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Synthesis of the (*S*,*S*,*S*)-diastereomer of the 15-membered biaryl ring system of RP 66453

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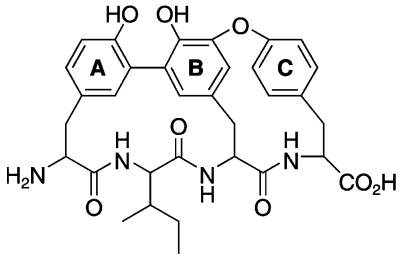
Abstract—The synthesis of the 15-membered biaryl ring system constituting an appropriately functionalized AB ring system of RP 66453 is detailed.

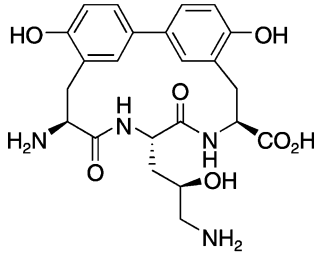
RP 66453 (**1**) is a secondary metabolite isolated from a *Streptomyces* strain while screening for compounds that bind to the neurotensin receptor. Although its connectivity structure was determined through spectroscopic methods, its relative and absolute stereochemistry have not been established. RP 66453 was found to possess a unique and highly strained bicyclic ring system consisting of a 15-membered ring containing an *endo* aryl–aryl bond and a 14-membered ring containing a diaryl ether.[1] The latter constitutes a cycloisodityrosine subunit possessing an amide orientation reversed relative to that found in preceding natural products,[2] and its 14-membered ring size makes it even more challenging to form than the 16-membered diaryl ether ring system of vancomycin[3] and related structures. We recently disclosed the first synthesis of the *S*,*S*-diastereomer of this reversed cycloisodityrosine BC subunit of **1** in efforts directed at its stereochemical assignment and total synthesis.[4]

Herein we report studies exploring the preparation of the 15-membered biaryl AB ring system of **1** conducted some time ago now, culminating in the synthesis of (*S*,*S*,*S*)-**2**. These studies complement an earlier disclosure of Zhu,[5] and define an optimal macrocyclization site and strategy, while exploring the atropisomer issues associated with this unique ring system.

The structure of the 15-membered ring of RP 66453 is similar to the ring system found in the biphenomycins, a series of antibiotics also isolated from *Streptomyces*. The α-carbons of the three biphenomycin amino acids were found to possess the *S* configuration through spectroscopic and synthetic studies.[6] Consequently, in the absence of a stereochemical assignment for **1** and with this related precedent, we pursued the preparation of (*S*,*S*,*S*)-**2**.



RP 66453 (**1**)



Biphenomycin B

It was envisioned that the 15-membered ring of **2** could be constructed through a sequence of Suzuki coupling of two appropriately functionalized tyrosines to form the biaryl linkage, followed by introduction of isoleucine and macrolactamization at one of the two amide bonds.

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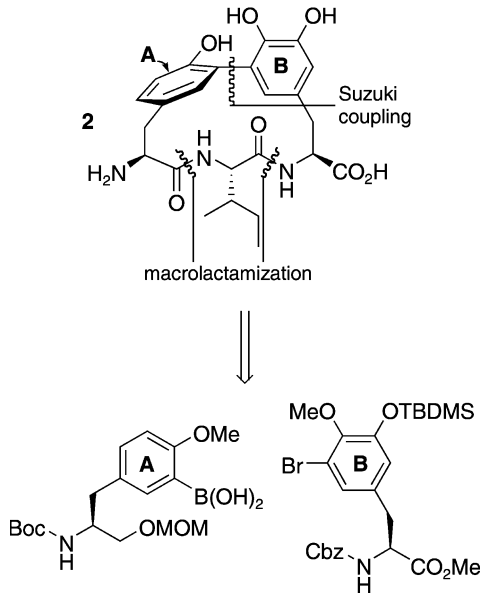
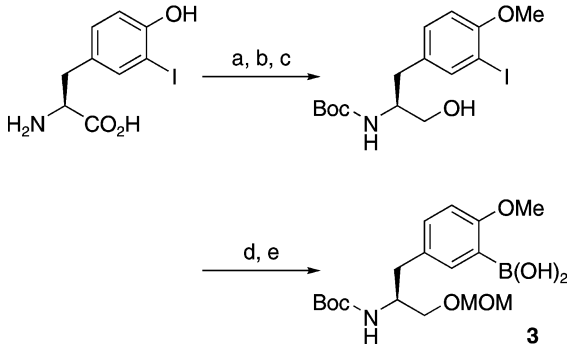
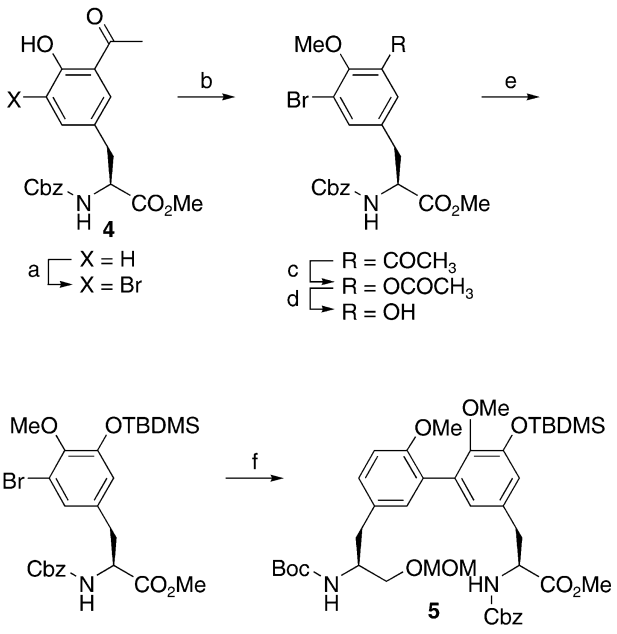


