Supplementary Material (ESI) for Organic and Biomolecular Chemistry

ELECTRONIC SUPPLEMENTARY MATERIAL

Synthesis of Macrocyclic Analogues of the Neuroprotective Agent Glycyl-L-Prolyl-L-Glutamic Acid (GPE)

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Experimental

General

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All reagents were used as supplied. Solvents were purified by standard methods. Analytical thin layer chromatography (TLC) was carried out on 0.20 mm pre-coated silica gel plates (ALUGRAM® SIL G/UV_{254}). Products were visualized by UV fluorescence and heating of plates dipped in anisaldehyde in ethanolic sulphuric acid or alkaline potassium permanganate solution. Flash chromatography was performed using Scharlau 60 (40-60 μm mesh) silica gel. Melting points in degrees Celsius (°C) were measured on an Electrothermal® melting point apparatus and are uncorrected. Optical rotations were measured at the sodium D line (589 nm), at 20 °C, with a Perkin Elmer 341 polarimeter using a 1 dm path length cell and are given in units of $10^{-1}degcm^2g^{-1}$. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer and the samples were prepared as thin films between sodium chloride plates. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AVANCE DRX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), a Bruker AVANCE 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) or a Bruker AC200 (^{1}H, 200 MHz; ^{13}C, 50 MHz) spectrometer at 298 K. For ^{1}H NMR data, chemical shifts are described in parts per million (ppm) relative to tetramethylsilane (δ 0.00), DOH (δ 4.75), CHD_2OD (δ 3.30) or $CHD_2S(O)CD_3$ (δ 2.50) and are reported consecutively as position (δ_H), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, q = quintet, s = sextet, dd = doublet of doublets, m = multiplet, and where br = broad), coupling constant (*J*/Hz) and assignment. For ^{13}C NMR data, chemical shifts (ppm) are

referenced internally to $CDCl_3$ (δ 77.0), CD_3OD (δ 49.1) and $(CD_3)_2S(O)$ (δ 39.4) or externally to 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) and are reported consecutively as position (δ_C), degree of hybridisation and assignment. Assignments were aided by DEPT135, COSY, NOESY, HSQC and HMBC experiments. When two sets of peaks arise in the NMR spectra due to *cis*/*trans* isomerisation about the glycine-proline amide bond, the chemical shift for the minor *cis* conformer is asterisked (*). Mass spectra were recorded on a VG-70SE mass spectrometer (EI, CI and FAB). High-resolution mass spectra were recorded at a nominal resolution of 5000. Analytical HPLC were performed on a Waters 600 system with a 2487 dual λ absorbance detector using an Phenomenex Jupiter C_{18} (150 × 4.6 mm; 5 μm) 90% A:10% B to 100% B over 35 mins at 1 mL/min (A = water/0.05% TFA, B = MeCN). Semi-preparative HPLC was performed using a Waters Xterra C_{18} (300 × 19 mm; 10 μm) starting at 90% A: 10% B to 100% B at 13 mL/min (A = water/0.05% TFA, B = MeCN) and adjusting the gradient as required. Fractions containing the purified compound were combined and lyophilised.

(*S*)-Ethyl *N*-*tert*-butoxycarbonylpyroglutamate[1i] 16

(*S*)-Pyroglutamic acid **15** (3.0 g, 15.5 mmol) was suspended in ethanol (40 cm^3) and cooled to 0 °C under a nitrogen atmosphere. Thionyl chloride (2.03 g, 17.0 mmol) was added dropwise and the solution was allowed to warm to room temperature overnight. The solution was cooled to 0 °C, neutralised with saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The combined organic layers were pooled, dried (Na_2SO_4), filtered and the solvent removed to give the crude ester[2] (2.53 g, 104%) that was used without further purification. To a solution of the ester (2.53 g) and dimethylaminopyridine (0.19 g, 1.55 mmol) in acetonitrile (30 cm^3) was added di-*tert*-butyl dicarbonate (3.71 g, 17.05 mmol). The resultant solution was stirred at room temperature for 18 h, concentrated *in vacuo* and purified by chromatography (SiO_2, 3:1, 2:1, hexanes-ethyl acetate) to give a yellow solid that was recrystallised from hexanes to afford carbamate **16** (3.35 g, 85%, in 2 steps) as a colourless solid: mp 53-54 °C (lit.[i] 53-54 °C); $[\alpha]_D$ -39.8 (*c* 0.5 in MeOH) [lit.[i] -46.3 (*c* 1.5 in MeOH)]; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.48 [9H, s, $C(CH_3)_3$], 1.96-2.06 (1H, m), 2.24-2.68 (3H, m), 4.22 (2H, q, *J* 7.2, OCH_2CH_3), and 4.58 (1H, dd, *J* 9.4 and 3.0, 5-H); δ_C (75 MHz; $CDCl_3$) 14.2 (CH_3, OCH_2CH_3), 21.5 (CH_2, 4-C), 27.9 [CH_3, $C(CH_3)_3$], 31.2 (CH_2, 3-C), 58.9 (CH, 5-C),

61.7 (CH_2, O*C*H_2CH_3), 83.5 [quat., $C(CH_3)_3$], 149.3 (quat., NCO_2), 171.3 (quat., 5-CO) and 173.2 (quat., 2-C).

N-tert-Butoxycarbonyl-(_S_)-allylglycine-5-allyl-L-proline ethyl ester 10

To a stirred solution of carbamate **16** (1.0 g, 3.89 mmol) in dry tetrahydrofuran (40 cm^3) was added a 1 mol L^{-1} tetrahydrofuran solution of lithium triethylborohydride (4.66 cm^3, 4.66 mmol) at –78 °C under at atmosphere of nitrogen. The solution was stirred for 1 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the cooling bath removed. The temperature was allowed to reach 0 °C then 30% aqueous hydrogen peroxide (35 drops) was added and stirring was continued at 0 °C for 50 min. The aqueous layer was extracted with ether, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed to give the crude mixture of aminols (1.30 g). The crude aminol mixture (0.363 g, *ca*. 1.40 mmol) was dissolved in dry dichloromethane (10 cm^3), allyltributylstannane (0.87 cm^3, 2.80 mmol) was added and the solution cooled to -78 °C under a nitrogen atmosphere. Boron trifluoride etherate (0.36 cm^3, 2.80 mmol) was added dropwise, and the solution was stirred at -78 °C for 2 h, then saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the reaction mixture warmed to room temperature. The aqueous layer was extracted with dichloromethane and the pooled organic extracts dried (Na_2SO_4) and filtered. Removal of the solvent *in vacuo* afforded an oil (1.28 g) that was purified by chromatography (SiO_2, 16:1, 10:1, 8:1, 6:1, 4:1, 3:1, hexanes-ethyl acetate) to afford alkene **17**[ii] [0.217 g, 54% over 2 steps] as a colourless oil. Alkene **17** was shown to be a 66:33 mixture of C(1)/C(5) *cis:trans* isomers together with minor component(s). Due to the complex nature of the NMR spectrum this compound was not characterized and used directly in the next step.

