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Tetrahedron
Tetrahedron 61 (2005) 7271–7276

A convenient and efficient synthesis of (*S*)-lysine and (*S*)-arginine homologues via olefin cross-metathesis

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Received 11 March 2005; revised 25 April 2005; accepted 5 May 2005

Available online 13 June 2005

Abstract—A convenient five step synthesis of (*S*)-homolysine, incorporating a key olefin cross-metathesis step in the chain extension methodology, has been developed, together with a six step related synthesis of a new homologue of arginine, (*S*)-bishomoarginine.

1. Introduction

Cationic amino acids, such as arginine and lysine, are important constituents of biologically active peptides,[1,2] and play a significant role in the binding of peptide substrates and their molecular targets. Homologues of these cationic amino acids are also valuable tools in the preparation of peptidic enzyme inhibitors and, in particular, for probing enzyme active site pockets in ligand based drug design.[3] For example, (*S*)-homolysine **1** (shown as the di-HCl salt), a nonproteinogenic amino acid, has been used as a lysine replacement residue in vasopressin[4] and in cyclic enkephalin analogues[5] as well as in the design of renin inhibitors.[6] Homoarginine is found in several proteins, including some within the brain,[7] and it has also been shown to inhibit arginine kinases.[8] In this context, extended homologues such as (*S*)-bishomoarginine **2** (shown as the di-HCl salt) would also be of considerable interest. However, no method for the preparation of **2** has been reported. Previous syntheses of its potential precursor homolysine **1**, produce either the racemic form[9] or an enantiomerically enriched form by excessive multistep methods from a chiral cyclic amino acid template,[10,11] or by constructing a chiral aldehyde template from serine and applying Wittig methodology to incorporate the desired sidechain.[12] Homolysine **1** was then finally produced by deprotection protocols in the synthesis. Facile access to both **1** and **2** in high enantiomeric purity would provide increased opportunities for the incorporation of these unnatural amino acids into drug discovery processes, including combinatorially-based and rational drug design programs.

2. Results and discussion

We report here an efficient synthesis of both (*S*)-homolysine **1** and (*S*)-bishomoarginine **2**. Our strategy (Scheme 1) incorporated the stereochemical element using commercially available (*S*)-allylglycine, thus avoiding the use of chiral templates. The reliable olefin cross-metathesis reaction[13] provided the necessary chain elongation and established guanidation methodology[14] was then applied for the required primary amine to guanidine functional group transformation. This strategy of amino acid chain elongation via olefin cross-metathesis could potentially be used to prepare a variety of unnatural amino acids and amino acid homologues rapidly, with the advantage of incorporating the C2-chiral stereocentre from the outset.

Therefore, the protected amine **5** was prepared[15] by treating the bromobutene **3** with di-*tert*-butyliminodicarboxylate and cesium carbonate affording the di-Boc-homoallylic amine **4**, which was then selectively deprotected with 2 equiv of TFA in dilute CH_2Cl_2 to give the *N*-Boc-allylamine **5** in an overall yield of 89% (Scheme 1).

Reaction of **5** with half an equivalent of the protected allylglycine derivative **6**[16] and Grubbs' ruthenium catalyst I in an analogous manner to reported cross-metatheses of allylglycines[17,18] afforded **7** in moderate yield (69%) as a