Construction of substituted tyrosine A began with 3-iodo-L-tyrosine (Scheme 1). The amine and phenol groups were first protected as the *t*-butyl carbamate and methyl ether, respectively. Conversion of the iodide to the boronic acid was unsuccessful when attempted with the unprotected carboxylic acid, so the acid was reduced and masked as the methoxymethyl ether. Deprotonation of the carbamate with isopropyl magnesium bromide, lithium–halogen exchange, and treatment of the resulting aryllithium with trimethyl borate afforded **3**, the boronic acid component for the Suzuki coupling.

Construction of tyrosine B started with bromination of **4**[7] with *N*-bromosuccinimide and protection of the phenol as the methyl ether (Scheme 2). Baeyer–Villiger oxidation with trifluoroperacetic acid, cleavage of the acetate, and protection of the resulting phenol as the TBDMS ether gave the second functionalized tyrosine. Suzuki coupling of the two tyrosine subunits was catalyzed by $Pd_2(dba)_3$ to give biaryl compound **5**[8] in



Scheme 1. *Reagents and conditions*: (a) Boc_2O, $NaHCO_3$, dioxane/H_2O, 25°C, 18 h, 99%; (b) NaH, MeI, 5% DMF–THF, 25°C, 3 days, 78%; (c) EtOCOCl, $NaBH_4$, THF/MeOH, 0°C, 20 min, 82%; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25°C, 8 h, 92%; (e) *i*-PrMgCl, *t*-BuLi, $(MeO)_3B$, THF, −78 to 25°C, 1 h, 99%.

