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Solution-Phase Peptide Synthesis; Synthesis of 'North-Western' and 'South-Eastern' Fragments of the Antifungal Cyclodepsipeptide Petriellin A

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The solution-phase synthesis of two highly modified peptides, a hexamer and a heptamer, that constitute the two halves of the antifungal cyclic depsipeptide, Petriellin A, is reported.

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Introduction

We have an ongoing interest in the chemistry of modified amino acids, in particular *N*-methyl α-amino acids[1–5] and β-amino acids.[6–9] Methodological developments in this area are continuing. In the next phase of our project, we are seeking to apply *N*-methyl amino acids in the synthesis of target peptides including some of the growing number of naturally occurring cyclic depsipeptides found to have antifungal activity.

Accordingly, our attention was captured by a report of the isolation and structural determination of Petriellin A **1** by Gloer et al.[10] We have completed the determination of the absolute configuration of Petriellin A[11] and an analysis of its solution conformation by NMR.[12] In the present paper, we report the successful assembly of the 'North-Western' and 'South-Eastern' hemispheres of Petriellin A by solution-phase peptide synthesis.

The retrosynthetic analysis for the ultimate target **1** was guided by several precepts as it was recognized there was no general rule that might guide the choice of cyclization site and therefore the particular acyclic precursor to be made. It was decided the tertiary *N*-methyl amide bonds would be formed as early as possible owing to expected lower amide coupling yields. These sites would therefore not be the subjects of major coupling or cyclization reactions. The two proline amide bonds were further discounted owing to the prospect of diketopiperazine-forming side reactions. Thus the primary disconnection (Fig. 1; the site for cyclization) was chosen as the amide bond between the alanine and pipecolic acid residues, which generates the acyclic precursor **2**. A further disconnection provides the initial 'North-West' fragment **3** and the 'South-East' fragment **4**. In the event that the 'North-West' and 'South-East' assembly strategy was unsuccessful, an orthogonal protecting group strategy would allow for, say, a 'North-East' 'South-West' combination of fragments. Thus disconnection of fragments **3** and **4** gave the four synthetic targets **5**–**8**. The synthesis of these compounds and their rapid assembly into the acyclic precursor **2** provide a high level of convergence that it was hoped would lead to an efficient high-yielding total synthesis.

Results and Discussion

*'North' Compound **5***

The synthesis of the dipeptide **5** was simple and direct (Scheme 1). Several related compounds were prepared at the same time as a means of trialling different coupling reagents and because at the corresponding point in the structures of Petriellins B, C, and D, there are structural variations requiring different dipeptides if they are to be synthesized later. In a first reaction, the isoleucine carbamate **9** was coupled to the proline ester **10** with benzotriazol-1-yl-*N*-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent to afford the dipeptide **11** in 95% yield. Attempts to couple carbamate **9** with pipecolinate **12** using BOP reagent failed. In this circumstance, use of bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP) as the coupling agent afforded the dipeptide **5** in 66% yield. These coupling reactions were critically dependent on structure. A similar coupling of the valine carbamate **13** with ester **12** using PyBroP proceeded in 85% yield to give dipeptide **14**. Also, the carbamate **15** was coupled with ester **12** with the same reagent to give the dipeptide **16** in 99% yield. This subunit is present in Petriellin A and was used later in the synthesis. Carbamate **17** was coupled to ester **10** using BOP reagent in 80% yield to give the dipeptide **18**. This dipeptide is also a subunit of Petriellin A and was used later.

*'West' Compound **6***

The West fragment **6** includes the D-phenyllactate residue. Although suitable precursors are commercially available, it was conveniently prepared. Thus D-phenylalanine **19** (Scheme 2) was diazotized to afford D-phenyllactic acid **20**. Acid **20** was then esterified under Fischer conditions in methanol to give methyl ester **21** in 99% yield. Treatment of the ester **21** with benzyl trichloroacetimidate and triflic acid afforded the benzyl ether **22**, which was then subjected to base hydrolysis. The acid **23** was isolated as the dicyclohexylammonium (DCHA) salt in 60% yield.

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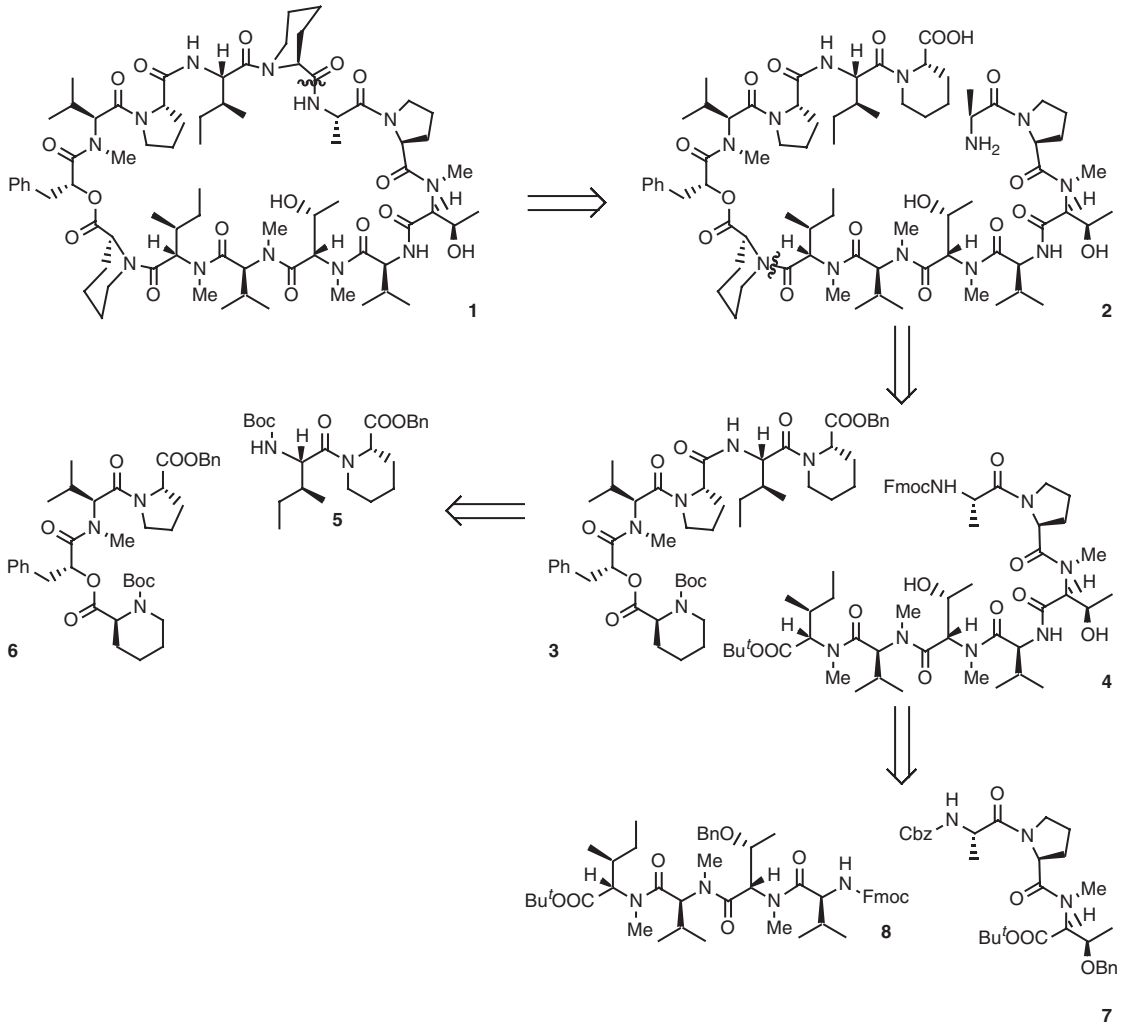


Fig. 1. Structure and retrosynthetic analysis for Petriellin A **1**.

In the first sequence (Scheme 3) aimed at preparing the 'West' fragment **6**, the D-phenyllactate **23** was coupled to the *N*-methyl valine **24** in 81% yield. Removal of the *tert*-butyl ester from dipeptide **25** was achieved with trifluoroacetic acid in CH_2Cl_2. The product acid **26** was not isolated but was used directly in a coupling reaction with *tert*-butyl proline **27** to provide the 'tripeptide' **28** in 99% yield. Hydrogenolysis of the benzyl ether **28** gave the secondary alcohol **29** but all attempts to couple the required pipecolic acid residue failed and so this approach was abandoned.

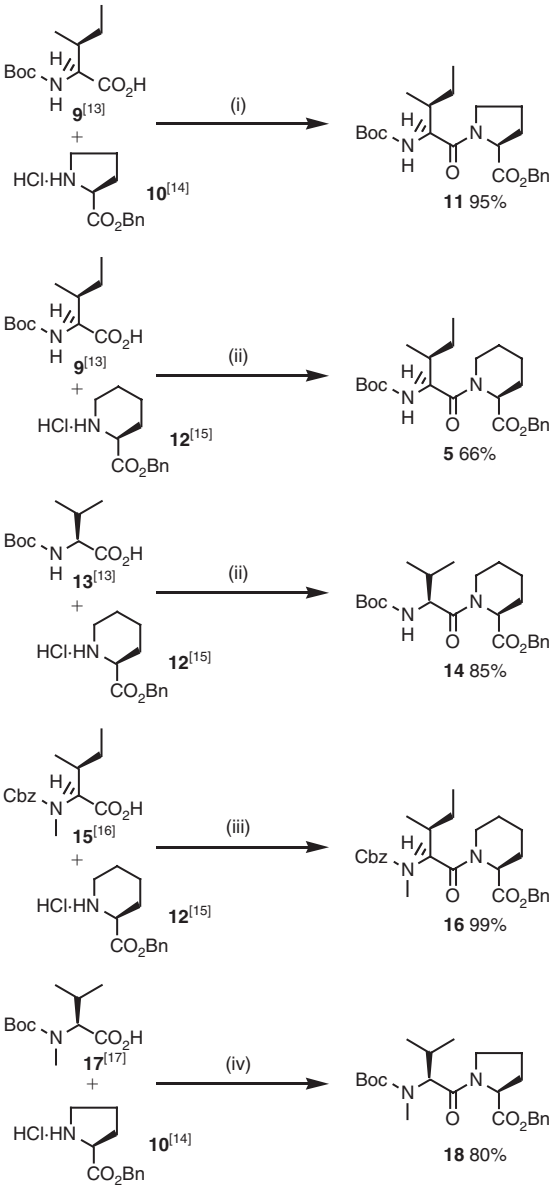
In the second approach to make the West fragment **6**, the problematic formation of the D-phenyllactate ester bond it was proposed to be solved via a Mitsunobu reaction. This reaction will normally result in inversion of the alcohol configuration and so the reaction partner was prepared from L-phenylalanine. Thus L-phenylalanine **30** was diazotized[18] (Scheme 4) and the product α-hydroxy acid was esterified to give the L-phenyllactate **31**. Mitsunobu reaction of the (*S*)-alcohol **31** and the carboxylic acid **32**[15] with triphenylphosphine and diethylazodicarboxylate (DEAD) gave the expected pseudo-dipeptide **33** in 69% yield. Hydrogenolysis of **33** gave the acid **34** in 95% yield ready for coupling to form the target **6**. The reaction partner for the coupling reaction was derived from the dipeptide **18** (Scheme 1), which was deprotected with trifluoroacetic acid to give the secondary amine **35**, which was not purified. Amine **35** was applied directly to the coupling reaction with acid **34** mediated by PyBroP to afford the target pseudo-tetrapeptide **6** in 70% yield.

*'North-West' Compound **3***

The retrosynthesis (Fig. 1) calls for joining of compounds **5** and **6** to give the pseudo-hexapeptide **3**. Accordingly, the orthogonally protected dipeptide **5** was deprotected with 50% trifluoroacetic acid in CH_2Cl_2 to give the secondary amine **36** in quantitative yield as the trifluoroacetate salt (Scheme 5). At the same time, the pseudo-tetrapeptide **6** was hydrogenolyzed to give the acid **37** (98% yield). The coupling reaction of compounds **36** and **37** with PyBroP gave the 'North-West' fragment **3** in 83% yield.

*'East' Compound **7***

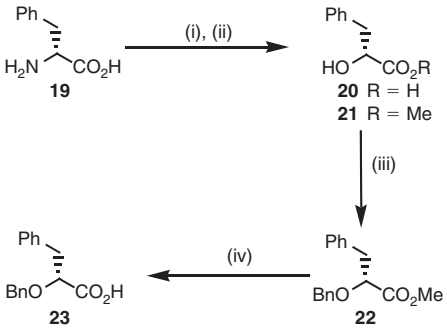
The East tripeptide **7** was a more challenging target owing to the side-chain protection required for the threonine residue and the potentially low-yielding coupling to form the amide bond between the *N*-methyl threonine and proline residues. The synthesis (Scheme 6) began with manipulation of the threonine residue. L-Threonine **38** was perbenzylated by the method of Mizoguchi et al.,[19] forming the ester **39**. Methanolysis[19] and



Scheme 1. Synthesis of dipeptide **5** and related dipeptides **11**, **14**, **16**, and **18**. Reagents and conditions: (i) BOP, Et_3N, CH_2Cl_2; (ii) PyBroP, Et_3N, CH_2Cl_2; (iii) PyBroP, Pr^i_2NEt, CH_2Cl_2; (iv) BOP, Pr^i_2NEt, CH_2Cl_2.

carbamoylation formed the acid **40**. The *O*-benzyl side-chain protection precludes side-chain interference in the formation of the 1,3-oxazolidin-5-one **41**[3,4] and reductive cleavage of this with trifluoroacetic acid and triethylsilane smoothly gives the *N*-methyl threonine **42** (86% yield). *tert*-Butyltrichloroacetimidate (TBTA)[20] in the presence of $BF_3{\cdot}Et_2O$ then gave the *tert*-butyl ester **43** (88% yield), and hydrogenolysis of the benzyl carbamate did not compromise the benzyl ether, allowing isolation of the secondary amine **44** (92% yield). This amine was also prepared via the 9-fluorenylmethoxycarbonyl (Fmoc)-carbamate (see Scheme 8).

