EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis of the rubiyunnanin B core aglycone

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201600741

Link to VoR: http://dx.doi.org/10.1002/ejoc.201600741

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Synthesis of the rubiyunnanin B core aglycone

Matthew J. Moschitto,[b] and Chad A. Lewis*[a]

Abstract: Rubiyunnanin B possesses an intriguing anticancer profile whose activity is dependent on the glycosylation of a fused tyrosinyl residue. We have developed a rapid synthesis of the rubiyunnanin B dityrosine core using a Suzuki coupling. Furthermore, the atropisomeric and isomeric products obtained were identified and their distribution controlled. The two major products obtained from the dityrosine coupling were discovered to be locked *cis/trans* isomers of the internal amide with atropisomerization quantifiable on the NMR timescale.

The macrocyclic peptides isolated from the *Rubiaceae* family[1] are intriguing natural products with some members possessing anticancer activity. The rubiyunnanins, a specific class of compounds from this family (Figure 1), are hexapeptidic macrocycles composed of two alanine amino acids (L-Ala, D-Ala), three modified tyrosine residues, two of which form a fused tyrosine dimer, and a third amino acid, which is alanine (rubiyunnanin A and B) or glutamine (rubiyunnanin D). The tyrosine dimer can either be formed from a carbon-oxygen bond (deoxybouvardin and rubiyunnanin C), a carbon-carbon bond (rubiyunnanin B), or a fused dihydrobenzofuran dimer (C-C and C-O bond formations, rubiyunnanin A).[2]

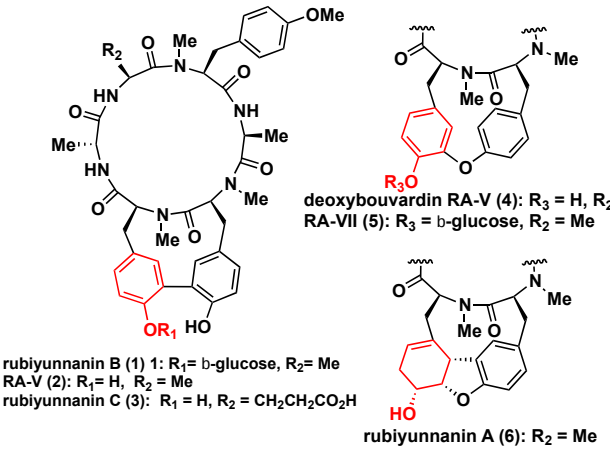


Figure 1. Rubiyunnanin family of macrocyclic peptides.

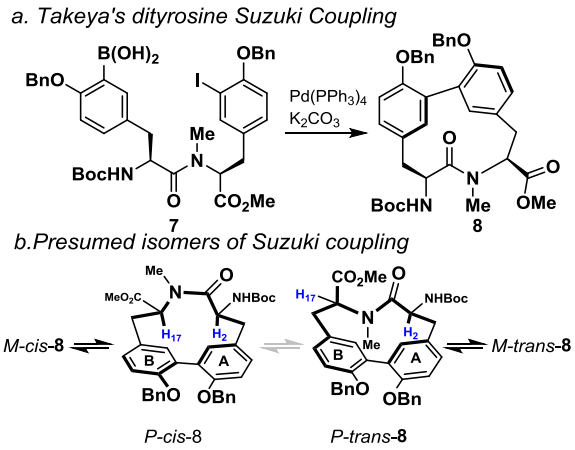
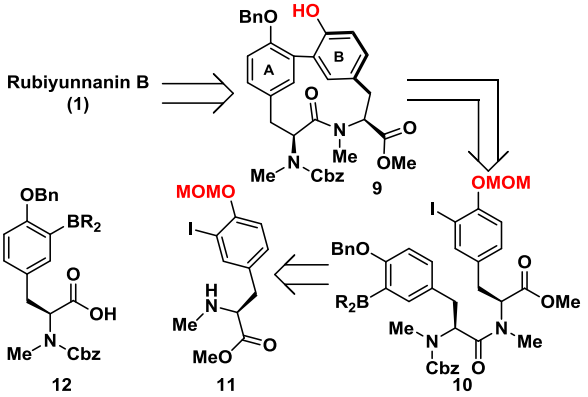