Keywords: (*S*)-Homolysine; (*S*)-Bishomoarginine; Metathesis; Cationic amino acid.
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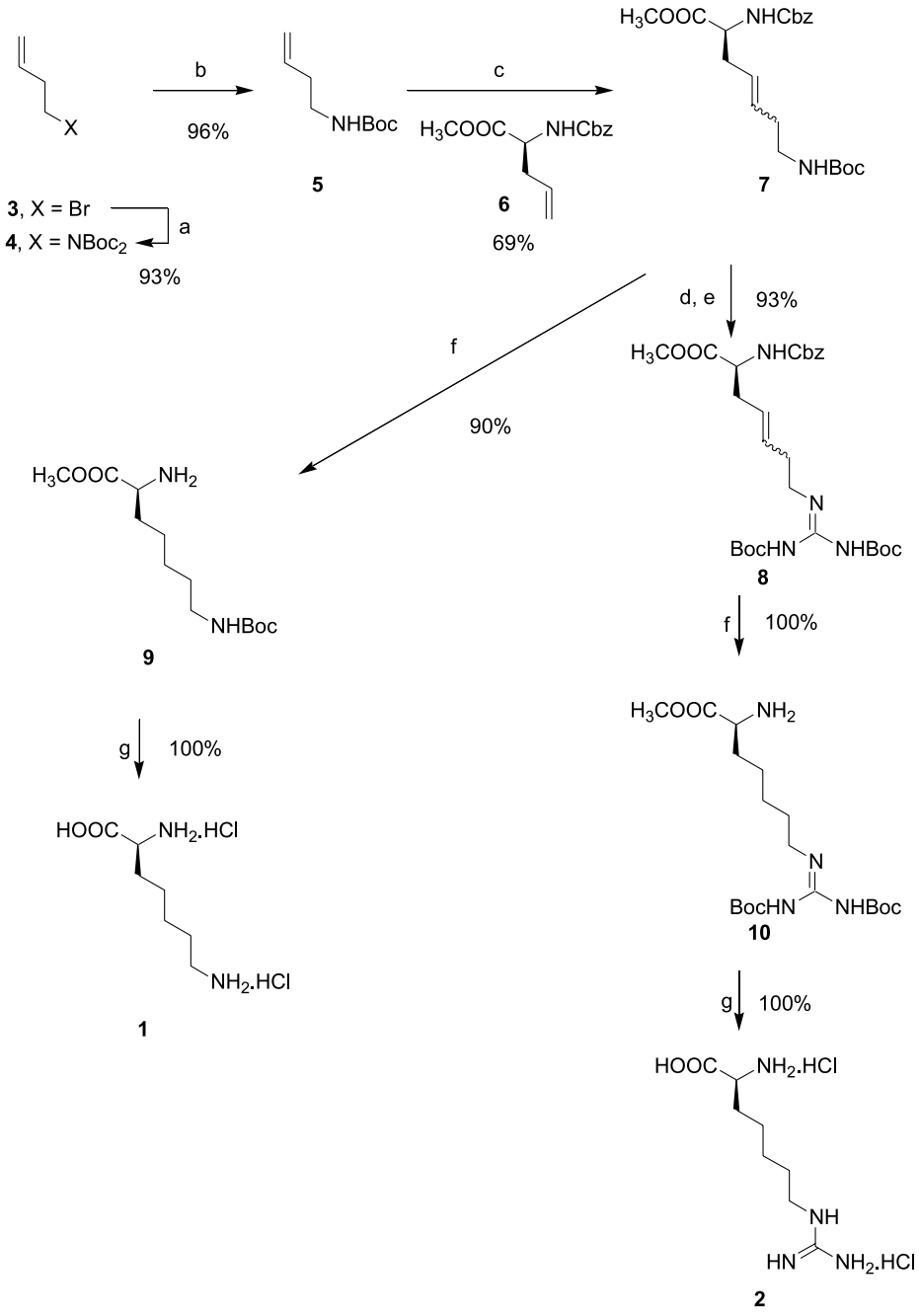
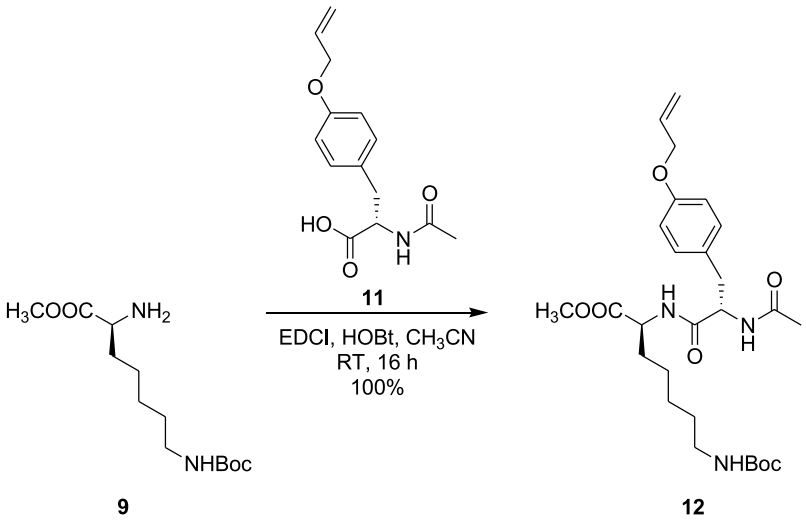
doi:10.1016/j.tet.2005.05.021