Meanwhile, L-proline trichloroethyl ester **45**[21] was coupled to the alanine carbamate **46** with BOP reagent to give the dipeptide **47** (80% yield). The trichloroethyl ester was removed by treatment with zinc metal in acetic acid, providing the acid **48** (96% yield).



Scheme 2. Preparation of D-phenyllactate **23**. Reagents and conditions: (i) aq. H_2SO_4, $NaNO_2$, 0°C to room temperature, 24 h; (ii) MeOH, 98% H_2SO_4 (cat.), reflux, 3 h; (iii) $BnO(C{=}NH)CCl_3$, CF_3SO_3H (cat.), 1:2 CH_2Cl_2/hexanes; (iv) MeOH, 2 M aq. KOH, 0°C.

The acid **48** was then coupled to the threonine **44** with PyBroP in a low-yielding reaction. Presumably, the coupling of the secondary amine **44** to the proline carboxylic acid is sterically demanding, accounting for this low yield (23%). Some of the threonine **44** starting material was recovered from this reaction (~52%) adding some weight to the suggestion this was a sterically difficult coupling reaction. The East tripeptide **7** was isolated in 23% yield (47% conversion).

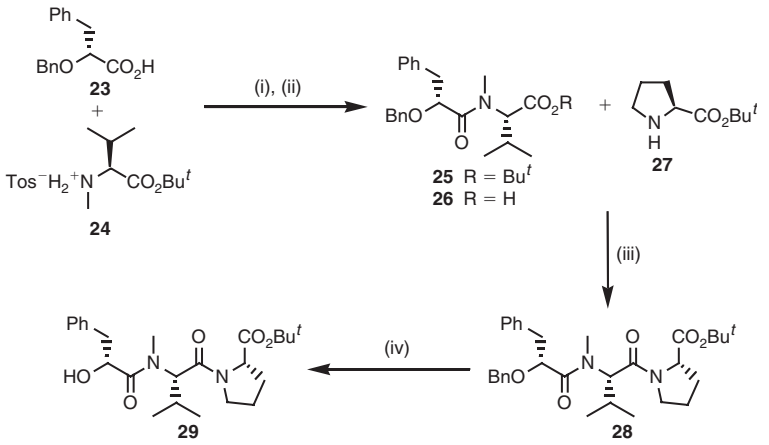
*'South' Compound **8***

The South fragment **8** is the most densely *N*-methylated fragment proposed in the retrosynthesis (Fig. 1). Two approaches were attempted; both approaches employed the C-terminal dipeptide **49**. The first approach (Schemes 7 and 8) seeks increased synthetic efficiency and describes a convergent sequence to tetrapeptide **8** using two dipeptides.

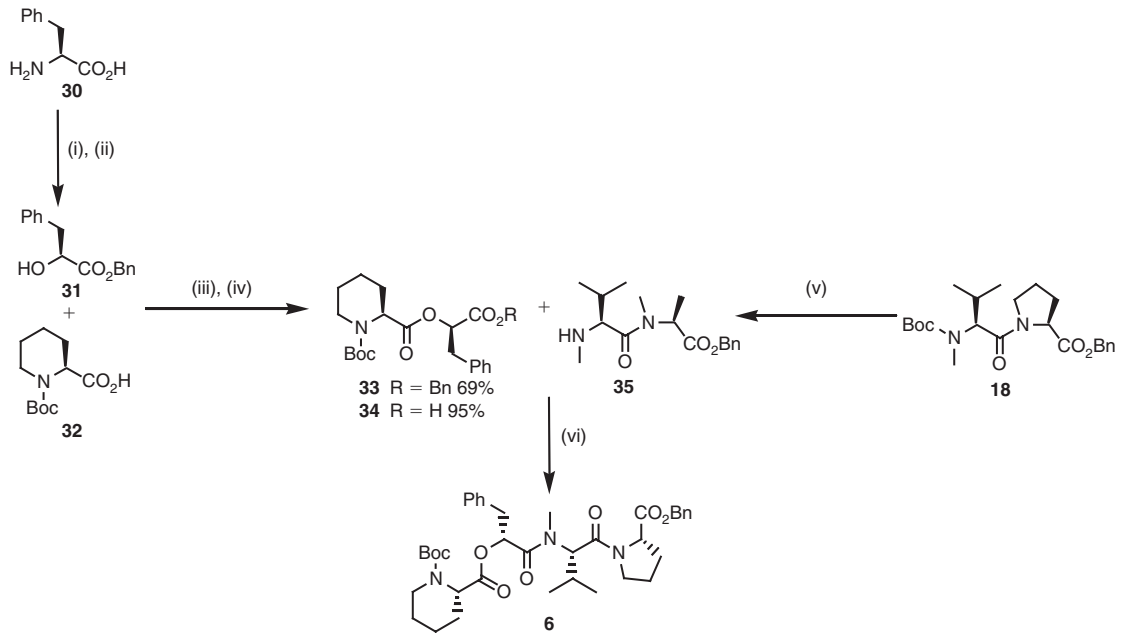
The first part of the tetrapeptide synthesis required the dipeptide **49** (Scheme 7). In this scheme, the *N*-methylisoleucine **50**[1,16] was esterified with TBTA, giving the *tert*-butyl ester **51** (83% yield), and hydrogenolysis of the benzyl carbamate gave access to the amine **52**, conveniently isolated as the crystalline tosylate salt (92% yield). This salt **52** was then coupled to the valine carbamate **53**[1,16] with PyBroP to give the target dipeptide **54** (77% yield). This orthogonally protected dipeptide was easily hydrogenolyzed to furnish the amine **49** ready for the coupling to form the tetrapeptide **8**.

Separately, the threonine carbamate **55** was converted to the 1,3-oxazolidin-5-one **56**, and reductive cleavage with trifluoroacetic acid and triethylsilane gave the *N*-methyl threonine **57**. The *tert*-butyl ester **58** was then formed with TBTA/$BF_3{\cdot}Et_2O$, and then treatment with diethylamine in DMF removed the Fmoc-carbamate, providing the amine **44**. Fmoc-valine **59** was then coupled to the *N*-methyl threonine **44** with PyBroP, giving the dipeptide **60** (83% yield). In preparation for the key coupling reaction, this *tert*-butyl ester **60** was treated with trifluoroacetic acid in CH_2Cl_2, providing the carboxylic acid **61**. In the presence of PyBroP, the acid **61** was coupled to the amine **49** giving the South tetrapeptide **8** in a 45% yield. The tetrapeptide **8** was accompanied by the dehydro tetrapeptide **62**[22] (15% yield).

That the side reaction had generated the dehydro structure **62** was evident from the mass spectrum (electrospray ionization mass spectrometry (ESMS) *m/z* 733 [M + H]). As the immediate synthetic steps before formation of **8** had not involved purification of intermediates, it was considered possible the alkene had formed either in the acidic deprotection of the ester **60** or



Scheme 3. Attempted synthesis of West fragment via pseudo-tripeptide **29**. Reagents and conditions: (i) PyBroP, Et_3N, CH_2Cl_2; (ii) 50% CF_3CO_2H/CH_2Cl_2; (iii) BOP, Et_3N, CH_2Cl_2; (iv) 10% Pd/C, H_2, EtOH.



Scheme 4. Synthesis of the West fragment **6**. Reagents and conditions: (i) H_2SO_4, H_2O, $NaNO_2$, 0°C to room temperature, 24 h[18]; (ii) K_2CO_3, BnBr, DMF; (iii) PPh_3, DEAD, CH_2Cl_2, 2 h, −20°C to room temperature; (iv) 10% Pd/C, H_2, MeOH; (v) 50% TFA/CH_2Cl_2; (vi) PyBroP, Pr^i_2NEt, CH_2Cl_2.

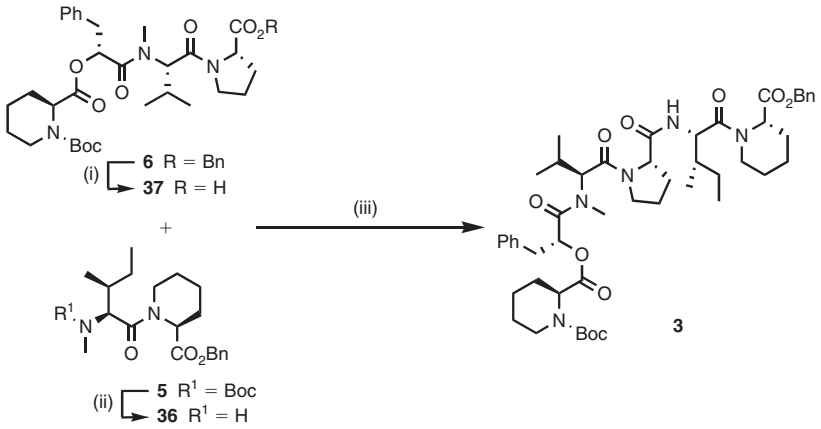
in the basic coupling reaction of the acid **61** with the amine **49**. The acid deprotection as the cause of the alkene formation was discounted by exposing a sample of the dipeptide **60** to trifluoroacetic acid for 2 h. ESMS of the reaction mixture failed to show any evidence of the dehydro compound **63** (Fig. 2) derived from the dipeptide.

The source of the dehydro tetrapeptide **62** seems to be the coupling reaction between the dipeptide **61** and the dipeptide **49**. It is suggested that the activated acid intermediate **64** (Fig. 2) is most acidic at the *N*-methyl threonine α-centre. The diisopropylethylamine is able to remove the α-proton and eliminate the benzyloxy group to form the alkene, which is able to couple to the dipeptide **49** and form the dehydro tetrapeptide **62**. This type of 'dehydration' has been noted by Okamoto et al.[23] and in related studies by Afzali-Ardakani and Rapoport.[24]

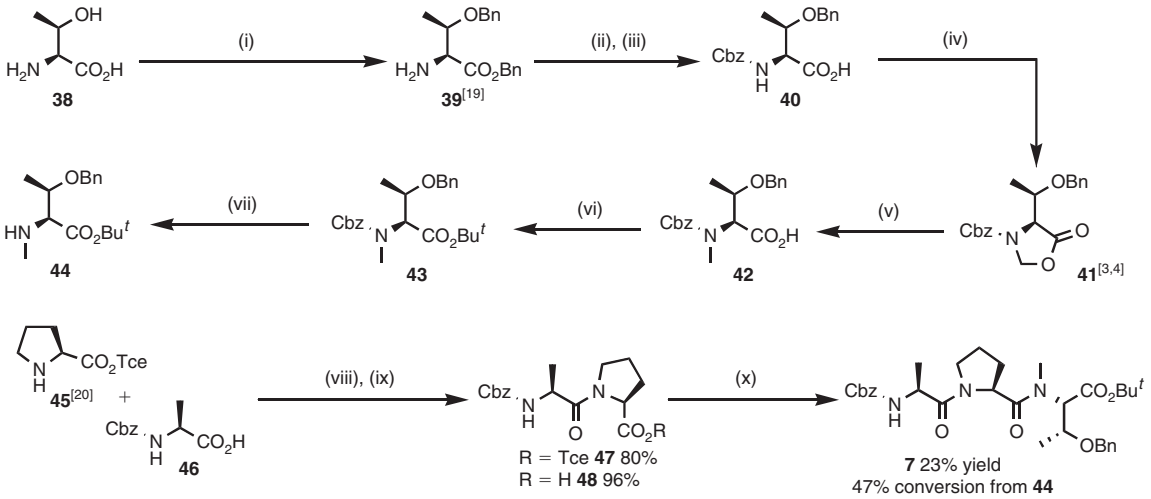
The formation of the dehydro compound **62** was minimized in the second approach to the tetrapeptide **8** (Scheme 9). In this scheme, the *N*-methyl threonine and the valine residues were added to the dipeptide **49** in a stepwise fashion, not as a dipeptide. Thus the *N*-methyl threonine **57** was coupled to the amine **49** with PyBroP to give the tripeptide **65** (57% yield). This tripeptide was accompanied by the dehydro tripeptide **66** (7% yield), which was removed by column chromatography. The tripeptide **65** was then deprotected with 33% diethylamine in DMF and the resulting amine was coupled to the valine carbamate **59**, giving the South tetrapeptide **8** in 94% yield.

'South-East' Compound ***4***

Formation of the South-East compound **4** was straightforward (Scheme 10) but purification was problematic. The carbamate **8** was deprotected with 33% diethylamine in DMF giving the amine **67**, which was not purified before coupling. Similarly, the *tert*-butyl ester **7** was treated with 50% trifluoroacetic acid



Scheme 5. Assembly of the North-West fragment **3**. Reagents and conditions: (i) 10% Pd/C, H_2, MeOH; (ii) 50% TFA/CH_2Cl_2; (iii) PyBroP, Pr^i_2NEt, CH_2Cl_2.



Scheme 6. Synthesis of the East tripeptide **7**. Reagents and conditions: (i) Ref. [19]; (ii) MeOH, NaOH[19]; (iii) K_2CO_3, H_2O, acetone, CbzCl; (iv) $(CH_2O)_n$, PhMe, camphorsulfonic acid (cat.), reflux; (v) CF_3COOH, Et_3SiH, $CHCl_3$; (vi) TBTA, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (vii) H_2, 5% Pd/C, MeOH, NH_4OAc; (viii) BOP, Pr^i_2NEt, CH_2Cl_2; (ix) Zn, AcOH, H_2O, EtOAc; (x) PyBroP, Pr^i_2NEt, **44**, CH_2Cl_2, 2 h.

in CH_2Cl_2 providing the acid **68**. The amine **67** and the acid **68** were coupled with PyBroP. TLC analysis of the reaction mixture showed the presence of by-products. Nevertheless, workup and column chromatography in the usual manner gave the expected heptapeptide **4** in ~78% yield and ~90% purity as determined from NMR spectra.