Figure 2. (a) Previous Suzuki coupling by Takeya results in two distinct sets of compounds. (b) Takeya's atropisomeric population.[3]

In a majority of the rubiyunnanins, the tyrosine dimer (dityrosine) forms a 12 membered macrocycle with an internal *cis*-amide. Deoxybouvardin (**4**) exhibits IC_{50} concentrations between 0.001 and 0.014 μg/mL against various cancer cell lines; however, the glycosylated variant, RA-XII, exhibits IC_{50} values substantially higher between 1.8 and 10 μg/mL.[2] Conversely, rubiyunnanin B possesses a glycosylated tyrosine with measured IC_{50} values between 3.6 and 31 μg/mL whereas the aglycone does not possess antitumor activity (IC_{50} > 100 μg/mL).[3,4]

Given the interesting bioactivity of rubiyunnanin B, we were keen to develop a synthesis of the core dityrosine to allow for analogue production. Although no synthesis of rubiyunnanin B has been reported, *neo*-RA-V has been prepared by the group of Takeya.[4] Their critical bond formation steps include a Suzuki dityrosine coupling, amide bond formation, and N-methylation of amides (Figure 2a). Suzuki coupling of the two tyrosine fragments[3] yielded the fused 12 member cycle, **8,** which was isolated as two isomers whose structures could not be differentiated by NMR spectroscopy but were chromatographically separable.



Scheme 1. Retrosynthesis of rubiyunnanin B.

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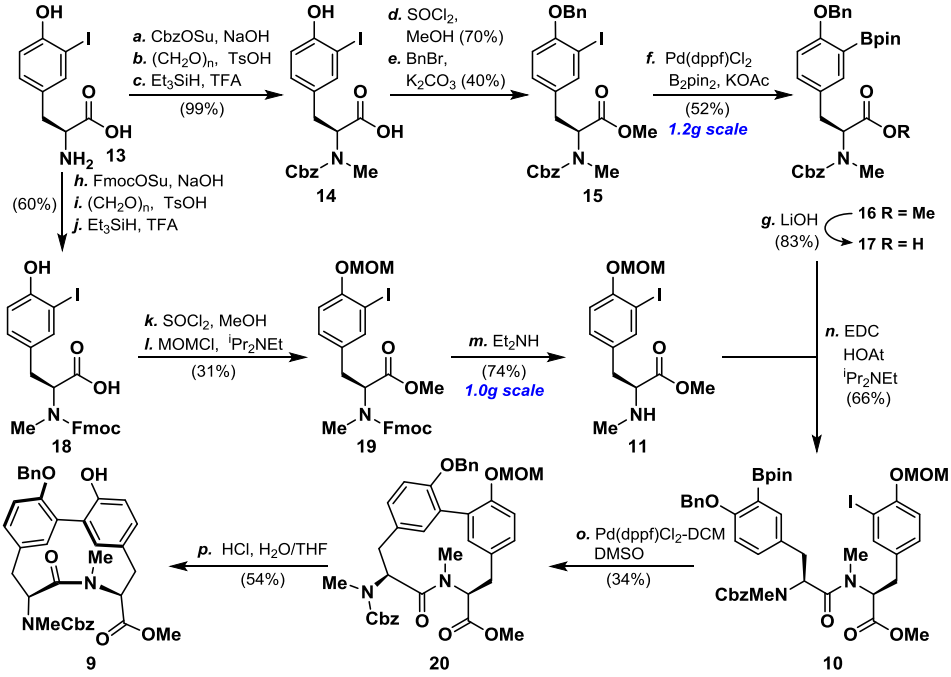


