An Approach to a Synthetic Carboxylate-binding Pocket Based on β-Avoparcin

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An approach to a macrocyclic lactam designed to bind to a carboxylate anion is described. The diaryl ether **8** was synthesised by Ullmann coupling of the protected 3-hydroxyphenylglycine derivative **7** and (*E*)-4-bromocinnamic acid methyl ester. Elaboration of an optically pure (*R*)-tyrosine synthon was achieved by transfer of electrophilic azide to the *N*-acyl oxazolidinone **12**. The synthesis of a model system is also described.

Peptide–peptide recognition phenomena are central to many biologically important systems. One of the best understood small peptide–peptide binding systems is that between antibiotics of the vancomycin group and nascent gram-positive bacterial cell walls. These antibiotics, typified by β-avoparcin[1] **1**, bind strongly and specifically to peptide sequences terminating in *N*-acyl-D-Ala-D-Ala,[2] and the solution structures of the resultant complexes have been studied extensively both in our group[3–5] and by others.[1,6,7] The vancomycin/*N*-acetyl-D-Ala-D-Ala complex, shown in Fig. 1, involves: an ion–ion interaction between the carboxylate group of the cell wall analogue and the protonated N-terminus of the antibiotic; three ion–dipole interactions between the cell-wall analogue carboxylate group and the amide NH groups of antibiotic residues 2, 3, and 4; two amide NH to amide carbonyl hydrogen bonds between the associated peptides; and two specific hydrophobic interactions between the alanine sidechains of the cell-wall analogue and aromatic rings in the antibiotic. Furthermore, the cell-wall analogue is bound into a cleft whose walls are determined by the crosslinked sidechains of the antibiotic.

The stereochemistry of the N-terminal tetrapeptide portion of vancomycin group antibiotics (*R,R,S,R*) has been rationalised in terms of the propensity of such a peptide to fold into a conformation ideally suited to binding a carboxylate anion on a D-amino acid.[8] In line with this analysis, we consider the minimal structural requirements for formation of such a 'carboxylate binding pocket' to be: (i), a tetrapeptide chain in which the third residue (from the N-terminus) is of opposite absolute configuration to the other three residues, and (ii), the sidechains of residues 2 and 4 should be crosslinked.

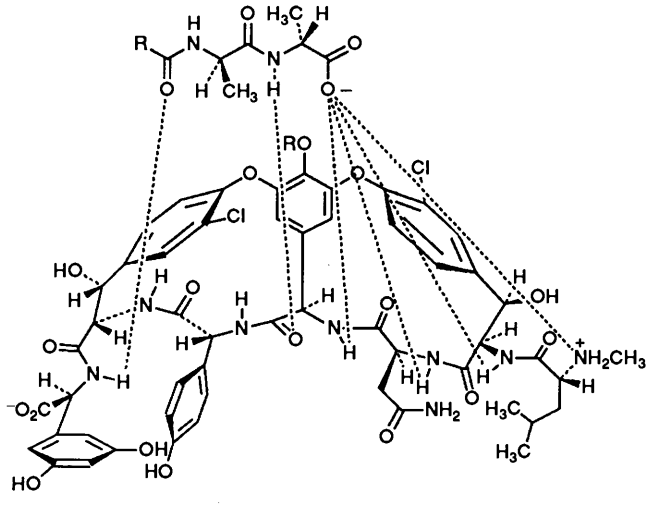
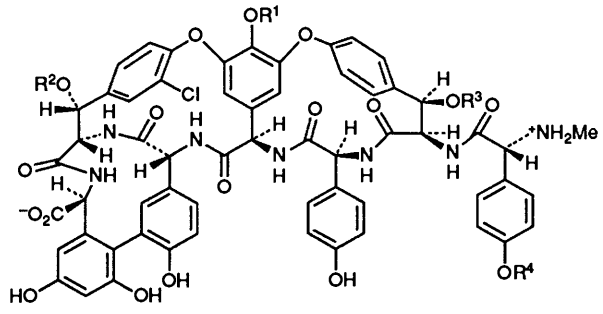
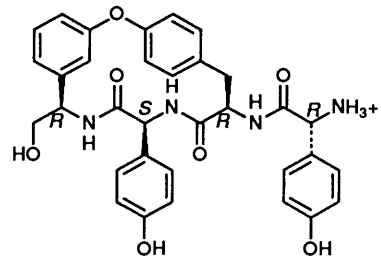


Fig. 1 The vancomycin/Ac-D-Ala-D-Ala complex; electrostatic interactions are represented as dotted lines



1 R^1–R^4 = sugars



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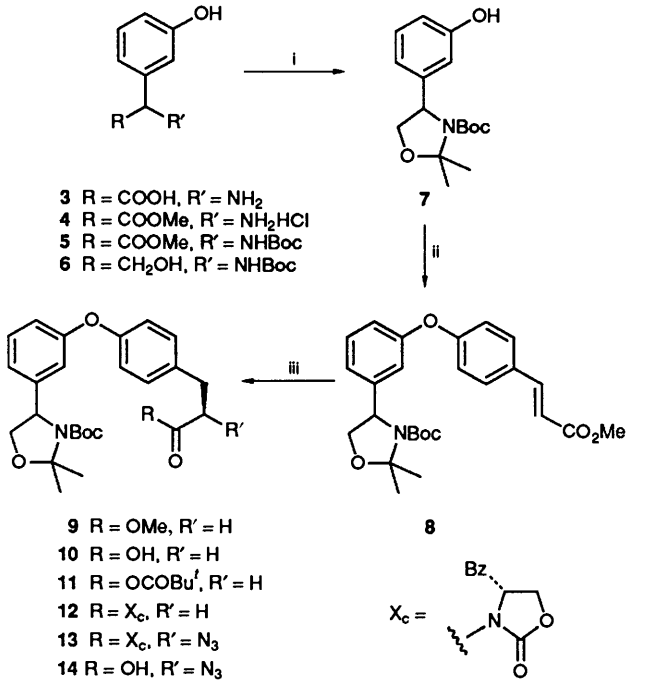
In order to test the validity of our prediction, we sought to synthesise the cyclic tetrapeptide **2**, whose structure resembles closely the N-terminal tetrapeptide portion of β-avoparcin **1**, and to test the binding of this compound to *N*-acyl-D-Ala. Previous syntheses of related systems have involved either construction of the peptide backbone, followed by oxidative crosslinking of the sidechains,[11–13] or initial construction of the diaryl ether promoted by nitro substituents, followed by cyclisation through one of the backbone peptide bonds.[9–10] The approach reported here was to synthesise the diaryl ether sidechain system in the absence of activating groups, then elaborate the amino acid functionalities and attempt macrocyclisation by peptide bond formation.

Discussion

Initially, (*R*)-3-hydroxyphenylglycine **3** was protected as its methyl ester **4** and *tert*-butoxycarbonyl (Boc) carbamate **5**. Lithium borohydride reduction of the ester **5**, followed by reaction with 2,2-dimethoxypropane gave the phenolic oxazolidine **7** in high yield.

