Flexible total synthesis of biphenomycin B†

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A total synthesis of the biaryl antibiotic biphenomycin B is reported which makes use of three independent building blocks (key steps were a clean Suzuki–Miyaura coupling of a free acid iodide, a novel 4-hydroxyornithine synthesis, and a high-yielding macrolactamization); a practical deprotection protocol allowed isolation of the target compound with excellent recovery and purity.

Natural products continue to be rich sources of new antibiotic lead structures.[1] The structurally related biarylcyclopeptide natural products biphenomycin B and A (**1**, **2**)[2] and arylomycin A and B (**3**, **4**)[3] represent an interesting case in this regard. Whilst the 15-membered ring compounds **1** and **2** inhibit protein biosynthesis with remarkable potency,[1] the 14-membered ring congeners **3** and **4** address the bacterial signal peptidase.[4] In order to enable investigations of this puzzling target dichotomy, we embarked on a total synthesis of biphenomycin B (Fig. 1).

To allow for broad variability of this newly projected synthesis,[5] it was planned to assemble **1** from three fully functionalized building blocks which can be individually varied. In a retrosynthetic sense, **1** could arise from a hydroxyornithine and an amino-acid derived biaryl, which was envisioned to be formed by a mild Suzuki–Miyaura coupling of suitable aromatic precursors.

Amino acid **6** was prepared from benzyl bromide **5**[6] in >96% ee using the asymmetric glycine enolate alkylation technology of Corey *et al.* (Scheme 1).[7] Boc-group and methyl-ester introduction and Pd^0-mediated borylation[8] delivered boronate **7** in excellent yield. Cbz-protection of **6** provided iodide **8**, which could be directly coupled to **7** under Pd^0 catalysis[9] to give biaryl acid **9** without protecting the free carboxylic acid. No epimerization was observed under optimized conditions (74% yield). In contrast, attempts at coupling the free acid of **7** with an ester derived from **6** remained unsuccessful.

The central hydroxyornithine amino acid[10] was elaborated from commercially available *trans*-4-hydroxyproline **10** (Scheme 2). **10** was *N*-Boc protected, smoothly converted to the *t*Bu ester using O-*tert*-butyl isourea[11] and silylated to provide the TBS ether **11**. Pyrrolidine **11** was subjected to a regioselective α-oxidation with cat. RuO_4 to cleanly give pyroglutamate **12** (89%),[12] which could be regioselectively ring

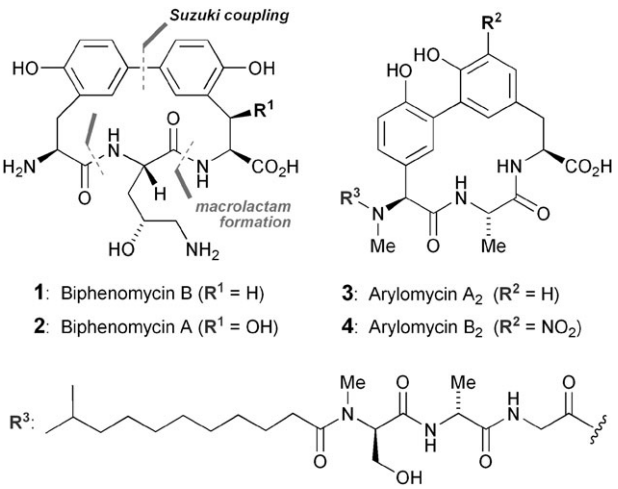
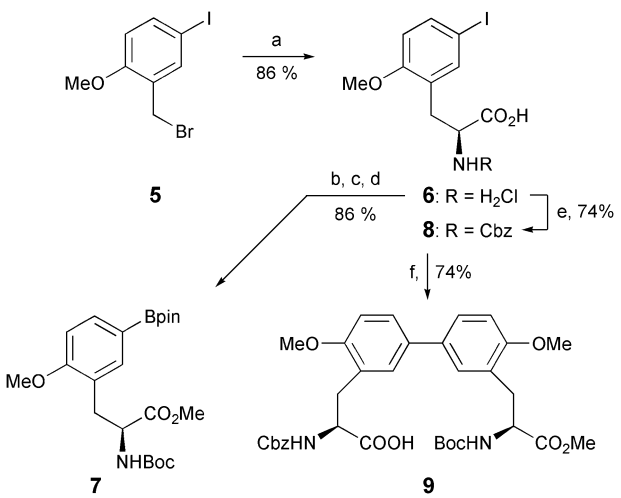


Fig. 1 Macrocyclic biaryl peptide antibiotics **1–4** and retrosynthetic disconnections of biphenomycin B (**1**).



