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Evidence for an Insertion-Homolysis Mechanism for Carbon-Sulphur Bond Formation in Penicillin Biosynthesis; 1. Synthesis of Tripeptide Probes

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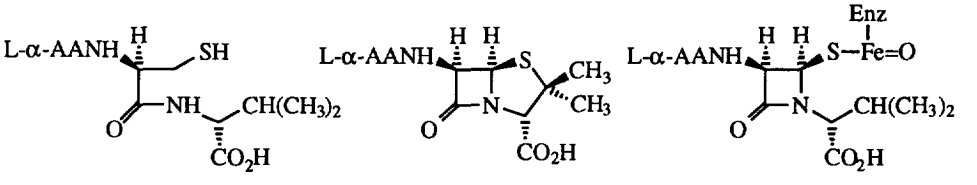
Abstract: Synthesis of four LLD-ACV analogues, in which the valine residue has been replaced by an amino acid containing a stereospecifically deuterated cyclopropane ring, is described.

As a result of a wide range of studies on the mechanism of isopenicillin N synthase (IPNS), which is responsible for the desaturative ring closure of an acyclic tripeptide LLD-ACV (**1**, L-α-AA=(*S*)-5-aminoadipoyl) into isopenicillin N (**2**), a stepwise mechanism has been proposed[1] in which an intermediate, enzyme-bound iron oxene species **3** mediates formation of the carbon-sulphur bond (figure 1). From the study of various analogues of **1** it has further been proposed[2] that for saturated substrates the closure of the second ring proceeds in three stages (scheme 1):

(i) Stereospecific insertion of the iron oxene into a C-H bond forming an iron-carbon bond;
(ii) Reversible homolytic dissociation of the iron-carbon bond to a diradical;
(iii) Coupling of the carbon-sulphur bond.

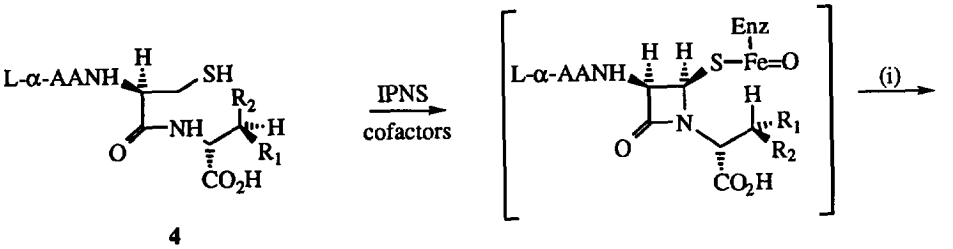


1 **2** **3**

Figure 1

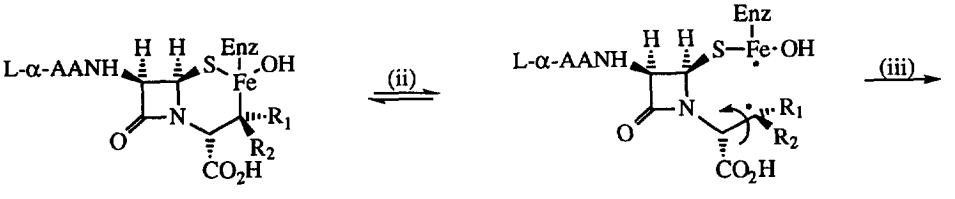
The stereochemistry of the so-formed carbon-sulphur bond of penicillin **6** is dictated in part by competition between the rate of coupling and the rate of bond rotation in the diradical **5** (scheme 1). Experiments which support this view and thus substantiate a diradical intermediate **5** have been reported,[3] in particular, the conversion by IPNS of either 3*R*- or 3*S*- monodeutero-aminobutyrate tripeptides **4b**, **4c** to the same α-deutero-β-methylpenicillin **6b**. This result can be rationalised by assuming that an iron oxene mediates homolytic cleavage of the weaker C3-^{1}H bond of either epimeric substrate to provide a common radical **5** (R_1=D, R_2=CH_3) which can readily rotate about the single bond indicated. Closure of the radical (or

its recombined metallocyclic equivalent) onto sulphur controlled by the enzyme's active site topology would then provide the observed single penam product. A similar course of events, with rotation in the diradical slowed by the methyl groups, would rationalise the observed stereospecific thiazolidine ring closure in the isotopically substituted natural substrate **4d** to **6d**.[4]

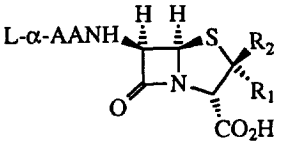


4

(a) $R_1 = R_2 = CH_3$
(b) $R_1 = D$, $R_2 = CH_3$
(c) $R_1 = CH_3$, $R_2 = D$
(d) $R_1 = {}^{13}CH_3$, $R_2 = {}^{12}CH_3$



5



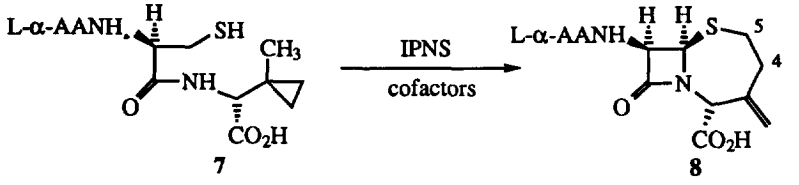
6

(a) $R_1 = R_2 = CH_3$
(b) $R_1 = D$, $R_2 = CH_3$
(d) $R_1 = {}^{13}CH_3$, $R_2 = {}^{12}CH_3$

Scheme 1

Conversion of **7** into **8** (scheme 2) suggested the intermediacy of cyclopropylcarbinyl radicals but did not rule out concerted mechanisms or identify whether the putative radical intermediate preceded or followed cyclopropane ring opening.[5] In this and the accompanying paper,† we report further experimental evidence to

† Following paper in this issue



Scheme 2

support our proposal and initial observations[6] that during the second step of the desaturase mode, insertion into a carbon-hydrogen bond to form an iron-carbon bond precedes reversible homolytic dissociation of the so-formed intermediate to a radical form.

In order to investigate the conversion of **7** into **8** in greater detail we decided to synthesise a series of stereospecifically labelled isotopomers **9**, **10**, **11** and **12** (figure 2) to probe the bonding in the homoallyl radicals or corresponding metallocyclic intermediates with particular reference to the nature of the iron-carbon bond. We reasoned that if the lifetimes of the postulated homoallyl radicals derived from **9** or **10** were sufficiently long, we should observe scrambling of the label between C4 and C5 of the 3-exomethylene homocepham metabolite. It is known from studies carried out on deuterium-labelled substrates that rearrangement of cyclopropylcarbinyl radicals is reversible and at room temperature the label is fully scrambled (scheme 3).[7,8] In comparison the significantly faster radical clocks, tripeptides **11** and **12** which contain a stereospecifically triply-deuterated cyclopropane ring require only rotation about a single bond to undergo scrambling of their stereochemical information.

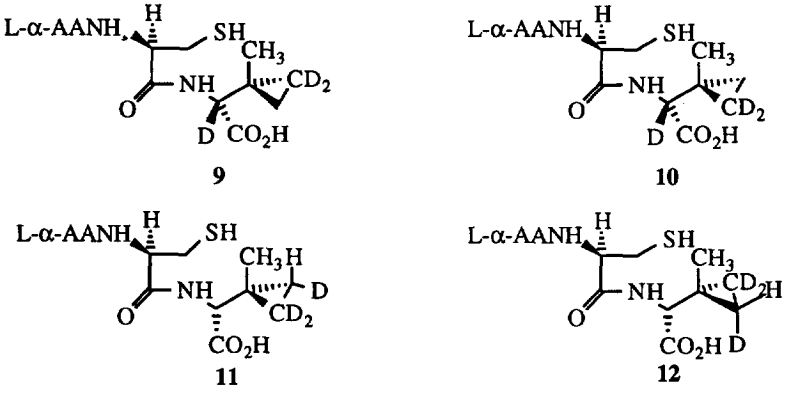
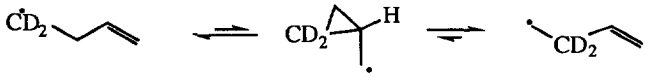


Figure 2

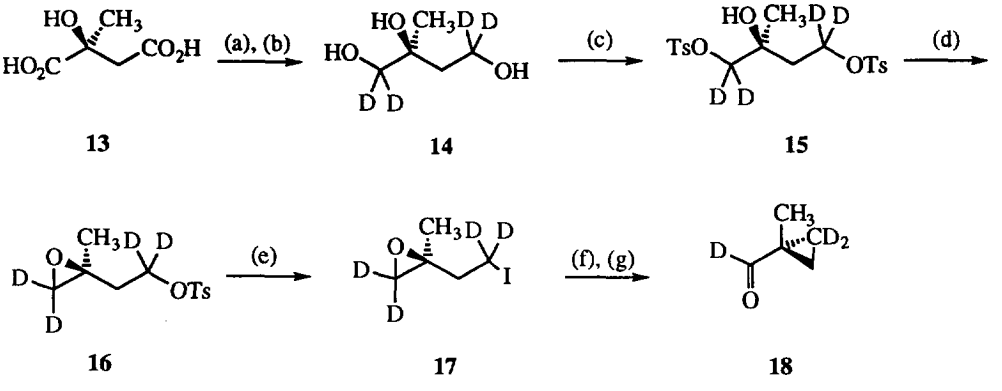


Scheme 3

Synthesis of Tripeptides 9-12.

The synthetic problems associated with the tripeptides **9** and **10** reduce to the preparation of stereospecifically deuterated methylcyclopropylglycines. Our synthesis of these key compounds utilises an approach whereby the stereochemistry of the deuterium labels can be directly and unambiguously inferred from the synthetic route. Specifically, **9** was synthesised by preparation of the deuterated epoxy-iodide **17** from *S*-citramalic acid **13** (scheme 4). This initially involved esterification of commercially available *S*-

citramalic acid using diazomethane[9] and incorporation of the deuterium label by reduction of the resulting diester with $LiAlD_4$. Although this strategy resulted in the introduction of an extra deuteron in the tripeptide, this was assumed not to effect the enzymatic reaction nor the analysis of any aspect of the results. Selective tosylation of the primary hydroxyls of the triol **14** was realised using two equivalents of *p*-toluenesulphonyl chloride at high concentration at 0°C in pyridine. Treatment of the resulting ditosylate **15** with caesium carbonate effected a 3-*exo*-tet cyclisation to afford epoxytosylate **16**. This was readily converted to the epoxy-iodide **17** using tetrabutylammonium iodide. Following a similar method to that of Arigoni[10] a 3-*exo*-tet cyclisation was performed by halogen-metal exchange using *tert*-butyllithium to produce the stereospecifically labelled (*S*)-1-methyl-(2,2-$^2H_2$)-cyclopropane-(α,α-$^2H_2$)-methanol as the sole product. Oxidation to the aldehyde **18** was achieved using the mild TPAP/NMO method of Griffith and Ley.[11,12]



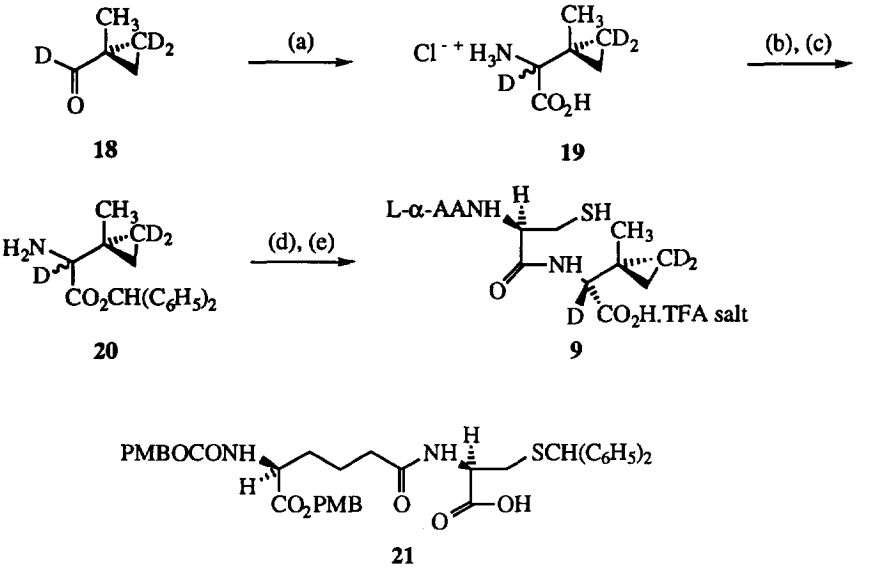
13 **14** **15** **16** **17** **18**

(a) CH_2N_2, CH_3OH (94%); (b) $LiAlD_4$, THF (57%); (c) *p*-$CH_3(C_6H_4)SO_2Cl$ (2.0 eq), pyridine (60%); (d) Cs_2CO_3 (2.3 eq), acetone (99%); (e) $^nBu_4N^+ I^-$, (2.0 eq) acetone, reflux (84%); (f) ^{t}BuLi, ether, -78°C; $Na_2SO_4.10H_2O$; (g) *N*-methylmorpholine-*N*-oxide, $^nPr_4N^+ RuO_4^-$ (5 mol%), CH_2Cl_2.

