A New Convergent Approach to Biphenomycin Antibiotics

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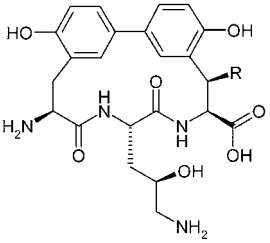
Abstract: A new, convergent approach to the biaryl key intermediate of Schmidt's biphenomycin B total synthesis has been accomplished via a palladacycle complex catalyzed Stille cross-coupling of two *o*-tyrosine building blocks.

Key words: biphenomycins, antibiotics, cyclopeptides, asymmetric synthesis, Stille coupling

The biphenomycins are a small family of cyclopeptide antibiotics isolated from the culture broths of *Streptomyces filipinensis*[1] and *S. griseorubiginosus*[2]. Their key structural feature is a 15-membered macrocycle containing a biaryl moiety (Figure 1). Among biphenomycins, biphenomycin A (**1a**) is the most abundant. It has been shown to exhibit high antibacterial activity both *in vitro* and in vivo, especially against Gram-positive bacteria. These include serious pathogens such as *Staphylococcus aureus*, *Enterococcus faecalis* or *Streptococcus pneumoniae*. Biphenomycin B (**1b**), the simplest representative of this family of cyclopeptide antibiotics, shows an *in vitro* antimicrobial activity closely related to that of **1a**. However, its potential in vivo activities are still undetected, presumably due to the paucity of material obtained from the natural source, which has precluded its further biological evaluation. In view of their promising antibacterial profiles coupled with their intriguing structural features, biphenomycins had attracted extensive synthetic studies[3] culminating in the stereoselective total syntheses of biphenomycin A (**1a**)[4] and biphenomycin B (**1b**)[5] by Schmidt and co-workers. However, neither biphenomycin derivatives nor close analogues thereof have been prepared and biologically evaluated so far.

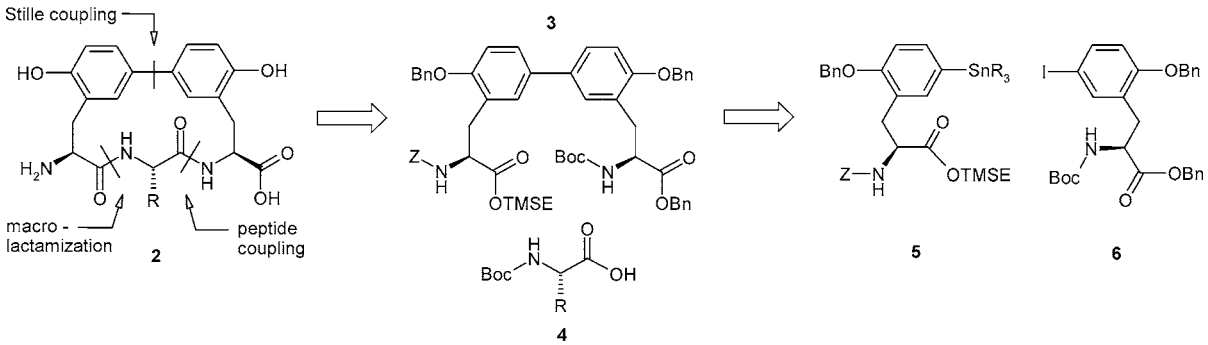


Biphenomycin A (**1a**): R = OH
Biphenomycin B (**1b**): R = H

Figure 1

Therefore, we recently have been engaged with the development of a new, convergent approach toward biphenomycin B (**1b**)[6] and related cyclopeptides **2** in general, that would be readily adaptable to parallel synthesis of a diverse set of analogues with modified biaryl moiety. The strategies of the total syntheses mentioned above are largely consecutive, i.e. 11 linear steps for key intermediate **3** of Schmidt's biphenomycin B total synthesis (vide infra), and thus unfavourable to this end.

