Pergamon

Tetrahedron Vol. 51, No. 16, pp. 4733-4762, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00157-3

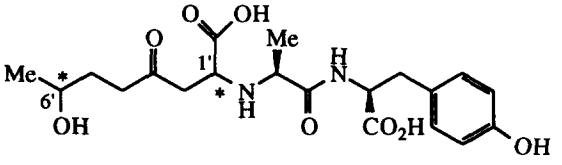
Carbon Based Nucleophilic Ring Opening of Activated Monocyclic β-lactams; Synthesis and Stereochemical Assignment of the ACE Inhibitor WF-10129

Jack E. Baldwin, Robert M. Adlington, Andrew T. Russell and Marie L. Smith

The Dyson Perrins Laboratory and the Oxford Centre for Molecular Sciences, South Parks Rd., Oxford, OX1 3QY, U.K.

Abstract: The preparation of γ-keto α-amino acids *via* carbon based nucleophilic ring opening of activated monocyclic β-lactams was examined and applied to the synthesis and stereochemical assignment of the dipeptide angiotensin converting enzyme (ACE) inhibitor, WF-10129.

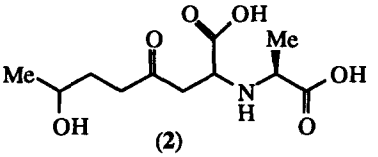
The angiotensin converting enzyme (ACE) inhibitor WF-10129 (**1**), was isolated by Ando *et al.* from a culture of the fungus *Doratomyces putredinis*.[1] Its IC_{50} for ACE was reported as 1.4 x 10^{-8}M, a potency comparable with that of the synthetic ACE inhibitor captopril (IC_{50}; 1.7 x 10^{-8}M[1]) making (**1**) amongst the most potent inhibitors of this enzyme isolated from a microbial source.



(**1**)

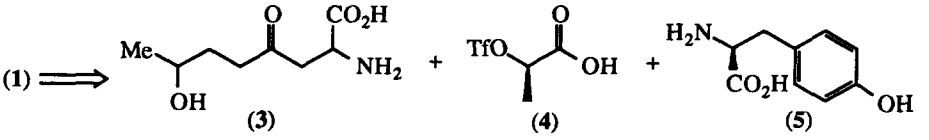
Possible diastereoisomers:
(**1a**) S, S, S, S; (**1b**) 6'R, 1'S, S, S
(**1c**) R, R, S, S; (**1d**) 6'S, 1'R, S, S

The structure of (**1**) was elucidated by spectroscopy and chemical degradation and was proposed to be a dipeptide composed of (L)-tyrosine and the novel amino acid (**2**), itself encompassing an (L)-alanine residue. It is of interest to note that (**1**) is therefore a substituted *N*-carboxyalkyl dipeptide, a structural feature which is shared with the synthetic ACE inhibitors enalapril[2] and lisinopril.[3] The relative and absolute stereochemistry at two centres (*), however, was not determined and to unambiguously prove the structure we required a synthetic strategy which would allow us to prepare any of the possible stereoisomers of (**2**).



(2)

Retrosynthetic analysis of (1) gives the novel amino acid (3), triflate (4) and (L)-tyrosine (5), Scheme 1.

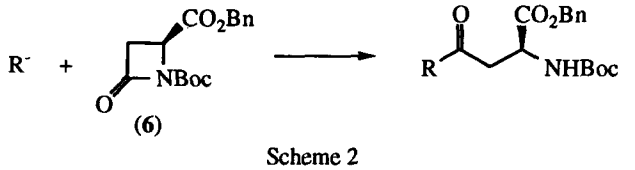


Scheme 1

As variously protected versions of both (4) and (5) are known the problem reduces to the stereochemically controlled preparation of the unusual γ-keto-α-amino acid (3).

Synthesis of γ-keto-α-amino acids via carbon based nucleophilic ring opening of activated monocyclic β-lactams

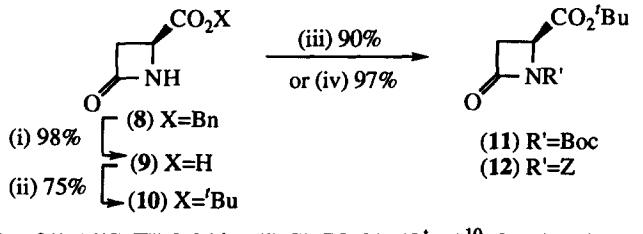
The cornerstone of our strategy was nucleophilic ring opening of activated monocyclic β-lactams such as (6) (prepared from β-lactam (8) which is available in 3 steps from aspartic acid[4-8]), Scheme 2. We began by examining various stabilised and unstabilised carbon nucleophiles in this rôle.



(6)

Scheme 2

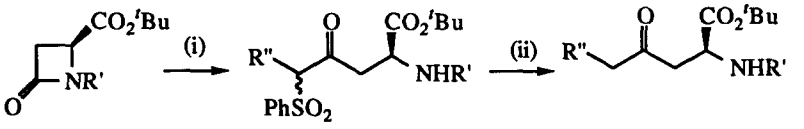
Firstly, we considered sulphone stabilised carbanions, however, early attempts to ring open (6) with a lithiated form of methylphenylsulphone (7),[9] indicated low selectivity for the β-lactam carbonyl over benzyl ester attack. *t*-Butyl esters such as (11) and (12) were therefore prepared, Scheme 3, and found to exhibit the desired chemospecificity.



(i) H_2, 10% Pd/C, THF, 24 h.; (ii) $Cl_3CC{=}NH(O^tBu)$[10] (2 eq.), $BF_3.Et_2O$ (cat.), THF/cyclohexane, R.T., 30 min.; (iii) Boc_2O[11] (2 eq.), DMAP (0.1 eq), MeCN, R.T., 24 h. or (iv) Z_2O[12] (2 eq.), DMAP (0.1eq.), MeCN, R.T., 15 min.

Scheme 3

Thus attack of the lithiated forms of methylphenyl sulphone (7)[9] and butylphenylsulphone[13] (13) occurred smoothly to give the β-ketosulphones (14). In view of the acidity of these products, it proved necessary to use 2 equivalents of sulphone to secure a high yield.¶ The sulphone group could then be reductively removed in high yield by treatment with Al amalgam,[14] Scheme 4 and Table 1.



(11) or (12) (14) (15)

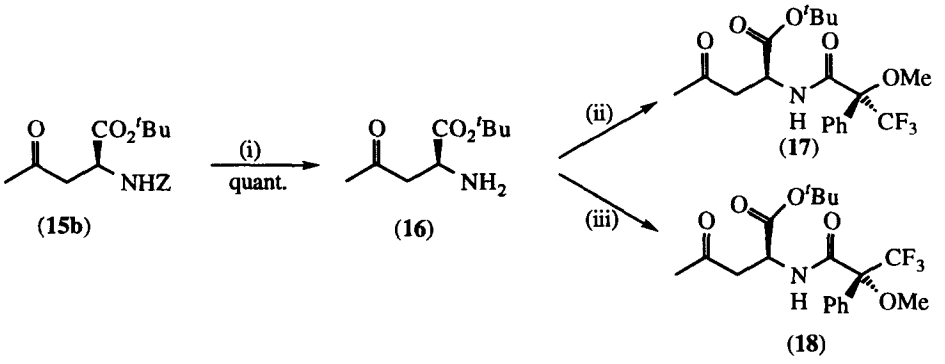
(i) $PhSO_2CH_2R"$ (2 eq.), ^nBuLi (2 eq.), THF, -78°C, 20 min.;
(ii) Al/Hg, deoxygenated THF:H_2O 9:1.

Scheme 4

Entry	Sulphone	R'	R"	% yield (14)	% yield (15)
a	(7)	Boc	H	81	90
b	(7)	Z	H	84	92
c	(13)	Boc	$^nC_3H_7$	80	90

Table 1

Hydrogenolysis of the benzyloxycarbonyl group in (15b) with 5% $Pd/CaCO_3$ as catalyst† was followed by coupling in turn to both enantiomers of Mosher's acid chloride,[15] Scheme 5. Examination of the ^1H and ^{19}F n.m.r. of the resulting diastereoisomers (17) and (18) revealed that no detectable racemisation had occurred during the sulphone addition.

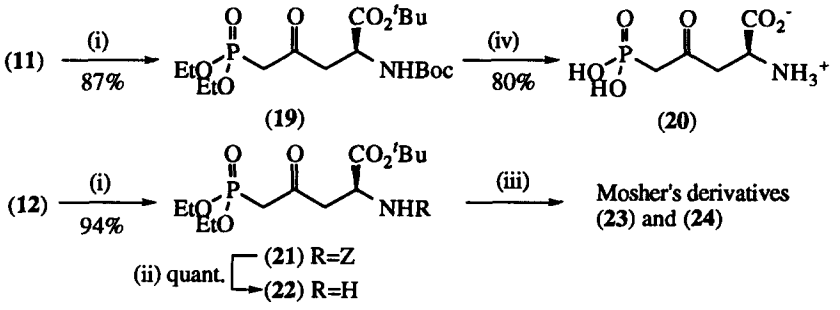


(i) H_2, 5% $Pd/CaCO_3$, EtOAc, R.T., 30min.; (ii) (R)-Mosher's acid chloride (1.2 eq.), DMAP (1.2 eq.), CH_2Cl_2, R.T., 24 h.; (iii) (S)-Mosher's acid chloride (1.2 eq.), DMAP (1.2 eq.), CH_2Cl_2, R.T., 24 h.

Scheme 5

¶ The unused equivalent could be recovered by column chromatography.
† Hydrogenolysis using 10% Pd/C led to decomposition.

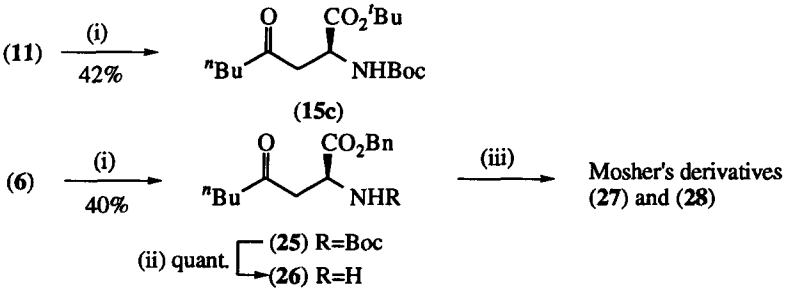
β-lactam ring opening with phosphonate stabilised carbon nucleophiles was also examined. Lithiated diethylmethylphosphonate ring opened (**11**) and (**12**) to afford (**19**) and (**21**) respectively. Hydrogenolysis of (**21**) to afford free amine (**22**) was again followed by formation of Mosher's derivatives[15] whose ^1H and ^{19}F n.m.r. again revealed that no detectable racemisation had occurred, Scheme 6. Additionally, (**19**) was smoothly deprotected to (2S)-4-oxo-5-phosphononorvaline (**20**).[16‡]



(i) $CH_3P(O)(OEt)_2$ (2 eq.), ^nBuLi (2 eq.), THF, -78°C, 30min.; (ii) H_2, 5% $Pd/CaCO_3$ EtOAc, R.T., 1 h.; (iii) (R) or (S)-Mosher's acid chloride (1.2 eq.), DMAP (1.2 eq.), CH_2Cl_2, R.T., 24 h.; (iv) TMSI (3 eq.), CH_2Cl_2, MeCN, R.T., 24h.

Scheme 6

To assess if organocuprates would react in an analogous fashion we attempted ring opening of (**11**) and (**6**) with a Lipshutz higher order cyano cuprate[17] and found that moderate yields of the requisite ketones could be obtained, Scheme 7. In the case of (**6**) no attack of the cuprate on the benzyl ester was observed. Deprotection of (**25**) afforded the free amine (**26**). Analysis of the Mosher's esters[15] as above indicated that no detectable racemisation had occurred. Furthermore, the specific rotation of (**15c**) prepared by this route [+19.4 (*c* 1, $CHCl_3$)] was found to be in agreement with that of the same compound prepared *via* the sulphone addition route, Scheme 4, [+20.8 (*c* 1, $CHCl_3$)].



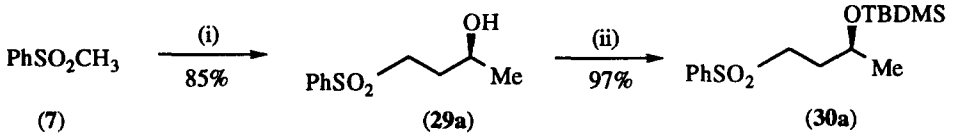
(i) $^nBu_2CuCNLi_2$, THF, -78°C to -50°C; (ii) TFA, R.T., 15 min. then aq. $NaHCO_3$; (iii) (R) or (S)-Mosher's acid chloride (1.2 eq.), DMAP (1.2 eq.), CH_2Cl_2, R.T., 24 h.

Scheme 7

‡ (**20**) possessed a specific rotation of -5.4 (*c* 0.25, H_2O). An authentic sample of (2R)-4-oxo-5-phosphononorvaline possessed a specific rotation of +6.0 (*c* 0.25, H_2O).

Synthesis of S, S, S, S WF-10129 (1a)

The sulphone addition route offered a promising entry into the required (2S) or (2R)-γ-keto-α-amino acids (**3**) for the synthesis of WF-10129. Regioselective ring opening, with stereochemical control of the secondary alcohol was predicted upon Babler's observation that reaction of racemic propylene oxide with the lithiated form of methylphenylsulphone (**7**) afforded (3RS)-1-phenylsulphonylbutan-3-ol.[13] In order to prepare (**1a**), the lithiated form of methylphenylsulphone (**7**) was reacted with (2S)-propylene oxide[18] to afford (**30a**) after protection of the hydroxy group of (**29a**) as its silyl ether.[19]

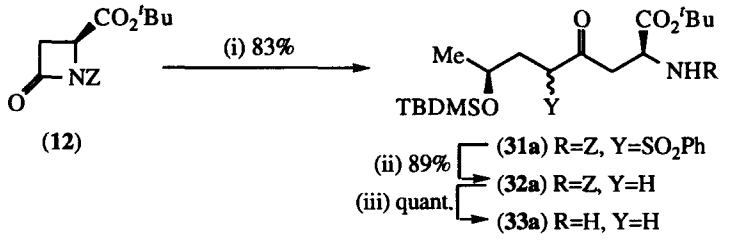


(7) (29a) (30a)

(i) ^{n}BuLi (1 eq.), (2S)-propylene oxide (1.2 eq.), THF, -78°C→R.T., 16 h.;
(ii) TBDMSCl (1.2 eq.), imidazole (2.5 eq.), DMF, R.T., 20 h.

Scheme 8

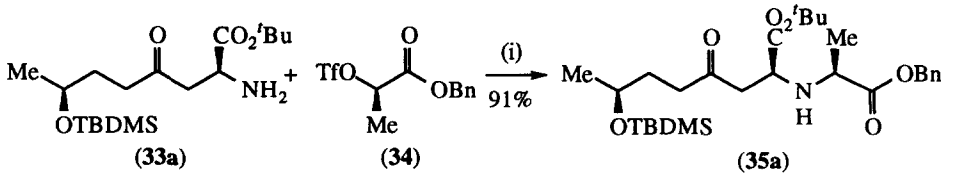
Ring opening of (**12**) with the metallated form of sulphone (**30a**) proceeded in high yield and was followed by reductive removal of the sulphone group.[14] Hydrogenolysis afforded the free amine (**33a**), Scheme 9.



(i) (**30a**) (2 eq.), ^{n}BuLi (2 eq.), THF, -78°C, 10 min.;
(ii) Al/Hg, deoxygenated THF: H_2O 9:1; (iii) H_2, 5%Pd/$CaCO_3$, EtOAc.

Scheme 9

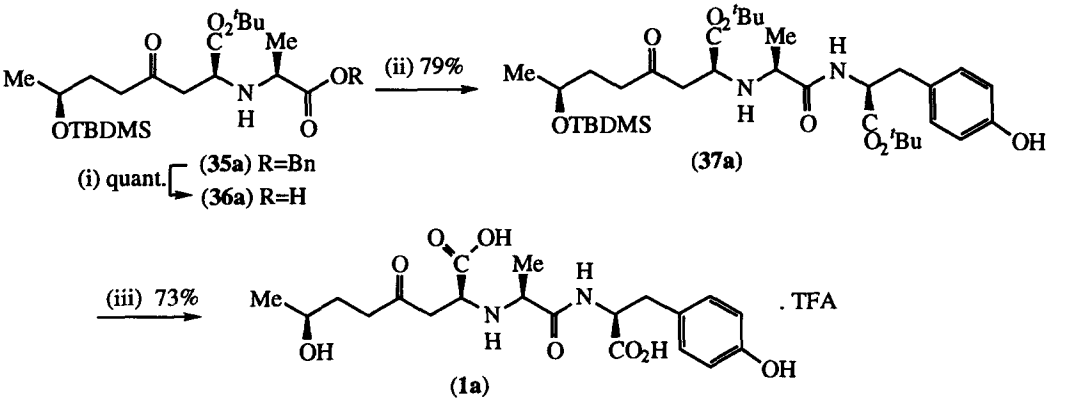
The next stage in the synthesis of (**1a**) involved S_N2 reaction between the amine (**33a**) and a protected form of the triflate (**4**) derived from (D)-lactic acid.[20] Hence, (R)-benzyl α-trifluoromethane sulphonyloxy propanoate (**34**) and the amine (**33a**) were successfully coupled[21] to give (**35a**), Scheme 10.



(i) NEt_3, **34** (2eq.)

Scheme 10

Hydrogenolysis of (**35a**) was followed by a DCC/HOBt mediated coupling to (L)-tyrosine ^{t}-butyl ester to afford the dipeptide (**37a**) which underwent complete deprotection on treatment with TFA/anisole affording (**1a**) as its TFA salt, Scheme 11.