Scheme 1. Synthesis of (*S*)-lysine and (*S*)-arginine homologues. Reagents and conditions: (a) $NH(Boc)_2$, Cs_2CO_3, LiI, 2-butanone, reflux, 48 h, 93%. (b) TFA (2 equiv), DCM, 3 h, RT, and then NaOH, 96%. (c) $RuCl_2(PCy_3)_2(=CHPh)$ 10 mol%, DCM, 16 h, 69%. (d) TFA/DCM (1:1), RT, 3 h. (e) $TfNC(NHBoc)_2$, Et_3N, DCM, RT, 16 h, 93%. (f) Pd/C, H_2, THF, RT, 16 h, 90% (9), 100% (10). (g) 10M HCl, RT, 48 h, 100%.

mixture of *E*/*Z* stereoisomers. It is interesting to note that a homo-dimer of the protected allylglycine **6** was not observed, as sometimes reported for similar cross-metathesis conditions with allylglycine derivatives.[19] Both the *E* and *Z* isomers were evident in the ^1H NMR spectrum from the doubling up of most signals, however the exact ratio could not be determined due to overlapping signals. Preparation of bishomoarginine **2** required removal of the acid labile *N*-Boc protecting group of **7** by treatment with TFA. Subsequent exposure to *N*-triflyl-*N*,*N*-di-*tert*-butoxy-carbonyl-protected guanidine (Aldrich Chemical Co.) and triethylamine then yielded the protected arginine analogue **8** in 93% yield. The alkene group and benzylcarbamate protecting group of **7** and **8** were then removed in one step by hydrogenation over Pd/C to yield the free amino esters **9** and **10**, in 90% and quantitative yields, respectively. Exposure of the amino ester derivatives **9** and **10** to 10 M HCl for 48 h resulted in the free amino acids **1** and **2**, as their corresponding dihydrochloride salts, in quantitative yield.

The specific rotation observed for **1** ($[\alpha]_D^{22}$ +10.9 (*c* 0.1 in 2 N HCl)), was in general accordance with the reported literature values for the enantiomeric hydrochlorides ($[\alpha]_D^{23}$ −10.6 (*c* 1, 1 N HCl) (*R*)-isomer[12] and $[\alpha]_D^{23}$ +14.4 (*c* 0.5, in 1 N HCl) (*S*)-isomer[11]), while the previously unreported **2** had an $[\alpha]_D^{22}$ of −23.3 (*c* 0.03 in 2 M HCl). Further evidence



Scheme 2. Synthesis of the diastereomeric dipeptide **12**.

for the enantiomeric purity of **1** was forthcoming from the peptide coupling reaction of its immediate precursor, **9**, with the known[20] chiral protected tyrosine derivative *O*-allyl-*N*-acetyl-(*S*)-tyrosine **11**[21] (Scheme 2). The dipeptide derivative **12** from this coupling showed a diagnostic sharp singlet peak in the ^{1}H NMR spectrum at δ 3.69, integrating for three protons. Our experience with these types of dipeptides has shown us that this methyl ester peak is indicative in delineating the presence of diastereomers, and in the case of **12**, the dr was calculated to be $>96\%$.[22] Consistent with this NMR analysis, the chiral GC analysis (Chirasil L-Val) of the *N*-pentafluoropropionyl, isopropyl esters of **1** and **2** showed a single peak, whereas the same derivatives of racemic lysine and arginine showed two well resolved peaks (see Section 4 for details).

3. Conclusion

The presented methodology provides a rapid and convenient synthesis of (*S*)-homolysine **1** in five steps in 55% overall yield which is an improvement over the previously reported procedure (nine steps, 22% overall yield) of Beaulieu et al.,[12] and that of Dong[11] (five steps, 51% overall yield). Bishomoarginine **2** was prepared in six steps, in 57% overall yield. The flexibility of the methodology also allows, in principle, for the synthesis of the corresponding (*R*)-amino acids, via the commercially available (*R*)-allylglycine.

4. Experimental

4.1. General

All NMR spectra were determined in $CDCl_3$ solution at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) unless otherwise stated. All compounds were determined to be $>95\%$ pure by ^{1}H NMR spectroscopy. Enantiomeric purities of amino acids was made on their *N*-pentafluoropropionyl isopropyl esters by gas chromatography on a fused silica capillary column coated with the stationary phase Chirasil L-Val.[23] Derivatisation of the amino acids was performed according to published procedures.[23]

Derivatisation: One milligram of the amino acids were transferred to 3 mL Pierce reaction-vials using methanol and brought to dryness under a stream of dry nitrogen. Esterification of the amino acids was undertaken by adding 250 μL of 3.5 N isopropanol/HCl and heating for 1 h at 110 °C. The samples were then allowed to cool to ambient temperature and were subsequently dried under a stream of dry nitrogen. Samples were then acylated with 250 μL of CH_2Cl_2 and 50 μL of pentafluoropropionic acid anhydride (PFPA) and heated at 110 °C for 15 min. After cooling, samples were dried completely under a stream of nitrogen.