In our convergent strategy cyclopeptides **2** are separated into a N_α-Boc amino acid **4** and key building block **3**, which is further subdivided into *o*-tyrosine derivatives **5** and **6** (Scheme 1). Subsequent segment coupling of these



Scheme 1 Retrosynthetic analysis of biphenomycin B analogues (**2**)

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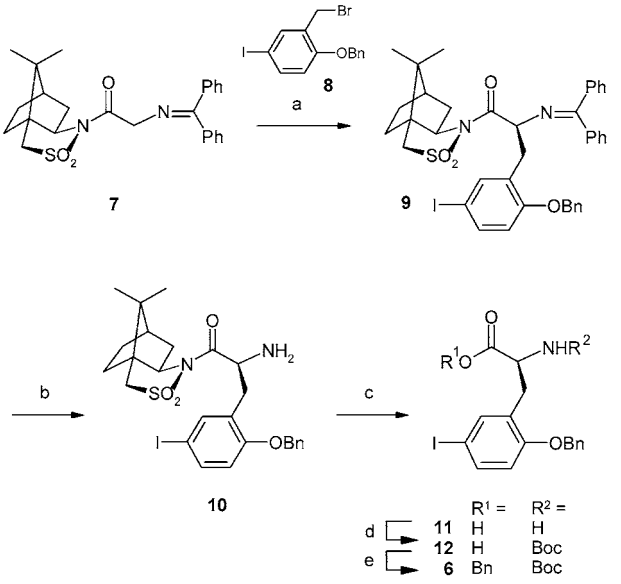
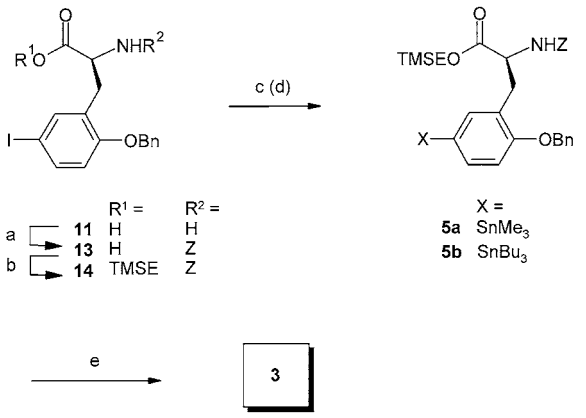
fragments involving a Stille cross-coupling reaction and a final macrolactamisation as key steps was envisioned to give the desired macrocycles. Herein we report a short and efficient asymmetric approach to *o*-tyrosine derivatives **5** and **6** as well as their subsequent cross-coupling to afford key building block **3**.

Building blocks **5** and **6** are both derived from (*S*)-2-benzyloxy-5-iodophenylalanine (**11**). This novel α-amino acid was synthesized following a diastereoselective pathway based on Oppolzer's camphor sultam as chiral auxiliary (Scheme 2). Thus successive treatment of chiral glycine equivalent **7**[7] with *n*-BuLi (THF, DMPU, –78 °C) and benzylbromide building block **8**[8] (–78 °C to r.t.) provided the alkylation product **9** in 84% yield and with high diastereoselectivity (ds ≥ 98:2 as determined by 500 MHz ^{1}H NMR).



Scheme 2 (a) (i) *n*-BuLi (1.05 equiv), THF, –78 °C; (ii) **7**, DMPU, –78 °C to r.t. (84%); (b) 0.01 M HCl, THF, 0 °C to r.t. (95%); (c) LiOH (2.0 equiv), H_2O_2 (4.0 equiv), THF, 0 °C to r.t. (81%); (d) Boc_2O, dioxane, aq $NaHCO_3$, r.t. (85%); (e) BnOH, EDCI, DMAP, CH_2Cl_2, 0 °C to r.t. (75%)

Deprotection of **9** under mild acidic conditions (0.01 M HCl, THF, 0 °C to r.t.) followed by lithium hydroperoxide-mediated cleavage of the chiral auxiliary (LiOH, H_2O_2, THF, 0 °C to r.t.) gave enantiomerically pure (*S*)-2-benzyloxy-5-iodophenylalanine (**11**)[9–11] in 77% overall yield. The chiral auxiliary could be recovered in 87% yield. Starting from α-amino acid **11**, building block **6** was readily obtained (64% overall yield) by introduction of a Boc group (Boc_2O, aq $NaHCO_3$, dioxane, r.t.) and subsequent esterification with benzyl alcohol (EDCl, cat. DMAP, CH_2Cl_2, 0 °C to r.t.). In an analogous sequence the *N*-Z protected amino acid 2-trimethylsilylethyl (TMSE) ester **14** was prepared (Scheme 3). Thus, protection of the amino group (Z-ONSu, aq Na_2CO_3, DMF, r.t.) and subsequent esterification ($TMSCH_2CH_2OH$, EDCl, cat. DMAP, CH_2Cl_2, 0 °C to r.t.) gave **14** in 65% overall yield.



