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Synthesis of the potent antitumoral marine alkaloid variolin B

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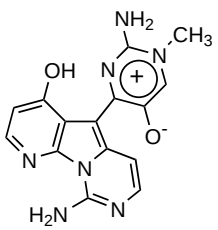
Abstract—The synthesis of the marine alkaloid variolin B has been completed in seven steps, starting from the iminophosphorane derived from ethyl α-azido-β-(4-methoxy-7-azaindol-3-yl) acrylate, available by condensation of 2-formyl-4-methoxy-7-aza-indole with ethyl azidoacetate. Formation of the annulated 2-aminopyrimidine ring is achieved by tandem aza-Wittig/carbodiimide-mediated cyclization whereas the 2-aminopyrimidine substituent at C-5 is formed using an acetyl group as C_2 moiety of the pyrimidine ring.

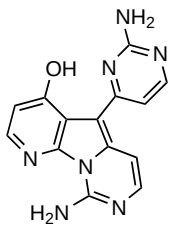
Marine organisms are among the most promising sources of new biologically active molecules.[1] Certain secondary metabolites are nontraditional guanidine-based alkaloids[2] that possess a broad spectrum of powerful biological activities. The guanidine moiety is frequently found in the guise of a 2-aminoimidazole ring[3] or a 2-aminopyrimidine ring.[4,5] In 1994, Blunt and Munro reported the isolation and structural elucidation of the variolins, which were isolated from the difficult to access Antarctic sponge *Kirkpatrickia varialosa*.[6,7] This new class of alkaloids is interesting from both the structural and biological points of view. Variolins have a common pyridopyrrolopyrimidine ring, strictly a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, which has no precedent in either terrestrial or marine natural products. Variolin B is the most active, having cytotoxic activity against the P388 murine leukemia cells, and also being effective against *Herpes simplex* type I.[6]

Recently, we have reported[8] a convenient method for the preparation of the core tricyclic of the variolins bearing suitable functionalities for the preparation of the natural products. Since then, three new strategies have been developed to synthesize the tricyclic pyrido[3′,2′:4,5] pyrrolo[1,2-*c*]pyrimidine ring system,[9–11] and very recently the total synthesis of variolin B has been reported.[12] This work has prompted us to report our efforts towards the synthesis of the variolin core structure and in this letter we present a new synthesis of variolin B.

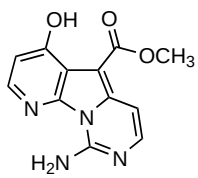
Formation of the annulated 2-aminopyrimidine ring is achieved from iminophosphorane **1**[8] by a tandem aza-Wittig/carbodiimide-mediated cyclization process. Thus, aza-Wittig reaction of **1** with α-methylbenzyl isocyanate in THF at room temperature provides the tricyclic pyrimidopyrrolopyridine **2**[13] in almost quantitative yield, thus completing the central core of the variolins. As far as the introduction of the second 2-aminopyrimidine ring at C-5 is concerned, bromination of **2** with bromine in pyridine at 0°C affords the 5-bromo derivative **3** in 93% yield. The conversion into



Variolin A



Variolin B



Variolin D

Keywords: phosphine imines; natural products; sponges; decarboxylation; pyrimidines.