Gas chromatography. Analysis of the *N*-pentafluoropropionyl-amino acid isopropyl esters were undertaken using a Varian model 3700 gas chromatograph with a flame ionization detector and a coiled, fused silica capillary column (25 m length) coated with the stationary phase Chirasil-L-Val. The temperature program consisted of a single ramp set at the following conditions: (1) initial temperature 50 °C for 2 min; (2) ramp at 4 °C/min to a ceiling at 200 °C and (3) a plateau at 200 °C for 10 min. High purity helium was used as a carrier gas. An authentic sample of D,L-lysine showed two peaks at retention times of 32.19 and 32.33 min, while L-homolysine **1** showed a single peak at a retention time of 33.57 min. An authentic sample of D,L-arginine showed two peaks at retention times of 32.12 and 32.26 min, while L-bishomoarginine **2** showed a single peak at a retention time of 29.30 min.

4.1.1. Di-*tert*-butyl *N*-3-butenyliminodicarboxylate (4). To a solution of di-*tert*-butyl iminodicarboxylate (868 mg, 4 mmol), cesium carbonate (2.61 g, 8 mmol) and lithium iodide (28 mg, 0.2 mmol) in 2-butanone (20 mL) was added 4-bromo-1-butene **3** (812 mg, 6 mmol) and the mixture was heated at reflux for 48 h. The reaction was allowed to cool, quenched with brine (40 mL) and then extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to yield the title compound **4** (1.01 g, 3.7 mmol, 93%) as a light brown oil. ν_{max}(neat) 2974 (s), 1735 (s), 1697 (s), 1129 (s) cm^{-1}. ^{1}H NMR: δ 5.84–5.70 (m, 1H, H3); 5.10–4.99 (m, 2H, H4); 3.62 (dd,

J=6.0, 8.7 Hz, 2H, H1); 2.36–2.29 (m, 2H, H2); 1.51 (s, 18H, 6×CH_3). ^{13}C NMR: δ 152.5, (CO); 135.0, (C3); 116.7, (C4); 82.0, (2×$C(CH_3)_3$); 45.6, (C1); 33.5, (C2); 28.0, (6×CH_3). MS (ES, +ve) m/z 272 (40%) [MH^+], 294 (30%) [MNa^+], 310 (55%) [MK^+]. HRMS (ES) calcd for $C_{14}H_{26}NO_4$ 272.1862, found 272.1848.

4.1.2. *tert*-Butyl *N*-3-butenylcarbamate (5). To a solution of **4** (708 mg, 2.60 mmol) in CH_2Cl_2 (21 mL) was added TFA (593 mg, 5.20 mmol) and the mixture was allowed to stir at rt for 5 min before being quenched with 2 M NaOH (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to yield the title compound **5**[15] (429 mg, 2.50 mmol, 96%) as a light brown oil. ν_{max}(neat) 2979 (s), 1799 (m), 1732 (s), 1697 (s), 1392 (m), 1367 (s), 1130 (s) cm^{-1}. ^{1}H NMR: δ 5.83–5.69 (m, 1H, H3); 5.13–5.05 (m, 2H, H4); 4.59 (br s, 1H, NH); 3.20 (dd, J=6.3, 12.6 Hz, 2H, H1); 2.24 (dd, J=6.9, 12.6 Hz, 2H, H2); 1.44 (s, 9H, 3×CH_3). ^{13}C NMR: δ 155.9, (CO); 135.3, (C3); 117.0, (C4); 82.0, ($C(CH_3)_3$); 39.6, (C1); 34.2, (C2); 28.4, (3×CH_3). MS (ES, +ve) m/z 116 (100%).