Scheme 3 (a) Z-ONSu, DMF, aq Na_2CO_3, r.t. (88%); (b) $TMSCH_2CH_2OH$, EDC, DMAP, 0 °C to r.t. (74%); (c) $Me_3SnSnMe_3$ (1.4 equiv), $Pd(OAc)_2$ (0.04 equiv), PPh_3 (0.08 equiv), toluene, Δ (80%); (d) $Bu_3SnSnBu_3$, cat. $PdCl_2(PMePh_2)_2$, KOAc, NMP, r.t. (68%); (e) **5b**, **6**, palladacycle-complex **23**, LiCl, NMP, 90 °C (64% from **6**)

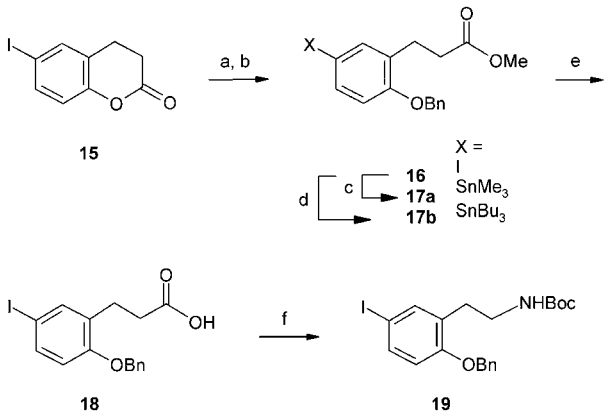
Subsequently, aryl iodide **14** was converted to the corresponding aryl stannanes **5a** and **5b** by treatment with either hexamethylditin or hexabutylditin [R_3SnSnR_3, cat. $Pd(OAc)_2$, PPh_3, toluene, 100 °C] according to Ortar et al.[12] However, whereas aryl trimethylstannane **5a** could be obtained in good yields (80%) the incorporation of the tributylstannyl group proceeded unsatisfactory (41% yield). Nevertheless preparation of **5b** still could be improved by stannylation according to a novel procedure reported by Masuda et al.[13] Thus treatment of **14** with hexabutylditin in the presence of cat. $PdCl_2(PMePh_2)_2$ (KOAc, NMP, r.t.) afforded **5b** in 68% yield.

We next focused our attention on optimising reaction conditions for the Stille cross-coupling of key building blocks **5** and **6**. To this end, we studied the reaction of the closely related model compounds **17** and **19**, which are more readily available than **5** and **6**.

Thus, both compounds **17** and **19** were prepared from readily accessible 6-iodochroman-2-one (**15**)[14] in three and four steps respectively, as indicated in Scheme 4.

Stille cross-coupling of aryl iodide **19** with stannanes **17a** and **17b**, respectively, to give biaryl **20** (Scheme 5) was performed under several well-established reaction conditions, as summarized in Table 1.

In situ generated $Pd(AsPh_3)_4$ (1 mol%) in the presence of LiCl (3.0 equiv, NMP, 65 °C)[15] or of cocatalytic CuI (10 mol%, DMF, 65 °C)[12] gave fair coupling yields (53–60%), both with trimethylstannane **17a** and tributylstannane **17b** (entries 1–4). $Pd(dppf)Cl_2$ catalysed cross-coupling of **17b** and **19** in the presence of cocatalytic CuBr (10 mol%), reaction conditions recently reported by Williams et al.,[16] gave product **20** in a comparable yield (49%) (entry 5). Appreciable amounts of biaryl **21** (8–13%) and alkylarenes **22** (2–10%), which arise from com-



Scheme 4 (a) NaOMe, MeOH, r.t.; (b) BnBr, K_2CO_3, acetone, Δ (88% from **15**); (c) $Me_3SnSnMe_3$, $Pd(OAc)_2$, PPh_3, toluene (83%); (d) $Bu_3SnSnBu_3$, $PdCl_2(PMePh_2)_2$, KOAc, NMP, r.t. (74%); (e) **16**, 1M NaOH, MeOH, r.t. (83%); (f) diphenyl phosphorazidate, NEt_3, *t*-BuOH, toluene, Δ (79%)

petitive stannane homocoupling and alkyl group transfer respectively, reactions that are frequently encountered with Stille couplings,[17] were isolated as the main side products.[18]

A markedly improved yield of cross-coupling product **20** could be accomplished, employing palladacycle catalyst **23**,[19] which is not yet widely applied for Stille cross-coupling reactions.[20]

Thus coupling of tributylstannane **17b** with **19** [**23** (5 mol%), LiCl (3.0 equiv), NMP, 90 C][20c] proceeded smoothly to give **20** in good yield (73%) (entry 7). Notably a distinct lower yield was observed for the coupling of trimethylstannane **17a** under analogous reaction conditions (entry 6). Apparently, this is due to a differing extent of alkyl group transfer occurring in either case (i.e. 9% versus 24% of the respective alkylarene **22**). Again, stannane homocoupling product **21** was isolated as the other main side product.