Scheme 4

Application of a modified Strecker reaction afforded the desired amino acid hydrochloride **19** as a 1:1 mixture of diastereoisomers at the α-amino centre (scheme 5). It proved essential to use the Greenlee modification[13] of the Strecker reaction to obtain acceptable yields in this particular system. The amino acid was then *N*-Boc protected with di-*tert*-butyldicarbonate[14] and the carboxyl group protected as its benzhydryl ester using diphenyldiazomethane.[15] After selective cleavage of the *N*-Boc group, the labelled amino acid benzhydryl ester **20** was coupled using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) to the protected dipeptide δ-(*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteine **21**.[16] The LLL and LLD configured diastereomers were separated using flash chromatography to give a stereochemically homogeneous LLD-tripeptide as the less polar component. Global deprotection of the LLD configured isomer using TFA/anisole furnished the desired tripeptide **9** as the trifluoroacetate salt.[17] Tripeptide **10** was synthesised in an analogous fashion starting from *R*-citramalic acid.

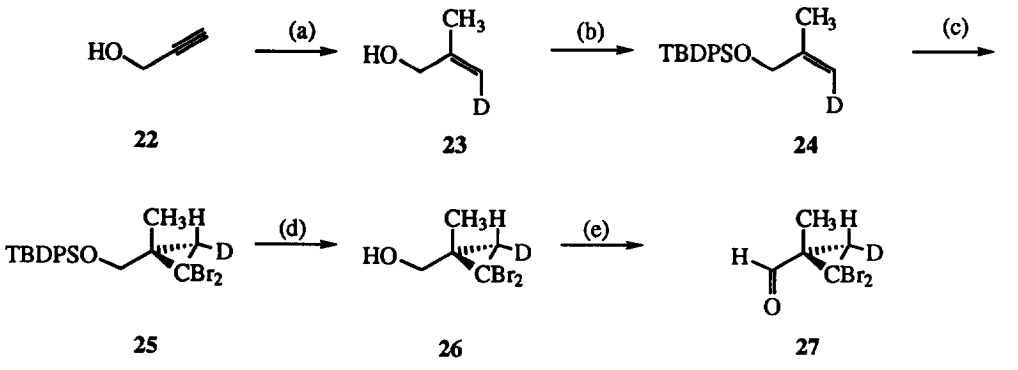
We next required the tripeptides **11** and **12** containing a stereospecifically triply-deuterated cyclopropane ring. The presence of the two extra deuterons in the cyclopropyl ring was essential to eliminate background resonances in the SCH_2CH_2 region of the ^1H NMR of the penam product thus enabling unambiguous assignment of the stereochemical integrity of the deuterium label.



(a) $[p\text{-}CH_3O(C_6H_4)]_2CHNH_2$, 4Å mol. sieves ; TMSCN; 6M HCl, reflux (84% from **17**); (b) $(Boc)_2O$, 1M NaOH followed by acidification; $(C_6H_5)_2CN_2$, CH_3CN (69%); (c) *p*-TsOH, ethanol, ether, 10% aqueous $NaHCO_3$ wash (82%); (d) **21**, EEDQ, THF, chromatographic separation of diastereomers (combined yield 97%); (e) TFA, anisole, 50°C (72%).

Scheme 5

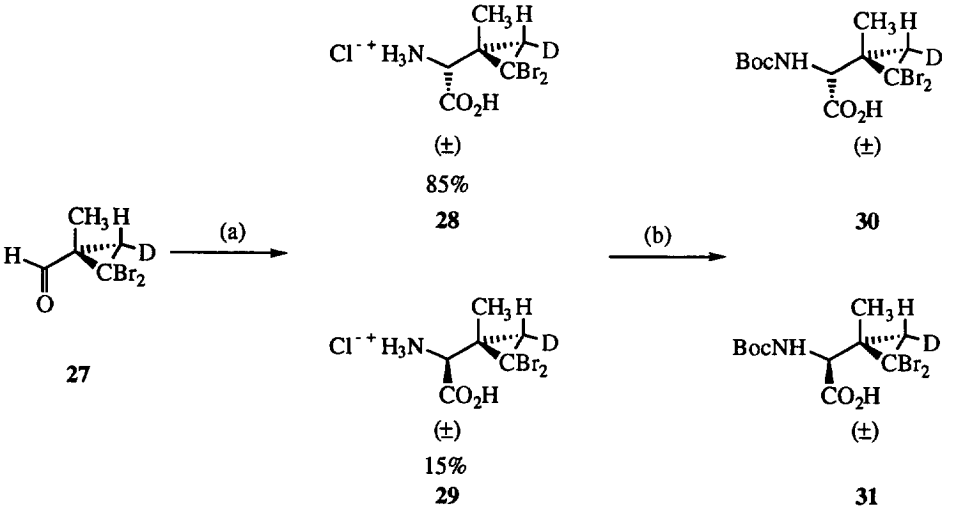
As with **9** and **10**, the synthetic challenge reduces to the preparation of the stereospecifically deuterated amino acids. In this synthetic approach the *Z* stereochemistry of the alkene system **23** was set up *via* a copper-catalysed Grignard reaction followed by deuterium incorporation with greater than 95% stereoselectivity (scheme 6).[18, 19] However, before cyclopropane construction was attempted the sensitive alcohol functionality was protected to avoid competing carbene insertion into the O-H bond. The TBDPS group was chosen due to its facile introduction and removal[20, 21] and its ability to withstand the conditions of carbene generation.[22] The dibromocyclopropane **25** was then prepared using bromoform and potassium *tert*-butoxide.[23, 24] Dibromocarbene is known to undergo a stereospecific cycloaddition with alkenes due to its predominantly singlet nature,[25-27] thus maintaining the stereochemical integrity of the deuterium label. Furthermore, introduction of the two bromine atoms precluded the handling of volatile intermediates and enabled the ready incorporation of two deuterons at a late stage in the synthesis. Cleavage of the silyl ether using 1M tetrabutylammonium fluoride (TBAF) in THF to give **26**, followed by oxidation of the alcohol using pyridinium chlorochromate[28] afforded the desired aldehyde **27** in 56% yield over five steps.



(a) CH_3MgBr, CuI, THF ; D_2O (74%); (b) TBDPSCl, imidazole, DMF (quantitative); (c) $CHBr_3$, ^tBuOK, pentane (89%); (d) TBAF, THF, RT (97%); (e) Pyridinium chlorochromate (PCC), CH_2Cl_2 (88%) .

Scheme 6

As with the previous syntheses the amino acid functionality in **28** and **29** was established using the Greenlee modification of the Strecker synthesis[13] to ensure acceptable yields (scheme 7). However, due to the steric demands of the dibromocyclopropane, a moderate degree of diastereoselectivity was observed (70% d.e. by ^1H NMR). That the major isomer had the $2R^*,1'S^*,3'S^*$ relative configuration as depicted in **28** was substantiated by incubation experiments.[29]

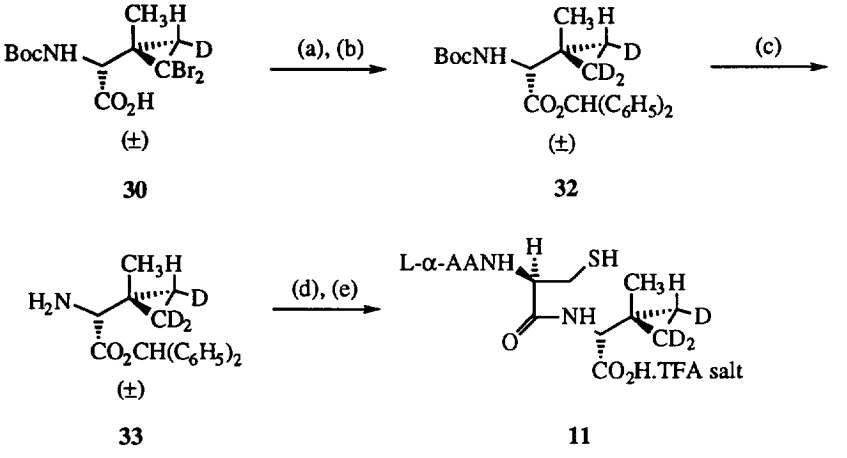


(a) $[p\text{-}CH_3O(C_6H_4)]_2CHNH_2$, 4Å mol. sieves ; TMSCN; 6M HCl, reflux (87%); (b) $(Boc)_2O$, 1M NaOH then acidification; chromatographic separation of diastereomers (79% **30**, 9% **31**).

Scheme 7

Following *N*-Boc protection of the amino group, the two diastereomers were successfully separated by flash chromatography. After formation of the benzhydryl ester of the major isomer **30**, the remaining deuterium atoms were introduced using triphenyltin deuteride[30-32] under radical conditions and the protecting groups manipulated to give the key amino ester **33** (scheme 8). This racemic amine was then coupled to the protected dipeptide δ-(*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteine **21** using EEDQ. The LLL and LLD configured diastereomers were separated using flash chromatography to give a stereochemically homogeneous LLD tripeptide as the less polar component.[17] Global deprotection using TFA/anisole was achieved as before to afford the desired tripeptide **11** as the trifluoroacetate salt. Tripeptide **12** was synthesised in an analogous manner from the minor isomer **31**.

Incubation of tripeptides **9** - **12** with IPNS is described in the following paper.



(a) $(C_6H_5)_2CN_2$, CH_3CN (77%); (b) $(C_6H_5)_3SnD$, AIBN, benzene, reflux (89%); (c) *p*-TsOH, ethanol, ether, 10% aqueous $NaHCO_3$ wash (quantitative); (d) **21**, EEDQ, THF, chromatographic separation of diastereomers (40%); (e) TFA, anisole, 50°C.

Scheme 8

EXPERIMENTAL

Melting points were obtained using a Büchi 510 capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20°C with a pathlength of 1dm. Concentrations are given in g/100ml. Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford. Infrared (IR) spectra were recorded as thin films, KBr discs or in $CDCl_3$ solution on a Perkin-Elmer 1750 Fourier transform spectrometer with major features of each spectrum reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

^1H NMR spectra were recorded at 200MHz and 500MHz on Varian Gemini 200 and Bruker AM500 spectrometers respectively. For ^1H NMR recorded in $CDCl_3$ and D_2O chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet and br, broad. Coupling constants are recorded in Hertz to the nearest 0.5Hz.

^{13}C NMR spectra were recorded at 50.31MHz and 125.77MHz on Varian Gemini 200 and Bruker AM500 spectrometers respectively using DEPT editing. Quaternary carbons are assigned from a broadband decoupled analysis used in conjunction with the DEPT program. Chemical shifts are quoted in parts per million and referenced to $CDCl_3$ unless otherwise stated. Spectra recorded in D_2O are referenced to internal 1,4-dioxan.