4.1.3. Methyl (2*S*)-2-benzyloxycarboxamido-4-pentenoate (6).[16] To a solution of methyl (2*S*)-2-amino-4-pentenoate hydrochloride[24] (422 mg, 2.56 mmol) and $NaHCO_3$ (645 mg, 7.68 mmol) in THF/water (3 mL/3 mL) was added benzyl chloroformate (482 mg, 2.82 mmol) and the mixture was allowed to stir at rt for 16 h. The reaction was quenched with 3% HCl (20 mL) and extracted with CH_2Cl_2 (3×20 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated to give the title known compound **6** (676 mg, 2.56 mmol, 100%) as a colourless oil. Spectral data matched closely with that in the literature[16] $[\alpha]_D^{20}$ +9.1 (c 0.15 in $CHCl_3$). ^{1}H NMR: δ 7.38–7.22 (m, 5H, ArH); 5.75–5.58 (m, 1H, H4); 5.56 (d, J=7.8 Hz, 1H, NH); 5.18–5.08 (m, 4H, $ArCH_2$ and C5); 4.47 (dd, J=6.3, 13.2 Hz, 1H, H2); 3.72 (s, 3H, OCH_3); 2.54 (AB_q, J=6.3, 13.8 Hz, 2H, H3).

4.1.4. Methyl (2*S*,4*E*/*Z*)-2-(benzyloxycarboxamido)-7-(*tert*-butoxycarboxamido)-4-heptenoate (7). To a solution of **5** (220 mg, 1.29 mmol) in CH_2Cl_2 (13 mL) was added, **6** (169 mg, 0.64 mmol) and $RuCl_2(PCy_3)_2$(=CHPh) (53 mg, 0.064 mmol). The mixture was heated at reflux for 16 h before the solvent was removed by rotary evaporation and the crude product purified by flash column chromatography (silica gel, 6:1, hexane/EtOAc) to yield the title compound **7** (180 mg, 0.44 mmol, 69%) as a brown oil. $[\alpha]_D^{24}$ −34.6 (c 0.3 in EtOH). ν_{max}(neat) 2345, 2225, 1684, 1630 cm^{-1}. ^{1}H NMR: δ 7.36–7.28 (m, 5H, ArH); 5.52–5.34 (m, 3H, H4, H5, NH); 5.11/5.10 (s, 2H, H4′); 4.61 (br s, 1H, NH); 4.49–3.90 (m, 1H, H2); 3.75/3.72 (s, 3H, OCH_3); 3.18–3.04 (m, 2H, H7); 2.62–2.40 (m, 2H, H3); 2.26–2.12 (m, 2H, H6); 1.43 (s, 9H, CH_3). ^{13}C NMR: δ 172.1/172.0, (C1); 155.8, (NCO_2′); 155.6, (NCO_2); 131.8, (C4); 130.4, (C5); 129.3, (ArC1′); 128.6/128.4, (ArC2′ and ArC6′); 128.0/126.8, (ArC3′ and ArC5′); 126.0/125.3, (ArC4′); 79.0, ($C(CH_3)_3$); 66.9, ($ArCH_2$); 53.6/53.4, (OCH_3); 52.3/52.2, (C2); 39.9/39.7, (C7); 35.5/35.2, (C3); 33.0/32.9, (C6); 28.3/28.1, (CH_3). MS (ES, +ve) m/z 297 (100%), 407 (20%) [MH^+], 429 (90%) [MNa^+]. HRMS (ES) calcd for $C_{21}H_{31}N_2O_6$ 407.2182, found 407.2171.

4.1.5. Methyl (2*S*,4*E*/*Z*)-2-(benzyloxycarboxamido)-7-(*N*,*N*′-di-*tert*-butoxycarbonyl-guanidino)-4-heptenoate (8). To a solution of **7** (52 mg, 0.128 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) and the resulting solution was allowed to stir at rt for 3 h before being evaporated to dryness and resuspended in CH_2Cl_2 (2 mL) and triethylamine (0.2 mL). To this solution was added *N*,*N*′-Bis(tert-butoxycarbonyl)*N*″-triflylguanidine methyl propanamide (75 mg, 0.192 mmol) and the resulting mixture was allowed to stir overnight under a nitrogen atmosphere. The mixture was concentrated and the crude product purified by flash column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to yield the title compound **8** (64 mg, 0.12 mmol, 93%) as a light brown/red oil. $[\alpha]_D^{23}$ +13.2 (c 0.05 in EtOH). ν_{max}(neat) 2925, 2851, 2352, 2336, 1866, 1644, 1403 cm^{-1}. ^{1}H NMR: δ 8.28 (br s, 1H, NH); 7.39–7.30 (m, 5H, ArH); 5.68–5.35 (m, 3H, H4, H5, NH); 5.09 (s, 2H, $ArCH_2$); 4.49–4.39 (m, 1H, H2); 3.74/3.72 (s, 3H, OCH_3); 3.49–3.35 (m, 2H, H7); 2.58–2.46 (m, 2H, H3); 1.89–1.82 (m, 2H, H6); 1.48/1.47 (s, 9H, CH_3). ^{13}C NMR: δ 171.59, (C1); 163.4, (CN_3); 156.0, (NCO'); 155.7, (NCO); 131.7, (C4); 130.1, (C5); 128.5, (ArC1′); 128.1, (ArC2′ and ArC6′); 126.6, (ArC3′ and ArC5′); 126.0, (ArC4′); 83.3, ($C(CH_3)_3$); 79.4, ($C'(CH_3)_3$); 67.0/66.9, ($ArCH_2$); 53.4, (OCH_3); 52.4/52.3, (C2); 40.3/40.1, (C7); 35.3/34.5, (C3); 31.8/30.1, (C6); 28.2/28.0, (C(CH_3)$_3$); 26.9/26.8, (C($C'H_3$)$_3$). MS (ES, +ve) m/z 549 (100%) [MH^+]. HRMS (ES) calcd for $C_{27}H_{41}N_4O_8$ 549.2924, found 549.2947.

