Application of the Suzuki Biphenyl Synthesis to the Natural Products Biphenomycin and Vancomycin

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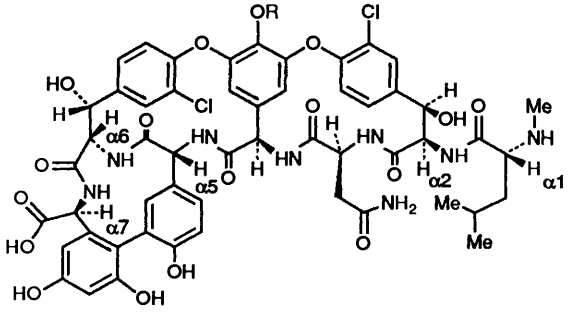
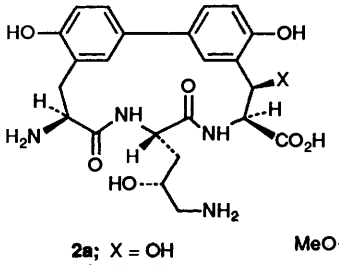
The synthesis of the unsymmetrical biphenyls **10** and **25** has been carried out by the palladium(0) catalysed coupling of the aryl boronic acid derivatives **5** and **20** with the aryl bromides **9** and **23** derived from (*R*)-4-hydroxyphenylglycine and (*S*)-tyrosine. In the former case unsuccessful attempts were made to bring about cyclization to compound **4** which is an analogue of the biphenyl ring system found in vancomycin. In the latter case, a variety of cyclization methods were used to give the cyclic products **34** and **35** which are analogues of the biphenomycin antibiotics.

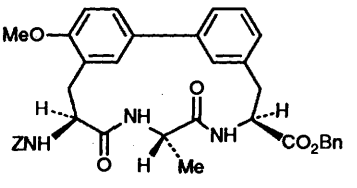
The palladium catalysed coupling of aryl bromides with aryl boronic acids has been shown to have great utility in the synthesis of unsymmetrical biphenyls.[1] The work of Snieckus[2] and others[3,4] has demonstrated that a wide range of substituted biphenyls can be prepared in this way. Our own interest in this methodology has focused on the biphenyl systems which are found in the glycopeptide antibiotics,[5] of which vancomycin **1** is a typical member, and in the biphenomycins **2**[6,7] which are also antibacterially active natural products. We have reported elsewhere on one of our approaches to the synthesis of analogues of the biphenomycins.[8] As our work was reaching a conclusion, a communication from Schmidt[9] and co-workers outlined the application of the boronic acid methodology to the synthesis of the biphenomycin analogue **3** and the same group has used the coupling of an arylzinc chloride to achieve a total synthesis of biphenomycin B **2b**.[10] In this paper we give details of our efforts in this field including the synthesis of some decarboxy analogues of biphenomycin B and an approach to the biphenyl system found in vancomycin.



1; R = *O*-α-L-vancosaminyl-(1→2)-*O*-β-D-glucopyranosyl

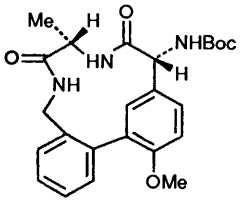


2a; X = OH
b; X = H



3; Z = Benzyloxycarbonyl
Bn = Benzyl

In the vancomycin molecule, residues 5, 6 and 7 pose an interesting synthetic challenge as they contain a cyclic peptide linked by a biphenyl bond between two phenylglycine derivatives. We determined to attempt the synthesis of the cyclic biphenyl derivative **4** which incorporates some of the features found in this region of vancomycin, *viz.* an (*R*)-4-hydroxyphenylglycine residue linked to an (*S*)-amino acid (alanine) corresponding to residues 5 and 6 of the natural product. A simple, unsubstituted aryl residue would provide the biphenyl bridging group. No attempt would be made to introduce the terminal carboxy to be found in residue 7 of the natural product and the phenolic group would be masked by methylation. Thus, the boronic acid derivative **5**[11] was chosen as a useful synthon which could be coupled with a brominated derivative of (*R*)-4-hydroxyphenylglycine giving a biphenyl derivative suitable for cyclization. Compound **5** was readily available, although in low yield, by a metallation reaction of 2-bromobenzyl alcohol with butyllithium followed by condensation with tributyl borate and an acidic work-up.



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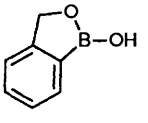

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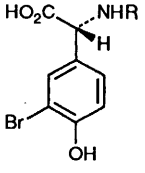
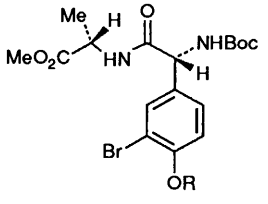


6; R = H
7; R = Boc

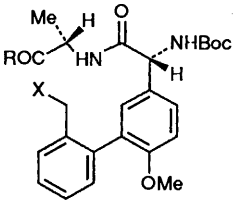
(*R*)-4-Hydroxyphenylglycine was converted into the 3-bromo derivative **6** which was then protected as the *N*-*tert*-butoxycarbonyl derivative **7**. Compound **7** was coupled with (*S*)-alanine methyl ester using dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBT) to give the peptide **8** which was *O*-methylated to give **9**. The boronic acid derivative **5** was then treated with the bromo peptide **9** using the Suzuki coupling conditions.[1] After column chromatography on silica gel, a single product was isolated from the reaction and this was identified as the desired unsymmetrical biphenyl **10**. Spectroscopic data were in accord with this structure and there

was no evidence (NMR or chromatographic) for formation of a diastereoisomer in this reaction.

When treated with a solution of hydrazoic acid in toluene under Mitsunobu conditions[12] (**CAUTION**: hydrazoic acid is toxic and explosive), the intermediate **10** was converted in good yield into the azide **11** which it was hoped could be progressed by a variety of methods to the desired cyclic product **4**. An abortive attempt was made to cyclize the amino ester **12** (formed by catalytic reduction of the azide **11**) by heating in dry DMF (*N*,*N*-dimethylformamide) containing HOBT. Alternatively, the acid **13** was prepared by saponification with aq. NaOH and then converted into an activated ester by treatment with DCC and *N*-hydroxysuccinimide.[13] Unfortunately, attempts to reduce this compound and then cyclize were also unsuccessful.



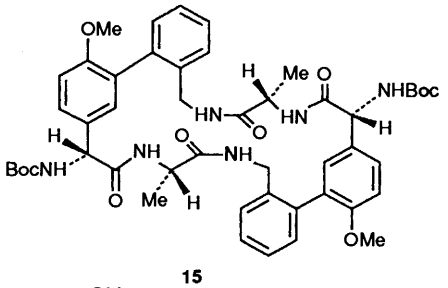
8; R = H
9; R = Me



10; X = OH, R = OMe
11; X = N_3, R = OMe
12; X = NH_2, R = OMe
13; X = N_3, R = OH
14; X = NH_2, R = OH

Hydrogenation of the sodium salt of the azido acid **13** gave the water soluble compound **14** which was difficult to characterize spectroscopically and which appeared to be a mixture of the ω-amino acid **14** and its sodium salt. The NMR spectrum of compound **14** at 295 K was quite complex although it simplified when recorded at 340 K suggesting that conformational isomers were present. In an attempt to bring about cyclization of compound **14** it was treated with diphenylphosphoryl azide (DPPA) in a dilute solution in DMF in the presence of base (Et_3N or $NaHCO_3$).[14] None of the desired product **4** could be identified in the complex reaction mixture. The only product isolated, in low yield, was tentatively assigned the dimeric structure **15** largely on the basis of mass spectral data (FAB mass spectrum, MH^+ 879). This compound **15** also displayed a complex NMR spectrum at ambient temperature which simplified somewhat on heating to 340 K.

Our failure to achieve the synthesis of the cyclic derivative **4** by this approach was disappointing. The application of this method of cyclization (DPPA) was successful when applied to the synthesis of the cyclic compound **16**[15] which is an analogue of the vancomycin binding pocket (residues 2, 3 and 4). Perhaps in the case of the biphenyl **14**, ring closure is rendered a more difficult process by the smaller size of ring to be formed (12 *vs.* 16 membered) and the strain imposed by the *ortho–meta* substituted biphenyl which it contains.



