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SYNTHESIS OF δ-L-α-AMINOADIPOYL-L-CYSTEINYL-D-ALLYLGLYCINE, AND EIGHT DEUTERATED ANALOGUES, SUBSTRATES FOR THE INVESTIGATION OF THE MECHANISM OF ACTION OF ISOPENICILLIN N SYNTHASE.

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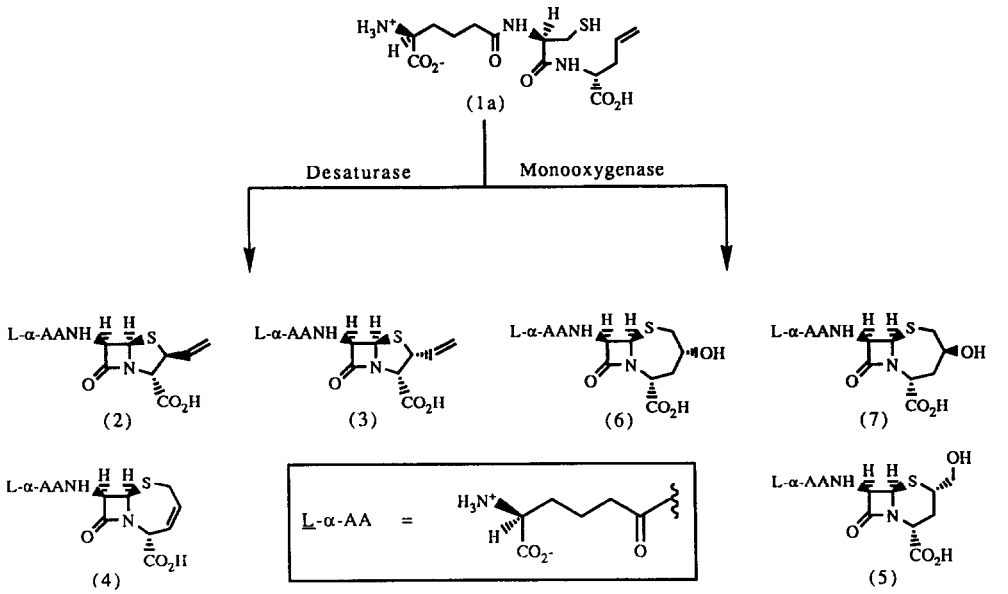
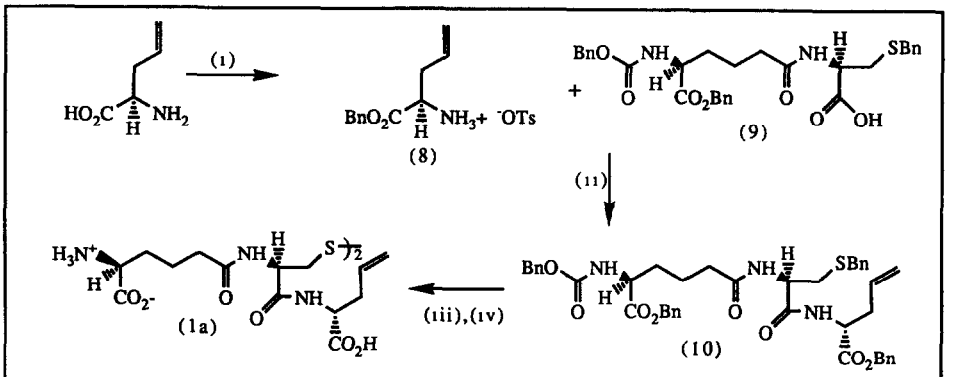
Abstract: The synthesis of δ-L-α-aminoadipoyl-L-cysteinyl-D-allylglycine (1a) from its component amino acids is described, along with the synthesis of eight analogues (1b-i) specifically deuterated at C-3 and/or C-5 of the allylglycine residue

The enzyme Isopenicillin N synthase (IPNS)[1,2] converts the modified substrate tripeptide δ-L-α-aminoadipoyl-L-cysteinyl-D-allylglycine (LLD-ACAllylglycine) (1) into 2S- and 2R-vinylpenam (2 and 3), homoceph-3-em (4), hydroxymethylcepham (5), and 4R- and 4S-hydroxyhomocepham (6 and 7) type products[3,4]. Herein we report full experimental details of the synthesis of the original LLD-ACAllylglycine tripeptide (1a), and in addition we report the synthesis of the eight deuterated tripepides (1b-i) that were required in order to further investigate the stereochemistry and mechanism of the closure of the second ring[5,6] of the β-lactam containing metabolites from this analogue of the natural substrate



The tripeptide (1a) was obtained as shown in scheme 1 Thus D-Allylglycine was refluxed with benzyl alcohol, benzene, and toluene-4-sulphonic acid, with azeotropic removal of water, to give the benzyl protected amino acid, toluene-4-sulphonic acid salt (8) This was coupled to benzyl protected "LL- AC" dipeptide[7] (9) using 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) and triethylamine according to the literature procedures[7], to give the fully protected tripeptide (10) Deprotection ($Na/NH_3(l)$), followed by a modified Hopkins work up[7], gave the tripeptide (1a) in

thiol form This was oxidised to the disulphide (O_2, pH9, 2hrs), then purified by reverse phase hplc.

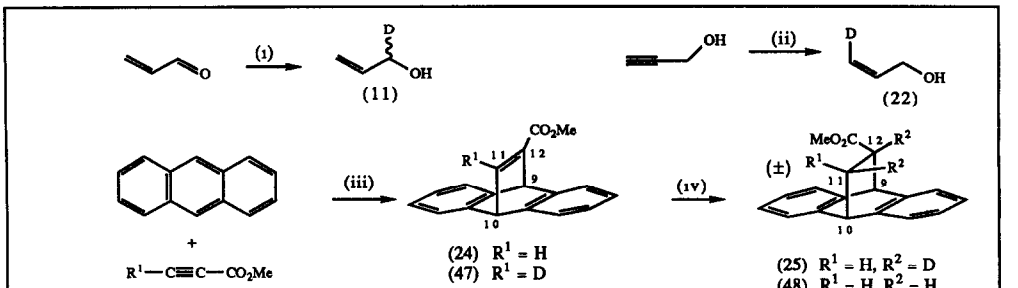


(i) $C_6H_5CH_2OH$, TsOH, Benzene, reflux (azeotropic removal of water). (ii) EEDQ, Et_3N, DCM. (iii) Na, NH_3 (l), followed by modified Hopkins' workup. (iv) O_2, pH 9 (NH_4OH), 2 h.

Scheme 1

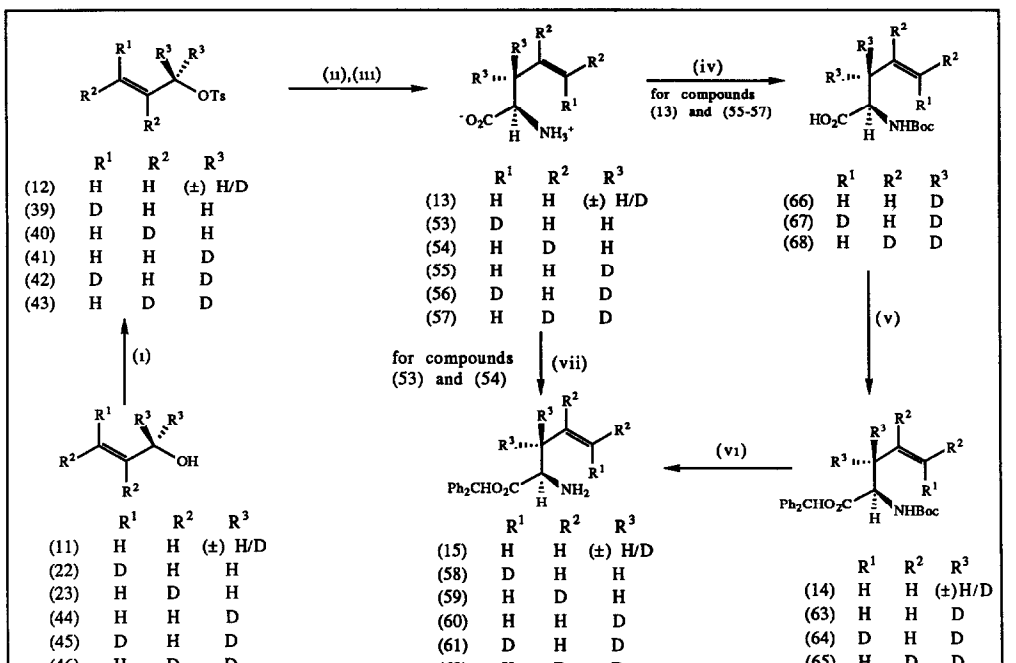
The racemic deuterated tripeptide (1b) was synthesised as shown in scheme 2, 3 and 4. Acid labile protecting groups (4-methoxybenzyl, and benzhydryl) were used for the final protected tripeptide instead of the previously reported benzyl protecting groups, as this allowed more facile separation of the diastereotopic protected LLD- and LLL-tripeptides. Thus acrolein was reduced with lithium aluminium deuteride in tetrahydrofuran to give the racemically deuterated allyl alcohol (11). This was tosylated with tosylchloride and NaOH in Et_2O[8] , and the resulting allyl tosylate (12) reacted with the O'Donnell synthon[9] (N,N-diphenylmethylene aminoacetonitrile) and sodium hydroxide under phase transfer conditions (no S_N2' attack of the synthon anion on the allyl tosylate was observed by high field NMR using this procedure). The resultant crude Schiff's base was hydrolysed with hydrochloric acid (1M) and the nitrile hydrolysed to the corresponding carboxylic acid with HCl (refluxing 6M) to give the amino acid, HCl salt (13) The amino acid was N-protected using BOC-ON[10], then carboxyl protected by treatment with diphenyldiazomethane[11], to give the diprotected amino acid (14) This was N-deblocked with toluene-4-sulphonic acid[12], followed by a basic work up, to give the benzhydryl ester free amine (15) This was coupled to the "LL- AC" dipeptide protected with acid labile groups (16), using EEDQ and triethylamine to give the fully protected, diastereotopic LLD- and LLL-tripeptides (17a and 17b) Separation of the isomers by column chromatography on silica gel followed by deprotection with trifluoroacetic acid and anisole (10 1, *reflux, 30min) of the less polar component gave the crude LLD-tripeptide* (1b) *as its trifloroacetate salt* Oxidation of the tripeptide to the disulphide (O_2, pH 9-10) and purification by reverse phase hplc gave the LLD-AC-3RS-[3-$^2H_1$]Allylglycine disulphide (1b). (Unlabelled LLD-ACAg tripeptide prepared in an analogous manner gave material identical in all respects to that of (1a) prepared as in scheme 1[see scheme 6]).

The tripeptides (1c,d) stereospecifically deuterated at C-3 of the allylglycine residue were then synthesised The key step in the synthesis was the use of the Ireland-Claisen rearrangement on the deuterated N-^{t}Boc-glycine allyl esters (18,19)[13] to give the specifically deuterated N-^{t}Boc allylglycines (20,21)(see scheme 5) The deuterated N-^{t}Boc-glycine allyl esters were prepared as shown in scheme 2,4 and 5. The deuterated alcohols (22,23) were obtained *via* the reduction of propargyl alcohol with $LiAlH_4$ followed by a D_2O quench[14] for (22), or for (23) from the methyl propiolate/anthracene Diels-Alder adduct (24), which was reduced with D_2(g) (1atm)/Pd on $CaCO_3$ to give the adduct (25), further reduced with $LiAlH_4/Et_2O$, to alcohol (26), and pyrolysed (350°C) to give the allyl alcohol (23) *via* a retro Diels-Alder process[15,16,17] The deuterated allyl alcohols were coupled to N-^{t}Boc-glycine using dicyclohexyl-carbodiimide (DCC) with dimethylaminopyridine (DMAP) catalysis to give the deuterated N-^{t}Boc-glycine allyl esters



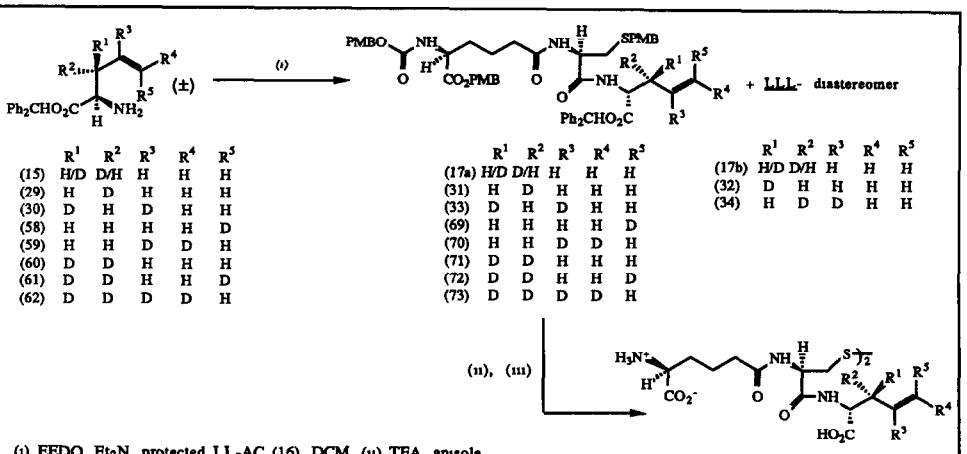
(i) $LiAlD_4$, THF, H_2O workup. (ii) $LiAlH_4$, THF, D_2O workup (iii) Reflux, xylene, 4 days. (iv) D_2 (g) or H_2 (g), $Pd/CaCO_3$, EtOAc (v) $LiAlD_4$ or $LiAlH_4$, Et_2O (vi) 350°C

Scheme 2



(i) TsCl, NaOH, Et_2O. (ii) $(C_6H_5)_2C{=}NCH_2CN$, NaOH, $C_6H_5CH_3$, H_2O, BTEAC. (iii) 1M HCl, 2h, then 6M HCl (reflux), 12h, followed by ion-exchange chromatography where necessary. (iv) BOC-ON, Et_3N, Dioxan, followed by H_3O^+ workup. (v) $(C_6H_5)_2CN_2$, EtOAc (vi) TsOH, EtOH, Et_2O, followed by aq $NaHCO_3$ workup. (vii) TsOH, H_2O, Acetone, followed by $(C_6H_5)_2CN_2$ Aq. $NaHCO_3$ workup.