4.1.6. Methyl (2*S*)-2-amino-7-(*tert*-butoxycarboxamido)-heptanoate (9). To a solution of **7** (25 mg, 0.061 mmol) in THF (4 mL) was added, palladium (10%) on activated carbon (13 mg, 0.006 mmol). The reaction vessel was evacuated, flushed with H_2 and allowed to stir at rt for 16 h. The resulting crude product was filtered through Celite and the solvent evaporated to yield the title compound **9** (15 mg, 0.055 mmol, 90%) as a colourless oil. $[\alpha]_D^{24}$ +9.6 (c 0.1, in EtOH). ν_{max}(neat) 2923, 2310, 2290, 1664, 1526 cm^{-1}. ^{1}H NMR: δ 4.55 (br s, 1H, NH); 3.72 (s, 3H, OCH_3); 3.44 (t, J=6.0 Hz, 1H, H2); 3.10 (dd, J=6.0, 12.6 Hz, 2H, H7); 1.80–1.68 (m, 4H, H3, H4); 1.44 (s, 9H, CH_3); 1.39–1.23 (m, 4H, H5, H6). ^{13}C NMR: δ 176.5, (C1); 155.9, (NCO); 79.9, ($C(CH_3)_3$); 54.2, (OCH_3); 51.8, (C2); 40.3, (C7); 34.7, (C3); 29.9, (C6); 28.3, (CH_3); 26.4, (C4); 25.3, (C5). MS (ES, +ve) m/z 219 (100%); 275 (90%) [MH^+]. HRMS (ES) Calcd for $C_{13}H_{27}N_2O_4$ 275.1971, found 275.1967.

4.1.7. Methyl (2*S*)-2-amino-7-(*N*,*N*-di-*tert*-butoxycarbonyl-guanidino)-heptanoate (10). To a solution of **8** (50 mg, 0.091 mmol) in THF (10 mL) was added, palladium (10%) on activated carbon (19 mg, 0.009 mmol). The reaction vessel was evacuated, flushed with H_2 and the mixture allowed to stir at rt for 16 h. The resulting crude mixture was filtered through Celite and the solvent was evaporated to yield the title compound **10** (28 mg, 0.091 mmol, 100%) as a red oil. $[\alpha]_D^{28}$ −15.3 (c 0.25, in EtOH). ν_{max}(neat) 2934, 2360, 2338, 1746, 1722, 1633, 1371, 1155 cm^{-1}. ^{1}H NMR: δ 8.34 (br s, 1H, NH); 3.79–3.76 (m, 1H, H2); 3.74 (s, 3H, OCH_3); 3.40 (t, J=6.6 Hz, 2H, H7); 1.92–1.82 (m, 4H, H3 and H4); 1.50 (s, 18H, 6×CH_3); 1.42–1.35 (m, 4H, H5 and H6). ^{13}C NMR: δ 171.6, (C1); 163.4, (CN_3); 156.1/153.3, (NCO); 83.1/79.3,

($C(CH_3)_3$); 54.2, (OCH_3); 52.1, (C2); 40.7, (C7); 35.3/34.5, (C3); 28.6/28.2, (CH_3); 28.0, (CH_3) 26.8/26.6, (C4); 26.1/26.0, (C5). MS (ES, +ve) *m/z* 417 (100%) [MH^+]. HRMS (ES) calcd for $C_{19}H_{37}N_4O_6$ 417.2713, found 417.2710.

