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Stereospecific Synthesis of Chlamydocin

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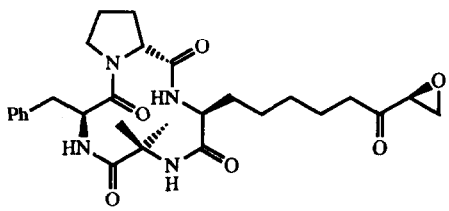
Abstract: A stereospecific synthesis of the cyclic tetrapeptide chlamydocin *via* free radical homologation from a (*S*)-2-amino-5-iodopentanoic acid containing cyclic tetrapeptide is described.

Introduction

The cyclic tetrapeptide chlamydocin[1] **1** is a constituent of a family of fungal metabolites which include HC-Toxin,[2] Cyl-2[3], WF-3161[4] and trapoxin A[5], all of which contain the residue (2*S*, 9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (AOE) **2** as a common structural feature. These compounds demonstrate significant bioactivity as cytostatic agents, detransformation agents and also as plant toxins. This broad range of biological activity has spurred workers to investigate both their *in vitro* and *in vivo* biological effects,[5,6] their solution conformation[7] (as an aid to drug design) and also to attempt syntheses of protected forms of the key residue (2*S*, 9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (AOE)[8] **2**. Syntheses of other related unnatural, cyclic tetrapeptide analogues have also appeared.[9]



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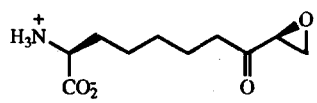

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Schmidt has published a rather lengthy route to chlamydocin **1**[10] and the related tetrapeptide WF-3161[11] from (*R*, *R*) tartaric acid, whilst syntheses of epimeric forms of chlamydocin have also been reported by Rich[12]. We believe that the major difficulty in the syntheses of such tetrapeptides is the lability of the epoxyketone functionality towards nucleophilic attack and as such the epoxyketone moiety needs to be introduced at a late stage in the synthesis. We proposed that a superior approach would be *via* addition of a free-radical **4** derived from a suitably functionalised cyclopeptide **3** to a chiral epoxyenone **5** (Figure 1). Reduction of the radical adduct **6** with tributyltin hydride should provide the epoxyketone containing cyclopeptide **7** and continue the propagation of the radical chain. In this way flexibility with respect to the pendant chain length and absolute configuration of the epoxyketone could readily be accommodated.

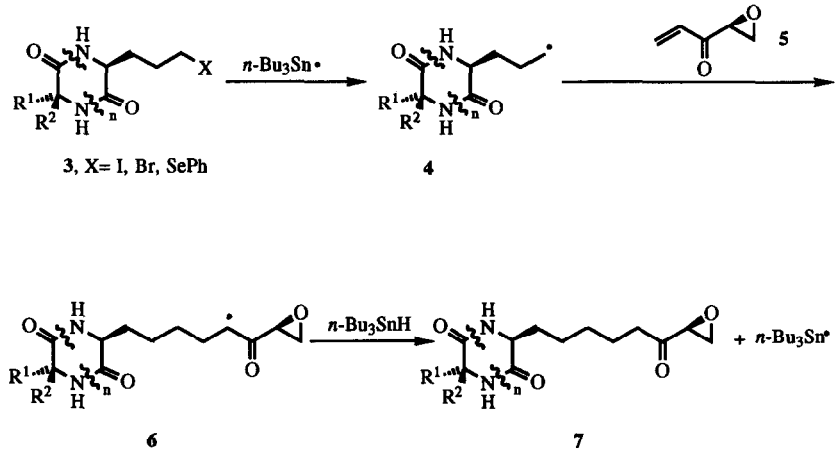


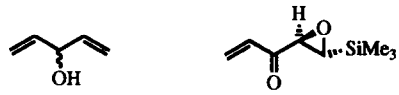
Figure 1

Using this approach we recently reported successful syntheses of protected (2*S*, 9*S*) and (2*S*, 9*R*) AOEs.[13] We now describe an extension of this methodology to the parent cyclotetrapeptide chlamydocin **1**.

Synthesis of a chiral epoxyenone (9) as a suitable radicophile

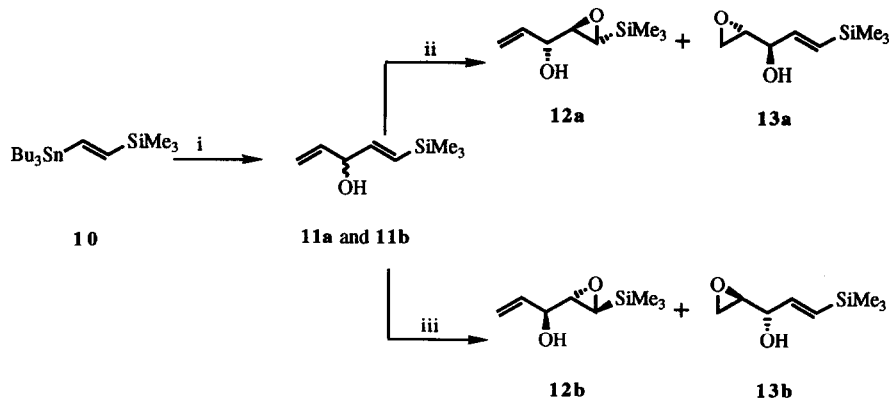
Initial efforts to synthesise the epoxyenone **5** from the divinyl alcohol **8** proved to be difficult due to the volatility and water solubility of the product. In addition, epoxidation of **8** was problematical partly because of the unreactive nature of the unsubstituted double bond. We decided, therefore, to investigate the synthesis of a radicophile bearing an appropriate substituent which would avoid these difficulties. Obviously, the one essential feature of such a substituent is that it should be easily removable under neutral reaction conditions. These conditions should be satisfied by the use of a trimethylsilyl group as a substituent which would decrease not only the water solubility and volatility of the radicophile but at the same time increase the nucleophilicity of the substituted alkene towards epoxidation. Additionally protodesilylation of trimethylsilyl substituted epoxides

can be achieved by use of TBAF hydrate.[14] Therefore, the trimethylsilylepoxyenone **9** was chosen as target radicophile for the proposed homolytic addition reaction.



8 **9**

Treatment of acrolein with the anion generated by the treatment of (*E*)1-tributylstannyl-2-trimethylsilylethene **10**[15] with *n*-butyllithium gave the divinylalcohols **11a** and **11b**. This mixture was then epoxidized using the Sharpless catalytic procedure. Use of (*D*)-diethyl tartrate as the chiral additive gave the (1*R*, 2*R*, 3*R*)- enantiomer **12a**. Examination of the crude reaction mixture by ^{1}H NMR spectroscopy showed traces of another minor product which was characterised as the product of epoxidation at the less substituted double bond, **13a**. This by-product was formed in much less than 5% yield if the reaction was carefully monitored (T~-20 °C). The kinetically resolved 3*S*- trimethylsilyldivinyl alcohol **11b** when resubjected to epoxidation using (*L*)-diethyl tartrate gave the (1*S*, 2*S*, 3*S*)-trimethylsilylepoxyvinyl alcohol **12b**. Again the less substituted epoxide **13b** was formed (Scheme 1).

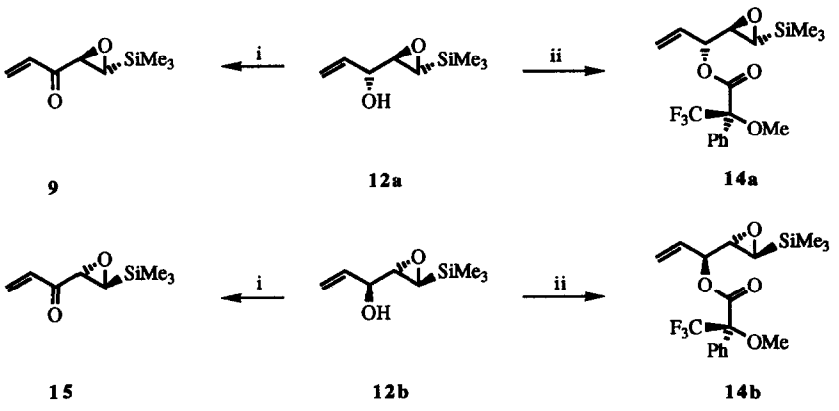


10 **11a and 11b** **12a** **13a** **12b** **13b**

i) *n*-BuLi, THF, -78 °C then acrolein, -78 °C; ii) (*D*)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, 4 Å mol. sieves, -23 °C, 17 h; iii) (*L*)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, 4 Å mol. sieves, -23 °C, 17 h.

Scheme 1

The enantiomeric excess of the epoxidation process was then evaluated by forming the Mosher's esters[16] **14a** and **14b** of the enantiomeric epoxy alcohols **12a** and **12b**. ^{1}H and ^{13}C NMR spectroscopic analyses of the derived Mosher's esters showed there was no cross-contamination. The trimethylsilylepoxy alcohols **12a** and **12b** were then oxidised using Swern's method with trifluoroacetic anhydride as the activating agent to give the epoxyenones **9** and **15** in isolated yields ranging from 65 to 85% (Scheme 2).

