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Syntheses of Fenanthroviridone, Gilvocarcin BE-12406X$_2$, and Antibiotic WS 5995B Based on the Palladium and Copper Catalyzed Coupling of Organostannanes with Bromoquinones

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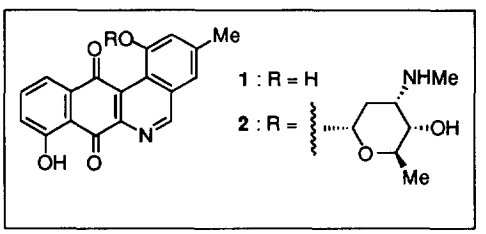
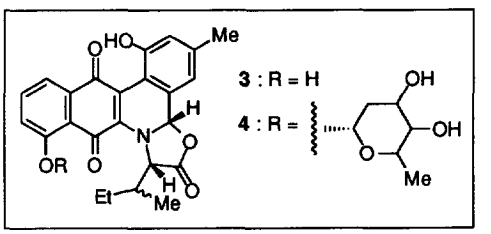
Abstract: A total synthesis of fenanthroviridone, gilvocarcin BE-12406X$_2$, antibiotic WS 5995B is described based on the palladium and copper catalyzed coupling reaction of sterically hindered aryl stannanes with a 2-bromonaphthoquinone. Copyright © 1996 Elsevier Science Ltd

We have recently developed a procedure for the selective alkylation, alkenylation, and arylation of naphthoquinones under mild conditions by using a variation of the palladium catalyzed Stille coupling reaction between 2-bromonaphthoquinones and tetraorganostannanes.[1] In most cases, the best results were obtained by using CuBr as the co-catalyst.[2] The alternative procedure, palladium-catalyzed coupling of stannylquinones with allyl or aryl electrophiles, has been recently developed by Liebeskind.[3]

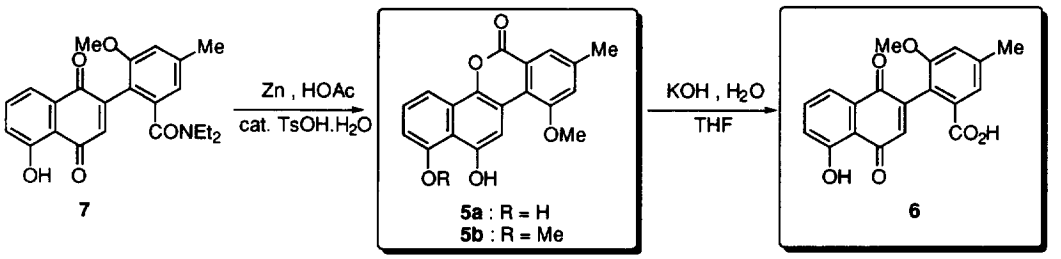




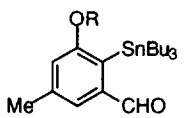
The benzo[*b*]phenanthridines are a small group of structurally related angucycline[4] natural products which have been isolated from different species of *Streptomyces*. Phenanthroviridone (**1**)[5] and its glycoside phenanthroviridine (**2**)[6] have been isolated from *S. murayamaensis*. Structurally more complex jadomycin A (**3**),[7a] and jadomycin B (**4**),[7b] were isolated from *S. venezuelae*. As part of a project aimed at the synthesis of jadomycins and determination of their stereochemistry, we decided first to demonstrate the application of our approach for the synthesis of phenanthroviridone (**1**).[8] Herein we report the concise synthesis of **1** by palladium catalyzed coupling of a sterically hindered arylstannane with a 2-bromonaphthoquinone. Additionally, as part of one of the unsuccessful approaches attempted for the synthesis of **1**, we have accomplished the syntheses of gilvocarcin BE-12406X$_2$ (**5a**)[9] and antibiotic WS 5995B (**6**).[10]

Gilvocarcin **5a** appeared to be a good starting point for the synthesis of **1**. Reduction of 2-aryl-1,4-naphthoquinone **7**[1c] with Zn in acetic acid containing a catalytic amount of TsOH.H$_2$O proceeded readily at 23 °C to give **5a**[11] in 75% yield. This is the first synthesis of natural occurring BE-12406X$_2$ (**5a**),[9b] the aglycon of gilvocarcin BE-12406A.[9a] Unfortunately, we failed to accomplished the required reduction of the lactone of **5a** to the aldehyde or the lactol under all the conditions examined. Although this approach for the preparation of **1** failed, the ready availability of **5a** allowed us to complete the synthesis of **6**, a cytotoxic pigment that cannot be