The residue-2 to residue-4 diaryl ether linkage was con-

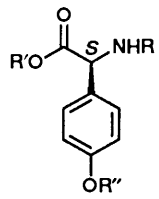


Scheme 1 *Reagents:* i, $Me_2C(OMe)_2$, CH_2Cl_2, *p*-TsOH; ii, K_2CO_3, pyridine; then CuCl; then 4-bromocinnamic acid methyl ester; iii, H_2, 10% Pd/C

structed using an Ullmann coupling reaction.[14–16] Deprotonation of the phenol **7** was effected with potassium carbonate, then transmetallation to copper(I) was followed by addition of 4-bromocinnamic acid methyl ester. Phenoxy displacement of bromide is presumed to have been promoted by π-complexation of the cinnamate to copper and by the presence of the α,β-unsaturated ester *para* to the desired position of attack. Yields of the diaryl ether **8** were in the range 50–60%, apparently dependent upon catalyst quality, with 10–30% recovery of starting materials. Palladium-catalysed hydrogenation and subsequent basic hydrolysis gave the saturated carboxylic acid in high yield.

Elaboration of the carboxylic acid **10** to form the required chiral centre of residue 2 was achieved efficiently using the methodology of Evans.[17–19] The chiral auxiliary, (*R*)-(+)-4-benzyl-1,3-oxazolidin-2-one, was attached in a one-pot reaction *via* the mixed anhydride **11**.[17] The intermediate anhydride was generated by treating the conjugate base of the carboxylic acid **10**, with trimethylacetyl chloride. Trimethylacetate displacement with (*R*)-4-benzyl-*N*-lithio-1,3-oxazolidin-2-one afforded the *N*-acyloxazolidinone **12** in 81% yield. Subsequent conversion to the chiral azide **13** was achieved by α- deprotonation of the oxazolidinone **11**, with potassium hexamethyldisilylamide then addition of the hindered electrophile 2,4,6-triisopropylbenzenesulphonyl azide[18] (trisyl azide; prepared in quantitative yield from trisyl chloride[20,21]). The reaction was quenched with glacial acetic acid and potassium acetate, and chromatography yielded the desired α-azido *N*-acyloxazolidinone **13** as a single diastereoisomer, in 85% yield (Scheme 1). None of the unwanted diastereoisomer was detected.

Residue 3 was protected as its di-*tert*-butyl ester ether **18** in three steps from (*S*)-4-hydroxyphenylglycine (4-HPG, **15**). Initially the amine was protected as its benzyloxycarbonyl (Cbz) carbamate **16**, in 76% yield, by reaction with benzyl chloroformate under weakly basic conditions. Formation of the di-*tert*-butyl ester ether **17** was achieved, in 53% yield, by shaking a suspension of the carbamate **16** in dichloromethane and liquefied 2-methylpropene, catalysed by sulphuric acid.[22] Hydrogenation of the carbamate **17** removed the Cbz group, and the amine was isolated (90%) as its hydrochloride **18**.



15 R = R' = R'' = H
16 R = Cbz, R' = R'' = H
17 R = Cbz, R' = R'' = Bu^t
18 R = H•HCl, R' = R'' = Bu^t

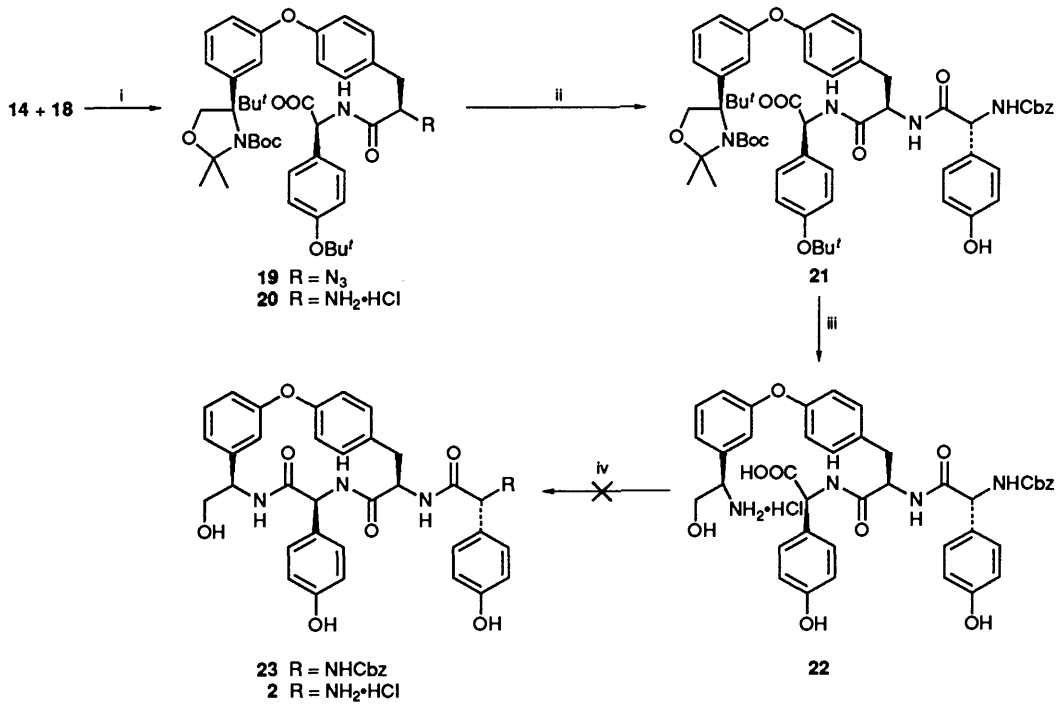
The *N*-acyloxazolidinone **13** was hydrolysed using lithium hydroperoxide[19] (no epimerisation was detected by ^1H NMR of either the hydrolysis product or the subsequent coupling product), and the crude product **14** was coupled immediately to the protected residue 3 amino acid **18**, promoted by *N,N'*-dicyclohexylcarbodiimide (DCC); the yield of peptide **19**, from **13**, was 90%. The azide **19** was catalytically hydrogenated under acidic conditions to give the amine hydrochloride **20**, which was coupled immediately to (*R*)-*N*-Cbz-4-HPG, the latter peptide coupling being induced using *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride.[23] Thus, the product tripeptide **21**, obtained in 76% yield from the protected dipeptide **19**, contained all four amino acid residues with the correct stereochemistry and suitable protecting groups (Scheme 2).

The deprotection of compound **21** was achieved by treatment with trifluoroacetic acid (TFA),[24] at room temperature, for 25 min. Quenching the reaction with water, or addition of ethyl methyl thioether[25] to the reaction solution, prevented removal of the residue 1 Cbz protecting group. The desired deprotected product was purified on a reverse phase medium pressure column, and converted to its hydrochloride **22** by ion-exchange chromatography.