Trifluoroacetic acid (2 cm^3) was added to a solution of alkenes **17** (0.22 g, 0.77 mmol) in dichloromethane (4 cm^3) and the solution was stirred at room temperature for 4 h, then the volatiles removed *in vacuo* to yield the *trifluoroacetate salts* **12** as an oil. Half of this material (0.383 mmol) was dissolved in dichloromethane (7 cm^3), *N-tert*-butoxycarbonyl-(*S*)-allylglycine **14**[iii,iv] (0.07 g, 0.32 mmol) and triethylamine (0.042 g, 0.42 mmol) were added and the solution cooled to 0 °C. *N, N'*-Dicyclohexylcarbodiimide (0.065 g, 0.316 mmol) was added, the mixture stirred overnight, then filtered through Celite™ to remove dicyclohexyl urea. The filtrate was subsequently washed with saturated aqueous sodium hydrogen carbonate, 2 M aqueous hydrochloric acid, dried ($MgSO_4$), filtered and the solvent removed to yield an oil

(0.113 g) which was purified by chromatography (SiO_2, 4:1, hexane-ethyl acetate) to afford *diene* **10** (0.064 g, 55%, 2 steps) as a colourless oil. Diene **10** was an inseparable mixture of diastereomers [C2/C5, *cis/trans,* 77:23]: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.21-1.26 (3H, m, OCH_2CH_3), 1.37 [6.93H, s, $C(CH_3)_3$], 1.41 [2.07H, s, $C(CH_3)_3$], 1.64-1.97 (4H, m, Proβ-H_2 and Proγ-H_2), 2.0-2.52 [3.77H, m, 2 x CH_2(allyl)], 2.75-2.95 [0.23H, m, CH_ACH_B(allyl)], 4.07-4.21 (2.23H, m, OCH_2CH_3 and Proα-H*), 4.32-4.48 (2.77H, Proδ-H, Glyα-H and Proα-H), 4.97-5.26 (5H, m, 2 x =CH_2, N-H) and 5.64-5.84 [2H, m, 2 x C(*H*)=CH_2]; δ_C (100 MHz; $CDCl_3$) 13.9* (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3), 26.8 (CH_2, Proβ-C), 28.3 [CH_3, $C(CH_3)_3$], 29.0* (CH_2, Proγ-C), 29.5 (CH_2, Proγ-C), 37.7* [CH_2, CH_2(allyl)Pro], 37.8 [CH_2, CH_2(allyl)Gly], 38.4* [CH_2, CH_2(allyl)Gly], 39.4* [CH_2, CH_2(allyl)Pro], 50.9 (CH, Glyα-C), 51.9* (CH, Glyα-C), 58.2 (CH, Proα-C), 58.5* (CH, Proα-C), 59.5 (CH, Proδ-C), 59.8* (CH, Proδ-C), 61.0 (CH_2, OCH_2CH_3), 61.9* (CH_2, OCH_2CH_3), 79.4* [quat., $C(CH_3)_3$], 79.7 [quat., $C(CH_3)_3$], 117.2* (CH_2, =CH_2), 118.3 (CH_2, =CH_2), 118.35 (CH_2, =CH_2), 118.7* (CH_2, =CH_2), 132.7* (CH, C(H)=CH_2), 133.2 [CH, C(H)=CH_2], 134.0 [CH, C(H)=CH_2], 134.7* [CH, C(H)=CH_2], 154.7* (quat., NCO_2), 155.3 (quat., NCO_2), 170.5* (quat., CO), 171.4 (quat., CO), 171.6* (quat., CO) and 172.1 (quat., CO); *m/z* (FAB+) 381.23896 (MH^+. $C_{20}H_{33}N_2O_5$ requires 381.23895).

***N-tert*-Butoxycarbonyl-5-allyl-L-proline *tert*-butyl ester 23**[v]

To a stirred solution of carbamate **22**[vi] (1.14 g, 3.98 mmol) in dry tetrahydrofuran (40 cm^3) was added a 1 mol L^{-1} tetrahydrofuran solution of lithium triethylborohydride (4.78 cm^3, 4.78 mmol) at –78 °C under at atmosphere of nitrogen. The solution was stirred for 1 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) added and the cooling bath removed. The temperature was allowed to reach 0 °C then 30% aqueous hydrogen peroxide[4] (30 drops) was added and stirring was continued at 0 °C for 30 min. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed to give the crude aminols (1.17 g). The mixture of crude aminols was dissolved in dry dichloromethane (20 cm^3) and added dropwise to a stirred solution of trimethylsilyl triflate (1.44 cm^3, 7.96 mmol) and allyltributylstannane (2.46 cm^3, 7.96 mmol) in dry dichloromethane (20 cm^3) at –78 °C under nitrogen. The solution was stirred at –78 °C for 2 h, saturated aqueous sodium hydrogen carbonate (15 cm^3) was added and the reaction