Scheme 3



	R^1	R^2	R^3	R^4	R^5
(15)	H/D	D/H	H	H	H
(29)	H	D	H	H	H
(30)	D	H	D	H	H
(58)	H	H	H	H	D
(59)	H	H	D	D	H
(60)	D	D	H	H	H
(61)	D	D	H	H	D
(62)	D	D	D	D	H

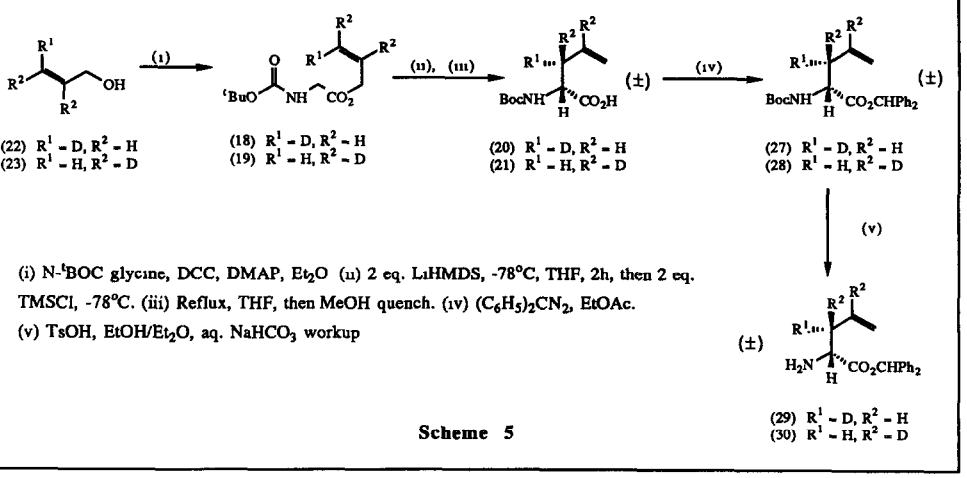
	R^1	R^2	R^3	R^4	R^5
(17a)	H/D	D/H	H	H	H
(31)	H	D	H	H	H
(33)	D	H	D	H	H
(69)	H	H	H	H	D
(70)	H	H	D	D	H
(71)	D	D	H	H	H
(72)	D	D	H	H	D
(73)	D	D	D	D	H

	R^1	R^2	R^3	R^4	R^5
(17b)	H/D	D/H	H	H	H
(32)	D	H	H	H	H
(34)	H	D	D	H	H

(i) EEDQ, Et_3N, protected LL-AC (16), DCM. (ii) TFA, anisole, reflux 30min. (iii) O_2, pH 9 (NH_4OH), 2h

	R^1	R^2	R^3	R^4	R^5
(1b)	H/D	D/H	H	H	H
(1c)	H	D	H	H	H
(1d)	D	H	D	H	H
(1e)	H	H	H	H	D
(1f)	H	H	D	D	H
(1g)	D	D	H	H	H
(1h)	D	D	H	H	D
(1i)	D	D	D	D	H

Scheme 4



(i) N-^{t}BOC glycine, DCC, DMAP, Et_2O (ii) 2 eq. LiHMDS, -78°C, THF, 2h, then 2 eq. TMSCl, -78°C. (iii) Reflux, THF, then MeOH quench. (iv) $(C_6H_5)_2CN_2$, EtOAc. (v) TsOH, EtOH/Et_2O, aq. $NaHCO_3$ workup

(22) R^1 = D, R^2 = H
(23) R^1 = H, R^2 = D

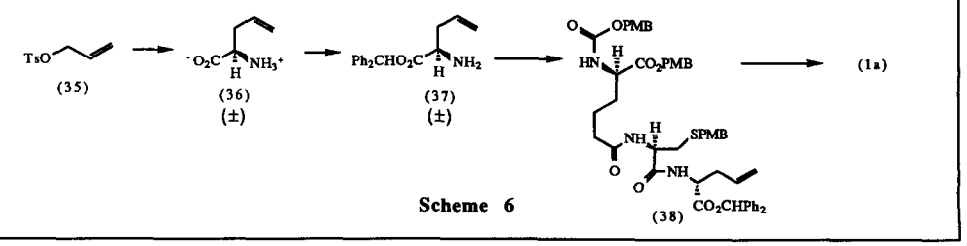
(18) R^1 = D, R^2 = H
(19) R^1 = H, R^2 = D

(20) R^1 = D, R^2 = H
(21) R^1 = H, R^2 = D

(27) R^1 = D, R^2 = H
(28) R^1 = H, R^2 = D

(29) R^1 = D, R^2 = H
(30) R^1 = H, R^2 = D

Scheme 5



(35) (36) (±) (37) (±) (38)

Scheme 6

Tripeptide	% deuterium incorperation (by mass spectrometry)	diastereomeric excess at C-3 (by nmr)
(1c)	$^2H_0 < 5\%$, $^2H_1 > 89\%$, $^2H_2 = 6\%$, $^2H_3 = 0$	90%
(1d)	$^2H_0 < 5\%$, $^2H_1 = 0\%$, $^2H_2 > 94\%$, $^2H_3 = 0$	90%

Table 1

Tosylates

Molecular ion cluster (MNH_4^+)

No	Observed	Calculated	% deuteration	Stereochemistry*
(39)	230 (4)	230 (0)	4% fully protio	E:Z ratio
	231 (100)	231 (100)	79% monodeuterated	approx. 1:12
	232 (34)	232 (13)	17% dideuterated	
(40)	231 (15)	231 (0)	13% monodeuterated	E:Z ratio
	232 (100)	232 (100)	87% dideuterated	approx. 15:1
	233 (13)	233 (13)		
(41)	231 (1)	231 (0)	99% dideuterated	no evidence of any
	232 (100)	232 (100)		proton background at C-1
	233 (9)	233 (13)		
(42)	232 (11)	232 (0)	10% dideuterated	only Z-isomer detectable,
	233 (100)	233 (100)	90% trideuterated	Z:E ratio
	234 (10)	234 (13)		>16·1
(43)	233 (5)	233 (0)	4% trideuterated	E:Z ratio
	234 (100)	234 (100)	96% tetradeuterated	> 25:1 by ^{1}H-nmr
	235 (8)	235 (13)		

Amino acid

Molecular ion cluster (MH^+)

No	Observed	Calculated	% deuteration	Stereochemistry*
(53)	116 (4)	116 (0)	4% fully protio	E:Z ratio
	117 (100)	117 (100)	78% monodeuterated	approx. 1:10
	118 (23)	118 (5)	18% dideuterated	
(54)	117 (14)	117 (0)	14% monodeuterated	E:Z ratio
	118 (100)	118 (100)	85% dideuterated	approx. 15·1
	119 (6)	119 (5)	1% trideuterated	
(55)	117 (2)	117 (0)	96% dideuterated	no evidence of any
	118 (100)	118 (100)		proton background at C-5
	119 (7)	119 (5)		
(56)	118 (10)	118 (0)	10% dideuterated	only Z-isomer detectable
	119 (100)	119 (100)	87% trideuterated	Z:E> 15:1
	120 (8)	120 (5)		
(57)	119 (5)	119 (0)	5% trideuterated	E.Z ratio
	120 (100)	120 (100)	94% tetradeuterated	> 25:1
	121 (8)	121 (5)		

* obtained from analysis of the olefinic region of the ^{1}H-nmr spectra.

Table 2.

(18,19) which were subjected to the slightly modified conditions for the Ireland-Claisen rearrangement to give the stereospecifically deuterated N-^{t}Boc allylglycines (20,21) in low yield but with high stereoselectivity. The N-^{t}Boc allylglycines (20,21) were then protected as their benzhydryl esters (27,28). The stereochemical purity of the assumed RR,SS and RS,SR enantiomerc pairs (20) and (21) was determined by ^{1}H n.m.r. to be greater than 90%, the major impurities being the opposite epimers at C-3. These were then N-deblocked with toluene-4-sulphonic acid to give the benzhydryl ester free amines (29, 30) and coupled to the dipeptide "LL-AC" protected with acid labile protecting groups (16) as described earlier. The diastereomeric protected tripeptides (31, 32) and (33, 34) were separated, and the LLD diastereoisomers were deprotected, oxidised to the disulphides (1c and 1d) and purified as previously described (scheme 4). The stereochemical purity and deuterium incorperation were determined by ^{1}H-nmr and mass spectral analysis and are shown in table 1.

The five tripeptides containing deuterium labels in the allylglycine residue (1e-i) were prepared as illustrated in scheme 2,3 and 4. The synthesis was developed initially with unlabelled allyltosylate (35) (scheme 6), *via* alkylation of the O'Donnel synthon under phase transfer conditions as described above to give a final tripeptide identical in all respects to (1a) derived as in scheme 1. The deuterated allyl tosylates (39,40,41,42,43) were prepared from the deuterated allyl alcohols (22,23,44,45,46) using tosyl chloride and powdered NaOH. The five deuterated allyl alcohols required were prepared as in scheme 2. The alcohols (22) and (23) were prepared as described earlier. Allyl alcohols (44,45,46) were prepared via the anthracene-methyl propiolate Diels-Alder adducts (24,47) in a similar fashion to that described above which were reduced either with deuterium (25) or hydrogen gas (48,49) using Pd on $CaCO_3$. The reduced adduct esters were reduced to the corresponding deuterated alcohols with $LiAlD_4$ (50,51,52) and the free allyl alcohols (44,45,46) released by a retro Diels-Alder reaction at 350 °C on the reduced adducts. The deuterated amino acids (53,54,55,56,57) were prepared by the alkylation of the O'Donnell synthon by reaction with the deuterated tosylates (39,40,41,42,43). This alkylated Schiffs' base was hydrolysed with HCl (1M), and the nitrile group hydrolysed by reflux in HCl (6M) (Scheme 3) to give the amino acids. The levels of deuteration and stereochemical purity of the allyl tosylates and amino acids are presented in table 2. The amino acids (53,54) were protected directly with diphenyldiazomethane to give the benzhydryl esters, free amines (58,59), while the amino acids (55,56,57) were converted to the benzhydryl ester amines (60,61,62) *via* the N-^{t}BOC amino acids (66,67,68) and N-^{t}BOC amino acid benzhydryl esters (63,64,65).

The amino acid free amines were coupled to the "LL-AC" dipeptide protected with acid labile protecting groups (16) as described earlier, the LLD-diastereoisomers (69,70,71,72,73) separated by column chromatography on silica gel, and then deprotected with trifluoroacetic acid-anisole to give the free thiol tripeptides (1e-i). The tripeptides were then oxidised to the disulphide with O_2 if purification by h.p.l.c. was necessary.

Experimental:

General Experimental.

Melting points were determined using a Gallenkamp capilliary apparatus and are uncorrected

Infra red spectra were recorded on a Perkin-Elmer 681 spectophotometer. Spectra are reported in wavenumbers (cm^{-1}) and are calibrated against polystyrene (υ_{max} 1602 cm^{-1}). Relevant strong (s), medium (m), and weak (w) absorbances are quoted.