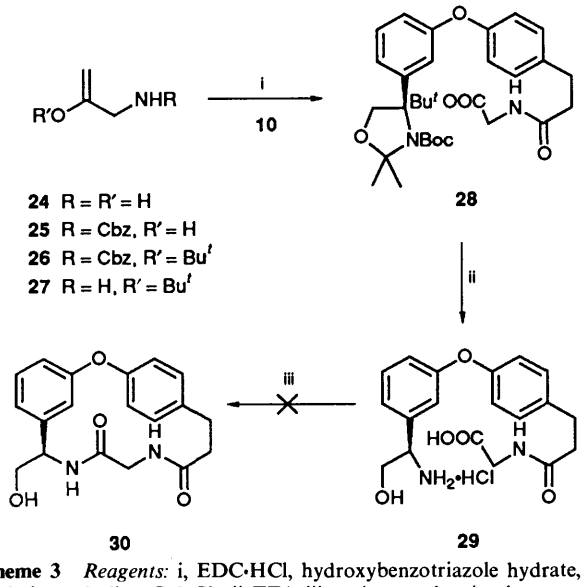
Attempts to cyclise compound **22** to the 16-membered macrocycle **23** were guided by previous successful syntheses of 13-, 14-, 16-, 17- and 19-membered macrocyclic lactams,[9,10,26–30] using DCC, EDC, diphenylphosphoryl azide,[31] benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate[32] or the Yamaguchi lactonisation reagent 2,4,6-trichlorobenzoyl chloride,[33] or by forming an activated pentafluorophenyl (PFP) ester[27] or pyridyl thioester.[34,35] Cyclisation attempts were carried out in the presence of only 1 equiv. or a slight excess of a hindered base because a large excess of base caused epimerisation of one or both 4-HPG α-centres. These attempts, as well as attempts to cyclise analogues with methyl or PFP esters at residue 3, afforded none of the desired macrocyclic lactam. Reaction mixtures and fractions obtained by HPLC were analysed by FAB mass spectrometry and ^1H NMR, providing evidence that adducts with the reagents had formed but neither cyclisation nor dimerisation had occurred.

In this light, a less strained model system was investigated lacking the conformational restrictions of chiral centres at residues 2 and 3. The new residue 3, glycine **24**, was protected in two steps. Benzyloxycarbonylation of the N-terminus, to give the carbamate **25** in 75% yield, and *tert*-butylation of the C-terminus, to give the ester **26** in 72% yield, were each achieved under analogous conditions to those described earlier for 4-HPG. Deprotection of the N-terminus by catalytic hydrogenation and coupling to the carboxylic acid **10** afforded the protected model peptide **28** (84%) which was deprotected quantitatively with neat TFA and purified by reverse-phase HPLC/ion-exchange chromatography.

Cyclisation attempts for the deprotected model peptide **29** were performed under analogous conditions to those described above for peptide **22**, but again yielded neither macrocyclic nor



Scheme 2 *Reagents:* i, DCC·HCl, CH_2Cl_2; ii, *N*-Cbz-4-HPG, EDC·HCl, CH_2Cl_2; iii, TFA; iv, various acyl activating reagents



Scheme 3 *Reagents:* i, EDC·HCl, hydroxybenzotriazole hydrate, *N*-methylmorpholine, CH_2Cl_2; ii, TFA; iii, various acyl activating reagents

dimeric material (Scheme 3). The reluctance of compounds **22** and **29** to cyclise through the peptide backbone, while previous studies have shown analogues to cyclise through sidechain groups,[9,10,26–30] can be attributed to the inability of the backbone to occupy the necessary conformation for peptide bond formation when the residue-3 carboxylate bears a bulky activating substituent.

The schemes presented herein demonstrate the preparative utility of both Ullmann diaryl ether coupling reactions and Evans amino acid synthesis, but emphasise the difficulty of macrocyclic lactamisation of conformationally restricted systems.

Experimental

General.—^{1}H NMR spectra were recorded on Bruker WM250 or AM400 spectrometers. ^{13}C NMR spectra were recorded on a Bruker AM400 spectrometer. All *J* values are in Hz. Infrared spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. Electron impact (EI) mass spectra were recorded on Kratos MS30, MS902 or MS50 double focussing spectrometers, while fast atom bombardment (FAB) mass spectra were recorded, in the positive-ion mode, on a Kratos MS50 spectrometer, using as the matrix glycerol–thioglycerol (1:1) containing *ca.* 1% acetic acid. Melting points were determined on a Reichert-Kofler block and are uncorrected. Optical rotations were determined on a Perkin-Elmer 241 polarimeter in a 1 cm^3 cell.

(E)-4-*Bromocinnamic Acid Methyl Ester.*—To a suspension of 4-bromocinnamic acid (10.1 g, 44.3 mmol) in methanol (100 cm^3), at 0 °C, was added slowly thionyl chloride (4.84 cm^3, 66.4 mmol), causing the solid to dissolve. The solution was refluxed for 3 h. On cooling, (*E*)-4-bromocinnamic acid methyl ester crystallised as white needles, which were removed by filtration. A second crop of needles was crystallised by reducing the volume of the filtrate (total yield 10.25 g, 96%), m.p. 89–90 °C (Found: M^+, 239.9782. $C_{10}H_9O_2Br$ requires 239.9786); ν_{max}(CHCl$_3$)/cm^{-1} 1708 (C=O); δ_H(400 MHz; $CDCl_3$) 3.79 (3 H, s, Me), 6.41 (1 H, d, *J* 16, 2-H), 7.36 (2 H, d, *J* 8, 3′-H and 5′-H), 7.50 (2 H, d, *J* 8, 2′-H and 6′-H) and 7.60 (1 H, d, *J* 16, 3-H); δ_C($CDCl_3$) 51.8 (Me), 118.5 (C-2), 124.5 (C-4′), 129.4 (C-2′) and (C-6′), 132.1 (C-3′ and C-5′), 133.2 (C-1′), 143.4 (C-3) and 167.1 (*C*OOMe); *m/z* (EI) 239 (M), 209 (M − OMe), 181 (M − COOMe) and 102 (181 − Br).

(R)-3-*Hydroxyphenylglycine Methyl Ester Hydrochloride* **4**.—(*R*)-3-Hydroxyphenylglycine **3** (1.01 g, 6.03 mmol) was methylated by an identical procedure to that used to prepare (*E*)-4-bromocinnamic acid methyl ester. The solvent was removed under reduced pressure, and the residue was recrystallised from methanol–diethyl ether to yield (*R*)-3-hydroxyphenylglycine methyl ester hydrochloride **4** (1.21 g, 92%) as colourless prisms, m.p. 188–189 °C (Found: M − HCl, 181.0734. $C_9H_{11}NO_3$ requires 181.0739); $[\alpha]_D$ −145° (18.0 g dm^{-3} in MeOH); ν_{max}(Nujol)/cm^{-1} 3600br (NH and OH) and 1740 (C=O); δ_H (250 MHz; CD_3OD) 3.80 (3 H, s, Me), 4.91 (3 H, br s, NH_3),

5.11 (1 H, s, CH_α), 6.9 (3 H, m, 2-H, 4-H and 6-H) and 7.29 (1 H, t, *J* 8, 5-H); $\delta_C(CD_3OD)$ 65.7 (Me), 124.3 (C-2 or C-4), 126.5 (C-4 or C-2), 128.1 (C-6), 140.0, (C-1), 142.7 (C-5), 167.8 (C-3) and 178.4 (CO_2Me); *m/z* (EI) 181 (M − HCl), 122 (181 − CO_2Me), 95 (122 − HCN) and 77 (95 − H_2O).

