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A Stille biaryl-coupling approach to dityrosines. Formal total synthesis of Hazimycin

Said Achab* and Laurence Velay

Institut de Chimie des Substances Naturelles, CNRS, 91 198 Gif-sur-Yvette, France

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Abstract—The Stille cross-coupling reaction between 3-tributylstannyltyrosine derivatives (**15**–**23**, **40**), and 3-iodotyrosines (**6**–**14**, **39**) afforded the corresponding dityrosines (**24**–**37**, **41**). Additionally, this method provided a short and improved access to Hazimycin (**3**) a naturally occurring anti-fungal agent.

Recently, the aryl–aryl coupling reaction has registered a number of valuable achievements in the area of dityrosine **1** and isodityrosine **2** natural products syntheses[1a] (Fig. 1). Structurally, compounds **1** and **2** (Fig. 1) belong to the family of tyrosine dimers. They have inspired significant interest[1] due to the diverse and potent biological activities they display.

Two groups of tyrosine dimers are generally encountered, the first comprises tyrosine units linked by a 3,3′-biaryl bond whereas the second, called isodityrosine, is characterized by a biaryl ether linkage (C3–O–C4′). With dityrosine **1** and isodityrosine **2** as the simplest members, each family includes a number of biologically interesting natural products. The acyclic antibiotic

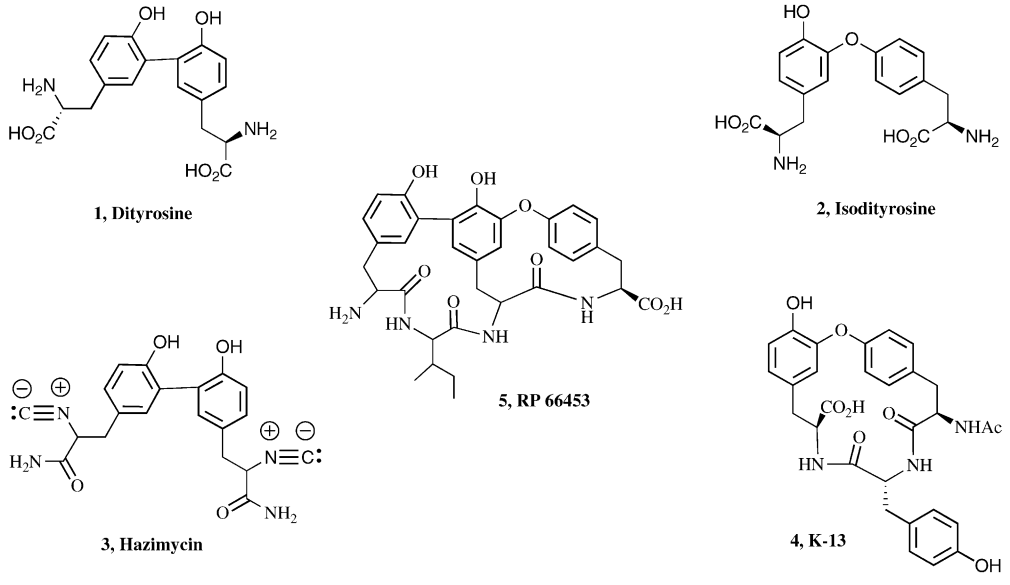

Figure 1.

Keywords: Dityrosines; Stille cross-coupling; Hazimycin; Stannyl tyrosines.
* Corresponding author. Tel.: +33 0169823092; fax: +33 0169823072; e-mail: achab@icsn.cnrs-gif.fr

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Hazimycin **3**,[2] and the macrocyclic ACE-inhibitor K-13 **4**,[3] that are typical to each group, bear respectively, a dityrosine or an isodityrosine unit. On the contrary, both units combine within the structure of the naturally occurring bicyclic secondary metabolite RP 66453 **5**.

Compared to dityrosines, the synthesis of isodityrosines has focused more attention as evidenced by the number of publications devoted to their preparations.[5] Consequently, only few protocols are available for the formation of dityrosines through construction of the C3–C3′ aryl–aryl bond. In this regard, the Suzuki-based aryl–aryl cross-coupling methodology[6] stands, to date, as the premier method to achieve this goal. Thus, formation of 3-boryltyrosine derivatives[7] followed by palladium-catalyzed cross coupling with a 3-halogenotyrosine has been successfully applied for accessing both acyclic dityrosine derivatives[8] and dityrosine-based macrocyclic peptides.[4d,e] In these transformations, yields range usually from moderate to good.

