The Synthesis of Biphenomycin B

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Biphenomycin B, a highly potent antibiotic against Gram-negative, β-lactam-resistant bacteria, which was previously isolated from culture filtrates of *Streptomyces griseorubiginosus* No. 43708, has now been synthesised.

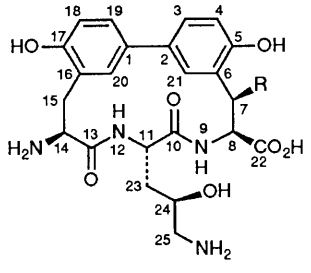
Biphenomycins A **1a** and B **1b** are cyclic tripeptides exhibiting high antibiotic activities against Gram-positive, β-lactam-resistant bacteria which have been isolated from culture filtrates of *Streptomyces griseorubiginosus* No. 43708.[1] These cyclopeptides, together with those of the vancomycin group, are unique in that they contain a biphenyl structural moiety. The compounds inhibit cell wall synthesis but, unlike the antibiotics of the vancomycin group, they apparently do not have any effect on binding to the D-Ala-D-Ala units of mucopeptide precursors. In the course of investigations relating to the site of attack for the inhibition of cell wall synthesis, the three-dimensional structure of biphenomycin A[2] in solution was examined. The reaction sequence described below represents the first synthesis of a natural cyclopeptide containing a biphenyl structural unit.

Biphenomycin B contains the two non-proteinogenic amino acids (*S,S*)-diisotyrosine **2** and (2*S*,4*R*)-hydroxyornithine. Only non-stereoselective syntheses of the latter amino acid were previously known[3] whereas we have already reported on the preparation of derivatives of the former, (*S,S*)-diisotyrosine.[4] In this process, the biphenyl unit was built up by the Pd^0-catalysed coupling of an arylboronic acid with an aryl bromide. However, the yields of arylboronic acid obtained varied so widely that we have now developed an alternative synthesis of diisotyrosine in which the biphenyl unit[5] is formed by the Pd^0-catalysed coupling of an aryl iodide with an arylzinc chloride. The stereoselective synthesis of a suitably protected hydroxyornithine is also described. The three stereogenic α-centres of both amino acids were formed from the corresponding didehydroamino acids by means of enantioselective hydrogenation using the $[Rh(cod)(dipamp)]^+ BF_4^-$ hydrogenation catalyst {cod = cycloocta-1,5-diene; dipamp = (*R,R*)-1,2-bis[2-(2-methoxyphenyl)phenylphosphino]ethane}.[6] The required substrates were prepared in turn by condensation of the appropriate aldehyde with a phosphorylglycine.[7]

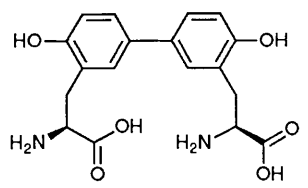
In the course of the total synthesis of biphenomycin B, it is necessary to mask two phenolic hydroxy groups, two amino groups, one hydroxy group, and one carboxy group with functions that are compatible with the protecting groups of the α-amino group of hydroxyornithine and a carboxy group of diisotyrosine which need to be cleaved during the peptide construction and ring closure steps. After numerous preliminary experiments we decided to protect the δ-amino and γ-hydroxy groups of the hydroxyornithine as a benzyloxycarbonyloxazolidine function and the other groups as benzyl ether, benzyl ester and benzyloxycarbonyl functions, respectively. We were fully aware of the difficulties to be encountered in the last step involving simultaneous cleavage of five *O*-benzyl bonds.

(*R*)-2,2-Dimethyl-4-(tosyloxymethyl)-1,3-dioxolane[8] **3**, prepared from mannitol, served as the starting material for the synthesis of the protected (2*S*,4*R*)-hydroxyornithine **9** (Scheme 1). Unambiguous conversion to the *Z*-compound **4**, opening of the dioxolane ring, acetylation of the primary hydroxy group (to give **5**), and aminal formation gave rise to an oxazolidine which could be converted by alkaline saponification to compound **6** possessing a free hydroxymethyl group. Oxidation of **6** gave the aldehyde **7** which was condensed with the phosphorylglycine to furnish the didehydroamino acid derivative **8**. The stereogenic centre in the α-position was formed with at least 98% diastereoisomeric excess (d.e.) by enantioselective hydrogenation.