(R)-N-tert-*Butoxycarbonyl*-3-*hydroxyphenylglycine Methyl Ester* **5**.[36]—To a stirring mixture of (*R*)-3-hydroxyphenylglycine methyl ester hydrochloride **4** (12.1 g, 55.7 mmol) in sodium hydroxide (1 mol dm^{-3}; 61 cm^3) was added *tert*-butyl alcohol (42 cm^3), then dropwise di-*tert*-butyl dicarbonate (12.8 cm^3, 55.7 mmol). The mixture was stirred at room temperature for 17 h, then extracted with diethyl ether, washed with hydrochloric acid (1 mol dm^{-3}), then brine, and dried. Solvent removal under reduced pressure afforded (*R*)-*N-tert*-butoxycarbonyl-3-hydroxyphenylglycine methyl ester **5** (16.6 g, 99%) as a yellow oil (Found: M^+, 281.1285. $C_{14}H_{19}NO_5$ requires 281.1263); $[\alpha]_D$ −108° (11.6 g dm^{-3} in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440br (NH and OH), 1740 and 1700 (C=O); δ_H(400 MHz; $CDCl_3$) 1.51 (9 H, s, Bu^t), 3.69 (3 H, s, Me), 5.22 (1 H, d, *J* 7, CH_α), 5.63 (1 H, d, *J* 7, NH), 6.4 (1 H, br s, OH), 6.76 (1 H, br d, *J* 8, 4-H or 6-H), 6.86 (2 H, m, 2-H and 6-H or 4-H) and 7.17 (1 H, t, *J* 8, 5-H); *m/z* (EI) 281 (M), 266 (M − Me), 222 (M − COOMe), 166 (222 − C_4H_8) and 122 (166 − CO_2).

N-tert-*Butoxycarbonyl*-2-*hydroxy*-1-(3-*hydroxyphenyl*)-*ethylamine* **6**.—To a stirring suspension of lithium borohydride (4.85 g, 223 mmol) in diethyl ether (300 cm^3), at 0 °C, was added a solution of (*R*)-*N-tert*-butoxycarbonyl-3-hydroxyphenylglycine methyl ester **5** (15.6 g, 55.4 mmol) in diethyl ether (100 cm^3). A white precipitate formed. The mixture was stirred at 0 °C for 7 h, then quenched by the addition of saturated sodium bisulphate until both layers were clear. The organic layer was washed with brine, and dried, and the solvent was removed under reduced pressure to yield the title compound **6** (12.48 g, 89%) as a colourless oil; $\nu_{max}(CHCl_3)$/cm^{-1} 3600–3300 (NH and OH) and 1685 (C=O); δ_H(400 MHz; $CDCl_3$) 1.40 (9 H, s, Bu^t), 3.7 (2 H, m, CH_2), 4.64 (1 H, br s, C*H*–NH), 5.49 (1 H, br s, NH), 6.7 (3 H, m, 2-H, 4-H and 6-H) and 7.12 (1 H, t, *J* 8, 5-H); *m/z* (FAB) 254 (M + H) and 198 (M − C_4H_8); *m/z* (EI) 222 (M − CH_2OH), 166 (222 − C_4H_8) and 122 (166 − CO_2).

N-tert-*Butoxycarbonyl*-2,2′-*dimethyl*-4-(3-*hydroxyphenyl*)-1,3-*oxazolidine* **7**.—To a solution of *N-tert*-butoxycarbonyl-2-hydroxy-1-(3-hydroxyphenyl)ethylamine **6** (233 mg, 0.92 mmol) in dichloromethane (5 cm^3) was added 2,2-dimethoxypropane (1 cm^3, 8.1 mmol), then toluene-*p*-sulphonic acid (one crystal). The solution was stirred at room temperature for 1 h, diluted with dichloromethane, washed with saturated sodium hydrogen carbonate, then brine, and dried. Solvent removal under reduced pressure yielded the title compound **7** (246 mg, 91%) as an amorphous white solid (Found: M^+, 293.1608. $C_{16}H_{23}NO_4$ requires 293.1627); $[\alpha]_D$ −70° (14.1 g dm^{-3} in $CHCl_3$); $\nu_{max}(CHCl_3)$ 3340br (OH) and 1675 (C=O); δ_H(400 MHz; $CDCl_3$) 1.19, 1.46, 1.59, 1.71 and 1.75 (15 H, singlets, Me_2 and Bu^t), 3.83 (1 H, m, one of CH_2), 4.25 (1 H, dd, *J* 9 and 7, other CH_2), 4.72 and 4.88 (1 H, br s, CH–N), 6.6–6.8 (3 H, m, Ar-H_3) and 7.13 (1 H, m, Ar-H); *m/z* (EI) 293 (M), 278 (M − Me), 222 (278 − C_4H_8) and 178 (222 − CO_2).

The Diaryl Ether **8**.—A mixture of the phenol **7** (4.79 g, 16.3 mmol) and potassium carbonate (11.3 g, 81.7 mmol) in dry pyridine (30 cm^3) was stirred, at room temperature, for 30 min. A suspension of copper(I) chloride in pyridine [freshly prepared by refluxing copper(II) chloride (1.10 g, 8.17 mmol) and copper metal (519 mg, 8.17 mmol) in pyridine (30 cm^3) for 1 h] was added, and the mixture was refluxed for 30 min. A solution of 4-bromocinnamic acid methyl ester (4.40 g, 18.2 mmol) in pyridine (20 cm^3) was added, and the mixture was refluxed for a further 17 h. The cooled mixture was diluted with diethyl ether, washed with hydrochloric acid (1 mol dm^{-3}), aqueous sodium hydroxide (3 mol dm^{-3}), then brine, and dried. Solvent removal under reduced pressure and flash chromatography (dichloromethane–diethyl ether, 1:0 then 19:1, then 1:1) yielded: (*a*), starting phenol **7** (469 mg, 10%); (*b*), starting bromide (1.43 g, 32%); and (*c*) product diaryl ether **8** (4.13 g, 56%) as a yellow oil (Found: M^+, 453.2142. $C_{26}H_{31}NO_6$ requires 453.2151); ν_{max}(neat)/cm^{-1} 1693 (C=O); δ_H(250 MHz; $CDCl_3$) 1.23, 144, 1.57, 1.63 and 1.70 (15 H, br s, Me_2 and Bu^t), 3.79 (3 H, s, OMe), 3.85 (1 H, dd, *J* 9 and 3, equatorial CH_2), 4.27 (1 H, dd, *J* 9 and 7, axial CH_2), 4.78 and 4.95 (1 H, br s, CH–N), 6.33 (1 H, d, *J* 16, 2-H), 6.9–7.2 (5 H, m, Ar-H_5), 7.31 (1 H, t, *J* 8, 5″-H), 7.47 (2 H, d, *J* 9, 2′-H and 6′-H) and 7.65 (1 H, d, *J* 16, 3-H); *m/z* (EI) 453 (M), 438 (M − Me), 422 (M − OMe), 338 (M − CO_2Me − C_4H_8).