(i) H_2, 10% Pd/C, EtOAc;
(ii) (L)-tyrosine ^{t}butylester (1 eq.), DCC (1.1 eq.), HOBt (1.1 eq.), CH_2Cl_2, 1 h.;
(iii) TFA, anisole, R.T., 1 h.;

Scheme 11

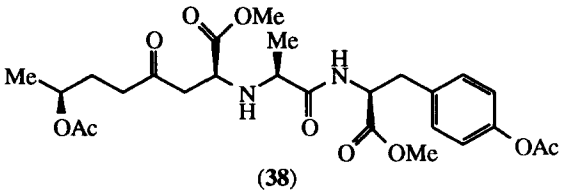
Synthesis of (1b), ent-(1c) and ent-(1d)

(**1b**) was prepared in an analogous manner to (**1a**). Hence, (2R)-1-phenylsulphonyl 3-^{t}butyldimethylsilyloxybutane (**30b**) was prepared from (2R)-propylene oxide and the lithiated form of methylphenylsulphone (**7**) followed by silyl protection of the hydroxy group. Ring opening of (**12**) with (**30b**) followed by desulphonation, Z-deprotection, S_N2 reaction with (**34**) and hydrogenolysis afforded (**36b**) which was subsequently coupled to (L)-tyrosine to afford (**37b**). Global deprotection afforded (**1b**). We elected to prepare the enantiomers of (**1c**) and (**1d**) by coupling the fragments (**33a**) and (**33b**) respectively with protected forms of (L)-lactic acid and (D)-tyrosine.

Comparison of the ^{1}H n.m.r and specific rotations of (**1a**), (**1b**), ent-(**1c**) and ent-(**1d**), Table 2, with that reported for WF-10129 (**1**) indicated that the stereochemistry was that of (**1a**) i.e. S at all stereocentres. Derivatisation of (**1a**) in an analogous manner to that carried out by Ando *et al.* [1] on the natural material gave (**38**), Fig. 1, whose ^{1}H n.m.r. was in agreement with that reported. Inhibition studies of (**1a**) and (**1b**) with ACE showed that both had similar potencies indicating that the stereochemistry of the hydroxyl centre is not critical for activity, Table 3.

	Optical rotation	
WF-10129	+12.9	(*c* 0.375, H_2O)
(1a)	+14.2	(*c* 0.375, H_2O)
(1b)	+3.9	(*c* 0.375, H_2O)
ent-(1c)	+6.2	(*c* 0.37, H_2O)
ent-(1d)	+2.5	(*c* 0.37, H_2O)

Table 2



(38)

Fig. 1

Inhibitor	IC_{50} (M)
Captopril	$3.6x10^{-8}$
(1a)	$5.5x10^{-8}$
(1b)	$7.4x10^{-8}$

Table 3

Summary

In summary we have established a flexible route to optically pure γ-keto α-amino acids[22,23] using carbon based nucleophilic ring opening of activated monocyclic β-lactams.[24] This methodology has been applied to a high yielding synthesis of the natural product WF-10129 (**1**)[1] whose stereochemistry has been assigned to be S at all stereocentres.

Acknowledgements

We wish to thank the SERC and Zeneca Pharmaceuticals Ltd for a CASE award (MLS), Fujiwara Pharmaceuticals Co. Ltd, Japan for supplying data on WF-10129 and performing inhibition studies on the synthetic samples and Marion Merrell Dow for a sample of (2R)-4-oxo-5-phosphononorvaline. We also thank the EPSRC mass spectrometry service (Swansea) for high resolution mass spectra, Mrs. E. McGuinness for high field n.m.r. experiments and Dr. N.P. Crouch for assistance with h.p.l.c.

EXPERIMENTAL SECTION

Melting points (m.p.) were obtained using a Büchi 510 capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20°C with a pathlength of 1dm.. Concentrations (*c*) are given in g/100ml. Microanalyses were performed in the Dyson Perrins Laboratory. Infrared (IR) spectra were recorded as thin films, KBr discs or in $CDCl_3$ solution on a Perkin-Elmer 1750 Fourier Transform spectrometer. The following abbreviations are used: m, medium; s, strong and br, broad. ^1H n.m.r. spectra were recorded at 200MHz and 500MHz on Varian Gemini 200 and Bruker AM500 spectrometers respectively. For ^1H n.m.r. recorded in $CDCl_3$ and D_2O chemical shifts (δ_H) are quoted in parts per million (p.p.m.) and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet and br, broad. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5Hz. ^{13}C n.m.r. spectra were recorded at 50.31MHz and 125.77MHz on Varian Gemini 200 and Bruker AM500 spectrometers respectively using DEPT editing. Chemical shifts (δC) are quoted in p.p.m. and referenced to $CDCl_3$ unless otherwise stated. Spectra recorded in D_2O are referenced to internal 1,4-dioxane. ^{19}F n.m.r. spectra were recorded at 235MHz on a Bruker AM250 spectrometer. Chemical shifts are

quoted in p.p.m. and referenced to $CFCl_3$. Low resolution mass spectra (m/z) were recorded on a V.G Micromass ZAB 1F (FAB/CI/DCI), V.G.Masslab 20-250 (CI/DCI/EI) or a V.G. BIO-Q (Electrospray), with only molecular ions (M^+), fragments from molecular ions and major peaks being reported. Flash chromatography was accomplished on silica gel using Baker silica gel (30-60 μm). Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254} which were visualised by the quenching of u.v. fluorescence (λmax=254nm), by staining with 10%w/v ammonium molybdate in 2M sulphuric acid or ninhydrin, followed by heat. All solvents were distilled before use. Anhydrous dichloromethane and anhydrous acetonitrile were obtained by distillation from calcium hydride under Ar. Anhydrous THF was obtained by distillation from sodium/benzophenone ketyl under nitrogen and anhydrous DMF by distillation from calcium hydride under reduced pressure. P.E. 30-40 refers to the the fraction of light petroleum ether boiling between 30-40°C. Solvents were evaporated at 40°C or below on a Büchi R110 Rotavapor; high boiling solvents were evaporated on a Büchi R110 Rotavapor fitted with a dry ice condenser at <2mmHg. Triethylamine was distilled from calcium hydride under Ar and stored over 4Å molecular sieves. All other reagents were purified in accordance with the instructions in D.D. Perrin and W.L.F. Armarego, 'Purification of Laboratory Chemicals', Pergamon Press, London, Third addition, 1988 or used as obtained from commercial sources.

(4S)-Benzyl *N*-(ᵗbutoxycarbonyl)-azetidin-2-one-4-carboxylate. (6) To a stirred solution of (4S)-benzyl azetidin-2-one-4-carboxylate[4-8] (8) 1.00g, 4.87mmol.) in anhydrous acetonitrile (20ml), under an inert atmosphere of Ar, was added di-*t*-butyldicarbonate (2.13g, 9.74mmol.) and DMAP (59mg, 0.48mmol.). The mixture was stirred at room temperature for seventeen hours before being concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (100ml) and washed with 1M $KHSO_4$ (40ml), saturated aqueous $NaHCO_3$ (40ml) and saturated aqueous brine (40ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash chromatography (SiO_2, P.E 30-40:ether; 60:40) afforded *(4S)-benzyl N-(ᵗbutoxycarbonyl)-azetidin-2-one-4-carboxylate* (6) as a colourless oil which solidified on standing (1.40g, 94%), m.p. 55-57°C (from P.E. 30-40:ether), (R_f 0.25, P.E 30-40:ether 60:40), (Found: C, 62.93; H, 6.30; N, 4.44. $C_{16}H_{19}NO_5$ requires C, 62.95; H, 6.27; N, 4.59%); $[\alpha]_D$ -74.5° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates), 2981br m (NH), 1821s, 1729s (C=O), 1337s, 1155s, 1047s and 736s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.46 (9H, s, $NHCO_2C(CH_3)_3$), 2.99 (1H, dd, *J* 3Hz, *J* 16Hz, 1 x CH_2CH), 3.25 (1H, dd, *J* 6Hz, *J* 16Hz, 1 x CH_2CH), 4.43 (1H, dd, *J* 3Hz, *J* 6Hz, CH_2CH), 5.23 and 5.27 (2H, ABq, *J* 12Hz, $CHCO_2CH_2(C_6H_5)$) and 7.30-7.40 (5H, m, $CHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) 27.74 ($NHCO_2C(CH_3)_3$), 41.23 (CH_2CH), 49.58 (CH_2CH), 67.60 ($CHCO_2CH_2(C_6H_5)$), 84.05 ($NHCO_2C(CH_3)_3$), 128.71 and 128.89 (Aromatic CH), 135.04 (Aromatic ipso C), 147.07 ($NHCO_2C(CH_3)_3$) and 162.53 and 169.43 ($CHCO_2CH_2(C_6H_5)$ and $C(O)CH_2CH$); m/z (desorption chemical ionisation, NH_3) 323[$(MNH_4)^+$, 15%], 223[100], 206[13], 178[15], 108[38], 91[75] and 57[14].

(4S)-Azetidin-2-one-4-carboxylic acid. (9) To a stirred solution of 10% Pd/C (cat.) in THF (20ml) was added (4S)-benzyl azetidin-2-one-4-carboxylate[4-8] (8) (1.00g, 4.88mmol.) as a solution in THF (10ml). The mixture was then stirred for fourteen hours under an atmosphere of hydrogen before being filtered through celite® and concentrated *in vacuo* to afford *(4S)-azetidin-2-one-4-carboxylic acid* (9) as a white crystalline solid (552mg, 98%), m.p. 99-100°C (from P.E.30-40:ethylacetate), (Found: C, 56.14; H, 7.98; N, 8.08. $C_4H_5NO_3$ requires C, 56.13; H, 7.65; N, 8.18%); $[\alpha]_D$ -115.0° (*c* 1.0 in H_2O); ν_{max} (FT IR, KBr

disc) 3338br s (NH and OH), 1747s (C=O), 1725s (C=O), 1421s, 1262s, 1213s, 1196s, 1167s, 1044s, 864s, 805s, 646s and 625s cm^{-1}; δ_H (200MHz; D_2O) 2.84 (1H, dd, *J* 2.5Hz, *J* 16Hz, 1 x CH_2CH), 3.15 (1H, dd, *J* 6Hz, *J* 16Hz, 1 x CH_2CH) and 4.10 (1H, dd, *J* 2.5Hz, *J* 6Hz, CH_2CH); δ_C (50MHz; D_2O) 41.72 (CH_2CH), 46.98 (CH_2CH), 170.91 (CO_2H) and 175.41 ($C(O)CH_2$); m/z (chemical ionisation, NH_3) 133[$(MNH_4)^+$, 100%], 122[9], 118[8], 88[20], 70[9] and 55[19].

(4S)-^{t}Butyl azetidin-2-one-4-carboxylate. (10) To a stirred solution of (4S)-azetidin-2-one-4-carboxylic acid (9) (850mg, 7.39mmol.) in anhydrous THF (8ml) and anhydrous cyclohexane (5ml) was added ^{t}butyltrichloroacetimidate[10] (3.20g, 14.74mmol.) as a solution in anhydrous cyclohexane (8ml) followed by dropwise addition of boron trifluoride etherate (260µl, cat.). The mixture was stirred for twenty five minutes, solid $NaHCO_3$ (500mg) was added and the mixture stirred for a further ten minutes before being filtered and concentrated *in vacuo*. The residue was then taken up in dichloromethane (50ml) and filtered through a plug of celite® to yield a yellow oil. Flash chromatography (SiO_2, P.E. 30-40:ether; 80:20) afforded *(4S)-^{t}butyl azetidin-2-one-4-carboxylate* (10) as a white solid (948mg, 75%) , m.p. 89-90°C (from P.E.30-40:ether), (R_f 0.25, P.E 30-40:ether 80:20), (Found: C, 42.02; H, 4.37; N, 12.00. $C_8H_{13}NO_3$ requires C, 41.75; H, 4.38; N, 12.17%); $[\alpha]_D$ -28.0° (*c* 0.5 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3352s (NH), 2975m, 1767s (C=O), 1733s (C=O), 1479m, 1412m, 1370s, 1285s, 1247s, 1157s, 1053s, 844s, 759m and 605s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.50 (9H, s, $CHCO_2C(CH_3)_3$), 3.05 (1H, ddd, *J* 2Hz, *J* 5Hz, *J* 15Hz, 1 x CH_2CH), 3.21 (1H, ddd, *J* 1Hz, *J* 6Hz, *J* 15Hz, 1 x CH_2CH), 4.08 (1H, dd, *J* 5Hz, *J* 6Hz, CH_2CH) and 6.12 (1H, d, *J* 1Hz, NH); δ_C (50MHz; $CDCl_3$) 27.79 ($CHCO_2C(CH_3)_3$), 43.28 (CH_2CH), 47.87 (CH_2CH), 82.63 ($CHCO_2C(CH_3)_3$), 167.30 ($CHCO_2C(CH_3)_3$) and 170.60 ($C(O)CH_2CH$); m/z (chemical ionisation, NH_3) 189[$(MNH_4)^+$, 100%], 172[$(M+H)^+$, 20], 144[22], 133[44], 88[11], 74[10], 70[11] and 61[13].

(4S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-azetidin-2-one-4-carboxylate. (11) To a stirred solution of (4S)-^{t}butyl-azetidin-2-one-4-carboxylate (10) (1.00g, 5.85mmol.) in anhydrous acetonitrile (15ml), under an inert atmosphere of Ar, was added di^{t}butyldicarbonate[11] (2.55g, 11.70mmol.) as a solution in anhydrous acetonitrile (10ml) followed by DMAP (71mg, 0.58mmol.). The reaction mixture was stirred at room temperature for twenty four hours before being concentrated *in vacuo*. The residue was taken up in dichloromethane (100ml) and washed with 1M aqueous $KHSO_4$ (2 x 50ml), saturated aqueous $NaHCO_3$ (50ml) and saturated aqueous brine (50ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash chromatography (SiO_2, P.E. 30-40:ether; 60:40) afforded *(4S)-^{t}butyl N-(^{t}butoxycarbonyl)-azetidin-2-one-4-carboxylate* (11) as a colourless oil which solidified on standing (1.42g, 90%), m.p. 45-47°C (from P.E.30-40:ether), (R_f 0.5, P.E 30-40:ether 50:50), (Found: C, 57.68; H, 7.88; N, 5.41. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%); $[\alpha]_D$ -52.0° (*c* 0.65 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2984m, 2259m, 1817s, 1729s (C=O), 1477s, 1396s, 1371s, 1338s, 1258s, 1152s, 1048s, 1000s, 840s and 774s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.40 and 1.51 (2 x 9H, 2 x s, $CHCO_2C(CH_3)_3$ and $NHCO_2C(CH_3)_3$), 2.92 (1H, dd, *J* 3Hz, *J* 16Hz, 1 x CH_2CH), 3.23 (1H, dd, *J* 6Hz, *J* 16Hz, 1 x CH_2CH) and 4.36 (1H, dd, *J* 3Hz, *J* 6Hz, CH_2CH); δ_C (50MHz; $CDCl_3$) 27.69 ($CHCO_2C(CH_3)_3$ and $NHCO_2C(CH_3)_3$), 41.10 (CH_2CH), 50.32 (CH_2CH), 82.73 and 83.54 ($NHCO_2C(CH_3)_3$ and $CHCO_2C(CH_3)_3$), 146.91 ($NHCO_2C(CH_3)_3$), 162.99 ($CHCO_2C(CH_3)_3$) and 168.45 ($C(O)CH_2CH$); m/z (chemical ionisation, NH_3) 289[$(MNH_4)^+$, 30%], 233[15], 189[100], 172[7], 144[12], 133[35], 74[8] and 57[42].

(4S)-^{t}-Butyl *N*-(benzyloxycarbonyl)-azetidin-2-one-4-carboxylate. (12) To a stirred solution (4S)-^{t}butyl azetidin-2-one-4-carboxylate (10) (828mg, 4.84mmol.) in anhydrous acetonitrile (5ml), under an inert atmosphere of Ar, was added dibenzyldicarbonate[12] (2.77g, 9.68mmol.) as a solution in anhydrous acetonitrile (7ml) followed by DMAP (59mg, 0.48mmol.). The reaction mixture was stirred at room temperature for fifteen minutes before being concentrated *in vacuo*. The residue was taken up in dichloromethane (70ml) and washed with 1M aqueous $KHSO_4$ (2 x 30ml), saturated aqueous $NaHCO_3$ (30ml) and saturated aqueous brine (30ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash chromatography (SiO_2, P.E. 30-40:ether; 70:30; 40:60; gradient elution) afforded *(4S)-^{t}-butyl N-(benzyloxycarbonyl)-azetidin-2-one-4-carboxylate* (12) as a white crystalline solid (1.44g, 97%), m.p.82-83°C (from P.E. 30-40:ether), (R_f 0.2, P.E 30-40:ether 70:30), (Found: C, 62.89; H, 6.12; N, 4.41. $C_{16}H_{19}NO_5$ requires C, 62.94; H, 6.27; N, 4.59%); $[\alpha]_D$ -86.9° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 2361m, 2343s, 1808s, 1743s (C=O), 1726s (C=O), 1467s, 1397s, 1366s, 1330s, 1316s, 1236s, 1152s, 1044s, 1000s and 771s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.43 (9H, s, $CHCO_2C(C\underline{H}_3)_3$), 2.98 (1H, dd, *J* 3Hz, *J* 17Hz, 1 x $C\underline{H}_2CH$), 3.30 (1H, dd, *J* 6, *J* 17Hz, 1 x $C\underline{H}_2CH$), 4.33 (1H, dd, *J* 3Hz, *J* 6Hz, $CH_2C\underline{H}$), 5.22 and 5.32 (2H, ABq, *J* 12Hz, $NHCO_2C\underline{H}_2(C_6H_5)$) and 7.34-7.42 (5H, m, $NHCO_2CH_2(C_6\underline{H}_5)$); δ_C (50MHz; $CDCl_3$) 27.76 ($CHCO_2C(\underline{C}H_3)_3$), 41.66 ($\underline{C}H_2CH$), 50.31 ($CH_2\underline{C}H$), 68.28 ($NHCO_2\underline{C}H_2(C_6H_5)$), 83.24 ($CHCO_2\underline{C}(CH_3)_3$), 128.53 and 128.78 (Aromatic $\underline{C}H$), 135.00 (Aromatic ipso $\underline{C}$), 148.20 ($NH\underline{C}O_2CH_2(C_6H_5)$), 162.58 ($CH\underline{C}O_2C(CH_3)_3$) and 168.27 ($\underline{C}(O)CH_2CH$); m/z (desorption chemical ionisation, NH_3) 323[$(MNH_4)^+$, 100%], 267[80], 250[12], 223[21], 206[81], 108[57] and 91[98].