Conclusions

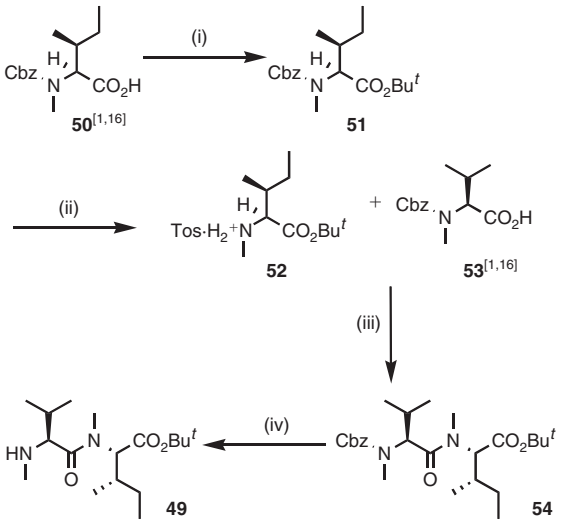
We have successfully assembled both hemispheres of the cyclic depsipeptide Petriellin A according to our retrosynthetic analysis (Fig. 1). Our solution-phase experimentation with the various intermediates in the synthesis has given us valuable experience in the chemistry and handling of the modified amino acids present in the natural product. Remarkably, in the chemistry described, there was no evidence of racemization of α-carbon stereocentres, a known problem in *N*-methyl amino acid synthesis.

In the next phase of experimentation, the hemispheres **3** and **4** can be deprotected and coupled to form the acyclic precursor and cyclization will give the natural product. These studies will be reported in due course.

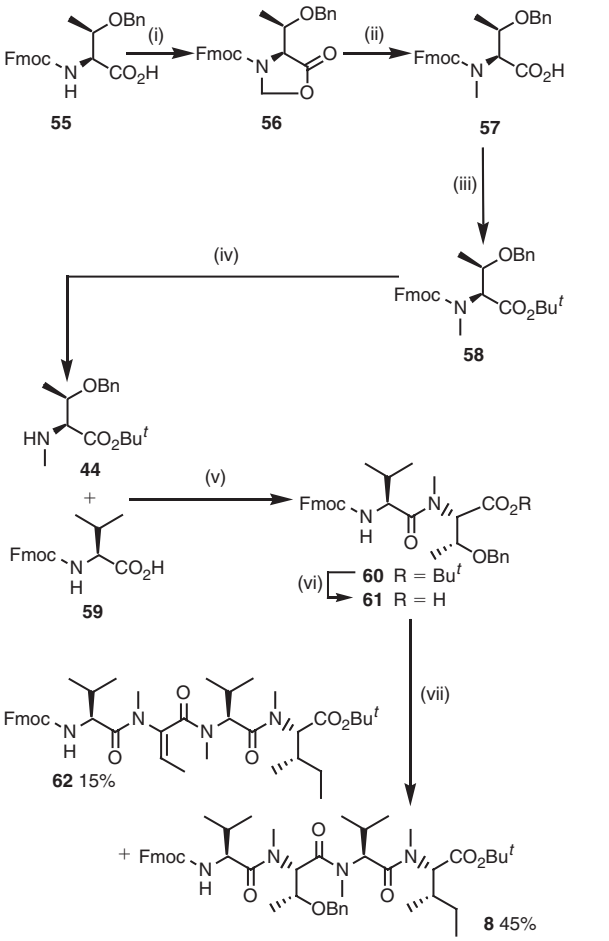
Experimental

General Methods

Melting points (mp) were recorded on a Reichert 'thermopan' hot stage apparatus and are uncorrected. Optical rotations were measured at the stated temperatures in the stated solvent on a Perkin–Elmer 141 polarimeter at the sodium d-line (589 nm); $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by Chemical and Microanalytical Services, Melbourne. Infrared spectra (ν_{max}) were recorded on a Bruker Vector 22 Fourier-Transform (FT-IR) spectrometer or a Perkin–Elmer 1720-X FT-IR spectrometer. Samples were analyzed as KBr disks (for solids) or as thin films on NaCl plates (for liquids or oils). Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterated chloroform ($CDCl_3$) at 20°C unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ_H 7.24) was used as the internal reference, while the central peak (δ_C 77.0) of the $CDCl_3$ triplet was used as the reference for



Scheme 7. Synthesis of the dipeptide **49**. Reagents and conditions: (i) TBTA, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (ii) H_2, 10% Pd/C, Bu^tOH, *p*-TsOH·H_2O; (iii) PyBroP, Pr^i_2NEt, CH_2Cl_2; (iv) H_2, 10% Pd/C, MeOH.



Scheme 8. Convergent synthesis of the South tetrapeptide **8**. Reagents and conditions: (i) $(CH_2O)_n$, PhMe, camphorsulfonic acid (cat.), reflux; (ii) CF_3COOH, Et_3SiH, $CHCl_3$; (iii) TBTA, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iv) 33% Et_2NH/DMF; (v) PyBroP, Pr^i_2NEt, CH_2Cl_2; (vi) 50% CF_3COOH/CH_2Cl_2; (vii) PyBroP, Pr^i_2NEt, **49**, CH_2Cl_2.

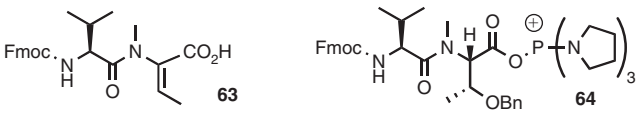


Fig. 2. Structures of proposed dehydrodipeptide **63** and proposed C-terminal activated dehydro precursor **64**.

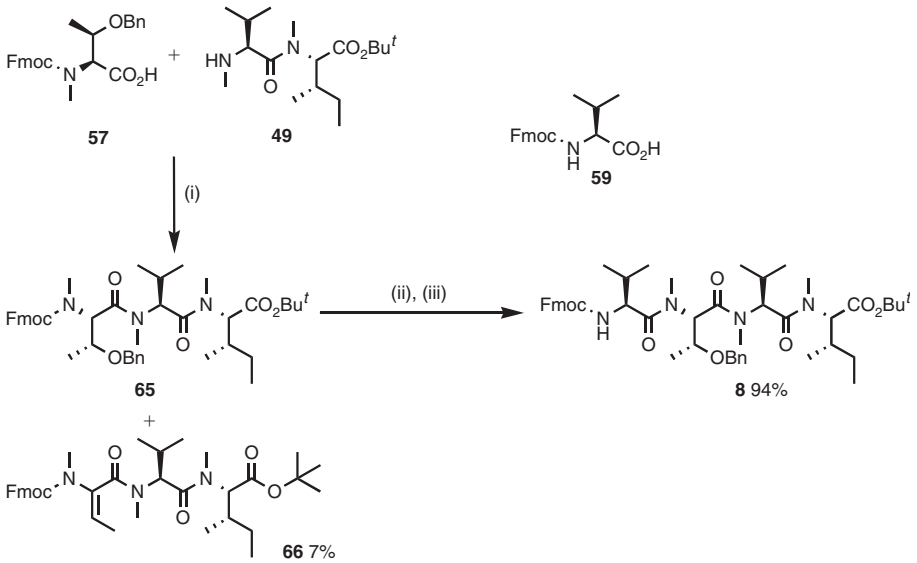
proton-decoupled ^{13}C NMR spectra. Low- and high-resolution mass spectra (LSIMS) were measured on a Kratos Concept mass spectrometer at 70 eV using a mobile phase consisting of water/methanol/acetic acid in a ratio of 0:99:1 or 50:50:1 in the positive mode unless otherwise indicated. ESMS was measured on a VG Bio-Q triple quadrupole mass spectrometer using acetonitrile/water mixtures as the mobile phase and 1% formic acid to form [M + 1] ions. Solvents were dried over standard drying agents[25] and freshly distilled before use. Ethyl acetate and hexane used for chromatography were distilled before use. All solvents were purified by distillation. Reactions were monitored by TLC on silica gel 60 F_{254} plates with detection by UV fluorescence or charring with a basic potassium permanganate stain. Flash column chromatography[26] was performed on silica gel 60 particle size 0.040–0.063 μm (230–400 mesh) supplied by Merck Chemicals.

*(S)-Benzyl 1-((2S,3S)-2-(*tert*-Butoxycarbonylamino)-3-methylpentanoyl)pyrrolidine-2-carboxylate* ***11***

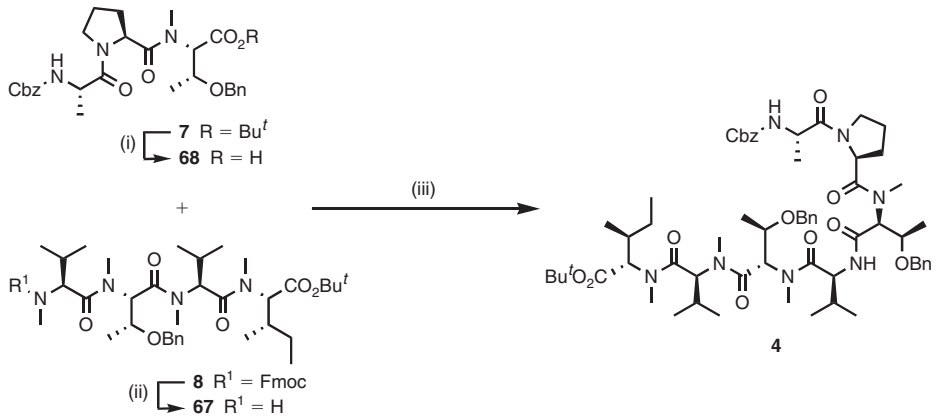
The carbamate **9** (870 mg, 3.8 mmol) was dissolved in CH_2Cl_2 (20 mL) and to the stirred solution was added the hydrochloride salt **10** (725 mg, 3.0 mmol) and BOP reagent (1.66 g, 3.8 mmol) at room temperature. To the stirred solution was added Et_3N (2 mL, 14.4 mmol) in one portion and the reaction mixture was left to stir at room temperature for 2.5 h. The reaction mixture was concentrated at reduced pressure and the residue was taken up in EtOAc (50 mL). The organic solution was washed successively with 10% citric acid solution (2 × 15 mL), water, 5% sodium bicarbonate solution (2 × 15 mL), water (×2), and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated at reduced pressure. The residue was purified by column chromatography (silica, 10% EtOAc/hexane, then 30% EtOAc/hexane elution) to provide the dipeptide **11** as a clear colourless gum (1.19 g, 95%). $[\alpha]_D^{18}$ −71.9 (*c* 1.0 in $CHCl_3$). (Found: C 66.0, H 8.4, N 6.5. $C_{23}H_{34}N_2O_5$ requires C 66.0, H 8.2, N 6.7%.) ν_{max} (NaCl)/cm^{-1} 3306, 3114, 3090, 3065, 3034, 3000–2800, 1747, 1707, 1643, 1502, 1434, 1389, 1366, 1317, 1276, 1249, 1169, 1098, 1044, 1018, 752, 699. δ_H 7.29 (5H, s, ArH), 5.17–5.12 (3H, m, NH and $ArCH_2$), 4.56–4.53 (1H, m, NCHCO), 4.25 (1H, t, *J* 8.4, NCHCO), 3.80–3.60 (2H, m, NCH_2), 2.21–0.80 (22H, m, aliphatic envelope). δ_C 171.7, 171.4, 155.7, 135.5, 128.4, 128.2, 128.0, 79.4, 66.7, 58.9, 56.1, 47.2, 37.8, 29.0, 28.2, 24.8, 24.1, 15.1, 11.1.

*(S)-Benzyl 1-((2S,3S)-2-(*tert*-Butoxycarbonylamino)-3-methylpentanoyl)piperidine-2-carboxylate* ***5***

The carbamate **9** (337 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and to the stirred solution was added hydrochloride salt **12** (372 mg, 1.5 mmol) and PyBroP reagent (490 mg, 1.05 mmol) at room temperature. To the stirred solution was



Scheme 9. Stepwise synthesis of the South tetrapeptide **8**. Reagents and conditions: (i) PyBroP, Pr^i_2NEt, CH_2Cl_2; (ii) 33% Et_2NH/DMF; (iii) PyBroP, Pr^i_2NEt, **59**, CH_2Cl_2.



Scheme 10. Synthesis of the South-East heptapeptide **4**. Reagents and conditions: (i) 50% CF_3COOH/CH_2Cl_2; (ii) 33% Et_2NH/DMF; (iii) PyBroP, Pr^i_2NEt, CH_2Cl_2.

added Et_3N (0.81 mL, 5.8 mmol) in one portion and the reaction mixture was left to stir at room temperature for 1 h. The reaction mixture was then filtered through a plug of silica gel, eluting with CH_2Cl_2. The filtrate was concentrated at reduced pressure and the residue was purified by column chromatography (silica, 40% ether/hexane elution) to provide the dipeptide **5** as a clear colourless gum (300 mg, 66%). $[\alpha]_D^{24}$ −48.0 (*c* 1.0 in $CHCl_3$). (Found: C 66.6, H 8.6, N 6.6. $C_{24}H_{36}N_2O_5$ requires C 66.6, H 8.4, N 6.5%.) ν_{max} (NaCl)/cm^{-1} 3419, 3320, 3100, 3064, 3033, 3000–2800, 1732, 1708, 1642, 1506, 1442, 1366, 1244, 1169, 1091, 1016, 919, 872, 816, 743, 695. δ_H (rotamers) 7.35–7.27 (5H, m, ArH), 5.46 (1H, d, *J* 5.0, NH), 5.30–5.26 (1H, m, NCHCO), 5.16–5.12 (2H, m, $ArCH_2$), 4.57–4.52 (1H, m, NCHCO), 3.90–3.85 (1H, m, NC*H*H), 3.24–3.10 (1H, m, NCH*H*), 2.29–2.24 and 1.80–0.77 (24H, 2 m, aliphatic envelope). δ_C (rotamers) 172.3, 172.0, 170.9, 170.7 (2), 155.8, 155.4, 135.6, 135.5, 128.6, 128.3, 128.2, 128.0, 127.9, 79.3, 79.2, 67.0, 66.8, 54.3, 52.5, 52.1 (2), 43.8, 43.4, 37.6, 28.3, 26.8, 26.6, 25.2, 25.1, 23.6, 21.0, 15.6, 11.3.