Low resolution mass spectra were recorded on a V. G. Micromass ZAB 1F (FAB/CI/DCI), a V. G. Masslab 20-250 (CI/DCI/EI), a V. G. TRIO 1 (GCMS) or V. G. BIO-Q (Electrospray) spectrometer with only molecular ions, fragments from molecular ions and major peaks being reported.

Flash chromatography was accomplished on silica gel using Sorbsil™ C60(40-63mm, 230-40 mesh). Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254} which were visualised by the quenching of u.v. fluorescence (λmax 254nm), and by staining with iodine, 10%w/v ammonium molybdate in 2M sulphuric acid, ninhydrin, anisaldehyde, 2,4-dinitrophenylhydrazine or bromocresol green, all followed by heat.

All solvents were distilled before use. Anhydrous dichloromethane, methanol and benzene were obtained by stirring over calcium hydride followed by distillation under argon. Anhydrous acetone was distilled from $CaSO_4$ under argon. Anhydrous diethyl ether and anhydrous THF were obtained by distillation from sodium/benzophenone ketyl under nitrogen and anhydrous DMF by distillation from calcium hydride under reduced pressure. Petroleum ether 30-40 refers to the fraction of light petroleum ether boiling between 30-40°C. Solvents were evaporated at 30°C or below on a Büchi R110 Rotavapor; high boiling solvents were evaporated on a Büchi R110 Rotavapor fitted with a dry ice condenser at <2mmHg. Kugelrohr distillations were performed at the recorded temperature and pressure.

Diazomethane,[9] 4,4'-dimethoxybenzhydrylamine[13] and triphenyltin (^2H)-hydride[31] were prepared by literature methods. All other reagents were purified in accordance with the instructions in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources.

Synthesis of (2S)-(1,1,4,4-$^2H_4$)-2-methylbutane-1,2,4-triol (14).

To a stirred solution of (*S*)-2-hydroxy-2-methylbutanedioic acid (*S*-citramalic acid, **13**) (5.92g, 40mmol) in methanol (50ml) cooled to 0°C was added a solution of diazomethane (*c.* 140mmol) in ether (250ml)[9] until the yellow colour just persisted. The excess diazomethane was quenched with the minimum volume of acetic acid at 0°C, and the reaction concentrated *in vacuo* to afford *dimethyl (S)-2-hydroxy-2-methylbutanedioate* as a pale yellow oil (6.62g, 94%), $[\alpha]_{20}^{D}$ +31.2° (*c.* 2.2, $CHCl_3$) (lit. [33] +27.3°, *c.* 2.11, $CHCl_3$), (Found: C, 47.4; H, 6.9. Calc. for $C_7H_{12}O_5$: C, 47.7; H, 6.9%); R_f 0.7 (CH_2Cl_2: methanol; 80: 20); ν_{max} (liquid film) 3496w (OH), 2957m, 1741s (ester C=O), 1439s, 1205s and 1014s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.44 (3H, s, $C(OH)C\underline{H}_3$), 2.68 and 2.97 (2H, AB, J_{AB} 16Hz, $C\underline{H}_2CO_2$), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.81 (3H, s, $CO_2C\underline{H}_3$); δ_C (125MHz; $CDCl_3$) 26.04 ($C(OH)\underline{C}H_3$), 43.91 ($\underline{C}H_2CO_2$), 51.33 ($CO_2\underline{C}H_3$), 52.59 ($CO_2\underline{C}H_3$), 72.39 ($\underline{C}(OH)CH_3$), 171.10 ($CH_2\underline{C}O_2$), 175.71 ($O_2\underline{C}C(OH)CH_3$); *m/z* (desorption chemical ionisation, NH_3) 194 (MNH_4^+, 100%), 177 (MH^+, 93).

To a stirred suspension of $LiAlD_4$ (3.6g, 86mmol) in anhydrous THF (150ml), cooled to 0°C under an inert atmosphere of argon, was added dimethyl (*S*)-2-hydroxy-2-methylbutanedioate (6.9g, 40mmol) as a solution in anhydrous THF (30ml) over 30 minutes. The reaction was stirred at room temperature for 3 hours, then cooled to 0°C, quenched with water (2ml) and 0.5M NaOH (2ml). The reaction was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to afford a colourless oil. The filtered aluminium residues were Soxhlet extracted with ethanol for 28 hours, concentrated *in vacuo* to afford a brown solid, then combined with the earlier product. Flash chromatography (SiO_2, CH_2Cl_2: methanol; 80: 20) afforded *(S)-(1,1,4,4-$^2H_4$)-2-methylbutane-1,2,4-triol (14)* as a colourless oil (2.79g, 57%), $[\alpha]_{20}^{D}$ -1.0°(*c.* 5.2, ethanol) (lit. [34] -1.1°, *c.*

5.2, ethanol), R_f 0.3 (CH_2Cl_2: methanol; 80: 20); ν_{max} (liquid film) 3351s (OH), 2975m, 1656m, 1103m and 912m cm^{-1}; δ_H (200MHz; CD_3OD) 1.16 (3H, s, C(OH)C$\underline{H}_3$), 1.71 and 1.75 (2H, AB, J_{AB} 16Hz, C$\underline{H}_2CD_2$); δ_C (125MHz; CD_3OD) 24.37 (C(OH)$\underline{C}H_3$), 41.34 ($\underline{C}H_2CD_2OH$), 58.51 (quintet, J_{CD} 21Hz, $CH_2\underline{C}D_2OH$), 69.77 (quintet, J_{CD} 22Hz, C(OH)(CH_3)$\underline{C}D_2OH$), 73.23 ($\underline{C}(OH)CH_3$); *m/z* (desorption chemical ionisation, NH_3) 142 (MNH_4^+, 100%), 125 (MH^+, 75), 89 (58).

Synthesis of (S)-(1,1,4,4-$^2H_4$)-2-hydroxy-2-methyl-1,4-butane-bis-(toluene-4-sulphonate) (15).

To a stirred solution of (*S*)-(1,1,4,4-$^2H_4$)-2-methylbutane-1,2,4-triol (**14**) (1.68g, 14mmol), in anhydrous pyridine (15ml), cooled to 0°C under an inert atmosphere of argon, was added *p*-toluenesulphonyl chloride (5.3g, 28mmol) in portions over 30 minutes. The mixture was then stirred at room temperature for 24 hours. The reaction was then diluted with ether (100ml), washed with 1M HCl (5 x 50ml), water (50ml) and brine (50ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a colourless oil. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 30: 70) afforded *(S)-(1,1,4,4-$^2H_4$)-2-hydroxy-2-methyl-1,4-butane-bis-(toluene-4-sulphonate) (15)* as a white crystalline solid (3.6g, 60%), m.p. 69-71°C (pentane, ether), $[\alpha]_{20}^{D}$ -1.1° (*c.* 1, $CHCl_3$), (Found: C, 52.65; H, 5.4. $C_{19}H_{20}D_4O_7S_2$ requires C, 52.75; H, 5.6%); R_f 0.4 (petroleum ether 30-40: ether; 40: 60); ν_{max} (KBr disc) 3509s (OH), 2983m, 1600w, 1352s (S=O), 1177s (S=O), 1098m, 1020m, 949m and 823s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.18 (3H, s, C(OH)C$\underline{H}_3$), 1.80 and 1.90 (2H, AB, J_{AB} 15Hz, C$\underline{H}_2CD_2$), 2.08 (1H, s, O$\underline{H}$), 2.47 (6H, s, 2x(C_6H_4)C$\underline{H}_3$), 7.35 to 7.41 (4H, m) and 7.76 to 7.81 (4H, m, aromatic C$\underline{H}$); δ_C (125MHz; $CDCl_3$) 21.52 (2x(C_6H_4)$\underline{C}H_3$), 23.94 (C(OH)$\underline{C}H_3$), 36.92 ($\underline{C}H_2CD_2OSO_2$), 65.50 (quintet, J_{CD} 22Hz, $CH_2\underline{C}D_2OSO_2$), 70.09 ($\underline{C}(OH)CH_3$), 77.00 (quintet, J_{CD} 22Hz, C(OH)(CH_3)$\underline{C}D_2OSO_2$), 127.83, 127.90, 129.89, 132.74, 133.12, 144.89 and 145.15($OSO_2(\underline{C}_6H_4)CH_3$); *m/z* (desorption chemical ionisation, NH_3) 450 (MNH_4^+, 33%), 278 (35), 89 (100).

Synthesis of (S)-(1,1,4,4-$^2H_4$)-3,4-epoxy-3-methylbutane-1-(toluene-4-sulphonate) (16).

To a stirred suspension of caesium carbonate (7.33g, 0.022mol) in anhydrous acetone (100ml) under an inert atmosphere of argon was added (*S*)-(1,1,4,4-$^2H_4$)-2-hydroxy-2-methyl-1,4-butane-*bis*-(toluene-4-sulphonate) (**15**) (6.7g, 0.015mmol) dropwise as a solution in anhydrous acetone (60ml) and the reaction was stirred at room temperature for 12 hours. Further caesium carbonate (3.75g, 0.012mol) was added and the reaction stirred at room temperature for a further 12 hours. The reaction was then concentrated *in vacuo* and partitioned between ether (300ml) and water (75ml). The organic layer was washed with water (2 x 75ml) and brine (50ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford *(S)-(1,1,4,4-$^2H_4$)-3,4-epoxy-3-methylbutane-1-(toluene-4-sulphonate) (16)* as a colourless oil which rapidly turned black after concentration (4.0g, 99%), (Found: C, 55.1; H, 5.9. $C_{12}H_{12}D_4O_4S$ requires C, 55.35; H, 6.2%); (R_f 0.7, petroleum ether 30-40: ether; 20: 80); ν_{max} (liquid film) 2980m, 2930m, 2172m, 1598m, 1362s (S=O), 1179 (S=O), 964m, 917s, 853s and 772s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.28 (3H, s, C$\underline{H}_3$C(O)CD_2), 1.88 and 1.98 (2H, AB, J_{AB} 15Hz, C$\underline{H}_2CD_2OSO_2$), 2.46 (3H, s, (C_6H_4)C$\underline{H}_3$), 7.36 and 7.80 (4H, AB, J_{AB} 8Hz, aromatic C$\underline{H}$); δ_C (125MHz; $CDCl_3$) 20.98 ($\underline{C}H_3C(O)CD_2$), 21.36 (C_6H_4)$\underline{C}H_3$), 35.40 ($\underline{C}H_2CD_2OSO_2$), 52.64 (quintet, J_{CD} 26Hz, $\underline{C}D_2(O)C(CH_3)$), 53.90 ($CH_3\underline{C}(O)CD_2$), 66.07 (quintet, J_{CD} 23Hz, $CH_2\underline{C}D_2OSO_2$), 127.69, 129.76, 133.16 and 144.75 (aromatic); *m/z* (desorption chemical ionisation, NH_3) 278 (MNH_4^+, 34%), 89 (100).

Synthesis of (S)-(1,1,4,4-$^2H_4$)-3,4-epoxy-1-iodo-3-methylbutane (17).

To a stirred solution of (*S*)-(1,1,4,4-$^2H_4$)-3,4-epoxy-3-methylbutane-1-(toluene-4-sulphonate) (**16**) (4.0g, 0.015mol) in anhydrous acetone (100ml) under an inert atmosphere of argon, tetrabutylammonium iodide (11.09g, 0.03mol) was added in one portion and the reaction was refluxed in the dark for 3 hours. The reaction was then allowed to cool and concentrated *in vacuo* to afford a white semi-solid mass. This was dissolved in water (200ml) and extracted with ether (3 x 400ml). The combined organic layers were washed with water (200ml) and brine (100ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a pale yellow oil. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(S)-(1,1,4,4-$^2H_4$)-3,4-epoxy-1-iodo-3-methylbutane (17)* (2.8g, 84%), $[\alpha]_{20}^{D}$ -11.7° (*c.* 1, $CHCl_3$), (R_f 0.3, petroleum ether 30-40: ether; 90: 10); ν_{max} (liquid film) 2980m, 2962m, 1620m, 1451m, 1391s, 1103m, 929s, 917s and 862m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.34 (3H, s, $C\underline{H}_3$), 2.09 and 2.23 (2H, AB, J_{AB} 14Hz, $C\underline{H}_2CD_2I$); δ_C (125MHz; $CDCl_3$) -1.69 (quintet, J_{CD} 23Hz, $CH_2\underline{C}D_2I$), 20.17 ($\underline{C}H_3C(O)CH_2$), 40.45 ($\underline{C}H_2CD_2$), 52.45 (quintet, J_{CD} 23Hz, $\underline{C}D_2(O)C(CH_3)$), 56.53 ($CH_3\underline{C}(O)CD_2$), *m/z* (desorption chemical ionisation, NH_3) 217 (MH^+, 68%), 89 (100).