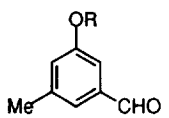
prepared by direct cleavage of the tertiary carboxamide of **7**.[1c] The synthesis of antibiotic WS 5995B (**6**)[12] was finally achieved in 67 % yield by saponification of lactone **5a** with aqueous KOH in THF at 23 °C, which proceeds with concomitant oxidation to the naphthoquinone in the presence of atmospheric oxygen.



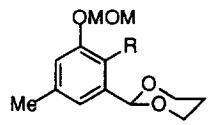
For the synthesis of **1**, substituted benzaldehyde stannanes **8a-b** were prepared from known 3-hydroxy-5-methylbenzoic acid (**9**)[13] by using the methodology developed by Comins.[14] Thus, **10a-b**[15a,b] were treated with the lithium amide derived from *N,N,N'*-trimethylethylenediamine, followed by addition of 3 equiv of BuLi to furnish the aryl lithiums, which were quenched with Bu_3SnCl to give **8a-b** in 85 and 76 % yield, respectively.[16] Alternatively, *ortho*-lithiation[17] of acetal **11** and stannylation provided fully protected stannane **12** (97% yield).[15c]



8a : R = Me
8b : R = MOM



10a : R = Me
10b : R = MOM

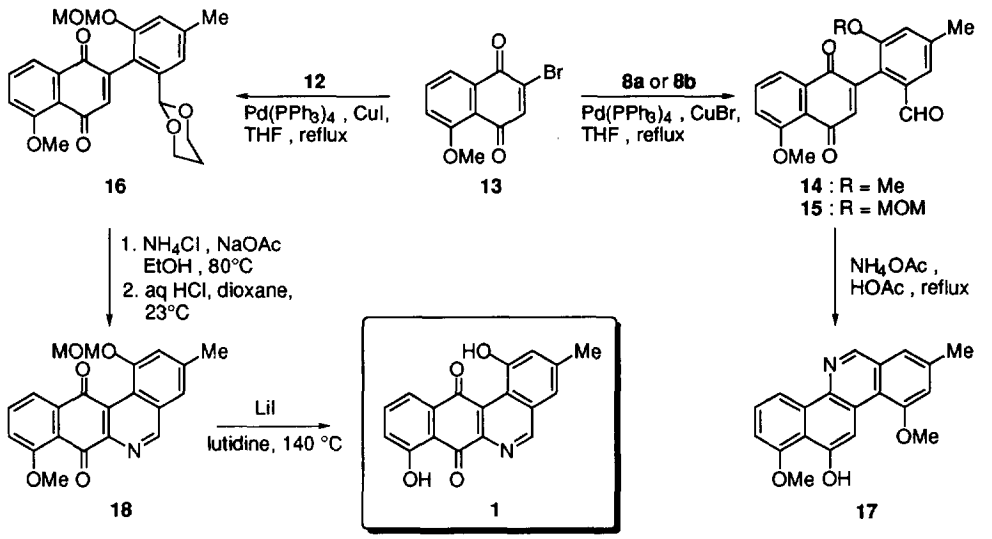


11 : R = H
12 : R = $SnBu_3$

Coupling of stannanes **8a-b** with 2-bromo-5-methoxy-1,4-napthoquinone (**13**) proceeded smoothly in THF under reflux in the presence of $Pd(PPh_3)_4$ and CuBr or CuI as the catalysts[1] to give **14** and **15** in 65 and 51% yields, respectively.[18a,b] Surprisingly, no reaction was observed in 1,4-dioxane at the same temperature. It is interesting to note that the more sterically hindered aryl stannane **12** coupled efficiently with **13** under these conditions to give **16** [$Pd(PPh_3)_4$ and CuI catalysts, THF, reflux; 85%].[18c]

Unfortunately, the naphthohydroquinone dianion derived from **14** failed to condense with the aldehyde to yield the carbocyclic ring system characteristic of the kinamycin family of antibiotics.[19] The alternative Michael-type reaction of an acyl anion equivalent derived from the aldehyde also failed because of the endocyclic nature of the cyclization. Interestingly, a Tishchenko-type transformation was uncovered upon treatment of **14** with catalytic 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and Et_3N (2 equiv) in DMF at 56°C for 21 h leading to **5b**[20] (45% yield). Similarly, reaction of **14** with aqueous NaCN in 1,4-dioxane led to **5b**, albeit in lower yield.