warmed to room temperature. The aqueous layer was extracted with dichloromethane and the pooled organic extracts dried ($MgSO_4$) and filtered. Removal of the solvent *in vacuo* gave an oil (3.855 g) that was purified by chromatography (SiO_2, 8:1, 7:1, hexane-ethyl acetate; gradient elution) to afford an oil (1.047 g) contaminated with tributylstannane residues. Further chromatography (SiO_2, 12:1, 10:1, 8:1, hexanes-ethyl acetate; gradient elution) gave *alkene* **23** (0.872 g, 70% over 2 steps) as a colourless oil. Alkene **23** was shown to be a 57:43 mixture of C(2)/C(5) *cis:trans* isomers[#]: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.41-1.45 [18H, m, 2 x $C(CH_3)_3$], 1.67-2.24 [5H, m, Proβ-H_2, Proγ-H_2 and CH_ACH_B(allyl)], 2.39-2.71 [1H, m, CH_ACH_B(allyl)], 3.79-4.18 (2H, m, Proα-H and Proδ-H), 4.99-5.08 (2H, m, $=CH_2$) and 5.67-5.85 [1H, m, $C(H)=CH_2$]; δ_C (75 MHz; $CDCl_3$) 26.6 (CH_2, Proγ-C), 27.4 (CH_2, Proγ-C), 27.8 (CH_2, Proγ-C), 27.86 [CH_3, $C(CH_3)_3$], 27.92 [CH_3, $C(CH_3)_3$], 28.25 [CH_3, $C(CH_3)_3$], 28.31 [CH_3, $C(CH_3)_3$], 28.4 (CH_2, Proβ-C), 29.4 (CH_2, Proβ-C), 30.2 (CH_2, Proβ-C), 38.1 [CH_2, CH_2(allyl)], 38.5 [CH_2, CH_2(allyl)], 38.98 [CH_2, CH_2(allyl)], 39.1 [CH_2, CH_2(allyl)], 57.4 (CH, Proδ-C), 58.0 (CH, Proδ-C), 60.6 (CH, Proα-C), 60.9 (CH, Proα-C), 79.5 [quat., $C(CH_3)_3$], 79.6 [quat., $C(CH_3)_3$], 80.7 [quat., $C(CH_3)_3$], 80.74 [quat., $C(CH_3)_3$], 116.9 (CH_2, $=CH_2$), 116.99 (CH_2, $=CH_2$), 117.0 (CH_2, $=CH_2$), 135.12 (CH, $C(H)=CH_2$), 135.2 (CH, $C(H)=CH_2$), 135.5 (CH, $C(H)=CH_2$), 153.7 (quat., NCO_2), 153.8 (quat., NCO_2), 154.3 (quat., NCO_2), 172.1 (quat., Proα-CO), 172.2 (quat., Proα-CO) and 172.3 (quat., Proα-CO); *m/z* (EI+) 312.2171 (M^+. $C_{17}H_{30}NO_4$ requires 312.2175).

(1*S*, 2*S*)-5-Allylproline *tert*-butyl ester (*trans*) 13b and (1*S*, 2*R*) 5-allylproline tert-butyl ester (*cis*) 13a.

To the above mixture of *cis* and *trans* alkenes **23** (0.24 g, 0.77 mmol) was added a 4 mol L^{-1} solution of hydrogen chloride in dioxane (4 cm^3) at 0 °C. The solution was stirred for 1 h at 0 °C then room temperature for 40 min at which time reaction was complete (by tlc). The mixture was cooled to 0 °C, neutralized with a saturated solution of aqueous sodium hydrogen carbonate and the product extracted with dichloromethane. Removal of the solvent *in vacuo* yielded an oil (0.142 g) which was purified by chromatography (SiO_2, 2:1, 5:4, 1:1, hexanes-

[#] Since the two isomers could not be separated, the stereochemistry was determined by ^1H NMR studies on the separated free amine as described in the next step.

ethyl acetate) to give (i) *amine*[τ] **13b** (*trans*) (0.051 g, 31%) as a colourless oil. This compound showed no NOE between the Proα-H atom at δ3.70 and the Proδ-H atom at δ3.26 : $[\alpha]_D$ -31 (*c* 0.47 in CH_2Cl_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.35-1.41 (1H, m, Proγ-H_AH_B), 1.43 [9H, m, $C(CH_3)_3$], 1.72-1.90 (2H, Proγ-H_AH_B and Proβ H_AH_B), 2.11-2.20 [3H, m, Proβ H_AH_B and CH_2(allyl)], 2.47 (1H, s, N-H), 3.26 (1H, p, *J* 6.5, Proδ-H), 3.70 (1H, dd, *J* 8.5 and 5.9, Proα-H), 4.98-5.10 (2H, m, $=CH_2$) and 5.73-5.84 [1H, m, $C(H)=CH_2$]; δ_C (75 MHz; $CDCl_3$) 27.9 [CH_3, $C(CH_3)_3$], 29.5 (CH_2, Proβ-C), 30.7 (CH_2, Proγ-C), 40.8 [CH_2, CH_2(allyl)], 57.6 (CH, Proδ-C), 59.7 (CH, Proα-C), 80.7 [quat., $C(CH_3)_3$], 116.1 (CH_2, $=CH_2$), 136.0 [CH, $C(H)=CH_2$], and 174.9 (quat., Proα-CO); (ii) *amine* **13a** (*cis*) (0.066 g, 41%) as a colourless oil. This compound showed an NOE between the Proα-H atom at δ3.57-3.62 and the Proδ-H atom at δ3.03-3.12: $[\alpha]_D$ –22.1 (*c* 0.66 in CH_2Cl_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.24-1.30 (1H, m, Proγ-H_AH_B), 1.42 [9H, m, $C(CH_3)_3$], 1.78-1.87 (2H, Proγ-H_AH_B and Proβ-H_AH_B), 1.98-2.07 (1H, m, Proβ-H_AH_B), 2.18-2.31 [3H, m, CH_2(allyl) and N-H), 3.03-3.12 (1H, m, Proδ-H), 3.57-3.62 (1H, m, Proα-H), 4.99-5.1 (2H, m, $=CH_2$) and 5.72-5.86 [1H, m, $C(H)=CH_2$]; δ_C (75 MHz; $CDCl_3$) 27.9 [CH_3, $C(CH_3)_3$], 30.4 (CH_2, Proβ-C), 31.1 (CH_2, Proγ-C), 39.9 [CH_2, CH_2(allyl)], 59.1 (CH, Proδ-C), 60.5 (CH, Proα-C), 80.8 [quat., $C(CH_3)$], 116.5 (CH_2, $=CH_2$), 135.5 [CH, $C(H)=CH_2$], and 174.3 (quat., Proα-CO); *m/z* (CI+) 212.1647 (MH^+. $C_{12}H_{22}NO_2$ requires 212.1651).

(2*S*, 5*S*)-*N*-*tert*-Butoxycarbonyl-α-allylglycine-5-allyl-L-proline *tert*-butyl ester 11

N,N'-Dicyclohexylcarbodiimide (0.057 g, 0.2761 mmol) was added to a stirred solution of *trans* amine **13b** (0.053 g, 0.251 mmol) and *N*-*tert*-butoxycarbonyl-α-allylglycine **14** (0.059 g, 0.2761 mmol) in dichloromethane (5 cm^3) and the mixture stirred overnight, then filtered through Celite™ to remove DCU. The reaction mixture was subsequently washed with saturated aqueous sodium hydrogen carbonate, 2M aqueous hydrochloric acid, dried ($MgSO_4$), filtered and the solvent removed to yield an oil (0.106 g) which was purified by chromatography (silica gel, hexane:ethyl acetate, 7:1, 5:1) to afford *diene* **11** (0.083 g, 81%) as a colourless oil: *m/z* (FAB+) 409.2707 (MH^+. $C_{22}H_{37}N_2O_5$ requires 409.2702).

