m*/*z*, 390.2029.

Methyl (3*S*,13*S*)-13-(acetylamino)-5,12-dioxo-4,11-diazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-3-carboxylate 7e. Yield 50%; mp 255–258 °C; δ_H −0.23 to −0.08 (1 H, m), 0.86–0.98 (1 H, m), 1.08–1.35 (3 H, m), 1.45–1.58 (1 H, m), 1.86–1.94 (1 H, m), 2.05 (3 H, s), 2.22–2.29 (1 H, m), 2.51 (1 H, t, *J* 13), 2.69 (1 H, t, *J* 12), 2.80–2.87 (1 H, m), 3.24 (1 H, dd, *J* 3.8 and 12.6), 3.40 (1 H, dd, *J* 3.6 and 13.2), 3.56–3.66 (1 H, m), 3.84 (3 H, s), 4.50–4.56 (1 H, m), 5.19–5.26 (1 H, m), 5.99 (1 H, d, *J* 9.6), 6.26 (1 H, br d, *J* 5.6), 6.54 (1 H, d, *J* 7.6), 6.89–6.95 (2 H, m), 7.09 (1 H, t, *J* 7.6) and 7.51 (1 H, s); δ_C 20.41, 23.06, 23.64, 25.77, 34.75, 36.63, 40.15, 40.42, 52.75, 52.92, 56.55, 128.43, 128.46, 128.76, 130.34, 136.94, 137.67, 169.41, 170.49, 172.32 and 172.78; HRMS (FAB+): $C_{21}H_{30}N_3O_5$ (M + H); Found: *m*/*z*, 404.2173. Calc.: *m*/*z*, 404.2185.

(±)-(*S,*R**)-7e.** δ_H 0.19–0.31 (1 H, m), 0.78–0.90 (1 H, m), 1.03–1.16 (1 H, m), 1.22–1.33 (1 H, m), 1.34–1.47 (2 H, m), 1.95–2.01 (1 H, m), 2.12 (1 H, s), 2.18–2.26 (1 H, m), 2.68–2.81 (2 H, m), 2.87–2.95 (1 H, m), 3.25–3.40 (3 H, m), 3.89 (3 H, s), 4.85–4.99 (2 H, m), 5.88 (1 H, d, *J* 10), 6.05 (1 H, br t, *J* 6), 6.95 (1 H, d, *J* 8), 7.03–7.09 (2 H, m) and 7.15 (1 H, t, *J* 8).

Methyl (3*S*,6*S*,13*S*)-13-(acetylamino)-6-[(*tert*-butoxycarbonyl)amino]-5,12-dioxo-4,11-diazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-3-carboxylate 7f. Yield 50%; mp 193–195 °C; δ_H −0.26 to −0.11 (1 H, m), 0.87–0.99 (1 H, m), 1.22–1.37 (3 H, m), 1.48 (9 H, s), 1.68–1.77 (1 H, m), 2.05 (3 H, s), 2.51–2.57 (1 H, m), 2.66–2.73 (1 H, m), 2.84–2.89 (1 H, m), 3.22–3.26 (1 H, m), 3.36–3.41 (1 H, m), 3.83 (3 H, s), 4.10 (1 H, br s), 4.51–4.57 (1 H, m), 4.66 (1 H, d, *J* 6.8), 5.09–5.16 (1 H, m), 6.20 (1 H, br s), 6.51 (1 H, d, *J* 7.6), 6.88–6.95 (3 H, m), 7.10 (1 H, t, *J* 7.6) and 7.50 (1 H, s); δ_C 19.87, 23.62, 25.22, 27.85, 28.44, 37.36, 40.01, 40.35, 52.78, 52.92, 54.35, 56.37, 81.18, 128.39, 128.47, 128.55, 130.47, 137.01, 137.75, 155.48, 169.48, 170.66, 171.49 and 172.17; HRMS (FAB+): $C_{26}H_{39}N_4O_7$ (M + H); Found: *m*/*z*, 519.2824. Calc.: *m*/*z*, 519.2819.