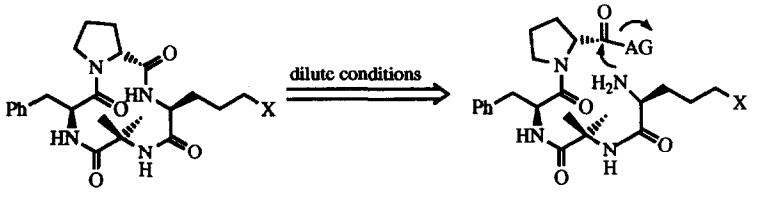


i) DMSO, TFAA, NEt_3, CH_2Cl_2, -65 to 20 °C;
ii) (*S*)-Mosher's acid chloride, NEt_3, DMAP, CH_2Cl_2.

Scheme 2

Synthesis of Chlamydocin 1

In order to evaluate our proposed homolytic coupling route to chlamydocin **1** we chose to synthesize a cyclopeptide radical precursor **16** by forming a peptide bond between the amino group of the AOE precursor and a prolinyl active ester of an acyclic tetrapeptide precursor **17** (Figure 2).

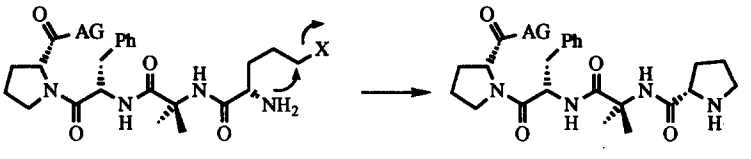


AG= activating group, X= halogen *etc.*

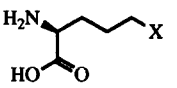
Figure 2

We considered the use of (*S*)-2-amino-5-iodopentanoic acid (AIP) **18a** as a residue in the acyclic tetrapeptide **17** to be unsuitable as there was a possibility that a competitive intramolecular nucleophilic displacement of the iodo group by the primary amino group in a 5-exo-tet[17] manner could occur to produce **19**

(Figure 3). The iodo substituent would also be unsuitable with respect to reduction in the vigorous hydrogenolysis conditions (to remove the benzyloxycarbonyl group) that would be employed during the cyclicpeptide forming reaction.



17 19

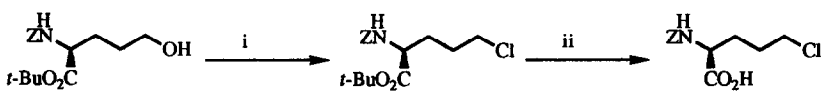


AG = activating group

18a X = I
18b X = Cl

Figure 3

We decided, therefore, to use (*S*)-2-amino-5-chloropentanoic acid (ACP) **18b** as a residue in the acyclic tetrapeptide in the hope that chloride would be a sufficiently poor leaving group such that macrolactamisation would be favoured. *N*-Z-(*S*)-2-amino-5-chloropentanoic acid **22** (Z-(*S*)-ACP) was synthesized from the protected hydroxyamino acid **20**[18] by initial chlorination (PPh_3, CCl_4, reflux, 79%)[19] to give the diprotected chloroaminoacid **21** followed by removal of the *t*-butyl ester by treatment with TFA in DCM (91%) (Scheme 3).

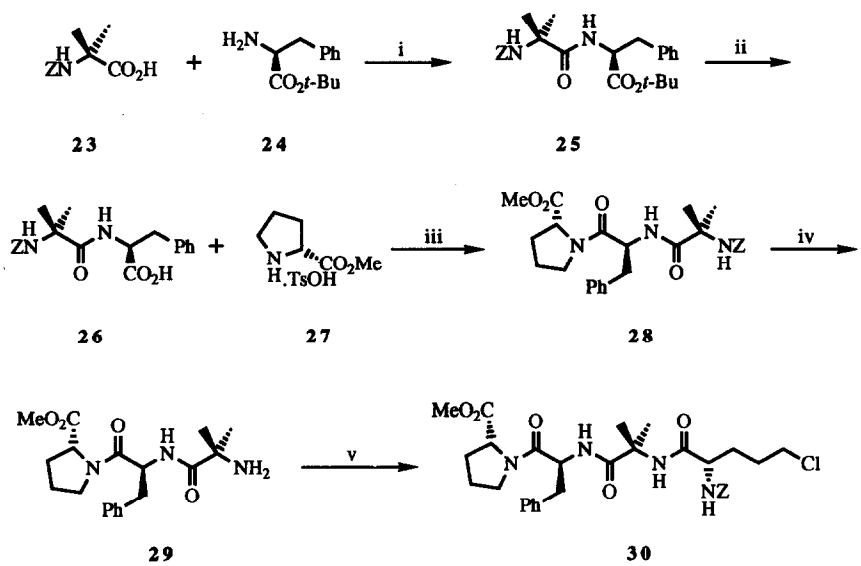


20 **21** **22**

i) PPh_3, CCl_4, reflux; ii) CH_2Cl_2:TFA.

Scheme 3

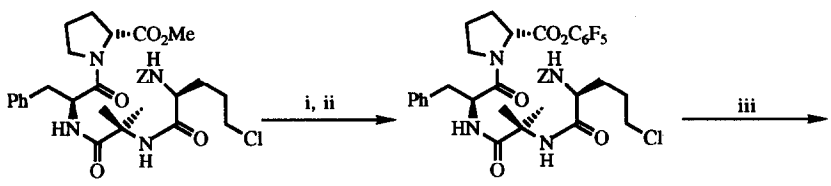
The acyclic tetrapeptide **29** was synthesized by initial condensation of Z-AIB (Z-aminoisobutyric acid) **23** to (*L*)-phenylalanine *t*-butyl ester **24** (DCC/HOBT),[20] deprotection of the resultant ester **25** (TFA) and coupling of the resulting dipeptide **26** (DCC, HOBT) to the methyl ester of (*D*)-proline **27** to give the tripeptide **28**. Hydrogenolysis of the tripeptide **28** followed by coupling with *N*-Z-(*S*)-2-amino-5-chloropentanoic acid **22** using BOP reagent[21] gave the required aminochloropentanoic acid (ACP) containing tetrapeptide **30** (Scheme 4).



i) DCC, HOBT, THF, 87%; ii) TFA, DCM; iii) DCC, HOBT, NEt_3, THF, 65%;
iv) H_2, Pd, MeOH; v) compound **22**, BOP reagent, $N(^iPr)_2Et$, DCM, 66% (over two steps).

Scheme 4

Tetrapeptide **30** was then saponified (NaOH, MeOH, followed by acidification, 85%) and subsequently reacted with pentafluorophenol using DCC as the coupling agent to give the activated substrate **31** for macrocyclization.[22] The unpurified pentafluorophenyl ester **31** was subjected to hydrogenolysis by addition of its solution in dioxane over 5 h to a suspension of palladium on carbon in dioxane at 95 °C through which was passed hydrogen gas. The resulting chlorocyclopeptide **32** formed in 55% yield from **30** was subjected to Finklestein exchange (NaI, methylethyl ketone (MEK), reflux) to form the iodoaminopentanoicacid (AIP) containing cyclopeptide **33** in 76% yield (Scheme 5).



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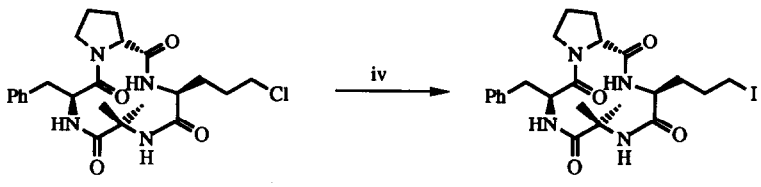
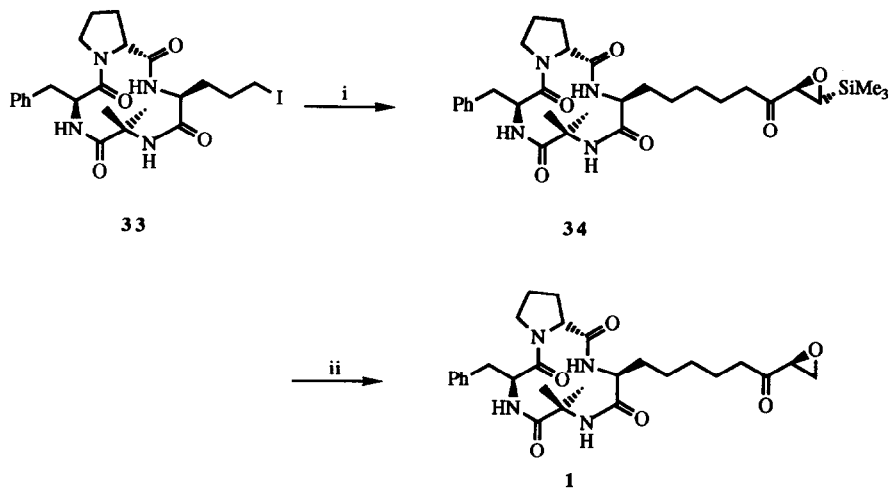


32 33

i) NaOH, MeOH; ii) C_6F_5OH, DCC, THF; iii) H_2, Pd/C, *N*-methyl morpholine, EtOH, 1,4-dioxane, 95 °C,55% over 3 steps; iv) NaI, methylethyl ketone, reflux, 76%.