The Saturated Ester **9**.—A solution of the α,β-unsaturated ester **8** (779 mg, 1.72 mmol) in methanol (20 cm^3) was hydrogenated over 10% palladium on charcoal (100 mg) for 16 h. The mixture was filtered through silica, and the solvent was removed under reduced pressure to give the saturated ester **9** (711 mg, 91%) as a colourless oil (Found: M^+, 455.2325. $C_{26}H_{33}NO_6$ requires 455.2308); ν_{max}(neat)/cm^{-1} 1735 and 1690 (C=O); δ_H(250 MHz; $CDCl_3$) 1.21, 1.44, 1.57, 1.62 and 1.68 (15 H, br s, Me_2 and Bu^t), 2.61 (2 H, t, *J* 8, 2-H), 2.92 (2 H, t, *J* 8, 3-H), 3.67 (3 H, s, OMe), 3.83 (1 H, dd, *J* 9 and 3, eq. CH_2–O), 4.25 (1 H, dd, *J* 9 and 7, ax. CH_2–O), 4.74 and 4.91 (1 H, br s, CH–N), 6.8–7.3 (8 H, m, aromatic); *m/z* (EI) 455 (M), 440 (M − Me), 340 (M − CO_2Me − C_4H_8).

The Saturated Carboxylic Acid **10**.—To a stirring solution of the ester **9** (6.04 g, 13.3 mmol) in THF (100 cm^3), at 0 °C, was added aqueous lithium hydroxide (2 mol dm^{-3}; 65 cm^3, 130 mmol). The mixture was stirred at room temperature for 17 h, then diluted with diethyl ether. The extract was washed successively with hydrochloric acid (1 mol dm^{-3}), saturated sodium hydrogen carbonate, brine, and then dried. Solvent removal under reduced pressure yielded the carboxylic acid **10** (5.85 g, 100%) as a pale yellow oil (Found: M^+, 441.2176. $C_{25}H_{31}NO_6$ requires 441.2151); ν_{max}(neat)/cm^{-1} 3500–2600 (COOH) and 1690 (C=O); δ_H(250 MHz; $CDCl_3$) 1.21, 1.45, 1.57, 1.62 and 1.67 (15 H, br s, Me_2 and Bu^t), 2.66 (2 H, t, *J* 8, 2-H), 2.93 (2 H, t, *J* 8, 3-H), 3.84 (1 H, dd, *J* 9 and 3, eq. CH_2–O), 4.25 (1 H, dd, *J* 9 and 7, ax. CH_2–O), 4.75 and 4.92 (1 H, br s, CH–N), 6.8–7.3 (8 H, m, aromatic); *m/z* (EI) 441 (M), 426 (M − Me), 326 (M − CH_2CO_2H − C_4H_8).

The N-*Acyloxazolidinone* **12**.[17]—To a solution of the carboxylic acid **10** (2.46 g, 5.56 mmol) in diethyl ether (26 cm^3) was added triethylamine (0.80 cm^3, 5.73 mmol). The mixture was stirred at 0 °C while trimethylacetyl chloride (0.71 cm^3, 5.73 mmol) was added dropwise (a white precipitate formed), and the mixture was stirred at 0 °C for 2 h. In a separate flask, to a cooled (−78 °C) solution of (*R*)-(+)-4-benzyl-1,3-oxazolidin-2-one (985 mg, 5.56 mmol) in THF (13 cm^3) was added dropwise butyllithium (1.6 mol dm^{-3} in hexane; 3.5 cm^3, 5.6 mmol) and the mixture was stirred, at −78 °C, for 10 min. This orange solution was added *via* a syringe to the cooled (−78 °C) solution of the anhydride. The mixture was allowed to warm to room temperature over *ca.* 30 min, and was stirred at room temperature for 1 h. The reaction was quenched with saturated ammonium chloride (5 cm^3), and the solvent was removed under reduced pressure to give a white slurry, which was extracted into dichloromethane, washed successively with hydrochloric acid (1 mol dm^{-3}), saturated sodium hydrogen

carbonate, brine, and then dried. Solvent removal under reduced pressure and flash chromatography (hexane–ethyl acetate, 2:1) yielded the *N*-acyloxazolidinone **12** (2.70 g, 81%) as a pale yellow oil (Found: M^+, 600.2820. $C_{35}H_{40}N_2O_7$ requires 600.2835); ν_{max}(neat)/cm^{-1} 1780 and 1690 (C=O); δ_H(400 MHz; $CDCl_3$) 1.21, 1.45, 1.57, 1.62 and 1.69 (15 H, br s, Me_2 and Bu^t), 2.76 (1 H, dd, *J* 13 and 10, one of CH_2Ph), 3.0 (2 H, m, 3-H), 3.3 (3 H, m, 2-H and one of CH_2Ph), 3.83 (1 H, dd, *J* 9 and 3, eq. CH_2OCMe_2), 4.18 (2 H, m, CH_2OCO), 4.24 (1 H, dd, *J* 9 and 7, ax. CH_2OCMe_2), 4.67 (1 H, m, $CHCH_2Ph$), 4.73 and 4.92 (1 H, br s, C*H*–NBoc), 6.8–7.3 (13 H, m, aromatic); *m/z* (EI) 600 (M), 585 (M − Me) and 543 (M − C_4H_9).

2,4,6-*Triisopropylbenzenesulphonyl Azide* (*Trisyl Azide*).[20,21]—To a solution of sodium azide (13.0 g, 200 mmol, 3.33 equiv.) in aqueous ethanol (300 cm^3) was added 2,4,6-triisopropylbenzenesulphonyl chloride (18.2 g, 60 mmol). The mixture was stirred at room temperature for 19 h, then diluted with ice-cold water (100 cm^3), extracted into diethyl ether, washed with brine, and dried. Solvent removal under reduced pressure and recrystallisation from hot methanol (50 cm^3) gave trisyl azide in three crops (total yield 18.6 g, 100%) as large colourless prisms, m.p. 41.5–43 °C (Found: M^+, 309.1514. $C_{15}H_{23}N_3O_2S$ requires 309.1511); ν_{max}(Nujol)/cm^{-1} 2120 (N_3); δ_H(400 MHz; $CDCl_3$) 1.3 (18 H, m, 3 × C*H*Me_2), 2.96 (1 H, sep, *J* 7, C-4–C*H*), 4.11 (2 H, sep, *J* 7, C-2–C*H* and C-6–C*H*), 7.29 (2 H, s, 3-H and 5-H); δ_C($CDCl_3$) 23.1 (C-4–CHMe_2), 24.4 (C-2–CHMe_2 and C-6–CHMe_2), 29.6 (C-2–*C*H and C-6–*C*H), 34.1 (C-4–*C*H), 123.9 (C-3 and C-5), 131.9 (C-4), 150.6 (C-2 and C-6) and 154.7 (C-1); *m/z* (EI) 309 (M), 281 (M − N_2) and 266 (M − C_3H_7).