Acknowledgements

We thank the Swedish Natural Research Council, the Crafoord Foundation, the Knut and Alice Wallenberg Foundation, and the Royal Physiographic Society for economic support.

References

1 A. V. R. Rao, M. K. Gurjar, K. L. Reddy and A. S. Rao, *Chem. Rev.*, 1995, **95**, 2135.
2 U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1988, 159.
3 I. Uchida, M. Ezaki, N. Shigematsu and M. Hashimoto, *J. Org. Chem.*, 1985, **50**, 1341.
4 R. Kannan and D. H. Williams, *J. Org. Chem.*, 1987, **52**, 5435.
5 J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243.
6 J. H. Burckhalter and V. C. Stephens, *J. Am. Chem. Soc.*, 1951, **73**, 56.
7 W. von Ried and B. Schleimer, *Liebigs Ann. Chem.*, 1961, **639**, 68.
8 Y. Omote, Y. Fujinuma and N. Sugiyama, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 1752.
9 R. F. Chapman and G. A. Swan, *J. Chem. Soc.* (*C*), 1970, 865.
10 R. Fitzi and D. Seebach, *Tetrahedron*, 1988, **44**, 5277.
11 U. Schmidt, R. Meyer, V. Leitenberger and A. Lieberknecht, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 929.
12 G. A. Brown and P. D. Edwards, *Tetrahedron Lett.*, 1990, **31**, 6581.
13 K. Undheim and M. Solbakken, PCT Int. Appl. WO 93/24522 PCT/GB93/01170 (*Chem. Abstr.*, 1994, **121**, 281231e).
14 A.-S. Carlström and T. Frejd, *Synthesis*, 1989, 414.
15 A.-S. Carlström and T. Frejd, *J. Org. Chem.*, 1990, **55**, 4175.
16 A.-S. Carlström and T. Frejd, *J. Org. Chem.*, 1991, **56**, 1289.
17 A.-S. Carlström and T. Frejd, *J. Chem. Soc., Chem. Commun.*, 1991, 1216.
18 A.-S. Carlström and T. Frejd, *Acta Chem. Scand.*, 1992, **46**, 163.
19 B. Basu and T. Frejd, *Acta Chem. Scand.*, 1996, **50**, 316.
20 B. Basu, S. K. Chattopadhyay, A. Ritzén and T. Frejd, *Tetrahedron: Asymmetry*, 1997, **8**, 1841.
21 A. Ritzén, B. Basu, S. K. Chattopadhyay, F. Dossa and T. Frejd, *Tetrahedron: Asymmetry*, 1998, **9**, 503.
22 J. M. Travins and F. A. Etzkorn, *J. Org. Chem.*, 1997, **62**, 8387.
23 M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
24 U. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler and J. Wild, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 770.
25 U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1984, 53.
26 E. P. Prokof'ev and E. I. Karpeiskaya, *Tetrahedron Lett.*, 1979, 737.
27 T. Shioiri, K. Ninomiya and S.-i. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
28 A. Ehrlich, H.-U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino and M. Bienert, *J. Org. Chem.*, 1996, **61**, 8831.
29 F. Cavelier-Frontin, G. Pèpe, J. Verducci, D. Siri and R. Jacquier, *J. Am. Chem. Soc.*, 1992, **114**, 8885.
30 M. Bodanszky and A. Bodanszky, *The Practise of Peptide Synthesis*, Springer-Verlag, Berlin, 1984.
31 S. Gladiali and L. Pinna, *Tetrahedron: Asymmetry*, 1991, **2**, 623.
32 D. Marcovici-Mizrahi, H. E. Gottlieb, V. Marks and A. Nudelman, *J. Org. Chem.*, 1996, **61**, 8402.

Paper 8/05350B