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Synthetic studies towards the 2-aminopyrimidine alkaloids variolins and meridianins from marine origin

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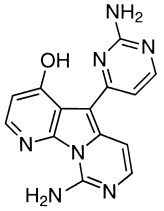
Abstract

A nine-step synthesis of 9-amino-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, a tricyclic ring system present in the marine alkaloids variolins is described. The natural marine products meridianins C–E have been synthesized for the first time starting from *N*-protected 3-acylindoles.

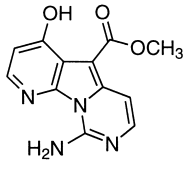
Keywords: phosphine imines; natural products; sponges; indolization; pyrimidines.

Certain secondary metabolites of marine organisms are nontraditional guanidine-based alkaloids[1] that possess a broad spectrum of powerful biological activities. The guanidine moiety is frequently found in the guise of an 2-aminoimidazol ring[2] or a 2-aminopyrimidine ring.[3]

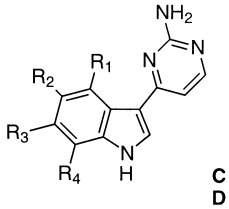
In 1994, Blunt and Munro reported the structure of variolins which were isolated from the Antarctic sponge *Kirkpatrickia varialosa*.[4] These alkaloids were isolated after the examination of extracts which were shown to be active against P388 murine leukemia cells. Subsequently, variolin B was found to be the most active in tests which included antiviral activity (Herpes simplex type I, polio type I).



Variolin B



Variolin D



Meridianins

C R_1= R_3= R_4= H, R_2= Br
D R_1= R_2= R_4= H, R_3= Br
E R_1= OH, R_2= R_3= H R_4= Br

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This new class of alkaloids is also interesting from both the structural and biogenetic points of view as the variolins are unique in their structural features; they represent the first example of natural products with a pyridopyrrolopyrimidine ring, strictly a pyrido[3′,2′:4,5] pyrrolo[1,2-*c*]pyrimidine. There is only one report dealing with the preparation of a thio-functionalized derivative of this ring system.[5]

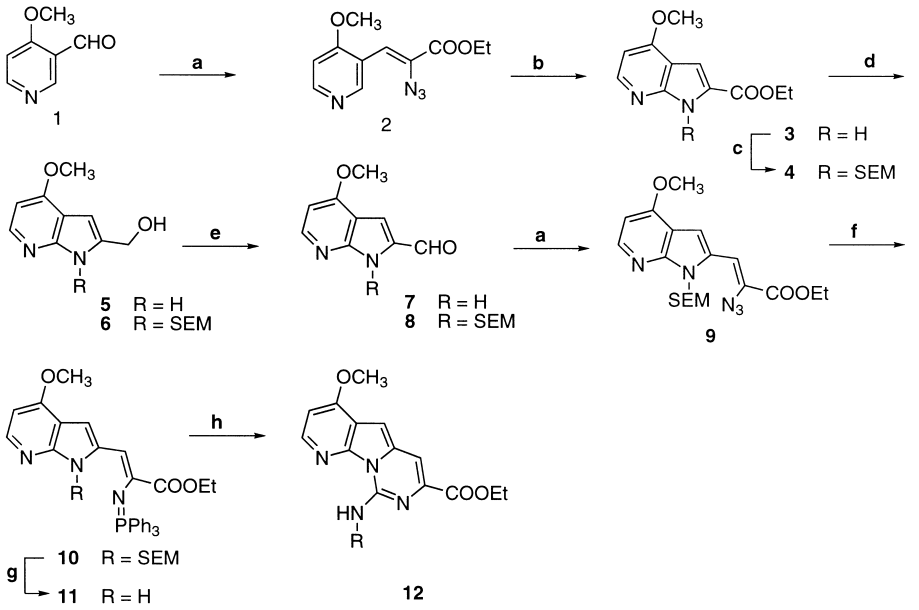
In connection with our synthetic efforts on the synthesis of alkaloids from a marine origin,[6] we became interested in the synthesis of the family of variolins and of the closely related meridianins. A recent report[7] dealing with the preparation of 3-heteroaryl-7-azaindoles prompted us to report our own results on the synthesis of the appropriately substituted pyridopyrrolo pyrimidine ring system and the first synthesis of meridianins C–E.