The Chiral Azide **13**.[18]—To a solution of potassium hexamethyldisilylamide (0.5 mol dm^{-3} in toluene; 2.0 cm^3, 1.0 mmol) in THF (3 cm^3), at −78 °C, was added, *via* a cannula, a cooled (−78 °C) solution of the *N*-acyloxazolidinone **12** (551 mg, 0.92 mmol) in THF (3 cm^3). The solution was stirred at −78 °C, for 30 min, then a cooled (−78 °C) solution of trisyl azide (341 mg, 1.10 mmol) in THF (3.8 cm^3) was added *via* a cannula. The solution was stirred at −78 °C for 2 min, then quenched by addition of glacial acetic acid (0.24 cm^3, 4.2 mmol), then potassium acetate (*ca.* 300 mg, 3.1 mmol) in THF (3 cm^3). The mixture was stirred at 30 °C for 1.5 h, then diluted with ethyl acetate, washed with hydrochloric acid, then brine, and dried. Solvent removal under reduced pressure and flash chromatography (hexane–ethyl acetate, 2:1) yielded the chiral azide **13** (588 mg, 85%) as a colourless oil; ν_{max}(neat)/cm^{-1} 2120 (N_3), 1785 and 1690 (C=O); δ_H(400 MHz; $CDCl_3$) 1.20, 1.44, 1.56, 1.62 and 1.69 (15 H, br s, Me_2 and Bu^t), 2.82 (1 H, dd, *J* 14 and 10, one of CH_2Ph), 3.00 (1 H, dd, *J* 14 and 9, one 3-H), 3.17 (1 H, dd, *J* 14 and 5, other 3-H), 3.32 (1 H, dd, *J* 13 and 3, other CH_2Ph), 3.83 (1 H, br d, *J* 10, eq. CH_2OCMe_2), 4.1–4.3 (3 H, m, ax. CH_2OCMe_2 and CH_2OCO), 4.62 (1 H, br s, $CHCH_2$-Ph), 4.73 and 4.90 (1 H, br s, C*H*–NBoc), 5.21 (1 H, dd, *J* 9 and 5, 2-H) and 6.8–7.3 (13 H, m, aromatic).

(S)-N-*Benzyloxycarbonyl*-4-*hydroxyphenylglycine* **16**.—To a solution of (*S*)-(+)-4-hydroxyphenylglycine **15** (499 mg, 2.99 mmol) and sodium hydrogen carbonate (0.63 g, 7.5 mmol) in water (5 cm^3) was added benzyl chloroformate (514 cm^3, 3.6 mmol, 1.2 equiv.). The mixture was stirred for 1 h, then washed with diethyl ether, acidified with hydrochloric acid (1 mol dm^{-3}), and extracted with ethyl acetate. Solvent removal under reduced pressure and recrystallisation from dichloromethane gave (*S*)-*N*-benzyloxycarbonyl-4-hydroxyphenylglycine **16** (684 mg, 76%) as a white solid (Found: M − COOH, 256.0956. $C_{15}H_{14}NO_3$ requires 256.0974); $[\alpha]_D$ +114° (*c* 11.5 g dm^{-3} in MeOH); ν_{max}/cm^{-1} 3380 (NH), 3400–2700 (CO_2H), 1730 and 1660 (C=O); δ_H(250 MHz; CD_3OD) 5.07 (2 H, s, CH_2Ph), 5.12 (1 H, s, CH_α), 6.75 (2 H, d, *J* 9, 3-H and 5-H), 7.21 (2 H, d, *J* 9, 2-H and 6-H) and 7.2–7.4 (5 H, m, Ph); *m/z* (FAB) 302 (M + H); *m/z* (EI) 256 (M − CO_2H), 166 (M − CO_2CH_2Ph), 151 (M − $NHCO_2CH_2Ph$), 107 (151 − CO_2).

The *R*-isomer was prepared by the same procedure from (*R*)-(−)-4-hydroxyphenylglycine, and had identical physical properties except for the optical rotation; $[\alpha]_D$ −119° (*c* 11.9 g dm^{-3} in MeOH).

(S)-N-*Benzyloxycarbonyl*-4-tert-*butoxyphenylglycine* tert-*Butyl Ester* **17**.[22]—(*S*)-*N*-Benzyloxycarbonyl-4-hydroxyphenylglycine **16** (686 mg, 2.28 mmol) was suspended in dichloromethane (6 cm^3). Liquefied 2-methylpropene (5 cm^3) and conc. sulphuric acid (few drops) were added, and the mixture was shaken in a pressure bottle, at room temperature, for 67 h. The 2-methylpropene was removed under a stream of nitrogen, and the solution was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate, then brine, and dried. Solvent removal under reduced pressure, followed by flash chromatography (hexane–ethyl acetate, 9:1, then 6:1, containing 1% triethylamine), yielded (*S*)-*N*-benzyloxycarbonyl-4-*tert*-butoxyphenylglycine *tert*-butyl ester **17** (497 mg, 53%) as a pale yellow oil (Found: M − Me, 398.1983. $C_{23}H_{28}NO_5$ requires 398.1967); ν_{max}($CHCl_3$)/cm^{-1} 3440 (NH) and 1710 (C=O); δ_H(400 MHz, [$^2H_6$]acetone) 1.32 (9 H, s, Bu^t), 1.38 (9 H, s, Bu^t), 5.09 (2 H, m, CH_2Ph), 5.19 (1 H, d, *J* 8, CH_α), 6.99 (2 H, d, *J* 9, 3-H and 5-H) and 7.3–7.4 (7 H, m, 2-H, 6-H and Ph); *m/z* (FAB) 414 (M + H); *m/z* (EI) 398 (M − Me), 312 (M − CO_2CMe_3), 256 (M − CO_2CMe_3 − C_4H_8) and 91 (C_7H_7).