Synthesis of (S)-1-methyl-(2,2-$^2H_2$)-cyclopropane-1-(^2H)-carbaldehyde (18).

To a stirred solution of (*S*)-(1,1,4,4-$^2H_4$)-3,4-epoxy-1-iodo-3-methylbutane (**17**) (2.10g, 10mmol) in anhydrous ether (40ml), cooled to -78°C under an inert atmosphere of argon, was added ^{t}BuLi (1.34$\underline{M}^{35}$ in pentane, 14.9ml, 20mmol) dropwise over 30 minutes. The reaction was stirred at -78°C for 30 minutes then allowed to warm to room temperature over 2 hours. The reaction was quenched with $Na_2SO_4.10H_2O$ (1.2g), then anhydrous Na_2SO_4 was added and the mixture filtered through a short column of silica. The volume was reduced to 5ml by careful distillation through a Vigreux column at ambient pressure under argon to afford *(S)-1-methyl-(2,2-$^2H_2$)-cyclopropane-(α,α-$^2H_2$)-methanol* as a solution in ether which enabled this volatile compound to be used directly in the next reaction, (R_f 0.3, petroleum ether 30-40: ether; 50: 50); δ_H (500MHz; $CDCl_3$) 0.24 and 0.34 (2H, br AB, J_{AB} 4Hz, $C\underline{H}_2CD_2$), 1.09 (3H, s, $CC\underline{H}_3$); δ_C (50MHz; $CDCl_3$) 10.32 ($\underline{C}H_2CD_2$) partially overlapping $CH_2\underline{C}D_2$ quintet), 17.53 ($\underline{C}CH_3$), 20.43 ($C\underline{C}H_3$), 69.99 (quintet, J_{CD} 23Hz, $\underline{C}D_2OH$); *m/z* (GCMS, chemical ionisation, NH_3) 108 (MNH_4^+, 52%), 90 (100), 73 (60).

To a stirred solution of (*S*)-1-methyl-(2,2-$^2H_2$)-cyclopropane-(α,α-$^2H_2$)-methanol (*ca.* one-fifth of material from previous experiment, 2mmol) in anhydrous CH_2Cl_2 (20ml) under an inert atmosphere of argon, crushed, freshly activated 4Å molecular sieves (1g) and *N*-methylmorpholine-*N*-oxide (NMO) (350mg, 3mmol) were added and the mixture was stirred at room temperature for 20 minutes. Tetrapropylammonium perruthenate (TPAP) (35mg, 0.10mmol, 5mol%) was added in one portion and the reaction was stirred for 2 hours. The reaction was then filtered through a short plug of silica (CH_2Cl_2 eluent) and the volume reduced to approximately 5ml by careful distillation through a Vigreux column at ambient pressure under argon to afford *(S)-1-methyl-(2,2-$^2H_2$)-cyclopropane-1-(^2H)-carbaldehyde (18)* as a solution in CH_2Cl_2 which enabled this sensitive volatile compound to be used directly in the next reaction, (R_f 0.7, petroleum ether 30-40: ether; 50: 50); ν_{max} ($CDCl_3$) 2960s, 2875s, 2240s, 1740s (C=O), 1440w, 1260s and 1100s cm^{-1}; δ_H (500MHz; $CDCl_3$) 0.90 and 1.15 (2H, br AB, J_{AB} 4Hz, $C\underline{H}_2CD_2$), 1.22 (3H, s, $CC\underline{H}_3$); *m/z* (GCMS, chemical ionisation, NH_3) 105 (MNH_4^+, 22%), 88 (21).

Synthesis of (2RS,1'S)-(2-^2H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropylglycine hydrochloride (19).

To a stirred solution of (*S*)-1-methyl-(2,2-$^2H_2$)-cyclopropane-1-(^2H)-carbaldehyde (**18**) (*ca.* 2mmol) in anhydrous CH_2Cl_2 (10ml), under an inert atmosphere of argon, were added freshly activated 4Å molecular sieves (0.6g) and 4,4'-dimethoxybenzhydrylamine[13] (490mg, 2.0mmol). The reaction was stirred at room temperature for 5 hours. Trimethylsilyl cyanide (TMSCN) (0.29ml, 2.2mmol) was added dropwise and the reaction stirred for 16 hours. The reaction mixture was then filtered and concentrated *in vacuo* to yield a yellow oil which was combined with 6M hydrochloric acid (50ml) and heated under reflux for 12 hours to afford a brown syrupy solution. The solution was allowed to cool to room temperature and washed with CH_2Cl_2 (3 x 25ml). The aqueous phase was concentrated *in vacuo* and lyophilised to afford *(2RS,1'S)-(2-^2H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine hydrochloride (19)* as a yellow solid (280mg, *ca.* 84% overall yield from (**17**)), m. p. 183-186°C (dec.) (ethanol, water), ν_{max} (KBr disc), 3050br s, 2674s, 1746s (C=O), 1586m, 1568s, 1408s, 1221s, 1051m and 844s cm^{-1}; δ_H (500MHz; D_2O, pH 1) 0.38 and 0.69 (1H, AB, J_{AB} 5Hz, 1 x CH_2CD_2), 0.45 and 0.46 (1H, AB, J_{AB} 5.5Hz, 1 x CH_2CD_2), 0.86 (3H, s, CCH_3); δ_C (50MHz; D_2O, pH 1) 12.17 and 13.37 (2 x br s , 2 x CH_2CD_2 partially overlapping 2 x CH_2CD_2 quintets), 16.18 (CCH_3), 17.39 (CCH_3), 61.25 (t, J_{CD} 22Hz, CDNH), 171.51 (C=O); *m/z* (desorption chemical ionisation, NH_3) 133 (free amino acid H^+, 100%), 87 (37).

Synthesis of (2RS,1'S)-(2-^2H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine benzhydryl ester (20).

To a stirred solution of (2*RS*,1'*S*)-(2-^2H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine hydrochloride (**19**) (170mg, 1.0mmol) in 1,4-dioxan: water (1: 1, 10ml), cooled to 0°C, was added 1M NaOH (3ml, 3.0mmol) dropwise, followed by di-*tert*-butyl dicarbonate (280mg, 1.3mmol) as a solution in 1,4-dioxan (1ml) and the reaction was stirred at room temperature for 3 hours. The reaction mixture was then concentrated *in vacuo* and diluted with water (20ml). The solution was washed at pH 10 with ethyl acetate (20ml), layered with ethyl acetate (20ml) and acidified to pH 3 with aqueous 1M potassium hydrogen sulphate. The aqueous phase was then further extracted with ethyl acetate (2 x 20ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a colourless oil. This compound was partially purified by flash chromatography (SiO_2, petroleum ether 30-40: ether: acetic acid 50:50:1) to afford a colourless oil which was dissolved in acetonitrile (5ml) and treated with diphenyldiazomethane (235mg, 1.2mmol) and stirred at room temperature for 2 hours. Acetic acid (0.2ml) was then added to the reaction and stirred for a further 30 minutes. The solution was concentrated *in vacuo* and flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(2RS,1'S)-(2-^2H)-*N-tert-*butyloxycarbonyl-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine benzhydryl ester* as a white crystalline solid (280mg, 69%), m. p. 108-110°C (pentane, ether), (Found: C, 72.25; H, 7.4; N, 3.4. $C_{24}H_{26}D_3NO_4$ requires C, 72.35; H, 7.35; N, 3.5%); (R_f 0.3, petroleum ether 30-40: ether; 90: 10); ν_{max} (KBr disc) 3771m (NH), 3135m, 2981m, 1747m, 1708s, 1393s, 1159s, 1083m, 988m and 745s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.31 and 0.43 (1H, AB, J_{AB} 5Hz, 1 x CH_2CD_2), 0.70 (0.5H, br s) and 1.07 (0.5H, br s, 1 x CH_2CD_2), 0.86 (3H, s, CCH_3), 1.45 (9H, s, $C(CH_3)_3$), 5.25 (1H, br s, CDNH), 6.93 (1H, s, $CH(C_6H_5)_2$), 7.35 (10H, br s, $CH(C_6H_5)_2$); δ_C (125MHz; $CDCl_3$) 11.74 and 12.43 (2 x br s, 2 x CH_2CD_2 partially overlapping 2 x CH_2CD_2 quintets), 18.34 (CCH_3), 18.93 (CCH_3), 28.27 ($C(CH_3)_3$), 60.03 (t, J_{CD} 22Hz, CDNH), 77.91 ($CH(C_6H_5)_2$), 79.71 ($C(CH_3)_3$), 127.01, 127.92, 127.95, 128.36, 128.43, 139.75, 139.92 ($CO_2CH(C_6H_5)_2$), 155.35 (CONH), 170.73 ($CO_2CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 421 (MNa^+, 14%), 399 (MH^+, 6), 167 (100), 131 (22), 57 (30).

To a stirred solution of (2*R S*,1'*S*)-(2-^2H)-*N-tert*-butyloxycarbonyl-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine benzhydryl ester (150mg, 0.37mmol) in ether (3ml), cooled to 0°C, was added *p*-toluenesulphonic acid monohydrate (140mg, 0.74mmol) as a solution in ethanol (3ml) and the reaction was then allowed to warm to room temperature. The reaction was concentrated *in vacuo*, redissolved in ether:

ethanol (1: 1, 6ml) and concentrated *in vacuo*. This procedure was repeated a further five times before TLC demonstrated that no starting material remained. The resulting white solid was then suspended in ethyl acetate (20ml) and washed with saturated aqueous $NaHCO_3$ (10ml). The aqueous layer was back-extracted with ethyl acetate (2 x 20ml) and the combined organic layers dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford *(2RS,1'S)-(2-^{2}H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine benzhydryl ester (20)* as a pale yellow oil (92mg, 82%), ν_{max} (liquid film) 3845w and 3714w (NH_2), 3034w, 2958m, 1734s (C=O, $CO_2CH(C_6H_5)_2$), 1496m, 1455m, 1001m, 862m and 701s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.38, 0.50 and 0.53 (1.5H, AB and A of AB, J_{AB} 5Hz, 3 x CH_2CD_2), 0.88 (3H plus 0.5H, s, 1 x CH_2CD_2 obscured and CCH_3), 3.13 (2H, br s, $CDNH_2$), 6.95 (1H, s, $CH(C_6H_5)_2$), 7.35 (10H, br s, $CH(C_6H_5)_2$); δ_C (125MHz; $CDCl_3$) 12.08 and 12.84 (2 x br s, 2 x CH_2CD_2 partially overlapping 2 x CH_2CD_2 quintets), 17.74 (CCH_3), 19.24 (CCH_3), 61.28 (t, J_{CD} 22Hz, $CDNH_2$), 77.67 ($CH(C_6H_5)_2$), 127.11, 127.94, 128.40, 128.47, 139.85 and 139.97 ($CO_2CH(C_6H_5)_2$), 172.49 ($CO_2CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 321 (MNa^+, 14%), 299 (MH^+, 7), 167 ($CH(C_6H_5)_2^+$, 100).

Synthesis of δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'S)-(2-^{2}H)-2-[(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl) glycine] (9).