Finally, we applied these optimised reaction conditions to the Stille cross-coupling of *o*-tyrosine building blocks **5b** and **6** (Scheme 3).[21]

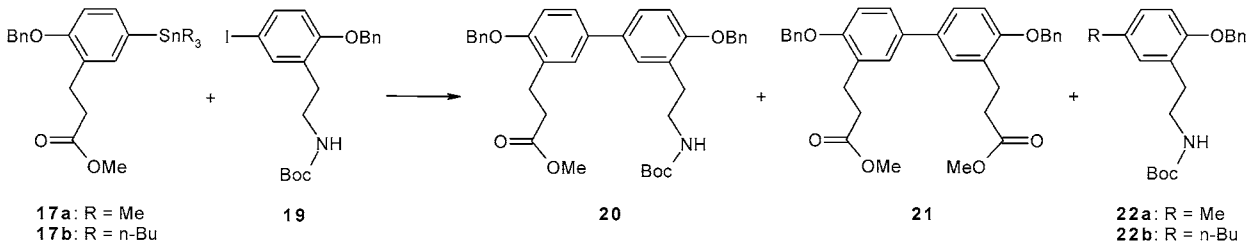
Indeed, the key intermediate **3** of Schmidt's biphenomycin B (**1b**) total synthesis could be obtained in good yield (64%) in addition to the respective stannane homocoupling and butyl transfer products (5% and 10% respectively). The ^1H NMR spectroscopic data of **3** are in full accordance with those reported in the literature.[5a] Apparently, neither racemisation during the preparation of building blocks **5b** and **6** nor epimerisation during their Stille cross-coupling occurred to an appreciable extent, since product **3** was attained as a single diastereomer [ds > 98:2 as determined by ^1H NMR (500 MHz) and HPLC from the crude reaction product].

In conclusion we disclose an efficient convergent approach to the key intermediate of Schmidt's biphenomycin B total synthesis. Efforts to adapt this strategy for the preparation of biphenomycin B analogues with modified biaryl moiety are currently in progress in our laboratory.

Table 1 Reaction Conditions and Results for the Stille Coupling Outlined in Scheme 5

Entry	R	Conditions	**20** Yield (%)[a]	**21** Yield (%)[b]	**22** Yield (%)[c]
1	Me	Pd_2dba_3, $AsPh_3$, CuI, DMF, 65 °C, 14 h	56	13	2
2	Bu	Pd_2dba_3, $AsPh_3$, CuI, DMF, 65 °C, 168 h	53	8	< 1
3	Me	Pd_2dba_3, $AsPh_3$, LiCl, NMP, 65 °C, 14 h	55	10	10
4	Bu	Pd_2dba_3, $AsPh_3$, LiCl, NMP, 65 °C, 168 h	60	8	9
5	Bu	$Pd(dppf)Cl_2$, MeCN, CuBr, 80 °C, 168 h	49	11	< 1
6	Me	Palladacycle **23**, LiCl, NMP, 90 °C, 14 h	56	13	24
7	Bu	Palladacycle **23**, LiCl, NMP, 90 °C, 14 h	73	13	9

[a] Yield of isolated, purified product **20** based on **19**.
[b] Yield of isolated, purified product **21** based on **17**.
[c] Yield of isolated, purified product **22** based on **19**.



Scheme 5

Acknowledgement

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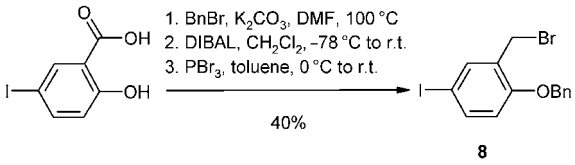
(8) Benzylbromide **8** was prepared from 5-iodo-salicylic acid in 40% overall yield as indicated in Scheme 6.