4.1.8. (2*S*)-2,7-Diaminoheptanoic acid dihydrochloride (1). A solution of **9** (16 mg, 0.058 mmol) in 10 M HCl (3 mL) was allowed to stir at rt for 48 h before evaporation of the solvent and drying of the residue (P_2O_5) to yield the title compound **1** (14 mg, 0.058 mmol, 100%) as a hygroscopic white solid. $[\alpha]_D^{22}$ +10.9 (*c* 0.1 in 2 M HCl) (lit.[11] $[\alpha]_D^{23}$ +14.4, and lit.[12] $[\alpha]_D^{23}$ −10.6 for the opposite (*R*)-enantiomer). ν_{max}(neat) 2927, 2870, 2851, 1734, 1559, 1541, 1457, 1103 cm^{-1}. ^1H NMR (D_2O): δ 3.90 (t, J=6.3 Hz, 1H, H2); 2.83 (t, J=7.5 Hz, 2H, H7); 1.80–1.70 (m, 2H, H3); 1.58–1.48 (m, 2H, H5); 1.32–1.22 (m, 4H, H6 and H4). ^{13}C NMR (D_2O, 125 MHz): δ 172.5, (C1); 53.1, (C2); 39.4, (C7); 29.6, (C3); 26.5, (C6); 25.3, (C4); 23.8, (C5). MS (ES, +ve) *m/z* 161 (100%) [MH^+]. HRMS (ES) calcd for $C_7H_{17}N_2O_2$ 161.1290, found 161.1294.

4.1.9. (2*S*)-2-Amino-7-guanidinoheptanoic acid dihydrochloride (2). A solution of **10** (34 mg, 0.082 mmol) in 10 M HCl (5 mL) was allowed to stir at rt for 48 h before evaporation of the solvent and drying of the residue (P_2O_5) to yield the title compound **2** (23 mg, 0.082 mmol, 100%) as a hygroscopic white solid. $[\alpha]_D^{20}$ −23.3 (*c* 0.03 in HCl). ν_{max}(neat) 2927, 2852, 1752, 1617, 1552, 1140 cm^{-1}. ^1H NMR (D_2O): δ 3.77 (t, J=6.3 Hz, 1H, H2); 3.14 (t, J=6.6 Hz, 2H, H7); 1.90–1.78 (m, 2H, H3); 1.64–1.52 (m, 2H, H5); 1.46–1.30 (m, 4H, H6 and H4). ^{13}C NMR (D_2O): δ 172.6, (C1); 53.1, (C2); 41.1, (C7); 29.8, (C3); 27.6, (C6); 25.5, (C4); 23.9, (C5). MS (ES, +ve) *m/z* 203 (100%) [MH^+]. HRMS (ES) calcd for $C_8H_{19}N_4O_2$ 203.1508, found 203.1500.

4.1.10. Methyl (2*S*,5*S*)-5-(4-allyloxybenzyl)-3,6-diaza-2-(5-[*tert*-butoxycarboxamido]pentyl)-4,7-dioxooctanoate (12). To a solution of *O*-allyl-*N*-acetyl-(*S*)-tyrosine **11**[21] (53 mg, 0.20 mmol) and **9** (65 mg, 0.24 mmol) in CH_3CN (10 mL), was added EDCI (38 mg, 0.20 mmol) and HOBt (30 mg, 0.22 mmol) and the resulting mixture was allowed to stir at rt for 16 h. The reaction was diluted with H_2O (20 mL) and the solid precipitate collected by vacuum filtration, then dissolved in EtOAc (30 mL) and the EtOAc solution was washed with water (3×30 mL). The crude product was purified by column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to afford **12** (103 mg, 0.20 mmol, 100%) as an off-white solid. Mp 96–103 °C. ν_{max}(neat) 2943, 2942, 1832, 1618, 1604, 1565, 1411, 1132 cm^{-1}. ^1H NMR: δ 7.11 (d, J=8.7 Hz, 2H, ArH2″ and ArH6″); 6.82 (d, J=8.7 Hz, 2H, ArH3″ and ArH5″); 6.50 (d, J=7.8 Hz, 1H, NH); 6.03 (m, 1H, H2‴); 5.39 (dd, J=1.8, 17.4 Hz, 1H, $H3_a$‴); 5.26 (dd, J=1.8, 9.3 Hz, 1H, $H3_b$‴); 4.66 (m, 2H, H2 and H5); 4.48 (m, 2H, H1‴); 3.69 (s, 3H, OCH_3); 2.98 (m, 4H, H5′ and $ArCH_2$); 1.96 (s, 3H, H8); 1.75 (m, 2H, H1′); 1.64 (m, 2H, H3′); 1.43 (s, 9H, $C(CH_3)_3$); 1.26 (m, 4H, H2′ and H4′). ^{13}C NMR: δ 172.2, C4; 171.2, C1; 170.2, C7; 157.5, NCO_2; 156.2, ArC4″; 133.2, C2″; 130.2, ArCH2″ and ArCH6; 128.6, ArC1″; 117.5, C3‴; 114.7, ArCH3″ and ArCH5″; 79.0, $C(CH_3)_3$; 68.7, C1‴; 54.5, C2; 54.4, C5; 52.2, C5′; 52.1, OCH_3; 40.0, C4′; 37.2, $ArCH_2$; 31.8, C1′; 28.3, $C(CH_3)_3$; 26.2, C8; 25.9, C3′; 22.9, C2′. Mass Spectrum (ES, +ve) *m/z* 520 (100%) [MH^+]. HRMS calcd for $C_{27}H_{41}N_3O_7$ 542.2842, found 542.2855.