To a stirred solution of (2*RS*,1'*S*)-(2-^{2}H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine benzhydryl ester (**20**) (93mg, 0.31mmol) in anhydrous CH_2Cl_2 (1ml), under an inert atmosphere of argon, was added δ-(*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteine[16] (**21**) (221mg, 0.31mmol) as a solution in anhydrous CH_2Cl_2 (3ml). 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (74mg, 0.31mmol) and anhydrous Na_2SO_4 (30mg) were then added, and the mixture stirred at room temperature for 24 hours. The reaction was then filtered and concentrated *in vacuo* to give an orange gum. This was dissolved in ethyl acetate (30ml), washed with 1M HCl (20ml), saturated aqueous $NaHCO_3$ (20ml) and water (20ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a white foam. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 80: 20) afforded a mixture of LLL and LLD-configured protected tripeptides (300mg, 97%); further flash chromatography enabled separation of the more polar LLL and less polar LLD diastereomers affording *(N-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-S-benzhydryl-L-cysteinyl-[(2R,1'S)-(2-^{2}H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine] benzhydryl ester* as a white foam; (R_f 0.3, less polar isomer, petroleum ether 30-40: ether; 20: 80); ν_{max} (KBr disc) 3305br m, 3031m, 2956m, 2837m, 1824m, 1723s, 1653s, 1614s, 1587m, 1516s, 1249s, 1174s and 823m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.30 and 0.66 (2H, AB, J_{AB} 5Hz, CH_2CD_2), 0.80 (3H, s, CCH_3), 1.60 to 1.74 (4H, m, $(CH_2)_2CH_2CONH$), 2.09 to 2.34 (2H, m, CH_2CONH), 2.72 (1H, A of ABX, J_{AB} 15Hz, J_{AX} 7Hz, 1xSCH_2), 2.81 (1H, B of ABX, J_{AB} 15Hz, J_{BX} 7Hz, 1xSCH_2), 3.80 (6H, s, 2 x OCH_3), 4.34 to 4.42 (1H, br m, cysteinyl CHNH), 4.50 to 4.61 (1H, br m, adipoyl CHNH), 5.03 (2H, s) and 5.08 (2H, s, 2 x $CH_2C_6H_4OCH_3$), 5.28 (1H, s, $SCH(C_6H_5)_2$), 5.49 (1H, d, *J* 7Hz, NH), 6.27 (1H, d, *J* 7Hz, NH), 6.83 to 6.90 (6H, m, NH, $CO_2CH(C_6H_5)_2$, and $C_6H_4OCH_3$), 7.18 to 7.47 (24H, m, aromatic CH); δ_C (125MHz; $CDCl_3$) 12.90 (br s , CD_2CH_2 partially overlapping CD_2CH_2 quintet), 18.15 (CCH_3), 18.81 (CCH_3), 21.13, 31.81, 34.19, 35.32 ($CH(CH_2)_3CONH$ and $CH_2SCH(C_6H_5)_2$), 52.09, 53.65, 54.57 (adipoyl αCH, cysteinyl αCH, $SCH(C_6H_5)_2$), 55.25 ($CH_2(C_6H_4)OCH_3$), 58.46 (t, J_{CD} 24Hz, CDNH), 66.68 and 66.96 ($CH_2(C_6H_4)OCH_3$), 78.09 ($CO_2CH(C_6H_5)_2$), 113.98, 114.07, 127.04, 127.39, 127.53, 127.98, 128.07, 128.38, 128.48, 128.57, 128.68, 129.91, 130.09 (aromatic), 139.54, 139.79, 141.81, 141.13, 156.15, 159.65, 159.85, 169.84, 170.01 (quaternary), 172.04 and 172.56 (CO_2 esters); *m/z* (fast atom bombardment, +ve Argon) 1017 (MNa^+, 100%), 995 (MH^+, 61).

To a stirred solution of (*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteinyl-[(2*R*,1'*S*)-(2-^{2}H)-2-(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine] benzhydryl ester (22mg, 0.02mmol) in distilled trifluoroacetic acid (1ml), was added distilled anisole (0.1ml) and the reaction

was heated to 50°C for 30 minutes. The reaction was then allowed to cool to room temperature, concentrated *in vacuo* and azeotroped with tetrachloromethane (5 x 1ml). The resulting white solid was dissolved in water (10ml) and washed with ethyl acetate (3 x 10ml). The aqueous layer was concentrated *in vacuo* and lyophilised to afford *δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'S)-(2-^{2}H)-2-[(1'-methyl-(2',2'-$^2H_2$) cyclopropyl)glycine] (9).*as the trifluoroacetate salt (6mg, 72%), ν_{max} (FT IR, KBr disc) 2967br s, 1674s, 1535m, 1433m, 1139s, 841m, 800m and 724m cm^{-1}; δ_H (200MHz; D_2O) 0.22 and 0.33 (2H, AB, J_{AB} 5Hz, CH_2CD_2), 0.84 (3H, s, CCH_3), 1.51 to 1.82 (4H, m, $(CH_2)_2CH_2CONH$), 2.16 to 2.25 (2H, m, $(CH_2)_2CH_2CONH$), 2.65 to 2.70 (2H, m, CH_2SH), 3.77 (1H, t, *J* 6Hz, αCH), 4.36 (1H, t, *J* 6Hz, αCH); δ_C (125MHz; D_2O) 11.57 (br s , CH_2CD_2 partially overlapping CH_2CD_2 quintet), 18.17 (CCH_3), 20.18 (CCH_3), 21.66, 30.58, 35.55, 39.74 (4 x CH_2), 53.39 and 55.22 (2 x αCH),171.60, 175.06, 176.52 and 177.61 (2 x CONH, 2 x CO_2) αCDNH triplet too weak to be observed; *m/z* (fast atom bombardment, +ve Argon) 379 (MH^+, 100%).

Synthesis of δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'R)-(2-^{2}H)-2-[(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl) glycine] (10).

The trifluoroacetate salt of *δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'R)-(2-^{2}H)-2-[(1'-methyl-(2',2'-$^2H_2$)-cyclopropyl)glycine] (10)* was synthesised in an analogous fashion from (*R*)-2-hydroxy-2-methylbutanedioic acid (*R*-citramalic acid). δ_H (500MHz; D_2O) 0.18 and 0.34 (2H, AB, J_{AB} 4.5Hz, CH_2CD_2), 0.85 (3H, s, CCH_3), 1.49 to 1.77 (4H, m, $(CH_2)_2CH_2CONH$), 2.22 to 2.26 (2H, m, $(CH_2)_2CH_2CONH$), 2.66 to 2.75 (2H, m, CH_2SH), 3.66 (1H, t, *J* 6Hz, αCH), 4.34 (1H, t, *J* 6Hz, αCH).

Synthesis of (Z)-(3-^{2}H)-2-methylprop-2-en-1-ol (23).[18, 19]

To a stirred solution of anhydrous propargyl alcohol (5.0g, 4.75ml, 0.09mol) in anhydrous THF (150ml) under an inert atmosphere of argon, was added copper (I) iodide (1.9g, 0.01mol) and the resulting pink suspension was cooled to -78°C. Methylmagnesium bromide (*c.* 0.25mol), which had been freshly prepared from methyl bromide (15ml) and magnesium (6.5g, 0.27mol), in anhydrous THF (250ml) was then added *via* cannula, at such a rate as to maintain the temperature below -60°C. The resulting grey suspension was allowed to warm slowly to room temperature over 18 hours. The reaction was again cooled to -78°C and treated with D_2O (10ml) to give a light green suspension. It was then allowed to warm slowly to room temperature over 3 hours, during which time it became grey in colour. The resulting suspension was transferred to a separating funnel and treated with an equivalent volume of ether (*c.* 500ml) followed by 1M hydrochloric acid (50ml) which caused the formation of a green gelatinous precipitate which was thoroughly extracted with ether (3 x 100ml). The combined organic phases were washed with 1M HCl (3 x 150ml) and the acid layers back-extracted with ether. The combined organic layers were then dried ($MgSO_4$, Na_2CO_3), filtered and the solvent removed by fractional distillation. The residue was then distilled through a short path distillation apparatus to afford (Z)-(3-^{2}H)-2-methylprop-2-en-1-ol (**23**) (4.8g, 74%), b. p. 114-116°C (ambient pressure), (lit. [18, 19] 112°C, 760 mmHg), (R_f 0.1, petroleum ether 30-40: ether; 95: 5); ν_{max} (FT IR, NaCl plates, liquid film) 3338br s (OH), 3042s, 1640m, 1448s 1070s, 1013s and 829s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.76 (4H, br s, CH_3 and OH), 4.05 (2H, s, CH_2OH), 4.85 (1H, br s, CHD); δ_C (50MHz, $CDCl_3$) 18.78 (CH_3), 66.23 (CH_2OH), 109.37 (t, J_{CD} 29Hz, CHD), 144.90 (CCH_3); *m/z* (electron impact) 73 (M^+, 41%), 58 (100).

Synthesis of (Z)-(3-^{2}H)-1-tert-butyldiphenylsilyloxy-2-methylprop-2-ene (24).

To a stirred solution of (Z)-(3-^{2}H)-2-methylprop-2-en-1-ol (**23**) (5.0g, 0.07mol) in anhydrous dimethylformamide (40ml) under an inert atmosphere of argon, were added *tert*-butyldiphenylsilyl chloride (28.9g, 0.11mol) and imidazole (14.3g, 0.21mol) and the reaction stirred at room temperature for 24 hours. The mixture was then extracted with pentane: ether (1: 1, 200ml) and the combined organic phases washed with 1M hydrochloric acid (50ml), saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml) then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a colourless oil. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 95: 5) afforded *(Z)-(3-^{2}H)-1-tert-butyldiphenylsilyloxy-2-methylprop-2-ene (24)* as a colourless oil (21.3g, quantitative), (Found: C, 77.0; H, 8.65. $C_{20}H_{25}DOSi$ requires C, 77.1; H, 8.4%); R_f 0.6 (petroleum ether 30-40: ether; 95: 5); ν_{max} (FT IR, NaCl plates, liquid film) 3071m, 2932s, 2858s, 1428s, 1113s, 999m, 826s and 702s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.09 (9H, s, $SiC(C\underline{H}_3)_3$), 1.70 (3H, br s, $CC\underline{H}_3$), 4.10 (2H, s, $C\underline{H}_2O$), 4.87 (1H, br s, C<u>H</u>D), 7.40 to 7.46 (6H, m, $SiC_6\underline{H}_5$), 7.70 to 7.74 (4H, m, $SiC_6\underline{H}_5$); δ_C (50MHz; $CDCl_3$) 18.86 ($C\underline{C}H_3$), 19.18 ($Si\underline{C}(CH_3)_3$), 26.72 ($SiC(\underline{C}H_3)_3$), 67.23 ($\underline{C}H_2O$), 108.99 (t, J_{CD} 29Hz, <u>C</u>HD), 127.83, 129.79, 133.91, 135.71 ($\underline{C}_6H_5$), 144.32 ($\underline{C}CH_3$); *m/z* (chemical ionisation, NH_3) 329 (MNH_4^+, 14%), 312 (MH^+, 30), 254 (63), 196 (100).