*(S)-Benzyl 1-((S)-2-(*tert*-Butoxycarbonylamino)-3-methylbutanoyl)piperidine-2-carboxylate* ***14***

The carbamate **13** (400 mg, 1.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and to the stirred solution was added hydrochloride salt **12** (362 mg, 1.4 mmol) and PyBroP reagent (857 mg, 1.8 mmol) at room temperature. To the stirred solution was added Et_3N (1.0 mL, 7.2 mmol) in one portion and the reaction mixture was left to stir at room temperature for 2 h. The reaction mixture was then filtered through a plug of silica gel, eluting with Et_2O. The filtrate was concentrated at reduced pressure and the residue was purified by column chromatography (silica, 30% ether/hexane elution) to provide the dipeptide **14** as a clear colourless gum (500 mg, 85%). $[\alpha]_D^{20}$ −36.8 (*c* 0.5 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3425, 3322, 3092, 3064, 3032, 3000–2800, 1739, 1708, 1642, 1500, 1437, 1387, 1366, 1282, 1224, 1171, 1089, 1044, 1017, 981, 751, 699. δ_H (rotamers) 7.31–7.23 (5H, m, ArH), 5.43–5.27 (2H, m, NH and NCHCO), 5.12–5.08 (2H, m, $ArCH_2$), 4.50 (1H, dd, *J* 4.5 and 8.9, NCHCO), 3.82–3.74 (1H, m, NC*H*H), 3.27–3.06 (1H, m, NCH*H*), 2.26–0.70 (22H,

m, aliphatic envelope). δ_C (rotamers) 171.9, 171.5, 170.6, 155.7, 155.4, 135.5, 135.3, 128.4, 128.2, 128.1, 128.0, 127.7, 79.1, 67.0, 66.8, 66.6, 54.6, 54.5, 52.3, 51.9, 43.5, 43.4, 31.7, 30.5, 28.1, 26.6, 26.3, 25.1, 20.8, 20.7, 19.6, 19.4, 16.7, 16.3.

(S)-Benzyl 1-((2S,3S)-2-((Benzyloxycarbonyl)(methyl)amino)-3-methylpentanoyl)piperidine-2-carboxylate ***16***

The benzyl carbamate **15** (700 mg, 2.6 mmol) was dissolved in CH_2Cl_2 (10 mL) and to the stirred solution was added the hydrochloride salt **12** (534 mg, 2.1 mmol) and PyBroP reagent (1.17 g, 2.5 mmol) at room temperature. To the stirred solution was added diisopropylethylamine (1.46 mL, 8.4 mmol) and the reaction mixture was left to stir for 2 h. The reaction mixture was filtered through a plug of silica gel, eluting with 30% ether/hexane, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 15% ether/hexane to give the dipeptide **16** as a clear colourless gum (1.0 g, 99%). $[\alpha]_D^{20}$ −118.7 (*c* 1.0 in CH_2Cl_2). (Found: C 69.9, H 7.8, N 5.7. $C_{28}H_{36}N_2O_5$ requires C 70.0, H 7.6, N 5.8%.) ν_{max} (NaCl)/cm^{-1} 3092, 3064, 3033, 3000–2800, 1739, 1694, 1648, 1454, 1397, 1337, 1303, 1263, 1192, 1150, 1110, 1017, 991, 751, 698. δ_H (rotamers) 7.32–7.22 (10H, m, ArH), 5.45–5.39, 5.24–4.78, 4.66–4.32, 4.21–4.16 and 3.84–3.80 (8H, 5 m, 2 × $ArCH_2$, 2 × NCHCO and NCH_2), 3.12–2.66, 2.39–2.08 and 1.64–0.77 (18H, 3 m, NCH_3, $CH(CH_3)CH_2CH_3$ and $NCH_2CH_2CH_2CH_2$). δ_C (rotamers) 170.9, 170.7, 170.5, 170.3, 170.0, 169.2 (2), 156.5, 156.4, 155.7, 155.2, 136.7, 136.5, 136.2, 136.0, 135.5, 135.4, 128.45, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 67.6, 67.3, 66.8, 59.7, 58.8, 58.1, 56.1, 55.4, 52.1, 43.5, 43.2, 39.8, 33.5, 33.3, 33.0, 29.7, 29.2, 28.9, 27.8, 27.6, 26.6, 25.3, 25.0, 24.9, 24.7, 24.4, 24.0, 21.0, 20.9, 20.8, 16.1, 15.9, 15.4, 10.7.

*(S)-Benzyl 1-((S)-2-(*tert*-Butoxycarbonyl(methyl)amino)-3-methylbutanoyl)pyrrolidine-2-carboxylate* ***18***

The carbamate **17** (1.64 g, 7.1 mmol) was dissolved in CH_2Cl_2 (40 mL) and to the stirred solution was added hydrochloride salt **10** (1.87 g, 8.2 mmol) and BOP reagent (3.74 g, 8.5 mmol) at room temperature. To the stirred solution was added Pr^i_2NEt (3.7 mL, 21.1 mmol) in one portion and the reaction mixture was left to stir at room temperature for 2.5 h. The reaction mixture was concentrated at reduced pressure and the residue was taken up in the minimum of CH_2Cl_2 (50 mL). The organic solution was then filtered through a silica plug, eluting with Et_2O. The filtrate was concentrated at reduced pressure and the residue was purified by column chromatography (silica, 30% Et_2O/hexane elution) to provide the dipeptide **18** as a clear colourless gum that crystallized (2.37 g, 80%). Recrystallization (Et_2O/hexane) gave a white solid, mp 83–84°C. $[\alpha]_D^{22}$ −154.1 (*c* 1.0 in $CHCl_3$). (Found: C 66.2, H 8.3, N 6.8. $C_{23}H_{34}N_2O_5$ requires C 66.0, H 8.2, N 6.7%.) ν_{max} (KBr)/cm^{-1} 3096, 3069, 3000–2800, 1742, 1678, 1637, 1446, 1384, 1320, 1268, 1168, 753, 705. δ_H (rotamers) 7.29 (5H, s, ArH), 5.19 (1H, d, *J* 12.3, ArC*H*H), 5.03 (1H, d, *J* 12.3, ArCH*H*), 4.55 and 4.32 (1H, 2d, *J* 11.0 and 10.7, NCHCO), 4.51–4.44 (1H, m, NCHCO), 3.84–3.55 (2H, m, NCH_2), 2.79–2.76 (3H, m, NCH_3), 2.26–1.86 (5H, m, $NCH_2CH_2CH_2$ and CH_3CH), 1.44–1.41 (9H, m, Bu^t), 0.89–0.81 (6H, m, CH_3CHCH_3). δ_C (rotamers) 171.8, 169.9, 169.9, 156.3, 155.3, 135.6, 128.4, 128.1, 80.1, 79.6, 66.8, 66.7, 66.6, 62.3, 60.6, 58.9, 47.2, 46.6, 29.5, 29.1, 29.0, 28.4, 28.3, 27.4, 27.3, 27.2, 24.8, 24.7, 19.4, 19.0, 18.4, 18.3.

(R)-Methyl 2-Hydroxy-3-phenylpropanoate ***21***

D-Phenyllactic acid **20**[18] (1.0 g, 6.0 mmol) was dissolved in dry MeOH (8 mL) and conc. H_2SO_4 (140 μL) was added. The solution was heated at reflux in a N_2 atmosphere for 3 h. The solution was diluted with Et_2O (70 mL) and then washed with 10% $NaHCO_3$ solution (2 × 15 mL) and brine (20 mL). The ethereal solution was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to give the ester **21** (1.1 g, 99%) as a clear oil that slowly solidified. This solid was recrystallized from Et_2O/hexane at ∼−5 to −10°C to give a solid, mp 49.5–50.5°C. $[\alpha]_D^{22}$ +6.1 (*c* 1.0 in $CHCl_3$). ν_{max} (KBr)/cm^{-1} 3284, 3023, 3000–2800, 1747, 1497, 1452, 1433, 1338, 1282, 1210, 1177, 1021, 978, 753, 702. δ_H 7.32–7.20 (5H, m, ArH), 4.45–4.41 (1H, m, HOC*H*CO), 3.73 (3H, s, OCH_3), 3.11 (1H, dd, *J* 4.5 and 13.9, PhC*H*H), 2.98–2.91 (2H, m, PhCH*H* and OH). δ_C 174.4, 136.3, 129.3, 128.2, 126.6, 71.2, 52.1, 40.4.

(R)-2-(Benzyloxy)-3-phenylpropanoic Acid ***23*** *(Dicyclohexylammonium Salt)*

The methyl ester **21** (1.0 g, 5.6 mmol) was dissolved in 1:2 CH_2Cl_2/hexane (18 mL) in an inert atmosphere and the solution was cooled to 0°C with an ice bath. Freshly distilled benzyl 2,2,2-trichloroacetimidate (2.4 mL, 12.9 mmol) was added to the solution with stirring, followed by trifluoromethanesulfonic acid (60 μL). The reaction mixture was left to stir for 1 h at 0°C and then a spatula of solid $NaHCO_3$ was added. The mixture was stirred for a further 10 min, and then it was filtered to remove trichloroacetamide. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (silica, 10% EtOAc/hexane). The appropriate fractions were pooled and concentrated at reduced pressure and the residue was purified by column chromatography (silica, 5% EtOAc/hexane) to give the benzyl ether **22** (1.06 g, 71%) as a clear colourless oil. The benzyl ether **22** (1.02 g, 3.8 mmol) was taken up in MeOH (25 mL) and the solution was cooled to 0°C. To the solution was added 2 M KOH (1.9 mL, 3.8 mmol) in water (3.1 mL) dropwise over 1 h. Once the addition was complete, the solution was stirred for a further 2 h at 0°C. The reaction mixture was then concentrated under vacuum to ∼10 mL. It was then diluted with water (20 mL). The aqueous solution was washed with Et_2O (2 × 20 mL) and the combined ethereal washings were discarded. The aqueous phase was acidified with 5 M HCl to pH ∼2 and it was then extracted with Et_2O (3 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was taken up in dry Et_2O (10 mL) and dicyclohexylamine (750 μL, 3.8 mmol) was added. A precipitate formed immediately. The mixture was cooled for several hours in an ice box, after which the salt **23** (1.0 g, 60%) was collected at the pump as fine white needles, mp 129–137°C. $[\alpha]_D^{20}$ +59.5 (*c* 1.0 in $CHCl_3$). ν_{max} (KBr)/cm^{-1} 3059, 3029, 3000–2800, 2525, 2465, 1625, 1562, 1498, 1454, 1397, 1315, 1102, 748, 701. δ_H 9.34 (2H, s, NH_2^+), 7.32–7.03 (10H, m, ArH), 4.71 (1H, d, *J* 12.1, ArC*H*H), 4.37 (1H, d, *J* 12.1, ArCH*H*), 3.98 (1H, dd, *J* 3.7 and 9.2, BnOC*H*), 3.17 (1H, dd, *J* 3.6 and 13.8, PhC*H*H), 3.08–2.87 (3H, m, PhCH*H* and $N(CH)_2$), 1.97–1.12 (20H, m, methylene envelope). δ_C 176.9, 139.6, 139.0, 129.4, 128.8, 127.8, 127.1, 126.9, 125.8, 82.0, 71.3, 52.3, 40.0, 29.0, 28.9, 25.1, 24.7.

*(S)-*tert*-Butyl 2-((R)-2-(Benzyloxy)-N-methyl-3-phenylpropanamido)-3-methylbutanoate* ***25***

Finely powdered salt **23** (1.0 g, 2.2 mmol) was suspended in dry Et_2O (minimum volume), TFA (0.2 mL) was added and the

solution was stirred vigorously for 15 min. The ethereal solution was filtered to remove the precipitate and concentrated at reduced pressure. The residue was taken up in CH_2Cl_2 (15 mL) and the valine ester **24** (1.0 g, 2.7 mmol) was added followed by PyBroP (1.25 g, 2.7 mmol). To the stirred solution at room temperature was added Et_3N (1.25 mL, 9.0 mmol) and stirring was continued for 3 h. The reaction mixture was diluted with Et_2O (100 mL) and then it was washed successively with 10% citric acid solution (2 × 20 mL), 5% $NaHCO_3$ solution (50 mL), water (30 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 20% EtOAc/hexane) to give the dipeptide **25** (760 mg, 81%) as a clear colourless gum. $[\alpha]_D^{25}$ −40.0 (*c* 1.0 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3106, 3088, 3063, 3029, 3002, 3000–2800, 1729, 1658, 1495, 1455, 1392, 1368, 1280, 1255, 1157, 1135, 1117, 986, 743, 699. δ_H (rotamers) 7.30–7.17 (10H, m, ArH), 4.84–4.80, 4.66–4.60, 4.55–4.45, 4.34–4.22 and 3.98–3.04 (4H, 5 m, OCHCO, NCHCO and $ArCH_2$), 3.25–2.86 (5H, m, $ArCH_2$ and NCH_3), 2.29–2.03 (1H, m, CH_3CHCH_3), 1.45–1.41 (9H, m, Bu^t), 0.97 (3H, dd, *J* 6.5 and 20.0, CH_3CHCH_3), 0.75 (3H, dd, *J* 6.5 and 22.8, CH_3CHCH_3). δ_C (rotamers) 171.6, 170.1, 169.0, 138.1, 137.5, 137.1, 129.4, 128.7, 128.2, 128.1, 127.6, 127.4, 126.5, 126.4, 82.3, 81.3, 78.0, 77.0, 70.7, 70.3, 65.9, 62.7, 38.4, 37.9, 30.8, 28.9, 27.9, 27.8, 27.6, 27.0, 19.8, 19.4, 19.0, 18.7.