[τ]Both **13a** and **13b** slowly decompose on exposure to air thus the crude reaction mixture was immediately used for the subsequent coupling step.

(1*S*, 2*S*)-*N*-Allyl-*N*-benzyloxycarbonylglycine-5-allylproline *tert*-butyl ester (*trans*) 29 and (1*S*, 2*R*)-*N*-allyl-*N*-benzyloxycarbonylglycine-5-allylproline *tert*-butyl ester (*cis*) 28.

To the above mixture of alkenes **13** (0.87 g, 0.77 mmol) was added a 4M solution of hydrogen chloride in dioxane (4 cm^3) at 0 °C. The solution was stirred for 1 h at 0 °C then room temperature for 35 min after which time reaction was complete (by tlc). The mixture was cooled to 0 °C, neutralized with a saturated solution of aqueous sodium hydrogen carbonate and the product extracted with dichloromethane. Removal of the solvent *in vacuo* yielded an oil (0.568 g) that was dissolved in dichloromethane (30 cm^3). To this was added triethylamine (0.54 cm^3, 4.0 mmol), *N*-allyl-*N*-benzyloxycarbonylglycine **27**[vii] (1.0 g, 4.0 mmol) and 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride) (EDCI) (0.77 g, 4.0 mmol) at 0 °C and the solution stirred for 16 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate, 2 M aqueous hydrochloric acid, dried ($MgSO_4$), filtered and the solvent removed to yield an oil (1.7 g) which was purified by chromatography (SiO_2, 5:1, 4:1, 3:1, 2:1, hexane-ethyl acetate) to afford (i) *diene* **29** (*trans*) (0.29 g, 24%) as a colourless oil. Diene **29** was shown to be a 1:1 *trans:cis* mixture of GlyC(O)-NPro conformers. In addition, restricted rotation about the GlyN-CO carbamate bond was also observed resulting in a 1:1 mixture of conformers: $[\alpha]_D$ -56.1 (*c* 0.77 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.43 [9H, s, $C(CH_3)_3$], 1.46 [9H, s, $C(CH_3)_3$], 1.48 [9H, s, $C(CH_3)_3$], 1.74-2.71 [6H, m, Proβ-H_2, Proγ-H_2 and CH_2(allyl)], 3.54 (0.5H, d, *J* 16.5, Glyα-H_AH_B), 3.58 (0.5H, d, *J* 16.5, Glyα-H_AH_B), 3.84-4.40 [5H, m, Glyα-H, CH_2(allyl), Proα-H and Proδ-H], 4.98-5.25 (6H, m, OCH_2Ph and 2 x $=CH_2$), 5.56-5.88 [2H, m, 2 x C(*H*)$=CH_2$] and 7.30-7.37 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 25.8 (CH_2, Proβ-C or Proγ-C), 25.9 (CH_2, Proβ-C or Proγ-C), 26.16 (CH_2, Proβ-C or Proγ-C), 26.2 (CH_2, Proβ-C or Proγ-C), 27.8 [CH_3, $C(CH_3)_3$], 28.3 (CH_2, Proβ-C or Proγ-C), 29.3 (CH_2, Proβ-C or Proγ-C), 29.4 (CH_2, Proβ-C or Proγ-C), 36.9 [CH_2, CH_2(allyl)], 37.0 [CH_2, CH_2(allyl)], 39.0 [CH_2, CH_2(allyl)], 39.3 [CH_2, CH_2(allyl)], 47.4 (CH_2, Glyα-C), 47.6 (CH_2, Glyα-C), 47.8 (CH_2, Glyα-C), 48.1 (CH_2, Glyα-C), 50.14 [CH_2, NCH_2(allyl)], 50.18 [CH_2, NCH_2(allyl)], 50.7 [CH_2, NCH_2(allyl)], 50.8 [CH_2, NCH_2(allyl)], 56.9 (CH, Proδ-C), 57.1 (CH, Proδ-C), 58.2 (CH, Proδ-C), 58.3, (CH, Proδ-C), 60.0 (CH, Proα-C), 60.1 (CH, Proα-C), 60.2 (CH, Proα-C), 60.3 (CH, Proα-C), 67.3 (CH_2, OCH_2Ph), 67.4 (CH_2, OCH_2Ph), 81.1 [quat., $C(CH_3)_3$], 82.3 [quat., $C(CH_3)_3$], 116.9 (CH_2, $=CH_2$), 117.1 (CH_2, $=CH_2$), 117.2 (CH_2, $=CH_2$), 117.6 (CH_2, $=CH_2$), 117.7 (CH_2, $=CH_2$), 118.1 (CH_2, $=CH_2$), 118.2, (CH_2, $=CH_2$), 127.6 (CH, Ph), 127.8 (CH, Ph), 127.9 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 133.3 [CH, C(H)$=CH_2$],

