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Microwave-Assisted Intramolecular Suzuki–Miyaura Reaction to Macrocycle, a Concise Asymmetric Total Synthesis of Biphenomycin B

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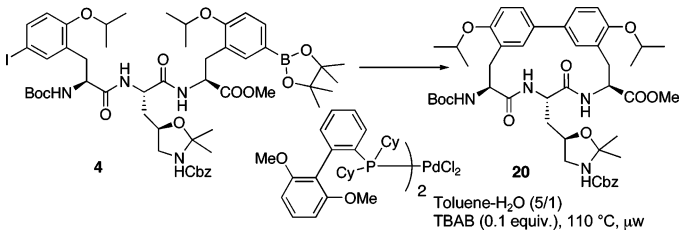
ABSTRACT



A concise and efficient total synthesis of biphenomycin B has been accomplished featuring a key microwave-assisted intramolecular Suzuki–Miyaura reaction for formation of the 15-membered *meta,meta*-cyclophane 20.

Biphenomycin A (**1**) and B (**2**, Figure 1) are cyclic tripeptides isolated from the culture broths of *Streptomyces filipinensis* and *S. griseorubuginosus*.[1] The absolute configuration of these 15-membered *meta,meta*-cyclophanes have been determined from detailed NMR studies.[2] Both compounds displayed potent activities against Gram-positive, β-lactam-resistant bacteria, such as *Streptococcus aureus*, *Enterococcus faecalis* or *Streptococcus*, although a detailed mode of action remained to be elucidated. Structurally, they belong to a growing family of macrocyclic natural products with an endo aryl−aryl bond(s) that included TMC-95 A (**3**, antitumor agent),[3,4] RP-66453 (antagonist of neurotensine receptor),[5,6] and vancomycin-type glycopeptide antibiotics.[7]

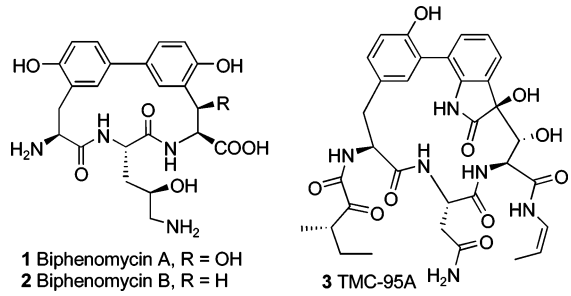


Figure 1. Structure of biphenomycins and TMC-95A.

The combination of structural novelty and potent antibiotic activity of biphenomycins provided motivation to contem-

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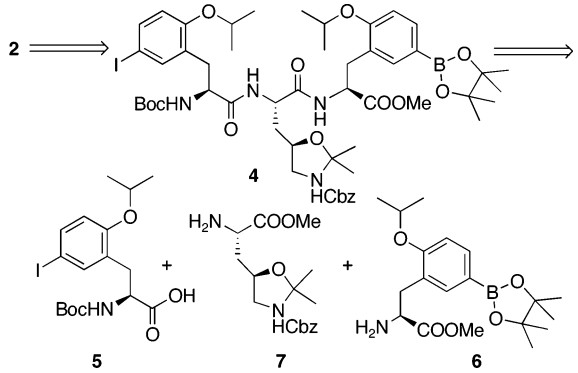
plate a total synthesis of these compounds, and indeed, a number of groups have been involved in such exercises.[8] However, only two total syntheses are known to date: The first one was reported by Schmidt in 1991,[9] and the second one was patented by scientists at Bayer in 2004.[10] Both groups employed macrolactamization technology for the key ring-closure step. We report herein a concise total synthesis of biphenomycin B (**2**) based on a novel strategy that is retrosynthetically depicted in Scheme 1. In a forward sense,