(S)-2-((R)-2-(Benzyloxy)-N-methyl-3-phenylpropanamido)-3-methylbutanoic Acid ***26***

The ester **25** (700 mg, 1.6 mmol) was dissolved in CH_2Cl_2 (3 mL). TFA (3 mL) was added and the reaction mixture was left to stand for ∼1 h. It was then concentrated at reduced pressure to give the residual acid **26**, which was taken up in CH_2Cl_2 (12 mL) and used immediately in the next step.

*(S)-*tert*-Butyl 1-((S)-2-((R)-2-(Benzyloxy)-N-methyl-3-phenylpropanamido)-3-methylbutanoyl)pyrrolidine-2-carboxylate* ***28***

To a stirred solution of the acid **26** was added the proline salt **27** (444 mg, 2.1 mmol), BOP reagent (947 mg, 2.1 mmol), and Et_3N (0.92 mL, 6.6 mmol). After stirring at room temperature for 2 h, the reaction mixture was filtered through a silica plug, eluting with CH_2Cl_2. The filtrates were concentrated at reduced pressure and the residue was purified by column chromatography (silica, 20% EtOAc/hexane) to give the 'tripeptide' **28** (850 mg, 99%) as a clear colourless oil. $[\alpha]_D^{25}$ −58.7 (*c* 1.0 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3106, 3087, 3063, 3030, 3000–2800, 1738, 1644, 1495, 1452, 1437, 1392, 1367, 1288, 1260, 1222, 1203, 1154, 1096, 1030, 744, 700. δ_H (rotamers) 7.29–7.14 (10H, m, ArH), 5.08–4.98 (1H, m, NCHCO), 4.64–4.52 (1H, m, ArCHH), 4.44 (1H, t, *J* 6.9, OCHCO), 4.34–4.29 (2H, m, ArCHH and NCHCO), 4.03–3.95, 3.71–3.63, 3.54–3.43 and 3.36–3.28 (2H, 4 m, NCH_2), 3.12–2.97 (2H, m, $ArCH_2$), 2.93–2.91 (3H, m, NCH_3), 2.27–1.81 (5H, m, CH_3CHCH_3 and $NCH_2CH_2CH_2$), 1.45–1.40 (9H, m, Bu^t), 0.99, 0.94, 0.85 and 0.64 (6H, 4d, *J* 6.5, 6.4, 6.8 and 6.7, CH_3CHCH_3). δ_C (rotamers) 171.7, 171.2, 169.2, 168.1, 137.4, 136.8, 129.4, 128.3, 128.2, 127.8, 127.7, 126.6, 126.4, 81.1, 78.5, 78.0, 71.1, 59.8, 59.6, 59.4, 47.4, 47.0, 38.4, 30.1, 29.2, 28.7, 27.9, 27.2, 19.0, 18.6.

(S)-Benzyl 2-Hydroxy-3-phenylpropanoate ***31***

L-Phenyllactic acid[18] (2.0 g, 12.0 mmol) was dissolved in DMF (20 mL) and finely powdered dry K_2CO_3 (3.3 g, 24.0 mmol) was added and the mixture was stirred vigorously. To the stirred mixture was added benzyl bromide (1.4 mL, 12.0 mmol) and the mixture was left overnight. The resulting turbid solution was diluted with H_2O (250 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (50 mL). The ethereal solution was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residual oil was purified by column chromatography (silica, 20% EtOAc/hexane) to give the benzyl ester **31** (2.65 g, 86%) as a clear colourless oil, which slowly solidified, mp 25–27°C. $[\alpha]_D^{22}$ −55.1 (*c* 1.0 in CH_2Cl_2). ν_{max} (KBr)/cm^{-1} 3435, 3115, 3088, 3062, 3032, 3000–2800, 1741, 1497, 1453, 1420, 1374, 1255, 1213, 1181, 1094, 1024, 991, 748, 700. δ_H 7.43–7.21 (10H, m, ArH), 5.22 (1H, d, *J* 12.1, ArCHH), 5.20 (1H, d, *J* 12.2, ArCHH), 4.55–4.51 (1H, m, HOCHCO), 4.17 (1H, dd, *J* 4.7 and 13.9, PhCHH), 3.10 (1H, br s, HOCHCO), 3.03 (1H, dd, *J* 6.7 and 13.9, PhCHH). δ_C 173.8, 136.1, 134.9, 129.3, 128.4, 128.3, 128.1, 126.5, 71.1, 67.0, 40.2.

*(S)-2-((R)-1-(Benzyloxy)-1-oxo-3-phenylpropan-2-yl) 1-*tert*-Butylpiperidine-1,2-dicarboxylate* ***33***

The carbamate **32**[15] (640 mg, 2.8 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL) and triphenylphosphine (1.32 g, 5.0 mmol) and the ester **31** (718 mg, 2.8 mmol) were added. The solution was cooled to −20°C with an ice–salt bath and DEAD (0.75 g, 4.8 mmol) was added. Stirring at −20°C was continued for 10 min and then the ice–salt bath was removed and stirring was continued for 2 h. Then the solution was filtered and the filtrate was concentrated at reduced pressure. The residue was purified by column chromatography (silica, 10% EtOAc/hexane) to give the ester **33** (910 mg, 69%) as a clear colourless gum. $[\alpha]_D^{24}$ −29.8 (*c* 1.0 in $CHCl_3$). (Found: C 69.5, H 7.3, N 3.2. $C_{27}H_{33}NO_6$ requires C 69.4, H 7.1, N 3.0%.) ν_{max} (NaCl)/cm^{-1} 3094, 3064, 3027, 3000–2800, 1748, 1696, 1485, 1452, 1403, 1368, 1330, 1275, 1160, 1081, 1035, 934, 871, 827, 747, 697. δ_H (rotamers) 7.30–7.14 (10H, m, ArH), 5.36–5.30 (1H, m, OCHCO), 5.09–4.99 and 4.79–4.77 (3H, 2 m, $ArCH_2$ and NCHCO), 3.96–3.81 (1H, m, NCHH), 3.22–3.07 (2H, m, $PhCH_2$), 2.88–2.72 (1H, m, NCHH), 2.17–2.01 and 1.57–1.22 (15H, 2 m, Bu^t and $NCH_2CH_2CH_2CH_2$). δ_C (rotamers) 171.3, 168.7, 155.2, 155.0, 135.2, 134.8, 129.4, 129.2, 128.3, 126.8, 126.4, 79.7, 73.2, 73.1, 66.9, 54.6, 53.4, 41.8, 40.6, 37.0, 28.2, 28.0, 26.7, 26.6, 24.6, 24.3, 20.3, 20.1.

*(S)-2-((R)-1-(((S)-1-((S)-2-(Benzyloxycarbonyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl) (Methyl)amino)-1-oxo-3-phenylpropan-2-yl) 1-*tert*-Butylpiperidine-1,2-dicarboxylate* ***6***

The carbamate **18** (1.56 g, 3.7 mmol) was dissolved in dry CH_2Cl_2 (5 mL), TFA (5 mL) was added and the reaction mixture was left to stand for ∼1 h. The solution was then concentrated at reduced pressure to give the amine **35** (TFA salt). Meanwhile, the benzyl ester **33** (1.87 g, 4.0 mmol) was taken up in MeOH (20 mL) and 10% Pd-on-C catalyst (480 mg) was added. The stirred mixture in an H_2 atmosphere was left for 4 h. The reaction mixture was then filtered through Celite with MeOH (40 mL) as eluent and the combined filtrates were concentrated under vacuum to give the free acid **34** (1.43 g, 95%) as a clear gum. The acid **34** (1.4 g, 3.7 mmol) was combined with the salt **35** (1.6 g, 3.7 mmol) in CH_2Cl_2 (15 mL). To the stirred solution was added PyBroP (1.82 g, 3.9 mmol) and the solution was cooled to 0°C with an ice bath. Pr^i_2NEt (1.95 mL,

11.2 mmol) was added and stirring was continued at 0°C for 5 min after which the ice bath was removed and stirring was continued for 1.5 h. The reaction mixture was then filtered through a silica plug, eluting with 30% EtOAc/hexane. The organic filtrates were evaporated to dryness at reduced pressure and the residue was purified by column chromatography (silica, 20% Et_2O/hexane, then 40% Et_2O/hexane) to give the depsipeptide **6** (1.76 g, 70%) as a colourless foam. $[\alpha]_D^{23}$ −138.0 (*c* 1.0 in $CHCl_3$). (Found: C 67.3, H 7.8, N 6.1. $C_{38}H_{51}N_3O_8$ requires C 67.3, H 7.6, N 6.2%.) ν_{max} (KBr)/cm^{-1} 3101, 3070, 3033, 3000–2800, 1745, 1695, 1650, 1447, 1409, 1263, 1164, 1088. δ_H (rotamers) 7.30–7.18 (10H, m, ArH), 5.42–5.40 (1H, m, OCHCO), 5.18 (1H, d, *J* 12.3, ArC*H*H), 5.08 (1H, d, *J* 12.4, ArCH*H*), 5.00–4.90 and 4.79–4.77 (2H, 2 m, NCHCO × 2), 4.77 (1H, dd, *J* 4.0 and 8.3, NCHCO), 4.00–3.55 and 3.11–2.97 (11H, 2 m, NCH_3, $PhCH_2$, NCH_2CH_2 and NCH_2), 2.33–0.65 (24H, m, $NCH_2CH_2CH_2CH_2$, $NCH_2CH_2CH_2$, CH_3CHCH_3, Bu^t). δ_C (rotamers) 171.9, 169.8, 169.7, 168.4, 155.5, 155.0, 135.7, 135.5, 129.4, 129.2, 128.6, 128.4, 128.14, 128.1, 127.1, 79.8, 72.3, 72.1, 66.7, 59.6, 59.1, 54.6, 53.5, 47.1, 45.9, 42.0, 40.8, 37.3, 37.1, 30.1, 29.1, 28.3, 27.1, 26.8, 24.8, 24.6, 20.6, 20.3, 19.1, 18.3.

(S)-2-((R)-1-(((S)-1-((S)-2-((2S,3S)-1-((S)-2-(Benzyloxycarbonyl)piperidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)(methyl)amino)-1-oxo-3-phenylpropan-2-yl) 1-tert-Butylpiperidine-1,2-dicarboxylate ***3***

The ester **6** (500 mg, 0.74 mmol) was dissolved in MeOH (6 mL) and 5% Pd-on-C catalyst (50 mg) was added. The slurry was stirred in an H_2 atmosphere overnight and then filtered through Celite with MeOH (20 mL) as eluent. The filtrates were concentrated at reduced pressure to give the acid **37** (425 mg, 98%) as a white foam. Meanwhile, the carbamate **5** (225 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and TFA (1 mL) was added and the reaction mixture was left to stand for ∼1 h. The solution was then concentrated at reduced pressure to give the amine **36** (TFA salt, 212 mg). To the free acid **37** (425 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) was added the salt **36** (212 mg, 0.46 mmol) followed by PyBroP (337 mg, 0.72 mmol). To the stirred solution was added Pr^i_2NEt (400 μL, 2.3 mmol) and the reaction mixture was left to stir overnight. The mixture was then diluted with EtOAc (50 mL) and washed successively with 10% citric acid solution (2 × 20 mL), water (20 mL), 5% sodium bicarbonate solution (20 mL), water (20 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica, 50% Et_2O/hexane, then 80% Et_2O/hexane) to give the 'hexamer' **3** (540 mg, 83%) as a white foam. $[\alpha]_D^{27}$ −134.0 (*c* 0.5 in $CHCl_3$). (Found: C 66.3, H 8.1, N 7.5. $C_{50}H_{71}N_5O_{10}$ requires C 66.6, H 7.9, N 7.8%.) (Found [M + H] 902.5255. $C_{50}H_{72}N_5O_{10}$ requires [M + H] 902.5279.) ν_{max} (NaCl)/cm^{-1} 3323, 3092, 3065, 3000–2800, 1738, 1690, 1644, 1519, 1448, 1419, 1369, 1319, 1255, 1194, 1158, 1088, 1050, 1026, 752, 697. δ_H (400 MHz, 1:4 $CDCl_3$/[D_6]acetone) 7.38–7.22 (11H, m, ArH and NH), 5.56–5.50 (1H, m, OCHCO), 5.44–5.40 (1H, m, NCHCO), 5.21–5.15 (2H, m, $ArCH_2$), 5.05–4.96 (1H, m, NCHCO), 4.90–4.84 (1H, m, NCHCO), 4.81–4.75 (1H, m, NCHCO), 4.53–4.42 (1H, m, NCHCO), 4.05–3.85 and 3.72–3.52 (4H, 2 m, NCH_2 × 2), 3.25–2.83 (11H, m, $PhCH_2$, NCH_3, NCH_2, NCH_2CH_2 × 2), 2.35–0.73 (37H, m, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2CH_2$ × 2, CH_3CHCH_3, $CH(CH_3)CH_2CH_3$ and Bu^t). δ_C (100 MHz, 1:4 $CDCl_3$/[D_6]acetone) 171.9, 171.4, 171.2, 171.0, 169.0, 155.0, 136.7, 136.5, 128.9, 128.6, 79.6, 72.9, 67.0, 60.7, 60.4, 55.0, 53.0, 52.4, 47.6, 44.0, 41.0, 37.7, 37.4, 30.0, 28.9, 28.3, 28.2, 27.6, 27.4, 26.9, 25.5, 25.3, 25.1, 24.1, 20.6, 19.7, 18.4, 15.7, 11.2. *m/z* (LSIMS) 902 ([M + H], 12%), 802 (10), 473 (100), 417 (95), 361 (15), 304 (33), 220 (44), 181 (15).