133.4 [CH, C(H)=CH_2], 133.6 [CH, C(H)=CH_2], 133.8 [CH, C(H)=CH_2], 134.9 [CH, C(H)=CH_2], 135.0 [CH, C(H)=CH_2], 136.5 (quat., Ph), 156.0 (quat., NCO_2), 156.37 (quat., NCO_2), 156.42, (quat., NCO_2), 167.1 (quat., Gly-CO), 167.3 (quat., Gly-CO), 167.4 (quat., Gly-CO), 167.6 (quat., Gly-CO) and 170.9 (quat., Proα-CO), 171.0 (quat., Proα-CO), 171.1 (quat., Proα-CO); *m/z* (EI+) 442.2455 (M^+. $C_{25}H_{34}N_2O_5$ requires 442.2468); (ii) a mixture of **28** and **29** (0.044 g, 4%); (iii) *diene* **28** (*cis*) (0.424 g, 36%) as a colourless oil. Diene **28** was shown to be a 1:1 *trans:cis* mixture of GlyC(O)-NPro conformers. In addition, restricted rotation about the GlyN-CO carbamate bond was also observed resulting in a 1:1 mixture of conformers: $[\alpha]_D$ -39.2 (*c* 0.57 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.43 [9H, s, $C(CH_3)_3$], 1.45 [9H, s, $C(CH_3)_3$], 1.47 [9H, s, $C(CH_3)_3$], 1.49 [9H, s, $C(CH_3)_3$], 1.69-2.49 [5.75H, m, Proβ-H_2, Proγ-H_2 and CH_2(allyl)], 2.78-2.84 [0.25H, m, CH_2(allyl)], 3.61-4.41 [6H, m, Glyα-H_2, CH_2(allyl], Proα-H and Proδ-H), 5.02-5.12 (6H, m, O*C*H_2Ph and 2 x =CH_2), 5.67-5.87 [2H, m, 2 x C(*H*)=CH_2] and 7.29-7.34 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 26.5 (CH_2, Proβ-C), 27.7 [CH_3, $C(CH_3)_3$], 27.8 [CH_3, $C(CH_3)_3$], 27.9 [CH_3, $C(CH_3)_3$], 29.4 (CH_2, Proβ-C or Proγ-C), 29.6 (CH_2, Proβ-C or Proγ-C), 29.7 (CH_2, Proβ-C or Proγ-C), 37.65 [CH_2, CH_2(allyl)], 37.7 [CH_2, CH_2(allyl)], 38.9 [CH_2, CH_2(allyl)], 47.2 (CH_2, Glyα-C), 47.6 (CH_2, Glyα-C), 47.7 (CH_2, Glyα-C), 48.0 (CH_2, Glyα-C), 50.2 [CH_2, NCH_2(allyl)], 50.3 [CH_2, NCH_2(allyl)], 50.8 [CH_2, NCH_2(allyl)], 50.9 [CH_2, NCH_2(allyl)], 57.8 (CH, Proδ-C), 58.5 (CH, Proδ-C), 60.2, 60.4 (CH, Proα-C), 60.5 (CH, Proα-C), 67.3 (CH_2, O*C*H_2Ph), 67.4 (CH_2, O*C*H_2Ph), 81.0 [quat., $C(CH_3)_3$], 82.2 [quat., $C(CH_3)_3$], 116.9 (CH_2, =CH_2), 117.0 (CH_2, =CH_2), 117.5 (CH_2, =CH_2), 118.0 (CH_2, =CH_2), 127.6 (CH, Ph), 127.8 (CH, Ph), 127.9 (CH, Ph), 128.0 (CH, Ph), 128.3 (CH, Ph), 133.3 [CH, *C*(H)=CH_2], 133.4 [CH, *C*(H)=CH_2], 133.5 [CH, *C*(H)=CH_2], 133.6 [CH, *C*(H)=CH_2], 134.1 [CH, *C*(H)=CH_2], 134.3 [CH, *C*(H)=CH_2], 134.8 [CH, *C*(H)=CH_2], 134.9 [CH, *C*(H)=CH_2], 136.5 (quat., Ph), 155.8 (quat., NCO_2), 155.9 (quat., NCO_2), 156.38 (quat., NCO_2), 156.44 (quat., NCO_2), 166.95 (quat., Gly-CO), 167.01 (quat., Gly-CO), 167.4 (quat., Gly-CO), 167.5 (quat., Gly-CO), 171.0 (quat., Proα-CO), 172.2 (quat., Proα-CO) and 171.3 (quat., Proα-CO); *m/z* (EI+) 442.2462 (M^+. $C_{25}H_{34}N_2O_5$ requires 442.2468).

N-tert-Butyloxy-(_S_)-allylglycyl-(_S_)-allylproline methyl ester[viii] 37

N,N'-Dicyclohexylcarbodiimide (0.1 g, 0.49 mmol) was added to a stirred solution of (*S*)-allylproline methyl ester **36**[ix] (0.1 g, 0.49 mmol), *N-tert*-butoxy-(*S*)-allylglycine **14** (0.12 g, 0.54

mmol), *N*-hydroxybenzotriazole (0.065 g, 0.486 mmol) and triethylamine (0.07 cm^3, 0.486 mmol) in dichloromethane (10 cm^3) at 0 °C. The mixture was stirred overnight at room temperature, refrigerated for 2 h and filtered through Celite™ to remove dicyclohexyl urea. The filtrate was washed with saturated aqueous sodium hydrogen carbonate, 2 M aqueous hydrochloric acid, dried (Na_2SO_4), filtered and the solvent removed to yield an oil which was purified by chromatography (SiO_2, 4:1, 3:1, hexane-ethyl acetate) to afford *diene*[2] **4** (0.041 g, *ca.* 23%) as a colourless oil. Diene **37** existed exclusively as the *trans* GlyC(O)-NPro conformer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.43 [9H, s, $C(CH_3)_3$], 1.94-2.15 (4H, m, Proβ-H_2, Proγ-H_2), 2.35 [1H, p, *J* 7.1, allyl-H_AH_B(Pro)], 2.50 [1H, p, *J* 7.2, allylH_AH_B(Pro)], 2.62 [1H, dd, *J* 14.0 and 8.4, allyl-H_AH_B(Gly)], 3.18 [1H, dd, *J* 14.1 and 6.5, allyl-H_AH_B(Gly)], 3.65-3.80 (5H, m, OCH_3 and Proδ-H_2), 4.46 (1H, dd, *J* 15.4 and 6.7, Glyα-H), 5.08-5.25 (5H, m, 2 x $=CH_2$ and N-H) and 5.63-5.86 (2H, m, 2 x $C(H)=CH_2$); δ_C (100 MHz; $CDCl_3$) 23.6 (CH_2, Proγ-C), 28.2 [CH_3, $C(CH_3)_3$], 35.0 (CH_2, Proβ-C), 36.3 [CH_2, CH_2(allyl)Gly], 37.7 [CH_2, CH_2(allyl)Pro], 48.5 (CH_2, Proδ-C), 51.6 (CH, Glyα-C), 52.2 (CH_3, OCH_3), 68.5 (quat., Proα-C), 79.6 [quat., $C(CH_3)_3$], 118.5 (CH_2, $=CH_2$), 119.1 (CH_2, $=CH_2$), 132.7 [CH, $C(H)=CH_2$], 133.0 [CH, $C(H)=CH_2$], 155.4 (quat., NCO_2), 170.2 (quat., Gly-CO) and 173.7 (quat., Pro-CO).