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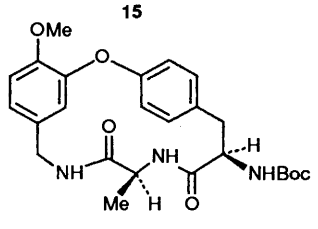

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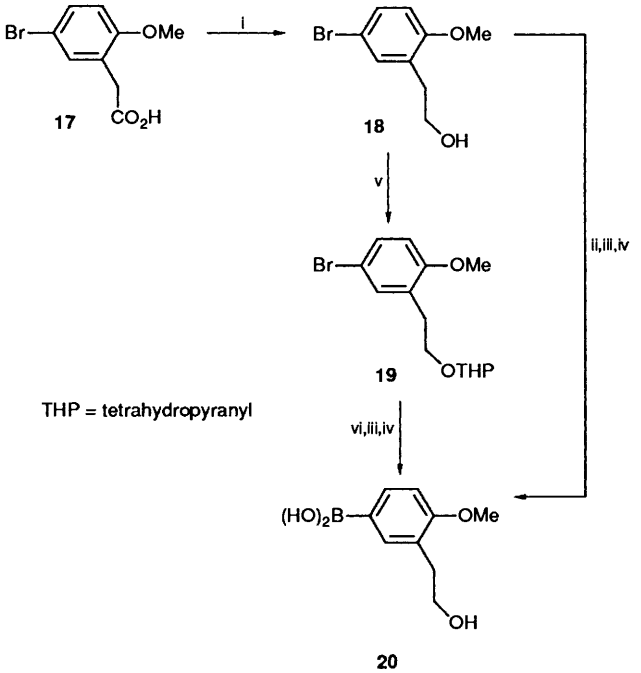
Another area of interest to us lay in the applicability of the boronic acid methodology to the synthesis of biphenomycin analogues. We have already reported on our investigation of the oxidative coupling of tyrosine derivatives with vanadium oxyhalides.[8] It seemed that the boronic acid methodology would give more flexibility in the choice of substituents and better yields of biphenyl.

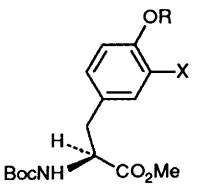
The decarboxy analogues **34** and **35** of biphenomycin B appeared to be readily accessible targets for which the boronic acid **20** would be a useful intermediate. A brominated derivative of (*S*)-tyrosine such as **23** could provide the second component required for the formation of the biphenyl linkage.

The synthesis of the aryl boronic acid **20** is outlined in Scheme 1. Reduction of the bromo acid **17** with borane gave an almost quantitative yield of the bromophenyl alcohol **18** which, when treated with butyllithium (two equiv.) followed by tributyl borate and an acidic work-up, gave the desired product **20** in 15% yield. A better procedure was then developed in which the alcohol **18** was protected as a tetrahydropyranyl (THP) ether **19** prior to the metallation reaction and condensation with tributyl borate. By treatment with acid during the work-up of this reaction the boronic acid **20** was generated from its butyl ester and the THP protecting group was removed. The crystalline boronic acid **20** was thus prepared from alcohol **18** in 64% overall yield.

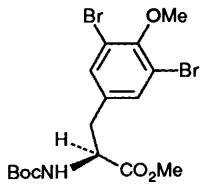


Scheme 1 *Reagents and conditions:* i, BH_3·THF; ii, 2 eq. BuLi; iii, $(BuO)_3B$; iv, H^+; v, dihydropyran/H^+; vi, 1 eq. BuLi

The second component **23** required for biphenyl formation was derived from *N*-Boc-(*S*)-tyrosine methyl ester **21** by bromination which gave a crude bromo compound **22**. After *O*-methylation of this crude product the mono bromo compound **23** was separated from a small amount of dibromo compound **24** by chromatography. The bromo compound **23** and boronic acid **20** were then coupled in 1,2-dimethoxyethane (DME) containing aq. sodium carbonate and a catalytic amount of tetrakistriphenylphosphine palladium.[3] The desired



21; R = H, X = H
22; R = H, X = Br
23; R = Me, X = Br



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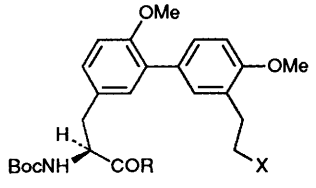
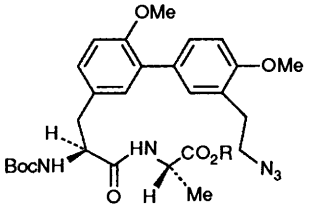
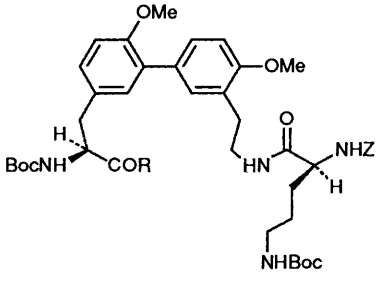


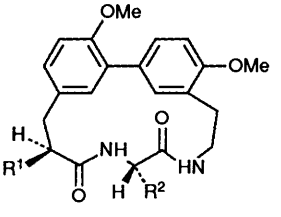
25; R = OMe, X = OH
26; R = OMe, X = N_3
27; R = OH, X = N_3
28; R = OMe, X = NH_3^+ TsO^-



29; R = Bn
30; R = Me
31; R = C_6F_5



32; R = OMe
33; R = C_6F_5



34; R^1 = BocNH, R^2 = Me
35; R^1 = BocNH, R^2 = $CH_2CH_2CH_2NHBoc$
36; R^1 = $NH_3^+CF_3CO_2^-$, R^2 = $CH_2CH_2CH_2NH_3^+CF_3CO_2^-$
37; R^1 = $NH_3^+CF_3CO_2^-$, R^2 = Me
38; R^1 = CH_3CONH, R^2 = Me

product **25** was obtained in 54% yield. There was some evidence for hydrolysis of the ester function in this reaction as it was possible to isolate an acid compound from the aqueous phase after work-up. Esterification of this material (potassium carbonate–dimethyl sulphate in DMF) gave a further quantity of the biphenyl **25** identical in all respects to that obtained earlier. When examined by HPLC using a chiral stationary phase, the biphenyl **25** showed no evidence of isomeric impurity. The hydroxy function of compound **25** was then converted into azide **26** using the Mitsunobu method.[12]

The conversion of the key intermediate **26** to biphenomycin analogues was then pursued in different ways. Thus compound **26** was saponified (1 mol dm^{-3} NaOH) and the azido acid **27** coupled with (*S*)-alanine benzyl ester and with (*S*)-alanine methyl ester giving the precursors **29** and **30**. Hydrogenolysis of **29** gave a zwitterionic intermediate which was used without purification in a cyclization reaction with diphenylphosphoryl azide in DMF. This reaction was carried out in dilute solution using *N*-methylmorpholine as base and the major product obtained, in 21% yield, was identified as the desired cyclic compound **34**. A small amount of material, probably a cyclodimer (MH^+ 995), was the only other product obtained from this reaction. Compound **34** was also prepared by a different process in which the alanyl methyl ester **30** was saponified and converted into the pentafluorophenyl ester **31**. Hydrogenation of **31** in dioxane–ethanol containing 4-pyrrolidinopyridine[16] at 90 °C brought about cyclization to the desired product **34** in 28% yield. In the NMR spectrum of compound **34** each proton could be differentiated by decoupling experiments. The protons of the $ArCH_2CH_2NH$ system appeared as complex multiplets centred on δ 2.7, 3.1, 3.2 and 3.9, consistent with their being in a cyclic system and experiencing different shielding effects from the neighbouring aryl and amide groups.

For the construction of the cyclic peptide **35** another approach was employed. The azide **26** was converted into amine **28** (isolated as a toluene-*p*-sulphonate salt) which was then coupled with δ-*N*-Boc-α-*N*-*Z*-(*S*)-ornithine to give the intermediate peptide **32** in good yield. Compound **32** was then saponified and converted into the pentafluorophenyl ester **33** which was used without purification and subjected to the reductive cyclization conditions described above.[16] A single product was isolated from the reaction and identified as the desired biphenomycin analogue **35**. Unfortunately, this alternative means of ring closure did not give an appreciably better yield of cyclic product.

When treated with trifluoroacetic acid in CH_2Cl_2, compounds **34** and **35** were readily converted into deprotected amine salts **36** and **37**. The amine **37** was also converted into the *N*-acetyl derivative **38**. None of the derivatives **36**, **37** or **38** showed useful levels of antibacterial activity.

Experimental

UV spectra were recorded on a Pye-Unicam SP7-500 instrument and extinction coefficients are reported in parentheses as $\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$. IR spectra were recorded for solutions in chloroform (except where noted otherwise) using a Perkin-Elmer 197. Unless stated otherwise, ^1H NMR spectra were recorded at 250 MHz on a Bruker WM250 for solutions in [$^2H_6$]-acetone using a tetramethylsilane as internal standard. Other ^1H NMR spectra were recorded on a Bruker WM400 (400 MHz) or a Perkin-Elmer R32 (90 MHz). *J* Values are given in Hz. Mass spectra were recorded using a VG 7070 or a VG ZAB instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. [α] Values are given in $10^{-1}\ cm^2\ g^{-1}$.