(S)-Benzyl 4-((R)-1-(Benzyloxy)ethyl)-5-oxooxazolidine-3-carboxylate ***41***

The ester **39**[19] (5.31 g, 17.7 mmol) was dissolved in methanol (100 mL), the solution was cooled to 0°C and 1 M aqueous NaOH (22 mL) was added. The basic solution was allowed to stir at 0°C for 10 min, then the ice bath was removed and the solution was left to stir for 1 h. The solution was concentrated at reduced pressure and the residue was then taken up in water (50 mL). To the aqueous solution was added solid K_2CO_3 (4.9 g, 35.5 mmol) followed by benzylchloroformate (3 mL, 21 mmol) and acetone (20 mL). The reaction mixture was stirred vigorously overnight and then it was diluted with water (100 mL) and washed with Et_2O (3 × 50 mL) and then CH_2Cl_2 (50 mL). The combined organic washings were back-extracted with water (50 mL) and the combined aqueous layers were acidified with 5 M HCl to pH 3. The aqueous layers were then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum to give the carbamate **40** as a syrup (5.35 g, 88%), which was used directly in the next step. The carbamate **40** (2.37 g, 9.5 mmol) was dissolved in toluene (80 mL) and camphorsulfonic acid (200 mg) was added followed by paraformaldehyde (3 g). The heterogeneous solution was heated to reflux for approx. 1 h (monitored by TLC with 10% EtOAc/hexane elution). The reaction mixture was concentrated at reduced pressure and the residue was passed through a plug of silica with 20% EtOAc/hexane as eluent. The filtrate was evaporated to dryness under vacuum to afford the oxazolidinone **41** as a clear colourless oil (2.94 g, 87%). A sample was purified by column chromatography (silica, 10% EtOAc/hexane elution). $[\alpha]_D^{25}$ +117.0 (*c* 1.0 in $CHCl_3$). (Found: C 67.6, H 6.0, N 3.7. $C_{20}H_{21}NO_5$ requires C 67.6, H 6.0, N 3.9%.) ν_{max} (NaCl)/cm^{-1} 3093, 3063, 3032, 3000–2800, 1804, 1718, 1456, 1411, 1379, 1361, 1306, 1239, 1212, 1165, 1123, 1057, 1028, 732, 697, 665. δ_H 7.40–7.25 (10H, m, ArH), 5.68 (1H, br s, NC*H*H), 5.24–5.14 (3H, m, $ArCH_2$ and NCH*H*), 4.59–4.40 (2H, m, $ArCH_2$), 4.37–4.16 (2H, m, NCHCO and CH_3CH), 1.34–1.26 (3H, m, CH_3CH). δ_C 171.7, 153.9, 137.4, 135.2, 128.45, 128.39, 127.6, 127.3, 79.2, 75.4, 71.1, 68.0, 60.6, 15.9.

(2S,3R)-tert-Butyl-3-(benzyloxy)-2-((benzyloxycarbonyl)(methyl)amino)butanoate ***43***

The oxazolidinone **41** (2.3 g, 6.5 mmol) was dissolved in $CHCl_3$ (30 mL) and Et_3SiH (3.0 mL, 18.8 mmol) was added with stirring. To the stirred solution was added trifluoroacetic acid (30 mL). The reaction mixture was then left to stand for 72 h. The resulting solution was diluted with toluene (150 mL) and then concentrated to dryness at reduced pressure. The residue was taken up in Et_2O (100 mL) and extracted with 5% $NaHCO_3$ solution (4 × 50 mL). The combined aqueous extracts were washed with Et_2O (100 mL) and acidified with 5 M HCl to pH 2. The aqueous layer was then extracted with CH_2Cl_2 (4 × 50 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give the acid **42** as a clear

gum (2.0 g, 86%). The acid **42** (1.57 g, 4.4 mmol) was taken up in a solution of cyclohexane (12 mL) and CH_2Cl_2 (4 mL) and cooled to 0°C with an ice bath. To the solution was added *tert*-butyl 2,2,2-trichloroacetimidate[20] (1.9 g, 8.7 mmol), followed by $BF_3{\cdot}Et_2O$ (20 μL). After 10 min, $NaHCO_3$ solid (a spatula tip) was added and stirring was continued for 5 min. The solution was then filtered to remove the trichloroacetamide by-product. The filtrate was then concentrated under reduced pressure and the residue was purified by column chromatography (silica, 10% Et_2O/hexane) to provide the ester **43** as a colourless gum (1.6 g, 88%). $[\alpha]_D^{19}$ +23.8 (*c* 1.0 in $CHCl_3$). (Found: C 69.5, H 7.8, N 3.3. $C_{24}H_{31}NO_5$ requires C 69.7, H 7.6, N 3.4%.) ν_{max} (NaCl)/cm^{-1} 3090, 3065, 3033, 3000–2800, 1741, 1704, 1497, 1479, 1455, 1399, 1369, 1313, 1259, 1216, 1141, 1089, 1054, 1029, 981, 771, 736, 698. δ_H (rotamers) 7.39–7.23 (10H, m, ArH), 5.23–5.12 (2H, m, $ArCH_2$), 4.96 and 4.72 (1H, 2d, *J* 4.5 and 5.2, NCHCO), 4.64–4.58 and 4.45–4.39 (2H, 2 m, $ArCH_2$), 4.35–4.16 (1H, m, CH_3CHO), 3.12–3.10 (3H, m, NCH_3), 1.45–1.43 (9H, m, Bu^t), 1.25–1.20 (3H, m, CH_3CHO). δ_C (rotamers) 168.7, 168.6, 157.5, 156.4, 138.3, 138.1, 136.7, 136.6, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 126.9, 81.6, 81.4, 75.3, 74.5, 71.4, 67.1, 67.0, 63.6, 63.4, 32.9, 32.8, 27.9, 27.1, 16.1, 15.9.

*(2S,3*R*)*-tert-*Butyl 3-(Benzyloxy)-2-(methylamino)butanoate* ***44***

The carbamate **43** (1.76 g, 4.2 mmol) was dissolved in methanol (15 mL) and ammonium acetate (332 mg, 4.3 mmol) was added by 5% Pd-on-C catalyst (176 mg) in a hydrogen atmosphere stirred at room temperature for 18 h. The reaction mixture was filtered through Celite with CH_2Cl_2 (150 mL) as eluent. The combined filtrates were washed with water (3 × 100 mL). The combined aqueous washings were back-extracted with CH_2Cl_2 (2 × 20 mL) and all the organic extracts were combined and dried ($MgSO_4$), filtered, and concentrated at reduced pressure to afford the amine **44** as an oily residue (1.10 g, 93%). This material was used in the next step without further purification.

(S)-1-((S)-2-(Benzyloxycarbonylamino)propanoyl)pyrrolidine-2-carboxylic Acid ***48***

The alanine acid **46** (2.97 g, 13.3 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution was cooled to 0°C with an ice bath. To the solution was added the proline ester trifluoroacetate salt **45**[21] (4.0 g, 11.1 mmol) and BOP reagent (5.89 g, 13.3 mmol). To the stirred solution was added Pr^i_2NEt (7.7 mL, 44.4 mmol) in one portion and the solution was left to stir with ice cooling for 5 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated at reduced pressure and the residue was taken up in EtOAc (50 mL). The organic layer was washed successively with 1 M HCl (30 mL), water (30 mL), 10% $NaHCO_3$ solution (2 × 30 mL), water (30 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was purified by column chromatography (silica, 60% Et_2O/hexane) to give the dipeptide **47** as a clear colourless gum (4.0 g, 80%). $[\alpha]_D^{20}$ −65.5 (*c* 1.0 in $CHCl_3$). (Found: C 48.0, H 4.7, N 6.1. $C_{18}H_{21}N_2O_5$ requires C 47.9, H 4.7, N 6.2%.) ν_{max} (NaCl)/cm^{-1} 3403, 3302, 3064, 3035, 3000–2800, 1761, 1716, 1651, 1525, 1448, 1376, 1335, 1245, 1157, 1097, 1056, 966, 913, 796, 713. δ_H (rotamers) 7.28 (5H, s, ArH), 5.74 (1H, d, *J* 7.9, NH), 5.08–4.43 (6H, m, NCHCO × 2, $ArCH_2$, CH_2CCl_3), 3.70–3.55 (2H, m, NCH_2), 2.26–1.96 (4H, m, $NCH_2CH_2CH_2$), 1.34 (3H, d, *J* 6.9, CH_3CH). δ_C (rotamers) 171.3, 170.0, 155.5, 136.3, 128.3, 127.9, 127.8, 94.6, 73.9, 66.5, 58.5, 48.1, 46.6, 28.8, 24.7, 18.1.

The carbamate **47** (2.5 g, 5.5 mmol) was dissolved in EtOAc (40 mL) with vigorous stirring and glacial AcOH (0.44 mL) was added followed by freshly activated zinc dust (3.93 g) and water (40 μL). After 20 min, a further aliquot of glacial AcOH (0.56 mL) was added and stirring was continued for 40 min. The reaction mixture was then filtered through a Celite plug with EtOAc (100 mL) as eluent. The filtrate was extracted with sat. $NaHCO_3$ solution (3 × 20 mL) and the combined aqueous extracts were acidified with 5 M HCl to pH ~2. The acidic aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give the acid **48** as a clear gum (1.7 g, 96%). A sample of the acid was dissolved in Et_2O and *tert*-butylamine (1 equiv.) was added, causing immediate precipitation of the *tert*-butylammonium salt, which was collected and recrystallized (acetone), mp 105–110°C. $[\alpha]_D^{20}$ −48.8 (*c* 1.0 in $CHCl_3$). (Found: C 61.3, H 8.2, N 10.7. $C_{20}H_{31}N_3O_5$ requires C 61.0, H 7.9, N 10.7%.) ν_{max} (KBr)/cm^{-1} 3431, 3000–2800, 2638, 2555, 1724, 1650, 1564, 1497, 1456, 1391, 1349, 1279, 1266, 1236, 1070, 1034, 754. δ_H (rotamers) 8.00 (3H, br s, NH_3), 7.29–7.22 (5H, m, ArH), 6.26 and 6.01 (each 0.5H, d, *J* 7.8, NH), 5.04–4.88 (2H, m, $ArCH_2$), 4.47–4.09 (2H, m, NCHCO × 2), 3.64–3.35 (2H, m, NCH_2), 2.18–1.69 (4H, m, $NCH_2CH_2CH_2$), 1.26–1.23 (12H, m, Bu^t and CH_3CH). δ_C (rotamers) 176.7, 171.1, 170.9, 155.7, 155.2, 136.4, 136.1, 128.3, 128.2, 127.9, 127.8, 127.7, 66.5, 66.4, 61.6, 61.4, 50.5, 48.5, 48.2, 46.7, 46.4, 31.5, 29.1, 27.8, 24.8, 22.3, 19.2, 17.6.

*(2S,3*R*)*-tert-*Butyl 3-(Benzyloxy)-2-((S)-1-((S)-2-(benzyloxycarbonylamino)propanoyl)-*N*-methylpyrrolidine-2-carboxamido)butanoate* ***7***

A sample of the amine **44** (856 mg, 3.1 mmol) was dissolved in CH_2Cl_2 (20 mL) and the dipeptide **48** (1.0 g, 3.1 mmol) was added in one portion followed by PyBroP reagent (1.49 g, 3.2 mmol) with stirring at room temperature. To the homogeneous mixture was added Pr^i_2NEt (2.2 mL, 12.6 mmol) and the reaction mixture was stirred at room temperature for 3 h. The solution was then diluted with EtOAc (100 mL) and the organic phase was washed successively with 5% citric acid solution (2 × 50 mL), brine (50 mL), 5% $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue (1.91 g) was purified by column chromatography (silica, 20% EtOAc/hexane, then 60% EtOAc/hexane) to give the tripeptide **7** as a clear gum (410 mg, 23%; 47% conversion from **44**). $[\alpha]_D^{20}$ −20.4 (*c* 1.0 in $CHCl_3$). (Found [M + H] 582.3189. $C_{32}H_{44}N_3O_7$ requires [M + H] 582.3179.) ν_{max} (NaCl)/cm^{-1} 3284, 3088, 3063, 3031, 3000–2800, 1726, 1646, 1523, 1498, 1455, 1369, 1300, 1249, 1215, 1161, 1118, 1090, 1067, 1029, 737, 698, 666. δ_H 7.31–7.20 (10H, m, ArH), 5.68 (1H, d, *J* 7.9, NH), 5.24 (1H, d, *J* 3.9, NCHCO), 5.09 (1H, d, *J* 12.4, ArC*H*H), 5.02 (1H, d, *J* 12.3, ArCH*H*), 4.94–4.90 (1H, m, NCHCO), 4.63–4.25 (4H, m, $PhCH_2$, CH_3CH, NCHCO), 3.73–3.56 (2H, m, NCH_2), 3.23 (3H, s, NCH_3), 2.28–1.92 (4H, m, $NCH_2CH_2CH_2$), 1.50–1.18 (15H, m, Bu^t and CH_3CH × 2). δ_C 172.9, 170.6, 168.9, 155.6, 138.5, 136.4, 128.4, 128.1, 127.9, 127.8, 127.3, 127.1, 81.5, 75.8, 71.6, 66.5, 61.1, 56.4, 48.2, 47.0, 34.1, 28.1, 28.0, 24.7, 18.0, 15.7. *m/z* (LSIMS) 582 ([M + H], 65%), 526 (40), 418 (25), 303 (100), 280 (35), 224 (67). Further elution gave the amine **44** (450 mg, 52%).