Proton nuclear magnetic resonance spectra were recorded on Brucker WH 300 (300MHz), Bruker AM 250 (250MHz), Brucker AM 500 (500MHz), or Varian Gemini 200 (200MHz) spectrometers. Chemical shifts (δ) are expressed in parts per million (ppm.). Spectra were referenced internally to residual proton in the solvent for chloroform (δ 7 27), acetonitrile (δ 1.95) or methanol (δ3.31), or for aqueous spectra 3-(trimethylsilyl)-[2,2,3,3-$^2H_4$]propionic acid, sodium salt (TSP) (δ 0.00), unless otherwise stated. Carbon nuclear magnetic resonance spectra were recorded on a Bruker AM 500 (126 MHz, multiplicities assigned by off resonsance proton decoupling or DEPT spectrum editing), Bruker AM 250

(63 MHz, multiplicities assigned by off resonance decoupling), or a Varian Gemini 200 (50MHz, multiplicities assigned by DEPT spectrum editing). Spectra were referenced internally to d_1-chloroform (δ 77.0) or d_3-methanol-Od (δ 49.0), or for aqueous samples, to added dioxan (δ 67.0). Unless otherwise quoted the pH of aqueous solutions was 6-8 All ^{1}H-nmr spectra in D_2O are HOD supressed unless otherwise stated.

Mass spectra were recorded on a ZAB-1F machine for fast atom bombardment (FAB), field desorption (FD), direct ammonia chemical ionisation (CI), and ammonia desorption chemical ionisation (NH_3 DCI). Gas chromatography-mass spectroscopy (GCMS) was performed on a VG Lab Base Trio 1 GC/MS system, DB5 column, ammonia direct chemical ionisation detection.

Microanalysis was performed on a Carlo Erba Strumentazone Elemental Analyser, model 1106 interfaced to a Commodore 8296-D computer.

Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Flash chromatography was performed using Merck silica gel 60 (40-63μm, 230-400 mesh). Preparative thin layer chromatography (plc) was carried out on glass plates using a 1.0mm layer of silica gel Merck blend 41 Thin layer chromatography was carried out on aluminium plates coated with 0.2mm Merck silica gel 60 F_{254}.

High pressure liquid chromatography (HPLC) was performed on two Gilson model 303 pumps, a Rheodyne 7125 injector, a Gilson HM Holochrome variable wavelength detector (220 nm) and a 250 x 9.4mm i d. column packed with Zorbax hypersil ODS, pump control from an Apple IIC computer and Gilson 702 gradient manager program. Stationary phase Zorbax Hypersil ODS, mobile phase 20% methanol·80% 50mM ammonium bicarbonate.

D-2-Aminopent-4-enoic acid, benzyl ester (toluene-4-sulphonate salt) (8).

D-2-Aminopent-4-enoic acid (0.40g, 3 5 mmol), benzyl alcohol (10 ml), toluene-4-sulphonic acid (0.79g, 4.2 mmol) and benzene (30 ml) were refluxed for 24h in a Deans`-Stark apparatus. After cooling the benzene and excess benzyl alcohol were removed in vacuo, and the gummy residue triturated with ether (3x100ml). Recrystalisation from dichloromethane/ether gave the title compound (0.87g, 67%), M.pt. 118-120°C; $[\alpha]_D^{20}$ +16.0° (c=2.0 in methanol); υ_{max} (nujol) 1750 cm^{-1} (C=O); δ_H (300MHz, $CDCl_3$), 2.30 (3H, s, Me-), 2.55 to 2.99 (2H, m, C$\underline{H}_2$-CH=), 4 08 to 4.12 (1H, m, Cα-H), 4 94 to 5.13 (4H, m, OC$\underline{H}_2$Ar, and CH=C$\underline{H}_2$), 5.49 to 5.63 (1H, m, C$\underline{H}$=CH$_2$), 7.07 and 7.74 (4H, A_2B_2, J_{AB} 8Hz, -C$_6\underline{H}_4$Me), 7 25 to 7 35 (5H, m, Ar).

[(N-benzyloxycarbonyl)-(α-benzyl)-δ-(L-α-aminoadipoyl)]-S-benzyl-L-cysteinyl-D-2-Aminopent-4-enoic acid, benzyl ester (10).

[(N-benzyloxycarbonyl)-(α-benzyl)-δ-(L-α-aminoadipoyl)]-S-benzyl-L-cysteine[7] (9) (0 268g, 0 46mmol), triethylamine (0 46mmol, 46.5mg, 64μl), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (0 113g, 0.46mmol), and D-2-aminopent-4-enoic acid, benzyl ester toluene-4-sulphonate salt (8) (0.173g, 0.46mmol) were stirred for 24 h at room temperature under argon in dry dichloromethane (10ml). The solvent was removed in vacuo and the oily residue re-dissolved in ethyl acetate (40ml), and sequentially washed with sodium bicarbonate (saturated solution, 30ml), HCl (1M, 30ml), NaCl (saturated solution, 30ml), dried (Na_2SO_4), filtered, and the solvent removed in vacuo Purification by column chromatography on silica gel [eluant dichloromethane:ethyl acetate 7:3], and crystalisation from dichloromethane gave the title compound (270mg, 77%). M.pt. 128-130°C. $[\alpha]_D^{20}$ -10° (c=1 0 in chloroform) υ_{max} (chloroform), 1740 s,1680 m, 1500 m. λ_{max} (chloroform), 257 nm (ε 1430 dm^{3}mol^{-1}cm^{-1}). δ_H (300 MHz, CD_3CN), 1.59 to 1 85 (4H, m, C$\underline{H}_2$C$\underline{H}_2$CH$_2$CO), 2.17 to 2.19 (2H, m, C$\underline{H}_2$CO), 2.42 to 2.57 (2H, m, C$\underline{H}_2$-CH=), 2.59 to 2.81 (2H, 8 lines, AB of ABX, C$\underline{H}_2$S), 3.72 (2H, s, SC$\underline{H}_2$Ar), 4 17 to 4.23 (1H, m, Cα-H), 4.43 to 4.53 (2H, m, 2xCα-H), 5.03 to 5.16 (8H, m, 3xOC$\underline{H}_2$Ar and CH=C$\underline{H}_2$), 5.62 to 5.74 (1H, m, C$\underline{H}$=CH$_2$), 6.13, 6.67 and 7.02 (3H, 3xd, J 8 Hz, 3xN$\underline{H}$), 7 23 to 7 41 (20H, complex m, Ar$\underline{H}$). δ_C (62 9 MHz, $CDCl_3$), 21.4 (t, γ-$\underline{C}$ of L-α-AA), 31.7, 33.2, 35 3, 36.2, and 36 5 (5xt, $\underline{C}H_2$), 51 9 (d, 2x$\underline{C}\alpha$), 53.7 (d, $\underline{C}\alpha$), 67 0, 67.2, and 67 3 (3xt, O$\underline{C}H_2$Ar), 119.6 (t, CH=$\underline{C}H_2$), 131.7 (d, $\underline{C}$H=CH$_2$), 127.2 to 138 0 (complex, Ar-$\underline{C}$), 156 1, 170 0, 170.2, 172 0, 172.3 (5xs, 5x$\underline{C}$O). m/z (F.D) 765 (M$^+$). Found: C, 67.53%, H, 6.19%; N, 5 51%; $C_{43}H_{47}N_3O_8S$ requires: C, 67 42%, H, 6.19%; N, 5.51%.

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-aminopent-4-enoic acid disulphide (1a).
The literature method[7] for the deprotection of the tripeptide (10) was essentially followed. Liquid ammonia (approx. 30ml) was distilled under argon from sodium, into a flask containing a solution of the tripeptide (0.22g, 0.29mmol) in dry tetrahydrofuran (10ml) Freshly cut sodium metal was added in small pieces to the stirred solution at -33°C, until the blue colour persisted for 10 minutes. The mixture was decolourised with ground, solid ammonium sulphate (approx. 10mg), and the ammonia allowed to evaporate under a stream of argon. The residue was re-dissolved in H_2SO_4 (0.05M, 50ml), filtered, the solid washed with further H_2SO_4 and to the combined filtrates was added Hopkins reagent[18], dropwise until no more precipitate formed. The white precipitate was collected by centrifugation and washed with water (3x100ml). The washed solid was suspended in water and H_2S gas passed through the suspension for 30 minutes, after which time the resultant black mixture was centrifuged, the supernatant decanted and filtered through celite. The clear aqueous solution was degassed in vacuo, and freeze dried to give the crude tripeptide in the thiol form (86mg, 81%) The crude thiol was oxidised by bubbling oxygen gas through an aqueous solution of the free thiol (pH 9-10) for 2 hours then the solution freeze dried. Preparative reverse phase HPLC (Gilson system, mobile phase 50mM ammonium bicarbonate:methanol, 8:2, flow rate 4 ml/min, retention time 6 minutes) followed by freeze drying gave the title compound in the disulphide form (60mg, 57%). δ_H (500 MHz, D_2O), 1.63 to 1.81 and 1.81 to 1.96 (4H, m, $CH_2CH_2CH_2CO$), 2.36 to 2 47 (3H, m, CH_2CO and HCHC=), 2.53 to 2 59 (1H, m, HCHC=), 2.94 and 3.20 (2H, AB of ABX, J 5,9,14 Hz, CH_2S), 3.73 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-aminoadipoyl), 4.25 (1H, dd, J 5,8 Hz, Cα-H of allylglycine), 4 61 (1H, dd, J 5,9 Hz, Cα-H of cysteine) 5 09 to 5 13 (2H, m, $CH=CH_2$), 5.68 to 5.78 (1H, m, $CH=CH_2$). δ_C (125.7 MHz, D_2O), 21 6, 30 8, 35.5, 36.8, and 39.2 (5xt, 5xCH_2), 53.5 and 55 3 (2xd, 3xCα), 118 8 (t, $CH=CH_2$), 134 4 (d, $CH=CH_2$), 160.8, 171.5, 176.5, 178.2 (4xs, 4xCO). m/z (positive argon FAB), 721 (MH^+).

9,10-Dihydro-9,10-ethenoanthracene-12-carboxylic acid, methyl ester (24).
The published procedures[15,16] for the preparation of the methyl propiolate adduct was followed. A mixture of anthracene (16.9g, 95mmol) and methyl propiolate (9 3g, 0.106mol) in anhydrous xylene (45ml) was refluxed under nitrogen for 6 days It was slowly cooled to room temperature and the excess anthracene removed by filtration. Addition of petrol to the mother liquour precipitated the crude title compound, which was removed by filtration and dried to a yellow crystaline solid. Purification by column chromatography on silica gel (eluant dichloromethane:petrol, 1:1 to 1 0) gave the title compound as a white crystaline solid (17.1g, 69%). M.Pt 171-174°C. Rf 0.5 (petrol·dichloromethane 1 1). δ_H (300MHz, $CDCl_3$), 3.75 (3H, s, CO_2CH_3), 5.26 (1H, d, J 6Hz, H-10), 5.72 (1H, d, J 2Hz, H-9), 6.91 to 7.53 (8H, m, ArH), 7 90 (1H, dd, J 2Hz, 6Hz, H-11) m/z (NH_3, DCI), 280 (MNH_4^+, 100), 281 (18)

9,10-Dihydro-9,10-ethenoanthracene-11-deutero-12-carboxylic acid, methyl ester (47).
The adduct was prepared as above from anthracene and 3-deutero-methyl propiolate[15] δ_H (300 MHz, $CDCl_3$), 3.77 (3H, s, CO_2CH_3), 5 27 (1H, br s, H-10), 5.70 (1H, br s, H-9), 7.04 to 7.52 (8H, m, ArH) m/z (NH_3 DCI), 280 (11), 281 (MNH_4^+, 100), 282 (22)

9,10-Dihydro-9,10-ethanoanthracene-12-carboxylic acid methyl ester (48).
The literature proceedure[17] was essentially followed. A solution of the adduct (24) (4 0g, 15mmol) was dissolved in ethyl acetate (100ml) and stirred with 5% palladium on calcium carbonate (0.1g) under an atmosphere of hydrogen gas. The reaction was initiated by raising the temperature to 60°C for a few minutes, then stirred for 48 h at room temperature until no trace of the starting material remained by tlc. The catalyst was removed by filtration through celite, and the solvent removed in vacuo to give the title compound in quantitative yield, Rf 0.4 (petrol:dichloromethane 1·1). δ_H (300 MHz, $CDCl_3$), 2.03 (1H, dd, J 12,3 Hz, H-11), 2 17 (1H, dd, J 3,3 Hz, H-11), 2 89 (1H, m, H-12), 3 61 (3H, s, CO_2CH_3), 4 35 (1H, d, J 3Hz, H-10), 4 70 (1H, d, J 3 Hz, H-9), 7.05 to 7.15 and 7.22 to 7.40 (8H, m, ArH) m/z (NH_3 DCI), 282 (MH^+, 100), 283 (18)

9,10-Dihydro-9,10-[cis-(11,12-$^2H_2$)]ethanoanthracene-12-carboxylic acid, methyl ester(25).
This was prepared in an analagous manner to that above for (48) using the adduct (24) and deuterium gas, in 93% yield δ_H (300 MHz, $CDCl_3$), 2.15 (1H, br d, J 3 Hz, H-11), 3.60 (3H, s, CO_2CH_3), 4.34 (1H, d, J 3 Hz, H-10), 4.68 (1H, s, H-9), 7 10 to 7.33 (8H, m, ArH). m/z (NH_3 DCI), 286 (4), 285 (21), 284 (MNH_4^+, 100), 283 (4).