(S)-4-tert-*Butoxyphenylglycine* tert-*Butyl Ester Hydrochloride* **18**.—A solution of (*S*)-*N*-benzyloxycarbonyl-4-*tert*-butoxyphenylglycine *tert*-butyl ester **17** (625 mg, 1.51 mmol) in methanol (25 cm^3) was hydrogenated over 10% palladium on charcoal (80 mg) for 1 h, then filtered through silica. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate. Hydrogen chloride in diethyl ether (1 mol dm^{-3}; 1.51 cm^3, 1.51 mmol) was added, and the solvents were removed under reduced pressure to give the title compound **18** as a white solid (475 mg, 100%) (Found: M − HCl − Me, 264.1606. $C_{15}H_{22}NO_3$ requires 264.1600); ν_{max}(Nujol)/cm^{-1} 1730 (C=O); δ_H(250 MHz; CD_3OD) 1.36 (9 H, s, Bu^t), 1.44 (9 H, s, Bu^t), 5.00 (1 H, s, CH_α), 7.10 (2 H, d, *J* 9, 3-H and 5-H) and 7.38 (2 H, d, *J* 9, 2-H and 6-H); *m/z* (FAB) 280 (M − Cl); *m/z* (EI) 264 (M − HCl − Me), 208 (264 − C_4H_8), 178 (M − HCl − CO_2CBu^t) and 122 (178 − C_4H_4).

Cleavage of the Chiral Auxiliary in the α-*Azido*-N-*acyloxazolidinone* **13** *and Coupling to Residue* 3: *Peptide* **19**.[19]—To a mixture of the α-azido-*N*-acyloxazolidinone **13** (462 mg, 0.72 mmol) in THF (10.5 cm^3) and water (2 cm^3) was added dropwise 30% hydrogen peroxide (0.33 cm^3, 2.88 mmol, 4 equiv.). A solution of lithium hydroxide monohydrate (60 mg, 1.44 mmol, 2 equiv.) in water (1.5 cm^3) was added, and the mixture was stirred at 0 °C for 40 min. Aqueous sodium sulphite (1.5 mol dm^{-3}; 2 cm^3) was added, then the mixture was diluted with ethyl acetate, washed with aqueous potassium hydrogen sulphite, then brine, and dried. Removal of the solvents under reduced pressure gave a colourless oil (515 mg), which was dried under high vacuum. This oil and (*S*)-4-*tert*-butoxyphenylglycine *tert*-butyl ester hydrochloride **18** (227 mg, 0.72 mmol) were stirred in dichloromethane (7.2 cm^3), and DCC hydrochloride (193 mg, 0.94 mmol, 1.3 equiv.) was added. The mixture was stirred at room temperature for 50 min, then filtered. Solvent was removed from the filtrate under reduced pressure, and flash chromatography of the residue (hexane–

ethyl acetate, 2:1, containing 1% triethylamine) yielded the peptide **19** (482 mg, 90%) as a yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH), 2120 (N_3), 1725 and 1675 (C=O); δ_H(400 MHz; [$^2H_6$]acetone) 1.33 and 1.40 (18 H, s, 2 × Bu^t), 1.23, 1.44, 1.53 and 1.64 (15 H, br s, Me_2 and NCO_2Bu^t), 3.03 (1 H, dd, *J* 14 and 8, CH_2Ar), 3.21 (1 H, dd, *J* 14 and 6, CH_2Ar), 3.82 (1 H, br d, *J* 9, C*H*CO_2Bu^t), 4.20 (1 H, dd, *J* 8 and 7, CH_2O), 4.32 (1 H, dd, *J* 9 and 7, CH_2O), 4.85 and 4.95 (1 H, br s, C*H*–NBoc), 5.35 (1 H, s, CH–N_3) and 6.8–7.4 (12 H, m, aromatic).

Hydrogenation of the Azide **19** *and Coupling to Residue* 1: *Peptide* **21**.[23]—A solution of the azide **19** (459 mg, 0.62 mmol) and trifluoroacetic acid (48 mm^3, 0.62 mmol) in methanol (6 cm^3) was hydrogenated over 10% palladium on charcoal (50 mg) for 2 h. The mixture was filtered through silica, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate, then brine, and dried. Hydrogen chloride in diethyl ether (1 mol dm^{-3}; 0.62 cm^3, 0.62 mmol) was added, and solvent removal under reduced pressure gave a yellow oil (477 mg). This oil and (*R*)-*N*-benzyloxycarbonyl-4-hydroxyphenylglycine (187 mg, 0.62 mmol) were stirred in dichloromethane (6.2 cm^3) while EDC hydrochloride (160 mg, 0.83 mmol, 1.35 equiv.) was added. The mixture was stirred at room temperature for 1.5 h, then filtered, diluted with dichloromethane, washed with hydrochloric acid (1 mol dm^{-3}), then brine, and dried. Solvent removal under reduced pressure, flash chromatography (chloroform–methanol, 100:1, containing 1% triethylamine), and preparative TLC (chloroform–methanol, 30:1, containing 1% triethylamine) of the mixed fractions yielded peptide **21** (460 mg, 74%) as a white amorphous solid; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450–3300 (NH), 1720 and 1675 (C=O); δ_H(250 MHz; [$^2H_6$]DMSO) 1.30 and 1.33 (18 H, s, 2 × Bu^t), 1.16, 1.39, 1.49 and 1.59 (15 H, br s, Me_2 and NCO_2Bu^t), 2.8–2.9 (2 H, m, CHCH_2Ar), 3.76 (1 H, dd, *J* 9 and 3, CH_2COCMe_2), 4.25 (1 H, dd, *J* 9 and 7, CH_2OCMe_2), 4.7–4.8 (2 H, m, C*H* – NBoc and C*H*CH_2Ar), 5.02 (2 H, s, OCH_2Ph), 5.1–5.2 (2 H, m, CH_α of residues 1 and 3), 6.66 (2 H, d, *J* 9, 3-H and 5-H of residue 1), 6.8–7.3 (14 H, m, aromatic), 7.73 (1 H, d, *J* 9, NH of residue 1 or 3), 8.28 (1 H, d, *J* 8, NH of residue 2) and 8.72 (1 H, d, *J* 7, NH of residue 3 or 1).

Deprotection of Peptide **21**: *Peptide* **22**.[24]—The protected peptide **21** (60 mg, 0.06 mmol) was dissolved in TFA (0.6 cm^3) and set aside at room temperature for 30 min. Water (*ca.* 3 cm^3) was added, and the solvents were removed by rotary evaporation and lyophilisation to give a white solid. Medium pressure chromatography (C18 silica, Whatman ODS 3; acetonitrile–water, 7:13, containing 0.1% TFA), followed by ion-exchange chromatography (C18 silica, Whatman ODS 3; 0.01 mol dm^{-3} hydrochloric acid; acetonitrile–water, 1:1) and lyophilisation, yielded peptide **22** as a white foam; δ_H(400 MHz; [$^2H_6$]DMSO) 2.7–3.0 (2 H, m, CHCH_2Ar), 3.58–3.77 (2 H, m, CH_2OH), 4.28 (1 H, br s, CH_α of residue 4), 4.71 (1 H, m, CH_α of residue 2), 5.01 (2 H, AB q, OCH_2Ph), 5.12 (1 H, d, *J* 8, CH_α of residue 1 or 3), 5.18 (1 H, d, *J* 8, CH_α of residue 3 or 1), 6.6–7.4 (21 H, m, aromatic), 7.74 (1 H, d, *J* 8, NH of residue 1 or 3), 8.24 (1 H, d, *J* 8, NH of residue 2), 8.38 (2 H, br d, *J* 12, NH_2) and 8.62 (1 H, d, *J* 8, NH of residue 3 or 1); *m*/*z* (FAB) 749 (M + H).