General procedure for ring opening of β-lactams with metallated sulphones. Preparation of (14a)-(14c) and (31a)-(31b) To a stirred solution of of sulphone (7), (13), (30a) or (30b) (2 eq.) in anhydrous THF (≈ 10ml per mmol. of β-lactam) at -78°C, under an inert atmosphere of Ar, was added ^{n}butyllithium (2eq.). After stirring at -78°C for ten minutes the mixture was warmed to 0°C and stirred at 0°C for ten minutes, before being recooled to -78°C, whereupon β-lactam (11) or (12) was added as a solution in anhydrous THF (≈ 5ml per mmol. of β-lactam). The reaction mixture was then stirred for a further thirty minutes at -78°C before being quenched by the addition of saturated aqueous NH_4Cl and diluted with ethyl acetate. The organic layer was separated and washed with saturated aqueous NH_4Cl and saturated aqueous brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

(2S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl pentanoate. (14a) The general procedure with β-lactam (11) (124mg, 0.46mmol.) and sulphone (7) followed by flash chromatography (SiO_2, P.E 30-40:ether; 50:50) afforded *(2S)-^{t}butyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl pentanoate* (14a) as a white crystalline solid (160mg, 81%), m.p. 171-172°C (from P.E 30-40:ether), (R_f 0.2, P.E 30-40:ether 60:40), (Found: C, 56.14; H, 6.68; N, 3.18. $C_{20}H_{29}NO_7S$ requires C, 56.19; H, 6.84; N, 3.28%); $[\alpha]_D$ +36.3° (*c* 0.4 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3359m (NH), 2360m, 1733s (C=O), 1707s (C=O), 1654s, 1528s, 1472s, 1448s, 1403s, 1369m, 1340m, 1310s, 1232s, 1050s, 729s and 687s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.44 and 1.45 (2 x 9H, 2 x s, $CHCO_2C(C\underline{H}_3)_3$ and $NHCO_2C(C\underline{H}_3)_3$), 3.15-3.37 (2H, m, $C\underline{H}_2CH$), 4.16 and 4.19 (2H, ABq, *J* 13Hz, $C\underline{H}_2SO_2(C_6H_5)$), 4.38 (1H, m, $CH_2C\underline{H}$), 5.42 (1H, d, *J* 8Hz, $N\underline{H}$), 7.54-7.73 (3H, m, meta and para $SO_2(C_6\underline{H}_5)$) and 7.80-7.93

(2H, m, ortho $SO_2(C_6\underline{H}_5)$); δ_C (125MHz; $CDCl_3$) 27.93 and 28.43 ($CHCO_2C(\underline{C}H_3)_3$ and $NHCO_2C(\underline{C}H_3)_3$), 46.68 ($\underline{C}H_2CH$), 50.24 ($CH_2\underline{C}H$), 67.08 ($\underline{C}H_2SO_2(C_6H_5)$), 80.14 and 82.73 ($CHCO_2\underline{C}(CH_3)_3$ and $NHCO_2\underline{C}(CH_3)_3$), 128.42, 129.47 and 134.42 (Aromatic $\underline{C}H$), 138.97 (Aromatic ipso $\underline{C}$), 155.80 ($NH\underline{C}O_2C(CH_3)_3$), 169.76 ($CH\underline{C}O_2C(CH_3)_3$) and 196.13 ($\underline{C}(O)CH_2SO_2(C_6H_5)$); m/z (desorption chemical ionisation, NH_3) 445[$(MNH_4)^+$, 12%], 428[$(MH)^+$, 5], 389[22], 333[90], 328[13], 272[18], 226[100], 86[45] and 57[49].

(2S)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl pentanoate. (14b) The general procedure with β-lactam (12) (477mg, 1.56mmol.) and sulphone (7) followed by flash chromatography (SiO_2, dichloromethane; dichloromethane:ether; 50:50; gradient elution) afforded *(2S)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl pentanoate* (14b) as a white crystalline solid (60mg, 84%), m.p. 85-86°C (from P.E. 30-40:ether), (R_f 0.1, dichloromethane); $[\alpha]_D$ +42.4° (*c* 1.0 in $CHCl_3$), (Found: C, 60.06; H, 5.77; N, 2.83. $C_{23}H_{27}NO_7S$ requires C, 59.86; H, 5.90; N, 3.03%); ν_{max} (FT IR, KBr disc) 3359br s (NH), 2360s, 2342s, 1733s (C=O), 1712s (C=O), 1707s (C=O), 1528s, 1340s, 1151s, 1064s, 1050s and 687s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.43 (9H, s, $CO_2C(\underline{CH}_3)_3$), 3.30 (1H, dd, *J* 4.5Hz, *J* 18Hz, 1 x $C\underline{H}_2CH$), 3.40 (1H, dd, *J* 4.5Hz, *J* 18Hz, 1 x $C\underline{H}_2CH$), 4.17 (2H, ABq, *J* 15Hz, $C\underline{H}_2SO_2(C_6H_5)$), 4.49 (1H, ddd, *J* 8Hz, *J* 4.5Hz, *J* 4.5Hz, $CH_2C\underline{H}$), 5.12 (2H, s, $C\underline{H}_2(C_6H_5)$), 5.58 (1H, d, *J* 8Hz, $N\underline{H}$), 7.34 (5H, s, $CH_2(C_6\underline{H}_5)$) and 7.48-7.90 (5H, m, $SO_2(C_6\underline{H}_5)$); δ_C (125MHz; $CDCl_3$) 27.82 ($CO_2C(\underline{C}H_3)_3$), 46.42 ($\underline{C}H_2CH$), 50.59 ($CH_2\underline{C}H$), 67.07 and 67.09 ($\underline{C}H_2SO_2(C_6H_5)$ and $\underline{C}H_2(C_6H_5)$), 82.90 ($CO_2\underline{C}(CH_3)_3$), 128.10, 128.19, 128.28, 128.54 and 129.37 (Aromatic $\underline{C}H$), 134.29 and 136.34 (2 x Aromatic ipso $\underline{C}$), 155.90 ($NH\underline{C}O_2CH_2(C_6H_5)$), 169.24 ($\underline{C}O_2C(CH_3)_3$) and 195.80 ($\underline{C}(O)CH_2SO_2(C_6H_5)$); m/z (desorption chemical ionisation, NH_3) 479[$(MNH_4)^+$, 15%], 423[43], 406[12], 362[18], 316[19], 271[9], 226[10], 175[8], 160[9], 112[10], 108[39], 91[100, 78[9] and 57[6].

(2S, 5RS)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl octanoate. (14c) The general procedure with β-lactam (11) (120mg, 0.44mmol.) and sulphone (13) followed by flash chromatography (SiO_2, P.E 30-40:ether; 60:40) afforded *(2S, 5RS)-^{t}butyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo-5-phenylsulphonyl octanoate* (14c) as a colourless oil (166mg, 80%), (R_f 0.2, P.E 30-40:ether 60:40), (Found: C, 58.82; H, 7.45; N, 2.69. $C_{23}H_{35}NO_7S$ requires C, 58.82; H, 7.51; N, 2.98%); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2981m, 1718s (C=O), 1499m, 1370s, 1311m, 1154s, 1084m and 707m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.84-0.91 (3H, m, $CH_2C\underline{H}_3$), 1.41 and 1.48 (2 x 9H, 2 x s, $CHCO_2C(C\underline{H}_3)_3$ and $NHCO_2C(C\underline{H}_3)_3$), 1.39-1.50 (2H, m, $C\underline{H}_2CH_3$), 1.80-1.91 (2H, m, $C\underline{H}_2CH_2CH_3$), 3.04-3.60 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 4.02-4.12 (1H, m, $C\underline{H}SO_2(C_6H_5)$), 4.32-4.46 (1H, m, $C\underline{H}CO_2C(CH_3)_3$), 5.28-5.41 (1H, m, $N\underline{H}$) and 7.51-7.82 (5H, m, $SO_2(C_6\underline{H}_5)$); δ_C (50MHz; $CDCl_3$) 13.50 ($CH_2\underline{C}H_3$), 19.81 ($\underline{C}H_2CH_3$), 27.63 and 28.15 ($CHCO_2C(\underline{C}H_3)_3$ and $NHCO_2C(\underline{C}H_3)_3$), 28.73 ($\underline{C}H_2CH_2CH_3$), 46.51 and 46.85 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 49.64 and 49.77 ($\underline{C}HCO_2C(CH_3)_3$), 74.73 and 74.83 ($\underline{C}HSO_2(C_6H_5)$), 79.83 and 82.36 ($CHCO_2\underline{C}(CH_3)_3$ and $NHCO_2\underline{C}(CH_3)_3$), 129.30, 129.51 and 134.56 (Aromatic $\underline{C}H$), 134.56 (Aromatic ipso $\underline{C}$), 155.56 ($NH\underline{C}O_2C(CH_3)_3$), 170.03 ($CH\underline{C}O_2C(CH_3)_3$) and 201.04 ($\underline{C}(O)CHSO_2(C_6H_5)$); m/z (desorption chemical ionisation, NH_3) 487[$(MNH_4)^+$, 12%], 470[$(MH)^+$, 12], 431[12], 375[55], 370[21], 314[21], 268[100], 127[43], 98[21], 78[20], 70[38] and 57[83].

(2S, 5RS, 7S)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo-5-phenylsulphonyl octanoate. (31a) The general procedure with β-lactam (12) (447mg, 1.47mmol.) and sulphone (30a) followed by flash chromatography (SiO_2, P.E 30-40:ether; 80:20) afforded *(2S, 5RS, 7S)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo-5-phenylsulphonyl octanoate* (31a) as a colourless oil (774mg, 83%), (R_f 0.3, P.E 30-40:ether 70:30), (Found: C, 60.67; H, 7.63; N, 1.95. $C_{32}H_{47}NO_8SSi$ requires C, 60.64; H, 7.47; N, 2.21%); ν_{max} (FT IR, Thin film, NaCl plates) 2956s, 2931s, 2897m, 2858s, 1724s (C=O), 1505s, 1427s, 1472s, 1394s, 1370s, 1324s, 1311m, 1220s, 1155s, 1084m, 1071s, 911s, 839m and 775s cm^{-1}; δ_H (200MHz; $CDCl_3$) -0.03 and -0.02 (6H, 2 x s, $Si(CH_3)_2$), 0.82 and 0.84 (9H, 2 x s, $SiC(CH_3)_3$), 0.89 and 1.08 (3H, 2 x d, 2 x *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.41 and 1.46 (9H, 2 x s, $CHCO_2C(CH_3)_3$), 1.87-2.12 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 3.13-3.95 (3H, m, $CH_2CHCO_2C(CH_3)_3$ and $CH(OSi(CH_3)_2C(CH_3)_3)$), 4.28-4.57 (2H, m, $CH_2CHCO_2C(CH_3)_3$ and $CHSO_2(C_6H_5)$), 5.12-5.21 (2H, m, $NHCO_2CH_2(C_6H_5)$), 5.54-5.66 (1H, m, NH) and 7.29-7.80 (10H, m, $SO_2(C_6H_5)$ and $NHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) -4.97, -4.96 and -3.99 ($Si(CH_3)_2$), 17.78 ($SiC(CH_3)_3$), 23.47 and 24.14 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 25.66 and 27.67 ($CHCO_2C(CH_3)_3$ and $SiC(CH_3)_3$), 35.92 and 36.66 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 46.47 and 46.76 ($CH_2CHCO_2C(CH_3)_3$), 50.18 ($CH_2CHCO_2C(CH_3)_3$), 65.50 ($CHSO_2(C_6H_5)$), 66.89 and 67.01 ($NHCO_2CH_2(C_6H_5)$), 70.85 and 72.01 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 82.52 ($CHCO_2C(CH_3)_3$), 128.23, 128.34, 128.70, 129.29, and 134.51 (Aromatic CH), 136.51 and 136.60 (Aromatic ipso C), 156.18 ($NHCO_2CH_2(C_6H_5)$), 169.80 ($CHCO_2C(CH_3)_3$) and 200.51 and 200.70 ($C(O)CHSO_2(C_6H_5)$); m/z (desorption chemical ionisation, NH_3) 651[$(MNH_4)^+$, 25%], 595[10], 400[20], 108[23], 91[100] and 57[28].

(2S, 5RS, 7R)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo-5-phenylsulphonyl octanoate. (31b) The general procedure with β-lactam (12) (489mg, 1.60mmol.) and sulphone (30b) followed by flash chromatography (SiO_2, P.E 30-40:ether; 80:20) afforded *(2S, 5RS, 7R)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo-5-phenylsulphonyl octanoate* (31b) as a colourless oil (808mg, 80%), (R_f 0.3, P.E 30-40:ether 70:30); ν_{max} (FT IR, Thin film, NaCl plates) 3432br m (NH), 2956s, 2931s, 2897m, 1728s (C=O), 1505s, 1449s, 1472s, 1370s, 1324s, 1311m, 1256s, 1155s, 1070s, 911s and 735s cm^{-1}; δ_H (200MHz; $CDCl_3$) -0.08, -0.04 and -0.01 (6H, 3 x s, $Si(CH_3)_2$), 0.81 and 0.85 (9H, 2 x s, $SiC(CH_3)_3$), 0.99 and 1.06 (3H, 2 x d, 2 x *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.41 and 1.47 (9H, 2 x s, $CHCO_2C(CH_3)_3$), 1.69-2.19 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 3.08-4.11 (3H, m, $CH_2CHCO_2C(CH_3)_3$ and $CH(OSi(CH_3)_2C(CH_3)_3)$), 4.28-4.60 (2H, m, $CH_2CHCO_2C(CH_3)_3$ and $CHSO_2(C_6H_5)$), 5.08-5.21 (2H, m, $NHCO_2CH_2(C_6H_5)$), 5.54-5.66 (1H, m, NH) and 7.28-7.82 (10H, m, $SO_2(C_6H_5)$ and $NHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) -5.25, -5.08, -4.87 and -4.21 ($Si(CH_3)_2$), 17.81 ($SiC(CH_3)_3$), 23.60 and 23.81 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 25.68 and 27.68 ($CHCO_2C(CH_3)_3$ and $SiC(CH_3)_3$), 35.64 and 36.40 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 46.14 and 46.95 ($CH_2CHCO_2C(CH_3)_3$), 50.12 ($CH_2CHCO_2C(CH_3)_3$), 65.34 ($CHSO_2(C_6H_5)$), 66.97 ($NHCO_2CH_2(C_6H_5)$), 71.02 and 71.51 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 82.65 ($CHCO_2C(CH_3)_3$), 128.34, 128.71, 129.39, and 134.53 (Aromatic CH), 136.51 and 136.67 (Aromatic ipso C), 156.20 ($NHCO_2CH_2(C_6H_5)$), 169.95 ($CHCO_2C(CH_3)_3$) and 199.97 and 200.99 ($C(O)CHSO_2(C_6H_5)$); m/z (desorption chemical ionisation, NH_3) 651[$(MNH_4)^+$, 28%], 595[12], 400[17], 108[25], 91[100] and 57[27].

General procedure for the preparation of γ-keto α-amino acids by Al/Hg reduction of β-ketosulphones. (15a)-(15c) and (32a)-(32b) To a stirred solution of β-ketosulphone in degassed THF:H_2O 9:1 (20mM solution) was added freshly prepared aluminium amalgam (24eq.).[14] The mixture was stirred at room temperature for five hours and then further aluminium amalgam (24eq.) was added. The reaction mixture was stirred for a further fifteen hours before being filtered through celite® (ether eluent), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

(2S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo pentanoate. (15a) The general procedure with β-ketosulphone (14a) (89mg, 0.21mmol.) followed by flash chromatography (SiO_2, P.E. 30-40:ether; 60:40) afforded *(2S)-^{t}butyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo pentanoate* (15a) as a white crystalline solid (54mg, 90%), m.p.72-74°C (from P.E.30-40:ether), (R_f 0.4, P.E 30-40:ether 60:40), (Found: C, 58.8; H, 9.1; N, 4.7. $C_{14}H_{25}NO_5$ requires C, 58.52; H, 8.77; N, 4.87%); $[\alpha]_D$ +14.5° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3463m, 2980m, 1733s (C=O), 1720 (C=O), 1497s, 1405m, 1368s, 1338s, 1249m, 1222s, 1158s and 1059 cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.44 (18H, s, $NHCO_2C(CH_3)_3$ and $CHCO_2C(CH_3)_3$), 2.19 (3H, s, $C(O)CH_3$), 2.90 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 3.12 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 4.35 (1H, ddd, *J* 5Hz, *J* 5Hz, *J* 9Hz, CH_2CH) and 5.45 (1H, d, *J* 9Hz, NH); δ_C (50MHz; $CDCl_3$) 27.69 and 28.15 ($CHCO_2C(CH_3)_3$ and $NHCO_2C(CH_3)_3$), 29.78 ($C(O)CH_3$), 45.46 (CH_2CH), 50.03 (CH_2CH), 79.79 and 82.05 ($CHCO_2C(CH_3)_3$ and $NHCO_2C(CH_3)_3$), 155.82 ($NHCO_2C(CH_3)_3$), 170.58 ($CHCO_2C(CH_3)_3$) and 206.93 ($C(O)CH_3$); m/z (chemical ionisation, NH_3) 288 [$(MH)^+$, 12%], 232[20], 193[40], 176[39], 132[21], 86[100] and 57[22].

(2S)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-4-oxo pentanoate. (15b) The general procedure with β-ketosulphone (14b) (344mg, 0.75mmol.) followed by flash chromatography (SiO_2, P.E. 30-40:ether; 50:50) afforded *(2S)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-4-oxo pentanoate* (15b) as a colourless oil (220mg, 92%), (R_f 0.3, P.E 30-40:ether 50:50), (Found: C, 63.88; H, 7.56; N, 4.32. $C_{17}H_{23}NO_5$ requires C, 63.57; H, 7.21; N, 4.36%); $[\alpha]_D$ +20.0° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 3345br m (NH), 3065m, 2979m, 1719s (C=O), 1509s, 1456s, 1395s, 1370s, 1256s, 1223s, 1156s, 1055s, 847s, 742s and 699s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.43 (9H, s, $CO_2C(CH_3)_3$), 2.15 (3H, s, $C(O)CH_3$), 2.90 (1H, dd, *J* 4Hz, *J* 16Hz, 1 x CH_2CH), 3.14 (1H, dd, *J* 4Hz, *J* 16Hz, 1 x CH_2CH), 4.44 (1H, td *J* 4Hz, *J* 8Hz, CH_2CH), 5.10 (2H, s, $CH_2(C_6H_5)$ 5.73 (1H, d, *J* 8Hz, NH) and 7.34 (5H, s, $NHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) 27.70 ($CO_2C(CH_3)_3$), 29.78 ($C(O)CH_3$), 45.33 (CH_2CH), 50.48 (CH_2CH), 66.89 ($CH_2(C_6H_5)$, 82.38 ($CO_2C(CH_3)_3$), 128.22 and 128.67 (Aromatic CH), 136.52 (Aromatic ipso C), 156.34 ($NHCO_2CH_2(C_6H_5)$), 170.20 ($CO_2C(CH_3)_3$) and 205.10 ($C(O)CH_3$); m/z (chemical ionisation, NH_3) 339[$(MNH_4)^+$, 8%], 322[$(MH)^+$, 112], 283[35], 266[75], 222[14], 176[20], 108[40], 91[100] and 86[33].