The synthesis of an (*S,S*)-diisotyrosine dibenzyl ether possessing four different protecting groups suitable for peptide construction is illustrated in Scheme 2. The biphenyl skeleton was formed by the Pd^0-catalysed coupling of the zinc compound **11** with the aryl iodide **12**. Key reactions for the formation of the amino acid moieties were the condensations



1a; R = OH
b; R = H



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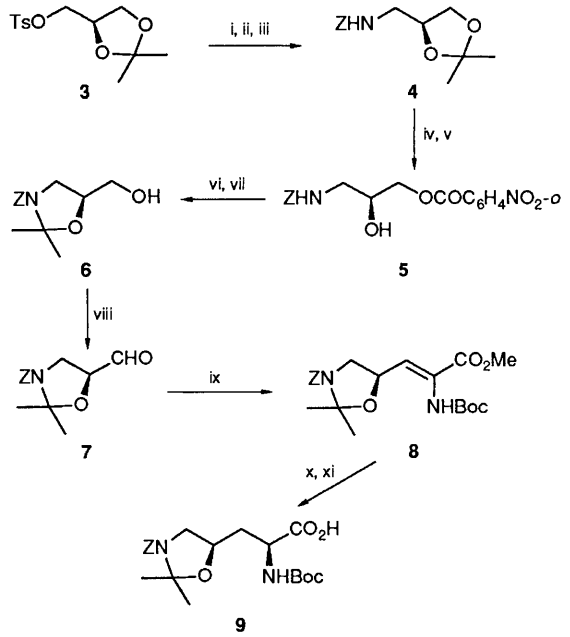
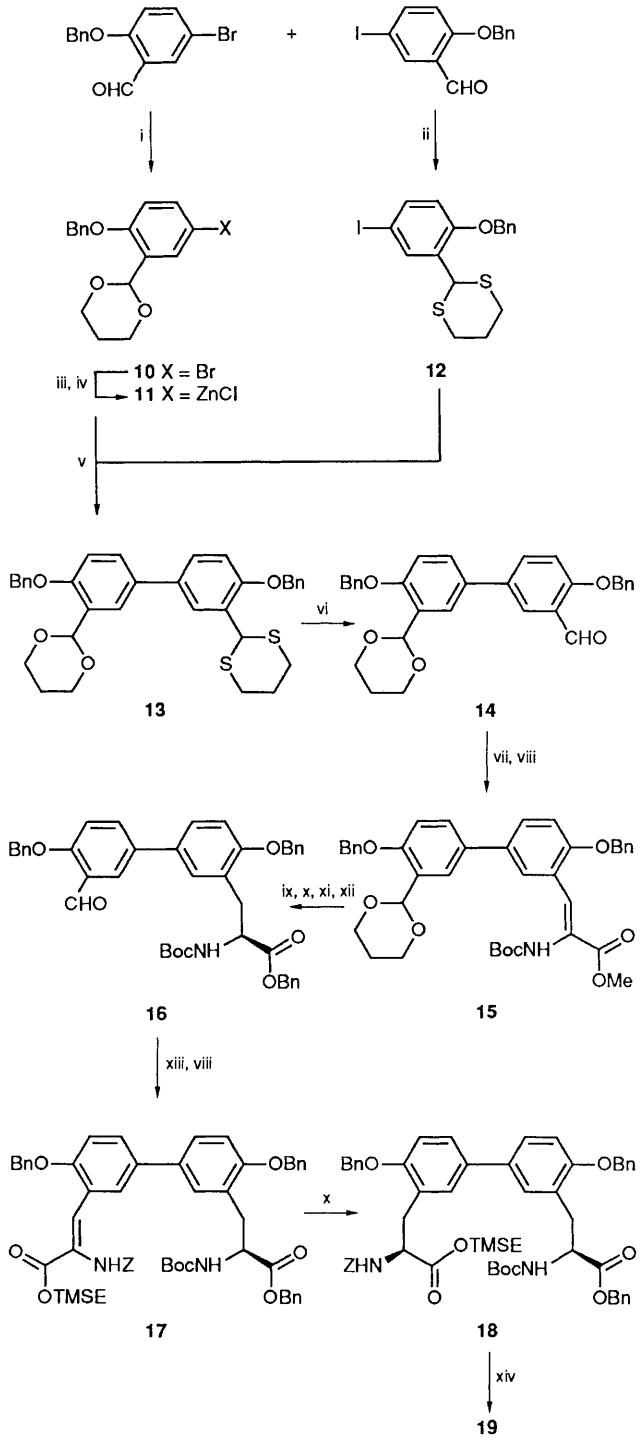


