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Studies toward the total synthesis of the variolins: rapid entry to the core structure

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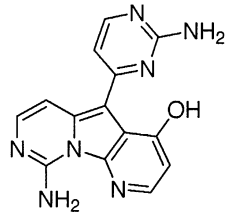
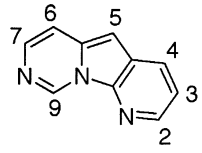
Abstract—The pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core structure of the variolins has been synthesized in three steps from commercially available materials. The key reaction involves the deoxygenation and concomitant cyclization of a triarylmethanol using the combination of triethylsilane and trifluoroacetic acid. Introduction of amine functionality as required for the natural products has been achieved in two steps.

The variolins are a new class of marine alkaloids isolated from the rare, difficult to access Antarctic sponge *Kirkpatricka varialosa*, with variolin B being a typical example.[1] All of the variolins contain a fused pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core **1**, with either a heterocyclic or ester group attached at the 5-position. The variolins display interesting biological activity, but further investigation has been hampered by the limited availability of natural material.



Variolin B



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While there has been no report to date on the total synthesis of the variolins, Alvarez and co-workers have published two reports[2] on the synthesis of bicyclic fragments of the variolin tricyclic core. More recently, a nine-step synthesis of 9-amino-7-ethoxycarbonyl-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine has been reported by the group of Fresneda and Molina.[3] This work has prompted us to report our efforts towards the synthesis of the variolin core structure and in this paper we present a short route to the 5-substituted core skeleton of the variolins.[4]

Our retrosynthetic strategy for the 5-substituted core structure **2** is outlined in Fig. 1. The extreme polarity of the variolins makes them difficult to handle so thiomethyl substituents have been used as synthetic equivalents for the amino groups.[5] Triarylmethane **4** should be obtained upon deoxygenation of the tertiary alcohol **5**, which in turn should be readily available from the reaction of the lithio species **6** with acid chloride **7**. The synthesis of the deoxy system **2** (R = H) was investigated initially as the starting material required, 2-chloronicotinoyl chloride (**7**, R = H), is commercially available.

The synthesis of triarylmethanol **5** (R = H) is detailed in Scheme 1.[†] As the lithiation of commercially available 4-chloro-2-thiomethylpyrimidine **8** is reported to be a difficult process, the chloride was converted to the iodide **9** by the literature method in 80% yield.[6] Addition of a pre-cooled (−95°C) solution of **7** (R = H) in THF to 3 equiv. of the lithio species **6**, generated by iodine-lithium exchange using *n*-butyllithium in THF at −95°C, gave the triarylmethanol **5** (R = H) in 52% yield.

Efficient functionalization of the tertiary alcohol proved difficult, which meant that attempts to deoxygenate the triarylmethanol **5** (R = H) using such methodologies were unproductive. Numerous methods were investigated for the direct conversion of the tertiary alcohol to the triarylmethane, but these resulted in either no reaction occurring or complete destruction of

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† All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectrometry. Yields are for isolated, chromatographically purified products.

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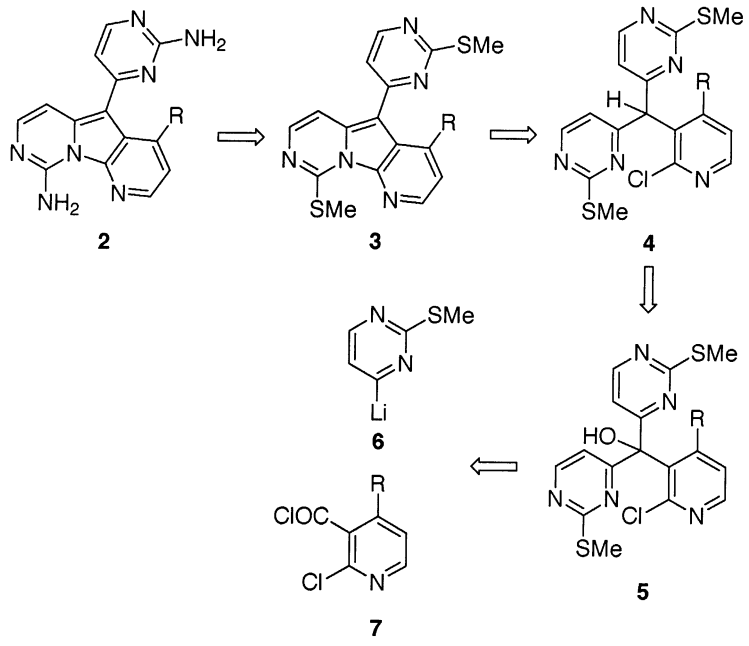


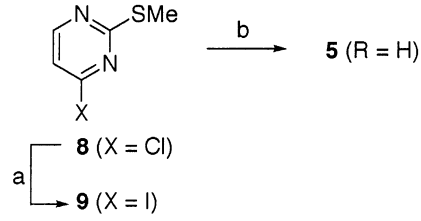
Figure 1. Retrosynthetic analysis of 5-substituted core **2** .

the starting material.[7] However, ionic hydrogenation of triarylmethanol **5** (R = H) with 1.2 equiv. of triethylsilane in trifluoroacetic acid (TFA) at reflux led to complete consumption of starting material and the generation of several products.[8] While examination of the crude material by ^{1}H NMR spectroscopy indicated that the desired triarylmethane **4** (R = H) was not present, we were encouraged to find that one of the reaction products had the desired core structure **3** (R = H).[9] It would appear that upon deoxygenation, triarylmethane **4** (R = H) is readily cyclized under the reaction conditions to afford the fused pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine skeleton.