(2S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo-octanoate. (15c) The general procedure with β-ketosulphone (14c) (100mg, 0.21mmol.) followed by flash chromatography (SiO_2, P.E. 30-40:ether; 70:30; 50:50; gradient elution) afforded *(2S)-^{t}butyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo-octanoate* (15c) as a colourless oil (63mg, 90%), (R_f 0.4, P.E 30-40:ether 50:50), (Found: C, 62.27; H, 9.58; N, 4.09. $C_{17}H_{31}NO_5$ requires C, 61.98; H, 9.48; N, 4.25%); $[\alpha]_D$ +20.8° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 3847m (NH), 3439s, 2977s, 2934s, 2875s, 1719br s (C=O), 1499s, 1393s, 1368s, 1252s and

1155s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.91 (3H, t, *J* 7Hz, $CH_2C\underline{H}_3$), 1.25-1.55 (4H, m, $C\underline{H}_2CH_3$ and $C\underline{H}_2CH_2CH_3$), 1.45 (18H, s, $CHCO_2C(C\underline{H}_3)_3$ and $NHCO_2C(C\underline{H}_3)_3$), 2.42 (2H, t, *J* 7Hz, $C\underline{H}_2CH_2CH_2CH_3$), 2.87 (1H, dd, *J* 4Hz, *J* 17Hz, 1 x $C\underline{H}_2CH$), 3.10 (1H, dd, *J* 4Hz, *J* 17Hz, 1 x $C\underline{H}_2CH$), 4.35 (1H, td, *J* 4Hz, *J* 8Hz, $CH_2C\underline{H}$) and 5.45 (1H, d, *J* 8Hz, $N\underline{H}$); δ_C (50MHz; $CDCl_3$) 13.62 ($CH_2\underline{C}H_3$), 22.09 ($CH_2\underline{C}H_2CH_3$), 25.67 ($CH_2\underline{C}H_2CH_2CH_3$), 27.72 and 28.18 ($CHCO_2C(\underline{C}H_3)_3$ and $NHCO_2C(\underline{C}H_3)_3$), 42.40 ($\underline{C}H_2CH_2CH_2CH_3$), 44.45 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 50.06 ($CH_2\underline{C}HCO_2C(CH_3)_3$), 79.71 and 82.01 ($CHCO_2\underline{C}(CH_3)_3$ and $NHCO_2\underline{C}(CH_3)_3$), 155.89 ($NH\underline{C}O_2C(CH_3)_3$), 170.68 ($CH\underline{C}O_2C(CH_3)_3$) and 209.60 ($\underline{C}(O)CH_2CH_2CH_2CH_3$); m/z (chemical ionisation, NH_3) 330 [$(MH)^+$, 50%], 274[33], 235[28], 230[31], 218[50], 174[14], 128[100], 85[33] and 57[56].

(2*S*, 7*S*)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate. (32a) The general procedure with β-ketosulphone (31a) (700mg, 1.11mmol.) followed by flash chromatography (SiO_2, P.E. 30-40:ether; 80:20) afforded *(2S, 7S)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate* (32a) as a colourless oil (485mg, 89%), (R_f 0.2, P.E 30-40:ether 80:20), m/z (high resolution) Found 494.2938, $C_{26}H_{43}NO_6Si+H^+$ requires 494.2938; $[\alpha]_D$ +25.2° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 3358br m (NH), 2956s, 1724s (C=O), 1505s, 1473m, 1457s, 1394m, 1370s, 1340s, 1256s, 1219s, 1157s and 776s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.02 and 0.04 (6H, 2 x s, $Si(C\underline{H}_3)_2$) 0.99 (9H, s, $SiC(C\underline{H}_3)_3$), 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.43 (9H, s, $CHCO_2C(C\underline{H}_3)_3$), 1.55-1.80 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.38-2.58 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.92 (1H, dd, *J* 4.5Hz, *J* 17.5Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.14 (1H, dd, *J* 4.5Hz, *J* 17.5Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.74-3.90 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$), 4.44 (1H, td, *J* 4.5Hz, *J* 8.5Hz, $CH_2C\underline{H}CO_2C(CH_3)_3$), 5.11 (2H, s, $NHCO_2C\underline{H}_2(C_6H_5)$), 5.72 (1H, d, *J* 8.5Hz, $N\underline{H}$) and 7.35 (5H, s, $NHCO_2CH_2(C_6\underline{H}_5)$); δ_C (50MHz; $CDCl_3$) -4.95 and -4.58 ($Si(\underline{C}H_3)_2$), 17.89 ($Si\underline{C}(CH_3)_3$), 23.52 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$), 25.74 and 27.71 ($CHCO_2C(\underline{C}H_3)_3$ and $SiC(\underline{C}H_3)_3$), 32.80 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.63 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 44.37 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 50.50 ($CH_2\underline{C}HCO_2C(CH_3)_3$), 66.87 ($NHCO_2\underline{C}H_2(C_6H_5)$), 67.42 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3$), 82.25 ($CHCO_2\underline{C}(CH_3)_3$), 128.20 and 128.67 (Aromatic $\underline{C}H$), 136.56 (Aromatic ipso $\underline{C}$), 156.36 ($NH\underline{C}O_2CH_2(C_6H_5)$), 170.28 ($CH\underline{C}O_2C(CH_3)_3$) and 209.10 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 494[$(MH)^+$, 27%], 438[8], 330[40], 306[7], 272[26], 229[10], 198[38], 108[30], 91[100], 74[25] and 57[13].

(2*S*, 7*R*)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate. (32b) The general procedure with β-ketosulphone (31b) (800mg, 1.26mmol.), followed by flash chromatography (SiO_2, P.E. 30-40:ether; 80:20) afforded *(2S, 7R)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate* (32b) as a colourless oil (592mg, 95%), (R_f 0.2, P.E 30-40:ether 80:20); $[\alpha]_D$ +3.2° (*c* 1.3 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 3431br, m (NH), 2957s, 2930m, 1719s (C=O), 1505s, 1370s, 1355m, 1219s, 1157s, 1068s, 837m and 776s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.01 and 0.03 (6H, 2 x s, $Si(C\underline{H}_3)_2$) 0.87 (9H, s, $SiC(C\underline{H}_3)_3$), 1.10 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.41 (9H, s, $CHCO_2C(C\underline{H}_3)_3$), 1.51-1.76 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.31-2.60 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)$), 2.78 (1H, dd, *J* 4Hz, *J* 18Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.13 (1H, dd, *J* 4Hz, *J* 18Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.71-3.89 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$), 4.43 (1H, td, *J* 4Hz,

J 8.5Hz, $CH_2CHCO_2C(CH_3)_3$), 5.09 (2H, s, $NHCO_2CH_2(C_6H_5)$), 5.76 (1H, d, *J* 8.5Hz, NH) and 7.33 (5H, s, $NHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) -5.02 and -4.61 ($Si(CH_3)_2$), 17.88 ($SiC(CH_3)_3$), 23.57 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 25.72 and 27.70 ($CHCO_2C(CH_3)_3$ and $SiC(CH_3)_3$), 32.80 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.60 ($CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 44.34 ($CH_2CHCO_2C(CH_3)_3$), 50.49 ($CH_2CHCO_2C(CH_3)_3$), 66.83 ($NHCO_2CH_2(C_6H_5)$), 67.31 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 82.20 ($CHCO_2C(CH_3)_3$), 128.19 and 128.65 (Aromatic CH), 136.56 (Aromatic ipso C), 156.36 ($NHCO_2CH_2(C_6H_5)$), 170.27 ($CHCO_2C(CH_3)_3$) and 209.08 ($C(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 494[$(MH)^+$, 29%], 438[10], 330[38], 306[5], 272[27], 229[12], 198[39], 108[33], 91[100], 74[24] and 57[10].

(2S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo octanoate. Cuprate route. (15c) To a stirred suspension of CuCN (122mg, 1.36mmol., 1.3 eq.) in anhydrous THF (2ml) at -78°C, under an inert atmosphere of Ar, was added ^{n}butyllithium (1.82ml of a 1.50M solution in hexanes, 2.72mmol., 2.6 eq.). The resulting mixture was allowed to warm to 0°C whereupon a clear tan solution was observed. The mixture was then recooled to -78°C and (4S)-^{t}butyl *N*-(^{t}butoxycarbonyl)-azetidin-2-one-4-carboxylate (11) (285mg, 1.05mmol.) was added as a solution in anhydrous THF (5ml). The reaction mixture was then stirred at -60°C for one hour before being quenched by the addition of a 9:1 saturated NH_4Cl:NH_4OH solution (5ml). The organics layer was separated, diluted with ether (50ml), washed with 9:1 saturated NH_4Cl:NH_4OH (3 x 20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Flash chromatography (SiO_2, P.E. 30-40:ether; 70:30; 50:50; gradient elution) afforded *(2S)-^{t}butyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo octanoate* (15c) as a colourless oil (145mg, 42%). ^{1}H n.m.r., t.l.c. analysis and I.R. were identical to (15c) prepared by the desulphonylation route above; $[\alpha]_D$ +19.4° (*c* 1 in $CHCl_3$).

(2S)-Benzyl *N*-(^{t}butoxycarbonyl)-2-amino-4-oxo octanoate. (25) The above procedure with β-lactam (6) (314mg, 1.03mmol.) followed by flash chromatography (SiO_2, P.E. 30-40:ether; 90:10; 70:30; gradient elution) afforded *(2S)-benzyl N-(^{t}butoxycarbonyl)-2-amino-4-oxo octanoate* (25) as a yellow oil (150mg, 40%), (R_f 0.3, P.E 30-40:ether 80:20), (Found: C, 66.13; H, 8.07; N, 3.56. $C_{20}H_{29}NO_5$ requires C, 66.09; H, 8.04; N, 3.85%); $[\alpha]_D$ -8.3° (*c* 0.5 in MeOH); ν_{max} (FT IR, Thin film, NaCl plates) 3035br m (NH), 2961m, 1742m (C=O), 1718s (C=O), 1499s, 1368s, 1251s, 1167s, 752s and 699m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.88 (3H, t, *J* 7Hz, CH_2CH_3), 1.18-1.63 (4H, m, $CH_2CH_2CH_3$), 1.43 (9H, s, $(NHCO_2C(CH_3)_3)$, 2.34 (2H, t, *J* 7Hz, $CH_2CH_2CH_2CH_3$), 2.90 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 3.15 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 4.55 (1H, td, *J* 5Hz, *J* 8Hz, CH_2CH), 5.14 and 5.18 (2H, ABq, *J* 14Hz, $CHCO_2CH_2(C_6H_5)$), 5.21 (1H, d, *J* 8Hz, NH) and 7.34 (5H, s, $CHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) 13.78 (CH_2CH_3), 22.16 ($CH_2CH_2CH_3$), 25.64 ($CH_2CH_2CH_2CH_3$), 28.26 ($NHCO_2C(CH_3)_3$), 42.46 ($CH_2CH_2CH_2CH_3$), 44.31 (CH_2CH), 49.66 (CH_2CH), 67.33 ($CHCO_2CH_2(C_6H_5)$), 80.04 ($NHCO_2C(CH_3)_3$), 127.40, 128.53 and 128.74 (Aromatic CH), 135.63 ($NHCO_2C(CH_3)_3$), 171.66 ($CHCO_2CH_2(C_6H_5)$ and 209.57 ($C(O)CH_2CH_2CH_2CH_3$); m/z (chemical ionisation, NH_3) 364 [$(MH)^+$, 7%], 325[11], 314[10], 308[47], 264[72], 228[11], 178[16], 172[10], 158[26], 128[92], 108[33], 91[100], 85[24] and 57[19].

(2S)-^{t}Butyl *N*-(^{t}butoxycarbonyl)-2-amino-5-diethylphosphono-4-oxo pentanoate. (19) To a stirred solution of diethyl methylphosphonate (168mg, 1.1mmol., 2 eq.) in anhydrous THF (2ml) at -78°C, under an inert atmosphere of Ar, was added ^{n}butyllithium (691µl of a 1.6M solution in hexanes, 1.1mmol., 2eq.). After stirring at -78°C for ten minutes the mixture was warmed to 0°C and stirred at 0°C for ten minutes, before being recooled to -78°C, whereupon (4S)-^{t}butyl *N*-(^{t}butoxycarbonyl)-azetidin-2-one-4-carboxylate (11) (150mg, 0.55mmol.) was added as a solution in anhydrous THF (5ml). The reaction mixture was then stirred for a further thirty minutes at -78°C before being quenched by the addition of saturated aqueous NH_4Cl (5ml) and diluted with dichloromethane (50ml). The organic layer was separated and washed with saturated aqueous NH_4Cl (2 x 10ml) and saturated aqueous brine (10ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash chromatography (SiO_2, P.E. 40-60:ethylacetate; 10:90) afforded *(2S)-^{t}butyl N-(^{t}butoxyoxycarbonyl)-2-amino-5-diethylphosphono-4-oxo pentanoate* (19) as a colourless oil (202mg, 87%), (R_f 0.2, P.E 40-60:ethylacetate 10:90), (Found: C, 50.7; H, 8.3; N, 3.5. $C_{18}H_{34}NO_8P$ requires C, 51.06; H, 8.09; N, 3.31%); $[\alpha]_D$ +16.2° (*c* 0.5 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 3303m (NH), 2978s, 2933s, 1722br s (C=O), 1502s, 1456s, 1395s, 1367s, 1252s, 1156s, 1028s, 971s, 851s and 799s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.34 (6H, t, *J* 6.5Hz, 2 x $OCH_2\underline{CH_3}$), 1.43 and 1.45 (2 x 9H, 2 x s, $CHCO_2C(\underline{CH_3})_3$ and $NHCO_2C(\underline{CH_3})_3$), 3.08 (2H, d, *J* 21.5Hz, $\underline{CH_2}P(O)(OEt)_2$), 3.09 (1H, dd, *J* 5Hz, *J* 17.5Hz, 1 x $C\underline{H_2}CH$), 3.27 (1H, dd, *J* 5Hz, *J* 17.5Hz, 1 x $C\underline{H_2}CH$), 4.02-4.22 (4H, m, 2 x $O\underline{CH_2}CH_3$), 4.58- (1H, m, $CH_2\underline{CH}$) and 5.49 (1H, d, *J* 8Hz, $N\underline{H}$); δ_C (50MHz; $CDCl_3$) 16.06 and 16.20 ($OCH_2\underline{CH_3}$), 27.93 and 28.43 ($CHCO_2C(\underline{CH_3})_3$ and $NHCO_2C(\underline{CH_3})_3$), 41.07, 43.62 (d, $J_{C,P}$ 128Hz, $\underline{CH_2}P(O)(OEt)_2$), 45.95 ($\underline{CH_2}CH$), 49.91 ($CH_2\underline{CH}$), 62.59 ($O\underline{CH_2}CH_3$), 79.77 and 82.22 ($CHCO_2\underline{C}(CH_3)_3$ and $NHCO_2\underline{C}(CH_3)_3$), 155.77 ($NH\underline{C}O_2C(CH_3)_3$), 170.36 ($CH\underline{C}O_2C(CH_3)_3$) and 200.35 ($\underline{C}(O)CH_2P(O)(OEt)_2$); m/z (FAB, +ve Na), 446[$(MNa)^+$, 100%], 424[$(M+H)^+$, 11], 324[14], 268[74], 251[50] and 222[42].

(2S)-^{t}Butyl *N*-(benzyloxycarbonyl)-2-amino-5-diethylphosphono-4-oxo pentanoate. (21) The above procedure with β-lactam (12) (60mg, 0.2mmol.) followed by flash chromatography (SiO_2, P.E. 40-60:ethylacetate; 10:90) afforded *(2S)-^{t}butyl N-(benzyloxycarbonyl)-2-amino-5-diethylphosphono-4-oxo pentanoate* (21) as a colourless oil (86mg, 94%) (R_f 0.2, P.E 40-60:ethylacetate 10:90); $[\alpha]_D$ +12.0° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 3281br m, 2987s, 2935s, 1721br s (C=O), 1510m, 1455m, 1396s, 1371s, 1343s, 1254s ,1163s, 1092s, 973s, 849m, 752m and 701s; δ_H (200MHz; $CDCl_3$) 1.31 (6H, t, *J* 7Hz, 2 x $OCH_2\underline{CH_3}$), 1.43 (9H, s, $CHCO_2C(\underline{CH_3})_3$), 3.06 (2H, d, *J* 23Hz, $\underline{CH_2}P(O)(OEt)_2$), 3.12 (1H, dd, *J* 4Hz, *J* 20Hz, 1 x $C\underline{H_2}CH$), 3.22 (1H, dd, *J* 4.5Hz, *J* 20Hz, 1 x $C\underline{H_2}CH$), 4.03-4.20 (4H, m, 2 x $O\underline{CH_2}CH_3$), 4.39-4.50 (1H, m, $CH_2\underline{CH}$), 5.10 (2H, s, $\underline{CH_2}(C_6H_5)$), 5.71 (1H, d, *J* 8Hz, $N\underline{H}$) and 7.34 (5H, s, $CH_2(\underline{C_6H_5})$); δ_C (50MHz; $CDCl_3$) 16.06 and 16.18 ($OCH_2\underline{CH_3}$), 27.66 ($CHCO_2C(\underline{CH_3})_3$), 41.13, 43.66 (d, $J_{C,P}$ 127.5Hz, $\underline{CH_2}P(O)(OEt)_2$), 45.78 ($\underline{CH_2}CH$), 50.36 ($CH_2\underline{CH}$), 62.60 and 62.71 ($O\underline{CH_2}CH_3$), 66.88 ($\underline{CH_2}(C_6H_5)$), 82.48 ($CHCO_2\underline{C}(CH_3)_3$), 128.23 and 128.67 (Aromatic $\underline{CH}$), 136.50 (Aromatic ipso $\underline{C}$), 156.29 ($NH\underline{C}O_2CH_2(C_6H_5)$), 169.94 ($CH\underline{C}O_2C(CH_3)_3$) and 200.18 ($\underline{C}(O)CH_2P(O)(OEt)_2$); m/z (FAB, +ve Na), 480[$(MNa)^+$, 94%], 458[$(MH)^+$, 80], 424[32], 402[100], 195[30] and 176[84].