Merck silica gel 60 (Art. 7729) was used for column chromatography. All organic solutions were dried over anhydrous magnesium sulfate. Hexane refers to the straight chain isomer and the following abbreviations are used; THF for tetrahydrofuran, DMF for *N*,*N*-dimethylformamide, DCC for dicyclohexylcarbodiimide, HOBT for *N*-hydroxybenzotriazole hydrate. α-*N*-Benzyloxycarbonyl-δ-*N*-*tert*-butoxycarbonyl-(*S*)-ornithine was purchased from Chemical Dynamics Corporation. Bio-gel P2 was purchased from Bio-Rad Laboratories.

1,3-*Dihydro*-2,1-*benzoxaborol*-1-*ol* **5**.—*o*-Bromobenzyl alcohol (2.8 g, 15 mmol) was dissolved in dry THF (30 cm^3) and cooled to −40 °C under argon. A solution of butyllithium (31 mmol) in hexane (21 cm^3) was added dropwise with stirring

and the resulting mixture kept at −40 °C for 15 min. Tributyl borate (8.1 cm^3, 30 mmol) was added with stirring and the reaction was allowed to warm to room temperature. After 1 h the solution was diluted with water (50 cm^3) and washed with ethyl acetate (20 cm^3). The aqueous phase was then adjusted to pH 1.5 by addition of dil. HCl and extracted with ethyl acetate (100 cm^3). The extract was dried and evaporated to a crude solid (1 g) which was recrystallized from hot water to give white crystals (0.6 g, 30%), m.p. 87–89 °C (lit.,[11] 96–98 °C) (Found: C, 63.0; H, 5.0. Calc. for $C_7H_7BO_2$: C, 62.75; H, 5.25%); δ_H(90 MHz) 4.98 (2 H, s), 7.2–7.45 (3 H, m), 7.6–7.8 (1 H, m) and 7.97 (1 H, s, exch D_2O).

(R)-3-*Bromo*-4-*hydroxyphenylglycine* **6**.—(*R*)-4-Hydroxyphenylglycine (8.8 g, 52 mmol) was suspended in glacial acetic acid (50 cm^3) and hydrobromic acid in acetic acid (45% w/v; 10 cm^3) was added. A solution of bromine (2.6 cm^3, 50 mmol) in acetic acid (10 cm^3) was then added dropwise with stirring over a period of 1 h to give a precipitate. The mixture was left at room temperature overnight after which the solid was filtered off and washed with a small volume of acetic acid and with ether. The *bromo acid* **6** was obtained as a white solid (6.3 g, 49%), m.p. 210 °C (decomp.) (Found: C, 39.2; H, 3.45; Br, 32.2; N, 5.6. $C_8H_8BrNO_3$ requires C, 39.05; H, 3.3; Br, 32.5; N, 5.7%); $[\alpha]_D^{20}$ −84 (*c* 0.5 in 0.25 mol dm^{-3} NaOH); δ_H(60 MHz, D_2O–NaOD) 6.55 (1 H, d, *J* 8), 7.0 (1 H, dd, *J* 8, 2) and 7.3 (1 H, d, *J* 2). We are grateful to Mr. A. Bicknell for details of this preparation.

(R)-(3-*Bromo*-4-*hydroxyphenyl*)-N-tert-*butoxycarbonylglycine* **7**.—(*R*)-3-Bromo-4-hydroxyphenylglycine (6.1 g, 25 mmol) was treated with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (6.3 g, 25.5 mmol) as described by Itoh *et al.*[17] The product **7** was obtained as a white foam (8.7 g, quantitative), $[\alpha]_D^{23}$ −114 (*c* 0.12 in $CHCl_3$); ν_{max}/cm^{-1} 3500, 3420, 3300, 1710 and 1650; δ_H(90 MHz) 1.38 (9 H, s), 5.15 (1 H, d, *J* 9, collapse to br s with D_2O), 6.4 (1 H, br, exch D_2O), 6.95 (1 H, d, *J* 8.5), 7.25 (1 H, dd, *J* 8.5, 2) and 7.57 (1 H, d, *J* 2); *m/z* (M^+, thioglycerol; FAB) 346 (MH^+), 290 ($MH^+ - C_4H_8$); TLC analysis, elution with 5% v/v MeOH–$CHCl_3$, R_f 0.1.

[(R)-(3-*Bromo*-4-*hydroxyphenyl*)-N-tert-*butoxycarbonylglycyl*]-(S)-*alanine Methyl Ester* **8**.—(*R*)-(3-Bromo-4-hydroxyphenyl)-*N*-*tert*-butoxycarbonylglycine **7** (4.6 g, 13.3 mmol) and (*S*)-alanine methyl ester hydrochloride (1.87 g, 13.3 mmol) were dissolved in dry DMF (25 cm^3). HOBT (1.8 g, 13.3 mmol) and triethylamine (2.15 cm^3, 15.3 mmol) were added and the mixture was stirred and cooled in an ice bath. A solution of DCC (3.15 g, 15.3 mmol) in dry THF (25 cm^3) was added dropwise with stirring and the mixture was stirred overnight at room temperature. The white precipitate was filtered off and washed with ethyl acetate. The combined filtrates were washed with 1 mol dm^{-3} HCl, aqueous sodium hydrogen carbonate and with brine. Drying, evaporation and chromatography on silica gel, eluting with 5% v/v MeOH–$CHCl_3$ (R_f 0.25), gave the product **8** as a foam (4.4 g, 78%), $[\alpha]_D^{20}$ −89.4 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3510, 3420, 1740, 1700 and 1680; δ_H 1.30 (3 H, d, *J* 7.2), 1.39 (9 H, s), 3.68 (3 H, s), 4.42 (1 H, dq, *J* 7.2, 7.2), 5.19 (1 H, br d), 6.41 (1 H, br, exch D_2O), 6.96 (1 H, d, *J* 8.3), 7.29 (1 H, dd, *J* 8.3, 2.1), 7.60 (1 H, d, *J* 2.1), 7.79 (1 H, br d, *J* 7.2 exch D_2O) and 9.0 (1 H, br, exch D_2O); *m/z* (M^+, thioglycerol; FAB) 431/433 (MH^+).

[(R)-(3-*Bromo*-4-*methoxyphenyl*)-N-tert-*butoxycarbonylglycyl*]-(S)-*alanine Methyl Ester* **9**.—Compound **8** (3.4 g, 7.9 mmol) was dissolved in dry DMF (25 cm^3) and potassium carbonate (1.4 g, 10 mmol) was added. The mixture was stirred and dimethyl sulphate (0.91 cm^3, 9.3 mmol) was added. After 3.5 h the mixture was diluted with ethyl acetate (100 cm^3) and with brine (50 cm^3). The organic phase was separated, washed with brine (2 × 50 cm^3) and dried. Evaporation and chromatography on silica gel, eluting with 1% v/v MeOH–$CHCl_3$ (R_f 0.13) gave the *product* **9** as a foam (3.07 g, 86%), $[\alpha]_D^{20}$ −87 (*c* 0.18 in MeOH) (Found: C, 48.7; H, 5.75; N, 6.4. $C_{18}H_{25}BrN_2O_6$ requires C, 48.55; H, 5.65; N, 6.3%); ν_{max}/cm^{-1} 3420, 1740, 1700 and 1680; δ_H 1.30 (3 H, d, *J* 7.2), 1.39 (9 H, s), 3.68 (3 H, s), 3.90 (3 H, s), 4.42 (1 H, dq, *J* 7.2, 7), 5.21 (1 H, br d, *J* 7.5), *ca.* 6.5 (1 H, br, exch D_2O), 7.05 (1 H, d, *J* 8.6), 7.42 (1 H, dd, *J* 8.6, 2.2), 7.66 (1 H, d, *J* 2.2) and 7.81 (1 H, d, *J* 7.2 exch D_2O); *m/z* (M^+, thioglycerol; FAB) 445/447 (MH^+).