Scheme 5

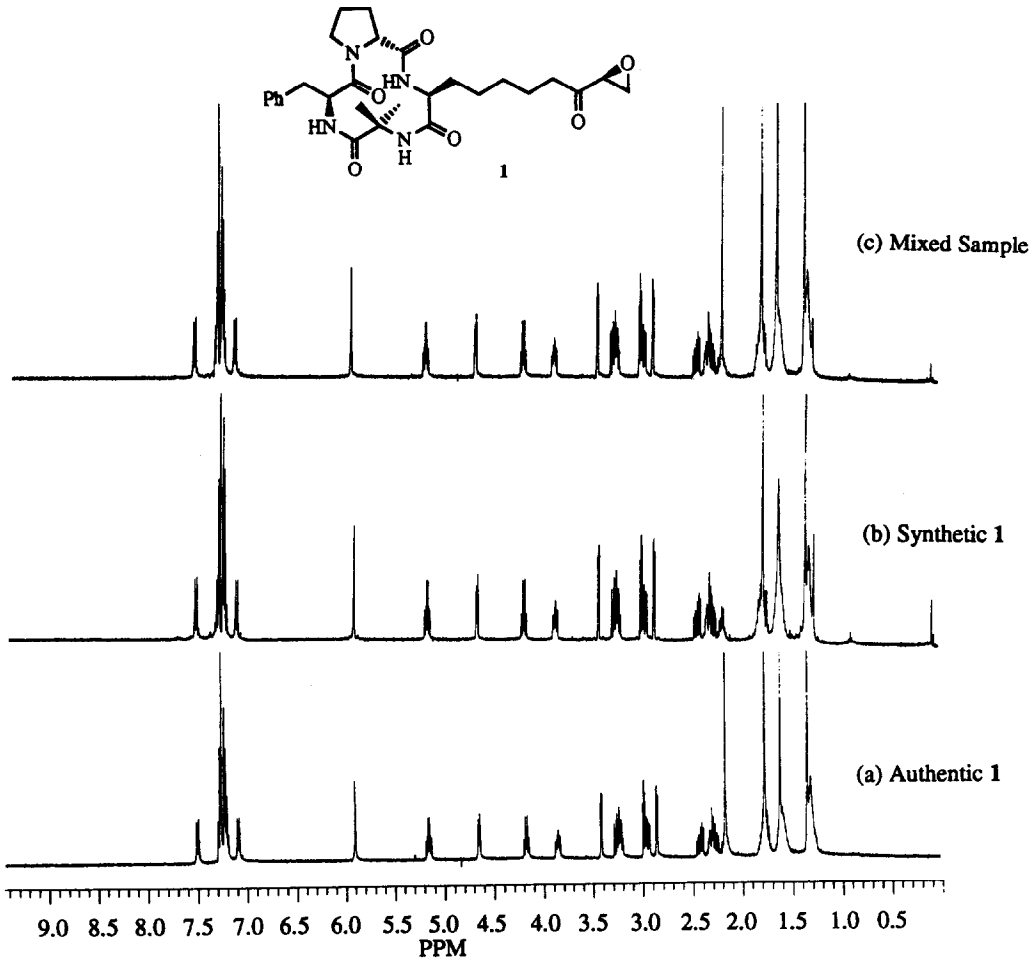
This peptide **33** when subjected to free radical homologation [silylepoxyenone **9**, (3.0 equiv.), tributyltin hydride(1.5 equiv.)] gave trimethylsilylAOE (TAOE) containing tetrapeptide **34** in a yield (60%) comparable to those previously found in our model studies[13] (Scheme 6). Desilylation of the silyl AOE **34** was slower than anticipated[13] (TBAF, 2 days, 21 °C) but gave chlamydocin **1** in a satisfactory yield of 68%. The synthetic material was identical to the natural material[23] (^{1}H NMR Figure 4, $[\alpha]_D$[1], CD) and showed a similar negative Cotton effect in the range 275-350 nm associated with (*S*) configured epoxyketone functionality.



33 34 1

i) reagent **9**, 3 equiv., Bu_3SnH, 1.5 equiv., benzene, reflux;
ii) TBAF.H_2O, DMSO, 2 days.

Scheme 6



500 MHz ^{1}H NMR spectrum ($CDCl_3$) of chlamydocin 1

Figure 4

In conclusion we have developed a new homolytic approach to the cyclic tetrapeptide chlamydocin 1 which could be readily applied to the synthesis of other related AOE containing peptides.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer with only selected absorptions being reported. Nuclear magnetic resonance (NMR) spectra were recorded on Brüker AM-500, Brüker WH-300, and Varian Gemini-200 spectrometers using the residual solvent peak as the internal reference. ^{1}H NMR data are reported with chemical shifts quoted in parts per million (δ p.p.m.) with coupling constants J±0.5 Hz. ^{13}C NMR spectra (0-200 p.p.m.) were run using DEPT editing where indicated, quartenary carbons were assigned from a broad band decoupled analysis used in combination with the DEPT programme. Mass spectra were recorded on a V.G. Micromass ZAB 1F (DCI), V.G. 20-250 (DCI/ CI) or a V.G. Trio 1 (GCMS) spectrometers. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a pathlength of 1dm with concentrations given in g/100 ml. Melting points were obtained using a Büchi capillary melting point apparatus and are uncorrected. Microanalyses were performed within the Dyson Perrins Laboratory, Oxford.

Flash chromatography was accomplished on silica gel using Sorbosil™ C60. Thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F_{254}, plates being visualised with UV (254 nm) or 10% w/v ammonium molybdate in 2M sulphuric acid followed by heat.

All solvents were distilled before use; tetrahydrofuran (THF) and 1,4-dioxane from sodium/benzophenone ketyl; dichloromethane from calcium hydride. Benzene and triethylamine were stored over sodium wire and potassium hydroxide respectively for at least 24h before use. *n*-Butyllithium was standardised by titration using 1,3-diphenylacetone-*p*-tosylhydrazone at -78 °C[24]. AIBN and aminoisobutyric acid (AIB) were supplied by Fluka, and other reagents were used as received without further purification. Reactions were performed at ambient temperature unless otherwise stated.

(*E*)-1-Tributylstannyl-2-trimethylsilylethene **10**[15]

A solution of tributyltin hydride (10.0 g, 9.24 ml, 34.4 mmol), trimethylsilylacetylene (3.38 g, 4.86 ml, 34.4 mmol) and AIBN (~100 mg) in deoxygenated benzene (100 ml) was refluxed for 24 h. The solvent was removed *in vacuo* and the residue purified by bulb-to-bulb distillation (~0.2 mmHg, 190 °C) to give the title compound **10** as a colourless oil (10.45 g, 78%); ν_{max}(thin film)/ cm^{-1} 3380 (s), 2927 (s), 2855 (s), 1280 (s); δ_H(200 MHz, $CDCl_3$) 0.08 (9H, s, -Si(CH_3)$_3$), 0.87-0.94 (15H, m, -Sn(CH_2(CH$_2$)$_2$CH$_3$)$_3$), 1.23-1.60 (12H, m, -Sn(CH$_2$(CH_2)$_2$CH$_3$)$_3$), 6.62 (1H, d, *J* 23 Hz, -CH-), 6.81 (1H, d, *J* 23 Hz, -CH-); *m/z* (in beam EI) 390 (M$^+$(^{120}Sn), 9%), 333 ((M-C$_4$H$_9$)$^+$, 32), 276 (100), 219 (47), 73 (19).

(*E*, 3*RS*)-3-Hydroxy-1-trimethylsilyl-1,4-pentadiene, **11a** and **11b**

n-Butyllithium (2.5 mol dm^{-3} solution in hexanes, 5.46 ml, 13.6 mmol) was added dropwise to a stirred cold (dry ice-acetone) solution of (*E*)-1-tributylstannyl-2-trimethylsilylethene **10** (4.82g, 12.4 mmol) in anhydrous THF (30 ml). After 30 min, the resulting yellow coloured anion was quenched by the dropwise addition of acrolein (1.15 ml, 965 mg, 17.2 mmol). The reaction mixture was allowed to warm to room

temperature, diluted with diethyl ether (100 ml), and washed with saturated aqueous ammonium solution (50 ml), water (50 ml) and brine (50 ml), dried (sodium sulphate) and the solvent removed, *in vacuo*. The residual oil was purified by flash column chromatography on silica gel using hexane-diethyl ether (10:1) mixture as eluent to give the title compounds **11a** and **11b** (1.72 g, 89%); R_f 0.3 [(petroleum ether (b.p. 30-40 °C)-diethyl ether (10:1)]; δ_H(200 MHz, $CDCl_3$) 0.08 (9H, s, $(CH_3)_3Si$-), 1.91 (1H, *b* s, -OH), 4.53-4.68 (1H, m, -CH(OH)), 5.15 (1H, dd, *J* 1.5, 10.5 Hz, CHHCHCH(OH)-), 5.25 (1H, dd, *J* 1.5, 18.5 Hz, CHHCHCH(OH)-), 5.80-5.97 (1H, m, $CH_2CHCH(OH)$-), 5.91 (1H, d, *J* 18.0 Hz, -CHCHSi$(CH_3)_3$), 6.07 (1H, dd, *J* 18.0, 4.5 Hz, -CHCHSi$(CH_3)_3$); δ_C(50.3 MHz, $CDCl_3$) 1.63 (-Si$(CH_3)_3$), 75.44 (-CH(OH)), 115.16 (CH_2CHCH(OH)-), 130.19 (-CHSi$(CH_3)_3$), 139.38 (-CHCHSi$(CH_3)_3$), 146.40 (-$CHCH_2$); *m/z* [CI, (NH_3)] 156 ((M-H_2O)NH_4^+, 100%), 139 (30), 90 (95). (Found C, 61.48; H, 10.43. $C_8H_{16}OSi$ requires C, 61.48; H, 10.32%).