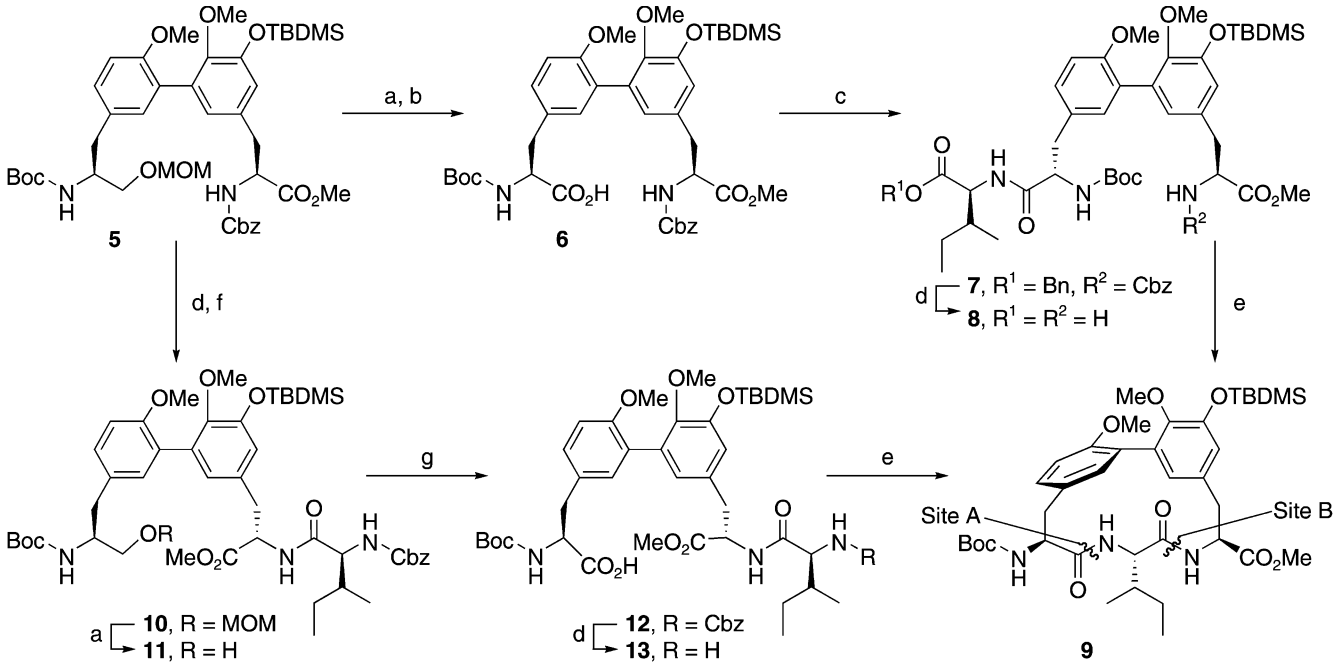


Scheme 2. *Reagents and conditions*: (a) NBS, CH_3CN, 25°C, 18 h, 99%; (b) K_2CO_3, MeI, DMF, 25°C, 5 h, 94%; (c) CF_3CO_3H, CH_2Cl_2, reflux, 2 days, 61%; (d) HCl, dioxane, 25°C, 2 h, 97%; (e) TBDMSOTf, lutidine, THF, 25°C, 4 h, 81%; (f) **3**, (*o*-tolyl)$_3$P, $Pd_2(dba)_3$, 1 M Na_2CO_3, toluene/MeOH, 85°C, 15 min, 95%.

superb yield, following a protocol we first used for formation of the vancomycin biaryl ring system.[9] Notably, this protocol provides excellent conversions even with highly hindered, electron-rich partners that fail to couple with alternative phosphine ligands, less active Pd catalysts, and at higher temperature or in alternative solvent systems.

Treatment of **5** with HCl cleaved both the MOM ether and the Boc groups, and the Boc group was reintroduced using di-*t*-butyl dicarbonate (Scheme 3). The unmasked alcohol was oxidized to the carboxylic acid with catalytic chromium trioxide in the presence of periodic acid,[10] and the carboxylic acid was coupled with isoleucine benzyl ester giving tripeptide **7**. Hydrogenolysis of the Cbz and benzyl protecting groups provided **8**, the first macrolactamization precursor. Without a serious effort at optimization, several peptide coupling agents were examined under high dilution reaction conditions (1 mM), with EDCI in the presence of HOAt and $NaHCO_3$ providing the best yield of **9**[11] (Table 1).

Alternatively, the Cbz group of **5** was removed by hydrogenolysis, and the resulting amine was coupled to Cbz-protected isoleucine. Treatment with HCl cleaved both the MOM ether and the Boc groups, necessitating replacement of the Boc group using di-*t*-butyl dicarbonate. Jones oxidation of the alcohol and deprotection of the isoleucine amine provided the alternative macrolactamization precursor **13**. Table 1 summarizes the results of cyclization of this second substrate (site A) with a range of peptide coupling reagents under condi-



Scheme 3. *Reagents and conditions*: (a) 3 M HCl/EtOAc, –10°C, 30 min, then Boc_2O, $NaHCO_3$, THF/H_2O, 69%; (b) cat. CrO_3, H_5IO_6, CH_3CN/H_2O, 0°C, 1 h, 61%; (c) Ile-OBn tosylate, EDCI, HOAt, $NaHCO_3$, DMF, 25°C, 90%; (d) 1 atm H_2, Pd/C, MeOH, 25°C, 15 h, 99%; (e) coupling reagent (see table), DMF, 1 mM; (f) Cbz-Ile, EDCI, HOAt, DMF, 93%; (g) Jones reagent, acetone, 10 mM, 0°C, 1 h, 55%.

tions analogous to those employed for **8**. Although most reagents examined for this closure were not as effective as the B site closure, FDPP was effective and significantly better than the comparable closure at the B site. Typically, this closure might have been expected to be the preferred site of macrolactamization by virtue of use of a less racemization prone activated carboxylate bearing an α-*N*-carbamate versus α-*N*-acyl group.