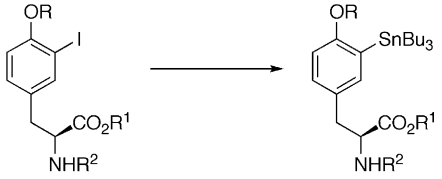
Although, natural or unnatural biaryls[9] are commonly made through the use of the Stille reaction,[10] there was no example upon the application of such a methodology to the synthesis of dityrosines. All these reasons led us to consider using the Stille reaction in our projected dityrosines synthesis. Accordingly, we decided to evaluate the usefulness of the Stille cross-coupling reaction en route to dityrosines. Furthermore, this method offers an interesting alternative to the Suzuki reaction as shown by its application to the formal total synthesis of Hazimycin **3** (Scheme 1).

Despite a large literature survey, we have been unable to find a significant number of publications reporting the preparation and use of 3-trialkylstannyl tyrosine derivatives. Indeed, the only contemporaneously related works, of which we became aware, were those of Konopelski et al.[11a] and of Albrecht and Williams.[11b] Konopelski reported the synthesis of stannane **20** (see Table 1) which they needed for their Diazonamide A synthesis[11a] whereas Williams described the preparation of stannane **17**, an intermediate in the synthesis of the proteasome's inhibitors TMC-95. We therefore set out to the preparation of the required 3-tri-*n*-butylstannane derivatives of tyrosine which were made through palladium-catalyzed reaction of 3-iodotyrosine derivatives (**6-14**) with hexabutyl-distannane[12] (see Table 1). Also, disclosed in Table 1 are some of the more reliable conditions we have found, to access the corresponding 3-organostannane derivatives of tyrosine[13] (**15–23**).

With the stannanes (**15–23**) in hand, we turned our attention toward developing an effective route for their conversion to dityrosines. First, we examined the effects of varying successively: the catalyst, the ligand and/or the solvent, on the outcome of the reaction. We identified a set of conditions that afforded the expected coupling products.

Next, we assessed the nature of the catalyst we needed, a choice which is often far from obvious and is made usually on a trial and error basis. Several catalysts including $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$ were tested and found to furnish low to modest yields of the corresponding dityrosines. Addition of some co-catalysts improved the yield; the additives, which we used, whether alone or combined to one another, comprise, CuI,[14] or CuI–$AsPh_3$[15,16b] or CuI–LiCl.[16] In this regard, use of the combination CuI–$AsPh_3$ proved to be very effective affording the dityrosines in usually decent yields (Table 2). Finally, we turned our attention to what would be the best solvents for these reactions. Solvents such as DMF, toluene, dioxane, and N-methyl-pyrrolidone were selected and evaluated. In these reactions, we were confronted with the occasional but seemingly unavoidable problem of tin-hydride exchange, and that did occur, sometimes, in a 20–30% yield. However, we were

Table 1. Synthesis of 3-tributylstannyltyrosine derivatives



6-14 **15-23**

Entry	R	R^1	R^2	Start. mater.	Conditions	Time (h)	Prod.	Yield (%)
1	MOM	*t*-Bu	Boc	**6**	A	2.5	**15**	74
					B	2		73
2	Me	*t*-Bu	Boc	**7**	B	2	**16**	73
3	Me	Me	Boc	**8**	B	2	**17**	66
4	Me	Bn	Ac	**9**	B	3	**18**	50
5	Ac	Bn	Ac	**10**	A	2	**19**	54
6	Ac	Me	Ac	**11**	A	2	**20**	55
7	Ac	Me	Boc	**12**	A	2.5	**21**	52
8	Ac	*t*-Bu	Boc	**13**	A	3	**22**	54
9	Me	Me	$-CO_2CH_2CCl_3$	**14**	A	1	**23**	50

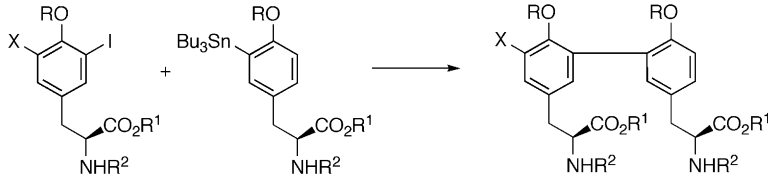
Reagents and conditions: A: $(Bu_3Sn)_2$ (2 equiv), DMF, 115 °C, $PdCl_2(PPh_3)_2$ (10 mol %); B: $(Bu_3Sn)_2$ (2 equiv), PhMe, reflux, $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %).

able to obtain the dityrosines (**24**–**37**) in a modest, but still decent yield, ranging from 30% to 50%. Apparently, in this transformation we took advantage of the beneficial withdrawing effect of both, the C-5 acetyl and C-4 acetate groups (entries 4, 5, and 9–14). In entries 1–3 and 6–9 the presence of a methoxy group at C-4 was found to be, somewhat detrimental to the coupling. And this is made clear through the opposite effect exercised by the methoxymethyloxy group that possesses both alkyl ether and acetal functionalities. Consequently this group has the ability to both complex and stabilizes the palladium reagents.