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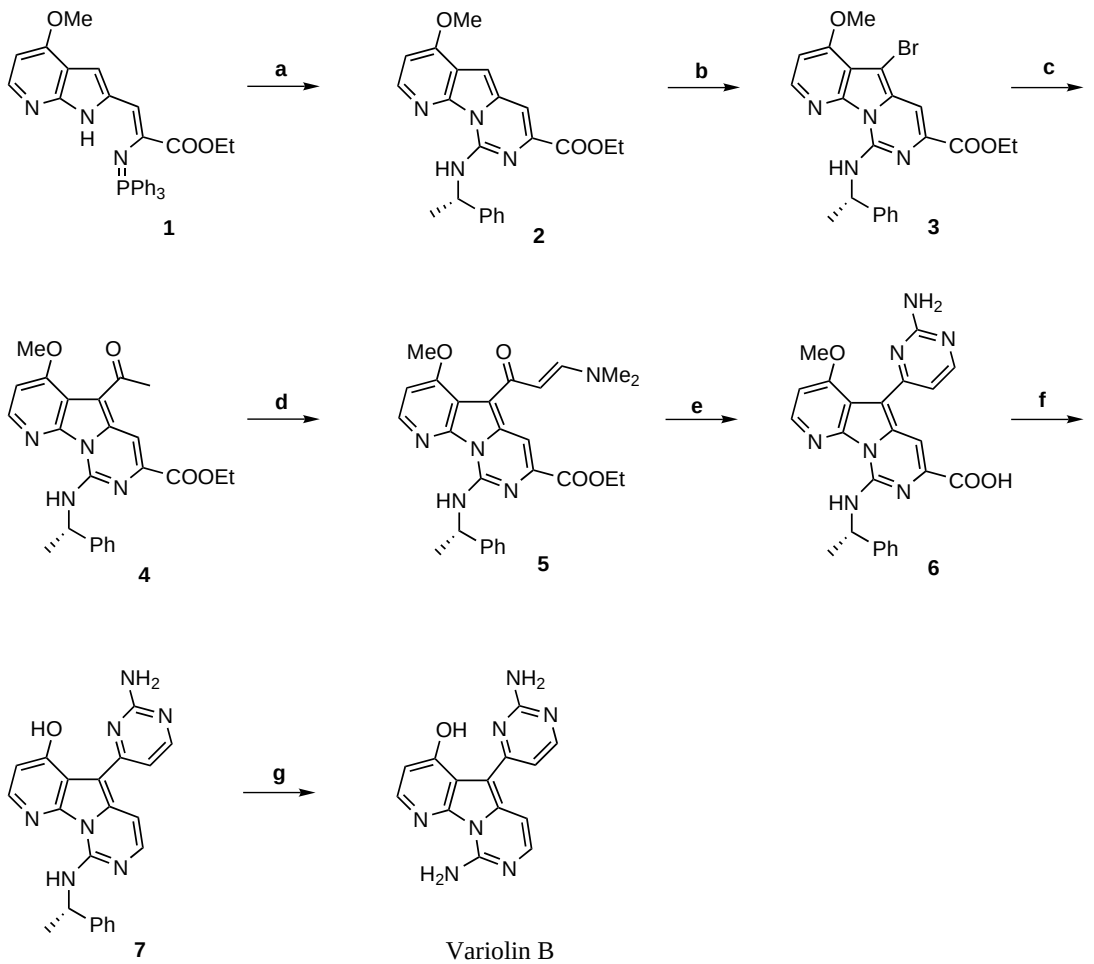
an acetyl group, used as a C_2 moiety for the construction of the pyrimidine ring, is achieved in 65% yield by coupling of **3** with (α-ethoxyvinyl)trimethyltin[14] in the presence of dichlorobis(triphenylphosphine)palladium-(II).[15] When compound **4** reacts with *N*,*N*-dimethylformamide dimethyl acetal in DMF at 110°C, the enaminone **5** is obtained in 45% yield. Switching to the more reactive *N*,*N*-dimethylformamide di-*ter*-butyl acetal produces the best yield at a lower reaction temperature. Thus, when compound **4** is treated with *N*,*N*-dimethylformamide di-*ter*-butylacetal in DMF at 80°C, the enaminone **5** is obtained in 70% yield. Conversion of **5** into **6**, which involves the formation of the north-east 2-aminopyrimidine ring and concomitant ester hydrolysis, is achieved in 89% yield in one step by treatment with guanidine hydrochloride in 2-methoxyethanol in the presence of anhydrous potassium carbonate.[16] All that remains for realization of the final goal are decarboxylation and *O*- and *N*-deprotection. Decarboxylation of **6**, essential to our objective of preparing variolin B, proved to be difficult. After several trials with various reagents and conditions (Cu/quinoline, $Cu_2Cr_2O_5$/BaO and Barton decarboxylation procedure) we were unable to accomplish this transformation. This series of frustating results was finally broken by using thermal treatment in diphenyl ether. Thus, when compound **6** is treated in diphenyl ether at 260°C for 5 h not only decarboxylation but also *O*-methyl deprotection take place to give **7** in 35% yield.[17] Finally, the *N*-protecting group is quantitatively removed by treatment of **7** in neat triflic acid at room temperature, to give variolin B, that was found to be identical in all respects with the natural product[6] (Scheme 1).