Synthesis of (±)-(1'R,3'R*)-1-tert-butyldiphenylsilyloxy-1-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl) methane (25).*

To a stirred solution of (Z)-(3-^{2}H)-1-*tert*-butyldiphenylsilyloxy-2-methylprop-2-ene (**24**) (6.22g, 0.02mol) in anhydrous pentane (100ml), cooled to 0°C, under an inert atmosphere of argon, potassium *tert*-butoxide (5.56g, 0.024mol) was added. Bromoform (1.92ml, 0.022mol) was then added dropwise and the reaction stirred for 1 hour at 0°C then for 1 hour at room temperature. This sequential addition of potassium *tert*-butoxide (5.56g, 0.024mol) and bromoform (1.92ml, 0.022mol) was repeated a further four times and the reaction was finally stirred at room temperature for 16 hours. The reaction mixture was then extracted into pentane: ether (1: 1, 250ml), washed thoroughly with water (3 x 100ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(±)-(1'R*,3'R*)-1-tert-butyldiphenylsilyloxy-1-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl) methane (25)* as a orange oil (8.57g, 89%), (Found: C, 52.0; H, 5.05. $C_{21}H_{25}Br_2DOSi$ requires C, 52.2; H, 5.2%), (R_f 0.3, petroleum ether 30-40: ether; 99: 1); ν_{max} (FT IR, NaCl plates, liquid film) 2960s, 2858s, 1472s, 1428s, 1113s, 960m, 888s and 702s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.11 (9H, s, $SiC(C\underline{H}_3)_3$), 1.38 (1H, s, C<u>H</u>D), 1.52 (3H, s, $CC\underline{H}_3$), 3.78 (2H, s, $C\underline{H}_2O$), 7.40 to 7.43 (6H, m, $Si(C_6\underline{H}_5)$), 7.67 to 7.72 (4H, m, $Si(C_6\underline{H}_5)_2$); δ_C (50MHz; $CDCl_3$) 19.20 ($Si\underline{C}(CH_3)_3$), 20.89 ($C\underline{C}H_3$), 26.74 ($SiC(\underline{C}H_3)_3$), 30.93 ($\underline{C}CH_3$), 32.01 (t, J_{CD} 30Hz, <u>C</u>HD), 35.85 ($\underline{C}Br_2$), 69.87 ($\underline{C}H_2O$), 127.83, 129.90, 133.61 and 135.76 ($Si\underline{C}_6H_5$); *m/z* (chemical ionisation, NH_3) 503, 501, 499 (MNH_4^+, 18, 30, 16%), 486, 484, 482 (MH^+, 9, 22, 11), 404 (24), 280 (33), 256 (100), 196 (25), 144 (34).

Synthesis of (±)-(1'R,3'R*)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanol (26).*

To a stirred solution of (±)-(1'*R**,3'*R**)-1-*tert*-butyldiphenylsilyloxy-1-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methane (**25**) (23.5g, 0.05mol) in anhydrous THF (100ml), under an inert atmosphere of argon, was added tetrabutylammonium fluoride (1M in THF, 100ml, 0.1mol) dropwise over 10 minutes during which time the reaction mixture turned dark brown. The reaction was stirred at room temperature for 1 hour then concentrated *in vacuo* to yield a black oil. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 50: 50) afforded *(±)-(1'R*,3'R*)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanol (26)* as a yellow solid (11.5g, 97%), m. p. 66-67°C (pentane, ether), (Found: C, 24.4; H, 3.0. $C_5H_7Br_2DO$ requires C, 24.5; H ,

3.3%); (R_f 0.3, petroleum ether 30-40: ether; 1: 1); ν_{max} (FT IR, KBr disc) 3255br s (OH), 1457m, 1020s and 881s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.47 (1H, s, C<u>H</u>D), 1.53 (3H, s, C<u>H</u>$_3$), 1.85 (1H, br s, O<u>H</u>), 3.72 and 3.88 (2H, AB, J_{AB} 12Hz, C<u>H</u>$_2$O); δ_C (50MHz; $CDCl_3$) 20.46 (<u>C</u>H$_3$), 31.20 (<u>C</u>CH$_3$), 32.20 (t, J_{CD} 30Hz, <u>C</u>HD), 35.71 (<u>C</u>Br$_2$), 69.58 (<u>C</u>H$_2$OH); *m/z* (chemical ionisation, NH_3) 265, 263, 261 (MNH_4^+, 48, 100, 54%), 247, 245, 243 (M^+,4, 8, 3), 186 (33).

Synthesis of (±)-(1'R,3'R*)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanal (27).*

To a stirred suspension of freshly prepared pyridinium chlorochromate[28] (5.32g, 24.6mmol) in anhydrous CH_2Cl_2 (100ml), under an inert atmosphere of argon, was added (±)-(1'*R**,3'*R**)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanol (**26**) (4.0g, 16.4mmol) as a solution in CH_2Cl_2 (20ml). The reaction slowly turned black and was stirred at room temperature for two hours. After this time further pyridinium chlorochromate (5.32g, 24.6mmol) was added and the reaction stirred for a further two hours. Anhydrous ether (100ml) was added to precipitate the chromium residues and the supernatant was decanted off the black gum. This was then thoroughly washed with ether (2 x 100ml) whereupon it became a black granular solid. The combined organic extracts were then filtered through a pad of Florisil® and the solvent removed *in vacuo* to afford *(±)-(1'R*,3'R*)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanal (27)* as a pale yellow oil (3.5g, 88%), (Found: C, 25.1; H, 2.6. $C_5H_5Br_2DO$ requires C, 24.8; H, 2.5%), (R_f 0.6, petroleum ether 30-40: ether; 1: 1); ν_{max} (FT IR, KBr disc) 3500-2000br m, 1755m (aldehyde C=O), 1622m, 1402s and 1134m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.55 (3H, s, C<u>H</u>$_3$), 1.84 (1H, s, C<u>H</u>D), 9.30 (1H, s, C<u>H</u>O); δ_C (50MHz; $CDCl_3$) 18.80 (<u>C</u>CH$_3$), 20.38 (<u>C</u>H$_3$), 28.15 (<u>C</u>Br$_2$), 32.04 (t, J_{CD} 30Hz, <u>C</u>HD), 198.8 (<u>C</u>=O); *m/z* (chemical ionisation, NH_3) 246, 244, 242 (MH^+, 49, 100, 53).

Synthesis of (±)-(2R,1'S*,3'S*)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (28) (major isomer) and (±)-(2R*,1'R*,3'R*)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (29) (minor isomer).*

To a stirred solution of (±)-(1'*R**,3'*R**)-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)methanal (**27**) (4.17g, 0.017 mol) in anhydrous CH_2Cl_2 (100ml) containing freshly activated 4Å molecular sieves (5g) under an inert atmosphere of argon, was added 4, 4'-*bis*methoxybenzhydrylamine (4.17g, 0.017mol) and the reaction stirred for 90 minutes at room temperature. Trimethylsilylcyanide (2.4ml, 0.019mol) was then added and stirring was continued for a further 90 minutes. The reaction mixture was then filtered and concentrated *in vacuo* to yield a yellow oil which was combined with 6<u>M</u> hydrochloric acid (300ml) and stirred under reflux for 18 hours to afford a brown syrupy solution. This was allowed to cool to room temperature, washed with CH_2Cl_2 (3 x 150ml), then concentrated *in vacuo* and lyophilised to afford a mixture of *(±)-(2R*,1'S*,3'S*)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (28)* and *(±)-(2R*,1'R*,3'R*)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (29)* (85: 15 mixture) as an orange solid (4.8g, 87%), m. p. 230°C (dec.), (ethanol, water); ν_{max} (FT IR, KBr disc), 3255m, 1755m (C=O), 1622 m, 1402s and 1134m cm^{-1}; δ_H (200MHz; D_2O, pH 1) 1.22 (3H, s, major and minor C<u>H</u>$_3$), 1.87 (1H, s, minor C<u>H</u>D), 1.92 (1H, s, major C<u>H</u>D), 3.82 (1H, s, major C<u>H</u>CO$_2$), 4.02 (1H, s, minor C<u>H</u>CO$_2$); δ_C (50MHz; D_2O) 17.88 (<u>C</u>H$_3$), 28.79 (<u>C</u>CH$_3$), 33.87 (<u>C</u>Br$_2$), 34.24 (t, J_{CD} 25Hz, <u>C</u>HD), 60.54 (<u>C</u>HCO$_2$), 171.18 (<u>C</u>O$_2$H); *m/z* (desorption chemical ionisation, NH_3) 291, 289, 287 (amino acid H^+, 51, 100, 50%), 243 (22), 163 (16), 101 (85), 83 (80).

Synthesis of (±)-(2R*,1'S*,3'S*)-N-tert-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl) glycine (30) and (±)-(2R*,1'R*,3'R*)-N-tert-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl) glycine (31).

(±)-(2*R**,1'*S**,3'*S**)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (**28**) and (±)-(2*R**,1'*R**,3'*R**)-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine hydrochloride (**29**) (85: 15 mixture) were converted to the corresponding free amino acids by chromatography on Dowex® 50-X8 cation-exchange resin (H^+ form, 2M NH_3 eluent). To a stirred solution of these amino acids (0.4g, 1.4mmol) in 1,4-dioxan: water (1: 1, 20ml) cooled to 0°C, 1M NaOH (1.4ml) was added followed by di-*tert*-butyl dicarbonate (0.4g, 1.82mmol) as a solution in 1, 4-dioxan (2ml) and the reaction stirred at room temperature for 3 hours. The reaction mixture was then concentrated *in vacuo* almost to dryness then diluted with water (10ml) and ethyl acetate (10ml) and acidified to pH 3 with aqueous 1M potassium hydrogen sulphate. The aqueous phase was further extracted with ethyl acetate (2 x 10ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a yellow solid. Flash chromatography (SiO_2, petroleum ether 30-40: ether: acetic acid; 74: 24: 2) enabled separation of diastereomers affording*(±)-(2R*,1'S*,3'S*)*-N-tert-*butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine (30)* as a white solid (0.42g, 79%), m. p. 162-164°C (pentane, ether), (Found: C, 33.9; H, 4.1; N, 3.4. $C_{11}H_{16}Br_2DNO_4$ requires C, 34.05; H, 4.4; N, 3.6%); (R_f 0.2, petroleum ether 30-40: ether: acetic acid; 74: 24: 2); ν_{max} (FT IR, KBr disc) 3314m (NH), 1708s (acid C=O), 1649s (carbamate C=O), 1478m, 1272s, 1094s, 1028s, 880m and 782s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.46 (3H, s, CCH_3), 1.48 (9H, s, $C(CH_3)_3$), 1.62 (1H, s, CHD), 4.34 (1H, br d, *J* 7.5Hz, $CHCO_2H$), 5.17 (1H, br d, *J* 7.5Hz, NH); δ_C (125MHz; $CDCl_3$) 19.50 (CCH_3), 28.31 ($C(CH_3)_3$), 30.37 (CCH_3), 33.96 (CBr_2), 34.35 (t, J_{CD} 24Hz, CHD), 59.98 (CHNH), 81.03 ($C(CH_3)_3$), 157.24 (CONH), 174.86 (CO_2H); *m/z* (desorption chemical ionisation, NH_3) 408, 406, 404 (MNH_4^+, 15, 31, 17%), 391, 389, 387 (MH^+, 7, 13, 6), 333 (M-$C(CH_3)_3$, 65), 289 (100), 83 (90), 57 (75);
and *(±)-(2R*,1'R*,3'R*)*-N-tert-*butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine (31)* as a white solid (50mg, 9%), m. p. 160-163°C (pentane, ether), (Found: C, 34.15; H, 4.55; N, 3.55. $C_{11}H_{16}Br_2DNO_4$ requires C, 34.05; H, 4.4; N, 3.6%), (R_f 0.3, petroleum ether 30-40: ether: acetic acid; 74: 24: 2); ν_{max} (FT IR, KBr disc) 3313m (NH), 3100m, 2992m, 2501m, 1708s (acid C=O), 1651s (carbamate C=O), 1416m, 1272s, 1093s, 1047s, 968m, 866m and 782s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.36 (3H, s, CCH_3), 1.44 (1H, s, CHD), 1.48 (9H, s, $C(CH_3)_3$), 4.78 (1H, br d, *J* 8Hz, $NHCHCO_2H$), 5.17 (1H, br d, *J* 8Hz, CHNH), *m/z* (fast atom bombardment, +ve Argon) 408, 406, 404, (MNH_4^+, 20, 40, 22%), 391, 389, 387 (MH^+, 11, 19, 10%), 333 ($M\text{-}C(CH_3)_3^+$, 100), 289 (60), 253 (31), 103 (47), 57 (76).