Scheme 2. Synthesis of rubiyunnanin B core aglycone. Reagents and conditions: a) CbzOSu, 1M NaOH/dioxane (1:1), 2 h; b) $(CH_2O)_n$, TsOH (0.1 equiv.), C_6H_6:DMF (25:1), 100 °C, 2h; c) Et_3SiH (3 equiv.), TFA:CH_2Cl_2 (1:1) 0 to 23 °C, 3h, 99% (three steps); d) $SOCl_2$, MeOH, 80 °C, 2h, 70%; e) BnBr, K_2CO_3, DMF, 50 °C, 12h, 40%; f) Pd(dppf)Cl_2.CH_2Cl_2 (5 mol%), B_2pin_2 (1.3 equiv.), K_2CO_3, DMSO, 80 °C, 52%; g) LiOH (2 equiv.), THF:H_2O,MeOH (3:1:1), 0 °C, 2h; h) FmocOSu, 1M NaOH/dioxane (1:1), 2 h; i) $(CH_2O)_n$, TsOH (0.1 equiv.), C_6H_6:DMF (25:1), 100 °C, 2h; j) Et_3SiH (3 equiv.), TFA:CH_2Cl_2 (1:1) 0 °C to 23 °C, 3h, 60% (three steps); k) $SOCl_2$, MeOH, 80 °C, 2h; l) MOMCl, iPr_2NEt, 31% (two steps); m) Et_2NH (20 equiv.), CH_2Cl_2, 74%; n) EDC-HCl (1.3 equiv), HOAt (1.5 equiv), **11** (1.3 equiv.), iPr_2NEt (2.1 equiv.), 0 °C to 23 °C, 48h, 66%; o) Pd(dppf)Cl_2·CH_2Cl_2 (0.15eq), K_2CO_3 (2 equiv.), DMSO, 80 °C, 4 h, 34% yield, 46:41:14 ratio (P-*cis*-**9a**:M-*trans*-**9b**:P-*trans*-**9a,** see Table 2; p) 4M HCl:THF (1:2), 50 °C, 2h, 54%. Abbreviations:; DMSO: dimethylsulfoxide; TFA: trifluoroacetic acid; DMF: N,N-dimethylformamide; THF: tetrahydrofuran; dppf: diphenylphosphinoethane; MOM: monomethyoxy methyl; EDC-HCl: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; HOAt: 1-Hydroxy-7-azabenzotriazole.

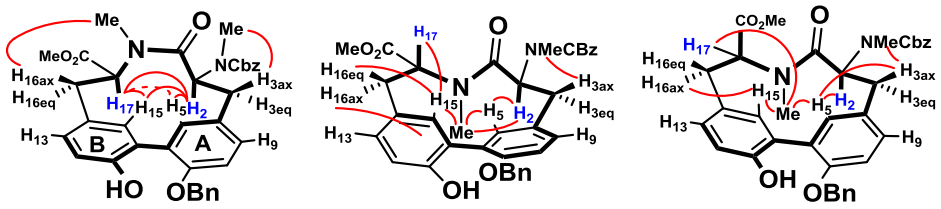
Compound P-*cis*-**9** was isolated in 50% yield while the second isomer was isolated in 15% yield. The minor structure could be converted to the major isomer by heating in toluene at 80 °C. The authors suspected the minor compound to be M-*cis*-**7**. Each compound, however, readily interconverted on the NMR timescale with a second set of compounds, which were believed to be atropisomers (M-*cis*-**8** and M-*trans*-**8,** Figure 2b).[5]

We sought to optimize the established synthesis and elucidate the three dimensional structure of the two compounds obtained from the Suzuki coupling (Scheme 1). Rubiyunnanin B will be obtained via macrocyclization and hydrogenolysis of the benzyl carbamate and benzyl ether. Similar to previous work, we will form the dityrosine dimer using a Suzuki coupling of aryl iodide **12** and aryl bis(pinicolato)boronic ester **11**. To avoid late stage N-methylation, both amino acids will be methylated prior to coupling. The A-ring Bpin-tyrosine will be installed through a Miyaura coupling from 3-iodotyrosine derivative. The B-ring tyrosine will be protected with a methoxy methyl ether (MOM) group derived from 3-iodotyrosine.