In conclusion, a total synthesis of variolin B has been completed in seven steps from the iminophosphorane **1**, available from 4-methoxypyridine in eight steps. Formation of the annulated 2-aminopyrimidine is achieved by tandem aza-Wittig/carbodiimide-mediated cyclization process, whereas the substituted 2-aminopyrimidine ring is formed using the Bredereck protocol.[18] Both methodologies introduce directly the necessary functionalities of variolin B.[19]



Scheme 1. *Reagents and conditions*: (a) $PhCH(CH_3)NCO$, THF, rt (100%); (b) Br_2, pyridine, 0°C (93%); (c) (α-ethoxyvinyl)trimethyltin, DMF, $PdCl_2(PPh_3)_2$ (65%); (d) DMF–DtBA, DMF, 80°C (70%); (e) $H_2N(C{=}NH)NH_2{\cdot}HCl$, K_2CO_3, 2-methoxyethanol, reflux (89%); (f) Ph_2O, 260°C (35%); (g) triflic acid, rt (90%).

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References

1. Foulkner, D. *J. Nat. Prod. Rep.* **2001**, *18*, 1–49.
2. Albizati, K. F.; Martin, V. A.; Agharahimin, M. R.; Stolze, D. A. In *Synthesis of Marine Natural Products in Biorganic Marine Chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, 1992; Vol. 6, pp. 158–248.
3. Molina, P.; Fresneda, P. M.; Sanz, M. A. *J. Org. Chem.* **1999**, *64*, 2540–2544 and references cited therein.
4. Franco, I. H.; Joffé, E. B. K.; Puricelli, L.; Tatian, M.; Seldes, A. M.; Palermo, J. A. *J. Nat. Prod.* **1998**, *61*, 1130–1132.
5. Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355–2363.
6. Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987–3992.
7. Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *56*, 3993–4000.
8. Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777–4780.
9. Mendiola, J.; Minguez, J. M.; Alvarez-Builla, J.; Vaquero, J. *Org. Lett.* **2000**, *2*, 3253–3256.
10. Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, 311–313.
11. Alvarez, M.; Fernandez, D.; Joule, J. A. *Tetrahedron Lett.* **2001**, 315–317.
12. Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, 8697–8699.
13. Spectroscopic data for **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (t, 3H, $J=7.2$ Hz, CH_3CH_2), 1.68 (d, 3H, $J=7$ Hz, H-12), 3.93 (s, 3H, CH_3O), 4.28 (qd, 2H, $J=2.6$, 7.2 Hz, CH_3CH_2), 5.61 (q, 1H, $J=7.2$ Hz, H-11), 6.51 (s, 1H, H-5), 6.64 (d, 1H, $J=5.6$ Hz, H-7), 7.12–7.31 (m, 3H, H*m*, H*p*), 7.47 (s, 1H, H-4), 7.50 (dd, 2H, $J=8.6$, 0.8 Hz, H*o*), 8.16 (d, 1H, $J=5.6$ Hz, H-8), 9.99 (d, 1H, $J=8$ Hz, NH). ^{13}NMR (50 MHz, $CDCl_3$) δ: 14.3 (CH_3CH_2), 28.8 (C-12), 50.2 (C-11), 55.6 (CH_3O), 61.1 (CH_3CH_2), 91.0 (C-5), 100.2 (C-7), 106.3 (C-4), 114.4 (C-5a), 126.5 (C*o*), 127.0 (C*p*), 127.7 (C*m*), 134.3 (C-4a), 137.0 (C*i*), 142.6 (C-8), 143.9 (C-9a), 147.0 (C-1), 159.1 (C-6), 165.8 (CO). IR (Nujol) ν: 3263 (m), 1718 (s), cm^{-1}. MS: m/z (%) (EI positive) 391 (M+1, 25), 390 (M, 93), 286 (84), 214 (95), 186 (43), 105 (100).
14. Sodersquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830–833.
15. Solberg, J.; Undheim, K. *Acta Chim. Scand.* **1989**, 52–68.
16. Spectroscopic data for **6**: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.68 (d, 3H, $J=6.9$ Hz, H-12), 4.01 (s, 3H, CH_3O), 5.65 (qn, 1H, $J=7.0$ Hz, H-11), 6.54 (s, 2H, NH_2), 6.86 (d, 1H, $J=5.3$ Hz, H-7), 7.20 (d, 1H, $J=5.5$ Hz, H-5′), 7.28 (t, 1H, $J=7.5$ Hz, H*p*), 7.38 (t, 2H, $J=7.5$ Hz, H*m*), 7.54 (d, 2H, $J=7.5$ Hz, H*o*), 8.06 (s, 1H, H-4), 8.23 (d, 1H, $J=5.3$ Hz, H-8), 8.45 (d, 1H, $J=5.5$ Hz, H-6′), 10.42 (d, 1H, $J=8.1$ Hz, NH). ^{13}NMR (50 MHz, DMSO-d_6) δ: 23.3 (C-12), 50.0 (C-11), 56.5 (CH_3O), 102.7 (C-7), 105.0 (C-5), 105.2 (C-5′), 111.3 (C-5a), 112.2 (C-4), 126.4 (C*o*), 127.4 (C*p*), 128.9 (C*m* and C-3), 134.6 (C-4a), 143.8 (C-8), 143.9 and 144.0 (C*i* or C-9a), 146.8 (C-1), 157.3 (C-6′), 160.0 (C-2′), 163.5 (C-4′), 166.8 (CO). IR (Nujol) ν: 3412 (m), 3218 (m), 1631 (s) cm^{-1}. MS: m/z (%) (EI positive) 456 (M+1, 18), 455 (M, 61), 400 (12), 395 (13), 365 (18), 351 (55), 292 (18), 105 (100).
17. Spectroscopic data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (d, 3H, $J=6.9$ Hz, H-12), 5.09 (brs, 2H, NH_2), 5.52 (qn, 1H, $J=6.9$ Hz, H-11), 6.79 (d, 1H, $J=5.4$ Hz, H-7), 6.94 (d, 1H, $J=6.6$ Hz, H-4), 7.04 (d, 1H, $J=5.7$ Hz, H-5′), 7.35–7.52 (m, 5H, Ph), 7.63 (d, 1H, $J=6.6$ Hz, H-3), 8.15 (d, 1H, $J=5.4$ Hz, H-8), 8.22 (d, 1H, $J=5.7$ Hz, H-6′), 11.15 (d, 1H, $J=7.5$ Hz, NH), 15.83 (s, 1H, OH). ^{13}NMR (75 MHz, $CDCl_3$) δ: 23.6 (C-12), 50.8 (C-11), 100.1 (C-4), 100.2 (C-5), 107.5 (C-5′), 107.8 (C-7), 111.6 (C-5a), 126.1 (C*o*), 127.2 (C*p*), 128.7 (C*m*), 138.0 (C-4a), 143.0 (C-8), 143.7 (C-9a), 144.4 (C-3), 149.1 (C-1), 159.0 (C-6′), 159.6 (C-2′), 160.1 (C-6), 160.7 (C-4′). IR (Nujol) ν: 3491 (m), 3412 (m), 3303 (m), 3176 (m), 1617 (m), 1575 (s), 1469 (m) cm^{-1}. MS: m/z (%) (EI positive) 398 (M+1, 8), 397 (M, 20), 293 (45), 252 (47), 149 (39), 105 (100).
18. Bredereck, H.; Effenberger, F.; Botsch, H.; Rehn, H. *Chem. Ber.* **1965**, *98*, 1081–1086.
19. All new compounds were characterized by ^{1}H and ^{13}C NMR, IR and mass spectrometry. Yields are for isolated, chromatographically purified products.