Synthesis of (±)-(2R,1'R*,3'R*)*-N-tert-*butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (32).*

To a stirred solution of (±)-(2*R**,1'*S**,3'*S**)-*N-tert*-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine (**30**) (0.10g, 0.25mmol) in acetonitrile (5ml), was added diphenyldiazomethane (0.063g, 0.32mmol) as a solution in acetonitrile (2ml) and the reaction was stirred at room temperature for 3 hours. Acetic acid (0.1ml) was then added to the reaction and stirring was continued for a further 30 minutes. The solution was then concentrated *in vacuo* to yield a yellow solid. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(±)-(2R*,1'S*,3'S*)*-N-tert-*butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine benzhydryl ester* as a white solid (0.11g, 77%), m. p. 128-129°C (pentane, ether), (Found: C, 51.7; H, 4.6; N, 2.7. $C_{24}H_{26}Br_2DNO_4$ requires C, 52.0; H, 4.9; N, 2.5%); (R_f 0.3, petroleum ether 30-40: ether; 70: 30); ν_{max} (FT IR, KBr disc) 3322m (NH), 2975w, 1737m (ester C=O), 1689s (carbamate C=O), 1536s, 1369m, 1161s, 961m and 701s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.25 (3H, s, CCH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.52 (1H, s, CHD), 4.46 (1H, d, *J* 8Hz, CHNH), 5.13 (1H, br d, *J* 8Hz, CHNH), 6.96 (1H, s, $CH(C_6H_5)_2$), 7.35 (10H, br s, $CH(C_6H_5)_2$); δ_C (125MHz; $CDCl_3$) 19.82 (CCH_3), 28.30 ($C(CH_3)_3$), 30.63

(CCH_3), 34.01 (CBr_2), 34.38 (t, J_{CD} 25Hz, CHD), 60.15 (CHNH), 78.58 (C$H(C_6H_5)_2$), 80.51 (C$(CH_3)_3$), 127.05, 127.51, 128.09, 128.21, 128.50, 128.54, 139.38, 139.61 ($CO_2CH(C_6H_5)_2$), 154.5 (CONH), 169.79 ($CO_2CH(C_6H_5)_2$); *m/z* (desorption chemical ionisation, NH_3) 574, 572, 570 (MNH_4^+, 11, 23, 12%), 557, 555, 553 (MH^+, 35, 75, 36), 343 (30), 167 (100).

To a stirred solution of (±)-(2*R**,1'*S**,3'*S**)-*N-tert*-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine benzhydryl ester (55mg, 0.1mmol) in anhydrous benzene (5ml) under an inert atmosphere of argon, was added triphenyltin (^{2}H)-hydride[30-32] (106mg, 0.3mmol) followed by AIBN (*ca.* 1mg). The mixture was heated under reflux for 1 hour, then concentrated *in vacuo* to afford a yellow solid. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(±)-(2*R**,1'*R**,3'*R**)*-N-tert-*butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (32)* (35mg, 89%) as a colourless oil which could be crystallised; m. p. 107-109°C (pentane, ether), (Found: C, 72.15; H, 7.3; N, 3.2. $C_{24}H_{26}D_3NO_4$ requires C, 72.35; H, 7.35; N, 3.5%); (R_f 0.3, petroleum ether 30-40: ether; 90: 10); ν_{max} (FT IR, KBr disc) 3443m (NH), 3035m, 2981m, 1715m , 1709s , 1588s, 1369m, 1251s, 1157s, 1054m, 984m and 645m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.43 (1H, s, CHD), 0.86 (3H, s, CCH_3), 1.45 (9H, s, C(CH_3)$_3$), 3.84 (1H, br d, *J* 8Hz, CHNH), 5.26 (1H, br d, *J* 8Hz, CHNH), 6.94 (1H, s, C$H(C_6H_5)_2$), 7.35 (10H, br s, CH(C_6H_5)$_2$); δ_C (125MHz; $CDCl_3$) 11.29 (quintet, J_{CD} 25Hz, CD_2), 12.20 (t, J_{CD} 25Hz, CHD), 18.38 (CCH_3), 20.00 (CCH_3), 28.32 (C(CH_3)$_3$), 60.41 (CHNH), 77.91 (C$H(C_6H_5)_2$), 79.80 (C$(CH_3)_3$), 127.14, 127.38, 128.00, 128.40, 128.48, 139.81, 139.97 ($CO_2CH(C_6H_5)_2$), 155.39 (CONH), 170.78 ($CO_2CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 421 (MNa^+, 42%), 399 (MH^+, 12), 351 (20), 167 (100), 131 (12), 87 (15), 57 (37).

*Synthesis of (±)-(2*R**,1'*R**,3'*R**)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (33).*

To a stirred solution of (±)-(2*R**,1'*R**,3'*R**)-*N-tert*-butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (**32**) (150mg, 0.37mmol) in ether (3ml), cooled to 0°C, was added *p*-toluenesulphonic acid monohydrate (140mg, 0.74mmol) as a solution in ethanol (3ml) and the reaction was stirred at room temperature for 1 hour. The mixture was then concentrated *in vacuo*, redissolved in ether: ethanol (1: 1, 5ml) and concentrated *in vacuo*. This procedure was repeated a further five times before TLC demonstrated that no starting material remained. The resulting white solid was then suspended in ethyl acetate (20ml) and washed with saturated aqueous $NaHCO_3$ (20ml). The aqueous layer was back-extracted with ethyl acetate (2 x 20ml) and the combined organic layers dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford *(±)-(2*R**,1'*R**,3'*R**)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (33)* as a pale yellow oil (113mg, quantitative), which was sufficiently pure (>95% by ^{1}H NMR) to be used directly in the following reaction; ν_{max} (FT IR, liquid film, NaCl plates) 3855w and 3712w (NH_2), 3032w, 2956w, 1737s (ester C=O), 1469m, 1455m, 1162s, 975m, 700s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.48 (1H, s, CHD), 0.89 (3H, s, CH_3), 1.63 (2H, s, CHNH_2), 2.91 (1H, s, CHNH_2), 6.95 (1H, s, C$H(C_6H_5)_2$), 7.35 (10H, br s, CH(C_6H_5)$_2$); δ_C (125MHz; $CDCl_3$) 10.70 to 11.16 (multiplet, J_{CD} 25Hz, CD_2), 12.34 (t, J_{CD} 25Hz, CHD), 17.84 (CCH_3), 19.73 (CH_3), 61.95 (CHNH_2), 77.47 (C$H(C_6H_5)_2$), 127.19, 127.26, 127.94, 128.43, 128.51, 140.16, 140.23 ($CO_2CH(C_6H_5)_2$), 173.44 ($CO_2CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 299 (MH^+, 7%), 167 ($CH(C_6H_5)_2^+$, 100), 87 (15).

Synthesis of δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'R,3'R)-3-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl) glycine] (11).

To a stirred solution of (±)-(2*R**,1'*R**,3'*R**)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (**33**) (93mg, 0.31mmol) in anhydrous CH_2Cl_2 (1ml), under an inert atmosphere of argon, was added δ-(*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteine[16]

(221mg, 0.31mmol) as a solution in anhydrous CH_2Cl_2 (3ml). 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (74mg, 0.31mmol) and Na_2SO_4 (30mg) were then added, and the mixture stirred at room temperature for 24 hours. The reaction was then filtered and concentrated *in vacuo* to afford an orange gum. This was dissolved in ethyl acetate (20ml), washed with 1M HCl (20ml), saturated aqueous $NaHCO_3$ (20ml) and water (20ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a white foam (232mg, 75%). Flash chromatography (SiO_2, petroleum ether 30-40: ether; 20: 80) enabled separation of the more polar LLL and less polar LLD diastereomers affording *(N-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-S-benzhydryl-L-cysteinyl-[(2R,1'R,3'R)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] benzhydryl ester* as a white foam (126mg, 40%), (R_f 0.3, less polar isomer, petroleum ether 30-40: ether; 20: 80); ν_{max} (FT IR, KBr disc) 3401br s, 3033w, 2926w, 1737s, 1718s, 1648s, 1516s, 1438m, 1303m, 1032s and 747s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.43 (1H, s, CHD), 0.89 (3H, s, CH_3), 1.54 to 1.72 (4H, m, $(CH_2)_2CH_2CONH$), 2.12 to 2.32 (2H, m, $(CH_2)_2CH_2CONH$), 2.72 (1H, A of ABX, J_{AB} 13Hz, J_{AX} 6Hz, 1xSCH_2), 2.83 (1H, B of ABX, J_{AB} 13Hz, J_{BX} 6Hz, 1xSCH_2), 3.79 (6H, s, 2 x $C_6H_4OCH_3$), 3.98 (1H, d, *J* 8Hz, αCHNH), 4.32 to 4.40 (1H, m, αCHNH), 4.49 to 4.53 (1H, m, αCHNH), 5.02 (2H, s) and 5.08 (2H, s, 2 x $OCH_2C_6H_4OCH_3$), 5.27 (1H, s, $SCH(C_6H_5)_2$), 5.44 (1H, d, *J* 7Hz, NH), 6.21 (1H, d, *J* 7Hz, NH), 6.83 to 6.89 (6H, m, NH, $CO_2CH(C_6H_5)_2$, *o*-H of $C_6H_4OCH_3$), 7.21 to 7.46 (24H, m, aromatic CH); δ_C (125MHz; $CDCl_3$) 12.80 to 13.21 (br m, CD_2CHD and CD_2CHD), 18.15 (CCH_3), 18.78 (CH_3), 21.34, 31.84, 34.16, 35.26 ($CH(CH_2)_3CONH$ and $CH_2SCH(C_6H_5)_2$), 52.03, 53.60, 54.57 (2 x αCHNH, and $SCH(C_6H_5)_2$), 55.28 (2 x $CH_2(C_6H_4)OCH_3$), 59.39 (αCHNH), 66.68 and 67.03 (2 x $CH_2(C_6H_4)OCH_3$), 78.10 ($CO_2CH(C_6H_5)_2$), 113.95, 114.04, 127.05, 127.39, 128.03, 128.38 128.44, 128.53, 128.68, 129.91, 130.09 (aromatic), 139.63, 139.73, 141.83, 141.09, 156.16, 159.64, 159.88, 169.84, 170.11 (quaternary), 172.14 and 172.55 (CO_2 esters); *m/z* (fast atom bombardment, +ve Argon) 995 (MH^+, 94%), 952 (100).

To a stirred solution of (*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteinyl-[(2*R*,1'*R*,3'*R*)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] benzhydryl ester (12mg, 0.01mmol) in trifluoroacetic acid (1ml), distilled anisole (0.1ml) was added and the reaction was heated to 50°C for 30 minutes. The reaction was then concentrated *in vacuo* and azeotroped with distilled toluene. The resulting white solid was dissolved in water (10ml) and washed with ethyl acetate (3 x 10ml). The aqueous layer was concentrated in vacuo then lyophilised to afford *δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'R,3'R)-3-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] (11)* as the trifluoroacetate salt (*ca.* 3mg); ν_{max} (FT IR, KBr disc) 2967br s, 1674s, 1535m, 1433m, 1139s, 841m, 800m and 724m cm^{-1}; δ_H (200MHz; D_2O) 0.27 (1H, s, CHD), 0.83 (3H, s, CH_3), 1.46 to 1.74 (4H, m, $(CH_2)_2CH_2CONH$), 2.13 to 2.21 (2H, m, $(CH_2)_2CH_2CONH$), 2.64 to 2.68 (2H, m, CH_2SH), 3.57 (1H, s, αCH), 3.70 (1H, t, *J* 4Hz, αCH), 4.36 (1H, t, *J* 6Hz, αCH); δ_C (125MHz; D_2O) 12.31 to 12.90 (m, CD_2CHD and CD_2CHD), 17.75 (CCH_3), 19.70 (CH_3), 21.70, 30.56, 35.53, 39.72 (4 x CH_2), 53.30, 55.12 and 55.12 (3 x αCH),172.36, 175.00, 176.57 and 177.74 (2 x CONH, 2 x CO_2), *m/z* (fast atom bombardment, +ve Argon) 379 (MH^+, 100%).