The proton NMR spectrum of the macrocycle **9** contains two complete sets of peaks for a pair of isomers that interconvert slowly relative to the NMR time scale. Consistent with the chromatographic detection of a single species for **9** (TLC, HPLC), the isomers were demonstrated to be interconverting, rather than stable or separable conformational isomers or atropisomers, by the presence of chemical exchange peaks in the ^1H–^1H ROESY NMR spectrum. Chemical exchange peaks have a sign opposite of NOE crosspeaks in the ROESY spectrum and clearly indicate one proton appearing at two different chemical shifts, diagnostic of slowly interconverting conformational isomers.[12]

While methoxy groups *ortho* to a biphenyl link do not usually hinder rotation about the biphenyl axis, the TBDMS group in **9** can create a buttressing effect, increasing the energy barrier to free rotation. Global deprotection of **9** with $AlBr_3$ in EtSH[13] provided **2**[14] in which the two aryl methyl ethers, the methyl ester, as well as the *N*-Boc and TBDMS protecting groups were effectively cleaved. Unlike the proton NMR spectrum of **9**, the NMR spectrum of **2** exhibits a single set of proton signals.

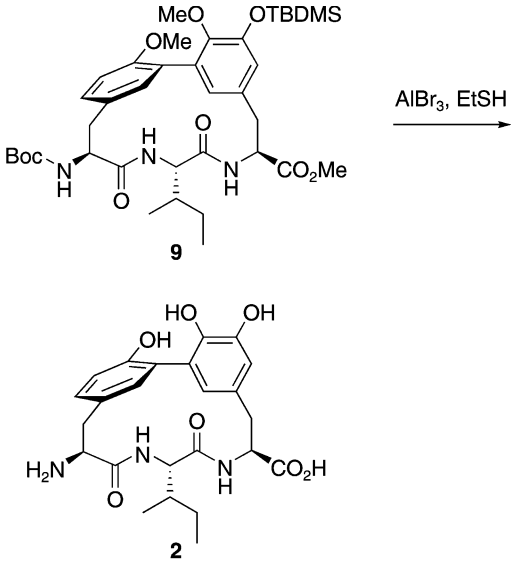


Table 1. Reaction conditions for macrolactamization

Coupling reagent	% yield of **9**	
	Site A	Site B
EDCI, HOAt, $NaHCO_3$	26	53
HATU	29	30
DEPBT	0	14
PyBOP, $NaHCO_3$	–	19
DPPA	0	–
FDPP	64	18

Conditions: 1 mM in DMF, 5 equiv. coupling reagent, 25°C, 3 days.

Thus, an appropriately functionalized derivative of the (*S*,*S*,*S*)-diastereomer of the 15-membered ring system of RP 66453 has been prepared by an unusually effective Suzuki coupling to form the aryl–aryl bond followed by macrolactamization. In route to the preparation of **2**, an optimal site of macrolactamization was identified, and the conformational and atropisomers issues associated with this unusual ring system were established. Extensions of these studies to **1** itself are in progress and will be disclosed in due course.