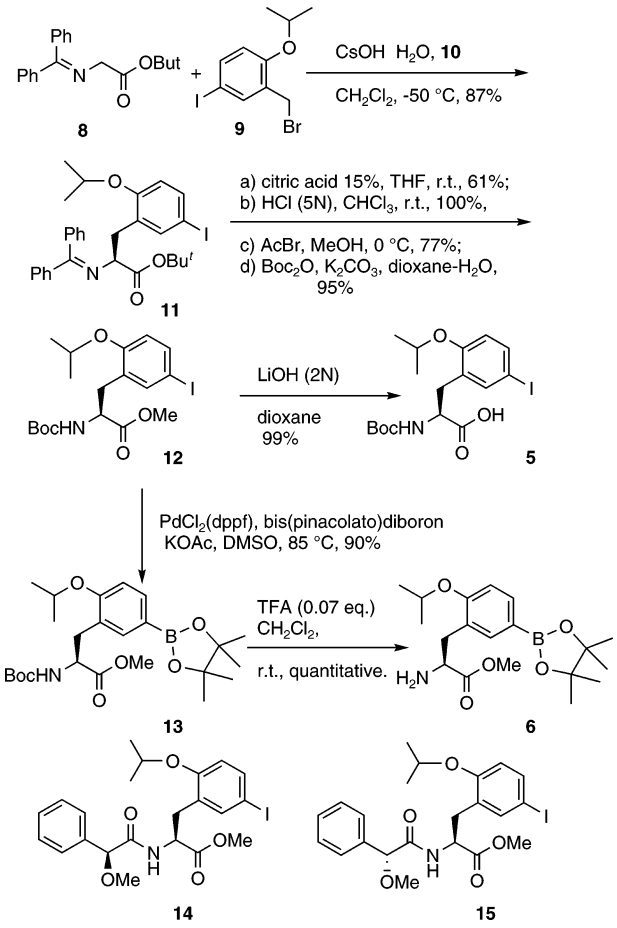
Scheme 1. Retrosynthetic Analysis of Biphenomycin B (**2**)



formation of the aryl−aryl bond with the concomitant ring closure to the 15-membered macrocycle by an intramolecular Suzuki−Miyaura reaction[11] of the linear tripeptide **4** was expected to provide the fully protected natural product. The tripeptide **4** in turn could be prepared from three non-proteinogenic amino acids, **5**, **6**, and **7**, by standard peptide chemistry.

The total synthesis began with the preparation of two substituted phenylalanine derivatives **5** and **6** (Scheme 2).

Scheme 2. Enantioselective Synthesis of Amino Acids **5** and **6**



Following Corey's procedure,[12] enantioselective alkylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester (**8**) with 2-isopropyloxy-5-iodo benzylbromide in the presence of a catalytic amount of *O*-(9)-allyl-*N*-(9′-anthracenylmethyl)-cinchonidinium bromide **10** (0.1 equiv) afforded the amino ester **11** in 87% yield.[13] A three-step sequence involving N-deprotection, transesterification, and *N*-*tert*-butyloxycarbonylation converted **11** into **12**. The synthesis diverged at this point. Hydrolysis of **12** provided the acid **5**, while palladium catalyzed cross-coupling between **12** and bis-(pinacolato)diboron following Miyaura's protocol afforded aryl boronate **13** in 90% yield.[14] Removal of the *N*-Boc function under carefully controlled conditions (0.07 equiv of TFA in CH_2Cl_2) provided the amino ester **6** in quantitative yield. The enantiomeric purity of amino ester **12** was determined to be higher than 95% by its transformation into the diastereomeric mandelate derivatives **14** and **15**.

A number of synthetic routes have been developed for the preparation of (2*S*,4*R*)-4-hydroxyornithine (**7**),[15] including

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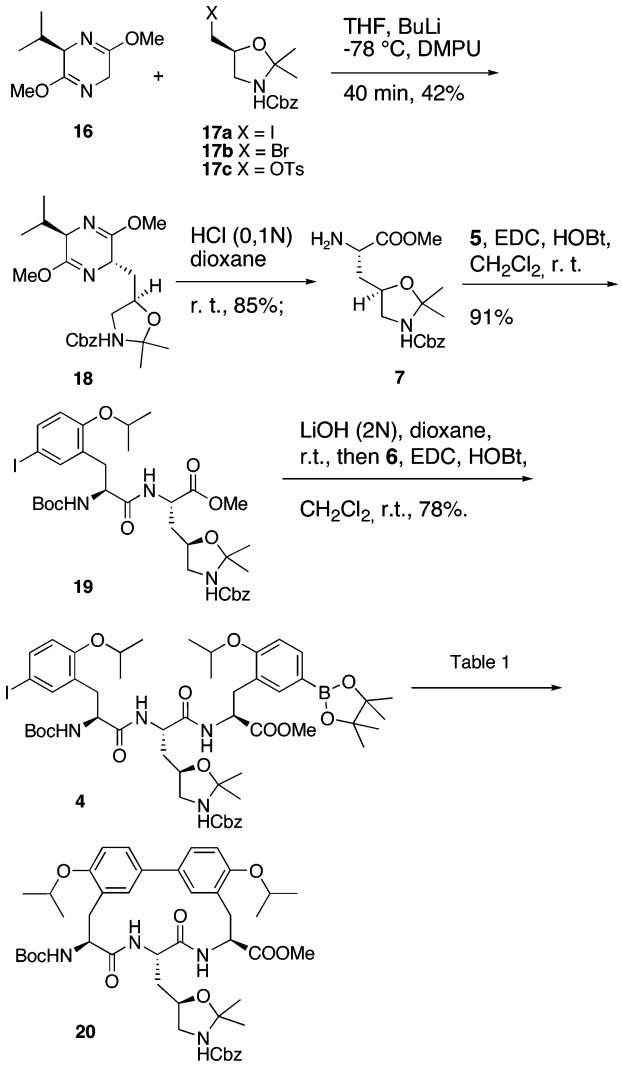
Scheme 3. Asymmetric Synthesis of (2*S*,4*R*)-4-Hydroxyornithine (**7**) and Construction of Tripeptide **4**