The synthesis of the A-ring tyrosine began with benzyl chloroformate protection of 3-iodotyrosoine (Scheme 2). A two step N-methylation procedure yielded known Cbz-N-Me-3I-tyrosine-OH (**14**). Esterification and benzyl protection afforded **15** which was converted to Bpin compound **16** in 52% yield using the Miyaura borylation protocol.[4] Construction of the B ring of rubiyunnanin B began from Fmoc-N-Me-3I-tyrosine-OH (**18**, prepared in the same manner), which was esterified and protected as the monomethoxy ether (31% yield). Deprotection of **19** proceeded cleanly with diethylamine in 77% yield. Coupling of acid **17** and amine **11** was accomplished with EDC and HOAt to yield **10** in 66% yield. Dipeptide **10** proved unstable to silica gel chromatography and was sufficiently pure to be used directly.

Initial attempts at the Suzuki coupling of **10** employing conditions used in the synthesis of arylomycin (Pd(dppf)Cl_2·CH_2Cl_2, K_2CO_3, DMSO, 80 °C) yielded **20** in modest recovery (34%).[6a] Purification by silica gel chromatography yielded two entities, whose mass spectra matched compound **20** (see Figure S1 in Supporting Information). ^{1}H NMR at 23 °C indicated multiple compounds with broadening of all peaks similar to what Takeya reported in the synthesis of *neo*-RA-V.[4] ^{1}H NMR at -40 °C revealed a defined set of two signals.

The comixture was then deprotected with 4M HCl at 50 °C for 2 hours in 54% yield. The resulting material was purified to yield three distinct species by LC/MS, whose mass spectra matched that of **9**. Analysis of ^{1}H NMR showed two major sets of compounds (*P-cis*-**9a** and *M-trans*-**9b**, *vide infra*), each of which exchanged with a second rotameric compound. In addition to the two major sets, a minor contributor (*P-trans*-**9a**) was observed and chromatographically separable. ROESY data indicated that *P-cis*-**9a** possessed a nOe correlation between α-protons (Figure 3, H_2 and H_{17}). Additional nOe correlations were observed between an axial β-proton (H_{2ax}) and the Cbz N-methyl as well as between an axial β proton (H_{16ax}) and the internal N-methyl. This supports an internal *cis*-amide as expected within the rubiyunnanin family. Furthermore, ring A is twisted above the biaryl plane with the B ring below. α-Proton H_2 has strong nOe correlations with both internal aryl protons (H_5 and H_{15}) whereas α-proton H_{17} shows a strong correlation to the ring B aryl proton (H_{15}) with a weak interaction to the A ring aryl proton (H_5). Strong four bond COSY correlations between β protons H_{2eq}, H_{16eq}, and H_{16ax} and aryl protons (and weak COSY



P-cis-**9a** *M-trans*-**9b** *P-trans*-**9a**

Figure 3: 3-D representations of compound **9**. nOe correlations are indicated with solid red line, weak nOe correlations are indicated with a dashed red line. The α protons, H_2 and H_{17}, are highlighted in blue.