We therefore decided to undertake the synthesis of various dityrosines bearing an electron-withdrawing group at C-3′. With the requisite iodides (entries 6–14) in hand, we investigated their ability to undergo palladium-catalyzed cross-coupling reactions with their stannanes counterparts; the results[17] we obtained are listed in Table 2.

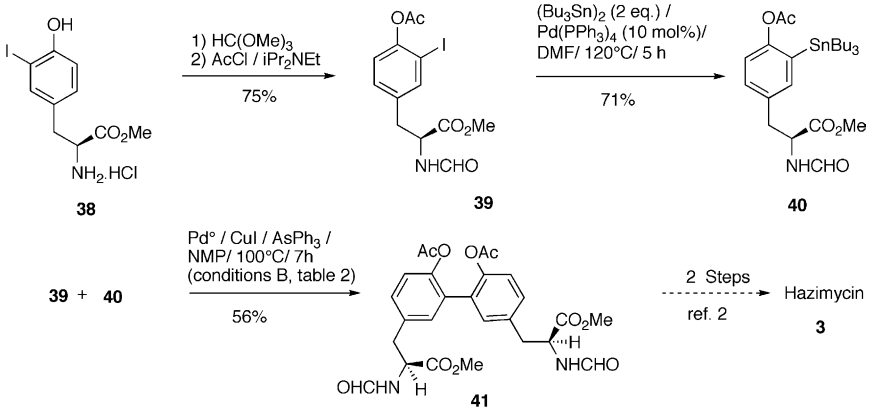
Looking for an application to this method, we thought of using it in the formal synthesis of Hazimycin **3**. To this end, we carried out the strategy described in Scheme 1. Thus, palladium-catalyzed cross-coupling between N-formyl-2-iodotyrosine[18] **39** and N-formyl-2-stannyltyrosine **40** provided the corresponding dityrosine **41** in an improved 56% yield. Dityrosine **41** was previously obtained in 6–11% yield and this synthesis[2] involved an oxidative coupling of N-formyl-L-tyrosine methyl ester

Table 2. Synthesis of dityrosines



Entry	3-Iodo-tyr				3-Bu_3Sn-tyr			Conditions	Di-tyr	Yield (%)
	R	R^1	R^2	X	R	R^1	R^2			
1	Me	Me	Ac	H	MOM	*t*-Bu	Boc	C	**24**	7–15
2	Me	Me	Boc	H	Me	*t*-Bu	Boc	D	**25**	13
3	Ac	*t*-Bu	Z	H	Me	*t*-Bu	Boc	B	**26**	21
4	Ac	Me	Boc	H	MOM	*t*-Bu	Boc	D	**27**	30
5	Ac	*t*-Bu	Z	H	Ac	Me	Ac	A	**28**	38–50
6	Me	Me	Boc	Ac	Me	Bn	Ac	D	**29**	19
7	Me	Me	Z	Ac	Me	*t*-Bu	Boc	D	**30**	20
8	Me	Me	Z	Ac	MOM	*t*-Bu	Boc	B	**31**	25–40
9	Ac	Me	Z	Ac	MOM	*t*-Bu	Boc	B	**32**	33–43
10	Me	*t*-Bu	Boc	Ac	Ac	Me	Z	D	**33**	37–40
11	Me	Me	Boc	Ac	Ac	Bn	Ac	D	**34**	37
12	Me	Me	Z	Ac	Ac	*t*-Bu	Boc	D	**35**	38
13	Me	*t*-Bu	Z	Ac	Me	Me	Boc	A	**36**	33
14	Me	*t*-Bu	Boc	Ac	Ac	Me	Ac	A	**37**	27, 40

Reagents and conditions: A: $PdCl_2(PPh_3)_2$ (10 mol%), $AsPh_3$ (20 mol%), CuI (20 mol%), DMF, 120 °C, 4 h; B: $PdCl_2$ $(PPh_3)_2$ (10 mol%), $AsPh_3$ (20 mol%), CuI (20 mol%), NMP, 100, 7 h; or dioxane, 100 °C, overnight; C: Pd $(PPh_3)_4$ (5 mol%), CuI (10 mol%), DMF, 110–120 °C, 3 h; D: $PdCl_2$ $(PPh_3)_2$ (5 mol%), $AsPh_3$ (10 mol%), CuI (10 mol%), DMF, 120 °C, 4–8 h.