(1*R*, 2*R*, 3*R*)-1,2-Epoxy-3-hydroxy-1-trimethylsilyl-4-pentene, **12a**

A cold (-20 °C) solution of (*D*)-diethyl tartrate (315 mg, 1.53 mmol), titanium isopropoxide (362 mg, 1.27 mmol) and *t*-butyl hydroperoxide (3.0 mol dm^{-3} solution in 2,2,4-trimethylpentane, 5.12 ml, 15.4 mmol) in anhydrous dichloromethane (100 ml) containing dried 4 Å molecular sieves was stirred under argon for 30 min. Subsequently, a solution of (*E*, 3*RS*)-3-hydroxy-1-trimethylsilyl-1,4-pentadiene **11a** and **11b** (4.00 g, 25.6 mmol) in anhydrous dichloromethane (25 ml) was added dropwise, the flask was charged with argon and then transferred to a freezer (-23 °C) for 17 h. The reaction mixture was allowed to warm to ~0 °C, water (5 ml) added, and stirred for a further 1 h. Sodium hydroxide in saturated brine (30% w/v, 5 ml) was then added, and the resulting emulsion was stirred for 1 h and then passed through a pre-washed (methanol) bed of Celite. The Celite bed was washed with dichloromethane (100 ml) and the combined filtrates were washed with water (100 ml) and brine (100 ml), dried (sodium sulphate) and solvent evaporated *in vacuo*. The residual oil was purified by flash column chromatography on silica gel using dichloromethane-petroleum ether (b.p. 30-40 °C) (4:1), neat dichloromethane and dichloromethane-diethyl ether (4:1) mixtures as eluents to give kinetically resolved starting material **11b** (2.01 g, 50%), trimethylsilylepoxyallyl alcohol **12a** as a colourless oil (1.83 g, 42%, 83% based on resolved starting material). Epoxytrimethylsilylallyl alcohol **13a** (128 mg, 3%) was also obtained as a byproduct. For (1*R*, 2*R*, 3*R*)-1,2-Epoxy-3-hydroxy-1-trimethylsilyl-4-pentene, **12a**: R_f 0.3 [diethyl ether-petroleum ether (b.p. 30-40 °C) (1:1)]; $[\alpha]_D^{23}$ -22.5 (*c* 1.0 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 0.08 (9H, s, -Si$(CH_3)_3$), 2.18 (1H, *b* s, -OH), 2.36 (1H, d, *J* 3.5 Hz, -CHSi$(CH_3)_3$), 2.97 (1H, t, *J* 3.5 Hz, -CHCHSi$(CH_3)_3$), 4.25-4.35 (1H, m, -CH(OH)-), 5.25 (1H, dd, *J* 1.0, 10.5 Hz, CH_2CH-), 5.37 (1H, dd, *J* 1.0, 17.5 Hz, CH_2CH-), 5.76-5.87 (1H, m, $CH_2CHCH(OH)$-); δ_C(50.3 MHz, $CDCl_3$) -4.03 (-Si$(CH_3)_3$), 47.61 (-CH(Si$(CH_3)_3$), 57.73 (-CHCH(Si$(CH_3)_3$)), 71.18 (-CH(OH)-), 117.22 (CH_2CH-), 136.24 (CH_2CH-); *m/z* [CI, (NH_3)] 190 (MNH_4^+, 8%), 155 (10), 134 (18), 91 (26), 90 (100).

(1*S*, 2*S*, 3*S*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene, **12b**

The title compound was synthesized using a method analogous to that used for the preparation of (1*R*, 2*R*, 3*R*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12a** using (*L*)-diethyl tartrate (395 mg, 1.92 mmol), titanium isopropoxide (455 mg, 1.60 mmol), *t*-butyl hydroperoxide (3 mol dm^{-3} solution in 2,2,4-trimethylpentane, 7.0 ml, 21.0 mmol) and largely kinetically resolved (*E*, 3*S*)-3-hydroxy-1-trimethylsilyl-1,4-pentadiene **11b** (5.0 g, 32 mmol), from runs of the previous protocol, to give unreacted starting material (800 mg, 16%) and the product **12b** as a colourless oil (4.1 g, 74%); $[\alpha]_D^{23}$ +22.1 (*c* 0.98 in $CHCl_3$); ^1H NMR data was identical to (1*R*, 2*R*, 3*R*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12a**.

(2'*R*, 1*R*, 2*R*, 3*R*)-1,2-Epoxy-3-(2'-methoxy-2'-phenyl-(3',3',3'-trifluoro)propionoyl) -1-trimethylsilyl-4-pentene, **14a**

(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl chloride (28 µl) was added to a stirred solution of (1*R*, 2*R*, 3*R*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12a** (24 mg, 0.14 mmol), triethylamine (68 mg, 93 µl, 0.67 mmol), 4-(*N*,*N*-dimethyl)aminopyridine (17 mg, 0.14 mmol) in anhydrous dichloromethane (2 ml). After 3 h the reaction was diluted with more dichloromethane (10 ml) and the resulting solution was washed with water (10 ml) and brine (10 ml), dried (sodium sulphate) and solvent was removed, *in vacuo*. The residue was purified by preparative thin layer chromatography using dichloromethane as the eluent to give the title compound **14a** as a colourless oil (48 mg, 88%); R_f0.6 (petroleum ether (b.p. 30-40 °C)-dichloromethane (3:2)); $[\alpha]_D^{25}$ +59.3 (*c* 2.0 in $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3022 (m), 1753 (s), 1252 (s), 1226 (s), 1171 (s), 1122 (s), 1020 (s); δ_H(200 MHz, $CDCl_3$) 0.07 (9H, s, (CH_3)$_3$Si-), 2.27 (1H, d, *J* 3.5 Hz, -C*H*Si(CH_3)$_3$), 3.02 (1H, m containing d, *J* 3.5Hz, -C*H*CHSi(CH_3)$_3$), 3.57 (3H, *ca* d, *J* 1.0 Hz, -OCH_3), 5.31-5.50 (3H, m, CH_2CH- and CH_2CH(O)-), 5.75-5.92 (1H, m, CH_2CHCH(O)-), 7.38-7.59 (5H, m, C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) -4.08 ((CH_3)$_3$Si-), 49.28 (-CHSi(CH_3)$_3$), 55.22 (-CHCHSi(CH_3)$_3$), 55.35 (-OCH_3), 76.80 (CH_2CHCH(O)-), 120.48 (CH_2CH-), 127.64, 128.52, 129.79 (CH-, aromatic), 131.32 (CH_2CH-), 132.21 (-*i*C-), 165.70 (-CO_2-); δ_F (235.2 MHz, $CDCl_3$) -73.4; *m/z* [CI, (NH_3)] 406 (MNH_4^+, 1.5%), 389 (MH^+, 1.5), 189 (100), 105 (24), 91 (12), 74 (16).

(2'*R*, 1*S*, 2*S*, 3*S*)-1,2-Epoxy-3-(2'-methoxy-2'-phenyl-(3',3',3'-trifluoro)propion-oyl)-1-trimethylsilyl-4-pentene, **14b**

The title compound was synthesized using a method analogous and on the same scale to that used for the preparation of (2'*R*, 1*R*, 2*R*, 3*R*)-**14a** using (1*S*, 2*S*, 3*S*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12b** to give the title compound **14b** as a colourless oil (47 mg, 86%); $[\alpha]_D^{25}$ +6.4 (*c* 2.0 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 0.03 (9H, s, (CH_3)$_3$Si-), 2.15 (1H, d, *J* 3.5 Hz, -C*H*Si(CH_3)$_3$), 2.94 (1H, m

containing d, *J* 3.5 Hz, -CHCH(Si(CH_3)$_3$)), 3.57 (3H, s, -OCH_3), 5.38-5.53 (3H, m, CH_2CH- and CH_2CHCH(O)-), 5.84-5.96 (1H, m, CH_2CHCH(O)-), 7.38-7.57 (5H, m, C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) -4.11 ((CH_3)$_3$Si-), 49.32 (-CHSi(CH_3)$_3$), 55.19 (-CHCHSi(CH_3)$_3$), 55.36 (-OCH_3), 77.00 (CH_2CHCH(O)-), 120.95 (CH_2CH-), 127.46, 128.49, 129.76 (CH-, aromatic), 131.54 (CH_2CH-), 132.21 (-*i*C-), 165.70 (-CO_2-); δ_F (235.2 MHz, $CDCl_3$) -73.4.