Acknowledgements

We thank Avexa Limited and the University of Wollongong for support, and Dr. Susan Cox and David Rhodes for their support in the initial development of this project and Prof. Colin Murray-Wallace and Dr. John Korth for assistance with the chiral GC study.

References and notes

1. Greenstein, J. P.; Winitz, M. In *Chemistry of the Amino Acids*, *Vol. 3*; Wiley: New York, 1961; pp 2463–2498.
2. Vizioli, J.; Salzet, M. *Trends Pharmacol. Sci.* **2002**, *23*, 494–496.
3. Beeson, C.; Dix, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 10275–10281.
4. Bodanszky, M.; Lindeberg, G. *J. Med. Chem.* **1971**, *14*, 1197–1199.
5. Schiller, P. W.; Nguyen, T. M. D.; Maziak, L. A.; Lemieux, C.; Wilkes, B. C. In Peptides (*Proceedings of the 19th European Peptide Symposium*); Theodoropoulos, D., Ed.; W. de Gruyter: Berlin, 1986; Vol. 1987, p 389.
6. Doherty, A. M.; Kaltenbronn, J. S.; Hudspeth, J. P.; Repine, J. T.; Roark, W. H.; Sircar, I.; Tinney, F. J.; Connolly, C. J.; Hodges, J. C. *J. Med. Chem.* **1991**, *34*, 1258–1271.
7. Hiramatsu, M. *Mol. Cell. Biochem.* **2003**, *244*, 57–62.
8. Pereira, C. A.; Alonso, G. D.; Ivaldi, S.; Bouvier, L. A.; Torres, H. N.; Flawia, M. M. *J. Eukaryotic Microbiol.* **2003**, *50*, 132–134.
9. Payne, L. S.; Boger, J. *Synth. Commun.* **1985**, *15*, 1277–1290.
10. Kennedy, K. J.; Lundquist, J. T. I. V.; Simandan, T. L.; Beeson, C. C.; Dix, T. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1937–1940.
11. Dong, Z. *Tetrahedron Lett.* **1992**, *33*, 7725–7726.
12. Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019–2022.
13. Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7717–7140.
14. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804–3805.
15. van Benthem, R. A. T. M.; Michels, J. J.; Hiemstra, H.; Speckamp, W. N. *Synlett* **1994**, 368–370.
16. Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6513–6520.
17. Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2499.
18. Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949–1950.
19. Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93–105.
20. Tous, G.; Bush, A.; Tous, A.; Jordan, F. *J. Med. Chem.* **1990**, *33*, 1620–1634.
21. The acid **11** was prepared by base hydrolysis of the ethyl ester derivative.[20] Subsequent reesterification using $SOCl_2$–ethanol yielded the ester, which had a specific rotation close to that of the starting ester of $[\alpha]_D^{22}$ +20.8, hence confirming the enantiomeric integrity of **11**.
22. The ^1H NMR of **12** contains small peaks adjacent to the

methyl ester signal which are assigned as either amide rotamers or a small quantity of a diastereomer. The dr for **12** of $>96\%$ is calculated from the NMR taking into account these peaks.

23. For conditions see: Murray-Wallace, C. V. *The Artefact* **1993**, 19–26.
24. McGrady, K. A. W.; Overberger, C. G. *Polym. J.* **1987**, *19*, 539–555.