9,10-Dihydro-9,10-[(Z)-(11-$^2H_1$)]ethanoanthracene-12-carboxylic acid, methyl ester(49).
This was prepared in an analagous manner to that for (48) above using the adduct (47) and hydrogen gas, in quantitative yield δ_H (300 MHz, $CDCl_3$), 2.00 (1H, br dd, J 3,12 Hz, H-11), 2.90 (1H, dd, J 3,12 Hz, H-12), 3.62 (3H, s, CO_2CH_3), 4 37 (1H, d, J 3 Hz, H-10), 4.70 (1H, d, J 3 Hz,H-9), 7.15 to 7 37 (8H, m, ArH). m/z (NH_3 DCI), 285 (4), 284 (21), 283 (MNH_4^+, 100).

9,10-Dihydro-9,10-ethanoanthracene-12-($^2H_2$-methanol) (50).
The literature procedures[16,17] were broadly followed. Thus the adduct (48) (3.4g, 13mmol) was dissolved in dry ether (100ml) and added dropwise to a refluxing suspension of lithium aluminium deuteride (0.5g, 12mmol) in ether (100ml), over two hours with vigorous stirring. The solution was then refluxed for 4 hours, at which time the reaction was complete. The reaction was quenched with 10% aqueous H_2SO_4 until effervescence ceased The layers were separated and the aqueous layer extracted with ether (2x40ml). The combined organic layers were washed with 10% H_2SO_4 (50ml), saturated $NaHCO_3$ solution (50ml), dried (Na_2SO_4), filtered, and the solvent removed in vacuo to give the title compound (2 9g, 95%). M.Pt 107-108°C (lit.[16,17] 108-110°C). Rf. 0.8 [petrol:ethyl acetate 1·1]. δ_H (300 MHz, $CDCl_3$), 1 06 to 1.10 (1H, m, H-11), 1 50 (br s, OH), 1.90 to 1.97 (1H, m, H-11), 2.10 to 2.15 (1H, m, H-12), 4 28 (1H, dd, J 3,13 Hz, H-10), 4 43 (1H, d, J 3 Hz, H-9), 7.13 to 7.30 (8H, m, ArH). m/z (NH_3 DCI), 255 (3), 256 (MNH_4^+, 100), 257 (20)

9,10-Dihydro-9,10-[cis-(11,12-$^2H_2$)]ethanoanthracene-12-methanol (26).
This was prepared from adduct (25) and lithium aluminium hydride in an analagous manner to that above for (50) in 92% yield. M.Pt. 109-110°C (lit.[16,17] 108-110°C). δ_H (300 MHz, $CDCl_3$), 1.01 (1H, br d, J 3 Hz, H-11), 1 48 (1H, br s, OH), 2.99 and 3 33 (2H, ABq, J 11Hz, CH_2OH), 4.27 (1H, d, J 3Hz, H-10), 4.42 (1H, br s, H-9), 7.10 to 7.32 (8H, m, ArH). m/z (GCMS), 257 (13), 256 (MNH_4^+, 95), 255 (0), 254 (5), 179 (75), 178 (100%)

9,10-Dihydro-9,10-[(Z)-(11-$^2H_1$)]ethanoanthracene-12-($^2H_2$-methanol) (51).
This was prepared from the adduct (49) with lithium aluminium deuteride in an analagous manner to that for (50) above in 99% yield. δ_H (300 MHz, $CDCl_3$), 1.50 (1H, br s, OH), 1 92 (1H, dd, J 3,13 Hz, H-11), 2.15 (1H, br dd, J 3,13 Hz, H-12), 4 27 (1H, d,J 3 Hz, H-10), 4 43 (1H, d, J 3 Hz, H-9), 7 13 to 7.30 (8H, m, ArH). m/z (NH_3, DCI) 256 (12), 257 (MNH_4^+, 100), 258 (19)

9,10-Dihydro-9,10-[cis-(11,12-$^2H_2$)]ethanoanthracene-12-($^2H_2$-methanol) (52).
This was prepared from adduct (25) and lithium aluminium deuteride in an analagous manner to that above in quantitative yield. δ_H (300 MHz, $CDCl_3$), 1 07 (1H, br d, J 3 Hz, H-11), 1.48 (1H, br s, OH), 4 28 (1H, d, J 3 Hz, H-10), 4 43 (1H, br s, H-9), 7 10 to 7.32 (8H, m, ArH) m/z (NH_3, DCI) 257 (8), 258 (MNH_4^+, 100), 259 (19)

[1,1-$^2H_2$]prop-2-en-1-ol (44).
Pyrolysis of the alcohol (50) (2 9g, 12mmol) was carried out in a Woods metal bath (290-300°C) at atmospheric pressure under argon according to the literature procedure[17]. The volatile allyl alcohol was slowly distilled off over a period of 30 minutes, and was colected in a receiver cooled to -78°C The colourless distillate alcohol (0 716g, 98%) was used directly without spectroscopic examination for the subsequent tosylation.

(E)-[2,3-$^2H_2$]prop-2-en-1-ol (23).
This was prepared from the alcohol (26) in an analogous manner to that for (44) above (71%)

(Z)-[1,1,3-$^2H_3$]prop-2-en-1-ol (45).
This was prepared from the alcohol (51) in an analogous manner to that for (44) above (52%).

(E)-[1,1,2,3-$^2H_4$]prop-2-en-1-ol (46).
This was prepared from the alcohol (52) in an analogous manner to that for (44) above (87%).

Prop-2-en-1-(toluene-4-sulphonate) (35).
The title compound was prepared according to the literature procedure[8]. Allyl alcohol (1.10g, 19.0mmol) was dissolved in dry ether (12ml) to which was added powdered NaOH (2.20g, 55mmol) and toluene-4-sulphonyl chloride (3.80g, 20mmol). The solution was stirred at 0°C for 1 hour then overnight at room temperature. The reaction mixture was poured onto ice and the product extracted into ether (3x50ml), the organic phase dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by column chromatography on silica gel [eluant petrol:dichloromethane 1:1] to give the title compound as a clear oil (3.57g, 88%). δ_H (500 MHz, $CDCl_3$), 2.45 (3H, s, ArC$\underline{H}_3$), 4 54 (2H, d, J 6 Hz, C$\underline{H}_2$), 5.26 (1H, d, J 10 Hz, CH=C$\underline{H}_2$), 5.33 (1H, d, J 17 Hz, CH=C$\underline{H}_2$), 5.79 to 5.86 (1H, m, C$\underline{H}$=CH$_2$), 7.35 and 7.80 (4H, A_2B_2, J 8 Hz, Ar$\underline{H}$). m/z (NH_3, DCI), 230 (MNH_4^+, 100), 231 (12), 232 (6).

1RS-[1-$^2H_1$]prop-2-en-1-(toluene-4-sulphonate) (12).
To a suspension of lithium aluminium deuteride (2.9mmol, 0.12g) in dry tetrahydrofuran (5ml) was added dropwise a solution of acrolein (0.56g, 10mmol) in dry tetrahydrofuran (2ml) over 30 minutes. Stirring was continued for 3 hours then the reaction quenched with water (approx 3ml), dried (Na_2SO_4), filtered, and the solvent volume adjusted to 20ml with dry ether to give a solution of 1RS-[1-$^2H_1$]prop-2-en-1-ol (11). This solution was then stirred with powdered NaOH (1 2g, 30mmol) and toluene-4-sulphonyl chloride (2 18g, 11mmol) as described for (35) above, to give the title compound (1.46g, 70%) δ_H (500 MHz, $CDCl_3$), 2.45 (3H, s, ArC$\underline{H}_3$), 4.52 to 4.60 (1H, br m, $\underline{H}$-1), 5.24 (1H, d, J 10 Hz, CH=C$\underline{H}_2$), 5 31 (1H, d, J 17 Hz, CH=C$\underline{H}_2$), 5 79 to 5.84 (1H, m, $\underline{H}$-2), 7.35 and 7.80 (4H, A_2B_2, J 8 Hz, Ar$\underline{H}$). m/z (NH_3, DCI), 232 (14), 231 (MNH_4^+, 100), 230 (0), 229 (2), 215 (2), 214 (MH^+, 15).

(Z)-[3-$^2H_1$]Prop-2-en-1-(toluene-4-sulphonate) (39).
A solution of propargyl alcohol (3.0g, 54mmol) in 1,2-dimethoxy ethane (80 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3.0g, 80mmol) in 1,2-dimethoxyethane (50ml) at 0°C. The solution was allowed to warm to room temperature, and stirred for 3 hours The reaction was then cooled to 0°C and D_2O (99.8%, 20ml) carefully added The reaction was dried (Na_2SO_4) and filtered through celite to give a clear solution of (Z)-[3-$^2H_1$]Prop-2-en-1-ol (22).The solution was stirred with powdered NaOH (6.43g, 0.16mol), and toluene-4-sulphonyl chloride (10 2g, 54mmol) according to the method described for (35) above, to give the title compound (4.81g, 42%), δ_H (500 MHz, $CDCl_3$), 2 45 (3H, s, ArC$\underline{H}_3$), 4 54 (2H, d, J 6 Hz, $\underline{H}$-1), 5 24 (1H, d, J 10Hz, CH=C$\underline{H}_2$), 5.79 to 5.84 (1H, m, $\underline{H}$-2), 7.35 and 7.80 (4H, A_2B_2, J 8 Hz, Ar$\underline{H}$) m/z (NH_3, DCI), 230 (4), 231 (MNH_4^+, 100), 232 (34), 233 (8)

(E)-[2,3-$^2H_2$]Prop-2-en-1-(toluene-4-sulphonate) (40).
This was prepared from alcohol (23) as described for (35) above (75%) δ_H (500 MHz, $CDCl_3$), 2.45 (3H, s, ArC$\underline{H}_3$), 4.53 (2H, s, C$\underline{H}_2$), 5 29 to 5 31 (1H, m, $\underline{H}$-3), 7 35 and 7.80 (4H, A_2B_2, J 8 Hz, Ar$\underline{H}$) m/z (NH_3, DCI), 231 (15),232 (MNH_4^+, 100), 233 (13), 234 (6).

[1,1-$^2H_2$]Prop-2-en-1-(toluene-4-sulphonate) (41).
This was prepared from alcohol (44) as described above for (35) (58%) Rf. 0.44 [petrol dichloromethane 1 1] δ_H (500

MHz, $CDCl_3$), 2.45 (3H, s, $ArCH_3$), 5.26 (1H, d, J 10 Hz, $CH=CH_2$),5.30 (1H, J 17Hz, $CH=CH_2$), 5.83 (1H, br dd, J 10,17 Hz, H-2), 7.35 and 7.81 (4H, A_2B_2, J 8 Hz, ArH). m/z (NH_3, DCI), 231 (1), 232 (MNH_4^+, 100), 233 (9).

(Z)-[1,1,3-$^2H_3$]Prop-2-en-1-(toluene-4-sulphonate) (42).
This was prepared from alcohol (45) as described above for (35) (48%). δ_H (500 MHz, $CDCl_3$), 2.45 (3H, s, $ArCH_3$), 5 26 (1H, d, J 10Hz, $CH=CH_2$), 5.83 (1H, br d, J 10 Hz, H-2) , 7.35 and 7.80 (4H, A_2B_2, J 8 Hz, ArH). m/z (NH_3, DCI), 232 (11), 233 (MNH_4^+, 100), 234 (10).