The *ortho*-lithiation of 4-methoxypyridine using mesityllithium as the metalating base[8] followed by reaction with *N*,*N*-dimethylformamide gave a 77% of 3-formyl-4-methoxypyridine **1**. Condensation of **1** with ethyl azidoacetate in the presence of NaOEt at –15°C provided the vinylazide **2** in 61% yield. When compound **2** was exposed to heat in *o*-xylene at reflux temperature for a short time, indolization took place by a nitrene insertion process to give the key intermediate 7-azaindole **3** in 67% yield.

The next task was to effect a pyrimido annelation which allows incorporation of the amine functionality, necessary for the preparation of the natural product, in the pyrimidine ring. Taking into account that the tandem aza-Wittig/heterocumulene-mediated ring-closure has been successfully applied to the synthesis of fused pyrimidines,[9] we decided to apply this methodology to build up the target tricyclic ring system. To this end, we required the 2-formyl-7-azaindole **7**, which was prepared from **3** by the following sequence: reduction with $AlLiH_4$/THF gave **5** in 93% yield which in turn was converted into **7** in 60% yield by reaction with MnO_2. However, in the reaction of **7** with ethyl azidoacetate under basic conditions, only numerous intractable decomposition products were formed. Therefore, we examined the same type of sequence of reactions, although we decided to protect the 7-azaindole ring prior to reduction/oxidation. The best results were obtained by the following three-step sequence: (a) N-SEM protection of **3** under standard conditions provided **4** in 94% yield: (b) reduction with $AlLiH_4$ in THF at reflux temperature gave **6** in 93% yield; and (c) oxidation with MnO_2 in CH_2Cl_2 at room temperature afforded **8** in 86% yield.

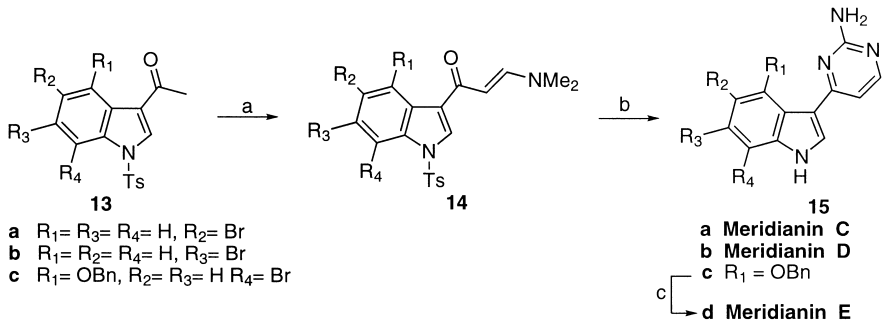
Condensation of N-SEM-protected 2-formyl-7-azaindole **8** with ethyl azidoacetate under the same conditions used for the preparation of **2** furnished the vinylazide **9** in 76% yield. The Staudinger reaction of **9** with triphenylphosphine in dry CH_2Cl_2 at room temperature gave the expected iminophosphorane derivative **10** in 82% yield. Treatment of the N-SEM-protected 7-azaindole **10** with tetrabutylammonium fluoride (TBAF)-SiO_2 under microwave heating for 1 min proved advantageous and cleanly removed the SEM group to give **11** in 70% yield, without affecting the iminophosphorane group. The use of TBAF/THF as deprotecting agent resulted even after an extended reaction time in a low yield of **11** with a considerable amount of the product derived from the hydrolytic cleavage of the iminophosphorane moiety. Aza-Wittig reactions of iminophosphorane **11** with several aromatic isocyanates and ethoxycarbonyl isothiocyanate in dry THF at room temperature directly gave the desired pyrimido annelation products **12** in yields higher than 90%, thus completing the tricyclic pyridopyrrolopyrimidine ring of the variolins bearing suitable functionalities for the preparation of the natural products[10] (Scheme 1).