{(R)-N-tert-*Butoxycarbonyl*-[3-(2-*hydroxymethylphenyl*)-4-*methoxyphenyl*]*glycyl*}-(S)-*alanine Methyl Ester* **10**.—The bromo compound **9** (1.25 g, 2.8 mmol) and tetrakistriphenylphosphinepalladium (0.15 g, 0.13 mmol) were dissolved in toluene (24 cm^3) under an atmosphere of argon. A solution of the boronic acid **5** (0.62 g, 4.6 mmol) in methanol (3 cm^3) was then added followed immediately by a solution of sodium carbonate (0.298 g, 2.8 mmol) in water (3 cm^3). The mixture was stirred vigorously under argon and heated at 90 °C for 4 h and then cooled and diluted with brine and ethyl acetate. The organic phase was separated, washed with brine and dried. Evaporation of solvent and chromatography on silica gel, eluting with ethyl acetate–hexane (1:1) (R_f 0.14), gave the *biphenyl* **10** as a foam (0.793 g, 60%), $[\alpha]_D^{23}$ −85.5 (*c* 0.5 in MeOH) (Found: C, 63.05; H, 6.4; N, 6.15. $C_{25}H_{32}N_2O_7$ requires C, 63.55; H, 6.8; N, 5.95%); λ_{max}(MeOH)/nm 282 (3250); ν_{max}/cm^{-1} 3400br, 1740, 1725 and 1680; δ_H($CDCl_3$) 1.33 (3 H, d, *J* 7, CH_3CH), 1.42 (9 H, s, C_4H_9), 2.1–2.5 (1 H, br, OH), 3.73 and 3.76 (6 H, two s, two OMe), *ca.* 4.4 (2 H, br, CH_2OH), 4.59 (1 H, dq, *J* 7, 7, CH_3CH), 5.12 (1 H, br d, ArC*H*), 5.65 (1 H, br, NH), 6.40 (1 H, br d, *J* 7, CH_3CHNH), 6.98 (1 H, d, *J* 8.5, ArH), 7.2–7.4 (5 H, m, ArH) and 7.55 (1 H, dd, *J* 8.9, 2, ArH); *m/z* (M^+, thioglycerol; FAB) 473 (MH^+).

{(R)-[3-(2-*Azidomethylphenyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonylglycyl*}-(S)-*alanine Methyl Ester* **11**.—The hydroxymethyl compound **10** (1.65 g, 3.5 mmol) was dissolved in dry THF (16 cm^3) and cooled in an ice bath. Triphenylphosphine (1.85 g, 7 mmol) was added with stirring followed by a solution of dimethyl azodicarboxylate (1.03 g, 7 mmol) in THF (2 cm^3) and a solution of hydrazoic acid (0.292 g, 6.8 mmol) in toluene (4 cm^3) [**CAUTION**: hydrazoic acid is toxic]. After 30 min at 0 °C the cooling bath was removed for 15 min and the solution was diluted with brine and extracted with ethyl acetate. Drying and evaporation followed by chromatography on silica gel, eluting with ethyl acetate–hexane (1:1) (R_f 0.3), yielded the *azide* **11** as a foam (1.4 g, 80%), $[\alpha]_D^{26}$ −75 (*c* 1 in $CHCl_3$) (Found: C, 60.4; H, 6.3; N, 13.75. $C_{25}H_{31}N_5O_6$ requires C, 60.35; H, 6.3; N, 14.05%); λ_{max}(MeOH)/nm 282 (3600); ν_{max}/cm^{-1} 3410, 2090, 1730, 1700sh and 1670; δ_H($CDCl_3$) 1.33 (3 H, d, *J* 7.2), 1.42 (9 H, s), 3.74 (3 H, s), 3.75 (3 H, s), 4.05–4.25 (2 H, m, CH_2N_3), 4.59 (1 H, dq, *J* 7.2, 7), 5.15 (1 H, br, collapse to s with D_2O), 5.6–5.8 (1 H, br, exch D_2O), 6.44 (1 H, d, *J* 7), 6.96 (1 H, d, *J* 8.5), 7.15–7.25 (2 H, m) and 7.3–7.45 (4 H, m); *m/z* (M^+ thioglycerol; FAB) 498 (MH^+).

{(R)-[3-(2-*Azidomethylphenyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonylglycyl*}-(S)-*alanine* **13**.—The azido ester **11** (0.429 g, 0.86 mmol) was dissolved in methanol (15 cm^3) and water (2 cm^3). An aqueous solution of NaOH (0.1 mol dm^{-3}) was added dropwise by means of a pH stat. apparatus which maintained the pH not greater than pH 12. After 1 h a total of 10.4 cm^3 (1.04 mmol) of the NaOH solution had been added and TLC analysis showed the absence of starting material. The solution was diluted with water (30 cm^3) and washed with ethyl

acetate. The aqueous layer was then acidified with dil. HCl and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give the acid **13** as a foam (0.37 g, 90%), $[\alpha]_D^{24}$ −70 (*c* 0.18 in MeOH); $\lambda_{max}(H_2O)$/nm 282 (3200); ν_{max}/cm^{-1} 3420, 3360, 2100, 1720 and 1675. TLC analysis, elution with ethyl acetate–ethanol–water (4:2:1), R_f 0.55.

Hydrogenation of the Azido Acid **13**.—The acid **13** (0.367 g, 0.75 mmol) was dissolved in methanol (10 cm^3) and water (4 cm^3). NaOH was added (1 mol dm^{-3} solution; 0.76 cm^3, 0.76 mmol) followed by 10% Pd–C (0.39 g) and the mixture shaken in an atmosphere of hydrogen for 1.5 h at room temperature and pressure. The catalyst was filtered off. Evaporation of the filtrate gave a crude solid which was purified on a column of Bio-gel P2 eluting with water. Fractions containing the product gave a positive reaction to ninhydrin and they were combined and freeze dried. The product **14** was obtained as a white solid (0.227 g, 62%), $[\alpha]_D^{25}$ −57 (*c* 0.22 in H_2O); $\lambda_{max}(H_2O)$/nm 280 (2700); ν_{max}(KBr)/cm^{-1} 1660; δ_H(400 MHz; [$^2H_6$]-DMSO, 340 K) 1.20 (3 H, d, *J* 7, CH_3CH), 1.38 (9 H, s, C_4H_9), 3.6–3.75 (approx. 5 H, m, $ArCH_2NH_2$, OMe), 4.04 (1 H, dq, *J* 7, 7, CH_3CH), 5.13 [1 H, d, *J* 8.4, ArCH(CO)NH], 6.95 [1 H, br, ArCH(CO)NH], 7.17 (1 H, d, *J* 8.5, ArH), 7.19 (1 H, dd, *J* 8.5, *ca.* 1, ArH), 7.2–7.4 (4 H, m, ArH), 7.60 (1 H, m, ArH) and 7.81 (1 H, br, CH_3CHNH); *m/z* (M^+, thioglycerol; FAB) 458 (MH^+ for free acid). TLC analysis eluting with ethyl acetate–ethanol–water (4:2:1) R_f 0.3. The sodium ion content was found to be 1%.

Attempted Cyclization of Amino Acid **14**.—(*a*) The amino acid **14** (0.18 g, 0.38 mmol) was dissolved in dry DMF (35 cm^3). The solution was cooled to −10 °C under argon and triethylamine (0.052 cm^3, 0.38 mmol) was added followed by diphenylphosphoryl azide (0.12 cm^3, 0.55 mmol) and the solution stored at *ca.* −8 °C for 48 h. The mixture was worked up as described by Brady[14] and purified by chromatography on silica gel, eluting with ethyl acetate–hexane 4:1 (R_f 0.12). The product **15** was obtained as a white solid (0.017 g, 10%), λ_{max}(MeOH)/nm 280 (5000); ν_{max}/cm^{-1} 3400, 3300, 1705 and 1650; *m/z* (M^+, thioglycerol; FAB) 879 (MH^+).

(*b*) When the reaction was carried out using $NaHCO_3$ (5 mol equiv.) as base, the product obtained was chromatographically identical with that obtained above.

5-*Bromo-2-methoxyphenylacetic Acid* **17**.—2-Methoxyphenylacetic acid (12.5 g, 75 mmol) was dissolved in glacial acetic acid (110 cm^3) and a solution of bromine (3.96 cm^3, 76 mmol) in acetic acid (40 cm^3) was added dropwise with stirring and simultaneous addition of mercuric acetate (26 g, 82 mmol). The reaction mixture was maintained at *ca.* 20 °C by a cold water bath. After 1 h the colourless mixture was poured into ice–water and the white precipitate was filtered off. The crude solid was partitioned between dil. HCl and ethyl acetate. The organic layer was washed with dil. HCl and with brine. Drying and evaporation gave the crude product which was purified by crystallization from ethyl acetate–hexane. The bromo compound **17** (11.5 g, 62%) had m.p. 133–135 °C (lit.,[18] m.p. 135 °C).