(E)-[1,1,2,3-$^2H_4$]Prop-2-en-1-(toluene-4-sulphonate) (43).
This was prepared from alcohol (46) as described above for (35) (65%). δ_H (500 MHz, $CDCl_3$), 2.46 (3H, s, $ArCH_3$), 5 30 to 5.32 (1H, br s, H-3), 7.34 and 7.81 (4H, A_2B_2, J 8 Hz, ArH) m/z (NH_3, DCI), 233 (5), 234 (MNH_4^+, 100), 235 (8)

2RS-2-Aminopent-4-enoic acid (36).
The tosylated allyl alcohol (35) (1 05g, 5 0mmol, 1.2eq.) was added dropwise over a period of 2 hours to a stirred solution of N-(diphenylmethylene) aminoacetonitrile (0.91g, 4mmol), benzyltriethylammonium chloride (0.15g, 0.7mmol), toluene (3ml) and 50% aqueous sodium hydroxide (3.2g) at 0°C. The mixture was slowly warmed to room temperature and stirred overnight. The resultant red solution was partitioned between dichloromethane (25ml) and water (25ml), the layers separated and the aqueous layer extracted with dichloromethane (3x25ml). The combined organic layers were washed with water (25ml), saturated brine (25ml), dried with Na_2SO_4, filtered and the solvent removed in vacuo to give the crude Schiff's base as a thick orange oil This was dissolved in ether (25ml), cooled to 0°C, and HCl (1N,40ml) added with stirring over 30 minutes. Stirring was continued overnight at room temperature, then the layers separated and the aqueous layer washed with ether (2x30ml). Conc HCl (11N, 40ml) was added and the mixture refluxed for 4 hours. After cooling the water was removed in vacuo and the residue applied to an ion-exchange resin (Dowex®-1 50W-X8(H)).The resin was washed with water (400ml) then elution with pyridine (1M,800ml) and removal of the solvent gave the title compound (0.27g, 59%). M.pt. 157 °C (lit.[19] 158-159°C). d_H (500 MHz, D_2O), 2 57 to 2 68 (2H,m,CH_2), 3.79 to 3.82 (1H,m,C_α-H), 5 26 to 5 28 (2H,m,$CH=CH_2$), 5.73 to 5 81 (1H,m,$CH=CH_2$). m/z (NH_3, DCI), 116 (MH^+, 100%), 117 (6)

Amino acids (13) and (53 to 57).

These were prepared from their respective allyltosylates (**12**) and (**39** to **43** respectively) in an analogous manner to that for (**36**) above.

2RS, 3RS-2-Amino-[3-$^2H_1$]pent-4-enoic acid (13).
Prepared from (12), (63%). M.Pt 155-157°C (lit.[19] 158-159°C) δ_H (300 MHz, D_2O), 2.58 and 2.64 (1H, br t and br s, R and S H-3), 3 79 (1H, m, H-2), 5.24 to 5.30 (2H, m, H-5), 5.70 to 5.80 (1H, m, H-4). m/z (NH_3 DCI), 118 (7), 117 (MH^+, 100%), 116 (3), 71 (23).

2RS-2-Amino-(Z)-[5-$^2H_1$]pent-4-enoic acid (53).
Prepared from (39), (54%) δ_H (500 MHz, D_2O), 2 57 to 2.68 (2H, m, CH_2), 3.80 to 3 83 (1H, m, H-2), 5 26 (1H, d, J 10 Hz, $CH=CHD$), 5.74 to 5.80 (1H, m, $CH=CHD$). m/z (NH_3, DCI), 116 (4), 117 (MH^+, 100%), 118 (23), 119 (1)

2RS-2-Amino-(E)-[4,5-$^2H_2$]pent-4-enoic acid (54).
Prepared from (40), (27%) δ_H (300 MHz, D_2O), 2.59 to 2.66 (2H, m, H-3), 3 80 to 3.84 (1H, m, H-2), 5.22 to 5.24 (1H, m, H-5) m/z (NH_3 DCI), 117 (14), 118 (MH^+, 100%), 119 (6).

2RS-2-Amino-[3,3-$^2H_2$]pent-4-enoic acid (55).
Prepared from (41), (64%). δ_H (300 MHz, D_2O), 3 83 (1H, br s, H-2), 5.27 to 5.37 (2H, m, H-5), 5.80 (1H, dd, J10,17 Hz, H-4) m/z (NH_3 DCI), 116 (1), 117 (2), 118 (MH^+, 100%), 119 (7)

2RS-2-Amino-(Z)-[3,3,5-$^2H_3$]pent-4-enoic acid (56).
Prepared from (42), (95%). δ_H (300 MHz, D_2O), 3.83 (1H, br s, H-2), 5.30 (1H, d, J 10 Hz, H-5), 5.80 (1H, br d, J 10 Hz, H-4) m/z (NH_3 DCI), 118 (10), 119 (MH^+, 100%), 120 (8).

2RS-2-Amino-(E)-[3,3,4,5-$^2H_4$]pent-4-enoic acid (57).
Prepared from (43), (88%). δ_H (300 MHz, D_2O), 3.76 (1H, br s, H-2), 5.21 (1H, br s, H-5). m/z (NH_3 DCI), 119 (5), 120 (MH^+, 100%), 121 (8), 122 (4)

N-tertbutyloxycarbonyl glycine [(E)-2,3-$^2H_2$]prop-2-en-1-yl ester (19).
The alcohol (23), (0.3g, 5mmol), N-tertbutyloxycarbonylglycine (0.88g, 5mmol), dicyclohexylcarbodiimide (1.03g, 5mmol) and N,N-dimethyl-4-aminopyridine (15mg) were stirred at room temperature in dry ether (10ml) for 24 hours. The precipitated white solid was removed by filtration and the solvent removed in vacuo to give an oil which was purified by column chromatography (eluant ethyl acetate:petrol (3:7)) to give the title compound (0.80g, 74%). υ_{max} (LF), 3380 (m), 2980 (m), 2940 (m), 1765 (s), 1715 (s), 1520 (m), 1340 (m), 1170 (m), 1010 (m), 980 (m), 890 (m). δ_H (500MHz, $CDCl_3$), 1.48 (9H, s, ^{t}Boc), 3.95 (2H, d, J 6 Hz, C$\underline{H}_2$CO), 4.67 (2H, s, C$\underline{H}_2$-CD=), 5.05 (1H, br d, J 6 Hz, N$\underline{H}$), 5.44 (1H, s, CD=CD$\underline{H}$). δ_C (50MHz, $CDCl_3$) 28.1 (q, C($\underline{C}H_3)_3$), 42.2 (t, $\underline{C}H_2$CD=), 65 7 (t, NH$\underline{C}H_2CO_2$), 79.9 (s,$\underline{C}(CH_3)_3$), 118.5 (d of t, CD=$\underline{C}$HD), 131 5 (t, $\underline{C}$D=CHD), 155.9 (s, O$\underline{C}$ONH), 170.3 (s, $\underline{C}O_2CH_2$) m/z (NH_3, DCI), 235 (MNH_4^+,12%), 218 (MH^+,15), 216 (1), 179 (30), 162 (28), 118 (100). $C_{10}H_{15}NO_4D_2$ requires C 55.56%, H 7.89%, N 6 45%, found C 55 65%, H 8.19%, N 6.14%

N-tertbutyloxycarbonylglycine [(Z)-3-$^2H_1$]prop-2-en-1-yl ester (18).
This was prepared from the alcohol (22) in DME and ether in an analogous manner to that for (19) above (30%) υ_{max} (LF), 3380 (m), 2980 (m), 2940 (m), 1760 (s), 1710 (s), 1520 (m), 1370 (m), 1170 (m), 1060 (m), 980 (m), 880 (m) δ_H (500MHz, $CDCl_3$), 1.46 (9H, s, ^{t}Boc), 3.94 (2H, d, J 6 Hz, NC$\underline{H}_2$CO), 4.65 (2H, d, J 6 Hz, =CH-C$\underline{H}_2$), 5.25 (1H, d, J 10 Hz, C$\underline{H}$D=CH), 5 87 to 5 95 (1H, m, CHD=C$\underline{H}$). δ_C (50MHz, $CDCl_3$) 28.0 (q, C($\underline{C}H_3)_3$), 42 1 (t, $\underline{C}H_2$CH=), 65.5 (t, NH$\underline{C}H_2CO_2$), 79 6 (s, $\underline{C}(CH_3)_3$), 118.3 (d of t, CH=$\underline{C}$HD), 131.6 (d, $\underline{C}$H=CHD), 156.0 (s, O$\underline{C}$ONH), 170.3 (s, $\underline{C}O_2CH_2$). m/z (NH_3, DCI), 234 (MNH_4^+,3%), 218 (3), 217 (MH^+, 8), 178 (20), 161 (35), 117 (100) $C_{10}H_{16}NO_4D$ requires C 55 54%, H 7 92%, N 6.48%, found C 55 43%, H 8.22%, N 6 75%.

N-tertbutyloxycarbonyl-(2R3R/2S3S)-2-amino-[3-$^2H_1$]pent-4-enoic acid (20)
The procedure of Bartlett[13] was followed with a few modifications. To a solution of the N-tertbutyloxycarbonylglycine (Z)-[3-$^2H_1$]prop-2-en-1-yl ester (18) (0.5g, 2.3mmol) in dry tetrahydrofuran (10ml) at -78^{o}C under nitrogen was added a solution of lithium hexamethyldisilazide (LiHMDS) (1 0M in tetrahydrofuran, 4.6mmol, 4 6ml), dropwise over 10 minutes The reaction was stirred for a further 10 minutes at -78^{o}C then distilled trimethylsilyl chloride (TMSCl) (4.6mmol, 0.58g) added, the reaction warmed to room temperature and then refluxed for 4 hours under nitrogen. The reaction was cooled to 0^{o}C and methanol (10ml) added over 10 minutes. The solvent was removed under reduced pressure, the residue dissolved in EtOAc (20ml), washed with HCl (1N, 10ml), and extracted into NaOH (2M, 3x20ml). The basic washings were acidified to pH 1-2 (1M HCl), saturated with sodium chloride, extracted with EtOAc (4x50ml), the organic phases combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give the title compound as a clear gum, which was recrystallised from EtOAc/petrol to give a white solid (0 21g, 39%) MPt 110-112^{o}C (lit [20] 109-111^{o}C) δ_H (500MHz, $CDCl_3$), 1.43 (9H, s, C($CH_3)_3$), 2.40 to 2 60 (1H, br m, $\underline{H}$-3), 4 11 to 4 18 (1H, br

m, NH), 4.55 to 4.59 (1H, br m, H-2), 5.13 to 5.17 (2H, m, CH=CH$_2$), 5.70 to 5.75 (1H, m, CH=CH$_2$). δ_C (125MHz, $CDCl_3$) 28.2 (q, C(CH$_3$)$_3$), 35.9 (d of t, CHDCH=CH$_2$), 56.0 (d, NHCHCO$_2$), 80.2 (s, C(CH$_3$)$_3$), 119.2 (t, CH$_2$=CH), 132.0 (d, CH=CH$_2$), 155.5 (s, CO$_2$H), 176.4 (s,OCONH). υ_{max} (dichloromethane) 3445 (m), 3085 (w), 2985 (m), 2940 (w), 1720 (s), 1505 (s), 1370 (m), 1165 (m), 1060 (m), 925 (m). m/z (NH_3, DCI), 235 (4), 234 (MNH_4^+,12%), 218 (8), 217 (MH^+,28), 179 (35), 178 (100), 161 (55), 117 (78), 71 (47). $C_{10}H_{16}NO_4D$ requires C 55.54%, H 7.92%, N 6.48%; found C 55.61%, H 8.25%, N 6.42%.

N-tertbutyloxycarbonyl-(2R3S/2S3R)-2-amino-[3,4-$^2H_2$]pent-4-enoic acid, benzhydryl ester (21). This was prepared from N-^{t}Boc-glycine (E)-[2,3-$^2H_2$]allyl ester (19) in an analogous manner to that described above for (20). Thus treatment of N-tertbutyloxycarbonyl glycine (E)-[2,3-$^2H_2$]prop-2-en-1-yl ester (19) (0.25g, 1.2mmol) with 2 equivalents of LiHMDS and TMSCl, followed by reflux, quenching with methanol, and purification gave the title compound as an off white solid (0.11g, 42%). MPt. 109-110^{o}C (lit.[20] 109-111^{o}C). υ_{max} (dichloromethane) 3450 (m), 3085 (w), 2985 (m), 2940 (w), 1720 (s), 1500 (s), 1360 (m), 1160 (m), 1060 (m), 930 (m). δ_H (500MHz, $CDCl_3$), 1.45 (9H, s, C(CH$_3$)$_3$), 2.41 to 2.62 (1H, br d, J 7 Hz, H-3), 4.10 to 4.19 (1H, br d, J 6 Hz, NH), 4.55 to 4.59 (1H, br m, H-2), 5 13 to 5.18 (2H, br s, CD=CH$_2$) δ_C (50MHz, $CDCl_3$) 28.3 (q, C(CH$_3$)$_3$), 36.0 (d of t, CHD-CD=CH$_2$), 56.0 (d, NHCHCO$_2$), 80.1 (s, C(CH$_3$)$_3$), 119.0 (t, CH$_2$=CD), 131 7 (t, CD=CH$_2$), 155.5 (s, CO$_2$H), 176.4 (s, OCONH). m/z (NH_3 DCI) 235 (MNH_4^+,15%), 219 (7), 218 (MH^+,25), 180 (20), 179 (100), 161 (48), 118 (85), 71 (45). $C_{10}H_{15}NO_4D_2$ requires C 55 28%, H 7.87%, N 6.44%; found C 55.44%, H 8.12%, N 6.22%.

