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Synthesis of variolin B

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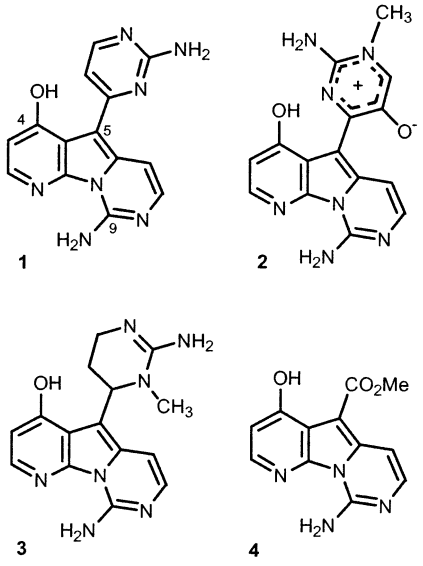
Abstract—The total synthesis of variolin B from 4-methoxy-7-azaindole is described. The preparation of the protected amino derivative **10** and a coupling reaction of the iodo derivative **12** with 2-acetylamino-4-trimethylstannylpyrimidine are the key steps of the sequence. The use of *N*-tosyldichloromethanimine for the cyclisation step afforded a good entry to the 9-aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system. Variolin B was obtained from the triply protected tetracyclic compound **13** in two steps.

Variolins **1**–**4** comprise a group of marine heterocyclic substances isolated from the Antarctic sponge *Kirkpatrickia variolosa*[1,2] They have a common tricyclic skeleton, which has no precedents in either terrestrial or marine natural products, a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, substituted at position 5. Pharmacological evaluation of these compounds showed important antiviral and antiproliferative activity against P388 leukaemia cells.[1,2] Variolin B (**1**) is the most active of the family, oxidation or reduction of the isolated D ring as in variolin A (**2**) or *N*-3′-methyl-3′,4′,5′,6′-tetrahydrovariolin B (**3**) reduces the activity. The importance of the aminopyrimidine ring at C5 of the above mentioned tricyclic system is corroborated by the lack of activity of variolin D (**4**).



Two total syntheses of variolin B,[3,4] and two syntheses of deoxyvariolin B,[5,6] as well as several methods[7–9] for the construction of the common tricyclic skeleton of these compounds have been reported. Our synthetic approach for the preparation of deoxyvariolin B[6] started from 7-azaindole and had two key steps: the introduction of the amino substituent of 9-aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine from a precursor pyrimidone by nucleophilic substitution of its *O*-silyl derivative with ammonia under strong conditions of temperature and pressure. Secondly, a Stille coupling of a tricyclic iodo derivative with a 4-trimethylstannyl-2-methylthiopyrimidine allowed introduction of the 5-substituent; subsequent oxidation of methylthio group followed by displacement with ammonia gave deoxyvariolin B.

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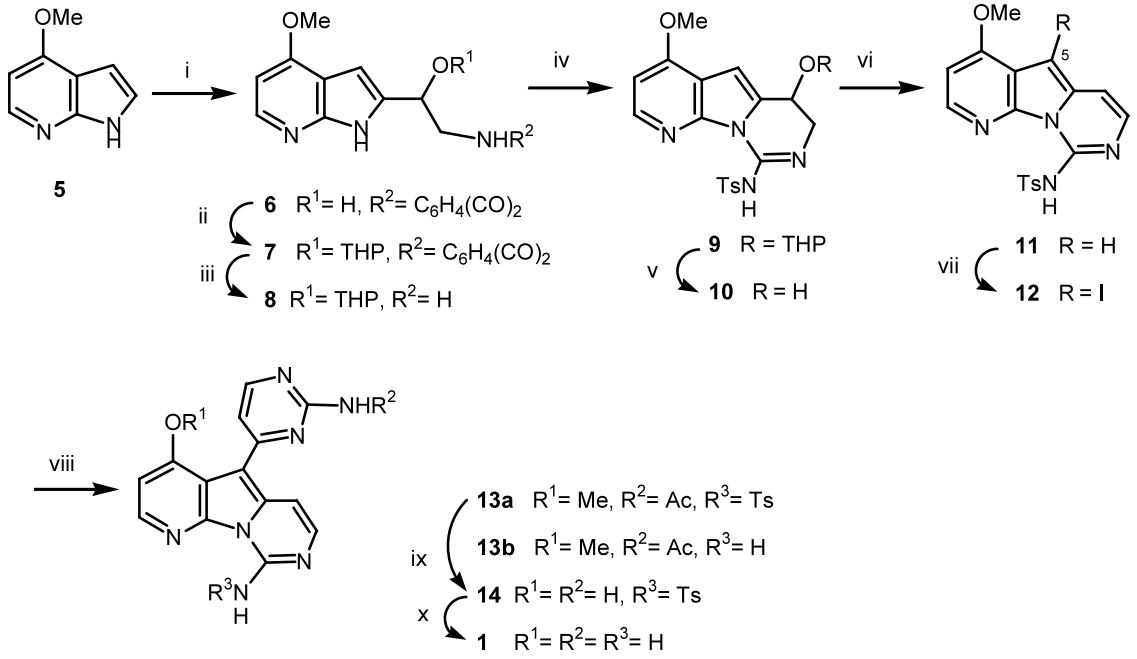
In this paper we describe a total synthesis of variolin B itself starting from 4-methoxy-7-azaindole.[10] The route used for the preparation of deoxyvariolin B[6] has been improved in this work with important changes in the above mentioned two key steps. The first change was in the reagent used for the formation of the tricyclic system, now with concomitant introduction of a protected amino group. This avoids pyrimidone formation and the need for a functional group transformation and hence a reduction in the number of synthetic steps. Secondly, the use of 2-acetylamino-4-trimethylstannylpyrimidine, not previously described, for the coupling reaction created a more convergent process avoiding two functional group interchanges at the end of the sequence.