(1*R*, 2*R*)-1,2-Epoxy-3-oxo-1-trimethylsilyl-4-pentene, **9**

Trifluoroacetic anhydride (2.74 g, 1.84 ml, 13.0 mmol) was added dropwise to a cold (-65 °C) stirred solution of dimethyl sulphoxide (1.36 g, 1.24 ml, 17.4 mmol) in anhydrous dichloromethane (50 ml) and stirring continued for 15 min. Subsequently a solution of (1*R*, 2*R*, 3*R*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12a** (1.50 g, 8.72 mmol) in anhydrous dichloromethane (10 ml) was added dropwise. Stirring was continued for a further 15 min, and then triethylamine (2.64 g, 3.64 ml, 26.1 mmol) was added dropwise. The reaction mixture was allowed to warm to ambient temperature over 1 h, diluted with dichloromethane (40 ml), washed with water (100 ml), brine (100 ml), dried (sodium sulphate) and the solvent was removed *in vacuo*. The residual oil was purified by flash column chromatography using petroleum ether (b.p. 30-40 °C)-diethyl ether (9:1) to give the product **9** as pale yellow oil (967 mg, 65%); R_f 0.4 [petroleum ether (b.p. 30-40 °C)-diethyl ether (9:1)]; $[\alpha]_D^{20}$ -43.3 (*c* 1.6 in $CHCl_3$); ν_{max}(thin film)/ cm^{-1} 2958 (s), 1696 (s), 1617 (s), 1406 (s), 1251 (s), 1187 (s), 845 (s); δ_H(200 MHz, $CDCl_3$) 0.13 (9H, s, -Si(CH_3)$_3$), 2.41 (1H, d, *J* 3.5 Hz, -CH(Si(CH_3)$_3$), 3.41 (1H, d, *J* 3.5 Hz, -CH(O)CH(Si(CH_3)$_3$), 5.81 (1H, *ca* t, *J* 6.5 Hz, -CHCH_2), 6.49-6.52 (2H, m, -CHCH_2); δ_C(50.3 MHz, $CDCl_3$) -4.00 (-Si(CH_3)$_3$), 50.38 (-CH(Si(CH_3)$_3$), 56.64 (CH(O)CH(Si(CH_3)$_3$), 128.92 (-CHCH_2), 130.50 (-CH_2), 197.60 (-C(O)-); *m/z* [CI, (NH_3)] 188 (MNH_4^+, 27 %), 171 (MH^+, 100), 155 (32), 90 (20). (Found C, 56.59; H, 8.31. $C_8H_{14}O_2Si$ requires C, 56.43; H, 8.29%).

(1*S*, 2*S*)-1,2-epoxy-3-oxo-1-trimethylsilyl-4-pentene, **15**

The title compound was synthesized using a method analogous to that used for the preparation of **9** using (1*S*, 2*S*, 3*S*)-1,2-epoxy-3-hydroxy-1-trimethylsilyl-4-pentene **12b** (815 mg, 4.74 mmol), dimethyl sulphoxide (739 mg, 670 µl, 9.46 mmol), trifluoroacetic anhydride (1.49 g, 1.00 ml, 7.07 mmol) and triethylamine (1.44 g, 1.97 ml, 14.2 mmol) to give the title compound **15** as a colourless liquid (685 mg, 85%); $[\alpha]_D^{20}$ +42.3 (*c* 1.6 in $CHCl_3$); ^1H NMR and ^{13}C NMR, same as for **9**.

t-Butyl (*S*)-2-(*N*-benzyloxycarbonylamino)-5-chloropentanoate, **21**

A solution of *t*-butyl (*S*)-2-(*N*-benzyloxycarbonylamino)-5-hydroxypentanoate **20**[18] (4.55 g, 14.1 mmol) and triphenylphosphine (5.53 g, 21.1 mmol) in carbon tetrachloride (50 ml) was refluxed under argon for 1 h. The reaction mixture was allowed to cool and the precipitated triphenylphosphine oxide removed

by filtration. The filtrate was concentrated and the residual oil was purified by flash column chromatography on silica gel using petroleum ether (b.p. 30-40 °C)-ethyl acetate (4:1) mixture as eluent to give **21** as a colourless oil (3.83 g, 79%); R_f0.6 ((petroleum ether (b.p. 30-40 °C)-ethyl acetate (1:1)); $[\alpha]_D^{20}$ +12.1 (*c* 1.66 in $CHCl_3$); ν_{max}(thin film)/ cm^{-1} 3336 (s), 2978 (s), 1719 (s), 1524 (s), 1155 (s); δ_H(200 MHz, $CDCl_3$) 1.48 (9H, s, $(CH_3)_3C$-), 1.75-2.05 (4H, m, -CH_2CH_2CH-), 3.54-3.60 (2H, m, -CH_2Cl), 4.25-4.38 (1H, m, -$CHCO_2(CH_3)_3$), 5.12 (2H, s, $PhCH_2$-), 5.32 (1H, d, *J* 8.0 Hz, -NH), 7.37 (5H, s, C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) 27.81 ($(CH_3)_3C$-), 28.01, 30.16 (-CH_2CH_2CH-), 44.26 (-CH_2Cl), 53.61 (-$CH(CO_2t$-Bu)), 66.90 (-CH_2Ph), 82.19 ($(CH_3)_3C$-), 128.23, 128.64 (-CH, aromatic), 136.43 (-*i*C-, aromatic), 156.32 (-N(H)CO_2CH_2Ph), 171.90 (-$CO_2C(CH_3)_3$); *m/z* [CI, (NH_3)] 344 (MH^+(^{37}Cl), 2%), 342 (MH^+(^{35}Cl), 5), 288 (24), 286 (24), 244 (3), 242 (10), 196 (17), 108 (22), 91 ($C_7H_7^+$, 100). (Found C, 59.80; H, 7.09; N, 4.10. $C_{17}H_{24}ClNO_4$ requires C, 59.73; H, 7.08; N, 4.10%).

(*S*)-2-(*N*-Benzyloxycarbonylamino)-5-chloropentanoic acid, **22**

A solution of *t*-butyl (*S*)-2-(*N*-benzyloxycarbonyl)-5-chloropentanoate **21** (3.41 g, 10.0 mmol) in a mixture of anhydrous dichloromethane:trifluoroacetic acid (1:1) (10 ml) was stirred for 16 h under argon. The solvent was removed, *in vacuo*, and residual trifluoroacetic acid removed by co-evaporation with toluene *in vacuo* (4 x 25 ml). The residue was purified by column chromatography using dichloromethane-ethyl acetate (1:1) mixture as eluent to give the title compound **22** as a colourless oil (2.60 g, 91%); R_f0.1 [(dichloromethane-ethyl acetate-acetic acid (200:50:1)]; $[\alpha]_D^{22}$ +5.8 (*c* 1.0 in $CHCl_3$); ν_{max}(thin film)/ cm^{-1} 3433 (s), 3200-2825 (*b* s), 1718 (s), 1588 (s), 1512 (s), 1454 (s), 1223 (s), 1141 (s); δ_H(200 MHz, $CDCl_3$) 1.82-2.12 (4H, m, -CH_2CH_2CH-), 3.54-3.60 (2H, m, -CH_2Cl), 4.43-4.50 (1H, m, -$CHCO_2H$), 5.14 (2H, s, $PhCH_2$-), 5.38 (1H, d, *J* 7.5 Hz, -NH), 7.37 (5H, s, C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) 28.17, 29.73 (-CH_2CH_2CH-), 44.05 (-CH_2Cl), 53.08 (-$CHCO_2H$), 67.31 (-CH_2Ph), 128.29, 128.49, 128.74 (-CH, aromatic), 136.08 (-*i*C-, aromatic), 156.40 (-N(H)CO_2CH_2Ph), 177.10 (-CO_2H); *m/z* [CI, (NH_3)] 305 (MNH_4^+(^{37}Cl), 1%), 303 (MNH_4^+(^{35}Cl), 5) 288 (MH^+(^{37}Cl), 3), 286 (MH^+(^{35}Cl), 9), 267 (43), 250 (100), 206 (90), 108 (34), 91 ($C_7H_7^+$, 76).

Z-AIB-(*L*)-Phe-O*t*-Bu, **25**

A solution of *N*-2-(benzyloxycarbonylamino)isobutyric acid **23** (5.0 g, 21.1 mmol), (*L*)-phenylalanine, *t*-butyl ester **24** (4.67 g, 21.1 mmol), 1-hydroxybenzotriazole (2.85 g, 21.1 mmol) and 1,3-dicyclohexylcarbodiimide (4.35 g, 21.1 mmol) in THF (100 ml) was stirred for 24 h. The reaction mixture was filtered to remove the precipitated dicyclohexylurea and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (150ml), refiltered, washed with 2N sodium hydroxide (150ml), 2N hydrochloric acid (250ml), water (2 x 200ml), dried (Na_2SO_4) and evaporated. The crude product was purified by crystallisation from methanol-petroleum ether (b.p. 40-60 °C) mixture to give the title compound **25** as a white crystalline solid (8.1 g, 87%); m.p. 121-122 °C; R_f0.4 [ethyl acetate-petroleum ether (b.p. 40-60 °C) (1:1)];

$[\alpha]_D^{20}$ +37.1 (*c* 1.3 in $CHCl_3$); ν_{max} ($CHCl_3$)/ cm^{-1} 3433 (m), 3021 (s), 1726 (s), 1675 (s), 1496 (s); δ_H(200 MHz, $CDCl_3$) 1.41 (9H, s, $-CO_2C(CH_3)_3$), 1.49 (6H, s, $-C(CH_3)_2$), 3.09 (2H, d, *J* 5.5 Hz, $PhCH_2$-), 4.68-4.78 (1H, m, $PhCH_2CH$-), 5.08 (2H, s, $PhCH_2O$-), 5.42 (1H, s, $(CH_3)_2CNH$-), 6.69 (1H, d, *J* 7.0 Hz, -NH), 7.15-7.35 (10H, m, 2 x C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) 25.07, 25.41 ($CH_3)_2C$-), 27.81 ($(CH_3)_3C$-), 37.78 ($PhCH_2CH$-), 53.57 ($PhCH_2CH$-), 56.77 ($(CH_3)_2C$-), 66.62 ($PhCH_2C(O)NH$-), 82.33 ($(CH_3)_3C$-), 127.03, 128.19, 128.42, 128.67, 129.71 (-CH-, aromatics), 136.37 (-*i*C-, aromatics), 155.07 ($-N(H)CO_2CH_2Ph$), 170.73, 173.94 ($-CO_2C(CH_3)_3$ and -N(H)C(O)-); *m/z* [direct CI, (NH_3)] 441 (MH^+, 100%), 385 (41), 192 (20), 148 (41), 81 (82). (Found C, 68.16; H, 7.39; N, 6.44. $C_{25}H_{32}N_2O_5$ requires C, 68.16; H, 7.32; N, 6.36%).