N-tertbutyloxycarbonyl-(2R3R/2S3S)-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (27). The N-tertbutyloxycarbonyl-(2R3R,2S3S)-2-amino-[3-$^2H_1$]pent-4-enoic acid (20) (0.21g, 0.98mmol) was disolved in EtOAc (10ml), to which was added diphenyldiazomethane (1 eq, 0.98 mmol, 0.18g) in EtOAc (2ml) dropwise with stirring at room temperature over 30 minutes. The reaction was stirred for two hours, the solvent removed under reduced pressure, and the residue purified by column chromatography [eluant dichloromethane, Rf 0 4] to give the title compound, which was recrystallised from dichloromethane/petrol (0.28g, 76%). The relative stereochemistry of the deuterium labelling was inferred from the synthetic route. MPt 79-80^{o}C. δ_H (500MHz, $CDCl_3$), 1.43 (9H, s, C(CH$_3$)$_3$), 2.50 to 2 54 (0.9H, br m, 2R3R/2S3S, H-3), 2.57 to 2.59 (0.1H, br m, 2S3R/2R3S, H-3), 4.48 to 4.52 (1H, br m, H-2), 5 39 to 5.43 (3H, m, CH$_2$=CH and NH), 5.54 to 5.60 (1H, m, CH$_2$=CH), 6.92 (1H, s, CHPh$_2$), 7.25 to 7.42 (10H, m, ArH). δ_C (125MHz, $CDCl_3$) 28.3 (q, C(CH$_3$)$_3$), 36.1 (br d, CHDCH=), 52.9 (d, NHCHCO$_2$), 76.7 (d, CHPh$_2$), 80.1 (s, C(CH$_3$)$_3$), 119.2 (t, CH$_2$=CH), 127.0, 127.2, 128 1, and 128 5 (4xd, 4x aromatic CH), 132.3 (d, CH=CH$_2$), 139.6 (s, ipso C), 155.5 (s, OCONH), 176 1 (s, CHCO$_2$). υ_{max} (dichloromethane) 3440 (w), 3060 (w), 2980 (w), 1745 (m), 1715 (s), 1500 (s), 1370 (m), 1165 (s). m/z (FD), 382 (M^+). $C_{23}H_{25}NO_4D$ requires C 72.22%, H 7.12%, N 3.66%; found C 72.56%, H 7 15%, N 3.41%

N-tertbutyloxycarbonyl-(2R3S/2S3R)-2-amino-[3,4-$^2H_2$]pent-4-enoic acid, benzhydryl ester (28). This was prepared from the treatment of N-tertbutyloxycarbonyl-(2R3S/2S3R)-2-amino-[3,4-$^2H_2$]pent-4-enoic acid (21) (0 11g, 0 5mmol) with diphenyldiazomethane as described above (68%). The stereochemistry of the deuterium labelling was inferred from the synthetic route. δ_H (500MHz, $CDCl_3$), 1 45 (9H, s, C(CH$_3$)$_3$), 2.47 to 2.50 (0.1H, m, 2R3R/2S3S H-3), 2 56 to 2.60 (0 9H, m, 2R3S/2S3R H-3), 4.50 to 4.55 (1H, br m, H-2), 5.40 to 5 46 (3H, m, CH$_2$=CD and NH), 6.93 (1H, s, CHPh$_2$), 7 27 to 7.40 (10H, m, ArH). δ_C (125MHz, $CDCl_3$) 28.1 (q, C(CH$_3$)$_3$), 36 0 (br d, CHDCD=), 53 0 (d, NHCHCO$_2$), 76 8 (d, CHPh$_2$), 80 0 (s, C(CH$_3$)$_3$), 119.2 (t, CH$_2$=CD), 127.0, 127.2, 128.1, and 128.5 (4xd, 4x aromatic CH), 132 0 (t, CD=CH$_2$), 139 8 (s, ipso C), 155.7 (s, OCONH), 176.4 (s, CHCO$_2$) υ_{max} (dichloromethane) 3440 (m), 3060 (m) 2980 (m), 1745 (m), 1720 (s), 1500 (s), 1370 (m), 1165 (s). m/z (FD), 383 (M^+). $C_{23}H_{25}NO_4D_2$ requires C 72 04%, H 7 09%, N 3.65%; found C 72 09%, H 7.02%, N 3.49%.

N-tertbutyloxycarbonyl-2RS-2-amino-[3,3-$^2H_2$]pent-4-enoic acid, benzhydryl ester (63).
The literature procedures[10] were followed with slight modification. The amino acid (55) (70mg, 0.6mmol) was dissolved in water (1ml), dioxan (1ml), and TEA (1.5 eq, 0.9mmol, 0.13ml), and BOC-ON (1 2eq, 0.7mmol, 0.16g) added. The solution was stirred overnight, after which time it became yellow and homogeneous. The reaction was partitioned between water (2ml) and EtOAc (2ml), the aqueous layer separated and washed with EtOAc (5ml), acidified to pH 3-4 with citric acid (10% aq.), and extracted with EtOAc (4x20ml). The organic phases were combined, dried (Na_2SO_4), filtered and the solvent removed in vacuo, to give the N-tertbutyloxycarbonyl-2RS-2-amino-[3,3-$^2H_2$]pent-4-enoic acid (66) as a crystaline solid (0.12g, 95%). δ_H (60MHz, $CDCl_3$), 1.45 (9H, s, Me_3C-), 4.0 to 4.2 (1H, br d, J 6 Hz, NH), 4.2 to 4.5 (1H, br d, J 6 Hz, H-2), 5.2 (2H, br m, H-5), 5.7 (1H, m, H-4).The solid (0.12g) was dissolved in EtOAc (10ml), and a solution of diphenyldiazomethane (1.2eq, 0.13g) in EtOAc (2ml) added dropwise over 1 hour. The reaction was stirred overnight, quenched with a little acetic acid, and the solvent removed in vacuo. Purification of the product by column chromatography (eluant dichloromethane, Rf. 0.4) gave the title compound as a white solid that was recrystallised from dichloromethane:petrol (0.11g, 48%). δ_H (60MHz, $CDCl_3$), 1.45 (9H, s, Me_3C-), 4.2 (1H, d, J 6 Hz, NH), 4.5 (1H, br d, J 6 Hz, H-2), 5.2 (2H, m, CH=CH_2), 5.6 (1H, m, H-4), 7 0 (1H, s, -CHPh_2), 7.1 to 7.4 (10H, m, ArH).

The amino acids (**13**, **56**, **57**) were treated in an analogous manner to give:

N-tertbutyloxycarbonyl-2RS/3RS-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (14).
Prepared from (13), (72%) δ_H (500 MHz, $CDCl_3$), 1.46 (9H, s, Me_3C-), 2.45 and 2.60 (1H, 2xbr s, R and S H-3), 4.51 to 4 59 (1H, br m, H-2), 5 00 to 5.10 (2H, br m, 2xH-5), 5.54 to 5.64 (1H, m, H-4), 6.93 (1H,s, CHPh_2), 7.18 to 7.38 (10H, m, ArH).

N-tertbutyloxycarbonyl-2RS-2-amino-[(Z)-3,3,5-$^2H_3$]pent-4-enoic acid, benzhydryl ester (64).
Prepared from (56) (43%). δ_H (500 MHz, $CDCl_3$), 1.50 (9H, s, Me_3C-), 4.25 (1H, br d, J 6 Hz, NH), 4.60 (1H, br d, J 6 Hz, H-2), 5 10 (1H, d, J 11 Hz, H-5), 5.60 (1H, br d, J 11 Hz, H-4), 6.95 (1H, s, CHPh_2), 7.2 to 7.5 (10H, m, ArH).

N-tertbutyloxycarbonyl-2RS-2-amino-[(E)-3,3,4,5-$^2H_4$]pent-4-enoic acid, benzhydryl ester (65).
Prepared from (57), (80%). δ_H (60MHz, $CDCl_3$), 1.45 (9H, s, Me_3C-), 4.4 to 4 5 (1H, br d, J 6 Hz, H-2), 4.9 to 5.1 (2H, br m, NH and H-5), 6.9 (1H, s, $CHPh_2$), 7.2 to 7.5 (10H, m, ArH).

2RS-2-aminopent-4-enoic acid, benzhydryl ester (37).
2RS-2-aminopent-4-enoic acid (36) (0.10g, 0 9mmol) and toluene-4-sulphonic acid (0.17g, 0.9mmol), were dissolved in a mixture of water (20ml) and acetone (20ml). Solid diphenyldiazomethane (0.3g, 1.7mmol) was added in portions and the solution stirred at room temperature for 2 hours. The acetone was removed in vacuo, the pH adjusted to 3 with HCl (1M) and the solution washed with EtOAc (10ml). The aqueous phase was then basified to pH 8-9 (saturated $NaHCO_3$) and extracted with EtOAc (3x25ml). The organic phases were combined, dried (Na_2SO_4), and the solvent removed in vacuo to give the title compound (0 17g, 70%). δ_H (500 MHz, $CDCl_3$), 2.41 to 2.62 (2H, m, H-3), 3 64 to 3 68 (1H, m, H-2), 5 06 to 5 14 (2H, m, H-5), 5.64 to 5.72 (1H, m, H-4), 6.91 (1H, s, CHPh_2), 7 26 to 7.40 (10H, m, ArH) m/z (NH_3, DCI), 282 (MH^+, 6%), 167 (100), 70 (23)

The amino acids (**53**) and (**54**) respectively were treated in an identical manner to give.

2RS-2-amino-[(Z)-5-$^2H_1$]pent-4-enoic acid, benzhydryl ester (58).
(60%). δ_H (500 MHz, $CDCl_3$), 2 41 to 2.61 (2H, m, H-3), 3.64 to 3.68 (1H, m, H-2), 5.08 (1H, d, J 10 Hz, H-5), 5 64 to 5.67 (1H, m, H-4), 6.93 (1H, s, CHPh_2), 7.26 to 7.40 (10H, m, ArH). m/z (NH_3, DCI), 283 (MH^+,3%), 167 (100), 71 (15).

2RS-2-amino-[(E)-4,5-$^2H_2$]pent-4-enoic acid, benzhydryl ester (59).
(65%). δ_H (500 MHz, $CDCl_3$), 2.43 to 2.61 (2H, m, H-3), 3.64 to 3 68 (1H, m, H-2), 5 09 (1H, br s, H-5), 6.94 (1H, s, C<u>H</u>Ph_2), 7.30 to 7.42 (10H, m, Ar<u>H</u>). m/z (NH_3, DCI), 284 (MH^+,7%), 167 (100), 72 (30).

2RS-2-amino-[3,3-$^2H_2$]pent-4-enoic acid, benzhydryl ester (60).
The literature procedure[12] was followed with minor modifications. The ^{t}Boc-amino acid benzhydryl ester (63) (50mg, 0 13mmol), was dissolved in ether and cooled to -5°C. Toluene-4-sulphonic acid (1eq, 25mg) in ethanol (3ml) was added over 30 minutes and the reaction stirred for a further 3 hours at room temperature. The solvent was removed <u>in vacuo</u> at 40°C, more ethanol (10ml) added and again removed <u>in vacuo</u>. The resultant toluene-4-sulphonate salt was recrystallised from dichloromethane to give a solid which was dissolved in EtOAc (10ml) and extracted with HCl (10%, 10ml) The aqueous layer was basified with saturated $NaHCO_3$ solution to pH 9-10, extracted with EtOAc (3x25ml), the organic phases combined, dried (Na_2SO_4), filtered and the solvent removed <u>in vacuo</u> to give the title compound (30mg, 81%) δ_H (300 MHz, $CDCl_3$), 3 65 (1H, br s, H-2), 5 02 to 5 15 (2H, 2xbr d, J 10,17 Hz, CH=C<u>H</u>$_2$), 5 62 (1H, br dd, J 10,17 Hz, H-4), 6.95 (1H, s, C<u>H</u>Ph_2), 7 22 to 7.42 (10H, m, Ar<u>H</u>).

The diprotected amino acids (**14**, **27**, **28**, **64**, **65**) were deprotected to their respective free amines in an analogous manner to give.

2RS,3RS-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (15).
Prepared from (14), (75%). δ_H (500 MHz, $CDCl_3$), 2 42 to 2.50 and 2.51 to 2 58 (1H, 2xbr m, CHD), 3.60 to 3 66 (1H, m, H-2), 5.00 to 5 15 (2H, m, C<u>H</u>$_2$=CH), 5.60 to 5.70 (1H, m, C<u>H</u>=CH$_2$), 6.95 (1H, s, C<u>H</u>Ph_2), 7 15 to 7 40 (10H, m, ArH)

2R3R/2S3S-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (29).
Prepared from (27), (78%). δ_H (500 MHz, $CDCl_3$), 2.47 (0 9H, overlapping dd, J 4 Hz, 2R3R/2S3S H-3), 2 50 to 2.53 (0 1H, m, 2R3S/2S3R H-3), 3 66 (1H, d, J 4 Hz, H-2), 5.10 to 5 15 (2H, m, CH=C<u>H</u>$_2$), 5.64 to 5 70 (1H, m, C<u>H</u>=CH$_2$), 6 93 (1H, s, C<u>H</u>Ph_2), 7.25 to 7 45 (10H, m, Ar<u>H</u>).