N-*Benzyloxycarbonylglycine* **25**.—To a stirring solution of glycine **24** (3.0 g, 40 mmol) and sodium hydrogen carbonate (8.4 g, 100 mmol, 2.5 equiv.) in water (67 cm^3) was added benzyl chloroformate (10 cm^3, 70 mmol, 1.75 equiv.), in 1 cm^3 portions, during 2.5 h. Stirring was continued for 1 h, then the mixture was acidified with conc. hydrochloric acid, extracted with ethyl acetate, washed with brine, and dried. Solvent removal under reduced pressure and recrystallisation from ethyl acetate–hexane gave *N*-benzyloxycarbonylglycine **25** as a white powder (6.31 g, 75%), m.p. 114–116 °C (Found: M$^+$, 209.0671. $C_{10}H_{11}NO_4$ requires 209.0688); ν_{max}(Nujol)/cm^{-1} 3340 (NH), 2600 (CO_2H), 1730 and 1680 (C=O); δ_H(400 MHz; CD_3OD) 3.82 (2 H, s, H_α), 5.09 (2 H, s, CH_2Ph) and 7.2–7.4 (5 H, m, Ph).

N-*Benzyloxycarbonylglycine* tert-*Butyl Ester* **26**.—To a suspension of *N*-benzyloxycarbonylglycine **25** (1.0 g, 4.8 mmol) in dichloromethane (10 cm^3) and liquefied 2-methylpropene (10 cm^3), at 0 °C, was added fuming sulphuric acid (few drops). The flask was sealed and the mixture was stirred vigorously at room temperature for 4 d. The mixture was poured into saturated sodium hydrogen carbonate, extracted with ethyl acetate, washed with brine, and dried. Solvent removal under reduced pressure and flash chromatography (hexane–ethyl acetate, 9:1, then 4:1, then 2:1) afforded *N*-benzyloxycarbonylglycine *tert*-butyl ester **26** as a colourless oil (913 mg, 72%) (Found: M − C_4H_8, 209.0676. $C_{10}H_{11}NO_4$ requires 209.0688); ν_{max}(neat)/cm^{-1} 3360 (NH) and 1730 C=O); δ_H(400 MHz; $CDCl_3$) 1.26 (9 H, s, Bu^t), 3.61 (2 H, br s, H_α), 4.90 (2 H, s, CH_2Ph), 5.87 (1 H, br s, NH) and 7.12 (5 H, br s, C_6H_5); *m*/*z* (EI) 209 (M − C_4H_8) and 91 (C_7H_7).

The Protected Model Peptide **28**.[23]—A solution of *N*-benzyloxycarbonylglycine *tert*-butyl ester **26** (100 mg, 0.38 mmol) in methanol (6 cm^3) was hydrogenated over 10% palladium on charcoal for 1.5 h. The mixture was filtered through Celite, hydrogen chloride in ether (1 mol dm^{-3}) was added to the filtrate, and the solvent was removed under reduced pressure. The residue (66 mg) and the carboxylic acid **10** (113 mg, 0.26 mmol) were dissolved in dichloromethane (3.5 cm^3). 1-Hydroxybenzotriazole hydrate (35 mg, 0.26 mmol, 1 equiv.) and *N*-methylmorpholine (86 cm^3, 0.78 mmol, 3 equiv.) were added, and the solution was cooled to 0 °C. EDC hydrochloride (100 mg, 2.0 equiv.) was added, and the mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate, washed with water (twice), saturated sodium hydrogen carbonate, citric acid, then brine, and dried. Solvent removal under reduced pressure and flash chromatography (hexane–ethyl acetate, 2:1) afforded the protected model peptide **28** (119 mg, 84%) as a colourless oil (Found: M − C_4H_8, 498.2337. $C_{27}H_{34}N_2O_7$ requires 498.2366); δ_H(400 MHz; $CDCl_3$) 1.19, 1.44, 1.54, 1.60 and 1.66 (24 H, br s, 2 × Bu^t and 2 × Me), 2.50 (2 H, t, *J* 8, ArCH_2CH_2CO), 2.92 (2 H, t, *J* 8, ArCH_2CH_2CO), 3.81 (1 H, dd, *J* 9 and 3, eq. CH_2O), 3.89 (2 H, d, *J* 4, Gly H_α), 4.22 (1 H, dd, *J* 9 and 7, axial CH_2O), 4.72 and 4.89 (1 H, br s, ArC*H*N), 6.18 (1 H, br s, NH), 6.8–6.9 (4 H, m), 6.97 (1 H, d, *J* 8), 7.1 (2 H, m), 7.23 (1 H, t, *J* 8), (8 aromatic); *m*/*z* (EI) 498 (M − C_4H_8), 454 (498 − CO_2), 439 (M − $CH_2CO_2Bu^t$) and 424 (M − $NHCH_2CO_2Bu^t$).

Deprotection of the Model Peptide **28**: *Peptide* **29**.[24]—The protected model peptide **28** (45 mg, 0.082 mmol) was dissolved in TFA (0.82 cm^3) and set aside at room temperature for 30 min. Water (*ca.* 5 cm^3) was added and the solvent was removed under reduced pressure to give a colourless oil. Medium pressure chromatography (C18 silica, Whatman ODS 3; 0.01 mol dm^{-3} hydrochloric acid; acetonitrile–water, 7:13) yielded the deprotected model peptide **29** (29 mg, 100%) as a pale yellow oil (Found: M − $2H_2O$, 322.1326. $C_{19}H_{18}N_2O_3$ requires 322.1317); δ_H(400 MHz; D_2O) 2.64 (2 H, t, *J* 7, ArCH_2CH_2CO), 2.95 (2 H, t, *J* 7, ArCH_2CH_2CO), 3.93 (2 H, s, Gly H_α), 3.8–4.0 (2 H, m, CH_2OH), 4.45 (1 H, br t, *J* 5, C*H*NH_2), 7.02 (2 H, d, *J* 8, 2′-H and 6′-H or 3′-H and 5′-H), 7.07 (1 H, d, *J* 9, 4″-H or 6″-H), 7.09 (1 H, s, 2″-H), 7.21 (1 H, d, *J* 8, 6″-H or 4″-H), 7.29

(2 H, d, *J* 8, 3′-H and 5′-H or 2′-H and 6′-H) and 7.48 (1 H, t, *J* 8, 5″-H); *m/z* (FAB) 359 (M + H).

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