Synthesis of δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'S,3'S)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine (12) from (31).

Synthesis of (±)-(2R,1R*,3'R*)-*N-tert-*butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^2H)-cyclopropyl) glycine benzhydryl ester.*

To a stirred solution of (±)-(2*R**,1'*R**,3'*R**)-*N-tert*-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^2H)-cyclopropyl)glycine (**31**) (0.18g, 0.47mmol) in acetonitrile (5ml), diphenyldiazomethane (0.11g, 0.56mmol) was added as a solution in acetonitrile (2ml) and the reaction was stirred at room temperature for 2 hours. Acetic acid (0.1ml) was then added to the reaction and stirred for a further 30 minutes. The solution was then concentrated *in vacuo* to yield a yellow solid. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90:

10) afforded *(±)-(2R*,1'R*,3'R*)*-N-tert-*butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl) glycine benzhydryl ester* (0.21g, 82%), m. p. 128-130 °C (pentane, ether); (Found: C, 51.85; H, 4.75; N, 2.35. $C_{24}H_{26}Br_2DNO_4$ requires C, 52.0; H, 4.9; N, 2.5%); (R_f 0.3, petroleum ether 30-40: ether; 70: 30); ν_{max} (FT IR, KBr disc) 3323m (NH), 2975w, 1737m (C=O, $CO_2CH(C_6H_5)_2$), 1688s (C=O, CONH), 1456s, 1352m, 1025s, 961m, 764 and 701s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.04 (3H, s, CCH_3), 1.38 (1H, s, CHD), 1.44 (9H, s, $C(CH_3)_3$), 4.82 (1H, d, *J* 8 Hz, CHNH), 5.44 (1H, br d, *J* 8Hz, CHNH), 7.02 (1H, s, $CH(C_6H_5)_2$), 7.40 (10H, br s, $CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 579, 577, 575 (MNa^+, 31, 65, 33%), 499, 497, 495 (22), 167 ($(C_6H_5)_2CH^+$), 100), 57 ($C(CH_3)_3^+$).

Synthesis of (±)-(±)-(2R,1'S*,3'S*)*-N-tert-*butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester.*

To a stirred solution of (±)-(2*R**,1'*R**,3'*R**)-*N-tert*-butyloxycarbonyl-2-(2',2'-dibromo-1'-methyl-(3'-^{2}H)-cyclopropyl)glycine benzhydryl ester (167mg, 0.3mmol) in anhydrous degassed benzene (20ml) under an inert atmosphere of argon, triphenyltin (^{2}H)-hydride[30-32] (317mg, 0.9mmol) was added in one portion followed by AIBN (2mg) and the reaction stirred under reflux for two hours. The reaction was then concentrated *in vacuo*. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 90: 10) afforded *(±)-(2R*,1'S*,3'S*)*-N-tert-*butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester* (120mg, quantitative) as a colourless oil which could be crystallised; m.p. 108-111°C (pentane, ether), (Found: C, 72.15; H, 7.25; N, 3.2. $C_{24}H_{26}D_3NO_4$ requires C, 72.35; H, 7.35; N, 3.5%); (R_f 0.3, petroleum ether 30-40: ether; 90: 10); ν_{max} (FT IR, KBr disc) 3443m (NH), 3035m, 2979m, 1713s, 1709s , 1610s, 1457m, 1249m, 1156m, 990m, 766m and 642m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.34 (1H, s, CHD), 0.86 (3H, s, CCH_3), 1.45 (9H, s, $C(CH_3)_3$), 3.84 (1H, d, *J* 8Hz, CHNH), 5.26 (1H, br d, *J* 8Hz, CHNH), 6.94 (1H, s, $CH(C_6H_5)_2$), 7.40 (10H, br s, $CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 421 (MNa^+, 23%), 399 (MH^+, 10), 167 (100), 57 (34).

Synthesis of (±)-(2R,1'S*,3'S*)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester.*

To a stirred solution of (±)-(2*R**,1'*S**,3'*S**)-*N-tert*-butyloxycarbonyl-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (120mg, 0.3mmol) in ether (5ml) and ethanol (5ml), cooled to 0°C, *p*-toluenesulphonic acid (144mg, 0.6mmol, 2.0 equivalents) was added as a solution in ethanol (5ml) and the reaction was then stirred at room temperature for 30 minutes. The reaction was then concentrated *in vacuo*, redissolved in ether: ethanol (2: 1, 15ml) and concentrated *in vacuo*. This procedure was repeated a further six times before TLC demonstrated that no starting material remained. The resulting white solid was then suspended in ethyl acetate (20ml), washed with saturated aqueous $NaHCO_3$ (10ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford *(±)-(2R*,1'S*,3'S*)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester* as a yellow oil (83mg, 92%), ν_{max} (FT IR, liquid film, NaCl plates) 3843w and 3722w (NH_2), 3031w, 2945w, 1735s (C=O, $CO_2CH(C_6H_5)_2$), 1564m, 1452m, 1324w, 1140m, 974m, 942m and 802s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.36 (1H, s, CHD), 0.89 (3H, s, CCH_3), 1.61 (2H, s, $CHNH_2$), 2.91 (1H, s, $CHNH_2$), 6.95 (1H, s, $CH(C_6H_5)_2$), 7.35 (10H, br s, $CH(C_6H_5)_2$); *m/z* (fast atom bombardment, +ve Argon) 299 (MH^+, 15%), 167 ($CH(C_6H_5)_2^+$, 100), 87 (19).

Synthesis of (N-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-S-benzhydryl-L-cysteinyl-[(2R,1'S,3'S)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] benzhydryl ester.

To a stirred solution of (±)-(2*R**,1'*S**,3'*S**)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine benzhydryl ester (83mg, 0.3mmol) in anhydrous CH_2Cl_2 (5ml), under an inert atmosphere of argon, [[N-4-methoxybenzyloxycarbonyl]-α-[4-methoxybenzyl]-δ-(L-α-aminoadipoyl)]-S-benzhydryl-L-cysteine[16] (214mg, 0.3mmol) was added. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (74mg, 0.3mmol) and Na_2SO_4 (30mg) were then added, and the reaction was stirred at room temperature for 20 hours. The reaction was then filtered, and concentated *in vacuo* to afford an orange gum. The gum was then dissolved in ethyl acetate (20ml), and washed with 1M HCl (10ml), saturated aqueous $NaHCO_3$ (10ml), water (10ml) and brine (10ml) then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a white foam. Flash chromatography (SiO_2, petroleum ether 30-40: ether; 10: 90) enabled separation of the more polar LLL and less polar LLD diastereomers affording *(N-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-S-benzhydryl-L-cysteinyl-[(2R,1'S,3'S)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] benzhydryl ester* (140mg 51%), (R_f 0.3, petroleum ether 30-40: ether; 80: 20); ν_{max} (FT IR, KBr disc) 3420br s, 3035w, 2940w, 1736s, 1718s, 1647s, 1488m, 1350m, 1143m, 902m and 845m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.29 (1H, s, CHD), 0.80 (3H, s, CCH_3), 1.66 to 1.83 (4H, 2 x m, $(CH_2)_2CH_2CONH$), 2.10 to 2.18 (2H, m, $(CH_2)_2CH_2CONH$), 2.76 (1H, A of ABX, J_{AB} 13Hz, J_{AX} 6Hz, 1xSCH_2), 2.80 (1H, B of ABX, J_{AB} 13Hz, J_{BX} 6Hz, 1xSCH_2), 3.80 (6H, s, 2 x OCH_3), 4.00 (1H, d, *J* 8Hz, αCHNH), 4.33 to 4.49 (1H, br m, αCHNH), 4.51 to 4.54 (1H, br m, αCHNH), 5.02 and 5.08 (2 x 2H, s, $OCH_2C_6H_4OCH_3$), 5.27 (1H, s, $SCH(C_6H_5)_2$), 5.44 (1H, d, *J* 8Hz, NH), 6.21 (1H, d, *J* 8Hz, NH), 6.83 to 6.89 (6H, m, NH, $CO_2CH(C_6H_5)_2$, *o*-H of $C_6H_4OCH_3$), 7.15 to 7.50 (24H, m, aromatic); *m/z* (fast atom bombardment, +ve Argon) 995 (MH^+, 74%), 952 (100).

Synthesis of δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'S,3'S)-3-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl) glycine] (12).

To a stirred solution of (*N*-4-methoxybenzyloxycarbonyl-α-4-methoxybenzyl-L-α-aminoadipoyl)-*S*-benzhydryl-L-cysteinyl-[(2*R*,1'*S*,3'*S*)-2-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine] benzhydryl ester (20mg, 0.01mmol) in distilled trifluoroacetic acid (1ml), distilled anisole (0.1ml) was added and the reaction was heated to 50°C for 30 minutes. The reaction was then concentrated *in vacuo* and azeotroped with distilled carbon tetrachloride (5 x 1ml). The resulting white solid was dissolved in water (15ml) and washed with ethyl acetate (3 x 5ml). The aqueous layer was concentrated *in vacuo* then lyophilised to afford *δ-(L-α-aminoadipoyl)-L-cysteinyl-[(2R,1'S,3'S)-3-(1'-methyl-(2',2',3'-$^2H_3$)-cyclopropyl)glycine](1 2)* as the trifluoroacetate salt (7mg), ν_{max} (FT IR, KBr disc) 2990br s, 1678s, 1580m, 1344m, 1140s, 764m and 724m cm^{-1}; δ_H (200MHz; D_2O) 0.21 (1H, s, CHD), 0.81 (3H, s, CCH_3), 1.51 to 1.92 (4H, 2 x m, $(CH_2)_2CH_2CONH$), 2.14 to 2.21 (2H, m, $(CH_2)_2CH_2CONH$), 2.64 to 2.68 (2H, m, CH_2SH), 3.57 (1H, s, αCH), 3.75 (1H, br t, *J* 6Hz, αCH), 4.35 (1H, t, *J* 6Hz, αCH); *m/z* (positive electrospray) 379 (MH^+, 100%).

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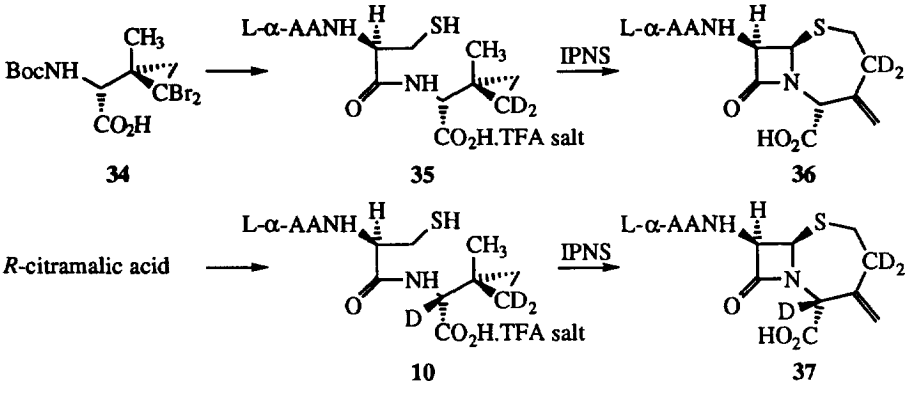
29. In order to establish the the stereochemistry of the major isomer **28** from the Strecker process the following experiments were performed. Firstly, schemes 6 and 7 were repeated using unlabelled

methallyl alcohol to yield **34** as the major product. Conversion to tripeptide **35** (scheme 8) followed by incubation with IPNS afforded (4,4-$^2H_2$)-3-exomethylene homocepham **36** as the sole product (see accompanying paper).



Likewise tripeptide **10** derived from *R*-citramalic acid was converted exclusively to the (2,4,4-$^2H_3$)-3-exomethylene homocepham **37**. Comparison of the ^1H NMR (500MHz, D_2O) indicated correspondence of these two products and hence stereochemical correspondence between tripeptides **10** and **35**. The major isomer **28** from the Strecker process can thus be assigned the (±)-2*R**,1'*S**,3'*S** stereochemistry.

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