Z-AIB-(*L*)-Phe-OH, **26**

A solution of Z-AIB-(*L*)-Phe-O*t*-Bu **25** (2.20 g, 5.0 mmol) in trifluoroacetic acid-dichloromethane (1:1) (10 ml) was stirred for 16 h. The solvent was removed *in vacuo*. Residual trifluoroacetic acid was removed by co-evaporation with toluene (4 x 25 ml), *in vacuo*, and then storing the resulting foam over sodium hydroxide pellets under high vacuum to yield **26** (1.91g, ~100%); $[\alpha]_D^{20}$ +30.3 (*c* 1.0 in $CHCl_3$).; ν_{max}($CHCl_3$)/ cm^{-1} 3433 (s), 3018 (s), 1722 (s), 1660 (s), 1456 (s); δ_H(200 MHz, $CDCl_3$) 1.43, 1.44 (2 x 3H, 2 x s, $-C(CH_3)_2$), 3.08-3.52 (2H, m, $PhCH_2$-), 4.71-4.86 (1H, m, $PhCH_2CH$-), 5.04 (2H, s, $PhCH_2O$-), 5.31 (1H, s, $(CH_3)_2CNH$-), 6.76 (1H, d, *J* 7.0 Hz, -NH), 7.14-7.33 (10H, m, 2 x C_6H_5-), 7.95 (1H, *b* s, $-CO_2H$); δ_C(50.3 MHz, $CDCl_3$) 24.54, 25.15 ($CH_3)_2C$-), 37.02 ($PhCH_2CH$-), 53.37 ($PhCH_2CH$-), 56.85 ($(CH_3)_2C$-), 66.98 ($PhCH_2O$-), 127.28, 128.20, 128.46, 128.73, 129.49 (-CH-, aromatics), 135.99 (-*i*C-, aromatics), 174.64, 175.37 ($-CO_2H$ and -N(H)C(O)-); *m/z* [direct CI, (NH_3)] 385 (MH^+, 40%), 277 (68), 192 (40), 148 (68), 91 ($C_7H_7^+$, 100).

Z-AIB-(*L*)-Phe-(*D*)-Pro-OMe, **28**

Triethylamine (920 mg, 1.27 ml, 9.10 mmol) was added dropwise to a cooled (ice bath), stirred solution of Z-AIB-(*L*)-Phe-OH **26** (3.50 g, 9.10 mmol), (*D*)-proline, methyl ester, tosylate salt **27** (2.80 g, 9.10 mmol) and 1-hydroxybenzotriazole (1.23 g, 9.10 mmol) in THF (50 ml). 1,3-Dicyclohexylcarbodiimide (1.87 g, 9.10 mmol) was added and stirring was continued for 16 h. The precipitated dicyclohexylurea by product was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (150 ml) and the resulting solution washed with hydrochloric acid (1 mol dm^{-3}, 150 ml), aqueous sodium hydroxide (1 mol dm^{-3}, 150 ml), water (150 ml), brine (150 ml) and dried (sodium sulphate). The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel using ethyl acetate-petroleum ether (b.p. 30-40 °C) (4:1) mixture and neat ethyl acetate as eluents to give the product **28** as a colourless solid (2.92 g, 65%); m.p. 96-98 °C [ethyl acetate-petroleum ether (b.p. 40-60 °C)]; R_f0.2 [ethyl acetate-petroleum ether (b.p. 40-60 °C) (2:1)]; $[\alpha]_D^{20}$ +39.9 (*c* 1.0 in $CHCl_3$); ν_{max}($CHCl_3$)/ cm^{-1} 3684 (s), 3428 (s), 3023 (s), 1741 (s), 1645 (s), 1498 (s), 1499 (s); δ_H(200 MHz,

$CDCl_3$) 1.49 and 1.52 (2 x 3H, 2 x s, $(CH_3)_2C$-), 1.80-1.92 (4H, m, -$CH_2CH_2CH(CO_2CH_3)N$- (Pro)), 2.68-3.18 (3H, m, $PhCH_2CH$- and -CHHNCO- (Pro)), 3.50-3.66 (1H, m, -CHHNCO- (Pro)), 3.67 (3H, s, $-CO_2CH_3$), 4.29-4.34 (1H, m, $-CH_2CH(CO_2CH_3)N$- (Pro)), 4.90-5.09 (1H, m, $PhCH_2CH$-), 5.09 (2H, s, $PhCH_2O$-), 5.48 (1H, s, $PhCH_2OC(O)NH$-), 6.93 (1H, d, *J* 8.0 Hz, $PhCH_2CH(NH)$-), 7.18-7.35 (10H, m, 2 x C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) 24.66, 24.91 ($(CH_3)_2C$-), 28.16, 29.72 (-$CH_2CH_2CH(CO_2CH_3)N$-), 37.58 ($PhCH_2CH$-), 44.34 (-CH_2N- (Pro)), 52.24 (-$CHCO_2CH_3$), 53.34 ($PhCH_2CH$-), 54.41 ($(CH_3)_2C$-), 57.15 ($-CO_2CH_3$), 67.13 ($PhCH_2O$-), 127.21, 128.19, 128.40, 128.63, 129.45 (-CH, aromatics), 136.05, 136.21 (-*i*C-, aromatics), 156.15 (-$N(H)CO_2CH_2Ph$), 170.69, 172.15, 173.50 (-CO_2Me and 2 x -C(O)N-); *m/z* [direct CI, (NH_3)] 496 (MH^+, 53%), 388 (100), 260 (10), 200 (12), 128 (21), 91 ($C_7H_7^+$, 23), 70 ($C_4H_7NH^+$ (Pro), 20). (Found C, 65.41; H, 6.47; N, 8.32. $C_{27}H_{33}N_3O_6$ requires C, 65.44; H, 6.71; N, 8.48%).

Z-(*L*)-ACP-AIB-(*L*)-Phe-(*D*)-Pro-OMe, **30**

Palladium on activated carbon (5%, ~1 g) was added to a stirred solution of Z-AIB-(*L*)-Phe-(*D*)-Pro-OMe **28** (1.20 g, 2.42 mmol) in methanol (30 ml) under a stream of argon. The reaction flask was evacuated with a water-pump and then filled with hydrogen gas. This procedure was repeated twice and stirring was continued for 3 h under an atmosphere of hydrogen. The reaction mixture was filtered through a pre-washed (methanol) Celite bed. The bed was washed with copious amounts of methanol, and the resulting methanolic solution was evaporated *in vacuo* to give crude H-AIB-(*L*)-Phe-(*D*)-Pro-OMe **29** (981 mg). The residue was dissolved in anhydrous dichloromethane (10 ml), (*S*)-2-(*N*-benzyloxycarbonylamino)-5-chloropentanoic acid (*N*-Z-ACP) **22** (727 mg, 2.54 mmol), BOP reagent[21] (1.13 g, 2.55 mmol) and diisopropylethylamine (660 mg, 890 µl, 5.11 mmol) were added. The reaction mixture was stirred for 16 h, the solvent removed *in vacuo* and the residue dissolved in ethyl acetate (100 ml). The resulting organic solution was washed with aqueous sodium hydroxide (1 mol dm^{-3}, 100 ml), hydrochloric acid (1 mol dm^{-3}, 100 ml), water (100 ml) and brine (100 ml), dried (sodium sulphate) and solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel using neat ethyl acetate as eluent to give the product **30** as an off-white foam (1.00 g, 66%); R_f 0.6 (ethyl acetate); $[\alpha]_D^{20}$ +35.7 (*c* 0.98 in $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3028 (s), 1733 (s), 1700 (s), 1684 (s), 1646 (s), 1499 (s), 1452 (s), 1225 (s); δ_H(200 MHz, $CDCl_3$) 1.48 and 1.54 (2 x 3H, 2 x s, $(CH_3)_2C$-), 1.80-1.98 (8H, m, -$CH_2CH_2CH(CO_2CH_3)N$- (Pro) and -$CH_2CH_2CH_2Cl$), 2.71-3.10 (3H, m, $PhCH_2CH$- and -CHHNCO- (Pro)), 3.54-3.67 (3H, m, -CHHNCO- (Pro) and -CH_2Cl), 3.68 (3H, s, $-CO_2CH_3$), 4.08-4.28 (1H, m, -CHC(O)- (ACP)), 4.29-4.34 (1H, m, $-CH_2CH(CO_2CH_3)N$- (Pro)), 4.86-4.98 (1H, m, $PhCH_2CH$-), 5.12 (2H, s, $PhCH_2O$-), 5.63 (1H, d, *J* 8.0 Hz, $PhCH_2OC(O)NH$-), 6.89 (1H, s, $-C(CH_3)_2NH$-) 7.00 (1H, d, *J* 8.0 Hz, $PhCH_2CH(NH)$-), 7.14-7.34 (10H, m, 2 x C_6H_5-); δ_C(50.3 MHz, $CDCl_3$) 24.21 (CH_2- (Pro)), 24.44 and 24.84 ($(CH_3)_2C$-), 28.24, 28.79, 29.73 (-CH_2 (Pro) and -$CH_2CH_2CH_2Cl$), 38.98 ($PhCH_2CH$-), 44.39 (-CH_2Cl), 46.67 (-CH_2N- (Pro)), 52.13 ($-CO_2CH_3$), 52.53 (-$CH(CO_2CH_3)$), 54.37 ($PhCH_2CH$-), 57.00 ($(CH_3)_2C$-), 58.74 (-CHC(O)- (ACP)), 67.05 ($PhCH_2O$-), 127.11, 128.16, 128.31, 128.52, 128.67,