2R3S/2S3R-2-amino-[3,4-$^2H_2$]pent-4-enoic acid, benzhydryl ester (30).
Prepared from (28), (84%). δ_H (500 MHz, $CDCl_3$), 2 46 to 2 50 (approx 0 1H, br m, 2S3S/2R3R C<u>H</u>D), 2 51 to 2 56 (approx 0 9H, br m, 2S3R/2R3S C<u>H</u>D), 3 66 (1H, m, Cα<u>H</u>), 4 98 to 5.06 (2H, m, CD=C<u>H</u>$_2$), 6 92 (1H, s, C<u>H</u>Ph_2), 7 27 to 7.40 (10H, m, Ar<u>H</u>)

2RS-2-amino-[(Z)-3,3,5-$^2H_3$]pent-4-enoic acid, benzhydryl ester (61).
Prepared from (64), (95%) δ_H (300 MHz, $CDCl_3$), 3.66 (1H, br s, H-2), 4.90 to 5 00 (1H, d, J 11 Hz, H-5), 5 58 (1H, br d, J 11 Hz, H-4), 6 95 (1H, s, C<u>H</u>Ph_2), 7 25 to 7 45 (10H, m, ArH).

2RS-2-amino-[(E)-3,3,4,5-$^2H_4$]pent-4-enoic acid, benzhydryl ester (62).
Prepared from (65), (98%) δ_H (300 MHz, $CDCl_3$), 3.61 (1H, br s, H-2), 5 01 (1H, br s, H-5), 6.85 (1H, s, C<u>H</u>Ph_2), 7 25 to 7 45 (10H, m, ArH)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(<u>L</u>-α-aminoadipoyl)]-S-(4-methoxybenzyl)-<u>L</u>-cysteine (16).
This was prepared *via* a modification of the literature procedure[7]. Dry triethylamine (1.87 mmol, 190 mg, 260 µl) was added to a solution of (N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(<u>L</u>-α-aminoadipic acid)[21] (0 83g, 1 87 mmol) in dry tetrahydrofuran (20ml) under argon and the solution cooled to -15°C After stirring for 15 min, isobutyl chloroformate (0 24ml, 1.87 mmol) was added and the mixture stirred at -15°C for 30 min A solution of S-(4-

chloroformate (0.24ml, 1.87 mmol) was added and the mixture stirred at -15°C for 30 min. A solution of S-(4-methoxybenzyl)-L-cysteine[22] (0.45g, 1.87 mmol) in water (20ml) and triethylamine (0 36ml, 2.57 mmol) was cooled to 0°C and added in one portion to the cold vigorously stirring reaction. The mixture was stirred at room temperature for 50 min then diluted with water (30ml) and washed with ether (3x30ml). The aqueous layer was acidified to pH 3 (1M HCl), and extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with brine (30ml) dried (Na_2SO_4), filtered, and the solvent removed in vacuo to give the crude title compound as a white foam (1.07g, 86%) This was used without further purification. δ_H (500 MHz, $CDCl_3$) 1.60 to 1 95 (4H, m, $CH_2CH_2CH_2CO$), 2.15 to 2.33 (2H, m, CH_2CO), 2.81 to 2 92 (2H, AB of ABX, CH_2S), 3.64 (2H, s, SCH_2Ar), 3.85, 3.86 and 3.88 (3x3H, 3xs, OMe), 4.35 to 4 41 (1H, m, Cα-H), 4.85 to 4.90 (1H, m, Cα-H), 4 98 to 5 08 (4H, m, $2xOCH_2Ph$), 5 71 (1H, d, J 8 Hz, NH), 6 76 (1H,.d, J 8 Hz, NH), 6.97 to 7.31 (12H, m, ArH)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-aminopent-4-enoic acid, benzhydryl ester (38).

Equimolar quantities of [(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteine, (protected AC) (16) (100mg, 0.15mmol), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (38mg, 0 15 mmol), and DL-2-aminopent-4-enoic acid, benzhydryl ester (37) (43mg, 0.15 mmol) were dissolved in dry dichloromethane (10ml) and stirred for 24 hours at room temperature under argon The dichloromethane was removed in vacuo and the residue dissolved in EtOAc (20ml). This was washed sequentially with saturated aqueous $NaHCO_3$ (20ml), dilute aqueous HCl (1M, 20ml) and saturated brine (20ml), dried (Na_2SO_4), filtered and the solvent removed in vacuo to give a residue that was purified by column chromatography on silica gel [eluant EtOAc/dichloromethane (1.4)], to give a 1·1 mixture of the two diastereomeric fully protected tripeptides (LLL and LLD) These could be separated by preparative tlc (or column chromatography) [eluant EtOAc petrol 1.1, Rf 0.4 and 0.35], the less polar band being identified as the LLD- isomer by comparison to authentic material. Removal of the solvent in vacuo gave the title compound (35mg, 25%). M.pt 141 to 142°C. δ_H (500 MHz, $CDCl_3$), 1.64 to 1.83 (4H, m, $CH_2CH_2CH_2CO$), 2 05 to 2.18 (2H, m, CH_2CO), 2.50 to 2.61 (2H, m, CH_2CH=), 2 61 to 2.83 (2H, AB of ABX, CH_2S), 3.70 (2H, s, SCH_2Ar), 3 76, 3.77 and 3 79 (3x3H, 3xs, OMe), 4 34 to 4 37 (1H, m, Cα-H), 4 46 to 4 50 (1H, m, Cα-H), 4 66 to 4.71 (1H, m, Cα-H), 4.97 to 5 09 (6H, m, $2xOCH_2Ph$ and $CH=CH_2$), 5.47 (1H, d, J 8 Hz, NH), 5.49 to 5 57 (1H, m, $CH=CH_2$), 6 26 (1H, d,J 7 Hz,NH), 6 80 to 6 89 and 7 23 to 7 34 (24H, m, NH, $CHPh_2$ and ArH) δc (125.7 MHz, $CDCl_3$), 21.2 (t, γ-C of α-aminoadipoyl), 31 7, 33.1, 35 2, 35 7 and 36 1 (5xt, CH_2), 51 9, 52 2, and 53.5 (3xd, 3xCα), 55.2 (3xq, OMe), 66 8 and 66 9 (2xt, OCH_2Ph), 78 1 (d, $OCHPh_2$), 113 8, 113 9 and 114.0 (3xd, Ar-C), 119.6 (t, $CH=CH_2$), 126.9 to 130.1 (11xd, Ar-C), 139 3, 139 4, 158 7, 159 5 and 159 7 (5xs, Ar-C), 131 5 (d, $CH=CH_2$), 156.1 (s, $NHCO_2$), and 169 9, 170 1, 172 0, and 172 3 (4xs, CO) m/z (FD) 931 (M^+)

The protected tripeptides (**17**), (**31**), (**33**), and (**69** to **73**) were prepared in an analagous manner·

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-3RS-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (17a).

Prepared from (15), (33%) MPt 140-142°C . δ_H (500 MHz, $CDCl_3$), 1.63 to 1.88 (4H, 2xm, $CH_2CH_2CH_2CO$), 2.06 to 2 25 (2H, m, CH_2CO), 2 48 (0 5H, t, J 6 Hz, 3R CHDCH=), 2.59 (0 5H, m, 3S CHDCH=), 2 61 to 2 83 (2H, AB of ABX, CH_2S), 3 70 (2H, s, SCH_2Ar), 3 76 and 3 77 (6H, 2xs, $2xOCH_3$), 3 79 (3H, s, OCH_3), 4.34 to 4.40 (1H, m, Cα-H), 4 42 to 4 47 (1H, m, Cα-H), 4 68 to 4.73 (1H, m, Cα-H), 4 97 to 5.09 (6H, m, $2xOCH_2Ph$ and $CH=CH_2$), 5.46 (1H, d, J 8 Hz, NH), 5 49 to 5 58 (1H, m, $CH=CH_2$), 6 27 (1H, d, J 7 Hz, NH), 6.80 to 6 92 and 7.20 to 7 34 (24H, m, NH, $CHPh_2$ and ArH). δc (125MHz, $CDCl_3$), 21 3 (t, γ-C of α-aminoadipoyl), 31.7, 33.0, 35 1, and 36 1 (4xt, $4xCH_2$), 36.2 (br d, CHD), 52 0, 52 1 and 53 5 (3xd, $3xC_\alpha$), 55 0 to 55 2 (3xq, 3xOMe), 66.7 and 66 8 (2xt, $2xOCH_2Ph$), 78.1 (d, $OCHPh_2$), 113 8, 113.9 and 114 0 (3xd, Ar-CH), 119 5 (t, $CH=CH_2$), 126.8 to 130.1 (11xd, Ar-CH), 139 3, 139.5, 158.7, 159 4 and 159 7 (5xs, Ar-C), 131 5 (d, $CH=CH_2$), 156 4 (s, $NHCO_2$), and 169 9 to 172.3 (4xs, 4xCO)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-3R-2-amino-[3-$^2H_1$]pent-4-enoic acid, benzhydryl ester (31).
Prepared from (29), (42%) δ_H (500 MHz, $CDCl_3$), 1.61 to 1.87 (4H, 2xm, $CH_2CH_2CH_2CO$), 2.06 to 2 22 (2H, m, CH_2CO), 2 50 (0.9H, t, J 6 Hz, 3R-CHD), 2.57 to 2 59 (0.1H, m, 3S-CHD), 2.61 to 2.83 (2H, AB of ABX, CH_2S), 3.70 (2H, s, SCH_2Ar), 3 77, 3.78 and 3.80 (9H, 3xs, $3xOCH_3$), 4.32 to 4.40 and 4.47 to 4 49 (2H, 2xm, $2xC_\alpha$-H), 4.70 to 4.73 (1H, m, C_α α-AA), 4 96 to 5.09 (6H, m, $2xOCH_2Ph$ and $CH=CH_2$), 5.45 (1H, d, J 8 Hz, NH), 5 51 to 5.55 (1H, m, $CH=CH_2$), 6 23 and 6.78 (2H, 2xbr d, 2xNH), 6.80 to 6.91 and 7.20 to7.42 (23H, m, $CHPh_2$ and ArH). m/z (FD) 932 (M^+).

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-3S-2-amino-[3,4-$^2H_2$]pent-4-enoic acid, benzhydryl ester (33).
Prepared from (30), (34%). δ_H (500 MHz, $CDCl_3$), 1.60 to 1.89 (4H, m, $CH_2CH_2CH_2CO$), 2 05 to 2.23 (2H, m, CH_2CO), 2 50 to 2 52 (0 1H, m, 3R-CHD), 2.56 to 2 60 (0.9H, m, 3S-CHD), 2.60 to 2.82 (2H, AB of ABX, CH_2S), 3 70 (2H, s, SCH_2Ar), 3 78 and 3.80 (9H, 3xs, 3xOMe), 4 32 to 4.35 and 4.46 to 4 50 (2H, 2xm, $2xC_\alpha$-H), 4 69 to 4.72 (1H, m, C_α of $CHCH_2S$), 4 95 to 5 10 (6H, m, $2xOCH_2Ph$ and $CD=CH_2$), 5.45 (1H, d, J 8 Hz, NH), 6.20 and 6.77 (2H, 2xbr d, 2xNH), 6 81 to 6.91 and 7.17 to 7.43 (23H, m, $CHPh_2$ and ArH). m/z (FD), 933 (M^+)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-amino-(Z)-[5-$^2H_1$]pent-4-enoic acid, benzhydryl ester (69).
Prepared from (58), (45%). δ_H (500 MHz, $CDCl_3$), 1.64 to 1.82 (4H, m, $CH_2CH_2CH_2CO$), 2.05 to 2.17 (2H, m, CH_2CO), 2 52 to 2.60 (2H, m, $CH_2CH=$), 2.61 to 2.83 (2H, AB of ABX, CH_2S), 3.70 (2H, s, SCH_2Ar), 3.76,3.77, and 3.79 (9H, 3xs, OMe), 4 35 to 4.38 and 4.48 to 4.52 (2H, 2xm, $2xC\alpha$-H), 4.73 to 4 76 (1H, m, Cα of $CHCH_2CH=$), 4 99 to 5.09 (5H, m, $2xOCH_2Ph$ and $CH=CHD$), 5 47 (1H, d, J 8 Hz, NH), 5 50 to 5 55 (1H, m, $CH=CHD$), 6 26 (1H, d, J 7 Hz, NH), 6.82 to 6 90 and 7.24 to 7 34 (24H, m, NH, $CHPh_2$ and ArH) m/z (FD) 932 (M^+).