Acknowledgements

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8. For **5**: $[\alpha]_D^{25}$ +20 (*c* 8.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32 (s, 5H), 7.16 (d, 1H, $J=7.4$ Hz), 7.03 (s, 1H), 6.86 (d, 1H, $J=8.4$ Hz), 6.61 (d, 1H, $J=1.9$ Hz), 6.57 (s, 1H), 5.31 (bs, 1H), 5.10 (s, 2H), 4.83 (bs, 1H), 4.64–4.58 (m, 3H), 3.91 (bs, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.50 (s, 3H), 3.46 (d, 2H, $J=9.2$ Hz), 3.33 (s, 3H), 3.05–2.98 (m, 2H), 2.85–2.76 (m, 2H), 1.41 (s, 9H), 1.00 (s, 9H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.1, 155.9, 155.6, 155.5, 148.8, 148.6, 136.4, 133.3, 132.4, 130.6, 129.7, 129.6, 128.7, 128.3, 127.6, 125.3, 121.4, 111.2, 97.0, 68.2, 67.1, 60.3, 55.8, 55.6, 54.9, 52.4, 51.8, 37.7, 37.0, 28.5, 25.9, 18.5, −4.4; IR (film) ν_{max} 3341, 2931, 1716, 1506, 1364, 1252, 1174, 1111, 1028, 841, 754 cm^{-1}; MALDIFTMS (DHB) m/z 819.3827 (M^++Na, $C_{42}H_{60}N_2O_{11}Si$ requires 819.3858).
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11. For **9**: $[\alpha]_D^{25}$ −4.8 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.02 (d, 1H, $J=6.5$ Hz), 6.89 (s, 1H), 6.76 (s, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.59 (s, 1H), 4.54 (d, 1H, $J=11.0$ Hz), 4.48 (d, 1H, $J=9.1$ Hz), 3.78 (s, 3H), 3.72 (s, 3H), 3.41 (s, 3H), 2.80 (m, 2H), 2.61 (m, 2H), 1.76 (m, 1H), 1.56 (m, 1H), 1.48 (s, 9H), 1.16 (m, 1H), 1.01 (s, 9H), 0.93 (d, 3H, $J=6.7$ Hz), 0.87 (m, 3H), 0.22 (s, 3H), 0.17 (s, 3H); and 7.17 (d, 1H, $J=6.5$ Hz), 6.87 (s, 1H), 6.76 (s, 1H), 6.67 (s, 1H), 6.28 (s, 1H), 4.89 (m, 1H), 4.41 (d, 1H, $J=9.5$ Hz), 4.06 (d, 1H, $J=12.1$ Hz), 3.75 (s, 3H), 3.69 (s, 3H), 3.51 (s, 3H), 3.32 (m, 1H), 3.23 (m, 1H), 3.05 (m, 1H), 3.01 (s, 1H), 1.71 (m, 1H), 1.46 (m, 1H), 1.45 (s, 9H), 1.12 (m, 1H), 1.01 (s, 9H), 0.95 (d, 3H, $J=6.7$ Hz), 0.86 (m, H), 0.21 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.5, 173.2, 172.1, 157.3, 149.6, 149.4, 149.3, 149.0, 135.6, 135.3, 135.1, 134.1, 133.5, 132.4, 131.2, 130.9, 130.4, 130.2, 129.6, 129.2, 125.8, 123.9, 122.4, 122.1, 112.1, 111.7, 80.8, 80.7, 60.8, 60.6, 59.2, 58.7, 58.6, 56.1, 55.4, 55.3, 53.1. 53.0, 52.2, 39.9, 39.4, 38.4, 38.1, 38.0, 34.8, 30.9, 28.9, 28.7, 26.5, 26.4, 26.3, 25.9, 19.4, 16.0, 15.6, 11.5, 11.3, −4.0, −4.1, −4.4; IR (film) ν_{max} 3293, 2960, 2412, 1747, 1713, 1644, 1427, 1252, 1177, 1029, 844, 756 cm^{-1}; MALDIFTMS (DHB) m/z 750.3727 (M^++Na, $C_{38}H_{57}N_3O_9Si$ requires 750.3756).
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14. For **2**: $[\alpha]_D^{25}$ −12 (*c* 0.63, 20% CH_3CN–H_2O); ^1H NMR (CD_3OD, 500 MHz) δ 7.03 (dd, 1H, $J=1.9$, 8.0 Hz), 6.90 (d, 1H, $J=1.8$ Hz), 6.84 (d, 1H, $J=8.1$ Hz), 6.65 (d, 1H, $J=1.5$ Hz), 6.61 (s, 1H), 4.58 (d, 1H, $J=9.1$ Hz), 4.49 (d, 1H, $J=9.5$ Hz), 4.25 (t, 1H, $J=3.7$ Hz), 3.34 (dd, 1H, $J=2.6$, 15.0 Hz), 2.93 (dd, 1H, $J=4.4$, 15.0 Hz), 2.84 (d, 1H, $J=14.0$ Hz), 2.57 (m, 1H), 1.81 (m, 1H), 1.61 (m, 1H), 1.18 (m, 1H), 0.99 (d, 1H, $J=6.6$ Hz), 0.90 (t, 1H, $J=7.4$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3, 172.9, 169.1, 154.3, 146.7, 141.5, 135.0, 133.5, 131.6, 128.7, 128.0, 126.1, 122.8, 117.6, 116.9, 59.6, 57.2, 55.0, 39.3, 36.7, 30.9, 26.5, 16.2, 11.4; IR (film) ν_{max} 3250 (broad), 1643, 1496, 1391, 1253, 1007, 664 cm^{-1}; MALDIFTMS (DHB) m/z 472.2074 (M^++Na, $C_{24}H_{29}N_3O_7$ requires 472.2078).