4-Methoxy-7-azaindole was transformed into alcohol **6** by formation of a 2-lithio-7-azaindole followed by condensation with 2-phthalimidoacetaldehyde.[11] A lithium-carboxylate was used as *N*-protecting and *ortho*-directing substituent for the preparation of the 2-lithio-7-azaindole as described by Katritzky for indole 2-lithiation.[12] Protection of alcohol **6** by reaction with dihydropyran and deprotection of the amino group by hydrazinolysis gave the amino-acetal **8** as a mixture of diastereomers. This mixture was used without separation in the cyclisation reaction outlined in Scheme 1.

We tested several *N*-substituted *C*,*C*-dichloro methanimines for the cyclisation of **8**, namely *N*-dichloroacetyl-, *N*-trityl- and *N*-tosyldichloro methanimines.[13] Only the *N*-tosyl-substituted dichloro methanimine (Cl_2C=NTs) was suitable for the synthetic sequence.

Reaction of amine **8** with the Cl_2C=NTs using diisopropylethylamine (DIPEA) as a base in DCM gave the tricyclic compound **9** as a diastereomeric mixture in a ratio of 1:1. The two singlets at 6.67 and 6.69 ppm for the proton at C5 were the most characteristic signals for assigning this ratio.[14] This cyclisation procedure avoids the strong conditions used for the introduction of the 9-amino group in our previous deoxyvariolin synthesis[6] and also more importantly avoided any possibility that the methoxy group might be substituted by amino as an undesirable side reaction. Removal of the *O*-THP protecting group of **9** by refluxing in 4N HCl gave the alcohol **10** characterised by its strong absorption at 3315 cm^{-1} and the presence of a singlet at 6.52 ppm for its C5 proton. The NH signals from **9** and **10** were broad which may indicate mixtures of tautomers, i.e. those shown as 9/10 and others in which the hydrogen resides on the endocyclic nitrogen. Elimination of the hydroxy group of **10** by formation of its mesylate and treatment with triethylamine (TEA) afforded the pyridopyrrolopyrimidine **11**. The ^1H NMR spectrum of **11** was characterised by the two singlets at 2.35 and 4.02 ppm for the *C*-methyl and *O*-methyl groups, the singlet for the proton at C5 at 6.57 ppm, and the three AB systems of the aromatic protons.[15]

Other alternatives to *N*-tosyl protection were tried. Thus, an *N*-dichloroacetyl protected, cyclised compound analogous to **9** was prepared (25%) by reaction with Cl_2C=NCOCHCl$_2$. However, it was not possible to bring about the necessary selective *O*-deprotection of the pyranyl group. Furthermore, an *N*-trityl protected, cyclised compound analogous to **9** was also prepared



Scheme 1. *Reagents and conditions*: (i) (a) *n*-BuLi, THF, −78°C; (b) CO_2, −78°C; (c) *t*-BuLi, THF, −78°C; (d) 2-phthalimidoacetaldehyde, THF, −78°C to rt (43%); (ii) DHP, HCl, benzene, $CHCl_3$, Δ (63%); (iii) $NH_2NH_2{\cdot}H_2O$, EtOH, Δ (quant.); (iv) TsN=C(Cl)$_2$, DIPEA, DCM (65%); (v) 4N HCl, DCM, rt (95%); (vi) MsCl, TEA, DCM, rt (71%); (vii) NIS, DCM, −30°C (95%); (viii) 2-acetylamino-4-trimethylstannylpyrimidine, $Pd_2(dba)_3$, PPh_3, LiCl, CuI, dioxane, Δ (75%); (ix) aq. HBr, Δ (60%); (x) h*v*, *p*-(OMe)$_2C_6H_4$, $NH_2NH_2{\cdot}H_2O$, MeOH (30%).

(45%) by reaction with $Cl_2C{=}NCPh_3$. Although selective deprotection of the alcohol was possible, the subsequent elimination of water was not possible under the several different reaction conditions applied. We speculate that the failure of that elimination process was probably due to the less acidic character of the proton at C7 as a consequence of the presence of the trityl substituent.

Regioselective iodination of **11** proceeded at C5, giving **12**, as was expected taking into account the differing reactivity of the three heterocyclic rings. A palladium-catalysed coupling reaction between **12** and 2-acetylamino-4-trimethylstannylpyrimidine afforded compound **13a**,[16] variolin B in heavily protected form.

