# The Synthesis of Biphenomycin A[1]

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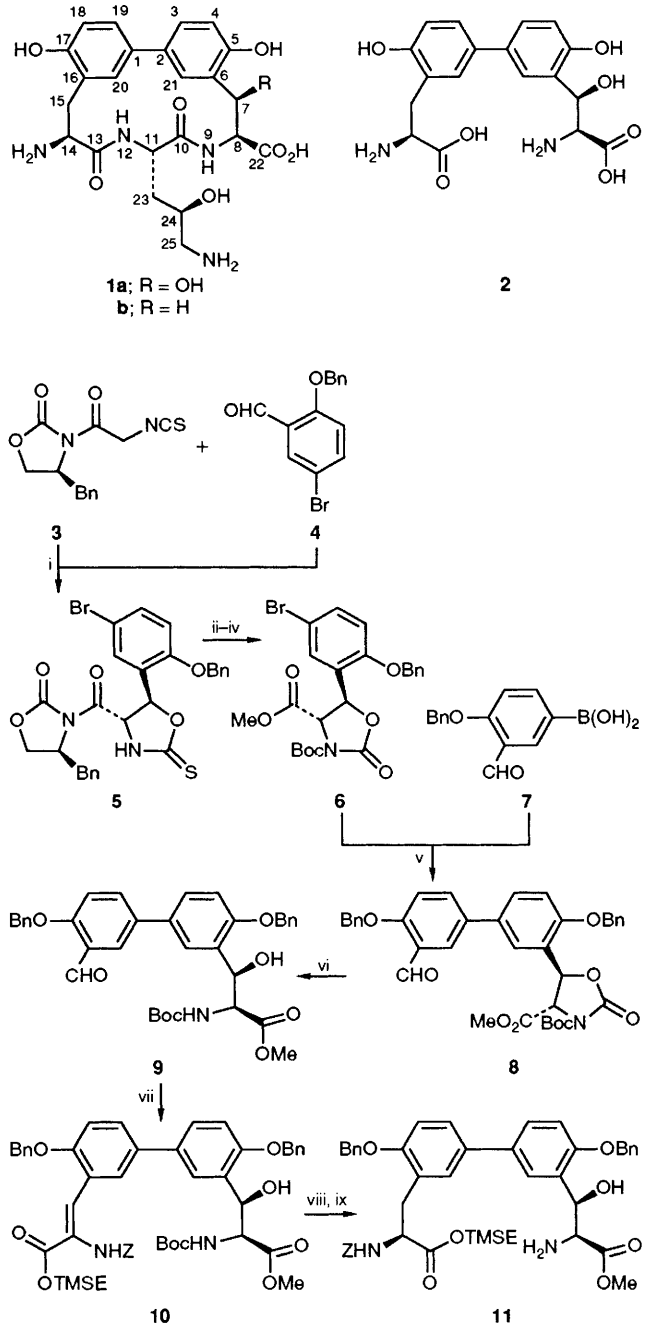
Biphenomycin A, a highly potent antibiotic against Gram-positive, β-lactam-resistant bacteria, which was previously isolated from culture filtrates of *Streptomyces griseorubiginosus* No. 43708, has now been synthesized.

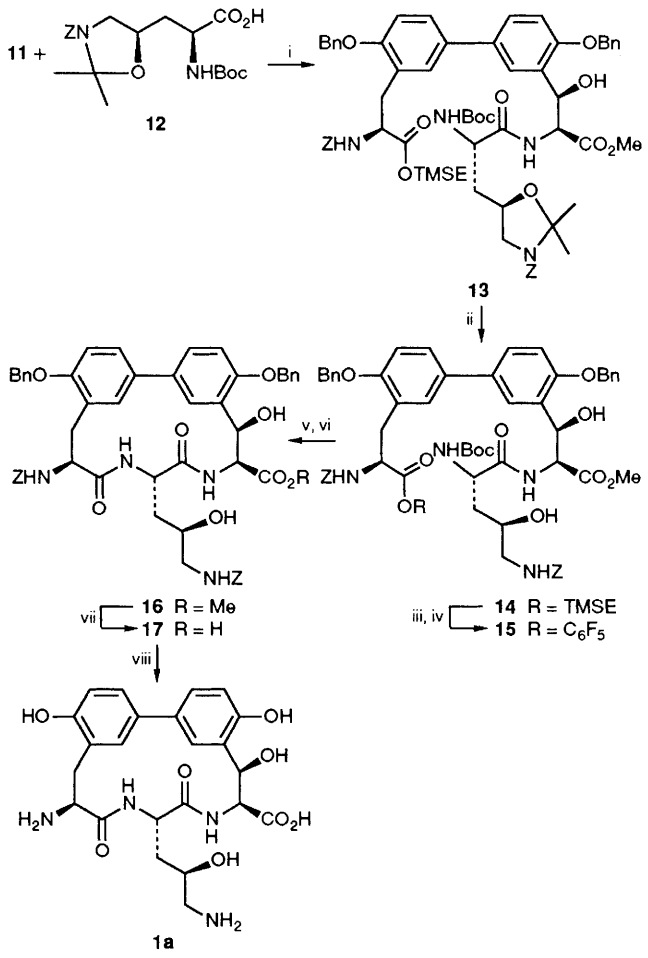
Biphenomycins A **1a** and B **1b** are cyclic tripeptides exhibiting high antibiotic activities against Gram-positive, β-lactam-resistant bacteria and have previously been isolated from culture filtrates of *Streptomyces griseorubiginosus* No. 43708 in the ratio of 10 : 1 (**1a** : **1b**).[2–4] These cyclopeptides, together with those of the vancomycin group, are unique in that they contain a biphenyl structural moiety. We have reported on the total synthesis of biphenomycin B[5] which contains the two non-proteinogenic amino acids (2*S*,4*R*)-hydroxyornithine and (*S*,*S*)-diisotyrosine. In place of the latter, the main metabolite biphenomycin A contains the corresponding hydroxy derivative **2** with an additional stereogenic centre *i.e.* the biphenyl