2-(5-*Bromo-2-methoxyphenyl*)*ethanol* **18**.—Compound **17** (11.25 g, 46 mmol) was dissolved in dry THF (60 cm^3) and added, with stirring and cooling in an ice bath, to a solution of 1 mol dm^{-3} borane in THF (98 cm^3). The reaction was maintained in an atmosphere of argon and after the initial reaction had subsided it was left at room temperature for 2.5 h and then quenched by careful addition of water. The solution was diluted with excess of water and ethyl acetate and the organic layer was then washed with water, aqueous sodium hydrogen carbonate and brine. Drying and evaporation gave the *alcohol* **18** as an oil (10.4 g, 98%), b.p. 100–104 °C/0.05 mmHg (Found: C, 46.9; H, 4.95; Br, 34.85. $C_9H_{11}BrO_2$ requires C, 46.8; H, 4.8; Br, 34.6%); ν_{max}/cm^{-1} 3550 and 3450br; $\delta_H(CDCl_3)$ 1.72 (1 H, br, exch D_2O), 2.88 (2 H, t, *J* 6.4), 3.76–3.83 (5 H, m), 6.72 (1 H, d, *J* 8.3) and 7.25–7.35 (2 H, m).

2-(5-*Bromo-2-methoxyphenyl*)*ethanyl Tetrahydropyranyl Ether* **19**.—The alcohol **18** (8.1 g, 35 mmol) was dissolved in dry dichloromethane (75 cm^3) and anhydrous toluene-*p*-sulphonic acid (0.002 g) was added. The solution was cooled in an ice bath and stirred while a solution of dihydropyran (6.4 cm^3, 70 mmol) in dichloromethane (10 cm^3) was added. The solution was then left at room temperature for 3 h when it was diluted with aqueous sodium hydrogen carbonate. The organic layer was separated, washed with brine and dried. Evaporation of solvent and chromatography on silica gel, eluting with CH_2Cl_2 (R_f 0.33), gave the *product* **19** as an oil (8.5 g, 77%) (Found: M^+, 314.0512. $C_{14}H_{19}{}^{79}BrO_3$ requires *M*, 314.0519); $\delta_H(CDCl_3)$ 1.45–1.90 (6 H, m), 2.90 (2 H, t, *J* 7), 3.40–3.50 (1 H, m), 3.60 (1 H, dt, *J* 9.5, 7), 3.70–3.80 (1 H, m), 3.80 (3 H, s), 3.86 (1 H, dt, *J* 9.5, 7), 4.61 (1 H, t, *J* 4), 6.70 (1 H, d, *J* 8.5), 7.29 (1 H, dd, *J* 8.5, 2.5) and 7.31 (1 H, d, *J* 2.5).

3-(2-*Hydroxyethyl*)-4-*methoxybenzeneboronic Acid* **20**.—(*a*) *From tetrahydropyranyl ether* **19**. Butyllithium (1.4 mol dm^{-3} solution in hexane; 19.5 cm^3) was added dropwise with stirring to a solution of compound **19** (8.2 g, 26 mmol) in dry THF (82 cm^3) under argon at −60 ± 5 °C. After 40 min tributyl borate (17.5 cm^3, 64 mmol) was added in one portion and the clear solution left to warm to room temperature for 1 h. Water was added to the solution which was then adjusted to pH 1 by addition of 5 mol dm^{-3} HCl. The mixture was extracted with ethyl acetate (2 × 100 cm^3) and the extract washed with brine, dried and evaporated to an oil. The oil was suspended in aqueous methanol and evaporated under reduced pressure giving a thick white gum which was redissolved in methanol (50 cm^3) containing 'Amberlite' IR-120 ion exchange resin (H^+, 10 g). The mixture was stirred at room temperature for 17 h and at 40 °C for 7 h. The resin was filtered off and the filtrate evaporated to dryness. The crude solid was dried *in vacuo* and triturated with ether–hexane giving the *boronic acid* **20** as a white solid (4.36 g, 85%), m.p. 207–210 °C (from aq. MeOH) (Found: C, 55.4; H, 6.6. $C_9H_{13}BO_4$ requires C, 55.15; H, 6.7%); δ_H([$^2H_6$]-acetone–D_2O) 2.85 (2 H, t, *J* 7.5), 3.72 (2 H, t, *J* 7.5), 3.84 (3 H, s), 6.95 (1 H, d, *J* 8.2), 7.69 (1 H, d, *J* 1.5) and 7.74 (1 H, dd, *J* 8.2, 1.5); *m/z* 195/196 (M^+).

(*b*) *From alcohol* **18**. The alcohol **18** (0.208 g, 0.9 mmol) was treated with butyllithium and tributyl borate as described above for the preparation of compound **5**. The *product* (0.027 g, 15%) had m.p. >200 °C and its NMR spectrum was identical with that in (*a*) above.

N-tert-*Butoxycarbonyl*-3-*bromo*-O-*methyl*-(S)-*tyrosine Methyl Ester* **23**.—*N-tert*-Butoxycarbonyl-(*S*)-tyrosine methyl ester (5.9 g, 20 mmol) was converted into the crude bromo compound **22** as described above for the preparation of compound **17**. Crude bromo compound **22** was obtained as a yellow gum (6.3 g) which was redissolved in dry DMF (40 cm^3). Potassium carbonate (2.75 g, 20 mmol) was added followed by dimethyl sulfate (1.93 cm^3, 20 mmol) and the mixture was stirred at room temperature overnight. The mixture was diluted with brine and extracted with ethyl acetate. The organic extract was washed with water and brine, dried and evaporated to a gum which was chromatographed on silica gel eluting with ethyl acetate-hexane (1:2). The first eluted component (R_f 0.46) was *N-tert*-butoxycarbonyl-3,5-dibromo-*O*-methyl-(*S*)-tyrosine methyl ester **24** obtained as a gum (0.35 g, 4%), $[\alpha]_D^{24}$ −4.4

(*c* 1 in MeOH); ν_{max}/cm^{-1} 3430, 1730sh and 1700; δ_H 1.35 (9 H, s), 2.94 (1 H, dd, *J* 13.9, 10), 3.16 (1 H, dd, *J* 13.9, 5), 3.70 (3 H, s), 3.84 (3 H, s), 4.41 (1 H, ddd, *J* 10, 8.5, 5), 6.35 (1 H, br d, *J* 8.5, exch D_2O) and 7.55 (2 H, s); *m/z* (M^+, 3-nitrobenzylalcohol–sodium acetate; FAB) 488/490/492 (MNa^+). The second eluted component (R_f 0.33) was the desired *product* **23** obtained as a gum (3.25 g, 42%), $[\alpha]_D^{23}$ +4.7 (*c* 1 in MeOH) (Found: M^+, 387.0683. $C_{16}H_{22}{}^{79}BrNO_5$ requires *M*, 387.0682); ν_{max}/cm^{-1} 3430, 1730sh and 1700; δ_H 1.35 (9 H, s), 2.91 (1 H, dd, *J* 13.9, 9), 3.09 (1 H, dd, *J* 13.9, 5.2), 3.69 (3 H, s), 3.87 (3 H, s), 4.35 (1 H, ddd, *J* 9, 8.5, 5.2), 6.21 (1 H, br d, *J* 8.5, exch D_2O), 7.02 (1 H, d, *J* 8.4), 7.25 (1 H, dd, *J* 8.4, 2) and 7.45 (1 H, d, *J* 2).

N-tert-*Butoxycarbonyl*-3-[3-(2-*hydroxyethyl*)-4-*methoxyphenyl*]-O-*methyl*-(S)-*tyrosine Methyl Ester* **25**.—The bromo compound **23** (1.9 g, 4.9 mmol) and tetrakistriphenylphosphinepalladium (0.185 g, 0.16 mmol) were dissolved in 1,2-dimethoxyethane (15 cm^3) under argon. A solution of sodium carbonate (0.54 g, 5 mmol) in water (3 cm^3) was added *via* syringe and after 2 min, a solution of the boronic acid **20** (1 g, 5 mmol) in 1,2-dimethoxyethane (11 cm^3) was added. The mixture was stirred and heated at 100 °C for 12 h after which it was cooled and diluted with water. The mixture was then extracted with ethyl acetate and the aqueous layer put to one side. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to give a gum (2 g). Chromatography on silica gel, eluting with ethyl acetate–hexane (1:2) (R_f 0.07), gave the *biphenyl* **25** as a white foam (0.93 g, 41%), $[\alpha]_D^{24}$ +6.7 (*c* 1 in MeOH) (Found: M^+, 459.2269. $C_{25}H_{33}NO_7$ requires *M*, 459.2257); λ_{max}(MeOH)/nm 256 (13 300), 289 (7800); ν_{max}/cm^{-1} 3200–3600, 3440, 1740 and 1710; δ_H 1.35 (9 H, s, C_4H_9), 2.88 (2 H, t, *J* 7.2, ArCH_2CH$_2$), 2.95 (1 H, dd, *J* 13.8, 8.5, ArCH*H*CHNH), 3.12 (1 H, dd, *J* 13.8, 5.5, ArC*H*HCHNH), 3.59 (1 H, t, *J* 5.5, OH), 3.67–3.75 (5 H, m, CH_2OH and OMe), 3.78 (3 H, s, OMe), 3.86 (3 H, s, OMe), 4.41 (1 H, ddd, *J* 8.5, 8.5, 5.5, C*H*NH), 6.15 (1 H, br d, *J* 8.5, N*H*), 6.95–7.02 (2 H, m, ArH), 7.15–7.22 (2 H, m, ArH) and 7.35–7.40 (2 H, m, ArH).