Reaction of **14** and **15** with ammonia under a variety of conditions failed to furnish the phenanthroviridine chromophore because of the higher reactivity of the aldehyde and subsequent reaction of the formed imine with the C-1 carbonyl of the quinone. Thus, benzo[*c*]phenanthridine **17**[21a] was obtained in the reaction of **14** with NH_4Cl and $CeCl_3.7H_2O$ as a Lewis acid[22] or with NH_4OAc in HOAc under refluxing conditions (22% unoptimized yield). Fortunately, the desired chromophore was achieved from **16** by reaction with ammonia (NH_4OH, MeOH, 23°C or NH_4Cl, EtOH, reflux) to give the aminoquinone which was treated with aqueous acid (10% aq HCl, 1,4-dioxane, 23°C, 3 h) to yield **18** (60-67%).[21b] The MOM group was not cleavaged under these mild hydrolysis conditions. Finally, reaction of **18** with LiI (2,6-lutidine, 140 °C, 6 h)[23] led to the natural chromophore phenanthroviridone (**1**) (63%). This new synthesis of **1** proceeded in 11 steps from benzoic acid **9** (longest sequence) in 20% overall yield, which compared very favorably in terms of efficiency with the previous reported synthesis.[8]



In summary, we have demonstrated that the palladium and copper-catalyzed coupling of bromo naphthoquinones with highly functionalized aryl stannanes allows for the development of an unified synthesis of natural occurring quinones and related metabolites such as phenanthroviridone (**1**), gilvocarcin BE-12406X$_2$ (**5**), and antibiotic WS 5995B (**6**). This coupling procedure is noteworthy in that highly congested nucleophiles react very efficiently leading to hindered biaryl-type products. The ready elaboration of functionalyzed 2-aryl-1,4-naphthoquinones such as **14-16** bearing either free or protected formyl group should allow for the synthesis of more complex members of this family, such as the jadomycins. A biomimetic synthesis of kinamycin metabolites from C-3 substituted derivatives of **14** or **15** could also be conceived. This route could also be adapted for the synthesis of benzo[*c*]phenanthridine alkaloids.[24] Progress towards these goals is underway.

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11. **5a**: Red solid; mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.12 (br s, 2H), 8.28 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.76 (s, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.46 (s, 1H, overlaps with the t), 6.90 (d, J = 7.6 Hz, 1H), 4.06 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 161.0, 160.1, 157.5, 155.2, 139.9, 138.0, 128.6, 126.0, 122.7, 122.0, 121.8, 118.9, 117.0, 114.4, 110.8, 110.0, 104.7, 56.4, 21.5. EI-MS *m/z* 322 (M^+, 100).

12. **6**: Red solid; mp >300 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.05 (s, 1H), 11.17 (s, 1H), 7.69-7.55 (m, 2H), 7.53 (s, 1H), 7.33-7.21 (m, 1H), 7.01 (s, 1H), 6.79 (s, 1H), 3.76 (s, 3H), 2.43 (s, 3H); EI-MS *m/z* 338 (M^+, 100).

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15. (a) **9→10a**: (1) MeI, K_2CO_3, acetone, reflux, 12 h, 86%; (2) $LiAlH_4$, THF, reflux, 1 h, 90%; (3) PCC, CH_2Cl_2, 23 °C, 2 h, 85%. (b) **9→10b**: (1) MeOH, H_2SO_4, 23 °C, 12 h, 94%; (2) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 24 h, 86 %; (4) $LiAlH_4$, THF, reflux, 1 h, 82%; (3) PCC, NaOAc, CH_2Cl_2, 23 °C, 2 h, 76%. (c) **9→11**: (1) MeOH, H_2SO_4, 23 °C, 12 h; (2) DHP, PPTS, CH_2Cl_2, 23 °C, 48 h; (3) $LiAlH_4$, THF, 23°C, 12 h; (4) PCC, NaOAc, CH_2Cl_2, 23 °C, 3 h, 89% overall (four steps); (5) 1,3-propanediol, *p*-TsOH, PhMe, reflux, 1 h, 74%; (6) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 24 h, 80%.