*Abbreviations*: Bn = benzyl; Boc = *tert*-butoxycarbonyl; TMSE = trimethylsilylethyl; Z = benzyloxycarbonyl

**Scheme 1** *Reagents and conditions*: i, **3**, $Sn(OTf)_2$, *N*-ethylpiperidine, tetrahydrofuran (THF), −78 °C, 1.5 h, **4**, 2 h, −78 °C, 75%; ii, MeOMgBr, MeOH, 0 °C, 3 min, 90%; iii, $(Boc)_2O$, dimethylaminopyridine (DMAP), $CH_2Cl_2$, room temp., 20 min, 90%; iv, $H_2O_2$, formic acid, $CH_2Cl_2$, 0 °C, 30 min, 90%; v, THF, $(Ph_3P)_4Pd$, reflux, 1 h, 12 mol $dm^{-3}$ $Na_2CO_3$, reflux 24 h, 50%; vi, $CsCO_3$, MeOH, room temp., 2 h, 80%; vii, *N*-benzyloxycarbonyl(dimethoxyphosphoryl) glycine trimethylsilylethyl ester, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), $CH_2Cl_2$, −78 °C, 15 h, 80%; viii, $[Rh(1.5\text{-cod})(dipamp)]^+$ $BF_4^-$, $H_2$, MeOH, room temp., 72 h, quant.; ix, 6 mol $dm^{-3}$ HCl, dioxane, room temp., 30 min, quant.

unit formally represents the dimer from (*S*)-*o*-hydroxyphenylalanine and (2*S*,3*R*)-*o*-hydroxyphenylserine. In this communication we describe the total synthesis of biphenomycin A. The key step for the construction of the biphenyl unit is the $Pd^0$-catalysed coupling[6] of an arylboronic acid containing an unprotected aldehyde function with a protected 2-hydroxy-5-



**Scheme 2** *Reagents and conditions*: i, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), hydroxybenzotriazole, $CH_2Cl_2$, −10 to 20 °C, 14 h, 80%; ii, AcOH–$H_2O$ (9 : 1), 50 °C, 2 h, 70%; iii, $Bu_4NF$, dimethylformamide, room temp., 30 min; iv, $C_6F_5OH$, EDC, $CH_2Cl_2$, −15 to 20 °C, 14 h, 95%; v, 6 mol $dm^{-3}$ HCl, dioxane, room temp., 30 min, evaporation, quant.; vi, $CHCl_3$–$NaHCO_3$ (aq.), 20 °C, 5 min, 70%; vii, 1 mol $dm^{-3}$ LiOH, dioxane, room temp., 30 min, evaporation, quant.; viii, trimethylsilyl bromide–thioanisole (1 : 1), $CF_3CO_2H$, 2 h, room temp., 60%

bromophenylserine. In the course of the synthesis it was necessary to mask two phenolic hydroxy groups, two amino groups, two hydroxy groups and one carboxy group with functions that are compatible with the protecting groups of the α-amino group of hydroxyornithine and the one carboxy group of the hydroxy diisotyrosine which needs to be cleaved during the peptide construction and ring closure steps.

The synthesis of a protected (*R*)-hydroxy-(*S,S*)-diisotyrosine **11** is illustrated in Scheme 1. The aryl bromide **6** represents a completely protected 2-hydroxy-5-bromophenylserine and can be constructed *via* **5** in excellent enantioselectivity and diastereoselectivity by the Evans method.[7] The $Pd^0$-catalysed coupling of **6**, with the boronic acid **7** containing an unprotected aldehyde function gives rise to the biphenyl derivative **8**. After opening of the oxazolidinone, the highly diastereoselective[8] construction of the *Z*-dehydroamino acid derivative **10** is achieved by condensation of **9** with an appropriate phosphorylglycine[9] and subsequent completely diastereoselective hydrogenation using the $[Rh(1,5\text{-cod})(dipamp)]^+$ $BF_4^-$ hydrogenation catalyst {cod = cycloocta-1,5-diene; dipamp = (*R,R*)-1,2-bis[2-(2-methoxyphenyl)-phenylphosphino]ethane}[10] gives rise to the biphenyl unit **11**. The further steps are illustrated in Scheme 2. The construction of the linear substrate **13** for the ring closure reaction is achieved starting from the hydroxyornithine derivative **12**.[5,11]

in analogy to the synthesis of biphenomycin B. The only exception is that the free carboxy group is now protected as a methyl ester (in place of a benzyl ester in the biphenomycin B synthesis). The ring closure reaction of the ω-aminopentafluorophenyl ester in the two phase system $CHCl_3$–$NaHCO_3$ (aq.) occurs within 5 min to give a 70% yield without dilution.[12] After saponification of the methyl ester **16**, the four benzylic protecting functions are cleaved by the method of Yajima[13] using trimethylsilyl bromide–thioanisole in trifluoroacetic acid. The synthesized product is separated by reversed phase chromatography and lyophilized. It is identical in every respect with the natural compound.

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