(*S*)-*N*-Benzyloxycarbonylallylglycyl-L-proline 50

N,N-Dicyclohexylcarbodiimide (0.103 g, 0.504 mmol) was added to a solution of *N*-benzyloxycarbonyl-(*S*)-allylglycine **49**[x] (0.114 g, 0.457 mmol), proline methyl ester hydrochloride **48** (0.083 g, 0.504 mmol), *N*-hydroxybenzotriazole (0.068 g, 0.504 mmol) and triethylamine (0.071 cm^3, 0.504 mmol) in dichloromethane (12 cm^3) at 0 °C. The mixture was stirred overnight, stored at 0 °C for 3 h and filtered thorough Celite™. The reaction mixture was washed with 2M aqueous hydrochloric acid, saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and the solvent removed to yield an oil which was purified by chromatography (silica gel, hexanes:ethyl acetate, 2:1, 1:1) to afford the *methyl ester of dipeptide* **50** (0.141 g) that was suspended in dioxane (4 cm^3). 1M Aqueous sodium hydroxide (1.95 cm^3, 1.95 mmol) was added and the mixture stirred at room temperature for 24 h. Water (5 cm^3) was added and the mixture extracted with dichloromethane. The aqueous layer was acidified with 31% hydrochloric acid and the product extracted with dichloromethane. The organic layers were pooled, washed with brine, dried ($MgSO_4$) and the solvent removed to afford an oil (0.152 g) that was purified by chromatography (silica gel, hexane:ethyl acetate, 3:1, then hexane:ethyl

acetate:acetic acid, 3:1:0.4, 2:1:0.3) to give *acid* **50** (0.102 g, 64%) as a colourless oil. Acid **50** was shown to be a 87:13 *trans:cis* mixture of conformers by ^{1}H NMR analysis (the ratio was estimated by integration of multiplets at δ 3.33-3.50 and 3.62-3.77 assigned to the Proδ-H_2 atoms of the minor and major conformers respectively): $[\alpha]_D$ -91 (*c* 0.26 in CH_2Cl_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.65* (0.13H, br s, Proβ-H_AH_B), 1.84-2.25 (3.87H, m, Proβ-H_AH_B,* Proβ-H_2, Proγ-H_2), 2.34-2.53 [2H, m, CH_2(allyl)], 3.33-3.50* (0.26H, m, Proδ-H_2), 3.62-3.77 (1.74H, m, Proδ-H_2), 4.30-4.58 (2H, m, Proα-H, Glyα-H), 4.93-5.15 (4H, m, OCH_2Ph, $=CH_2$) 5.71-5.85 (1H, m, $C(H)=CH_2$), 6.0 (0.13H, br d, *J* 8.5, N-H), 6.06* (0.13H, br d, *J* 8.7, N-H), 7.26-7.31 (5H, m, Ph) and 8.01 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 22.1* (CH_2, Proγ-C), 24.8 (CH_2, Proγ-C), 28.6 (CH_2, Proβ-C), 31.2* (CH_2, Proβ-C), 36.6 [CH_2, CH_2(allyl)], 37.8* [CH_2, CH_2(allyl)], 46.7* (CH_2, Proδ-C), 47.3 (CH_2, Proδ-C), 52.1 (CH, Glyα-C), 52.3* (CH, Glyα-C), 59.2 (CH, Proα-C), 66.6 (CH_2, OCH_2Ph), 67.1* (CH_2, OCH_2Ph), 119.1 (CH_2, $=CH_2$), 127.9, 128.0, 128.4, 128.5 (CH, Ph), 132.4 (CH, $C(H)=CH_2$), 136.1* (quat., Ph), 136.3 (quat., Ph), 156.1 (quat., NCO_2), 170.8* (quat., Glyα-CO), 171.4 (quat., Glyα-CO) and 174.6 (quat., Proα-CO); *m/z* (EI+) 346.1527 (M^+. $C_{18}H_{22}N_2O_5$ requires 346.1529).

(*S*)-*N*-Benzyloxycarbonylallylglycyl-L-prolyl-L-γ-(*R*)-allylglutamic acid dibenzyl ester 52

To an ice cold solution of acid **50** (0.134 g, 0.387 mmol) and triethylamine (0.062 cm^3, 0.461 mmol) in dichoromethane (10 cm^3) was added dropwise ethyl chloroformate (0.045 cm^3, 0.464 mmol). The solution was stirred at 0 °C for 40 min then an ice cold solution of trifluoroacetate **51** [prepared by treatment of the Boc derivative[xi] (0.217 g, 0.464 mmol) and triethylamine (0.062cm^3, 0.464 mmol) in dichloromethane (5 cm^3) was added dropwise and the mixture stirred overnight. The solution was subsequently washed with 2M aqueous hydrochloric acid, saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and the solvent removed to yield an oil which was purified by chromatography (silica gel, hexane:ethyl acetate, 2:1) to give *protected tripeptide* **52** (0.162 g, 60%) as a colourless oil. Tripeptide **52** was shown to be a 89:11 *trans:cis* mixture of conformers by ^{1}H NMR analysis (the ratio was estimated by