Scheme 1 Synthesis of biaryl building block **9**. Reagents and conditions: (a) $Ph_2C{=}GlyO^tBu$, *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (10 mol%), CsOH (10 equiv.), CH_2Cl_2, −50 °C, 24 h; then 4 M HCl in dioxane, 86%, 96% ee; (b) Boc_2O (1.5 equiv.), 2 M NaOH (2 equiv.), dioxane/H_2O (1 : 1), 16 h, 92%; (c) MeI (1.5 equiv.), K_2CO_3 (2 equiv.), acetone, 56 °C, 16 h, 97%; (d) $(pinB)_2$ (1.2 equiv.), $PdCl_2(dppf)$ (5 mol%), KOAc (3 equiv.), DMSO, 80 °C, 16 h, 96%; (e) CbzCl (1.2 equiv.), Na_2CO_3 (1.5 equiv.), dioxane/H_2O (1 : 1), 16 h, 74%; (f) **7** (1.2 equiv.), $Pd(OAc)_2$ (20 mol%), P(o-tolyl)$_3$ (40 mol%), Cs_2CO_3 (3 equiv.), dioxane/H_2O (9 : 1), 80 °C, 16 h, 74%. Pin = pinacolato, dppf = *bis*-diphenylphosphinoferrocene.

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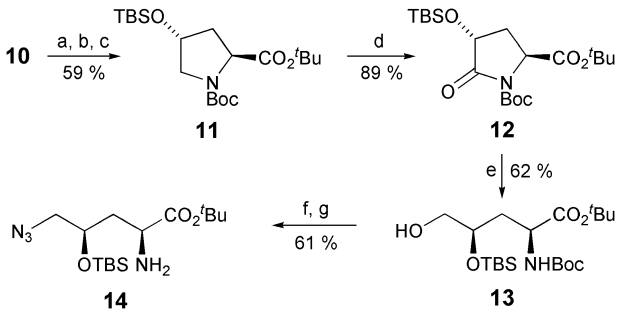


Scheme 2 Protected hydroxyornithine synthesis. Reagents and conditions: (a) Boc_2O (1 equiv.), NaOH (1.2 equiv.), THF/H_2O (2 : 1), 16 h, 93%; (b) *O-tert*-butyl *N*,*N*-diisopropylisourea (2 equiv.), THF, 60 °C, 16 h, 68%; (c) TBSCl (1.2 equiv.), DMAP (0.1 equiv.), imidazole (2.6 equiv.), 16 h, 94%; (d) $RuO_2{\cdot}nH_2O$ (25 mol%), $NaIO_4$ (3 equiv.), $EtOAc/H_2O$ (1 : 2), 16 h, 89%; (e) $NaBH_4$ (5 equiv.), $MeOH/NaP_i$ buffer (1 : 1, pH = 7.0), 0 °C → RT, 8 h, 62%; (f) PPh_3 (3 equiv.), DIAD (3 equiv.), HN_3 (5 equiv.), 4 h, 87%; (g) TBSOTf (1.5 equiv.), 2,6-lutidine (2 equiv.), CH_2Cl_2, 15 min, then TBAF (1 equiv.), THF/H_2O (10 : 1), 70%.