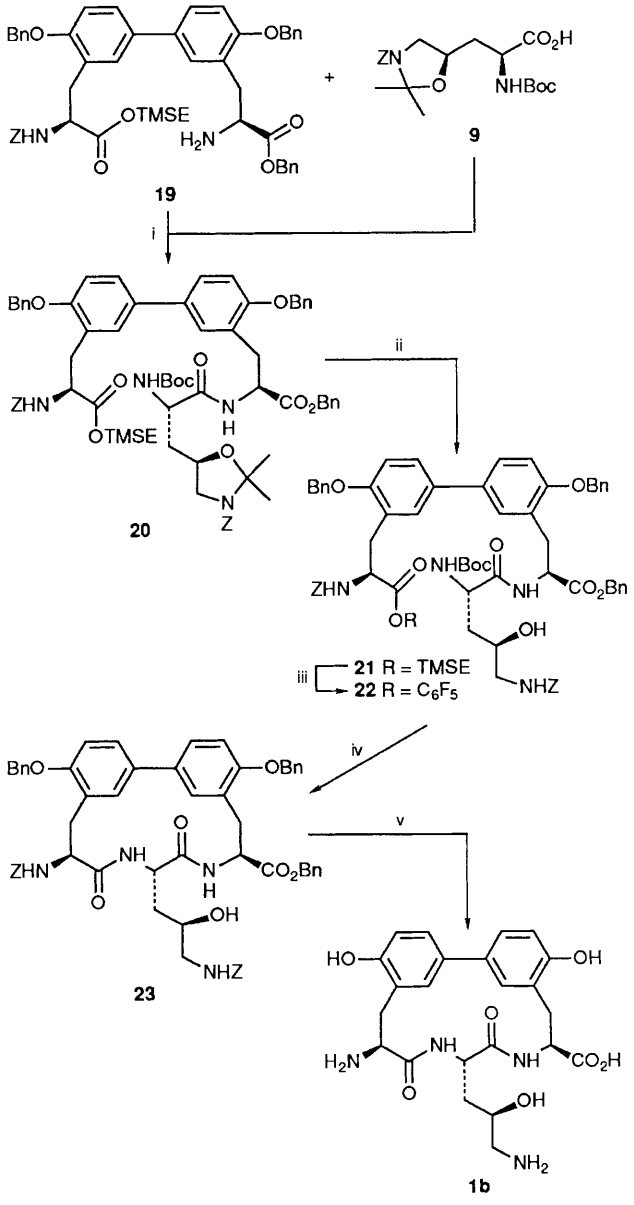
Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; Bz = benzoyl; Z = benzyloxycarbonyl; Ts = *p*-$MeC_6H_4SO_2$.

Scheme 1 *Reagents and conditions*: i, NaN_3, dimethylformamide (DMF), 70 °C, 6 h, 82%; ii, Pd–C, MeOH, room temp., 5 h, 82%; iii, ZCl, dioxane, $NaHCO_3$, room temp., 12 h, 85%; iv, 1 mol dm^{-3} HCl, dioxane, 70 °C, 2 h, 90%; v, *o*-$NO_2C_6H_4COCl$, CH_2Cl_2, pyridine, room temp., 1 day, 75%; vi, $Me_2C(OMe)_2$, $BF_3{\cdot}Et_2O$, acetone, 20 °C, 1 day, 79%; vii, 1 mol dm^{-3} LiOH, tetrahydrofuran (THF), room temp., 1 h, 92%; viii, dimethyl sulphoxide (DMSO), dicyclohexylcarbodiimide (DCC), Cl_2CHCO_2H, C_6H_6, 0 to 20 °C, 2 h, 62%; ix, methyl *N*-*tert*-butoxycarbonyl(dimethoxyphosphoryl)glycinate, $KOBu^t$, CH_2Cl_2, −60 to 20 °C, 12 h, 82%; x, $[Rh(cod)(dipamp)]^+BF_4^-$, H_2, MeOH, 20 °C, 2 days, 99%; xi, 1 mol dm^{-3} LiOH, THF, room temp., 1 h, 95%