(2S)-4-oxo-5-phosphononorvaline.[16] (20) To a stirred solution of (2S)-^{t}butyl *N*-(^{t}butoxyoxycarbonyl) 2-amino-5-diethylphosphono-4-oxo pentanoate (19) (50mg, 0.12mmol.) in

acetonitrile:dichloromethane 50:50 (2ml) was added TMSI (135µl, 0.94mmol.). The reaction mixture was stirred at room temperature for eighteen hours then concentrated *in vacuo*. To the residue was added methanol (5ml) and the mixture was stirred at room temperature for one hour then concentrated *in vacuo*. The resulting brown residue was partitioned between ether (20ml) and water (50ml). The aqueous layer was separated and washed with ether (3 x 20ml) then concentrated *in vacuo* to afford a yellow oil which was purified by ion exchange on Dowex 50W-X8(H) resin 100-200 mesh (precharged with 2M HCl and washed with H_2O) eluting with 2M NH_4OH to afford *(2S)-4-oxo-5-phosphononorvaline* (20) as a white solid (20mg, 80%), m.p. 110-112°C (authentic sample of enantiomer m.p. 113-115°C); $[\alpha]_D$ -5.4° (*c* 0.25 in H_2O) (authentic sample of the enantiomer $[\alpha]_D$ +6.0 (*c* 0.25 in H_2O); ν_{max} (FT IR, KBr disc) 3427br s (OH), 3143m, 2931s, 1708s (C=O), 1651m, 1634m, 1623m, 1144s and 1060s cm^{-1}; δ_H (200MHz; D_2O) 3.15 (2H, d, J_{HP} 21.5Hz, $CH_2P(O)(OH)_2$), 3.43-3.46 (2H, m, CH_2CH) and 4.32 (1H, t, *J* 5.5Hz, CH_2CH); δ_C (125MHz; D_2O) 45.51 (CH_2CH), 47.74 (d, $J_{C,P}$ 114Hz, $CH_2P(O)(OH)_2$), 51.53 (CH_2CH), 174.48 ($CHCO_2$) and 207.57 ($C(O)CH_2P(O)(OH)_2$); m/z (negative ion electrospray) 210[(M-H$^-$), 100%].

(2S)-^{t}Butyl-2-amino-4-oxo pentanoate. (16) To a stirred suspension of 5% Pd/$CaCO_3$ (cat.) in ethylacetate (0.5ml) was added (2S)-^{t}butyl *N*-(benzyloxycarbonyl)-2-amino-4-oxo-pentanoate (15b) (30mg, 0.93mmol.) as a solution in ethyl acetate (2ml). The resulting mixture was stirred under an atmosphere of H_2 for 1 hour before being filtered through a plug of celite® and concentrated *in vacuo* to afford *(2S)-^{t}butyl-2-amino-4-oxo pentanoate* (16) as a pale yellow oil (17mg, quant.); δ_H (200MHz; $CDCl_3$) 1.47 (9H, s, $CO_2C(CH_3)_3$), 2.20 (3H, s, $C(O)CH_3$), 2.72-2.98 (2H, m, CH_2CH) and 3.69-3.73 (1H, m, CH_2CH).

(2S)-^{t}Butyl-2-amino-5-diethylphosphono-4-oxo pentanoate.(22) The above procedure with (2S)-^{t}butyl *N*-(benzyloxycarbonyl)-2-amino-5-diethylphosphono-4-oxo pentanoate (21) (40mg, 0.09mmol.) afforded *(2S)-^{t}butyl-2-amino-5-diethylphosphono-4-oxo pentanoate* (22) as a pale yellow oil (28mg, quant.); δ_H (200MHz; $CDCl_3$) 1.34 (6H, t, *J* 7Hz, 2 x OCH_2CH_3), 1.45 (9H, s, $CHCO_2C(CH_3)_3$), 3.10-3.52 (4H, m, CH_2CH and $CH_2P(O)(OEt)_2$) and 4.05-4.38 (5H, m, 2 x OCH_2CH_3 and CH_2CH).

(2S)-Benzyl-2-amino-4-oxo octanoate. (26) To (2S)-benzyl *N*-(^{t}butoxycarbonyl)-2-amino 4-oxo octanoate (25) (15mg, 0.04mmol.) was added trifluoroacetic acid and the mixture was stirred at room temperature for fifteen minutes before being concentrated *in vacuo*. The residue was taken up in ethyl acetate (50ml)/saturated aqueous $NaHCO_3$ (20ml). The organics were separated and the aqueous layer washed with ethylacetate (2 x 50ml). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford *(2S)-benzyl 2-amino 4-oxo octanoate* (26) as a yellow oil (11mg, quant.); δ_H (200MHz; $CDCl_3$) 0.90 (3H, t, *J* 7Hz, CH_3), 1.20-1.40 (2H, m, CH_2CH_3), 1.45-1.61 (2H, m, $CH_2CH_2CH_3$), 2.25-2.40 (2H, m, $CH_2CH_2CH_2CH_3$), 3.41 (2H, m, CH_2CH), 3.75-3.94 (1H, m, CH_2CH), 5.10-5.18 (2H, m, $CHCO_2CH_2(C_6H_5)$) and 7.33-7.37 (5H, m, $CH_2(C_6H_5)$).

General procedure for the preparation of Mosher's acid derivatives. (17), (18), (23), (24), (27) and (28) To a stirred solution of amine in anhydrous dichloromethane (≈1ml per 0.05mmol.of amine), under an inert atmosphere of Ar, was added (R) or (S)-Mosher's acid chloride (1.2 eq.) as a solution in anhydrous dichloromethane (≈0.5ml per 0.05mmol. of amine) followed by DMAP (1.2 eq.). The reaction

mixture was stirred at room temperature for twenty four hours before being concentrated *in vacuo*. ^{1}H n.m.r. of the residue confirmed that the amine had been completely consumed. The residue was taken up in ether and washed with 1M HCl, saturated aqueous Na_2CO_3 and saturated aqueous brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the Mosher's acid derivative.

Mosher's acid derivative. (17) The general procedure with (2S)-^{t}butyl 2-amino-4-oxo pentanoate (16) (21mg, 0.11mmol.) and (R)-Mosher's acid chloride afforded the (S, S)-Mosher's acid derivative (17) (48mg crude mass) as a yellow oil; δ_H (200MHz; $CDCl_3$) 1.45 (9H, s, $CHCO_2C(CH_3)_3$), 2.08 (3H, s, $C(O)CH_3$), 2.91 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 3.15 (1H, dd, *J* 5Hz, *J* 17Hz, 1 x CH_2CH), 3.53 (3H, d, *J* 2Hz, OCH_3), 4.69 (1H, td, *J* 5Hz, *J* 8Hz, CH_2CH) and 7.32-7.60 (6H, m, C_6H_5 and NH); δ_F (235MHz; $CDCl_3$) -70.54 (s, CF_3).

Mosher's acid derivative (18). The general procedure with (2S)-^{t}butyl 2-amino-4-oxo pentanoate (16) (20mg, 0.11mmol.) and (S)-Mosher's acid chloride afforded the (S, R)-Mosher's acid derivative (18) (47mg crude mass) as a yellow oil; δ_H (200MHz; $CDCl_3$) 1.45 (9H, s, $CHCO_2C(CH_3)_3$), 2.19 (3H, s, $C(O)CH_3$), 2.98 (1H, dd, *J* 5Hz, *J* 18Hz, 1 x CH_2CH), 3.22 (1H, dd, *J* 5Hz, *J* 18Hz, 1 x CH_2CH), 3.35 (3H, s, OCH_3), 4.71 (1H, td, *J* 5Hz, *J* 8Hz, CH_2CH), 7.32-7.68 (5H, m, C_6H_5) and 7.88 (1H, d, *J* 8Hz, NH); δ_F (235MHz; $CDCl_3$) -71.07 (s, CF_3).

Mosher's derivative (23) The general procedure with (2S)-^{t}butyl 2-amino-5-diethylphosphono-4-oxo pentanoate (22) (23mg, 0.07mmol.) and (R)-Mosher's acid chloride afforded the (S, S)-Mosher's acid derivative (23) (50mg crude mass) as a yellow oil; δ_H (500MHz; $CDCl_3$) 1.29 (6H, dt, *J* 3.5Hz, *J* 7Hz, 2 x OCH_2CH_3), 1.45 (9H, s, $CHCO_2C(CH_3)_3$), 2.97 (1H, dd, *J* 11.5Hz, *J* 13.5Hz, 1 x $CH_2P(O)(OEt)_2$), 2.99 (1H, dd, *J* 11.5Hz, *J* 13.5Hz, 1 x $CH_2P(O)(OEt)_2$), 3.11 (1H, dd, *J* 4Hz, *J* 18.5Hz, 1 x CH_2CH), 3.32 (1H, dd, *J* 5Hz, *J* 18.5Hz, 1 x CH_2CH), 3.50 (3H, d, *J* 1.5Hz, OCH_3), 4.04-4.11 (4H, m, 2 x OCH_2CH_3), 4.71 (1H, ddd, *J* 4Hz, *J* 5Hz, *J* 8Hz, CH_2CH), 7.36-7.53 (5H, m, C_6H_5) and 7.56 (1H, d, *J* 8Hz, NH); δ_F (235MHz; $CDCl_3$) -70.58 (s, CF_3).

Mosher's derivative (24) The general procedure with (2S)-^{t}butyl 2-amino-5-diethylphosphono-4-oxo pentanoate (22) (22mg, 0.07mmol.) and (S)-Mosher's acid chloride afforded the (S, R)-Mosher' acid derivative (24) (53mg crude mass) as a yellow oil; δ_H (500MHz; $CDCl_3$) 1.34 (6H, t, *J* 7Hz, 2 x OCH_2CH_3), 1.43 (9H, s, $CHCO_2C(CH_3)_3$), 3.11 (2H, d, *J* 22Hz, 1 x $CH_2P(O)(OEt)_2$), 3.20 (1H, dd, *J* 4Hz, *J* 18.5Hz, 1 x CH_2CH), 3.35 (1H, dd, *J* 4.5Hz, *J* 18.5Hz, 1 x CH_2CH), 3.35 (3H, d, *J* 1Hz, OCH_3), 4.03-4.12 (4H, m, 2 x OCH_2CH_3), 4.71 (1H, ddd, *J* 4Hz, *J* 4.5Hz, *J* 8Hz, CH_2CH), 7.39-7.52 (5H, m, C_6H_5) and 7.56 (1H, d, *J* 8Hz, NH); δ_F (235MHz; $CDCl_3$) -72.17 (s, CF_3).

Mosher's acid derivative. (27) The general procedure with (2S)-benzyl 2-amino-4-oxo octanoate (26) (22mg, 0.08mmol.) and (R)-Mosher's acid chloride afforded the (S, S) Mosher's acid derivative (27) (51mg crude mass) as a yellow oil; δ_H (200MHz; $CDCl_3$) 0.92 (3H, t, *J* 7Hz, CH_2CH_3), 1.15-1.50 (4H, m, $CH_2CH_2CH_2CH_3$), 2.25 (2H, t, *J* 7Hz, $CH_2CH_2CH_2CH_3$), 2.90 (2H, dd, *J* 4Hz, *J* 17Hz, 1 x CH_2CH), 3.20 (2H, dd, *J* 4Hz, *J* 17Hz, 1 x CH_2CH), 3.48 (3H, s, OCH_3), 4.34 (1H, ddd, *J* 4Hz, *J* 4Hz, *J* 8Hz, CH_2CH),

5.12 and 5.23 (2H, ABq, J_{AB} 14Hz, $CH_2(C_6H_5)$), 7.20-7.60 (10H, m, 2 x (C_6H_5)) and 8.22 (1H, d, *J* 8Hz, NH); δ_F (235MHz; $CDCl_3$) -70.57 (s, CF_3).

Mosher's acid derivative. (28) The general procedure with (2S)-benzyl 2-amino-4-oxo octanoate (26) (21mg, 0.08mmol.) and (S)-Mosher's acid chloride afforded the (S, R) Mosher's acid derivative (28) (50mg crude mass) as a yellow oil; δ_H (200MHz; $CDCl_3$) 0.89 (3H, t, *J* 7Hz, CH_3), 1.20-1.59 (4H, m, $CH_2CH_2CH_2CH_3$), 2.40 (2H, t, *J* 8Hz, $CH_2CH_2CH_2CH_3$), 2.85-3.20 (2H, m, CH_2CH), 3.29 (3H, s, OCH_3), 4.85 (1H, td, *J* 4Hz, *J* 8Hz, CH_2CH), 5.12 and 5.18 (2H, ABq, J_{AB} 13Hz, $CH_2(C_6H_5)$), 7.31-7.63 (10H, m, 2 x (C_6H_5)) and 7.94 (1H, d, *J* 8Hz, NH); δ_F (235MHz; $CDCl_3$) -71.14 (s, CF_3).

(3S)-1-Phenylsulphonyl-3-hydroxybutane. (29a) To a stirred solution of methylphenylsulphone (7) (700mg, 4.49mmol.) in anhydrous THF (10ml), under an inert atmosphere of Ar, and cooled to -78°C was added ^{n}butyllithium (3.1ml of a 1.45M solution in hexanes, 4.48mmol., 1 eq.). The reaction mixture was stirred at -78°C for fifteen minutes and then at 0°C for ten minutes before being recooled to -78°C whereupon (S)-propylene oxide (471µl, 6.72mmol., 1.5 eq.) was added. The mixture was allowed to warm to room temperature over one hour and then stirred at room temperature for a further sixteen hours before being quenched by the addition of saturated aqueous NH_4Cl (10ml) and being diluted with dichloromethane (50ml), washed with saturated aqueous NH_4Cl (20ml) and saturated aqueous brine (20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Flash chromatography (SiO_2, dichloromethane:ether; 80:20) afforded *(3S) 1-phenylsulphonyl-3-hydroxybutane* (29a) as a colourless oil (814mg, 85%); $[\alpha]_D$ +22.8° (*c* 1.0 in $CHCl_3$). ^{1}H n.m.r data was in accordance with that previously reported for the racemate.[13]

(3R)-1-Phenylsulphonyl-3-hydroxybutane. (29b) The procedure above with methylphenylsulphone (7) (753mg, 4.83mmol.) and (R)-propylene oxide afforded *(3R)-1-phenylsulphonyl-3-hydroxybutane* (29b) as a colourless oil (902mg, 87%); $[\alpha]_D$ -23.4° (*c* 1.0 in $CHCl_3$). ^{1}H n.m.r data was in accordance with that previously reported for the racemate.[13]

(3S)-1-Phenylsulphonyl 3-^{t}butyldimethylsilyloxybutane. (30a) To a stirred solution of (3S)-1-phenylsulphonyl-3-hydroxybutane (29a) (780mg, 3.64mmol.) in anhydrous DMF (25ml), under an inert atmosphere of Ar, was added ^{t}butyldimethylsilylchloride (660mg, 4.37mmol., 1.2 eq.) and imidazole (620mg, 9.11mmol., 2.5 eq.) The reaction mixture was then left to stir at 35°C for fourteen hours before being concentrated *in vacuo* and the residue being taken up in dichloromethane (80ml), washed with 1M HCl (2 x 40ml), saturated aqueous $NaHCO_3$ (40ml), saturated aqueous brine (40ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash chromatography (SiO_2, P.E. 30-40:ether; 80:20) afforded *(3S)-1-phenylsulphonyl 3-^{t}butyldimethylsilyloxybutane* (30a) as a colourless oil (1.16g, 97%), (R_f 0.3, P.E. 30-40:ether; 80:20), (Found: C, 58.53: H, 8.88. $C_{16}H_{28}O_3SSi$ requires C 58.49; H, 8.59%); $[\alpha]_D$ +11.7° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, Thin film, NaCl plates) 2956s, 2931s, 2857s, 2742s, 1448s, 1307s, 1148s, 1088s, 1021s, 838s, 777s and 690s cm^{-1}; δ_H (200MHz; $CDCl_3$) -0.01 and 0.01 (6H, 2 x s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.10 (3H, d, *J* 6Hz, $CHCH_3$), 1.71-1.93 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)$), 3.20-3.32 (2H, m, $CH_2SO_2(C_6H_5)$), 3.80-3.90 (1H, m, $CH(OSi(CH_3)_2C(CH_3)_3)$), 7.53-7.70 (3H, m, meta and para $SO_2(C_6H_5)$ and 7.89-7.93 (2H, m, ortho $SO_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) -5.16 and -4.65 ($Si(CH_3)_2$),

17.74 ($SiC(CH_3)_3$), 23.28 ($CHCH_3$), 25.60 ($SiC(CH_3)_3$), 33.01 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)$), 52.60 ($CH_2SO_2(C_6H_5)$), 66.40 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 128.16, 129.45 and 138.84 (Aromatic CH) and 139.26 (Aromatic ipso C); m/z (chemical ionisation, NH_3) 329[$(MH)^+$, 100%], 271[66], 197[66], 152[20], 135[30]. 90[18] and 74[22].

(3R)-1-Phenylsulphonyl 3-^{t}butyldimethylsilyloxybutane. (30b) The procedure above with (3R)-1-phenylsulphonyl-3-hydroxybutane (29b) (880mg, 4.11mmol.) afforded *(3R)-1-phenylsulphonyl 3-^{t}butyldimethylsilyloxybutane* (30b) as a colourless oil (1.31g, 97%); $[\alpha]_D$ -11.0° (*c* 1 in $CHCl_3$). All other physical and spectroscopic data were identical to that given for (29a) above.

(2S, 7S)-^{t}Butyl-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate. (33a) To a stirred suspension of 5% Pd/$CaCO_3$ in ethyl acetate (1ml) was added (2S, 7S)-^{t}butyl *N*-(benzyloxycarbonyl) 2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (32a) (212mg, 0.43mmol.) as a solution in ethyl acetate (1ml). The resulting mixture was stirred under an atmosphere of H_2 for one hour before being filtered through a plug of celite® and concentrated *in vacuo* to afford *(2S, 7S)-^{t}butyl-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate* (33a) as a white foam (153mg, quant.); δ_H (200MHz; $CDCl_3$) 0.04 and 0.05 (6H, 2 x s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.46 (9H, s, $CHCO_2C(CH_3)_3$), 1.59-1.80 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.18 (2H, br s, NH_2), 2.38-2.64 (2H, m, $CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.80-3.00 (2H, m, $CH_2CHCO_2C(CH_3)_3$) and 3.72-3.89 (2H, m, $CH(OSi(CH_3)_2C(CH_3)_3$ and $CH_2CHCO_2C(CH_3)_3$).