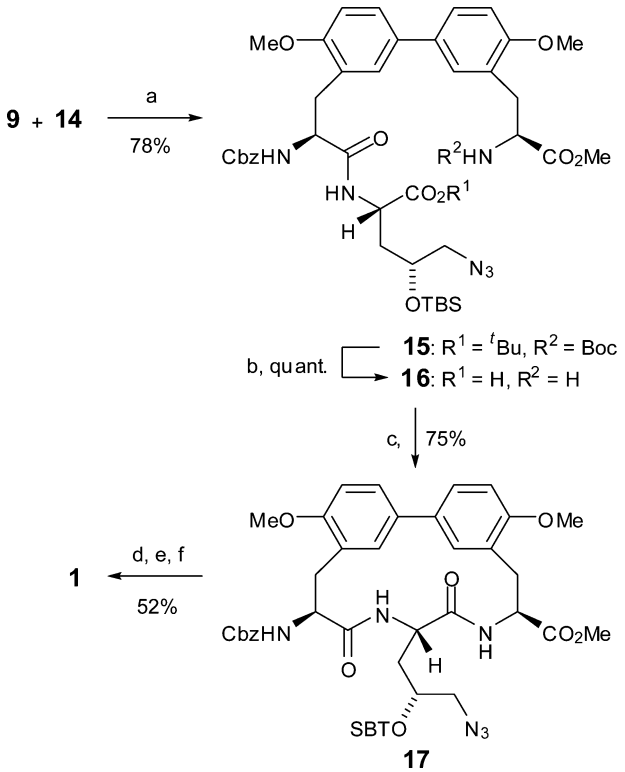
opened to alcohol **13** in buffered MeOH (62%). Alcohol **13** was converted to azido amine **14** in a two step sequence involving a Mitsunobu reaction with hydrazoic acid[13] and selective Boc-group cleavage with TBSOTf[14] (61%, 20% from **10**).

Biaryl acid **9** was then coupled to amine **14** under standard conditions (78%, Scheme 3), and the resulting dipeptide **15** was simultaneously Boc- and *t*Bu-deprotected with TESOTf[15] in remarkable yield and selectivity. Ring closure to the macrolactam **17** was then achieved with excellent results using HATU/HOAt[16] under pseudo-high dilution conditions (75%).

The protecting groups on **17** had been initially chosen to allow orthogonal deprotection[17] for future derivatizations, but to liberate biphenomycin B (**1**) all of them had to be removed. It was found that the OTBS and azido functions in **17** would react under the strongly Lewis-acidic conditions necessary to cleave the phenylmethyl ethers. Therefore, deprotection commenced with reducing the azide to the amine (PMe_3) under basic conditions with concomitant methyl ester cleavage in quantitative yield.

Aqueous HCl was subsequently used to remove the TBS group. The resulting 2-amino alcohol could then be treated with an excess of BBr_3, which cleanly cleaved the Cbz and OMe groups. In unprotected form the side chain now proved to be inert, presumably due to *in situ* protection as a cyclic boronate. Serendipitously, under these conditions the product precipitated from the reaction mixture, which allowed easy removal of all excess reagent. The recovered crude product was desalted and further purified by prep. HPLC, which provided synthetic biphenomycin B (**1**) in 52% yield from **17**, in all aspects (^1H, ^{13}C, IR, mp, HRMS, $[\alpha]^D$) matching the data reported for the natural product.[1,5]

In summary, we report a streamlined and flexible total synthesis of biphenomycin B which provides the target molecule in high purity in only 11 steps and 14% yield from benzyl bromide **5**. Importantly, in contrast to previous syntheses, stereochemical and structural variations in all three amino acid subunits can be liberally accessed. These results will significantly facilitate exploiting biphenomycin B and its biarylpeptide natural product scaffold.



Scheme 3 Completion of the total synthesis of biphenomycin B (**1**). Reagents and conditions: (a) EDC·HCl (1.5 equiv.), HOBt (1.5 equiv.), $EtN(iPr)_2$ (2.2 equiv.), CH_2Cl_2, 16 h, 78%; (b) TESOTf (20 equiv.), 2,6-lutidine (40 equiv.), CH_2Cl_2, 6 h, quant.; (c) slow addition to HATU (1.5 equiv.), HOAt (1.5 equiv.), $EtN(iPr)_2$ (2.2 equiv.), CH_2Cl_2, 30 h, 75%; (d) PMe_3 (9 equiv., 1 M in toluene), THF/0.1 M NaOH (9 : 1), 8 h, quant.; (e) 1 M HCl, 16 h, quant.; (f) BBr_3 (1 M in CH_2Cl_2, 20 equiv.), 24 h, 52% (prep. HPLC). EDC = *N*-ethyl-*N*-dimethylaminopropyl carbodiimide; HOBt = 1-hydroxybenzotriazole; HATU = 7-aza-1-hydroxybenzotriazoluronium hexafluorophosphate; HOAt = 7-aza-1-hydroxybenzotriazole.

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