integration of the doubles at δ 8.04 and 7.10 assigned to the GluN-H atoms of the minor and major conformers respectively): $[\alpha]_D$ -31.2 (*c* 0.462 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.90-1.99 (2H, m, Proβ-H_AH_B, Proγ-H_AH_B), 2.06-2.13 (3H, m, Proγ-H_AH_B, Gluβ-H_2), 2.19-2.26 (1H, m, Proβ-H_AH_B), 2.33-2.42 [3H, m, CH_2(allyl), CH_AH_B(allyl)], 2.47-2.54 (1H, m, CH_ACH_B(allyl)], 2.63 (1H, p, *J* 6.7, Gluγ-H), 3.56-3.72 (2H, m, Proδ-H_2), 4.18* (0.11H, q, *J* 6.2, Glyα-H), 4.38* (0.11H, d, *J* 7.7, Proα-H), 4.54-4.66 (2.78H, Glyα-H, Proα-H), Gluα-H), 4.86-5.18 (10H, m, 3 x OCH_2Ph, 2 x $=CH_2$), 5.60-5.81 (3H, m, 2 x C(*H*)=CH_2, GlyN-H), 7.10 (0.89H, d, *J* 7.4, GluN-H), 7.26-7.39 (15H, m, Ph) and 7.10* (0.11H, d, *J* 7.9, GluN-H); δ_C (100 MHz; $CDCl_3$) 22.0* (CH_2, Proγ-C), 24.9 (CH_2, Proγ-C), 27.5 (CH_2, Proβ-C), 31.3* (CH_2, Proβ-C), 31.4* (CH_2, Gluβ-C), 32.9 (CH_2, Gluβ-C), 35.65* [CH_2, CH_2(allyl)], 35.71* [CH_2, CH_2(allyl)], 35.9 [CH_2, CH_2(allyl)], 36.9 [CH_2, CH_2(allyl)], 41.0 (CH, Gluγ-C), 41.9* (CH, Gluγ-C), 46.9* (CH_2, Proδ-C), 47.3 (CH_2, Proδ-C), 50.7 (CH, Gluα-C), 51.3* (CH, Gluα-C), 51.8 (CH, Glyα-C), 52.4* (CH, Glyα-C), 59.9 (CH, Proα-C), 60.8* (CH, Proα-C), 66.31* (CH_2, OCH_2Ph), 66.4 (CH_2, OCH_2Ph), 66.8 (CH_2, OCH_2Ph), 67.0* (CH_2, OCH_2Ph), 67.2 (CH_2, OCH_2Ph), 117.7, 119.0, 119.8* (CH_2, $=CH_2$), 127.9, 128.0, 128.14, 128.22, 128.24, 128.31, 128.42, 128.46, (CH, Ph), 131.7,* 132.2, 134.2 (CH, C(H)=CH_2), 135.2, 135.3,* 135.7, 136.0,* 136.2 (quat., Ph), 155.8 (quat., NCO_2), 156.2* (quat., NCO_2), 170.7* (quat., CO), 170.9 (quat., CO) 171.2 (quat., CO), 171.5 (quat., CO), 171.6* (quat., CO), 174.3* (quat., Gluγ-CO) and 174.4 (quat., Gluγ-CO); *m/z* (EI+) 695.3170 (M^+. $C_{40}H_{45}N_3O_8$ requires 695.3207).

_N_-Allyl-_N_-benzyloxycarbonylglycyl-L-proline methyl ester 54

1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (EDCI) (0.453 g, 2.36 mmol) was added to a solution of proline methyl ester hydrochloride **48** (0.356 g, 2.15 mmol), acid **55** (0.590 mmol, 2.35 mmol) and triethylamine (0.481 g, 4.73 mmol) in dichloromethane (20 cm^3) at 0 °C. The resultant solution was stirred for 19 h, washed with 2M aqueous hydrochloric acid

and saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed to yield an oil which was purified by chromatography (silica gel, hexanes:ethyl acetate, 2:1, 1:1) to afford *protected dipeptide* **54** (0.508 g, 66%) as a colourless oil. Dipeptide **54** was shown to be a 76:24 *trans:cis* mixture of conformers by ^{13}C NMR analysis (the ratio was estimated by integration of signals at δ 22.0 and 24.5, 24.7, assigned to the Proγ-C atoms of the minor and major conformers respectively). In addition, restricted rotation about the GlyN-CO carbamate bond was also observed resulting in a further 1:1 mixture of conformers: $[\alpha]_D$ -54.6 (*c* 1.17 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.81-2.14 (4H, m, Proβ-H_2, Proγ-H_2), 3.29-3.58 (2H, m, Proδ-H_2), 3.64, 3.66, 3.69* (3H, s, OCH_3), 3.84-4.20 [4H, m, CH_2(allyl), Glyα-H_2], 4.40-4.48 (1H, m, Proα-H), 5.07-5.17 (4H, m, OCH_2Ph, $=CH_2$), 5.69-5.81 (1H, m, C(H)=CH_2) and 7.24-7.30 (m, 5H, Ph); δ_C (100 MHz; $CDCl_3$) 22.0* (CH_2, Proγ-C), 24.62, 24.73 (CH_2, Proγ-C), 28.66, 28.73 (CH_2, Proβ-C), 31.1,* 31.3* (CH_2, Proβ-C), 45.93, 45.98 (CH_2, Proδ-C), 46.5* (CH_2, Proδ-C), 47.5, 48.0 (CH_2, Glyα-C), 50.0, 50.6 [CH_2, CH_2(allyl)], 50.0,* 50.6* [CH_2, CH_2(allyl)], 52.0, (CH_3, OCH_3), 52.31,* 52.5* (CH_3, OCH_3), 58.4,* 58.5* (CH, Proα-C), 58.8 (CH, Proα-C), 67.2, 67.3 (CH_2, OCH_2Ph), 117.0, 117.5 (CH_2, $=CH_2$), 127.5, 127.7, 127.8, 128.3, (CH, Ph), 133.2, 133.4 (CH, C(H)=CH_2) 136.4, 136.5 (quat., Ph), 155.8, 156.3, (quat., NCO_2), 167.1 (quat., Gly-CO), 167.4,* 167.5* (quat., Gly-CO). 172.0,* 172.2* (quat., Pro-CO) and 172.3, 172.4 (quat., Pro-CO); *m/z* (EI+) 360.1676 (M^+. $C_{19}H_{24}N_2O_5$ requires 360.1685).

_N_-Allyl-_N_-benzyloxycarbonylglycyl-L-proline 55

To a solution of protected dipeptide **54** (0.474 g, 1.31 mmol) in dioxane (13 cm^3) was added 1M aqueous sodium hydroxide (6.71 cm^3, 6.71 mmol) and the mixture stirred at room temperature for 20 h. Water (10 cm^3) was added and the mixture extracted with dichloromethane. The aqueous layer was acidified with 10% HCl and the product extracted with dichloromethane. The organic layers were pooled, dried ($MgSO_4$) and the solvent removed to afford an oil (0.456 g) contaminated with 2-hydroxy-1,4-dioxane. Subsequent purification by chromatography (silica gel, hexanes:ethyl acetate, 1:1, 1:2, 1:3,) gave *acid* **55** (0.250 g, 55%) as a colourless oil: Acid **55** was shown to be a 86:14 *trans:cis* mixture of conformers by ^{13}C NMR analysis (the ratio was estimated by integration of signals at δ 22.1