(2S, 7R)-^{t}Butyl-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate. (33b) The above procedure with (2S, 7R)-^{t}butyl *N*-(benzyloxycarbonyl)-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (32b) (187mg, 0.38mmol.) afforded *(2S, 7R)-^{t}butyl-2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate* (33b) as a white foam (136mg, quant.); δ_H (200MHz; $CDCl_3$) 0.05 (6H, 2 x s, $Si(CH_3)_2$) 0.89 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.47 (9H, s, $CHCO_2C(CH_3)_3$), 1.55-1.80 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.40-2.51 (2H, m, $CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.95-3.27 (4H, m, NH_2 and $CH_2CHCO_2C(CH_3)_3$) and 3.72-3.98 (2H, m, $CH(OSi(CH_3)_2C(CH_3)_3$ and $CH_2CHCO_2C(CH_3)_3$).

General procedures for the preparation of (1a), (1b), ent-(1c) and ent-(1d) from (33a) and (33b)

General procedure for the coupling affording (35). To a stirred solution of amine (33a) or (33b) in anhydrous dichloromethane (≈ 7ml per mmol. of amine), under an inert atmosphere of Ar, was added triethylamine (2eq.) followed by (R) or (S)-benzyl α-trifluoromethanesulphonyloxy propanoate[20] (2eq.) as a solution in anhydrous dichloromethane (≈ 5ml per mmol of amine). The resulting mixture was stirred at room temperature for twelve hours before being diluted with dichloromethane and washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure for the hydrogenolysis of (35) to afford (36). To a stirred suspension of 10% Pd/C (cat.) in ethyl acetate (≈ 3ml per mmol. of ester) was added (35) as a solution in ethylacetate (≈ 3ml per

mmol. of ester). The resulting mixture was stirred under an atmosphere of H_2 for one hour before being filtered through a plug of celite® and concentrated *in vacuo*.

General procedure for the coupling of tyrosine to (36) to afford (37). To a stirred solution of (36) in anhydrous dichloromethane (≈ 4ml per mmol. of carboxylic acid) was added 1-hydroxybenzotriazole (1.1eq.), DCC (1.1eq.) and tyrosine *t*-butyl ester (1eq.). The reaction mixture was then stirred at room temperature for one hour before being diluted with CH_2Cl_2 washed with 1M HCl, saturated aqueous $NaHCO_3$ and saturated aqueous brine. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* .

General procedure for full deprotection. Preparation of (1a), (1b), ent-(1c) and ent-(1d) To a stirred solution of (37) (≈ 30mg, 0.046mmol.) in anisole (0.5ml) was added TFA (2ml) and the mixture was stirred at room temperature for two hours before being concentrated *in vacuo*. The residue was taken up in water (30ml) and washed with Et_2O (10ml). The aqueous layer was then lyophilised three times. Further purification could be achieved by h.p.l.c. as indicated by Ando *et al.*[1]

Synthesis of (1a)

***N*-((1S, 6S)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester. (35a)** The general procedure with (2S, 7S)-^{t}butyl 2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (33a) (145mg, 0.40mmol.) and (R)-benzyl α-trifluoromethanesulphonyloxy propanoate (34) followed by flash chromatography (SiO_2, P.E 30-40:ether; 70:30) afforded *N-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester* (35a) as a colourless oil (190mg, 91%), (R_f 0.25, P.E 30-40:ether 70:30); $[\alpha]_D$ -8.2° (*c* 1.3 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 2931m, 1738br s (C=O), 1456s, 1369s, 1256s and 776m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.04 and 0.05 (6H, 2 x s, $Si(CH_3)_2$) and 0.89 (9H, s, $SiC(CH_3)_2$), 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.34 (3H, d, *J* 7Hz, $NHCHCH_3$), 1.45 (9H, s, $CH_2CHCO_2C(CH_3)_3$), 1.58-1.85 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.48 (2H, d of ABq, *J* 6Hz, *J* 15Hz, $CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.70-2.92 (2H, m, $CH_2CHCO_2C(CH_3)_3$), 3.42-3.63 (2H, m, $CH_2CHCO_2C(CH_3)_3$ and $NHCHCH_3$), 3.83 (1H, m, $CH(OSi(CH_3)_2C(CH_3)_3)$), 5.16 and 5.18 (2H, ABq, *J* 12Hz, $NHCHCO_2CH_2(C_6H_5)$ and 7.28-7.37 (5H, m, $NHCHCO_2CH_2(C_6H_5)$); δ_C (50MHz; $CDCl_3$) -4.95 and -4.61 ($Si(CH_3)_2$), 17.92 ($SiC(CH_3)_3$), 18.96 and 23.53 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $NHCHCH_3$), 25.74 and 27.85 ($CHCO_2C(CH_3)_3$ and $SiC(CH_3)_3$), 32.80 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.81 ($CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 46.24 ($CH_2CHCO_2C(CH_3)_3$), 55.40 and 56.21 ($NHCHCH_3$ and $CH_2CHCO_2C(CH_3)_3$), 66.49 ($NHCHCO_2CH_2(C_6H_5)$), 67.49 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 81.54 ($CHCO_2C(CH_3)_3$), 128.34 and 128.74 (Aromatic CH), 136.04 (Aromatic ipso C), 173.19 and 174.97 ($CHCO_2C(CH_3)_3$ and $NHCHCO_2CH_2(C_6H_5)$) and 208.75 ($C(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 522[$(MH)^+$, 100%], 420[10], 288[31], 236[17], 180[20], 173[15], 108[11], 91[52] and 70[10].

***N*-((1S, 6S)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine. (36a)** The general procedure with *N*-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester (35a) (170mg, 0.33mmol.) afforded *N-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-*

^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine (36a) as a white foam (139mg, quant.), (Found: C, 58.44; H, 9.75; N 3.06. $C_{21}H_{41}NO_6Si$ requires C, 58.44; H, 9.57; N, 3.06%); $[\alpha]_D$ +17.7° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 1757s (C=O), 1715m, 1320s and 838m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.03 and 0.05 (6H, 2 x s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.44 (3H, d, *J* 7Hz, $NHCHCH_3$), 1.47 (9H, s, $CH_2CHCO_2C(CH_3)_3$), 1.55-1.88 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.54-2.60 (2H, m, $CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.70-2.95 (2H, m, $CH_2CHCO_2C(CH_3)_3$), 3.32 (1H, q, *J* 7Hz, $NHCHCH_3$), 3.42-3.52 (1H, m, $CH_2CHCO_2C(CH_3)_3$), 3.75-3.90 (1H, m, $CH(OSi(CH_3)_2C(CH_3)_3)$) and 5.25 (2H, br s, NH and OH); δ_C (125MHz; $CDCl_3$) -4.95 and -4.58 ($Si(CH_3)_2$), 17.89 ($SiC(CH_3)_3$), 18.68 and 23.53 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $NHCHCH_3$), 25.74 and 27.82 ($CH_2CHCO_2C(CH_3)_3$ and $SiC(CH_3)_3$), 32.72 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.73 ($CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 44.64 ($CH_2CHCO_2C(CH_3)_3$), 56.43 and 56.60 ($NHCHCH_3$ and $CH_2CHCO_2C(CH_3)_3$), 67.36 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 82.92 ($CH_2CHCO_2C(CH_3)_3$), 171.91 and 175.59 ($NHCHCO_2H$ and $CH_2CHCO_2C(CH_3)_3$) and 208.78 ($C(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 432[$(MH)^+$, 20%], 343[23], 211[30], 90[100].

***N*-((1S, 6S)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanyl-L-tyrosine^t-butylester. (37a).** The general procedure with *N*-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine (36a) (119mg, 0.28mmol.) and (L)-tyrosine *t*-butylester followed by flash chromatography (SiO_2, P.E. 30-40:ether; 30:70) afforded *N-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanyl-L-tyrosine ^{t}butylester* (37a) as a colourless oil (144mg, 79%), (R_f 0.2, P.E 30-40:ether 20:80), m/z (high resolution) Found 651.404, $C_{34}H_{58}N_2O_8Si+H^+$ requires 651.404; $[\alpha]_D$ -5.8° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 3347br m (NH and OH), 2932s, 2858s, 1728s (C=O), 1657s, 1615s, 1516s, 1451s, 1371s, 1256s, 1156s and 878s cm^{-1}; δ_H (500MHz; $CDCl_3$) 0.06 and 0.07 (6H, 2 x s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_2$), 1.14 (6H, 2 x d, 2 x *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $NHCHCH_3$), 1.43 and 1.46 (2 x 9H, 2 x s, $CH_2CHCO_2C(CH_3)_3$ and $NHCHCO_2C(CH_3)_3$), 1.61-1.77 (2H, m, $CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.39-2.54 (2H, m, $CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.75-2.83 (2H, m, $CH_2CHCO_2C(CH_3)_3$), 3.00 (1H, dd, *J* 7.5Hz, *J* 14Hz, 1 x $CH_2(C_6H_4)OH$) , 3.15 (1H, dd, *J* 5.5Hz, *J* 14Hz, 1 x $CH_2(C_6H_4)OH$), 3.21-3.25 (1H, m, $NHCHCH_3$), 3.32-3.38 (1H, m, $CH_2CHCO_2C(CH_3)_3$), 3.83-3.87 (1H, m, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 4.68 (1H, ddd, *J* 5.5Hz, *J* 7.5Hz, *J* 8Hz, $NHCHCH_2(C_6H_4)OH$), 6.28 (1H, br s, OH), 6.71 and 7.02 (2 x 2H, 2 x d, 2 x *J* 8.5Hz, $(C_6H_4)OH$) and 7.91 (1H, d, *J* 8Hz, $NHCH(CO_2C(CH_3)_3)CH_2(C_6H_4)OH$); δ_C (50MHz; $CDCl_3$) -4.90 and -4.61 ($Si(CH_3)_2$), 17.92 ($SiC(CH_3)_3$), 19.68 and 23.52 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $NHCHCH_3$), 25.75 ($SiC(CH_3)_3$), 27.88 ($CH_2CHCO_2C(CH_3)_3$ and $NHCHCO_2C(CH_3)_3$)), 32.80 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 37.03 and 38.81 ($CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $CH_2(C_6H_4)OH$) 45.93 $CH_2CHCO_2C(CH_3)_3$), 53.29, 56.50 and 57.48 ($NHCHCH_3$, $CH_2CHCO_2C(CH_3)_3$ and $CHCH_2(C_6H_4)OH$), 67.59 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 81.93 ($CH_2CHCO_2C(CH_3)_3$ and $NHCHCO_2C(CH_3)_3$), 115.45 and 130.48 (Aromatic CH), 127.65 and 155.03 (2 x Aromatic ipso C), 171.23, 173.29 and 175.49 ($CH_2CHCO_2C(CH_3)_3$, $NHCHCO_2C(CH_3)_3$ and NHC(O)) and 209.07 ($C(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (desorption chemical ionisation, NH_3) 651[$(MH)^+$, 10%], 343[42], 309[65], 253[100], 225[50], 211[49], 155[20] and 89[20].

***N*-((1S, 6S)-6-Hydroxy-1-carboxylic acid-3-oxo-heptyl)-L-alanyl-L-tyrosine (1a) (trifluoromethane sulphonate salt).** The general procedure with *N*-((6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanyl-L-tyrosine^t-butylester (37a) (30mg, 0.046mmol.) afforded *N-((1S, 6S)-6-hydroxy-1-carboxylic acid-3-oxo-heptyl)-L-alanyl-L-tyrosine (1a) (trifluoromethane sulphonate salt)* as a white powder (18mg, 73%), m.p. 95-97°C, (Found C, 49.35; H, 5.70; N, 5.40. $C_{22}F_3H_{29}N_2O_{10}$ requires C, 49.07; H, 5.43; N, 5.20%; $[\alpha]_D$ +14.2° (*c* 0.375 in H_2O); ν_{max} (FT IR, KBr disc) 3386br m (NH and OH), 1775m, 1717s, 1674s, 1616s, 1518s, 1448s, 1384s, 1201s and 1141s cm^{-1}; δ_H (500MHz; D_2O) 1.05 (3H, d, *J* 6.5Hz, CH(OH)C$\underline{H}_3$), 1.42 (3H, d, *J* 7Hz, NHCHC$\underline{H}_3$), 1.54-1.60 (2H, m, C$\underline{H}_2$CH(OH)CH$_3$), 2.44 (2H, t, *J* 7.5Hz, C$\underline{H}_2$CH$_2$CH(OH)CH$_3$), 2.69 (1H, dd, *J* 11Hz, *J* 14Hz, 1 x C$\underline{H}_2$(C$_6$H$_4$)OH), 2.82-2.88 (2H, m, 1 x C$\underline{H}_2$CHCO$_2$H and CH$_2$C$\underline{H}$CO$_2$H), 3.03 (1H, dd, *J* 5Hz, *J* 18Hz, 1 x C$\underline{H}_2$CHCO$_2$H), 3.20 (1H, dd, *J* 5Hz, 14Hz, 1 x C$\underline{H}_2$(C$_6$H$_4$)OH) 3.66-3.70 (1H, m, C$\underline{H}$(OH)CH$_3$), 3.95 (1H, q, *J* 7Hz, NHC$\underline{H}$CH$_3$), (NHC$\underline{H}$CO$_2$H obscured by HOD signal) and 6.73 and 7.06 (4H, 2 x d, 2 x *J* 8.5Hz, (C$_6\underline{H}_4$)OH); δ_C (125MHz; $CDCl_3$) 16.96 and 22.48 (CH(OH)$\underline{C}$H$_3$ and NHCH$\underline{C}$H$_3$), 32.25 ($\underline{C}$H$_2$CH(OH)CH$_3$), 37.06, 38.82 and 42.40 ($\underline{C}$H$_2$CHCO$_2$H, $\underline{C}$H$_2$CH$_2$CH(OH)CH$_3$ and $\underline{C}$H$_2$(C$_6$H$_4$)OH), 55.50, 57.72 and 58.31 (3 x NH$\underline{C}$HCO), 67.65 ($\underline{C}$H(OH)CH$_3$), 116.22 and 131.40 (Aromatic $\underline{C}$H), 129.33 and 155.26 (2 x Aromatic ipso $\underline{C}$), 169.66, 171.45 and 175.00 (CH$_2$CH$\underline{C}$O$_2$H, NHCH$\underline{C}$O$_2$H and $\underline{C}$(O)NH) and 211.55 ($\underline{C}$(O)CH$_2$CH$_2$CH(OH)CH$_3$); δ_F (235MHz; $CDCl_3$) -77.65 (s, C$\underline{F}_3$); m/z (FAB) 463[(MK$^+$, 6%], 447[(MNa$^+$, 10], 407[37], 361[15], 309[35], 253[56], 155[100], 136[21], 107[26], 99[79], 83[20], 70[30] and 55[33].

The derivative (38) was prepared from (1a) according to the procedure of Ando *et al.*[1]; δ_H (200MHz; $CDCl_3$) 1.22 (6H, 2 x d, 2 x *J* 6Hz, CH(OCOCH$_3$)C$\underline{H}_3$ and NHCHC$\underline{H}_3$), 1.70-1.90 (2H, m, C$\underline{H}_2$CH(OCOCH$_3$)CH$_3$), 2.03 and 2.29 (2 x 3H, 2 x s, 2 x OCOC$\underline{H}_3$), 2.38-2.50 (2H, m, C$\underline{H}_2$CH$_2$CH(OCOCH$_3$)CH$_3$), 2.79 (2H, d, *J* 5.5Hz, C$\underline{H}_2$CHCO$_2$CH$_3$), 3.15-3.27 (3H, m, C$\underline{H}_2$(C$_6$H$_4$)OH and NHC$\underline{H}$CH$_3$), 3.55 (1H, t, *J* 6Hz, CH$_2$C$\underline{H}$CO$_2$CH$_3$), 3.70 and 3.75 (2 x 3H, 2 x s, 2 x CO$_2$C$\underline{H}_3$), 4.72-4.93 (2H, m, C$\underline{H}$(OCOCH$_3$)CH$_3$ and NHC$\underline{H}$CH$_2$), 7.00 and 7.17 (2 x 2H, 2 x d, 2 x *J* 8.5Hz, (C$_6\underline{H}_4$)OCOCH$_3$) and 7.93 (1H, d, *J* 8Hz, NHCHCO$_2$CH$_3$).

Synthesis of (1b)

***N*-((1S, 6R)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester. (35b)** The general procedure with (2S, 7R)-^{t}butyl 2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (33b) (136mg, 0.38mmol.) and (R)-benzyl 2-trifluoromethanesulphonyloxypropanoate (34) followed by flash chromatography (SiO_2, P.E 30-40:ether; 70:30) afforded *N-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester* (35b) as a colourless oil (160mg, 81%), (R_f 0.25, P.E 30-40:ether 70:30), m/z (high resolution) Found 522.325. $C_{28}H_{47}NO_6Si+H^+$ requires 522.325; $[\alpha]_D$ -25.7° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 2930m, 1736br s (C=O), 1473s, 1369s, 1153s, 1084m, 837s and 776m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.04 and 0.05 (6H, 2 x s, Si(C$\underline{H}_3$)$_2$), 0.89 (9H, s, SiC(C$\underline{H}_3$)$_2$), 1.12 (3H, d, *J* 6Hz, CH(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)C$\underline{H}_3$), 1.33 (3H, d, *J* 7Hz, NHCHC$\underline{H}_3$), 1.44 (9H, s, CH$_2$CHCO$_2$C(C$\underline{H}_3$)$_3$), 1.55-1.80 (2H, m, C$\underline{H}_2$CH(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)CH$_3$), 2.42-2.55 (2H, m, C$\underline{H}_2$CH$_2$CH(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)CH$_3$), 2.80 (2H, ABq, *J* 12.5Hz, C$\underline{H}_2$CHCO$_2$C(CH$_3$)$_3$), 3.50-3.62 (2H, m, CH$_2$C$\underline{H}$CO$_2$C(CH$_3$)$_3$ and NHC$\underline{H}$CH$_3$), 3.75-3.88 (1H, m, C$\underline{H}$(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)), 5.12 and 5.18

(2H, ABq, *J* 15Hz, $NHCHCO_2C\underline{H}_2(C_6H_5)$ and 7.30 (5H, s, $NHCHCO_2CH_2(C_6\underline{H}_5)$); δ_C (50MHz; $CDCl_3$) -4.97 and -4.61 ($Si(\underline{C}H_3)_2$), 17.92 ($Si\underline{C}(CH_3)_3$), 18.97 and 23.56 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and $NHCH\underline{C}H_3$), 25.75 and 27.85 ($CO_2C(\underline{C}H_3)_3$ and $SiC(\underline{C}H_3)_3$), 32.83 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.92 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 46.30 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 55.41 and 56.16 ($NH\underline{C}HCH_3$ and $CH_2\underline{C}HCO_2C(CH_3)_3$), 66.47 ($NHCHCO_2\underline{C}H_2(C_6H_5)$), 67.52 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)CH_3$), 81.54 ($CH_2CHCO_2\underline{C}(CH_3)_3$), 128.38 and 128.74 (Aromatic $\underline{C}H$), 136.03 (Aromatic ipso $\underline{C}$), 173.25 and 174.97 ($CH_2CH\underline{C}O_2C(CH_3)_3$ and $NHCH\underline{C}O_2CH_2(C_6H_5)$) and 208.72 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 522[$(MH)^+$, 8%], 343[10], 236[12], 180[100] and 91[23].