The aqueous layer, obtained above, was evaporated to dryness and the residue dried over phosphorus pentoxide. The dry solid was then suspended in DMF (10 cm^3) and potassium carbonate (0.266 g, 2 mmol) and dimethyl sulfate (0.2 cm^3, 2 mmol) added. The mixture was stirred overnight at room temperature, diluted with water and extracted with ethyl acetate. The extract was dried and evaporated to give a gum which was purified by chromatography as described above, yielding a sample of the *biphenyl* **25** (0.17 g, 8%), $[\alpha]_D^{24}$ +6.8 (*c* 1 in MeOH), identical (IR and NMR) to that described above.

3-[3-(2-*Azidoethyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonyl*-O-*methyl*-(S)-*tyrosine Methyl Ester* **26**.—The biphenyl alcohol **25** (1.2 g, 2.6 mmol) was converted into the azide **26** using the procedure described above for compound **11**. The azide **26** was obtained as a colourless gum (0.98 g, 77%), $[\alpha]_D^{24}$ +6.3 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3440, 2100, 1740 and 1710; δ_H 1.35 (9 H, s), 2.94 (2 H, t, *J* 7.2), 2.95 (1 H, dd, *J* 13.7, 8.5), 3.12 (1 H, dd, *J* 13.7, 5.3), 3.54 (2 H, t, *J* 7.2), 3.69 (3 H, s), 3.79 (3 H, s), 3.89 (3 H, s), 4.51 (1 H, ddd, *J* 8.5, 8, 5.3), 6.15 (1 H, d, *J* 8, exch D_2O), 6.95–7.05 (2 H, m), 7.15–7.25 (2 H, m) and 7.40–7.45 (2 H, m); *m/z* (M^+, 3-nitrobenzyl alcohol–sodium acetate; FAB) 507 (MNa^+); TLC analysis, elution with ethyl acetate–hexane (1:2) R_f 0.35.

3-[3-(2-*Azidoethyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonyl*-O-*methyl*-(S)-*tyrosine* **27**.—A solution of the biphenyl derivative **26** (0.484 g, 1 mmol) was dissolved in methanol (7 cm^3) and aqueous NaOH (0.5 mol dm^{-3}; 2.1 cm^3, 1.05 mol equiv.) was added over 3 h. The solution was left overnight at room temperature when TLC (ethyl acetate–ethanol–water, 4:2:1) showed one component R_f 0.67 and no starting material. The solution was diluted with water, acidified with 5 mol dm^{-3} HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give the acid **27** as a white foam (0.47 g, 100%), $[\alpha]_D^{24}$ +17.4 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3440, 2200–3500, 2100 and 1705. This material was used without further purification (see below).

3-[3-(2-*Azidoethyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonyl*-O-*methyl*-(S)-*tyrosyl*-(S)-*alanine Benzyl Ester* **29**.—The acid **27** (0.47 g, 1 mmol) was coupled with (*S*)-alanine benzyl ester hydrochloride (0.24 g, 1.1 mmol) using DCC and HOBT as described above for compound **8**. The product **29** was obtained as a white foam (0.544 g, 86%), $[\alpha]_D^{25}$ −2.1 (*c* 1 in MeOH); λ_{max}(MeOH)/nm 255 (14 600) and 289 (8500); ν_{max}(cm^{-1} 3420, 2100, 1740, 1700sh and 1680; δ_H 1.33 (9 H, s, C_4H_9), 1.38 (3 H, d, *J* 7.2, CH_3CH), 2.85 (1 H, dd, *J* 14, 9, ArCH*H*CHNH), 2.94 (2 H, t, *J* 7.3, ArCH_2CH$_2$N$_3$), 3.14 (1 H, dd, *J* 14, 4.7, ArC*H*HCHNH), 3.52 (2 H, t, *J* 7.3, ArCH$_2$CH_2N$_3$), 3.75 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.44 (1 H, ddd, *J* 9, 8, 4.7, ArCH$_2$C*H*NH), 4.52 (1 H, dq, *J* 7.2, 7, CH$_3$C*H*), 5.15 (2 H, AA′, PhCH$_2$), 5.97 (1 H, br d, *J* 8, exch D_2O, NH), 6.90–7.01 (2 H, m, ArH), 7.12–7.22 (2 H, m, ArH), 7.30–7.45 (7 H, m, ArH) and 7.66 (1 H, br d, exch, D_2O, NH); *m/z* (M^+, 3-nitrobenzyl alcohol–sodium acetate; FAB) 654 (MNa^+). TLC analysis, elution with ethyl acetate–hexane (1:2) R_f 0.18.

3-[3-(2-*Azidoethyl*)-4-*methoxyphenyl*]-N-tert-*butoxycarbonyl*-O-*methyl*-(S)-*tyrosyl*-(S)-*alanine Methyl Ester* **30**.—The acid **27** (0.47 g, 1 mmol) and (*S*)-alanine methyl ester hydrochloride (0.153 g, 1.1 mmol) were coupled as described above for compound **8**. The product **30** was obtained as a white foam (0.462 g, 83%), $[\alpha]_D^{27}$ −1 (*c* 1 in MeOH); λ_{max}(MeOH)/nm 256 (13 900) and 289 (5600); ν_{max}/cm^{-1} 3430, 2100, 1740, 1700 and 1670; δ_H([$^2H_6$]-DMSO) 1.28–1.33 (12 H, m), 2.67 (1 H, dd, *J* 13.5, 11), 2.87 (2 H, t, *J* 7.2), 2.93 (1 H, dd, *J* 13.5, 4), 3.50 (2 H, t, *J* 7.2), 3.61 (3 H, s), 3.72 (3 H, s), 3.83 (3 H, s), 4.18 (1 H, ddd, *J* 11, 8, 4), 4.30 (1 H, dq, *J* 7, 7), 6.90 (1 H, d, *J* 8 exch D_2O), 6.96 (1 H, d, *J* 8.4, CH *ortho* to OMe), 7.01 (1 H, d, *J* 8.4, CH *ortho* to OMe), 7.18–7.25 (2 H, m), 7.32 (1 H, d, *J* 2), 7.35 (1 H, dd, *J* 8.4, 2), 8.40 (1 H, d, *J* 7 exch D_2O); *m/z* (M^+, thioglycerol; FAB) 456 ($MH^+ - C_4H_8 - CO_2$); TLC analysis, elution with ethyl acetate–hexane (1:2) R_f 0.1.

(11S,14S)-14-tert-*Butoxycarbonylamino*-5,19-*dimethoxy*-11-*methyl*-9,12-*diazatricyclo*[14.3.1.1^{2,6}]*henicosa*-1(20),2,4,6(21),-16,18-*hexaene*-10,13-*dione* **34**.—(*a*) The biphenyl benzyl ester **29** (0.237 g, 0.37 mmol) was dissolved in methanol (20 cm^3)–water (2 cm^3) in which 10% Pd–C (0.1 g) was suspended. The mixture was hydrogenated at room temperature and pressure for 55 min after which the catalyst was filtered off. Evaporation of the filtrate gave an off-white solid (0.2 g) which was dissolved in dry DMF (100 cm^3) under argon and cooled to −25 °C. *N*-Methylmorpholine (0.062 cm^3, 0.56 mmol) was added followed by diphenylphosphoryl azide (0.12 cm^3, 0.56 mmol). The reaction mixture was stored at −10 °C for 4 d and evaporated nearly to dryness. After partitioning between water (100 cm^3) and ethyl acetate (100 cm^3), the organic layer was washed with brine, dried and evaporated to give a crude solid (0.3 g). Chromatography on silica gel, eluting with 2% v/v MeOH–$CHCl_3$ (R_f 0.1), gave the *cyclic compound* **34** as a white solid (0.04 g, 21%), m.p. 265–267 °C (decomp.) (Found: C, 65.1; H, 6.95; N, 8.3. $C_{27}H_{35}N_3O_6$ requires C, 65.2; H, 7.1; N, 8.45%); $[\alpha]_D^{25}$ +21 (*c* 1 in $CHCl_3$); λ_{max}(MeOH)/nm 288 (6400) and 256 (11 300); ν_{max}/cm^{-1} 3430, 1700sh and 1660; δ_H(400 MHz; $CDCl_3$–CD_3OD) 1.34 (3 H, d, *J* 7, CH_3CH), 1.45 (9 H, s, C_4H_9),