Abbreviation: TMSE - trimethylsilylethyl

Scheme 2 *Reagents and conditions*: i, propane-1,3-diol, $BF_3{\cdot}Et_2O$, toluene, 4 h, reflux, 81%; ii, propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, $CHCl_3$, room temp., 24 h, 94%; iii, Mg, THF, 3 h, reflux; iv, $ZnCl_2$, THF, 1 h, reflux; v, $PdCl_2(PPh_3)_2$, Bu^i_2AlH, room temp., 3 h, 79%; vi, *N*-bromosuccinimide (NBS), 2,6-lutidine, acetonitrile, H_2O, 0 °C, 5 min, 74%; vii, methyl *N*-*tert*-butoxycarbonyl(dimethoxyphosphoryl)glycinate, LiCl, 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU), acetonitrile, 1 h, room temp., 99%; viii, NEt_3, C, EtOH–$CHCl_3$ (1 : 1), 2 days, room temp., 95%; ix, LiOH, H_2O, dioxane, room temp., 12 h, quant.; x, $[Rh(cod)(dipamp)]^+BF_4^-$, H_2, MeOH, room temp., 72 h, quant.; xi, BnOH, DCC, 4-dimethylaminopyridine (DMAP), ethyl acetate, −15 to 20 °C, 12 h, 82%; xii, pyridinium-*p*-toluene sulphonate, acetone, H_2O, reflux, 6 h, 84%; xiii, *N*-benzyloxycarbonyl(dimethoxyphosphoryl)glycine trimethylsilylethyl ester, LiCl, DBU, acetonitrile, 2 h, room temp., 93%,; xiv, 6 mol dm^{-3} HCl, dioxane, 2 h, 20 °C, quant.



Scheme 3 *Reagents and conditions*: i, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), hydroxybenzotriazole, CH_2Cl_2, 15 to 20 °C, 14 h, 71%; ii, AcOH–H_2O (9 : 1), 50 °C, 7 h, 85%; iii, Bu_4NF, DMF, room temp., 1 h, C_6F_5OH, EDC, CH_2Cl_2, −15 to 20 °C, 14 h, 95%; iv, 6 mol dm^{-3} HCl, dioxane–CH_2Cl_2 (1 : 1), 0 °C, evaporation, $CHCl_3$–$NaHCO_3$, 20 °C, 5 min, 85%; v, trimethylsilyl trifluoromethane sulphonate, thioanisole, CF_3CO_2H, 30 min, room temp., 70%

of the aldehydes **14** and **16** with an appropriate (dialkoxyphosphoryl)glycine ester to furnish the didehydroamino acid derivatives **15** and **17**, respectively. The protecting groups at the amino and carboxy groups, which are required later in the sequence, were introduced with the phosphonic acid reagent. The initially formed *E*–*Z*-mixtures of **15** and **17** were isomerised to the respective *Z*-compounds by treatment with triethylamine on carbon. Details of this isomerisation procedure will be reported later. The enantioselectivities in the subsequent hydrogenations of **15** and **17** to provide the trimethylene acetal of **16** and the (*S,S*)-diisotyrosine derivative **18**, respectively, were in excess of 99%.

The synthesis of biphenomycin B is depicted in Scheme 3. Following cleavage of the Boc group from **18**, the amine **19** was coupled with the hydroxyornithine derivative **9** to furnish the linear peptide **20**. After conversion of the trimethylsilylethyl ester **20** into the pentafluorophenyl ester, attempts to

bring about ring closure met with little success. The mass spectra of some of the reaction products were indicative of a cleavage of the hydroxyornithine. Thus, we first opened the oxazolidine ring to obtain compound **21**. After conversion of **21** into the pentafluorophenyl ester **22** and cleavage of the Boc group, cyclisation in the two-phase system chloroform–aqueous sodium hydrogen carbonate[9] without dilution in 0.1 mol dm^{-3} solution produced the cyclopeptide **23** in 85% yield within a few minutes. Cleavage of the five benzyl groups was effected by the method of Yajima[10] using trimethylsilyl trifluoromethane sulphonate–thioanisole in trifluoroacetic acid. The synthesised product was separated by reversed phase chromatography and lyophilised. The NMR and mass spectra were identical to those of the natural product.

The configuration of diisotyrosine in the natural product was unequivocally analysed by NMR spectroscopy and assigned as *S,S*.[1,2] For further confirmation of this structural proposal, we have also synthesised the cyclopeptide having the 8*S*,14*R*-configuration at diisotyrosine. The ^{13}C NMR spectra of this product,† however, show significant discrepancies in comparison to the spectrum of the natural product; hence the *S,S*-configuration of diisotyrosine in the natural product has been proven by synthesis.

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† ^{13}C NMR data for (8*S*,11*S*,14*R*,24*R*)-**1b**: δ 173.44, 170.12, 169.87, 155.48, 154.91, 133.41, 133.28, 131.29, 130.32, 128.17, 127.97, 123.38, 122.92, 117.49, 117.12, 66.15, 56.63, 55.22, 52.25, 45.03, 40.09, 33.84 and 32.14.

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