(2S,3S)-tert-*Butyl 2-((Benzyloxycarbonyl)(methyl)amino)-3-methylpentanoate* ***51***

The amino acid **50**[1,16] (1.1 g, 3.9 mmol) was dissolved in hexane (10 mL) and CH_2Cl_2 (2 mL) and the solution was cooled to 0°C with an ice bath. The solution was vigorously stirred while adding *tert*-butyl 2,2,2-trichloroacetimidate (2.5 g, 11.4 mmol) in one portion followed by $BF_3{\cdot}Et_2O$ (40 μL). Vigorous stirring was continued for 10 min and then $NaHCO_3$ solid (one spatula) was added and stirring again continued for 10 min. The reaction mixture was then filtered to remove trichloroacetamide. The filtrate was further filtered through a silica plug with 15% EtOAc/hexane as eluent. Concentration of the filtrate at reduced pressure gave a residue, which was purified by column chromatography (silica, 10% EtOAc/hexane) to give the ester **51** (1.1 g, 83%) as a clear colourless oil. $[\alpha]_D^{20}$ −65.3 (*c* 1.0 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3098, 3063, 3034, 3000–2800, 1732, 1705, 1498, 1456, 1401, 1369, 1309, 1258, 1227, 1210, 1166, 1142, 975, 768, 733, 697, 665. δ_H (rotamers) 7.33–7.24 (5H, m, ArH), 5.23–5.05 (2H, m, $ArCH_2$), 4.46 and 4.26 (each 0.5H, d, *J* 10.5, NCHCO), 2.88 (3H, s, NCH_3), 1.99–1.85 (1H, m, C*H*CH_3), 1.42–1.36 (9H, m, Bu^t), 1.11–0.80 (8H, m, CH(C*H*$_3$)C*H*$_2$C*H*$_3$). δ_C (rotamers) 170.4, 170.0, 156.8, 156.4, 138.8, 128.3, 127.8, 127.6, 81.2, 67.2, 63.6, 63.4, 33.7, 33.3, 30.1, 27.9, 25.2, 25.0, 15.6, 10.7, 10.4.

*(2S,3S)-1-*tert-*Butoxy-*N*,3-dimethyl-1-oxopentan-2-aminium 4-Methylbenzenesulfonate* ***52***

The ester **51** (1.2 g, 3.6 mmol) was dissolved in *tert*-butanol (20 mL) and *p*-toluenesulfonic acid monohydrate (680 mg, 3.6 mmol) was added, followed by 10% Pd-on-C (173 mg). The mixture was stirred in an H_2 atmosphere until TLC analysis (20% EtOAc/hexane) showed complete reaction (~2 h). The reaction mixture was filtered through Celite eluting with *tert*-butanol (40 mL). The filtrate was concentrated at reduced pressure. The residue was taken up in a minimum of MeOH and this solution was diluted with Et_2O to effect precipitation of the salt **52** (1.23 g, 92%) as fine needles, mp 130–132°C. $[\alpha]_D^{22}$ +19.6 (*c* 1.0 in MeOH). (Found: C 58.1, H 8.4, N 3.6. $C_{18}H_{31}NO_5S$ requires C 57.9, H 8.4, N 3.8%.) ν_{max} (KBr)/cm^{-1} 3000–2800, 2511, 2462, 1729, 1597, 1480, 1400, 1376, 1366, 1240, 1164, 1121, 1060, 1039, 1022, 822, 681. δ_H (D_2O) 7.54 (2H, d, *J* 8.2, ArH), 7.20 (2H, d, *J* 8.2, ArH), 3.70 (1H, d, *J* 3.7, NCHCO), 2.57 (3H, s, NCH_3), 2.23 (3H, s, $ArCH_3$), 1.93–1.80 (1H, m, C*H*CH_3), 1.44–1.14 (11H, m, Bu^t and C*H*$_2$C*H*$_3$), 0.83–0.77 (6H, m, CH(C*H*$_3$)CH$_2$C*H*$_3$). δ_C (D_2O) 167.0, 142.0, 139.2, 129.0, 125.0, 85.9, 65.2, 35.3, 31.8, 26.8, 25.5, 20.1, 13.2, 10.6.

(2S,3S)-tert-*Butyl 2-((S)-2-((Benzyloxycarbonyl)(methyl)amino)-*N*,3-dimethyl-butanamido)-3-methylpentanoate* ***54***

The acid **53** (900 mg, 3.4 mmol) was dissolved in CH_2Cl_2 (13 mL) and the salt **52** (1.0 g, 2.7 mmol) was added followed by PyBroP reagent (1.6 g, 3.4 mmol). To the stirred solution was added Pr^i_2NEt (2.4 mL, 13.6 mmol) at room temperature. The solution was stirred for 3.5 h and then filtered through a silica plug with 40% EtOAc/hexane as eluent. The combined filtrates were concentrated at reduced pressure and the residue was purified by column chromatography (silica, 10% EtOAc/hexane) to give the dipeptide **54** (930 mg, 77%) as a clear colourless syrup. $[\alpha]_D^{22}$ −165.6 (*c* 1.0 in CH_2Cl_2). (Found: C 67.1, H 9.3, N 6.5. $C_{25}H_{40}N_2O_5$ requires C 66.9, H 9.0, N 6.2%.) ν_{max} (KBr)/cm^{-1} 3085, 3066, 3033, 3000–2800, 1731, 1697, 1651, 1456, 1396, 1303, 1258, 1212, 1164, 1135, 978, 768, 698. δ_H (rotamers) 7.31–7.25 (5H, m, ArH), 5.27–4.96 (2H, m, $ArCH_2$), 4.84–4.06 (2H, m, NCHCO × 2), 2.98–2.73 (6H, m, NCH_3 × 2), 2.46–2.24 and 1.99–1.81 (2H, 2 m, C*H*CH_3 × 2), 1.41–1.34 (9H, m, Bu^t), 1.23–1.22 and 0.99–0.61 (14H, 2 m, CH(C*H*$_3$)C*H*$_2$C*H*$_3$ and C*H*$_3$CHC*H*$_3$). δ_C (rotamers) 171.0, 170.4, 170.1, 170.0, 169.8, 169.2, 156.9, 156.4, 155.9, 155.1, 136.7, 136.5, 136.2, 136.1, 128.5, 128.4, 128.3, 127.9, 127.6, 127.4, 82.1, 81.4, 81.2, 67.7, 67.3, 67.2, 64.6, 64.1, 61.1, 61.0, 60.7, 60.4, 60.2, 33.8, 33.7, 33.0, 32.9, 31.2, 30.7, 29.6, 29.4, 29.2, 28.9, 27.9, 27.6, 27.4, 27.2, 24.9, 24.7, 24.0, 19.9, 19.2, 18.2, 16.0, 15.8, 10.6.

(2S,3S)-tert-*Butyl 2-((S)-*N*,3-Dimethyl-2-(methylamino) butanamido)-3-methylpentanoate* ***49***

The carbamate **54** (360 mg, 0.8 mmol) was dissolved in MeOH (5 mL) and 10% Pd-on-C catalyst (50 mg) was added. The mixture was stirred in an H_2 atmosphere and monitored by TLC (silica, 20% EtOAc/hexane). When the reaction was complete (~1 h), the mixture was filtered through Celite with MeOH (10 mL) as eluent and the combined methanolic filtrates were concentrated under vacuum to give the amine **49**, which was used directly in subsequent reactions.

*(S)-(9*H*-Fluoren-9-yl)methyl 4-((*R*)-1-(Benzyloxy)ethyl)-5-oxooxazolidine-3-carboxylate* ***56***

To a sample of the carbamate **55**[13] (2.0 g, 4.6 mmol) in toluene (40 mL) was added camphorsulfonic acid (60 mg) and dry paraformaldehyde (3.0 g). The reaction mixture was then heated to reflux for 30–60 min. The mixture was cooled, filtered to remove solids, and the filtrate was concentrated at reduced pressure. The residue was taken up in the minimum of 40% EtOAc/hexane and it was then filtered through a silica plug, eluting with 30% EtOAc/hexane to provide the oxazolidinone **56** as a clear colourless oil (2.0 g, 97%). A small portion was further purified by column chromatography (silica, 50% ether/hexane elution) to give the oxazolidinone **56** as a colourless glass. $[\alpha]_D^{22}$ +107.0 (*c* 1.0 in $CHCl_3$). (Found [M + H] 444.1814. $C_{27}H_{26}NO_5$ requires [M + H] 444.1811.) ν_{max} (NaCl)/cm^{-1} 3089, 3066, 3033, 3000–2800, 1807, 1718, 1451, 1414, 1379, 1359, 1317, 1238, 1210, 1166, 1126, 1108, 1058, 1028, 757, 740, 698, 666, 620. δ_H 7.77–7.24 (13H, m, ArH), 5.59–3.60 (9H, m, NCH_2O, $PhCH_2$, NCHCO, CH_2CH, C*H*OBn), 1.29–1.23 (3H, m, C*H*$_3$CH). δ_C 171.8, 154.0, 143.2, 141.3, 137.5, 128.3, 127.92, 127.89, 127.7, 127.4, 127.2, 124.4, 120.0, 79.3, 75.5, 71.2, 67.9, 67.0, 60.6, 47.1, 15.8, 15.2.

(2S,3R)-tert-*Butyl 2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-3-(benzyloxy)butanoate* ***58***

The oxazolidinone **56** (1.40 g, 3.2 mmol) was dissolved in chloroform (15 mL) and triethylsilane (1.5 mL, 9.4 mmol) was added with stirring. To the homogeneous solution was added trifluoroacetic acid (15 mL). The solution was then stirred to maintain homogeneity overnight. The solution was diluted with toluene (100 mL) and then it was concentrated under vacuum. This procedure was twice repeated with toluene aliquots (50 mL). The residue obtained was subjected to column chromatography (silica, 94:6:0.5 CH_2Cl_2/MeOH/H_2O elution), which removed traces of triethylsilane and provided the acid **57** as a clear gum (1.20 g, 85%). The acid **57** (1.20 g, 2.7 mmol) was dissolved in a solution of cyclohexane (10 mL) and CH_2Cl_2 (2 mL) and cooled to 0°C with an ice bath. To the solution was added TBTA (1.47 g, 6.7 mmol), followed by $BF_3{\cdot}Et_2O$ (20 μL).

After 10 min, solid sodium bicarbonate (a spatula tip) was added and stirring was continued for 5 min. The reaction mixture was then filtered to remove trichloroacetamide, and the filtrate was concentrated at reduced pressure. The residue was purified by column chromatography (silica, 20% ether/hexane elution) to give the ester **58** as a clear colourless gum (1.22 g, 90%). $[\alpha]_D^{24}$ +20.0 (*c* 1.0 in $CHCl_3$). (Found: C 74.2, H 7.1, N 2.6. $C_{31}H_{35}NO_5$ requires C 74.2, H 7.0, N 2.8%.) ν_{max} (NaCl)/cm^{-1} 3089, 3066, 3032, 3003, 3000–2800, 1740, 1702, 1479, 1452, 1400, 1369, 1313, 1249, 1140, 1109, 1088, 1067, 1054, 1030, 987, 757, 740, 697. δ_H (rotamers) 7.78–7.24 (13H, m, ArH), 4.95–4.22 (7H, m, $CHCH_2$, $ArCH_2$, CH_3CH, NCHCO), 3.14–3.05 (3H, m, NCH_3), 1.46 (9H, s, Bu^t), 1.22 and 1.13 (3H, 2d, *J* 6.4 and 6.3, CH_3CHO). δ_C (rotamers) 168.9, 168.7, 157.6, 156.4, 144.1, 143.9, 141.3, 138.4, 138.2, 128.2, 127.9, 127.6, 127.3, 127.2, 127.1, 127.0, 125.0, 124.9, 119.9, 81.8, 81.6, 75.5, 74.5, 71.6, 71.5, 67.7, 67.5, 63.6, 63.4, 47.2, 33.0, 32.7, 28.0, 16.0.

*(2S,3*R*)*-tert-*Butyl 2-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy) carbonylamino)-*N*,3-dimethylbutanamido)-3-(benzyloxy)butanoate **60***

The ester **58** (520 mg, 1.0 mmol) was dissolved in 33% Et_2NH/DMF solution (6 mL) for 1 h and then the mixture was concentrated at reduced pressure to give crude amine **44**, which was used directly. The amine **44** was taken up in CH_2Cl_2 (6 mL) and the acid **59** (457 mg, 1.4 mmol) was added, followed by PyBroP (630 mg, 1.4 mmol). The solution was stirred and cooled to 0°C with an ice bath, and then Pr^i_2NEt (540 μL, 3.1 mmol) was added and the reaction mixture was stirred overnight at 0°C. The reaction mixture was then diluted with Et_2O (30 mL) and the ethereal solution was washed successively with water (15 mL), 5% citric acid solution (15 mL), brine (15 mL), 5% $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by column chromatography (silica, 20% EtOAc/hexane) to give the dipeptide **60** (510 mg, 82%) as a clear colourless gum. $[\alpha]_D^{22}$ +16.0 (*c* 1.0 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3302, 3089, 3066, 3038, 3000–2800, 1727, 1643, 1525, 1506, 1499, 1479, 1451, 1369, 1299, 1247, 1160, 1110, 1080, 1030, 758, 738, 698. δ_H 7.75–7.24 (13H, m, ArH), 5.81 (1H, d, *J* 9.2, NH), 5.43 (1H, q, *J* 4.2, CH_3CHO), 4.72–4.20 (7H, m, $CHCH_2$, $ArCH_2$, NCHCO × 2), 3.30 (3H, s NCH_3), 2.20–2.09 (1H, m, CH_3CHCH_3), 1.44–1.39 (9H, m, Bu^t), 1.17, 1.08 and 1.01 (9H, 3d, *J* 6.2, 6.6 and 6.6, CH_3CHCH_3 and CH_3CHO). δ_C 173.6, 168.2, 156.2, 143.7, 143.6, 141.0, 138.1, 128.0, 127.4, 127.2, 127.0, 126.8, 124.9, 124.1, 119.7, 81.5, 75.0, 71.4, 66.7, 60.9, 55.4, 46.9, 33.9, 31.0, 27.8, 27.6, 19.2, 17.4, 15.7.