129.36 (-CH, aromatics), 136.34, 136.42 (-*i*C-, aromatics), 156.51 (-N(H)CO_2CH_2Ph), 169.99, 170.96, 172.42, 173.77 (-CO_2CH_3 and 3 x -C(O)N-); *m/z* [direct CI, (NH_3)] 631 ($MH^+(^{37}Cl)$, 2%), 629 ($MH^+(^{35}Cl)$, 6), 593 (38), 464 (10), 130 (42), 91 ($C_7H_7^+$, 100), 70 (48), 58 (38).

cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-ACP-), **32**

Aqueous sodium hydroxide (1.0 mol dm^{-3}, 2.30 ml) was added to a stirred solution of *N*-Z-(*L*)-ACP-AIB-(*L*)-Phe-(*D*)-Pro-OMe **30** (725 mg, 1.15 mmol) in methanol (5 ml). After 8 h methanol was evaporated *in vacuo*, the residue was partitioned between aqueous sodium hydroxide (1 mol dm^{-3}, 50 ml) and diethyl ether (50 ml), and the aqueous layer was removed, acidified and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with water (50 ml), brine (50 ml), dried (sodium sulphate) and solvent was evaporated *in vacuo* to give a saponified tetrapeptide. This tetrapeptide (606 mg, 0.98 mmol) was dissolved in anhydrous THF (5 ml) and pentafluorophenol (552 mg, 335 µl, 3.0 mmol) and 1,3-dicyclohexylcarbodiimide (203 mg, 0.98 mmol) were added. After stirring the reaction mixture overnight the precipitated dicyclohexylurea was removed by filtration, the filtrate concentrated, *in vacuo*, and the resultant residue dissolved in ethyl acetate (50 ml). The resulting solution was washed with aqueous potassium carbonate (1 mol dm^{-3}, 50 ml), water (50 ml) and brine (50 ml). Ethyl acetate was removed and the residue **31** (696 mg, 0.89 mmol) dissolved in anhydrous 1,4-dioxane (10 ml). This solution was added over 5 h to anhydrous 1,4-dioxane (500 ml) at 95 °C containing ethanol (10 ml), *N*-methyl morpholine (89 mg, 97 µl, 0.88 mmol) and 10 % palladium on activated charcoal (~ 1 g). During the addition hydrogen gas was passed through the suspension by means of an aeration tube. After the addition was complete the reaction mixture was stirred for a further 1 h. The reaction mixture was then cooled, concentrated, *in vacuo*, to about 10 ml. The catalyst was removed by filtration through a pre-washed (methanol) Celite bed and the bed was subsequently washed with copious amounts of methanol. The methanolic solution was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate (b.p. 30-40 °C) (3:2) mixture to give the title compound **32** as a white foam (295 mg, 55% from **30**); R_f0.3 [ethyl acetate-petroleum ether (b.p. 40-60 °C) (1:1)]; $[\alpha]_D^{20}$ -75.1 (*c* 1.1 in $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3301 (m), 3020 (s), 1682 (s), 1625 (m), 1521 (s); δ_H(500 MHz, $CDCl_3$) 1.34 (3H, s, CH_3-), 1.68-1.87 (5H, m, CHH (Pro) and -$CH_2CH_2CH_2Cl$), 1.77 (3H, s, CH_3-), 1.91-1.99 (1H, m, CHH (Pro)), 2.14-2.22 (1H, m, -CHH (Pro)), 2.30-2.35 (1H, m, -CHH (Pro)), 2.96 (1H, dd, *J* 6.0, 13.5 Hz, PhCHH-), 3.20-3.25 (1H, m, -CHHN(CO)CH- (Pro)), 3.26 (1H, dd, *J* 10.0, 13.5 Hz, PhCHH-), 3.51-3.58 (2H, m, -CH_2Cl), 3.84-3.89 (1H, m, -CHHN(CO)CH- (Pro)), 4.22-4.27 (1H, m, -CH(NH)CO (ACP)), 4.67 (1H, dd, *J* 2.5, 8.0 Hz, CHCO (Pro)), 5.12-5.19 (1H, m, $PhCH_2CH$-), 5.91 (1H, s, -$NHC(CH_3)_2$), 7.17 (1H, d, *J* 10.0 Hz, -NHCO-), 7.19-7.34 (5H, m, C_6H_5-), 7.47 (1H, d, *J* 10.0 Hz, -NHCO-); δ_C(125.8 MHz, $CDCl_3$) 23.49 (-CH_3), 24.73 (-CH_2CH_2Cl), 25.01 (CH_2- (Pro)), 26.44 (-CH_3), 26.48, 28.54 (-$CH_2CH_2CH_2Cl$ and -CH_2 (Pro)), 35.80 ($PhCH_2$-), 44.21 (-CH_2Cl), 47.03 (-$CH_2N(CO)$-), 53.47 and 53.72 ($PhCH_2CH$- and -CH_2CH- (ACP)), 57.76 (-CH(CO)- (Pro)), 58.88 ($(CH_3)_2C$-), 126.73, 128.61, 129.02 (-CH, aromatic), 136.99 (-*i*C-, aromatic), 171.98, 172.91, 173.89, 175.52 (4 x -CON-); *m/z* [direct CI, (NH_3)] 480 ($MNH_4^+(^{35}Cl)$, 2%),

465 ($MH^+(^{37}Cl)$, 7), 463 ($MH^+(^{35}Cl)$, 32), 225 (100), 120 (13), 99 (14), 70 (33), 58 (26). (Found C, 59.58; H, 6.94; N, 11.90. $C_{23}H_{31}ClN_4O_4$ requires C, 59.67; H, 6.75; N, 12.10%).

cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-AIP[#]-), **33**

Sodium iodide (478 mg, 3.30 mmol) was added to a solution of cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-ACP-) **32** (148 mg, 0.32 mmol) in dry 2-butanone (5 ml) and the reaction mixture refluxed overnight under an atmosphere of argon. The reaction mixture was partitioned between ethyl acetate (50 ml) and aqueous sodium thiosulphate (5% w/v, 50 ml). The organic layer was separated and then washed with water (50 ml) and brine (50 ml), dried (sodium sulphate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel using ethyl acetate-petroleum ether (b.p. 30-40 °C) (1:1) and ethyl acetate-petroleum ether (b.p. 30-40 °C) (2:1) mixtures as eluents to give the title compound **33** as a white foam (134 mg, 76%); R_f 0.4 [ethyl acetate-petroleum ether (b.p. 40-60 °C) (1:1)]; $[\alpha]_D^{20}$ -81.2 (*c* 1.6 in $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3298 (m), 3020 (s), 1682 (s), 1625 (m), 1524 (s); δ_H(500 MHz, $CDCl_3$) 1.35 (3H, s, CH_3-), 1.74-1.93 (6H, m, CH_2 (Pro) and -$CH_2CH_2CH_2$I), 1.78 (3H, s, CH_3-), 2.16-2.19 (1H, m, -CHH (Pro)), 2.32-2.35 (1H, m, -CHH (Pro)), 2.96 (1H, dd, *J* 5.5, 13.5 Hz, PhCHH-), 3.16-3.24 (3H, m, -CH_2I and -CHHN(CO)CH- (Pro)), 3.27 (1H, dd, *J* 10.0, 13.5 Hz, PhCHH-), 3.85-3.89 (1H, m, -CHHN(CO)CH- (Pro)), 4.22-4.24 (1H, m, -CH(NH)CO (AIP)), 4.65-4.68 (1H, m, CH(NH)CO (Pro)), 5.15-5.20 (1H, m, $PhCH_2CH$-), 5.90 (1H, s, -NHC$(CH_3)_2$), 7.18 (1H, d, *J* 10.5 Hz, -NHCO-), 7.20-7.30 (5H, m, C_6H_5-), 7.44 (1H, d, *J* 9.5 Hz, -NHCO-); δ_C(50.3 MHz, $CDCl_3$) 5.21 (-CH_2I), 23.34 (-CH_3), 24.82 (CH_2- (Pro)), 26.25 (-CH_3), 29.25 ($ICH_2CH_2CH_2$- and -CH_2- (Pro)), 33.75 ($ICH_2CH_2CH_2$-), 35.67 ($PhCH_2$-), 46.88 (-CH_2N(CO)-), 53.33 ($PhCH_2CH$- and -CH_2CH- (AIP)), 57.69 (-CH(CO)- (Pro)), 58.75 ($(CH_3)_2C$-), 126.88, 128.74, 129.14 (-CH, aromatic), 137.08 (-*i*C-, aromatic), 172.20, 173.14, 174.17, 175.76 (4 x -CON-); *m/z* [direct CI, (NH_3)] 572 (MNH_4^+, 2%), 555 (MH^+, 30), 429 (24), 225 (100), 120 (14), 70 (35), 58 (28). (Found C, 49.91; H, 5.77; N, 9.84. $C_{23}H_{31}IN_4O_4$ requires C, 49.83; H, 5.64; N, 10.11%).

cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-TAOE[§] -), **34**

A solution of tributyltin hydride (92 mg, *ca* 57% w/w, *ca* 0.18 mmol) in deoxygenated benzene (5 ml) was added using a syringe pump to a refluxing solution of cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-AIP-) **33** (67 mg, 0.12 mmol), (1*R*, 2*R*)-1,2-epoxy-3-oxo-1-trimethylsilyl-4-pentene **9** (62 mg, 0.36 mmol) and AIBN (~10 mg) in deoxygenated anhydrous benzene (10 ml) over a period of 5 h. The reaction mixture was refluxed for a further 30 min, cooled, and the solvent was then removed *in vacuo* and the residue dissolved in acetonitrile (20 ml) and washed with hexane (2 x 20 ml). Acetonitrile was evaporated *in vacuo* and the residue purified by flash column chromatography on silica gel using petroleum ether (b.p. 40-60 °C)-ethyl acetate (2:1)

[#] AIP= (*S*)-2-amino-5-iodopentanoic acid

[§] TAOE= (2*S*, 9*R*, 10*R*)-2-amino-8-oxo-9,10-epoxy-10-trimethylsilyldecanoic acid

mixture as eluent to give the title compound **34** as an oil (43 mg, 60%); R_f 0.5 [petroleum ether (b.p. 40-60 °C)-ethyl acetate (1:1)]; $[\alpha]_D^{20}$ -94.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3299 (s), 2933 (s), 1681 (s), 1624 (s), 1522 (s), 1253 (m), 846 (m); δ_H(200 MHz, $CDCl_3$) 0.11 (9H, s, -Si(CH_3)$_3$), 1.12-1.96 (10H, m, -(CH_2)$_4$$CH_2$C(O)- and -$CH_2$ (Pro)), 1.34 (3H, s, -CH_3), 1.77 (3H, s, -CH_3), 2.15-2.40 (4H, m, -(CH_2)$_4$$CH_2$C(O)- and -$CH_2$- (Pro)), 2.35 (1H, d, *J* 3.5 Hz, -CH(Si(CH_3)$_3$)), 2.95 (1H, dd, *J* 5.5, 13.5 Hz, PhCHH-), 3.21-3.33 (2H, m, PhCHH- and -CHHN(CO)CH- (Pro)), 3.24 (1H, d, *J* 3.5 Hz, -COCH(O)CH(Si(CH_3)$_3$)), 3.79-3.87 (1H, m, -CHHN(CO)CH- (Pro)), 4.10-4.24 (1H, m, -CH(NH)CO (TAOE)), 4.66 (1H, br d, *J* 5.5 Hz, CH(NH)CO (Pro)), 5.10-5.25 (1H, m, PhCH$_2$CH-), 5.92 (1H, s, -NHC(CH_3)$_2$), 7.09 (1H, d, *J* 10.0 Hz, -NHCO-), 7.20-7.32 (5H, m, C_6H_5-), 7.48-7.58 (1H, m, -NHCO-); δ_C(50.3 MHz, $CDCl_3$) -3.99 (-Si(CH_3)$_3$), 23.00, 24.57, 24.82, 28.61, 33.91, 34.84 (-CH_2(Pro)- (TAOE)), 23.40 (-CH_3), 26.25 (-CH_3), 35.67 (PhCH_2-), 46.84 (-CH_2N-), 50.81 (-CHSi(CH_3)$_3$), 53.31, 54.21 (-CHC(O)N- (TAOE) and PhCH$_2$CH-), 57.18 (-CHC(O)CH(Si(CH_3)$_3$), 57.68 (-CH(CO)- (Pro)), 58.68 (-C(CH_3)$_2$), 126.83, 128.73, 129.16 (-CH, aromatic), 137.17 (-*i*C-, aromatic), 172.08, 173.04, 174.63, 175.89 (4 x -CON-); *m/z* [direct CI, (NH_3)] 599 (MH^+, 5%), 429 (100), 328 (16), 229 (15), 120 (45), 91 ($C_7H_7^+$, 27), 70 ($C_4H_7NH^+$ (Pro), 93), 58 (68).

Chlamydocin, **1**

Tetrabutylammonium fluoride hydrate (92 mg, 0.35 mmol) was added to a solution of cyclo(-(*D*)-Pro-(*L*)-Phe-AIB-(*L*)-TAOE-) **34** (40 mg, 6.7 μmol) in DMSO (1 ml). The reaction mixture was stirred for 48 h, diluted with ethyl acetate (10 ml), washed with water (10 ml), and brine (10 ml), dried (sodium sulphate), filtered and solvent removed *in vacuo*. The residue was purified by preparative thin layer chromatography using ethyl acetate-petroleum ether (b.p. 30-40 °C) (1:1) mixture as eluent to give the title compound **1** as a colourless syrup (24 mg, 68%); R_f0.2 [petroleum ether (b.p. 40-60 °C)-ethyl acetate (1:1)]; $[\alpha]_D^{21}$ -145.3 (*c* 0.27 in C_6H_6)(lit.,[1] -147.5 (*c* 0.3 in C_6H_6) ; $\nu_{max}(CHCl_3)$/ cm^{-1} 3300 (m), 1681 (s), 1626 (m), 1515 (m); δ_H(500 MHz, $CDCl_3$) [fig. 4] 1.26-1.33 (4H, m, -$CH_2$$CH_2$- (AOE)), 1.35 (3H, s, -$CH_3$), 1.58-1.82 (6H, m, -$CH_2$- (Pro) and -$CH_2$$CH_2$- (AOE)) 1.78 (3H, s, -$CH_3$), 2.16-2.21 (1H, m, -CHH- (Pro)), 2.25-2.35 (2H, m, -CHH- (Pro) and -CH_2CHHC(O)- (AOE)), 2.40-2.47 (1H, m, -CH_2CHHC(O)- (AOE)), 2.87 (1H, dd, *J* 2.5, 6.0 Hz, CHH(O)CHC(O)CH_2- (AOE)), 2.96 (1H, dd, *J* 5.5, 13.5 Hz, PhCHH-), 2.99 (1H, dd, *J* 5.0, 6.0 Hz, CHH(O)CHC(O)CH_2- (AOE)), 3.20-3.25 (1H, m, -CHHN(CO)CH- (Pro)), 3.27 (1H, dd, *J* 10.0, 13.5 Hz, PhCHH-), 3.42 (1H, dd, *J* 2.5, 5.0 Hz, -C(O)CH(O)CH_2 (AOE)), 3.84-3.89 (1H, m, -CHHN(CO)CH- (Pro)), 4.16-4.21 (1H, m, -CH(NH)CO (AOE)), 4.67 (1H, dd, *J* 8.5, 2.5 Hz, CH(NH)CO (Pro)), 5.14-5.19 (1H, m, PhCH$_2$CH-), 5.91 (1H, s, -NHC(CH_3)$_2$), 7.10 (1H, d, *J* 10.5 Hz, -NHCO-), 7.20-7.32 (5H, m, C_6H_5-), 7.50 (1H, d, *J* 10.5 Hz, -NHCO-); δ_C(125.8 MHz, $CDCl_3$) 22.87 (-CH_2- (AOE)), 23.53 (-CH_3), 24.74, 25.06, 25.27 (-CH_2- (AOE), -CH_2- (Pro)), 26.60 (-CH_3), 28.81, 29.67 (-CH_2- (AOE), -CH_2- (Pro)), 35.91, 36.30 (PhCH_2- and -C(O)CH_2-), 45.93 (CH_2(O)CHC(O)-), 47.04

(-$\underline{C}H_2N(CO)$-), 53.36, 53.56, 54.39, 57.87 ($PhCH_2\underline{C}H$-, -$C(O)\underline{C}H(O)CH_2$, -$\underline{C}HC(O)N$- (AOE), -$\underline{C}H(CO)N$- (Pro)), 58.92 (-$\underline{C}(CH_3)_2$), 126.71, 128.60, 129.08 (-$\underline{C}H$, aromatic), 137.20 (-*i*$\underline{C}$-, aromatic), 171.85, 172.89, 174.32, 175.65 (4 x -$\underline{C}ON$-); *m/z* [direct CI, (NH_3)] 544 (MNH_4^+, 13%), 527 (MH^+, 100), 511 (27).

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