and 24.6, 24.7, assigned to the Proγ-C atoms of the minor and major conformers respectively). In addition, restricted rotation about the GlyN-CO carbamate bond was also observed resulting in a further 1:1 mixture of conformers $[\alpha]_D$ -117 (*c* 0.8 in CH_2Cl_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.88-2.25 (4H, m, Proβ-H_2, Proγ-H_2), 3.30-3.69 (2H, m, Proδ-H_2), 3.75-4.26 [4H, m, CH_2(allyl), Glyα-H_2], 4.50-4.58 (1H, m, Proα-H), 5.10-5.22 (4H, m, OCH_2Ph, $=CH_2$), 5.73-5.82 (1H, m, C(H)=CH_2), 7.33-7.34 (m, 5H, Ph) and 7.84 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 22.1* (CH_2, Proγ-C), 24.6, 24.7 (CH_2, Proγ-C), 27.9, 28.0 (CH_2, Proβ-C), 31.1,* 31.3* (CH_2, Proβ-C), 46.5 (CH_2, Proδ-C), 46.7* (CH_2, Proδ-C), 47.5, 48.1 (CH_2, Glyα-C), 47.7,* 48.2* (CH_2, Glyα-C), 50.2, 50.7 [CH_2, CH_2(allyl)], 50.5,* 50.9* [CH_2, CH_2(allyl)], 58.6* (CH, Proα-C), 59.5 (CH, Proα-C), 67.6 (CH_2, OCH_2Ph), 117.3, 117.9 (CH_2, $=CH_2$), 127.6, 127.9, 128.0, 128.4, (CH, Ph), 133.0, 133.2 (CH, C(H)=CH_2) 136.3 (quat., Ph), 155.9, 156.5, (quat., NCO_2), 156.7* (quat., NCO_2), 167.8* (quat., Gly-CO), 168.9, 169.0 (quat., Gly-CO), 173.6, 173.7 (quat., Pro-CO) and 174.4* (quat., Pro-CO); *m/z* (EI+) 346.1524 (M^+. $C_{18}H_{22}N_2O_5$ requires 346.1529).

_N_-Allyl-_N_-benzyloxycarbonylglycyl-L-prolyl-L-γ-(_R_)-allylglutamic acid dibenzyl ester 56

To an ice cold solution of acid **55** (0.288 g, 0.655 mmol) and triethylamine (0.150 cm^3, 0.80 mmol) was added dropwise ethyl chloroformate (0.075 cm^3, 0.786 mmol). The solution was stirred at 0 °C for 40 min then an ice-cold solution of *trifluoroacetate* **51** (0.359 g, 0.768 mmol) and triethylamine (0.150 cm^3, 0.80 mmol) in dichloromethane (15 cm^3) was added dropwise and the mixture stirred overnight. The solution was subsequently washed with 2M aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed to yield an oil which was purified by chromatography (silica gel, hexane:ethyl acetate, 1:1) to give *fully protected tripeptide* **56** (0.432 g, 94%) as a colourless oil. Tripeptide **56** was shown to be a 85:15 *trans:cis* mixture of conformers by ^{13}C NMR analysis (the ratio was estimated by integration of signals at δ 22.1 and 24.9 assigned to the Proγ-C atoms of the minor and major conformers respectively). In addition, restricted rotation about the GlyN-CO carbamate bond was also observed resulting in a further 1:1 mixture of conformers: $[\alpha]_D$ -38.7 (*c* 0.73 in CH_2Cl_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.75-2.33 [8H, m, Proβ-H_2, Proγ-H_2, Gluβ-H_2, CH_2(allyl)], 2.55-2.66 (1H, m, Gluγ-H), 3.25-3.63 (m, 2H, Proδ-H_2), 3.77-4.19 [4H, m, Glyα-H_2, CH_2(allyl)], 4.32* (0.15H, d, *J* 7.7, Proα-H), 4.46-4.60 (1.85H, m, Proα-H, Gluα-H),

4.99-5.15 (10H, m, 3 x OCH_2Ph, 2 x $=CH_2$), 5.57-5.82 (2H, m, 2 x C(*H*)$=CH_2$) and 7.19-7.34 (16H, m, 3 x Ph, GluN-H); δ_C (75 MHz; $CDCl_3$) 22.2* (CH_2, Proγ-C), 24.9 (CH_2, Proγ-C), 27.2* (CH_2, Proβ-C), 27.5 (CH_2, Proβ-C), 31.8* [CH_2, CH_2(allyl)], 32.7 [CH_2, CH_2(allyl)], 35.9 (CH_2, Gluβ-C), 36.0* (CH_2, Gluβ-C), 41.2 (CH, Gluγ-C), 41.9* (CH, Gluγ-C), 46.4 (CH_2, Proδ-C), 46.9* (CH_2, Proδ-C), 47.6,* (CH_2, Glyα-C), 48.3 (CH_2, Glyα-C), 48.2,* (CH_2, Glyα-C), 50.4 [CH_2, CH_2(allyl)], 50.7, 50.9 (CH_2, Gluα-C), 51.2,* [CH_2, CH_2(allyl)], 51.4* (CH_2, Gluα-C), 59.96* (CH, Proα-C), 60.0 (CH, Proα-C), 60.4* (CH, Proα-C), 66.3 (CH_2, OCH_2Ph), 66.4* (CH_2, OCH_2Ph), 66.5* (CH_2, OCH_2Ph), 67.0 (CH_2, OCH_2Ph), 67.1* (CH_2, OCH_2Ph), 67.35 (CH_2, OCH_2Ph), 67.4 (CH_2, OCH_2Ph), 117.0 (CH_2, $=CH_2$), 117.1* (CH_2, $=CH_2$), 117.5 (CH_2, $=CH_2$), 117.6 (CH_2, $=CH_2$), 117.8* (CH_2, $=CH_2$) 118.0* (CH_2, $=CH_2$), 127.56,* 127.63,* 127.77,* 127.85,* 128.08, 128.13, 128.17, 128.35, 128.39, 128.43 (CH, Ph), 133.3 (CH, C(H)$=CH_2$), 133.5* (CH, C(H)$=CH_2$), 134.0* (CH, C(H)$=CH_2$), 134.2* (CH, C(H)$=CH_2$), 134.3 (CH, C(H)$=CH_2$), 135.2* (quat., Ph), 135.3 (quat., Ph), 135.7 (quat., Ph),, 136.4 (quat., Ph), 136.6* (quat., Ph), 155.9* (quat., NCO_2), 156.5, (quat., NCO_2), 168.4 (quat., Gly-CO), 170.9,* 171.0, 171.4, 171.8* (quat., Pro-CON, Gluα-CO), 174.3* (quat., Gluγ-CO) and 174.4 (quat., Gluγ-CO); *m/z* (FAB+) 696.3280 (MH^+. $C_{40}H_{46}N_3O_8$ requires 696.3285).

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