16. Colorless oil. Satisfactory spectroscopic and analytical data were obtained for stannanes **8a-b** and **12**.

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18. (a) **14**: Orange solid; mp 194-196 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.78 (dd, J = 7.5, 1.6 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.37-7.30 (m, 2H), 7.06 (br s, 1H), 6.80 (s, 1H), 4.04 (s, 3H), 3.78 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.2, 183.8 (2C), 159.4, 157.0, 143.0, 140.86, 139.4, 134.8, 133.1, 132.5, 130.8, 124.3, 120.0, 119.5, 117.6, 117.3, 56.3, 56.0, 21.4; EI-MS *m/z* 336 (M^+, 100). (b) **15**: Orange solid; mp 190-191 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.76 (dd, J = 7.5, 1.6 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 7.41 (br s, 1H), 7.36-7.31 (m, 2H), 6.79 (s, 1H), 5.12 (s, 2H), 4.04 (s, 3H), 3.38 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.2, 184.0 (2C), 159.6, 155.0, 143.3, 141.1, 139.4, 135.5, 134.8, 132.8, 132.2, 130.2, 126.0, 121.0, 119.8, 117.8, 94.7, 56.5 (2C), 21.5; EI-MS *m/z* 366 (M^+, 23), 321 (100). (c) **16**: Orange solid; mp 105-106 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 6.9 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.17 (br s, 1H), 6.98 (br s, 1H), 6.84 (s, 1H), 5.29 (s, 1H), 4.10-4.02 (m, 2H), 4.02 (s, 3H), 3.80-3.63 (m, 2H), 3.33 (s, 3H), 2.36 (s, 3H), 2.15-1.95 (m, 1H), 1.30-1.24 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.6, 183.6, 159.4, 154.3, 144.6, 140.4, 139.4, 137.4, 134.8, 134.7, 120.3, 120.0, 119.5, 117.3, 115.5, 100.0, 94.5, 67.1, 67.0, 56.4, 56.0, 25.4, 21.7 (one signal was not observed); EI-MS *m/z* 424 (M^+, 70), 379 (100).

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20. **5b**: Red solid; mp 266-267 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.41 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 7.96 (br s, 1H), 7.48 (dd, J = 8.6, 7.8 Hz, 1H), 7.18 (br s, 1H), 6.94 (d, J = 7.8 Hz, 1H), 4.10 (s, 3H), 4.09 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 157.4, 155.5, 149.8, 139.9, 139.3, 126.4, 125.7, 123.1, 122.4, 121.6, 117.8, 116.0, 115.1, 114.7, 107.6, 105.7, 56.2, 55.9, 21.6; EI-MS *m/z* 336 (M^+, 100).

21. (a) **17**: Red solid; mp 226-227 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.57 (s, 1H), 9.13 (s, 1H), 9.10 (d, J = 8.3 Hz, 1H), 8.85 (s, 1H), 7.60 (t, J = 8.3 Hz, 1H), 7.46 (br s, 1H), 7.05 (m, 2H), 4.13 (s, 6H), 2.58 (s, 3H); EI-MS *m/z* 319 (M^+, 100). (b) **18**: Red solid; mp 166-167 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 7.75-7.65 (m, 2 H), 7.51 (br s, 1 H), 7.44 (br s, 1 H), 7.28 (dd, J = 7.0, 2.4 Hz, 1 H), 5.32 (s, 2 H), 4.04 (s, 3 H), 3.62 (s, 3 H), 2.57 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.8, 181.2, 159.9, 156.7, 154.1, 145.0, 142.2, 138.4, 135.1, 131.7, 129.2, 121.7, 120.9, 120.6, 118.9, 118.3, 117.0, 95.7, 56.6 (2C), 22.1; EI-MS *m/z* 363 (M^+, 100).

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23. This procedure gave **1** more reproducibly and in higher yield than deprotection with BBr_3 (CH_2Cl_2).

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