one from this laboratory.[16] In the course of this study, an alternative and highly diastereoselective synthesis was developed on the basis of Schöllkopf's bislactim ether technology (Scheme 3).[17] Initial experiments on the alkylation of metalated bislactim ether **16** with (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine (**17a**) under standard Schöllkopf's conditions failed to provide the homologated product (Table 1, entries 3 vs 4). After survey of different reaction parameters varying the nature of electrophiles (X = Br, I, OTs),[18] nucleophiles (lithium salt, potassium salt, and cuprates),[19,20] the reaction temperature and the additives, the optimized conditions consist of performing the alkylation of lithiated bislactim ether with bromide **17b** in THF at −78 °C in the presence of *N*,*N*-dimethylpropylurea (DMPU).[20] Under these conditions, compound **18** was obtained in 42% yield with an excellent diastereoselectivty (de > 95%). Hydrolysis of **18** under mild acidic conditions (0.1 N HCl, dioxane, room temperature) provided the desired amino ester **7** ready for peptide coupling.

The construction of the linear tripeptide proceeded without event (Scheme 3). Coupling of (*S*)-*N*-Boc-(2-isopropyloxy-5-iodo) phenylalanine (**5**) with (2*S*,4*R*)-4-hydroxyornithine methyl ester (**7**) (EDC, HOBt, CH_2Cl_2) provided dipeptide **19** in 91% yield. Subsequent hydrolysis of the methyl ester (2N LiOH, dioxane-H_2O, $v/v = 1/1$) followed by amidation with amino acid **6** (EDC, HOBt, CH_2Cl_2) afforded the tripeptide **4** in 78% overall yield.

With the properly functionalized tripeptide **4** in hand, we set out to examine the desired macrocyclization by way of an intramolecular Suzuki−Miyaura reaction.[21−23] No cyclization took place when **4** was submitted to the conditions that we developed previously [Pd(dppf)Cl_2, toluene/H_2O = 30/1, 90 °C, 0.001 M] for the synthesis of RP-66453.[5] Since very few examples existed in the literature dealing with this type of cyclization, a detailed survey of reaction conditions varying the solvents (toluene, DMSO, DME, water), the ligands (Figure 2), the bases (K_2CO_3, Cs_2CO_3, K_3PO_4), and the temperatures (90 °C, 110 °C) was carried out. However, even after extensive optimization of reaction parameters, the yield of the desired macrocycle **20** was limited to 20% [Pd(dba)$_2$ (0.06 equiv), ligand **21** (0.06 equiv), or catalyst **24** (0.06 equiv), toluene−water = 30/1, *M* = 0.001 M, 90 °C,

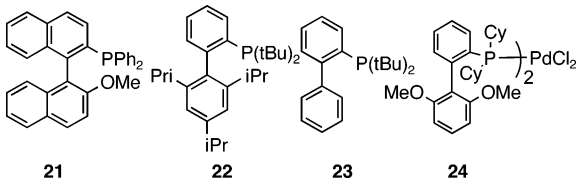


Figure 2. Structure of ligands for Suzuki−Miyaura reaction.

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(22) Aryl−aryl bond formation from bis-arylhalide by a palladium-catalyzed, diboron-mediated cyclization, see: Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477−3480.

(23) Aryl−aryl bond formation via intramolecular Stille reaction, see: Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032−9034.

15 h], which is of course synthetically nonsignificant. The presence of water was found to be essential, which might promote the hydrolysis of arylboronate ester to the arylboronic acid, facilitating the transmetalation and therefore the Suzuki−Miyaura cross-coupling reaction.