2.68–2.78 (1 H, m, ArC*H*HCH$_2$NH), 2.94 (1 H, dd, *J* 14, 2.5, ArCH*H*CHNHBoc), 3.05–3.15 (1 H, m, ArCH*H*CH$_2$NH), 3.15–3.25 (1 H, m, ArCH$_2$C*H*HNH), 3.22 (1 H, dd, *J* 14, 8, ArC*H*HCHNHBoc), 3.80 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.85–3.95 (1 H, m, ArCH$_2$CH*H*NH), 4.36 (1 H, dd, *J* 8, 2.5, ArCH$_2$C*H*NH), 4.51 (1 H, q, *J* 7, CH$_3$C*H*), 6.83 (1 H, d, *J* 8.5, ArH *ortho* to OMe), 6.84 (1 H, d, *J* 8.3, ArH *ortho* to OMe), 6.85 (1 H, d, *J* 2), 7.01 (1 H, dd, *J* 8.3, 2), 7.07 (1 H, d, *J* 1.7) and 7.50 (1 H, dd, *J* 8.7, 1.7); *m/z* (M$^+$, thioglycerol; FAB) 498 (MH$^+$). The second eluted component was obtained as a white solid (0.009 g); δ_H($CDCl_3$) 1.24 (3 H, d, *J* 7), 1.35 (9 H, s), 2.7–3.0 (4 H, m), 3.3–3.45 (1 H, m), 3.45–3.60 (1 H, m), 3.71 (3 H, s), 3.84 (3 H, s), 4.25–4.35 (1 H, m), 4.42 (1 H, dq, *J* 8, 7), 5.55 (1 H, br d, *J* 8, exch D_2O), 6.45 (1 H, br), 6.82 (1 H, d, *J* 8.3), 6.85 (1 H, d, *J* 8.5), 6.95 (1 H, d, *J* 8), 7.04 (1 H, dd, *J* 8.3, 2), 7.1 (1 H, d, *J* 2), 7.19 (1 H, d, *J* 2) and 7.45 (1 H, dd, *J* 8.5, 2); *m/z* (M$^+$, thioglycerol; FAB) 995 (MH$^+$); TLC analysis, elution with 2% v/v MeOH–$CHCl_3$ R_f 0.03.

(*b*) The biphenyl methyl ester **30** (0.45 g, 0.81 mmol) was dissolved in methanol (7 cm^3) and NaOH (0.5 mol dm^{-3}; 1.72 cm^3, 0.86 mmol) added. The solution was left overnight at room temperature, acidified with 5 mol dm^{-3} HCl and extracted with ethyl acetate. Drying and evaporation of the extract gave a white foam (0.43 g) which was dissolved in dry DMF (3 cm^3) containing pentafluorophenol (0.147 g, 0.8 mmol). The solution was cooled at 0 °C and a solution of DCC (0.163 g, 0.8 mmol) in dry THF (2 cm^3) was added dropwise. The mixture was left at *ca.* 5 °C for 3 d, filtered, and the filtrate evaporated to dryness. The resulting crude pentafluorophenyl ester **31** was obtained as a gum (0.6 g) which was dissolved in dry dioxane (30 cm^3) and the solution added dropwise to a stirred suspension of 10% Pd–C (0.6 g) in dioxane (125 cm^3)–ethanol (2 cm^3) containing 4-pyrrolidinopyridine (0.118 g, 0.8 mmol), under an atmosphere of hydrogen. The addition was carried out over 1.3 h and the mixture was heated at 90 °C during this time. After a further 2 h at 90 °C the catalyst was filtered off and the filtrate evaporated to dryness. The mixture was partitioned between water and ethyl acetate and the organic layer was washed with 0.1 mol dm^{-3} NaOH, 1 mol dm^{-3} HCl and with brine. Drying and evaporation gave a crude product (0.3 g) which was chromatographed as described above to give the *cyclic compound* **34** as a white solid (0.113 g) having spectral properties identical with those described above.

(11S,14S)-5,19-*Dimethoxy*-11-*methyl*-10,13-*dioxo*-9,12-*diazatricyclo*[14.3.1.1^{2,6}]*henicosa*-1(20),2,4,6(21),16,18-*hexaene*-14-*ylammonium Trifluoroacetate* **37**.—The cyclic compound **34** (0.085, g, 0.17 mmol) was suspended in dry dichloromethane (5 cm^3) and trifluoroacetic acid (2 cm^3) added. After 1 h at room temperature the solution was evaporated to dryness and azeotroped with chloroform giving the *trifluoroacetate* **37** as a white solid (0.079 g, 90%), m.p. >230 °C (from MeOH) (Found: C, 56.45; H, 5.45; N, 7.9. $C_{24}H_{28}F_3N_3O_6$ requires C, 56.35; H, 5.55; N, 8.2%); $[\alpha]_D^{29}$ +60 (*c* 0.5 in MeOH); λ_{max}(MeOH)/nm 258 (12 800) and 288 (7600); ν_{max}(KBr)/cm^{-1} 1700sh, 1660sh and 1640; δ_H(CD_3OD) 1.38 (3 H, d, *J* 7), 2.60–2.70 (1 H, m), 3.06 (1 H, dd, *J* 14.9, 6, ArCH*H*CHNH$^+$$_3$), 3.12–3.22 (2 H, m), 3.36 (1 H, dd, *J* 14.9, 2.7, ArC*H*HCHNH$^+$$_3$), 3.79 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.80–3.90 (1 H, m), 4.16 (1 H, dd, *J* 6, 2.7), 4.60 (1 H, q, *J* 7, CH$_3$C*H*), 6.88 (1 H, d, *J* 8.5, ArH *ortho* to OMe), 6.96 (1 H, d, *J* 8.3, ArH *ortho* to OMe), 6.99 (1 H, d, *J* 2.3 ArH), 7.06 (1 H, dd, *J* 8.3, 2.3 ArH), 7.15 (1 H, d, *J* 2.1, ArH), 7.22 (1 H, dd, *J* 8.5, 2.1 ArH) and 8.4 (1 H, br d, *J* 7.8, NH); *m/z* (M$^+$, thioglycerol; FAB) 398 (MH$^+$ for free amine).

(11S,14S)-14-*Acetamido*-5,19-*dimethoxy*-11-*methyl*-9,12-*diazatricyclo*[14.3.1.1^{2,6}]*henicosa*-1(20),2,4,6(21),16,18-*hexaene*-10,13-*dione* **38**.—The trifluoroacetate **37** (0.04 g, 0.08 mmol) was dissolved in dry DMF (1 cm^3). 4-Dimethylaminopyridine (catalytic, <1 mg) and pyridine (0.024 cm^3, 0.3 mmol) were added, the solution was cooled in ice and acetic anhydride (0.016 cm^3, 0.16 mmol) was added. The mixture was stirred overnight at room temperature and diluted with water and ethyl acetate. The precipitate was filtered off and dried *in vacuo*, giving the N-*acetyl derivative* **38** as a white solid (0.031 g, 90%), m.p. >260 °C (from trifluoroacetic acid–ether) (Found: C, 63.7; H, 6.2; N, 8.7. $C_{24}H_{29}N_3O_5$·$\frac{1}{5}C_2HF_3O_2$ requires C, 63.4; H, 6.3; N, 9.1%); δ_H(trifluoroacetic acid) 1.60 (3 H, d, *J* 7), 2.49 (3 H, s), 2.65–2.80 (1 H, m), 3.18–3.30 (1 H, m), 3.35–3.60 (3 H, m), 4.00 (3 H, s) and 4.02 (3 H, s), overlapping 4.0–4.06 (*ca.* 1 H, m), 4.92 (1 H, q, *J* 7), 5.28–5.35 [1 H, m, ArCH$_2$C*H*(CO)], 7.00 (1 H, br s, ArH), 7.05–7.20 (4 H, m) and 7.50 (1 H, dd, *J* 8.2, *ca.* 1); *m/z*, (M$^+$, thioglycerol–trifluoroacetic acid; FAB), 440 (MH$^+$).

