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Syntheses of Fenanthroviridone, Gilvocarcin BE-12406X₂, and Antibiotic WS 5995B Based on the Palladium and Copper Catalyzed Coupling of Organostannanes with Bromoquinones

Óscar de Frutos and Antonio M. Echavarren*

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Abstract: A total synthesis of fenanthroviridone, gilvocarcin BE-12406X₂, 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 angucycline⁴ 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),⁷ and jadomycin B (4),⁷ 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-12406X₂ (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-1,4naphthoquinone 7^{1c} with Zn in acetic acid containing a catalytic amount of TsOH.H₂O proceeded readily at 23 °C to give $5a^{11}$ in 75% yield. This is the first synthesis of natural occurring BE-12406X₂ (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 3hydroxy-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 Bu₃SnCl to give **8a-b** in 85 and 76 % yield, respectively.¹⁶ Alternatively, *ortho*-lithiation¹⁷ of acetal **11** and stannylation provided fully protected stannane **12** (97% yield).^{15c}



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 catalysts¹ 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 NH₄Cl and CeCl₃.7H₂O as a Lewis acid²² or with NH₄OAc in HOAc under refluxing conditions (22% unoptimized yield). Fortunately, the desired chromophore was achieved from 16 by reaction with ammonia (NH₄OH, MeOH, 23°C or NH₄Cl, 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 2C% 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-12406X₂ (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; ¹H 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); ¹³C 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).
- 6: Red solid; mp >300 °C (dec); ¹H NMR (200 MHz, CDCl₃) & 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, K₂CO₃, acetone, reflux, 12 h, 86%; (2) LiAlH₄, THF, reflux, 1 h, 90%; (3) PCC, CH₂Cl₂, 23 °C, 2 h, 85%. (b) 9→10b: (1) MeOH, H₂SO₄, 23 °C, 12 h, 94%; (2) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, reflux, 24 h, 86 %; (4) LiAlH₄, THF, reflux, 1 h, 82%; (3) PCC, NaOAc, CH₂Cl₂, 23 °C, 2 h, 76%. (c) 9→11: (1) MeOH, H₂SO₄, 23 °C, 12 h; (2) DHP, PPTS, CH₂Cl₂, 23 °C, 48 h; (3) LiAlH₄, THF, 23°C, 12 h; (4) PCC, NaOAc, CH₂Cl₂, 23 °C, 3 h, 89% overall (four steps); (5) 1,3-propanediol, *p*-TsOH, PhMe, reflux, 1 h, 74%; (6) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, reflux, 24 h, 80%.
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- 18. (a) 14: Orange solid; mp 194-196 °C; ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) 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); ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) δ 191.2, 184.0 (2C), 159.6, 155.0, 143.3, 141.1, 139.4, 135.5, 134.8, 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; ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) 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* 242 (M⁺, 70), 379 (100).
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- 20. **5b**: Red solid; mp 266-267 °C; ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) 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); ¹H NMR (200 MHz, CDCl₃) 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); ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) 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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