Table 1: Important ^{1}H NMR data for comparison of isomers of **9**.

compound	δ (ppm)						$J_{3ax,2}$ (Hz)	$J_{16ax,17}$ (Hz)	Strong cosy correlation[a]	Weak cosy correlation[b]
	H_2	H_{17}	H_{3ax}	H_{3eq}	H_{16ax}	H_{16eq}				
P-*cis*-**9a**	5.52	5.60	4.12	2.45	3.06	3.61	9.0	15.0	H_5-H_{3eq} H_{13}-H_{16eq} H_{13}-H_{16ax}	H_5-H_{3ax}
M-*trans*-**9b**	5.65	5.81	3.56	2.80	3.08	3.51	9.0	12.0	H_5-H_{3eq} H_{13}-H_{16eq}	H_{13}-H_{16ax} H_5-H_{3ax}
P-*trans*-**9a**	5.56	3.91	3.51	2.73	3.41	3.13	11.4	5.9	H_5-H_{3ax}	H_{15}-H_{16ax}

[a] Four bond correlations are indicated, strong COSY correlation indicates a high intensity cross peak between corresponding protons; [b] four bond correlations indicated, weak cosy correlation indicates a weak cross peak between corresponding protons; any couplings not indicated signify that no cross peak was seen; see Supporting Information for additional detail.

interactions with H_{2eq} and aryl protons) confirm the orientation of the rings as per the Karplus equation for benzylic four bond coupling (see Table 1).[7] We therefore believe that *P-cis*-**9a** is oriented in a manner shown in Figure 3.

P-cis-**9a** exchanges with a second compound, *P-cis*-**9a-rot** (not shown), as evidenced by exchange peaks present in ROESY data. This compound contains similar correlations, between each α-proton and the α-proton to the aryl ring, as well as an identical pattern in four bond COSY couplings. This second compound therefore cannot be an atropisomer or *trans*-amide isomer. It is possible that this second compound (P-*cis*-**9a-rot**) is a rotamer at the Cbz N-methyl, although no correlations could confirm this hypothesis.

The second isomeric compound isolated was determined to be a H_{17} epimer. This compound (*M-trans*-**9b**) contains a *trans*-amide. Strong nOe correlations are observed between the internal N-methyl and protons H_2, H_5, H_{15}, and H_{16ax}. The epimerized α-proton H_{17} correlates only with H_{15}. Large coupling constants ($J_{16ax\text{-}17}$ = 12.0 Hz) also support this conformation. These data are also supported by four bond COSY correlations, which indicate that only one proton (H_{2ax}) is perpendicular to the aryl ring. It is likely that ring B in this compound resides above the biaryl plane whereas ring A is canted below. We therefore believe this compound, *M-trans*-**9b** is oriented as shown in Figure 3.

^{1}H NMR indicated a third compound was also formed. This isomer was separable from *P-cis*-**9a** and *M-trans*-**9b** by preparatory TLC, and its structure assigned *P-trans*-**9a**. The isomer was present in small quantities when Pd(dppf)Cl_2·CH_2Cl_2 (15 mol%) was used at a ratio of 42:44:4 (*P-cis*-**9a**: *M-trans*-**9b**: *P-trans*-**9a**) but increased to 23:34:44 when catalyst loading of Pd(dppf)Cl_2·CH_2Cl_2 was increased (*vide infra*, see Supporting Information). A nOe was not observed between α-protons H_2 and H_{17} indicating a *trans* isomer. H_5 showed correlations to an axial β-proton (H_{3ax}), α-proton H_2 and the internal N-methyl. This suggested that the A ring is canted above the biaryl plane. The B ring aryl proton H_{15} has correlations with axial β-proton H_{16ax} and with the internal N-methyl. It does not show a correlation with H_{17} indicating that the B ring is canted below the biaryl plane. H_{17} retains the same stereochemistry as *P-cis*-**9a**, which is supported by the smaller coupling constant between H_{16ax} and H_{17} ($J_{16ax,17}$ = 5.9 Hz). The position of the rings is also supported by long range four bond COSY couplings.