***N*-((1S, 6R)-6-ᵗButyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanine (36b).** The general procedure with *N*-((1S, 6R)-6-ᵗbutyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanine benzyl ester (35b) (140mg, 0.27mmol.) afforded *N-((1S, 6R)-6-ᵗbutyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanine* (36b) as a white foam (116mg, quant.); $[\alpha]_D$ -6.0° (*c* 0.5 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 1753s and 1718s (C=O), 1372s, 1257s, 1149s, 1030s, 838m and 777s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.04 and 0.06 (6H, 2 x s, $Si(C\underline{H}_3)_2$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 1.14 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.44 (3H, d, *J* 7Hz, $NHCHC\underline{H}_3$), 1.48 (9H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$), 1.52-1.88 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.53 (2H, t, *J* 7.5Hz, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.65-2.90 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.20 (2H, br s, O<u>H</u> and N<u>H</u>), 3.33 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), 3.42 (1H, dd, *J* 4Hz, *J* 8Hz, $CH_2C\underline{H}CO_2C(CH_3)_3$) and 3.78-3.90 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$); δ_C (50MHz; $CDCl_3$) -4.99 and -4.58 ($Si(\underline{C}H_3)_2$), 17.92 ($Si\underline{C}(CH_3)_3$), 18.94 and 23.56 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and $NHCH\underline{C}H_3$), 25.74 and 27.85 ($CH_2CHCO_2C(\underline{C}H_3)_3$ and $SiC(\underline{C}H_3)_3$), 32.73 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.79 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 44.85 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 56.56 ($NH\underline{C}HCH_3$ and $CH_2\underline{C}HCO_2C(CH_3)_3$), 67.28 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)$), 82.88 ($CH_2CHCO_2\underline{C}(CH_3)_3$), 172.24 and 175.62 ($NHCH\underline{C}O_2H$ and $CH_2CH\underline{C}O_2C(CH_3)_3$) and 208.93 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 432[$(MH)^+$, 25%], 343[40], 211[27] and 90[100].

***N*-((1S, 6R)-6-ᵗButyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanyl-L-tyrosineᵗ-butylester. (37b)** The general procedure with *N*-((1S, 6R)-6-ᵗbutyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanine (36b) (95mg, 0.22mmol.) and (L)-tyrosine *t*-butylester followed by flash chromatography (SiO_2, P.E. 30-40:ether; 30:70) afforded *N-((1S, 6R)-6-ᵗbutyldimethylsilyloxy-1-ᵗbutyloxycarbonyl-3-oxo-heptyl)-L-alanyl-L-tyrosineᵗ-butylester* (37b) as a colourless oil (120mg, 84%), (R_f 0.3, P.E 30-40:ether 30:70); $[\alpha]_D$ -32.5° (*c* 0.75 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 3347s (NH and OH), 2932s, 2858s, 1729s (C=O), 1662s, 1516s, 1371s, 1156s, 911s, 898s and 731s cm^{-1}; δ_H (500MHz; $CDCl_3$) 0.081 and 0.086 (6H, 2 x s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $SiC(C\underline{H}_3)_2$), 1.16 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$) 1.18 (3H, d, *J* 7Hz, $NHCHC\underline{H}_3$), 1.43 and 1.46 (2 x 9H, 2 x s, $CH_2CHCO_2C(C\underline{H}_3)_3$ and $NHCHCO_2C(C\underline{H}_3)_3$), 1.60-1.78 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.40-2.52 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.62 (2H, dd, *J* 3.5Hz, *J* 18Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 2.83 (1H, dd, *J* 11.5Hz, *J* 18Hz, 1 x $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.03 (1H, dd, *J* 7Hz, *J* 14Hz, 1 x $C\underline{H}_2(C_6H_4)OH$) , 3.08 (1H, dd, *J* 5.5Hz, *J* 14Hz, 1 x $C\underline{H}_2(C_6H_4)OH$), 3.23 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), 3.28-3.31 (1H, m, $CH_2C\underline{H}CO_2C(CH_3)_3$), 3.85-3.91 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$), 4.69

(1H, ddd, *J* 5.5Hz, *J* 7Hz, *J* 9Hz, NHC<u>H</u>$CH_2(C_6H_4)OH$), 6.72 and 7.02 (2 x 2H, 2 x d, 2 x *J* 8.5Hz, ($C_6\underline{H}_4$)OH) and 7.88 (1H, d, *J* 9Hz, N<u>H</u>$CH(CO_2C(CH_3)_3)CH_2(C_6H_4)OH$); δ_C (50MHz; $CDCl_3$) -4.68 and -4.42 ($Si(\underline{C}H_3)_2$), 18.14 ($Si\underline{C}(CH_3)_3$), 19.87 and 23.43 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and $NHCH\underline{C}H_3$), 25.92 ($SiC(\underline{C}H_3)_3$), 28.07 and 28.80 ($CH_2CHCO_2C(\underline{C}H_3)_3$ and $NHCHCO_2C(\underline{C}H_3)_3$), 32.96 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 37.06 and 38.88 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3CH_3$ and $\underline{C}H_2(C_6H_4)OH$) 46.07 $\underline{C}H_2CHCO_2C(CH_3)_3$), 53.23, 56.71 and 57.74 ($NH\underline{C}HCH_3$, $CH_2\underline{C}HCO_2C(CH_3)_3$ and $\underline{C}HCH_2(C_6H_4)OH$), 67.81 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)$), 81.79 ($NHCHCO_2\underline{C}(CH_3)_3$ and $CH_2CHCO_2\underline{C}(CH_3)_3$), 115.39 and 130.51 (Aromatic <u>C</u>H), 128.01 and 155.27 (2 x Aromatic ipso <u>C</u>), 170.83, 173.10 and 175.21 ($NHCH\underline{C}O_2C(CH_3)_3$, $CH_2CH\underline{C}O_2C(CH_3)_3$) and <u>C</u>O(NH)) and 208.42 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (desorption chemical ionisation, NH_3) [651$(MH)^+$, 6%], 386[10], 343[35], 309[37], 253[100], 229[20], 211[32], 155[20], 136[11], 89[25].

***N*-((1<u>S</u>, 6<u>R</u>)-6-Hydroxy-1-carboxylic acid-3-oxo-heptyl)-<u>L</u>-alanyl-<u>L</u>-tyrosine (1b) (trifluoromethane sulphonate salt).** The general procedure with *N*-((6<u>R</u>)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-<u>L</u>-alanyl-<u>L</u>-tyrosine^t-butylester (37b) (31mg, 0.048mmol.) afforded *N-((1<u>S</u>, 6<u>R</u>)-6-hydroxy-1-carboxylic acid-3-oxo-heptyl)-<u>L</u>-alanyl-<u>L</u>-tyrosine (1b) (trifluoromethane sulphonate salt)* as a white powder (19mg, 76%), m.p. 105-107°C; $[\alpha]_D$ +3.9° (*c* 0.375 in H_2O); ν_{max} (FT IR, KBr disc) 3420br m (NH and OH), 1720s, 1674s, 1616s, 1518s, 1447s, 1384s, 1201s and 1142s cm^{-1}; δ_H (500MHz; D_2O) 1.04 (3H, d, *J* 6.5Hz, CH(OH)C<u>H</u>$_3$), 1.40 (3H, d, *J* 7Hz, NHCHC<u>H</u>$_3$), 1.54-1.58 (2H, m, C<u>H</u>$_2$CH(OH)CH_3), 2.40 (1H, ddd, *J* 15Hz, *J* 8Hz, *J* 6.5Hz, 1 x C<u>H</u>$_2$CH$_2$CH(OH)CH_3), 2.47 (1H, ddd, *J* 15Hz, *J* 8.5Hz, *J* 6.5Hz, 1 x C<u>H</u>$_2$CH$_2$CH(OH)CH_3), 2.66 (1H, dd, *J* 11Hz, *J* 14Hz, 1 x C<u>H</u>$_2(C_6H_4)OH$), 2.84-2.88 (2H, m, 1 x C<u>H</u>$_2$CHCO$_2$H and CH$_2$C<u>H</u>CO$_2$H), 3.05 (1H, dd, *J* 6.5Hz, *J* 20Hz, 1 x C<u>H</u>$_2$CHCO$_2$H), 3.20 (1H, dd, *J* 4.5Hz, 14Hz, 1 x C<u>H</u>$_2(C_6H_4)OH$) 3.65-3.68 (1H, m, C<u>H</u>(OH)CH_3), 3.96 (1H, q, *J* 7Hz, NHC<u>H</u>CH_3), (NHC<u>H</u>CO$_2$H obscured by HOD signal) and 6.71 and 7.05 (4H, 2 x d, *J* 8.5Hz, ($C_6\underline{H}_4$)OH); δ_C (125MHz; $CDCl_3$) 16.82 and 22.49 (CH(OH)<u>C</u>H$_3$ and NHCH<u>C</u>H$_3$), 32.26 ($\underline{C}H_2CH(OH)CH_3$), 37.01, 38.69 and 42.23 ($\underline{C}H_2CHCO_2H$, $\underline{C}H_2CH_2CH(OH)CH_3$ and $\underline{C}H_2(C_6H_4)OH$), 54.84, 56.73 and 58.37 (3 x NH<u>C</u>HCO), 67.60 (<u>C</u>H(OH)CH_3), 116.20 and 131.42 (Aromatic <u>C</u>H), 129.22 and 155.27 (2 x Aromatic ipso <u>C</u>), 169.54, 171.10 and 174.82 ($CH_2CH\underline{C}O_2H$, NHCH<u>C</u>O$_2$H and <u>C</u>(O)NH) and 211.04 ($\underline{C}(O)CH_2CH_2CH(OH)CH_3$); m/z (FAB) 463[(MK$^+$, 4%], 447[(MNa$^+$, 17], 425[9], 407[55], 361[14], 337[5], 309[45], 253[66], 242[17], 172[12], 155[100], 136[20], 126[14], 107[30], 99[80], 83[20], 70[30] and 55[32].

Synthesis of ent-(1c)

***N*-((1<u>S</u>, 6<u>S</u>)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-<u>D</u>-alanine benzyl ester. (35c).** The general procedure with (2<u>S</u>, 7<u>S</u>)-^{t}butyl 2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (33a) (150mg, 0.42mmol.) and (<u>S</u>)-benzyl 2-trifluoromethanesulphonyloxypropanoate followed by flash chromatography (SiO_2, P.E 30-40:ether; 70:30) afforded *N-((1<u>S</u>, 6<u>S</u>)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-<u>D</u>-alanine benzyl ester* (35c) as a colourless oil (182mg, 83%), (R_f 0.3, P.E 30-40:ether 70:30); $[\alpha]_D$ +12.2° (*c* 0.6 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 2930m, 1737br s (C=O), 1470s, 1369s, 1256s, 1153s, 837s and 776m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.04 and 0.05 (6H, 2 x s, Si$(\underline{C}H_3)_2$), 0.89 (9H, s, SiC$(\underline{C}H_3)_2$), 1.12 (3H, d, *J* 6Hz, CH(OSi$(CH_3)_2$C$(CH_3)_3$)C<u>H</u>$_3$),

1.31 (3H, d, *J* 7Hz, NHCHC$\underline{H}_3$), 1.44 (9H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$), 1.55-1.82 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.35-2.61 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.62-2.88 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.50 (1H, q, *J* 7Hz, NHC$\underline{H}$CH$_3$), 3.65 (1H, t, *J* 6.5Hz, $CH_2C\underline{H}CO_2C(CH_3)_3$), 3.75-3.90 (1H, m, C$\underline{H}$(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)), 5.12 and 5.20 (2H, ABq, *J* 12.5Hz, $NHCHCO_2C\underline{H}_2(C_6H_5)$ and 7.37 (5H, s, $NHCHCO_2CH_2(C_6\underline{H}_5)$); δ_C (50MHz; $CDCl_3$) -4.95 and -4.61 ($Si(\underline{C}H_3)_2$), 17.91 ($Si\underline{C}(CH_3)_3$), 18.64 and 23.57 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and NHCH$\underline{C}$H$_3$), 25.74 and 27.83 ($CO_2C(\underline{C}H_3)_3$ and $SiC(\underline{C}H_3)_3$), 32.77 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 39.31 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 46.05 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 55.02 and 55.90 (NH$\underline{C}HCH_3$ and $CH_2\underline{C}HCO_2C(CH_3)_3$), 66.56 ($NHCHCO_2\underline{C}H_2(C_6H_5)$), 67.52 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)CH_3$), 81.63 ($CH_2CHCO_2\underline{C}(CH_3)_3$), 128.31, 128.41 and 128.71 (Aromatic $\underline{C}$H), 135.96 (Aromatic ipso $\underline{C}$), 172.99 and 174.98 ($CH_2CH\underline{C}O_2C(CH_3)_3$ and $NHCH\underline{C}O_2CH_2(C_6H_5)$) and 208.48 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 522[$(MH)^+$, 100%], 420[12], 288[23], 236[12], 180[48], 173[18], 108[17], 91[48] and 70[11].

***N*-((1*S*, 6*S*)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine.** **(36c)** The general procedure with *N*-((1*S*, 6*S*)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine benzyl ester (35c) (100mg, 0.19mmol.) afforded *N-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine* (36c) as a white foam (83mg, quant.), $[\alpha]_D$ -0.8° (*c* 1.0 in $CHCl_3$); ν_{max} 2957m, 2897m, 1759s and 1719s (C=O), 1375s and 1157m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.03 (6H, s, $Si(C\underline{H}_3)_2$), 0.87 (9H, s, $SiC(C\underline{H}_3)_3$), 1.11 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.38 (3H, d, *J* 7Hz, NHCHC$\underline{H}_3$), 1.45 (9H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$), 1.60-1.80 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.32-2.65 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 3.02-3.20 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.45 (1H, q, *J* 7Hz, NHC$\underline{H}$CH$_3$), 3.72-3.98 (2H, m, $CH_2C\underline{H}CO_2C(CH_3)_3$ and C$\underline{H}$(OSi(CH$_3$)$_2$C(CH$_3$)$_3$)) and 6.99 (2H, br s, O$\underline{H}$ and N$\underline{H}$); δ_C (50MHz; $CDCl_3$) -4.92 and -4.61 ($Si(\underline{C}H_3)_2$), 15.96 ($Si\underline{C}(CH_3)_3$), 17.89 and 23.53 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and NHCH$\underline{C}$H$_3$), 25.74 and 27.73 ($CH_2CHCO_2C(\underline{C}H_3)_3$ and $SiC(\underline{C}H_3)_3$), 32.73 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 38.71 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 43.37 ($\underline{C}H_2CHCO_2C(CH_3)_3$), 54.99 and 56.53 (NH$\underline{C}HCH_3$ and $CH_2\underline{C}HCO_2C(CH_3)_3$), 67.49 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)$), 83.37 ($CH_2CHCO_2\underline{C}(CH_3)_3$), 169.96 and 174.88 (NHCH$\underline{C}$O$_2$H and $CH_2CH\underline{C}O_2C(CH_3)_3$) and 208.01 ($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (chemical ionisation, NH_3) 432[$(MH)^+$, 5%], 343[51], 229[28], 211[55] and 90[100].

***N*-((1*S*, 6*S*)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine^t-butylester** **(37c)** The general procedure with *N*-((1*S*, 6*S*)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine (36c) (70mg, 0.16mmol.) and (D)-tyrosine *t*-butylester followed by flash chromatography (SiO_2, P.E. 30-40:ether; 30:70) afforded *N-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine^t-butylester* (37c) as a colourless oil (84mg, 81%), (R_f 0.3, P.E 30-40:ether 30:70); $[\alpha]_D$ +10.2° (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2931s, 2858s, 1718s (C=O), 1462m, 1372s, 1257s, 1154s, 895s and 777m cm^{-1}; δ_H (500MHz; $CDCl_3$) 0.041 and 0.047 (6H, 2 x s, $Si(C\underline{H}_3)_2$), 0.88 (9H, s, $SiC(C\underline{H}_3)_2$), 1.10 (3H, d, *J* 7Hz, NHCHC$\underline{H}_3$) 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.43 (18H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$ and NHCHCO$_2$C(C$\underline{H}_3$)$_3$), 1.59-1.80 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.42-2.61 (2H, m,

$CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.76-2.91 (3H, m, $CH_2CHCO_2C(CH_3)_3$ and 1 x $CH_2(C_6H_4)OH$), 3.16-3.28 (2H, m, $NHCHCH_3$ and 1 x $CH_2(C_6H_4)OH$), 3.62 (1H, t, *J* 6Hz, $CH_2CHCO_2C(CH_3)_3$), 3.76-3.88 (1H, m, $CH(OSi(CH_3)_2C(CH_3)_3)$), 4.63-4.78 (1H, m, $NHCHCH_2(C_6H_4)OH$), 6.72 and 7.02 (2 x 2H, 2 x d, 2 x *J* 8.5Hz, $(C_6H_4)OH$) and 7.76 (1H, d, *J* 8.5Hz, $NHCH(CO_2C(CH_3)_3)CH_2(C_6H_4)OH$); δ_C (125MHz; $CDCl_3$) -4.69 and -4.41 ($Si(CH_3)_2$), 18.06 ($SiC(CH_3)_3$), 19.24 and 23.56 ($CH(OSi(CH_3)_2C(CH_3)_3)CH_3$ and $NHCHCH_3$), 25.87 ($SiC(CH_3)_3$), 27.96 and 28.01 ($CH_2CHCO_2C(CH_3)_3$ and $NHCHCO_2C(CH_3)_3$), 33.04 ($CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 37.42 and 39.31 ($CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3CH_3$ and $CH_2(C_6H_4)OH$) 43.83 $CH_2CHCO_2C(CH_3)_3$), 53.48, 55.61 and 55.86 ($NHCHCH_3$, $CH_2CHCO_2C(CH_3)_3$ and $CHCH_2(C_6H_4)OH$), 67.66 ($CH(OSi(CH_3)_2C(CH_3)_3)$), 81.80 and 81.89 ($NHCHCO_2C(CH_3)_3$ and $CH_2CHCO_2C(CH_3)_3$), 115.38 and 130.46 (Aromatic CH), 128.00 and 155.20 (2 x Aromatic ipso C), 170.61, 172.24 and 174.82 ($NHCHCO_2C(CH_3)_3$, $CH_2CHCO_2C(CH_3)_3$ and CO(NH)), 208.49 ($C(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (desorption chemical ionisation, NH_3) [651$(MH)^+$, 15%], 343[51], 309[100], 253[89], 211[34] and 89[27].