Scheme 1.

as the key step. Dityrosine **41** being two steps away from product **3**, access to this compound, as indicated in Scheme 1, represents a formal total synthesis of the latter.

In conclusion, we reported herein the synthesis of various dityrosines using a Stille cross-coupling approach extending thereby the currently available methodologies for accessing this class of compounds. Furthermore, the usefulness of this method was substantiated by the direct formal total synthesis of the anti-fungal antibiotic, Hazimycin **3**, in good overall yield.

Acknowledgements

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13. Representative procedure: To a solution of iodide **6** (1.2 g,1.6 mmol) in DMF (20 ml), was added $Pd(PPh_3)_2Cl_2$ (120 mg, 10 mol%) followed by hexabutylditin (2.5 ml), the mixture was stirred and warmed at 120 °C for 2.5 h. The reaction mixture was cooled to room temperature, extracted in Et_2O, washed three times with brine and then evaporated to dryness to afford an oily residue (4.3 g). Purification by silica gel column chromatography eluting with hexanes: 10% EtOAc:1% Et_3N gave tributylstannane **15** (1.18 g) as a colorless oil, in 74% yield. $[\alpha]_D^{25}$ +23.0 (*c* 0.4, $CHCl_3$); I.R. (ν cm^{-1}): 3368–3443, 2957, 2930, 1719; MS (EI) *m/z*: 614 (M^+-n-Bu, 100); 612 (M^+-n-Bu, 77); ^1H NMR, (300 MHz, $CDCl_3$) δ ppm: 0.87 (t, 9H, J = 7.3 Hz); 1.03 (t, 6H, J = 7.5 Hz); 1.28 (m, 6H); 1.39 (s, 9H); 1.43 (s, 9H); 1.51 (m, 6H); 2.99 (dl, 2H, J = 5.7 Hz); 3.5 (s, 3H); 4.38–4.42 (m, 1H); 4.97 (dl, 1H, J = 7.9 Hz); 5.12 (s, 2H); 6.97 (d, 1H, J = 8.3 Hz); 7.08 (ddl, 1H, J=2.1, 8.3 Hz); ^{13}C NMR, (DMSO-d_6, 75.4 MHz), δ ppm: 9.46, 13.6, 26.7, 27.7, 28.2, 28.8, 36.1, 55.5, 56.1, 78.1, 80.2, 93.8, 111.2, 129.1, 130.6, 130.7, 137.4, 155.4, 160.0, 171.4.
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17. Dityrosine **27**: To a solution of stannane **15** (102 mg, 0.15 mmol) and iodide **12** (64 mg, 1 equiv) in DMF (4 ml) was added CuI (3 mg, 10 mol%) and $AsPh_3$ (10 mg, 5 mol%) followed by $Pd(PPh_3)_2Cl_2$ (5 mg, 5 mol%). The reaction mixture was warmed at 120 °C for 4.5 h. Then, the reaction mixture was cooled to room temperature, diluted with DCM and washed successively with 10% aqueous NH_4OH and brine, evaporation of the solvent provided 230 mg of a yellow colored residue. Column chromatography on silica gel, eluting with hexanes: 30% EtOAc furnished the dityrosine **27** as a colorless gum in 30% yield. $[\alpha]_D^{25}$ +32.3 (*c* 4.7, $CHCl_3$); I.R. (ν cm^{-1}): 3385, 2978, 2932, 1761, 1715; MS (EI) *m/z*: 660 (M^+–C_4H_8, 40); 543 (660-BocNH$_2$, 70); ^1H NMR, (300 MHz, DMSO-d_6), δ ppm: 1.33–1.37 (2s, 27H); 2.0 (s, 3H); 2.89 (m, 3H); 3.05 (ddl, 1H, J = 5.0 Hz, 13.5 Hz); 3.34 (s, 3H); 3.64 (s, 3H); 4.01 (m, 1H); 4.21 (m, 1H); 5.01 (s, 2H); 7.01 (sl, 1H); 7.12 (dd, 2H, J = 6.8 Hz); 7.21 (sl, 1H); 7.28 (d, 1H, J = 8.5 Hz); 7.33 (d, 1H, J = 8.5 Hz); ^{13}C NMR, (DMSO-d_6, 75.4 MHz), δ ppm: 20.7, 27.7, 28.3, 35.9, 51.9, 55.3, 55.6, 56.3, 78.3, 78.5, 80.5, 94.8, 115.4, 122.7, 127.7, 129.1, 130.1, 130.6, 131.0, 131.6, 132.0, 134.9, 146.9, 152.9, 155.6, 168.8, 171.4, 172.7.
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