Other products from the triethylsilane/TFA reaction have been identified and are shown in Fig. 2. These products had not been deoxygenated, which leads to the conclusion that they were the result of rearrangements, most likely triggered by TFA. Indeed, when triarylmethanol **5** (R = H) was refluxed in neat TFA, compounds **10**, **11**, and **12** were formed in the ratio of 14:1:4.

The propensity of triarylmethanol **5** (R = H) to rearrange in acid made it difficult to optimize the formation of **3** (R = H). However, decreasing the amount of TFA present in the reaction mixture had a significant effect on the yield of the core structure **3** (R = H), as summarized in Table 1. Any further reduction in the quantity of TFA used beyond that in entry 4 of the Table 1 did not lead to further improvement in the yield.

Preliminary investigations into the conversion of the thiomethyl groups into amines were undertaken so as to ensure that they were appropriate synthetic equivalents. This is commonly achieved by the oxidation of the thiomethyl group to either the sulfoxide or sulfone, followed by displacement with an amine.[5] Indeed, when



Scheme 1. (a) 55% HI solution, 48 h, 80%; (b) *n*-BuLi, THF, −95°C, 30 min then **7** (R = H), −95°C, 3.5 h, 52%.

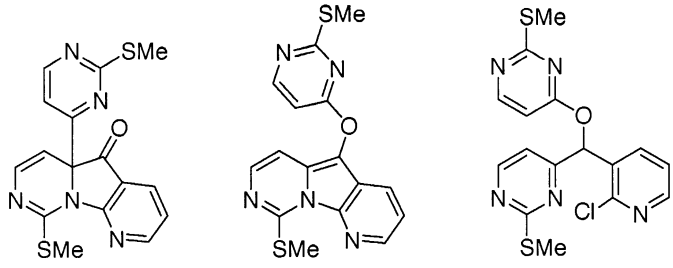


Figure 2. Side-products from Et_3SiH/TFA reaction with **5** (R = H).

core structure **3** (R = H) was treated with *meta*-chloroperbenzoic acid and the resulting material heated at 85°C in neat 4-methoxybenzylamine, the desired diamine **13** was obtained in 55% yield for the two steps.[10]

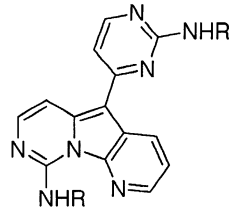


Table 1. Optimization of the reaction conditions for the synthesis of **3** (R = H)[a]

Entry	Equivalents of Et_3SiH	Equivalents of TFA	Yield of **3** (R = H)
1	2.0	8.3	15
2	4.0	8.2	18
3	8.0	8.2	22
4	8.1	4.3	34
5	7.8	2.0	33

[a] Reactions were performed at reflux under an atmosphere of argon using 1.3 mmol of **5** (R = H). All yields refer to isolated pure products.

In conclusion, the synthesis of the 5-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine skeleton of the variolins has been completed in only three steps, starting from commercially available materials. The key step in the synthesis was the one-pot deoxygenation/cyclization of triarylmethanol **5** (R = H). Introduction of amine functionality as required for the natural products has been achieved using an oxidation/substitution procedure. Efforts are currently focussed on adapting this strategy so that the total synthesis of the variolins can be completed.

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3. Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777–4780.
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6. Majeed, A. J.; Antonsen, Ø.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993–1006.
7. Some of the reagent systems investigated include $Me_3SiCl/NaI/MeCN, NaCNBH_3/ZnI_2, Pd–C/AlCl_3$/cyclohexene, $P/I_2/HI$, $H_2/Pd–C$, $LiAlH_4/AlCl_3$, $NaBH_4$/TFA, and H_2/Adams' catalyst/TFA.
8. For a review of ionic hydrogenation see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651.
9. Selected spectroscopic data for compound **3** (R = H): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H), 2.73 (s, 3H), 7.34 (d, $J = 5.4$ Hz, 1H), 7.51 (dd, $J = 4.6$, 8.1 Hz, 1H), 7.82 (d, $J = 6.3$ Hz, 1H), 8.06 (d, $J = 6.3$ Hz, 1H), 8.51 (d, $J = 5.4$ Hz, 1H), 8.60 (dd, $J = 1.7$, 4.6 Hz, 1H), 8.64 (dd, $J = 1.7$, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.9, 101.5, 108.4, 113.0, 120.8, 120.9, 128.1, 137.6, 140.0, 141.9, 143.1, 155.2, 156.7, 161.0, 172.5; HRMS: calcd for $C_{16}H_{13}N_5^{32}S_2$ (M^+) 339.0612, found 339.0617.
10. Selected spectroscopic data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.81 (s, 3H), 4.69 (d, $J = 5.9$ Hz, 2H), 4.89 (d, $J = 5.4$ Hz, 2H), 5.52 (br, exchangeable, 1H), 6.89–6.93 (m, 4H), 6.98 (d, $J = 5.4$ Hz, 1H), 7.33–7.42 (m, 6H), 7.63 (d, $J = 6.8$ Hz, 1H), 8.27 (dd, $J = 1.0$, 5.2 Hz, 1H), 8.31 (d, $J = 5.4$ Hz, 1H), 8.56 (br d, $J = 7.8$ Hz, 1H), 10.36 (br t, non-exchangeable, $J = 5.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3, 45.1, 55.3 ($2\times CH_3$), 100.6, 101.5, 107.9, 113.9, 114.0, 120.0, 121.9, 128.4, 128.6, 128.8, 130.3, 131.4, 138.4, 139.5, 143.0, 143.4, 149.0, 157.4, 158.7, 158.9, 162.1, 162.2; HRMS: calcd for $C_{30}H_{27}N_7O_2$ (M^+) 517.2226, found 517.2242.