***N*-((1S, 6S)-6-Hydroxy-1-carboxylic acid-3-oxo-heptyl)-D-alanyl-D-tyrosine (ent-1c) (trifluoromethane sulphonate salt).** The general procedure with *N*-((1S, 6S)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine ^{t}butylester (37c) (30mg, 0.046mmol.) afforded *N-((1S, 6S)-6-hydroxy-1-carboxylic acid-3-oxo-heptyl)-D-alanyl-D-tyrosine ent-(1c) (trifluoromethane sulphonate salt)* as a white powder (19mg, 77%), m.p. 92-94°C; $[\alpha]_D$ +6.2° (*c* 0.37 in H_2O); ν_{max} (FT IR, KBr disc) 3382br m (NH and OH), 1780m, 1720s, 1673s, 1616s, 1559s, 1518s, 1448s, 1385s, 1350s, 1200s and 1142s cm^{-1}; δ_H (500MHz; D_2O) 1.16 (3H, d, *J* 6.5Hz, $CH(OH)CH_3$), 1.40 (3H, d, *J* 7Hz, $NHCHCH_3$), 1.62-1.75 (2H, m, $CH_2CH(OH)CH_3$), 2.45-2.52 (2H, m, $CH_2CH_2CH(OH)CH_3$), 2.66 (1H, dd, *J* 10.5Hz, *J* 14Hz, 1 x $CH_2(C_6H_4)OH$), 3.04-3.89 (3H, m, CH_2CHCO_2H and CH_2CHCO_2H), 3.25 (1H, dd, *J* 5Hz, 14Hz, 1 x $CH_2(C_6H_4)OH$) 3.78-3.82 (1H, m, $CH(OH)CH_3$), 4.06 (1H, q, *J* 7Hz, $NHCHCH_3$), ($NHCHCO_2H$ obscured by HOD signal) and 6.84 and 7.16 (4H, 2 x d, *J* 8.5Hz, $(C_6H_4)OH$);δ_C (125MHz; $CDCl_3$) 16.02 and 22.50 ($CH(OH)CH_3$ and $NHCHCH_3$), 32.26 ($CH_2CH(OH)CH_3$), 36.21, 38.79 and 40.95 (CH_2CHCO_2H, $CH_2CH_2CH(OH)CH_3$ and $CH_2(C_6H_4)OH$), 54.85 and 56.00 (3 x NHCHCO), 66.92 ($CH(OH)CH_3$), 115.90 and 130.87 (Aromatic CH), 128.61 and 154.95 (2 x Aromatic ipso C), 169.57, 170.93 and 174.53 (CH_2CHCO_2H, $NHCHCO_2H$ and C(O)NH) and 210.96 ($C(O)CH_2CH_2CH(OH)CH_3$); m/z (negative ion electrospray) 423[$(M-H^-)$, 100%].

Synthesis of ent-(1d)

***N*-((1S, 6R)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine benzyl ester. (35d)** The general procedure with (2S, 7R)-^{t}butyl 2-amino-7-^{t}butyldimethylsilyloxy-4-oxo octanoate (33b) (160mg, 0.45mmol.) and (S)-benzyl 2-trifluoromethanesulphonyloxypropanoate followed by flash chromatography (SiO_2, P.E 30-40:ether; 70:30) afforded *N-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine benzyl ester* (35d) as a colourless oil (192mg, 82%), (R_f 0.3, P.E 30-40:ether 70:30); $[\alpha]_D$ -4.1° (*c* 0.7 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2957m, 2930m, 2895m, 2857m, 1737br s (C=O), 1473s, 1456m, 1152s, 1063s, 837s and 776s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.03 and 0.04 (6H, 2 x s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_2$), 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 1.29 (3H, d, *J* 7Hz, $NHCHCH_3$), 1.43 (9H, s, $CH_2CHCO_2C(CH_3)_3$), 1.55-

1.80 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.32-2.65 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.70-2.88 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.46 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), 3.63 (1H, t, *J* 6Hz, $CH_2C\underline{H}CO_2C(CH_3)_3$), 3.73-3.89 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$), 5.10 and 5.18 (2H, ABq, *J* 12.5Hz, $NHCHCO_2C\underline{H}_2(C_6H_5)$ and 7.35 (5H, s, $NHCHCO_2CH_2(C_6\underline{H}_5)$); m/z (chemical ionisation, NH_3) 522[$(MH)^+$, 100%], 420[12], 288[30], 180[20] and 91[32].

***N*-((1S, 6R)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine. (36d).** The general procedure with *N*-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine benzyl ester (35d) (120mg, 0.23mmol.) afforded *N-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine* (36d) as a white foam (99mg, quant.), m/z (high resolution) Found 432.2781, $C_{21}H_{41}NO_6Si+H^+$ requires 432.2781; $[\alpha]_D$ -25.64° (*c* 0.85 in $CHCl_3$); ν_{max} 2958m, 1754s and 1719s (C=O), 1372s, 1257m, 1157m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.04 and 0.05 (6H, 2 x s, $Si(C\underline{H}_3)_2$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 1.13 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.42 (3H, d, *J* 7Hz, $NHCHC\underline{H}_3$), 1.46 (9H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$), 1.50-1.82 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.53 (2H, t, *J* 7.5Hz, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.85-2.97 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 3.39 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), 3.68-3.90 (2H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$ and $CH_2C\underline{H}CO_2C(CH_3)_3$); m/z (chemical ionisation, NH_3) 432[$(MH)^+$, 33%], 343[55], 211[15] and 90[100].

***N*-((1S, 6R)-6-^{t}Butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine^t-butylester (37d)** The general procedure with *N*-((6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanine (36d) (70mg, 0.16mmol.) and (D)-tyrosine *t*-butylester followed by flash chromatography (SiO_2, P.E. 30-40:ether; 30:70) afforded *N-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine ^{t}butylester* (37d) as a colourless oil (83mg, 80%), (R_f 0.3, P.E 30-40:ether 30:70); $[\alpha]_D$ -19.2° (*c* 0.6 in $CHCl_3$); ν_{max} (FT IR, $CDCl_3$ solution, NaCl plates) 2932m, 1724s (C=O), 1661s, 1516s, 1371s, 1256s, 1156s, 923s and 839s cm^{-1}; δ_H (500MHz; $CDCl_3$) 0.00, 0.04 and 0.05 (6H, 3 x s, $Si(C\underline{H}_3)_2$), 0.88 (9H, s, $SiC(C\underline{H}_3)_2$), 1.10 (3H, d, *J* 7Hz, $NHCHC\underline{H}_3$) 1.12 (3H, d, *J* 6Hz, $CH(OSi(CH_3)_2C(CH_3)_3)C\underline{H}_3$), 1.43 (18H, s, $CH_2CHCO_2C(C\underline{H}_3)_3$ and $NHCHCO_2C(C\underline{H}_3)_3$), 1.59-1.75 (2H, m, $C\underline{H}_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.48 (2H, m, $C\underline{H}_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 2.77 (2H, m, $C\underline{H}_2CHCO_2C(CH_3)_3$), 2.86 (1H, dd, *J* 8Hz, *J* 14Hz, $C\underline{H}_2(C_6H_4)OH$), 3.10 (1H, dd, *J* 5.5Hz, *J* 14Hz, 1 x $C\underline{H}_2(C_6H_4)OH$), 3.21 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), 3.61 (1H, t, *J* 6Hz, $CH_2C\underline{H}CO_2C(CH_3)_3$), 3.82 (1H, m, $C\underline{H}(OSi(CH_3)_2C(CH_3)_3)$), 4.67 (1H, m, $NHC\underline{H}CH_2(C_6H_4)OH$), 6.72 and 7.01 (2 x 2H, 2 x d, 2 x *J* 8.5Hz, $(C_6\underline{H}_4)OH$) and 7.77 (1H, d, *J* 8.5Hz, $N\underline{H}CH(CO_2C(CH_3)_3)CH_2(C_6H_4)OH$); δ_C (125MHz; $CDCl_3$) -4.72 and -4.41 ($Si(\underline{C}H_3)_2$), 18.05 ($Si\underline{C}(CH_3)_3$), 19.26 and 23.60 ($CH(OSi(CH_3)_2C(CH_3)_3)\underline{C}H_3$ and $NHCH\underline{C}H_3$), 25.87 ($SiC(\underline{C}H_3)_3$), 27.94 and 27.99 ($CH_2CHCO_2C(\underline{C}H_3)_3$ and $NHCHCO_2C(\underline{C}H_3)_3$), 32.98 ($\underline{C}H_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$), 37.44 and 39.21 ($\underline{C}H_2CH_2CH(OSi(CH_3)_2C(CH_3)_3CH_3$ and $\underline{C}H_2(C_6H_4)OH$) 43.68 $\underline{C}H_2CHCO_2C(CH_3)_3$), 53.50, 56.60 and 55.87 ($NH\underline{C}HCH_3$, $CH_2\underline{C}HCO_2C(CH_3)_3$ and $\underline{C}HCH_2(C_6H_4)OH$), 67.55 ($\underline{C}H(OSi(CH_3)_2C(CH_3)_3)$), 81.80 and 81.89 ($NHCHCO_2\underline{C}(CH_3)_3$ and $CH_2CHCO_2\underline{C}(CH_3)_3$), 115.37 and 130.41 (Aromatic $\underline{C}H$), 127.85 and 155.32 (2 x Aromatic ipso $\underline{C}$), 170.63, 172.26 and 174.97 ($NHCH\underline{C}O_2C(CH_3)_3$, $CH_2CH\underline{C}O_2C(CH_3)_3$) and $\underline{C}O(NH)$) and 208.64

($\underline{C}(O)CH_2CH_2CH(OSi(CH_3)_2C(CH_3)_3)CH_3$); m/z (desorption chemical ionisation, NH_3) [651$(MH)^+$, 10%], 617[10], 343[40], 309[100], 253[90], 229[20], 211[30] and 89[25].

***N*-((1S, 6R)-6-Hydroxy-1-carboxylic acid-3-oxo-heptyl)-D-alanyl-D-tyrosine (ent-1d) (trifluoromethane sulphonate salt).** The general procedure with *N*-((1S, 6R)-6-^{t}butyldimethylsilyloxy-1-^{t}butyloxycarbonyl-3-oxo-heptyl)-D-alanyl-D-tyrosine ^{t}butylester (37d) (30mg, 0.046mmol.) afforded *N-((1S, 6R)-6-hydroxy-1-carboxylic acid-3-oxo-heptyl)-D-alanyl-D-tyrosine (ent-1d) (trifluoromethane sulphonate salt)* as a white powder, (19mg, 77%), m.p. 89-91°C; $[\alpha]_D$ +2.5° (*c* 0.37 in H_2O); ν_{max} (FT IR, KBr disc) 3400br m (NH and OH), 1775m, 1719s, 1673s, 1518s, 1448s, 1384s, 1201s and 1141s cm^{-1}; δ_H (500MHz; D_2O) 1.05 (3H, d, *J* 6.5Hz, $CH(OH)C\underline{H}_3$), 1.43 (3H, d, *J* 7Hz, $NHCHC\underline{H}_3$), 1.52-1.65 (2H, m, $C\underline{H}_2CH(OH)CH_3$), 2.35-2.99 (2H, m, $C\underline{H}_2CH_2CH(OH)CH_3$), 2.79 (1H, dd, *J* 10Hz, *J* 14Hz, 1 x $C\underline{H}_2(C_6H_4)OH$), 2.85-2.98 (3H, m, $C\underline{H}_2CHCO_2H$ and $CH_2C\underline{H}CO_2H$), 3.20 (2H, dd, *J* 4.5Hz, 14Hz, 1 x $C\underline{H}_2(C_6H_4)OH$) 3.65-3.68 (1H, m, $C\underline{H}(OH)CH_3$), 3.94 (1H, q, *J* 7Hz, $NHC\underline{H}CH_3$), ($NHC\underline{H}CO_2H$ obscured by HOD signal) and 6.74 and 7.06 (4H, 2 x d, *J* 8.5Hz, $(C_6\underline{H}_4)OH$); δ_C (125MHz; $CDCl_3$) 16.17 and 22.20 ($CH(OH)\underline{C}H_3$ and $NHCH\underline{C}H_3$), 31.96 ($\underline{C}H_2CH(OH)CH_3$), 36.15, 38.68 and 40.77 ($\underline{C}H_2CHCO_2H$, $\underline{C}H_2CH_2CH(OH)CH_3$ and $\underline{C}H_2(C_6H_4)OH$), 49.30, 54.82, 55.83 (3 x $NH\underline{C}HCO$), 67.30 ($\underline{C}H(OH)CH_3$), 115.97 and 130.93 (Aromatic $\underline{C}H$), 128.84 and 154.97 (2 x Aromatic ipso $\underline{C}$), 169.75, 171.50 and 174.76 ($CH_2CH\underline{C}O_2H$, $NHCH\underline{C}O_2H$ and $\underline{C}(O)NH$) and 211.05 ($\underline{C}(O)CH_2CH_2CH(OH)CH_3$); m/z (negative ion electrospray) 423[$(M-H^-)$, 100%].)

REFERENCES AND NOTES

1. Ando, T.; Okada, S.; Uchida, I.; Hemmi, K.; Nishikawa, M.; Tsurumi, Y.; Fujie, A.; Yoshida. K.; Okuhara, M. *J. Antibiot*, **1987**, *40*, 468.
2. Patchett, A.A.; Harris, E.; Tristram, E.W.; Wyvratt, M.J.; Wu, M.T.; Taub, D.; Peterson, E.R.; Ikeler, T.J.; ten Broeke, J.; Payne, L.G.; Ondeyka, D.L.; Thorsett, E.D.; Greenlee, W.J.; Lohr, N.S.; Hoffsommer, R.D.; Joshua, H.; Ruyle, W.V.; Rothrock, J.W.; Aster, S.D.; Maycock, A.L.; Robinson, F.M.; Hirschmann, R. *Nature*, **1980**, *288*, 280.
3. Wu, M.T.; Douglas, A.W.; Ondeyka, D.L.; Payne, L.G.; Ikeler, T.J.; Joshua, H.; Patchett, A.A.; *J. Pharm. Sci.*, **1985**, *74*, 352.
4. Salzmann, T.N.; Ratcliffe, R.W.; Christensen, B.G.; Bouffard, F.A.*J. Am. Chem. Soc.*, **1980**, *102*, 6161.
5. Birkofer, L.; Schramm, J. *Liebigs Ann. Chem.*, **1975**, 2195.
6. Labia, R.; Morin, C.*Chem. Lett.*, **1984**, 1007.
7. Zervas, L.; Winitz, M.; Greenstein, J.P. *J. Org. Chem.*, **1957**, *22*, 1515.
8. Baldwin, J.E.; Adlington, R.M.; Gollins, D.W.; Schofield, C.J. *Tetrahedron*, **1990**, *46*, 4733.
9. Trost, B.M.; Curran, D.P. *Tetrahedron Lett.*, **1981**, *22*, 1287.
10. Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.*, **1988**, *29*, 2483.
11. Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 296.
12. Sennyey, G.; Barcelo, G.; Senet, J.-P. *Tetrahedron Lett.*, **1986**, *27*, 5375.
13. Babler, J.H. *J. Org. Chem.*, **1987**, *52*, 4614.

14. Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.*, **1965**, *87*, 1345.
15. Dale, J.A. ; Dull, D.L.; Mosher, H.S. *J. Org. Chem.*, **1969**, *34*, 2541.
16. Whitten, J.P.; Baron, B.M.; Muench, D.; Miller, F.; White, H.S.; McDonald, I.A., *J. Med. Chem.*, **1990**, *33*, 2961; Rudisill, D.E.; Whitten, J.P., *Synthesis*, **1994**, 851.
17. Lipshutz, B.H.; Parker, D.; Kozlowski, J.A.*J. Org. Chem.*, **1983**, *48*, 3334.
18. Seebach, D.; Pohmakotr, M.; *Helv. Chim. Acta*, **1979**, *62*, 843.
19. Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.*, **1972**, *94*, 6190.
20. Escher, R.; Bünning, P. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 277;
Vedejs, E.; Engler, D.A.; Mullins, M.J. *J. Org. Chem.*, **1977**, *42*, 3109.
21. Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem. Int. Ed. Engl.*, **1983**, *22*, 65.
22. Baldwin, J.E.; Adlington, R.M.; Godfrey, C.R.A.; Gollins, D.W.; Smith, M.L.; Russell, A.T. *Synlett*, **1993**, 51.
23. For other studies on the synthesis of γ-keto α-amino acids, see Ben-Ishai, D.; Altman, J.; Bernstein, Z.; Peled, N. *Tetrahedron*, **1978**, *34*, 467.
Jackson, R.F.W.; James, K.; Wythes, M.J.; Wood, A. *J. Chem. Soc., Chem. Commun.*, **1989**, 644.
Jackson, R.F.W.; Wood, A.; Wythes, M.J. *Synlett*, **1990**, 735.
Jackson, R.F.W.; Wishart, N.; Wood, A.; James, K.; Wythes, M.J. *J. Org. Chem.*, **1992**, *57*, 3397.
Aubrey, N.; Plante, R.; Déziel, R. *Tetrahedron Lett.*, **1990**, *31*, 6311.
Burger, K.; Rudolph, M.; Neuhauser, H. *Liebigs Ann. Chem.*, **1991**, 1365.
24. For the ring opening of simpler β-lactams by alkyl lithiums to provide β-amino ketones see: Kano, S.; Ebata, T.; S. Shibuya, S. *Chem. Pharm. Bull.*, **1979**, *27*, 2450

(*Received in UK* 12 *January* 1995; *revised* 15 *February* 1995; *accepted* 17 *February* 1995)