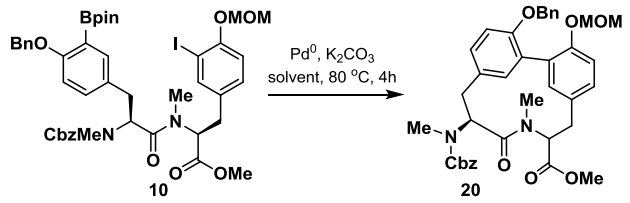
Broad ^{1}H NMR signals in **20** could be a result of isomerization between eight distinct compounds and their Cbz N-methyl rotamers. **20a** could consist of both atropisomers and *cis/trans* isomers resulting in four different compounds *P-cis*-**20a,** *M-cis*-**20a**, *P-trans*-**20a**, and *M-trans*-**20a** (see Figure S2 for detailed depictions)**.** If epimerization has occurred, it is also possible that four more compounds may be observed: *P-cis*-**20b,** *M-cis*-**20b**, *P-trans*-**20b**, and *M-trans*-**20b.** Exchange between each set, due to either atropisomerism or *cis/trans* amide exchange, would lead to broadening. Deprotection of the material, however, results in only two **9a** compounds: *P-cis*-**9a** and *M-trans*-**9b.** Decreasing the steric bulk of the *ortho* position of an atropisomeric compound should encourage more rotational freedom that would bolster broadening of ^{1}H NMR signals; this, however, was not observed.[7] The lack of broadening could be explained by a critical hydrogen bond between the newly deprotected phenol and the benzyl ether, thus stabilizing the atropisomer isolated.[9] Rubiyunnanin B would be able to adopt this same critical hydrogen bond, thus stabilizing the ring.

In order to efficiently produce the rubiyunnanin architecture, the reduction or elimination of the unwanted stereoisomers is essential. Increasing the loading of Pd(dppf)$_2$·CH_2Cl_2 decreased epimerization but also reduced yield; reaction time was unaltered. Changing catalyst and solvent to Pd(PPh_3)$_4$ in THF:water reduced epimerization but also resulted in low yield (Table 2, entry 3). A more electron rich phosphine, Pd(P^tBu_3)$_2$, resulted in almost a 90:10:0 ratio of epimers favoring *P-cis*-**9a**, however, in a combined yield of only 13% (Table 2, entry 4).

Mild Suzuki conditions pioneered by the Buchwald group, involving the use of Xphos Pd G2, resulted in >99:1 ratio of epimers and completion of the reaction in 30 minutes at 40 °C.[10] Optimization of the reaction conditions by eliminating silica gel chromatography of **20** and directly exposing the crude reaction mixture to 4M HCl at 50 °C for 30 minutes resulted in an

increase of *P-cis*-**9a** to 56% yield over two steps (Figure 4). The facile

Table 2: Suzuki coupling of **10**



entry	catalyst (eq)	solvent	**20** Yield[a]	Ratio **9**[b]
1	Pd(dppf)Cl_2-DCM (0.15)	DMSO	34%	46:41:13
2	Pd(dppf)Cl_2-DCM (0.30)	DMSO	18%	46:22:35
3	$Pd(PPh_3)_4$(0.30)	THF:H_2O (6:1)	15%	73:24:4
4	$Pd(P^tBu_3)_2$ (0.15)	DMSO	13%	90:10:0

[a] Isolated yields of **20** after flash chromatography; [b] ratio: (P-*cis*-**9a**:M-*trans*-**9b**:P-*trans*-**9a**) determined by LC/MS analysis of **9** and **20** and ^{1}H NMR analysis of **9** after deprotection using 4M HCl in THF).

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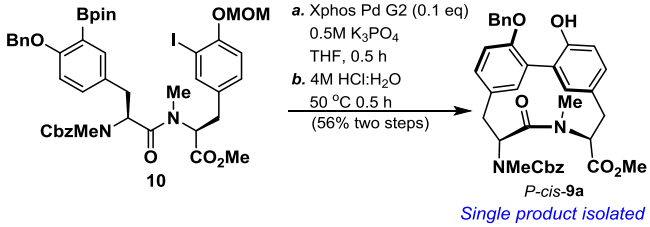

Figure 4. Final optimization for the synthesis of the rubiyunnanin B aglycone.

coupling conditions streamline the preparation of the rubiyunnanins and allow for further exploration of their syntheses.