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-amino-(E)-[4,5-$^2H_2$] pent-4-enoic acid, benzhydryl ester (70).
Prepared from (59), (48%). δ_H (500 MHz, $CDCl_3$), 1.62 to 1.80 (4H, m, $CH_2CH_2CH_2CO$), 2.05 to 2.18 (2H, m, CH_2CO), 2.50 to 2.60 (2H, m, $CH_2CD=$), 2 62 to 2.85 (2H, AB of ABX, CH_2S), 3.71 (2H, s, SCH_2Ar), 3.77, 3 78 and 3.80 (9H, 3xs, OMe), 4.34 to 4.38 and 4 48 to 4 52 (2H, 2xm, $2xC\alpha$-H), 4.73 to 4.76 (1H, m, Cα of $CHCH_2CD=$), 4.97 to 5 10 (5H, m, $2xOCH_2Ph$ and $CD=CHD$), 5.48 (1H, d, J 8 Hz, NH), 6.23 (1H, d, J 8 Hz, NH), 6.82 to 7.36 (24H, m, NH, $CHPh_2$ and ArH) m/z (FD) 933 (M^+)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-amino-[3,3-$^2H_2$]pent-4-enoic acid, benzhydryl ester (71).
Prepared from (60), (48%). δ_H (500 MHz, $CDCl_3$), 1.61 to 1.85 (4H, m, $CH_2CH_2CH_2CO$), 2.08 to 2.22 (2H, m, CH_2CO), 2 61 to 2 85 (2H, AB of ABX, CH_2S), 3.70 (2H, s, SCH_2Ar), 3.76, 3.77 and 3.79 (9H, 3xs, OMe), 4.34 to 4.39 and 4.48 to 4.53 (2H, 2xm, $2xC\alpha$-H), 4 73 (1H, d, J 8 Hz, $NHCHCD_2$), 4.96 to 5 10 (6H, m, $2xOCH_2Ph$ and $CH=CH_2$), 5.48 (1H, d, J 8 Hz, NH), 5 52 (1H, dd, J 10,17 Hz, $CH=CH_2$), 6.26 (1H, d, J 7 Hz, NH), 6.79 to 6.91 and 7.24 to 7.34 (24H, m, NH, $CHPh_2$ and ArH) m/z (FD.) 933 (M^+)

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-amino-(Z)-[3,3,5-$^2H_3$] pent-4-enoic acid, benzhydryl ester (72).
Prepared from (61), (62%). δ_H (300 MHz, $CDCl_3$), 1 62 to 1.80 (4H, m, $CH_2CH_2CH_2CO$), 2.05 to 2 18 (2H, m, CH_2CO), 2 62 to 2 85 (2H, AB of ABX, CH_2S), 3.71 (2H, s, SCH_2Ar), 3 76, 3.77 and 3.79 (9H, 3xs, OMe), 4 36 and 4 50 (2H,

2xm, 2xCα-H), 4.72 (1H, d, Cα of CHCD$_2$), 4.97 to 5 10 (5H, m, 2xOCH$_2$Ph and CH=CHD), 5.48 (1H, br d, J 10Hz, CH=CHD), 6.01 and 6 34 (2H, 2xd, J 7,8 Hz, 2xNH), 6.77 to 6.93 and 7.21 to7.41 (24H, m, NH, CHPh$_2$ and ArH). m/z (FD) 934 (M^+).

[(N-4-methoxybenzyloxycarbonyl)-(α-4-methoxybenzyl)-δ-(L-α-aminoadipoyl)]-S-(4-methoxybenzyl)-L-cysteinyl-D-2-amino-(E)-[3,3,4,5-$^2H_4$]pent-4-enoic acid, benzhydryl ester (73).
Prepared from (62), (40%). δ_H (300 MHz, $CDCl_3$), 1.62 to 1.85 (4H, m, CH$_2$CH$_2$CH$_2$CO), 2.08 to 2.22 (2H, m, CH$_2$CO), 2 61 to 2.85 (2H, AB of ABX, CH$_2$S), 3.70 (2H, s, SCH$_2$Ar), 3.76, 3.77 and 3.79 (9H, 3xs, OMe), 4.34 to 4.39 and 4.48 to 4.53 (2H, 2xm, 2xCα-H), 4.73 (1H, d, J 8 Hz, Cα of CHCD$_2$), 4.96 to 5.10 (5H, m, 2xOCH$_2$Ph and CD=CHD), 5.48 (1H, d, J 8 Hz, NH), 6.26 (1H, d, J 8 Hz, NH), 6.79 to 6.91 and 7.24 to7.37 (24H, m, NH, CHPh$_2$ and ArH). m/z (FD) 935 (M^+)

General procedure for the Deprotection of Tripeptides with Acid Labile Protection: Preparation of δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Aminopent-4-enoic acid disulphide (1a).
The fully protected tripeptide (38), (35mg) was thoroughly dried, dissolved in freshly distilled TFA (1ml), and dry anisole (100μl) and the solution refluxed for 30 minutes under argon. The reaction mixture was allowed to cool, and the TFA removed by azeotroping with toluene (3x5ml) in vacuo. The gummy residue was partitioned between H_2O (10ml) and EtOAc (5ml), the aqueous layer separated, washed with EtOAc then freeze dried to give the crude tripeptide in the free thiol form.Where further purification was neccessary the crude tripeptide was oxidised to the disulphide by bubbling O_2 through an aqueous solution of the tripeptide at pH 9-10 (dilute NH_3 solution) for 2 hours. Preparative HPLC (Gilson system· 50mM NH_4HCO_3:MeOH, 8·2, flow rate 4ml/min, retention time 6.1 mins), gave the title compound, identical in all respects (^{1}H,^{13}C nmr, FAB mass spectrometry) to the compound derrived from the benzyl protected tripeptide (10).

Protected tripeptides (**17a**), (**31**), (**33**), and (**69** to **73**) were treated in an identical manner to give:

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-3RS-2-Amino-[3-$^2H_1$]pent-4-enoic acid (disulphide) (1b).
Prepared from (17a), (61%). δ_H (500 MHz, D_2O), 1.67 to 1.84 and 1.84 to 1 91 (4H, m, CH$_2$CH$_2$CH$_2$CO), 2.38 to 2.45 (2 5H, m, CH$_2$CO and CHDCH=CH$_2$), 2.55 (0.5H, overlapping dd, J 6,6 Hz, CHDCH=CH$_2$), 2 95 and 3.21 (2H, AB of ABX, J 5,9,14 Hz, CH$_2$S), 3.74 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4.25 (1H, m, Cα-H of D-Ag), 4.73 (1H, dd, J 5,9 Hz, Cα-H of Cys), 5.10 to 5.16 (2H, m, CH=CH$_2$), 5 71 to 5.78 (1H, m, CH=CH$_2$). m/z (+ve Ar FAB) 723 (MH^+)

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-[3R-$^2H_1$]pent-4-enoic acid (disulphide) (1c).
Prepared from (31), (75%). δ_H (500 MHz, D_2O), 1.68 to 1.80 and 1.80 to 1.91 (4H, m, CH$_2$CH$_2$CH$_2$CO), 2.38 to 2.43 (3H, m, CH$_2$CO and 3R CHDCH=CH$_2$), 2.55 (0.1H, br m, 3S CHDCH=CH$_2$), 2.95 and 3.19 (2H, AB of ABX, J 5,9,14 Hz, CH$_2$S), 3.74 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4.26 (1H, d, J 8 Hz, Cα-H of D-Ag), 4.72 (1H, dd, J 5,9 Hz, Cα-H of L-cys), 5.11 to 5.16 (2H, m, CH$_2$=CH), 5.70 to 5.80 (1H, m, CH=CH$_2$) m/z (+ve Argon FAB) 722 (3), 723 (MH^+, 100), 724 (20), 725 (5), 755 (MNa^+).

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-3S-2-Amino-[3,4-$^2H_2$]pent-4-enoic acid (disulphide) (1d).
Prepared from (33), (75%). δ_H (500 MHz, $CDCl_3$), 1 63 to 1 78 and 1.78 to 1.94 (4H, m, CH$_2$CH$_2$CH$_2$CO), 2 38 to 2.45 (2H, m, CH$_2$CO), 2.45 to 2.50 (0.1H, m, 3R-CHD), 2.57 (0.9H, d, J 5 Hz, 3S-CHD), 2.95 and 3.18 (2H, AB of ABX, J 5,9,14 Hz, CH$_2$S), 3.75 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4.32 (1H, d, J 5 Hz, Cα-H of D-Ag), 4.72 (1H, dd, J 5,9 Hz, Cα-H of L-cys), 5 13 (2H, br s, CH$_2$=CD). m/z (+ve Ar FAB), 723 (3), 724 (0), 725 (MH^+, 100), 726 (15)

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-(Z)-[5-$^2H_1$]pent-4-enoic acid (free thiol) (1e).
Prepared from (69), (75%). δ_H (500 MHz, D_2O), 1.61 to 1.78 and 1.78 to 1.94 (4H, m, $CH_2CH_2CH_2CO$), 2 27 to 2 34 (3H, m, CH_2CO and HCHCH=), 2.39 to 2 43 (1H, m, HCHCH=), 2.76 and 2.82 (2H, AB of ABX, J 5.5,7,14 Hz, CH_2S), 3.97 (1H, overlapping dd, Cα-H of L-α-AA), 4.39 (1H, dd, J 6,9 Hz, Cα-H of D-Ag), 4.44 (1H, dd, J 5.5,7 Hz, Cα-H of L-cys), 5 07 (1H, d, J 10 Hz, CH=CHD), 5.68 (1H, m, CH=CHD). m/z (+ve Ar FAB) 363 (MH^+).

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-(E)-[4,5-$^2H_2$]pent-4-enoic acid (disulphide) (1f).
Prepared from (70), (55%). δ_H (500 MHz, D_2O), 1.65 to 1.80 and 1.80 to 1.97 (4H, m, $CH_2CH_2CH_2CO$), 2.26 to 2 35 (3H, m, CH_2CO and HCHCD=), 2.56 (1H, A of ABX, J 5,14 Hz, HCHCD=), 2.96 and 3.20 (2H, AB of ABX, J 5,9,14 Hz, CH_2S), 3 73 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4.26 (1H, dd, J 5,8 Hz, Cα-H of D-Ag), 4.72 (1H, dd, J 5,9 Hz, Cα-H of L-cys), 5.13 (1H,br s,CD=CHD) m/z (+ve Ar FAB) 725 (MH^+).

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-[3,3-$^2H_2$]pent-4-enoic acid, (free thiol) (1g).
Prepared from (71), (50%). δ_H (500 MHz, D_2O), 1.57 to 1.73 and 1.73 to 1.94 (4H, m, $CH_2CH_2CH_2CO$), 2.25 to 2 34 (2H, m, CH_2CO), 2 75 and 2.82 (2H, AB of ABX, J 5.5,7,14 Hz, CH_2S), 3.93 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4 37 (1H, s, Cα-H of D-Ag), 4.41 (1H, dd, J 5.5,7 Hz, Cα-H of L-cys), 5.04 to 5.08 (2H, m, $CH=CH_2$), 5.65 (1H, m, $CH=CH_2$). m/z (+ve Ar FAB) 364 (MH^+)

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-[3,3,5-$^2H_3$]pent-4-enoic acid (free thiol) (1h).
Prepared from (72), (77%) δ_H (500 MHz, D_2O), 1.59 to 1.77 and 1.77 to 1.95 (4H, m, $CH_2CH_2CH_2CO$), 2 26 to 2.35 (2H, m, CH_2CO), 2 78 and 2 84 (2H, AB of ABX, J 5 5,7,14 Hz, CH_2S), 3.95 (1H, overlapping dd, J 6.6 Hz, Cα-H of L-α-AA),4.40 (1H, s, Cα-H of D-Ag), 4 46 (1H, dd, J 5.5,7 Hz, Cα-H of L-cys), 5.07 (1H, d, J 10 Hz, CH=CHD), 5.69 (1H, br d,J 10 Hz, CH=CHD) m/z (+ve Ar FAB) 365 (MH^+).

δ-(L-α-aminoadipoyl)-L-cysteinyl-D-2-Amino-(E)-[3,3,4,5-$^2H_4$]pent-4-enoic acid (free thiol) (1i).
Prepared from (73), (80%) δ_H (500 MHz, D_2O), 1 56 to 1.75 and 1.75 to 1.92 (4H, m, $CH_2CH_2CH_2CO$),2 28 to 2 35 (2H, m, CH_2CO), 2.77 and 2.83 (2H, AB of ABX, J 5 5,7,14 Hz, CH_2S), 3.85 (1H, overlapping dd, J 6,6 Hz, Cα-H of L-α-AA), 4.37 (1H, s, Cα-H of D-Ag), 4 43 (1H, dd, J 5.5,7 Hz, Cα-H of L-cys), 5 06 (1H, br s, CD=CHD). m/z (+ve Ar FAB) 366 (MH^+).

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