3-{3-{2-[N$^{\alpha}$-*Benzyloxycarbonyl*-N$^{\delta}$-tert-*butoxycarbonyl*-(S)-*ornithylamino*]*ethyl*}-4-*methoxyphenyl*}-N-tert-*butoxycarbonyl*-O-*methyl*-(S)-*tyrosine Methyl Ester* **32**.—The biphenyl azide **26** (0.24 g, 0.5 mmol) was dissolved in methanol (6 cm^3) and THF (6 cm^3) containing toluene-*p*-sulphonic acid monohydrate (0.095 g, 0.5 mmol) and 10% Pd–C (0.122 g). The mixture was hydrogenated at room temperature and pressure for 30 min and the catalyst was filtered off. Evaporation of the filtrate gave the crude amino tosylate **28** as a gum (0.315 g) which was dissolved in dry DMF (2 cm^3) containing HOBT (0.067 g, 0.5 mmol), and α-*N*-benzyloxycarbonyl-δ-*N*-*tert*-butoxycarbonyl-(*S*)-ornithine (0.184 g, 0.5 mmol). Triethylamine (0.07 cm^3, 0.5 mmol) was added followed by a solution of DCC (0.112 g, 0.5 mmol) in THF (1 cm^3) with cooling in ice. The mixture was left overnight at room temperature and worked up as described for compound **8**. Chromatography [silica gel, eluting with ethyl acetate (1:1) R_f 0.1], gave the *biphenyl derivative* **32** as a white solid (0.339 g, 84%), m.p. 132–134 °C (from ethyl acetate) (Found: C, 63.7; H, 7.6; N, 7.0; $C_{43}H_{58}N_4O_{11}$ requires C, 64.0; H, 7.25; N, 6.95%); $[\alpha]_D^{25}$ +18.3 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 3430 and 1710br; δ_H 1.35 (9 H, s), 1.40 (9 H, s), 1.47–1.60 (2 H, m, CH$_2$C*H*$_2$CH$_2$NHBoc), 1.60–1.90 (2 H, m, C*H*$_2$CH$_2$CH$_2$NHBoc), 2.80–2.90 (2 H, m, ArC*H*$_2$CH$_2$NH), 2.96 (1 H, dd, *J* 13.9, 9, ArC*H*HCHCO), 3.09 (1 H, dd, *J* 13.9, 5.3), 3.0–3.10 (2 H, m, CH$_2$C*H*$_2$NHBoc), 3.38–3.55 (2 H, m, ArCH$_2$C*H*$_2$NH), 3.69 (3 H, s), 3.79 (3 H, s), 3.87 (3 H, s), 4.10–4.25 (1 H, m, C*H*CH$_2$CH$_2$CH$_2$NHBoc), 4.42 (1 H, ddd, *J* 9, 8, 5.3, ArCH$_2$C*H*CO), 5.95 (1 H, br, NH), 6.19 (1 H, d, *J* 8, NH), 6.40 (1 H, d, *J* 8, NH), 6.96 (1 H, d, *J* 8.5, ArH), 6.99 (1 H, d, *J* 8.3, ArH), 7.18 (1 H, dd, *J* 8.3, 2), 7.21 (1 H, d, *J* 2) and 7.30–7.40 (8 H, m, 7 × ArH, 1 × NH); *m/z* (M$^+$, thioglycerol; FAB) 807 (MH$^+$), 707 (MH$^+$ − CO_2 − C_4H_8) and 607 (MH$^+$ − 2CO_2 − 2C_4H_8).

(11S,14S)-14-tert-*Butoxycarbonylamino*-5,19-*dimethoxy*-11-(3-tert-*butoxycarbonylaminopropyl*)-9,12-*diazatricyclo*[14.3.1.1^{2,6}]*henicosa*-1(20),2,4,6(21),16,18-*hexaene*-10,13-*dione* **35**.—Compound **32** (0.317 g, 0.4 mmol) was dissolved in THF (5 cm^3) and methanol (5 cm^3) and treated with NaOH (1 mol dm^{-3}; 0.41 cm^3, 0.41 mmol) at room temperature. After 16 h the mixture was worked up as described in the preparation of compound **34**(*b*) above. The resulting crude product was converted into the pentafluorophenyl ester **33** by treatment with pentafluorophenol (0.092 g, 0.5 mmol) and DCC (0.106 g, 0.5 mmol) in DMF (4 cm^3) and THF (3 cm^3) and cyclization of the pentafluorophenyl ester **33** was brought about using the conditions described above for compound **34**(*b*). Chromatographic purification (silica gel, eluting with 2% v/v MeOH–$CHCl_3$, R_f 0.12) gave the *cyclic product* **35** as white needles (0.102 g, 32%), m.p. 234–236 °C (from MeOH) (Found: C, 63.6; H, 7.4; N, 8.5. $C_{34}H_{48}N_4O_8$ requires C, 63.7; H, 7.55; N, 8.75%); $[\alpha]_D^{23}$ +39.5 (*c* 0.5 in $CHCl_3$); λ_{max}(MeOH)/nm 257 (10 600)

and 289 (6200); ν_{max}/cm^{-1} 3430, 3300, 1695 and 1660; δ_H-(400 MHz; CD_3OD) 1.43 (9 H, s) 1.45 (9 H, s), 1.40–1.48 (2 H, m, $CH_2CH_2CH_2NHBoc$), 1.60–1.68 (2 H, m, $CH_2CH_2CH_2$-NHBoc), 2.70–2.80 (1 H, m, ArCHHCH$_2$NH), 2.93 (1 H, dd, *J* 14, 2.5, ArCHHCHCO) 3.0–3.15 (2 H, m, ArCHHCH$_2$NH and CHHNHBoc), 3.24 (1 H, dd, *J* 14, 8, ArCHHCHCO), 3.15–3.25 (2 H, m, ArCH$_2$CHHNH and CHHNHBoc), 3.78 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.90–4.00 (1 H, m, ArCH$_2$CHHNH), 4.35 (1 H, dd, *J* 8, 2.5, ArCH$_2$CHCO), 4.50–4.60 (1 H, m, NHCHCO), 6.82–6.90 (3 H, m, ArH), 7.0 (1 H, dd, *J* 8, *ca.* 2), 7.09 (1 H, d, *J ca.* 2) and 7.48 (1 H, dd, *J* 8, 2); *m/z* (M^+, 3-nitrobenzyl alcohol–sodium acetate; FAB) 641 (MH^+) and 663 (MNa^+).

(11S,14S)-11-(3-*Aminopropyl*)-5,19-*dimethoxy*-10,13-*dioxo*-9,12-*diazatricyclo*[14.3.1.1^{2,6}]*henicosa*-1(20),2,4,6(21),16,18-*hexaene*-14-*amino bistrifluoroacetate* **36**.—The cyclic derivative **35** (0.024 g, 0.03 mmol) was suspended in dichloromethane (2 cm^3) and cooled in ice. Trifluoroacetic acid (1 cm^3) was added and the solution kept at 0 °C for 1 h when it was evaporated to dryness. The residue was triturated with ether and dissolved in water; freeze drying of the aqueous solution gave the bistrifluoroacetate **36** (0.02 g, 78%), $[\alpha]_D^{26}$ +49.5 (*c* 0.5 in MeOH); λ_{max}(MeOH)/nm 258 (12 400) and 288 (7600); ν_{max}(KBr)/cm^{-1} 1674; δ_H(CD_3OD) 1.60–1.90 (4 H, m, $CH_2CH_2CH_2NH_3^+$), 2.65–2.80 (1 H, m), 2.90–3.00 (2 H, m, $CH_2CH_2CH_2NH_3^+$), 3.10 (1 H, dd, *J* 15, 6, ArCHHCHCO), 3.10–3.22 (2 H, m), 3.37 (1 H, dd, *J* 15, 2.5, ArCHHCHCO), 3.80 (3 H, s), 3.85 (3 H, s), 3.85–3.95 (1 H, m), 4.20 (1 H, dd, *J* 6, 2.5, ArCH$_2$CHCO), 4.55 (1 H, t, *J* 6, NHCHCO), 6.90 (1 H, d, *J* 8), 6.97 (1 H, d, *J* 2), 6.98 (1 H, d, *J* 8), 7.10 (1 H, dd, *J* 8, 2), 7.13 (1 H, d, *J* 2) and 7.51 (1 H, dd, *J* 8, 2); *m/z* (M^+, thioglycerol; FAB) 441 (MH^+).

Acknowledgements

We thank Mr. E. A. Cutmore and Mr. J. W. Tyler for the NMR spectra, Mr. G. Powell for the microanalytical results and Mr. G. D. Risbridger for the mass spectra. We also thank Prof. R. Ramage, Dr. T. Smale and Dr. R. Southgate for helpful discussions during the course of this work.

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Paper 1/03548G
Received 12*th July* 1991
Accepted 9*th August* 1991