Further work is needed to install the glycoside and complete the macrocyclic ring. Both steps have precedent given work done by Romesberg[6a] and Takeya.[4] We have presented a synthesis of the dityrosinyl core of rubiyunnanin B that takes advantage of a palladium catalyzed Suzuki coupling to forge the biaryl bond. This coupling resulted in multiple isomers which were characterized by in-depth NMR spectroscopy as product **9a** with internal *cis* and *trans*-amides, and epimerized product, **9b** with an internal *trans*-amide. Optimization of the coupling resulted in the major product (P-*cis*-**9a**) being the sole isolable product. Two step coupling and deprotection yielded the aglycone of the dityrosine peptide of rubiyunnanin B. The streamlined approach to the core of the rubiyunnanins and NMR studies allows access to these rare and understudied compounds.

Experimental Section

Dipeptide 10: CbzMeN-3Bpin-tyrosine(OBn)-OMe (220.0 mg, 0.40 mmol) was dissolved in THF:MeOH:H_2O (3.20 mL, 3:1:1 ratio) and cooled to 0 °C. LiOH·H_2O (37.30 mg, 0.79 mmol, 2.0 eq.) was added and the reaction is stirred at 0 °C for 2 hours. Upon completion, the solution was carefully acidified to pH 2 by the addition of 1 M HCl (10 mL) and extracted with EtOAc (2 x 10 mL). After drying over Na_2SO_4, the solution was concentrated to yield CbzMeN-3Bpin-tyrosine(OBn)-OH (180.0 mg, 0.33 mmol, 83 % yield) which was used in the next reaction without purification.

CbzMeN-3Bpin-tyrosine(OBn)-OH (220 mg, 0.40 mmol) was dissolved in THF (2.00 mL), and EDC-HCl (100.50 mg, 0.52 mmol, 1.3 eq.) and HOAt (82.30 mg, 0.61 mmol, 1.5 eq) were added at 0 °C. The reaction was stirred for 5 minutes before HNMe-3I-tyrosine(OMOM)-OMe (200.00 mg, 0.524 mmol, 1.3 eq) in 0.50 mL of THF and DIPEA (0.14 mL, 0.85 mmol, 2.1 eq.) was added. The reaction was allowed to warm to room temperature and stirred under argon for 48 hours. Upon completion, the reaction was diluted with EtOAc (10 mL), washed with 1M HCl (2 x 10 mL) and saturated sodium bicarbonate solution (10 mL). The solution was dried over Na_2SO_4 and concentrated *in vacuo* to yield 230 mg (0.254 mmol, 63 % yield) of **10** as an unstable white solid, yet sufficiently pure to be used in the next step.

Dityrosine *P-cis*-**9a**: **10** (20 mg, 0.03 mmol) was dissolved in 0.2 mL THF and 0.2 mL of 0.5M K_3PO_4 solution. The reaction was degassed by sparging with argon over sonication for 15 minutes. Xphos Pd G2 was added and the reaction heat at 40 °C for 30 minutes. The reaction was cooled and diluted with 1.0 mL 1M HCl. The aqueous layer was extracted with EtOAc (2 x 3.00 mL), and the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The material could be purified at this point by flash chromatography (3:1 hexanes/EtOAc, v/v) but was used in the next step without purification. **HRMS** ($DART^+$) calc'd for $C_{38}H_{41}N_2O_8$ 653.2863, found 653.2858. **TLC** R_f**=** 0.67 (1:1 hexanes/EtOAc, v/v). Crude **20** was dissolved in THF (0.2 mL) and 4M HCl (0.1 mL) was added. The reaction was heated at 50 °C for 30 minutes and then cooled. Concentration and purification by flash chromatography (3:1 hexanes/EtOAc, v/v) yielded **9** (8.50 mg, 0.014 mmol, 56% yield) as a single diastereomer.