As far as the construction of the second 2-aminopyrimidine ring is concerned, we have performed the synthesis of 3-(2-aminopyrimidin-4-yl)indoles in a parallel study. This method has



Scheme 1. *Reagents and conditions*: (a) N_3CH_2COOEt, NaEtO, EtOH, –15°C, **2** (61%), **9** (76%); (b) *o*-xylene, reflux (67%); (c) NaH, DMF, SEMCl (94%); (d) $AlLiH_4$, THF, reflux, **5** (93%), **6** (93%); (e) MnO_2, CH_2Cl_2, rt, **7** (60%), **8** (86%); (f) Ph_3P, CH_2Cl_2, rt (82%); (g) TBAF–SiO_2, THF, MW (70%); (h) RNCO, THF, rt (90%)

been successfully applied for the synthesis of the alkaloids meridianins isolated from the tunicate *Aplidinium meridianum*, which show cytotoxicity towards murine tumor cell lines.[3] As shown in Scheme 2, the synthesis of these alkaloids was realized through a four-step procedure.



Scheme 2. *Reagents and conditions*: (a) DMF–DMA, DMF, 110°C, **14a** (74%), **14b** (83%), **14c** (41%); (b) $H_2N(=NH)NH_2{\cdot}HCl$, 2-methoxyethanol, K_2CO_3, **15a** (72%), **15b** (78%), **15c** (82%); (c) H_2, Pd/C 10%, EtOH (88%)

N-Tosyl-3-acylindoles **13** were used for the construction of the 2-aminopyrimidine ring. The best results for the preparation of **13a** and **13b** were obtained when the corresponding brominated indole[11] was *N*-protected by the *p*-toluenesulfonyl group (90–94%) and then acylated with acetyl chloride in the presence of $SnCl_4$ (80–85%). However, the preparation of **13c** was carried out by an initial acylation of the 4-benzyloxy-7-bromoindole (89%) followed by *N*-protection (55%). When compounds **13** were treated with dimethylformamide dimethylacetal in DMF at 110°C the corresponding enaminones **14** were obtained in yields ranging from 41 to 83%. Direct conversion

of **14a** and **14b** into **15a** meridianin C and **15b** meridianin D, which involves formation of the 2-aminopyrimidine ring and *N*-tosyl deprotection, was achieved in 72–78% yield in one step by treatment with guanidine chlorohydrate in the presence of anhydrous Na_2CO_3.[12] Meridianin E was obtained in a straightforward manner from **15c** by standard *O*-benzyl deprotection (H_2, Pd/C) (Scheme 2).

In conclusion, we have developed a new approach to the synthesis (nine steps) of the appropriately substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine ring system present in the marine alkaloids variolins, and the first synthesis of the alkaloids meridianins starting from *N*-protected 3-acylindoles.

Acknowledgements

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10. Spectroscopy data for **12** (R = 4-$CH_3C_6H_4$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 3H, J = 6.9 Hz, CH_3CH_2O), 2.36 (s, 3H, CH_3-Ar), 4.0 (s, 3H, CH_3O), 4.43 (q, 2H, J = 6.9 Hz, CH_3CH_2O), 6.7 (s, 1H, H-5), 6.72 (d, 1H, J = 5.7 Hz, H-7), 7.21 (d, 2H, J = 8.1 Hz, H*m*), 7.65 (s, 1H, H-4), 7.96 (d, 2H, J = 8.1 Hz, H*o*), 8.25 (d, 1H, J = 5.7 Hz, H-8), 11.87 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (CH_3CH_2O), 20.8 (CH_3-Ar), 55.7 (CH_3O), 61.2 (CH_3CH_2O), 91.7 (C-5), 100.4 (C-7), 107.4 (C-4), 114.4 (C-5a), 120.1 (C*o*), 129.4 (C*m*), 132.6 (C*p*), 134.1 (C-4a), 136.2 (C-3), 136.3 (C*i*), 142.7 (C-8), 143.5 (C-9a), 144.4 (C-1), 159.4 (C-6), 165.6 (COOEt). IR (nujol) ν 3300 (m), 1715 (s), 1636 (m), 1605 (s) cm^{-1}. Anal. calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.94; H, 5.43; N, 14.75.
11. The previously unreported 4-benzyloxy-7-bromoindole was prepared from 5-bromo-2-hydroxybenzaldehyde by the following five-step sequence: (a) *O*-benzyl protection with benzyl bromide in the presence of HNa (96%); (b) condensation with ethyl azidoacetate (75%); (c) indolization by heating in toluene at reflux temperature (66%); (d) hydrolysis of the ester group with LiOH/THF/H_2O (100%); (e) decarboxylation by heating at 230°C in quinoline in the presence of copper (72%).
12. The spectroscopic data for the meridianins C–E were identical to those reported[3] for the natural products.