The controlled microwave heating technique was next applied to the tripeptide **4** with the hope to increase the cyclization efficiency (Table 1).[24] Since it is well-known that the reaction medium needs to have a high dielectric constant in order to take advantage of the microwave heating effect and that toluene is almost transparent to the microwave irradiation, we focused on the solvent effect in this study by taking advantage of the best ligand−base combination defined under thermal conditions [K_2CO_3 − **21**/$Pd(dba)_2$ or **24**]. As observed, the toluene−H_2O system remained to be the solvent of choice and gave better yield of the cyclization product than MeCN and DMSO under otherwise identical conditions (Table 1, entries 1, 6, 7). On the other hand, increasing the proportion of water increased the product yield (entries 3 vs 4). Under optimized conditions (catalyst **24**, toluene/H_2O = 5/1, 0.1 equiv of tetrabutylammonium bromide), the intramolecular Suzuki−Miyaura reaction of **4** afforded macrocycle **20** in 50% yield. The particularly high efficiency of 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine as the ligand in the Suzuki−Miyaura coupling reaction has been demonstrated recently by Buchwald.[25] It was postulated that **24**, after being in situ reduced to Pd(0)L_2, would first dissociate to Pd(0)L. Being highly reactive, this monoligated complex is capable of catalyzing the difficult coupling reactions by facilitating the oxidative addition as well as the transmetalation steps. It is nevertheless interesting to note that, with microwave irradiation, palladium acetate [$Pd(OAc)_2$] under "ligandless" conditions was able to promote the cyclization affording **20** in 33% yield.

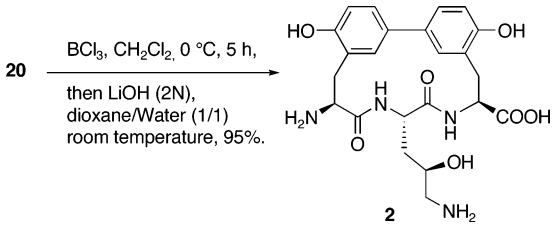
Table 1. Microwave-Assisted Intramolecular Suzuki−Miyaura Reaction of Tripeptide **4**[a]

entry	ligand	solvent	additive	T (°C)	yield (%)[b]
1	**21**	tol−H_2O[c]		90	27
2	**21**	tol−H_2O[c]		110	29
3	**24**	tol−H_2O[c]		110	40
4	**24**	tol−H_2O[d]	TBAB[e]	110	50
5	**24**	tol−H_2O[f]	TBAB[g]	110	50
6	**24**	MeCN		80	32
7	**24**	DMSO		110	0
8	$Pd(OAc)_2$	tol−H_2O		110	33

[a] General reaction conditions: concentration 0.001 M, $Pd(dba)_2$ (0.06 equiv) as palladium source, potassium carbonate as base. Reaction time: 30 min with a Discover microwave reactor from CEM. Irradiation power: 20 W. Ramp time: 2 min. [b] Yield referred to isolated yield; [c] v/v = 30/1. [d] v/v = 5/1. [e] 0.1 equiv. [f] v/v = 1/5. [g] 1 equiv.

Unmasking all the functional groups from **20** is the last step of the planned total synthesis of biphenomycin B (**2**). There are a number of different protective groups in compound **20** that included: *N*-Boc and *N*-Cbz functions, an oxazolidine, two isopropyl ethers, and a methyl ester. Much to our delight, the global deprotection can be realized in one operation. Thus, treatment of a CH_2Cl_2 solution of **20** with BCl_3 (1 M solution in CH_2Cl_2) followed by workup with dry methanol and saponification of the crude product (2N LiOH, dioxane−H_2O, v/v = 1/1) provided the biphenomycin B (**2**) in higher than 95% yield after purification by reverse-phase preparative high-performance liquid chromatography (HPLC) (Scheme 4). The spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS) of the synthetic material were identical to those of the natural product.

Scheme 4. Deprotection of **20** to Biphenomycin B (**2**)



In conclusion, a concise and efficient total synthesis of biphenomycin B (**2**) has been accomplished. Formation of an aryl−aryl bond with the concomitant formation of the 15-membered *meta*,*meta*-cyclophane and minimum protective group manipulation are the characteristic features of the present synthesis. We also documented the first example of microwave-assisted *intramolecular* Suzuki−Miyaura cross-coupling reaction[26] for the formation of the macrocycle. We expect that this reaction would find applications in the synthesis of other natural products and in the diversity-oriented synthesis of biaryl-containing macrocycles.[27]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **5**, **6**, **7**, **19**, **4**, **20**, **2**. Synthesis and physical data of **20**, **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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