P-cis-**9a: [α]^D** = -21.9 (*c* 0.85, $CDCl_3$) **^{1}H NMR**: (600 MHz, $CDCl_3$) δ 7.35 – 7.40 (m, 10H), 7.06 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 5.60 (dd, *J* = 11.6, 4.4 Hz, 1H), 5.52 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.24 (d, *J* = 11.6 Hz, 1H), 5.16 (d, *J* = 11.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.12 (m, 1H), 3.61 (dd, *J* = 16.3, 4.5 Hz, 3H), 3.60 (s, 3H), 3.06 (dd, *J* = 16.8, 11.6 Hz, 1H), 2.98 (s, 3H), 2.70 (s, 3H), 2.45 (dd, *J* = 14.8, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers) δ 172.1, 171.3, 156.2, 153.6, 152.3, 140.7, 139.9, 136.4, 136.1, 131.3, 129.5, 129.0, 128.6, 128.4, 128.3, 127.5-128.5, 127.5-128.5, 127.5-128.5, 127.7, 127.6, 126.0, 115.6, 111.0, 71.0, 71.0, 67.9, 67.9, 60.6, 56.7, 52.5, 34.7, 34.7, 32.7, 32.7, 29.8, 29.7. **IR** (cm^{-1}) 3339, 2926, 2850, 1741, 1694, 1650, 1217, 735. **HRMS** ($DART^+$) calc'd for $C_{36}H_{37}N_2O_7$ 609.2601, found 609.2593. **TLC** R_f **=** 0.56 (1:1 hexanes/EtOAc, v/v)

M-trans-**9b: ^{1}H NMR** (600 MHz, CDC_3) δ 7.41–7.30 (m, 10H), 7.11 (m, 1H), 7.05 (dd, *J* = 9.23, 1.78 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.62 (bs, 2H), 5.81 (dd, *J* = 10.8, 4.0 Hz, 1H), 5.65 (dd, *J* = 12.2, 3.6 Hz, 1H), 5.23 (d, *J* = 11.8 Hz, 1H), 5.20 (m, 1H), 5.17 (m, 1H), 5.16 (m, 1H), 3.76 (*s*, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.08 (m, 1H), 3.01 (s, 3H), 2.96 (s, 3H), 2.82 (m, 1H); **^{13}C NMR** δ 171.6, 171.5, 156.0, 152.8, 152.6, 138.2, 136.8, 136.4, 135.8, 130.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.5, 128.5, 128.1, 127.6, 126.7, 126.7, 115.6, 112.0, 71.4, 71.4, 68.0, 68.0, 55.7, 55.2, 52.6, 32.5, 32.5, 30.9, 30.9, 30.3, 29.8

Acknowledgements

The authors would like to acknowledge Ivan Keresztes for assistance with NMR spectroscopy and structural determination, David Kiemle for NMR spectroscopy and Professors Brett Fors and Bruce Ganem for insightful discussions. This project was supported by Cornell University.

Keywords: Macrocyclic Peptide • Synthesis • Suzuki couplings• Atropisomerism

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Layout 2:

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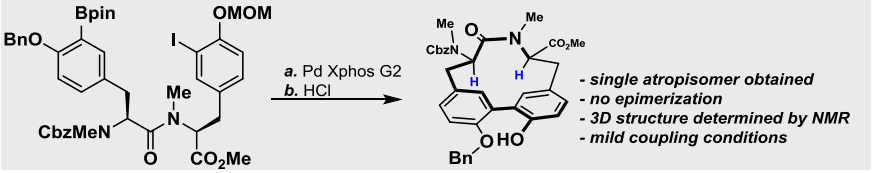

Rubiyunnanin B, a macrocyclic peptide possesses an intriguing anticancer profile. Currently, no synthesis of the dityrosinyl core exists. We have developed a rapid synthesis of the core of rubiyunnanin B and have characterized and controlled the distribution of the products formed from a biaryl Suzuki coupling.

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Synthesis and structural determination of the rubiyunnanin B core aglycone