(5S,8S,11S,14S)-tert-*Butyl 8-((*R*)-1-(Benzyloxy)ethyl)-14-*sec*-butyl-1-(9*H*-fluoren-9-yl)-5,11-diisopropyl-7,10,13-trimethyl-3,6,9,12-tetraoxo-2-oxa-4,7,10,13-tetraazapentadecan-15-oate **8** (Convergent Approach)*

The dipeptide **60** (130 mg, 0.22 mmol) was dissolved in 50% TFA/CH_2Cl_2 (2 mL) for ~1 h. The solution was then concentrated at reduced pressure and the residue was taken up in toluene (10 mL) and reconcentrated to leave the acid **61**, which was left under high vacuum overnight. Meanwhile, the dipeptide **54** (100 mg, 0.22 mmol) was dissolved in MeOH (3 mL) and 10% Pd-on-C catalyst (20 mg) was added. The reaction mixture was stirred in an H_2 atmosphere and the reaction was monitored by TLC (silica, 20% EtOAc/hexane, ~1 h to completion). The mixture was then filtered through Celite with MeOH (5 mL) as eluent and the combined filtrates were concentrated to dryness under vacuum. The residual amine **49** was combined with the acid **61** in CH_2Cl_2 (5 mL), to which was added PyBroP (111 mg, 0.24 mmol) and the mixture was cooled to 0°C with an ice bath. To the cooled solution was added Pr^i_2NEt (113 μL, 0.65 mmol) and stirring was continued at 0°C for 30 min, when the ice bath was removed, and the reaction mixture was left overnight. The solution was diluted with EtOAc (50 mL) and it was then washed successively with dilute HCl (10 mL), water (10 mL), 5% $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum to give a residue, which was filtered through a plug of silica with 30% EtOAc/hexane as eluent to afford the crude tetramer **8**. Further elution with 60% EtOAc/hexane gave the tetramer **62**. The tetramer **8** was further purified by column chromatography (silica, 20% Et_2O/hexane, then 40% Et_2O/hexane) to give the tetramer **8** (82 mg, 45%) identical in all respects with the material described below. The crude tetramer **62** was also purified by column chromatography (silica, 70% Et_2O/hexane) and was isolated as a clear colourless gum (224 mg, 15%). *m*/*z* (ESMS) 771 ([M + K], 10%), 755 ([M + Na], 100), 731 ([M + H], 28), 532 (55), 500 (10), 419 (26), 329 (8). δ_H (rotamers) 7.75–7.24 (8H, m, ArH), 5.40–4.18 (8H, m, NH, $CHCH_2$, C=$CHCH_3$, NCHCO × 3), 3.40–2.96 (9H, m, NCH_3 × 3), 2.39–0.77 (26H, m, $CH(CH_3)CH_2CH_3$, C=$CHCH_3$, CH_3CHCH_3 × 2).

(5S,8S,11S)-tert-*Butyl 5-((*R*)-1-(Benzyloxy)ethyl)-11-sec-butyl-1-(9*H*-fluoren-9-yl)-8-isopropyl-4,7,10-trimethyl-3,6,9-trioxo-2-oxa-4,7,10-triazadodecan-12-oate **65***

The amine **49** (0.8 mmol) was taken up in CH_2Cl_2 (4 mL) and the acid **57** (429 mg, 1.0 mmol) was added, followed by PyBroP (450 mg, 1.0 mmol). The stirred reaction mixture was cooled to 0°C with an ice bath and Pr^i_2NEt (420 μL, 2.4 mmol) was added. The mixture was stirred at 0°C for 20 min and then the ice bath was removed, and stirring was continued overnight. The solution was diluted with Et_2O (20 mL) and it was then washed successively with brine (10 mL), 5% citric acid solution (10 mL), brine (10 mL), 5% $NaHCO_3$ solution (10 mL), and brine (10 mL). The ethereal layer was then dried ($MgSO_4$), filtered, and concentrated at reduced pressure to leave a pale yellow residue that was purified by column chromatography (silica, 40% Et_2O/hexane) to afford the tripeptide **65** (340 mg, 57%) as a clear colourless gum. $[\alpha]_D^{28}$ −150.4 (*c* 1.0 in $CHCl_3$). (Found [M + H] 742.4439. $C_{44}H_{60}N_3O_7$ requires [M + H] 742.4431.) ν_{max} (NaCl)/cm^{-1} 3088, 3066, 3030, 3000–2800, 1731, 1705, 1643, 1472, 1454, 1394, 1369, 1300, 1258, 1163, 1094, 1088, 757, 740, 697, 666. δ_H (rotamers) 7.76–7.13 (13H, m, ArH), 5.14–3.81 (9H, m, $CHCH_2$, CH_3CHO, $ArCH_2$, NCHCO × 3), 3.03–2.11 and 2.00–1.91 (11H, 2 m, NCH_3 × 2, $CHCH_3$, CH_3CHCH_3), 1.45–1.41 (9H, m, Bu^t), 1.25–1.17 and 0.98–0.68 (17H, 2 m, CH_3CHO, $CH(CH_3)CH_2CH_3$, CH_3CHCH_3). δ_C (rotamers) 170.6, 170.5, 170.0, 169.9, 169.7, 169.2, 168.9, 168.7, 157.0, 156.6, 144.1, 144.0, 143.7, 141.4, 141.1, 138.24, 138.2, 128.2, 127.6, 127.5, 127.3, 125.0, 124.84, 124.8, 124.4, 119.9, 119.6, 119.5, 81.2, 71.1, 70.5, 70.4, 70.2, 67.5, 66.5, 60.9, 60.6, 60.4, 60.2, 59.9, 59.1, 57.8, 57.5, 47.3, 47.1, 33.4, 32.8, 32.7, 31.8, 31.1, 31.0, 30.4, 30.2, 29.8, 29.6, 29.5, 29.3, 28.0, 27.9, 27.4, 24.6, 24.5, 19.2, 19.0, 18.1, 17.6, 17.2, 16.4, 16.3, 16.2, 15.9, 14.0, 11.7, 10.6. Further elution gave the dehydro tripeptide **66** (35 mg, 7%). *m*/*z* (ESMS) 634 ([M + H], 100%).

(5S,8S,11S,14S)-tert-*Butyl 8-((R)-1-(Benzyloxy)ethyl)-14-*sec*-butyl-1-(9H-fluoren-9-yl)-5,11-diisopropyl-7,10,13-trimethyl-3,6,9,12-tetraoxo-2-oxa-4,7,10,13-tetraazapentadecan-15-oate **8** (Stepwise Approach)*

The tripeptide **65** (330 mg, 0.4 mmol) was dissolved in 33% Et_2NH/DMF solution (3 mL) for 1 h and then it was concentrated at reduced pressure. The residue was taken up in CH_2Cl_2 (3 mL) and the carbamate **59** (226 mg, 0.7 mmol) was added followed by PyBroP (311 mg, 0.7 mmol). The stirred solution was cooled to 0°C with an ice bath and Pr^i_2NEt (230 μL, 1.33 mmol) was added and the reaction mixture was stirred overnight. The solution was diluted with Et_2O (20 mL) and the ethereal solution was washed successively with water (10 mL), 5% citric acid solution (10 mL), brine (10 mL), 5% $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum to give a pale yellow residue, which was purified by column chromatography (silica, 20% Et_2O/hexane, then 40% Et_2O/hexane) to afford the tetramer **8** (350 mg, 94%) as a clear colourless gum. $[\alpha]_D^{22}$ −131.0 (*c* 1.0 in $CHCl_3$). (Found [M + H] 841.5110. $C_{49}H_{69}N_4O_8$ requires [M + H] 841.5115.) ν_{max} (NaCl)/cm^{-1} 3094, 3064, 3029, 3000–2800, 1724, 1679, 1639, 1524, 1455, 1394, 1346, 1332, 1257, 1216, 1154, 1088, 1030, 738. δ_H (rotamers) 7.75–7.17 (13H, m, ArH), 5.62–5.53 and 5.13–3.98 (11H, 2 m, NH, C*H*CH_2, CH_3CHO, $ArCH_2$, NCHCO × 4), 3.09–2.70 (9H, m, NCH_3 × 3), 2.42–0.75 (26H, m, $CH(CH_3)CH_2CH_3$, CH_3CHCH_3 × 2, CH_3CHO). δ_C (100 MHz, 1:4 $CDCl_3$/[D_6]acetone) 171.9, 169.8, 169.3, 169.1, 156.8, 144.8, 144.6, 141.8, 139.3, 128.8, 128.2, 128.0, 127.7, 127.6, 125.8, 120.5, 81.4, 71.9, 70.4, 67.1, 61.4, 58.1, 57.7, 56.7, 47.7, 33.2, 31.6, 31.4, 31.0, 28.2, 28.0, 25.1, 19.4, 18.2, 17.5, 16.6, 10.7. *m/z* (ESMS) 879 ([M + K], 13%), 863 ([M + Na], 100), 841 ([M + H], 45), 640 (65), 527 (100), 500 (5), 412 (10), 316 (8).

(3S,6S,9S,12S,15S,16S)-tert-*Butyl 3,9-bis((R)-1-(Benzyloxy)ethyl)-1-((S)-1-((S)-2-(benzyloxycarbonylamino)propanoyl)pyrrolidin-2-yl)-6,12-diisopropyl-2,8,11,14,16-pentamethyl-1,4,7,10,13-pentaoxo-2,5,8,11,14-pentaazaoctadecane-15-carboxylate **4***

The ester **7** (270 mg, 0.46 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and TFA (1 mL) was added and the reaction mixture was left to stand for ∼1 h. The solution was then concentrated at reduced pressure to give the free acid **68**. Meanwhile, the carbamate **8** (350 mg, 0.42 mmol) was dissolved in 33% Et_2NH/DMF (2.4 mL) and stirred at room temperature for 1 h. The solution was then evaporated under vacuum to give the free amine **67**. The free acid **68** and the amine **67** were combined in CH_2Cl_2 (3 mL) and the solution was cooled to 0°C with an ice bath. To the stirred solution was added PyBroP (260 mg, 0.56 mmol), followed by Pr^i_2NEt (242 μL, 1.4 mmol). The reaction mixture was stirred at 0°C for 30 min, the ice bath was removed and stirring was continued overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed successively with water (20 mL), 10% citric acid solution (20 mL), water (20 mL), 5% sodium bicarbonate solution (20 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica, 60% Et_2O/hexane, then 5% MeOH/Et_2O) to give the crude heptamer **4**. This material was further purified by column chromatography (silica, 60% Et_2O/hexane, then Et_2O) to give the heptamer **4** (365 mg, 78%) as a clear colourless gum. $[\alpha]_D^{18}$ −136.0 (*c* 0.5 in $CHCl_3$). (Found [M + H] 1126.6749. $C_{62}H_{92}N_7O_{12}$ requires [M + H] 1126.6804.) ν_{max} (NaCl)/cm^{-1} 3403–3346, 3087, 3064, 3032, 3000–2800, 1723, 1675, 1639, 1500, 1451, 1395, 1254, 1154, 1093, 742, 694, 660. δ_H (rotamers) 8.70 (1H, d, *J* 8.4, NH), 7.59–7.17 (15H, m, ArH), 6.12 (1H, d, *J* 8.0, NH), 5.58–5.55 (1H, m, NCHCO), 5.15–4.28 (13H, m, NCHCO × 5, $ArCH_2$ × 3, CH_3CHOBn × 2), 4.00–3.52 (2H, m, NCH_2), 3.07–2.71 (9H, m, NCH_3 × 3), 2.25–0.69 (45H, m, $NCH_2CH_2CH_2$, CH_3CHOBn × 2, CH_3CHCH_3 × 2, $CH(CH_3)CH_2CH_3$, Bu^t, $CHCH_3$). δ_C (100 MHz, 1:4 $CDCl_3$/[D_6]acetone) 174.0, 172.2, 171.3, 171.0, 170.5, 170.2, 168.5, 156.0, 139.6, 139.2, 128.9, 128.8, 128.74, 128.7, 128.3, 128.1, 81.4, 72.0, 71.7, 71.2, 70.2, 66.4, 65.6, 61.4, 58.0, 57.4, 56.3, 54.9, 48.9, 48.0, 33.2, 31.3, 31.2, 30.8, 28.0, 26.0, 25.1, 20.1, 19.3, 18.3, 17.7, 17.1, 16.6, 16.1, 10.7. *m/z* (ESMS) 1164 ([M + K], 10%), 1148 ([M + Na], 80), 1126 ([M + H], 100), 564 ([M + 2H]/2, 18), 536 (12), 496 (8), 463 (9).

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[13] Compounds **9**, **13**, and **55** were commercial products.
[14] Compound **10** was prepared from commercial *tert*-butyl carbamoyl proline by benzylation (K_2CO_3, BnBr, DMF) followed by treatment with HCl(g) in ether to give the hydrochloride **10**.
[15] Compound **12** was prepared from racemic pipecolinic acid by resolution via tartrate salts (D. S. Perlow, J. M. Erb, N. P. Gould, R. D. Tung, R. M. Freidinger, P. D. Williams, D. F. Veber, *J. Org. Chem.* **1992**, *57*, 4394). The resolved salt was then carbamoylated (E. Ponnusamy, U. Fotadar, A. Spisni, D. Fiat, *Synthesis* **1986**, 48; L. Kisfaludy, F. Korenczki, A. Katho, *Synthesis* **1982**, 163). The Boc-carbamate **32** was benzylated (K_2CO_3, BnBr, DMF) followed by treatment with HCl(g) in ether to give the hydrochloride **12**.
[16] Compound **15** was identical to material described by J. R. McDermott, N. L. Benoiton, *Can. J. Chem*. **1973**, *51*, 1915.
[17] Compound **17** was identical to material described by S. T. Cheung, N. L. Benoiton, *Can. J. Chem*. **1977**, *55*, 906.
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