Scheme 6

(9) **(*S*)-2-Amino-3-(2-benzyloxy-5-iodophenyl)propionic acid(11)**: Colourless crystals, mp 228–230 °C (decomp.). $[\alpha]_D^{20}$ = –11.8 (*c* 0.11, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 2.89 (dd, *J* = 9.2/14.3 Hz, 1 H, C*H*$_2$CH), 3.41 (dd, *J* = 4.7/14.3 Hz, 1 H, C*H*$_2$CH), 3.89 (dd, *J* = 4.7/9.2 Hz, 1 H, CH$_2$C*H*), 5.18 (s, 2 H, OCH$_2$), 6.86 (d, *J* = 8.6 Hz, 1 H, H$_{arom}$), 7.28–7.49 (m, 5 H, H$_{arom}$), 7.54 (dd, *J* = 2.2/8.6 Hz, 1 H, H$_{arom}$), 7.57 (d, *J* = 2.2 Hz, 1 H, H$_{arom}$); ^{13}C NMR (125 MHz, CD_3OD): δ = 33.5, 56.2, 71.3, 83.9, 115.9, 128.7, 128.9, 129.2, 129.8, 138.2, 138.8, 141.0, 158.3, 173.6; MS (MALDI): *m/z* = 398 [M + 1]. HRMS (CI, CH_5^+): Anal. Calcd for $C_{16}H_{16}NO_3I$ (M + H$^+$): 398.0253; Found: 398.0253.

(10) The enantiomeric purity of **11** was determined via its Fmoc derivative by HPLC (ChiraDex®Gamma (5-μm) LiChroCART® 250 × 4 mm (Merck) MeCN–triethylamine–AcOH, 1000:7:0.5, 1 mL/min) according to Armstrong et al. to be > 98% ee. See: Tang, Y.; Zukowski, J.; Armstrong, D. W. *J. Chromatogr. A* **1996**, *743*, 261.

(11) The absolute configuration of **11** was determined to be *S* by conversion into (*S*)-*o*-tyrosine, whose absolute configuration has been unambiguously established. Lit.: Dugave, C. *J. Org. Chem.* **1995**, *60*, 601.

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(18) In addition to **20**, **21** and **22** small amounts of the respective aryl iodide homocoupling product **i** (1–7%) and in case of entries 1–4 product **ii** (3–6%), which arises from aryl transfer by the arsine, were also obtained (Figure 2).

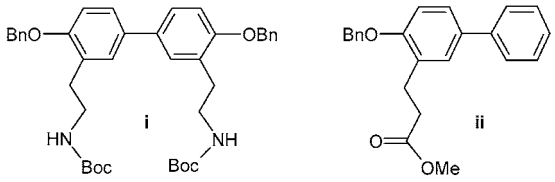

Figure 2

(19) For the preparation of **23** (Figure 3), see: Herrmann, W. A.; Broßmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844; *Angew. Chem.* **1995**, *107*, 1989.

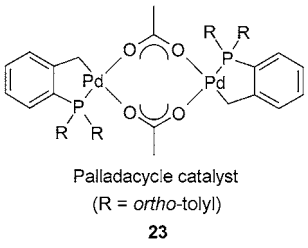

Figure 3

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(21) Stille coupling of **5b** and **6**: A solution of **5b** (29.5 mg, 37 mol) in degassed NMP (0.14 mL) was added to a stirred mixture of anhydrous LiCl (4.3 mg, 102 mol), **6** (20.0 mg, 34 mol) and **23** (1.6 mg, 1.7 mol) in degassed NMP (0.2 mL) at room temperature. The reaction mixture was heated at 90 °C for 14 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of silica gel. The filtrate was washed with aqueous 1.3 M phosphate buffer pH 7.0 and water, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by prep. HPLC (LiChrosorb® Si 60 5 μm, *n*-

heptane–EtOAc, 85:15) to give 20.9 mg (64%) **3** as a colourless solid.
3: $[\alpha]_D^{20}$ = +10.3 (*c* = 0.95, $CHCl_3$); lit.[5a]: $[\alpha]_D$ = +11.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ = –0.03 [s, 9 H, $Si(CH_3)_3$], 0.85–0.91 (m, 2 H, CH_2CH_2Si), 1.35 [s, 9 H, $C(CH_3)_3$], 3.06–3.14 (m, 2 H, $CHCH_2$), 3.18–3.26 (m, 2 H, $CHCH_2$), 4.05–4.21 (m, 2 H, CH_2CH_2Si), 4.56–4.67 (m, 2 H, $CHCH_2$), 4.95–5.17 (m, 8 H, OCH_2Ph), 5.38 (d, 1 H, *J* = 7.8 Hz, NHBoc), 5.61 (d, 1 H, *J* = 7.7 Hz, NHZ), 6.91 (d, 1 H, *J* = 8.6 Hz, H_{arom}), 6.94 (d, 1 H, *J* = 8.6 Hz, H_{arom}), 7.19–7.38 (m, 20 H, $H_{arom.}$), 7.42–7.48 (m, 4 H, H_{arom}).