2-Acetylamino-4-trimethylstannylpyrimidine was prepared in an 80% yield by stannylation of 2-acetylamino-4-chloropyrimidine using hexamethylditin, $Pd(PPh_3)_4$ as catalyst, and dioxane as a solvent at reflux temperature.[17]

Simultaneous deprotection of the methoxy and 3′*N*-acetyl groups was achieved by treatment of **13a** with an aqueous solution of hydrobromic acid at reflux for 10 min to give **14** in a 60% yield.[18]

The *N*-tosyl deprotection was a more difficult process. Treatment with aqueous HBr,[19] HBr and AcOH in phenol at reflux temperature,[20] aqueous HI, HF,[21] Mg and NH_4Cl in EtOH,[22] Red-Al in toluene at different temperatures,[23] NaOH in MeOH or DCM, Na in liquid ammonia,[24,25] Na in naphthalene,[26] all failed to bring about N9-tosyl deprotection of **13**. Finally, the tosyl group of **13a** was removed with Li–naphthalene in THF[27] but in only 3% yield—traces of **13b** were detected by HPLC-MS. A reductive photolysis of the tosyl group was possible using a high pressure Hg lamp with a Pyrex filter, $NaBH_4$ as a reducing agent and 1,4-dimethoxybenzene as an electron source.[28] This procedure allowed the removal of the tosyl group from **11** in a 64% yield. Finally, the preparation of variolin B **1** was completed, starting from **14**, using the reductive photolysis procedure with H_2NNH_2. H_2O as a reducing agent instead of $NaBH_4$, in a 30% yield.[29]

The described procedure constitutes a versatile route for the synthesis of variolin B and will be used for the preparation of analogues of the natural product. The coupling of iodo compound **12** with other organometallic derivatives will afford analogues of variolin B differing in ring D. Nucleophilic substitution of the methoxy group will give a series of compounds differing from the natural compound in the substituent at position 4 of the tricyclic system.

Acknowledgements

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14. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.18–1.82 (m, 6H, H3′, H4′, and H5′); 2.38 (s, 3H, Me); 3.40–3.60 (m, 2H, H6′); 3.64–3.80 (m, 2H, H-7); 3.97 (s, 3H, Me); 4.41 and 4.90 (2dd, $J=3.2$ and 3.4 Hz and 2.6 and 1.9 Hz, 1H, H2′); 4.90–5.05 (m, 1H, H6); 6.67 and 6.69 (2s, 1H, H5); 7.26 (d, $J=8.4$ Hz, 2H, Ts); 8.10 (d, $J=8.4$ Hz, 2H, Ts); 8.40 (d, $J=2.8$ Hz, 1H, H3); 8.42 (d, $J=2.8$ Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) 18.6, 19.3 (t); 21.6 (q); 25.2, 25.3 (t); 30.0, 30.2 (d); 43.3 and 44.9 (t); 55.6 (q); 61.9 and 62.3 (t); 62.7 and 63.5 (d); 95.5 and 96.4 (d); 101.3 and 101.4 (d); 102.9 (d); 111.9 (s); 126.2 (s); 126.4 (d); 129.2 (d); 129.3 (s); 132.2 (s); 142.5 (s); 147.6 and 150.0 (d); 159.7 (s).
15. ^1H NMR (CD_3OD, 300 MHz) δ 2.35 (s, 3H, Me); 4.02 (s, 3H, OMe); 6.57 (s, 1H, H5); 6.63 (d, $J=7.5$ Hz, 1H, H6); 6.94 (d, $J=6.0$ Hz, 1H, H3); 6.98 (d, $J=7.5$ Hz, 1H, H7); 7.29 (d, $J=8.1$ Hz, 2H, Ts); 8.01 (d, $J=8.1$ Hz, 2H, Ts); 8.30 (d, $J=6.0$ Hz, 1H, H2). ^{13}C NMR (DMSO-d_6, 75 MHz): 21.0 (q); 55.9 (q); 93.0 (d); 102.1 (d); 113.9 (s); 120.2 (d); 124.4 (d); 125.5 (s); 125.9 (d); 128.2 (s); 129.3 (d); 132.6 (s); 142.3 (s); 143.9 (s); 145.1 (d); 158.4 (s).
16. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, Me); 2.45 (s, 3H, Me); 4.05 (s, 3H, OMe); 6.92 (d, $J=5.2$ Hz, 1H, H3); 7.30 (d, $J=8.4$ Hz, 2H, Ts); 7.43 (d, $J=5.2$ Hz, 1H, H5′); 7.56 (d, $J=6.8$ Hz, 1H, H7); 7.95 (bs, 1H, H6); 8.13 (d, $J=8.4$ Hz, 2H, Ts); 8.32 (d, $J=5.2$ Hz, 1H, H6′); 8.49 (d, $J=5.2$ Hz, 1H, H2); 8.69 (bs, 1H, NH); 13.28 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) 21.9 (q); 25.3 (q); 56.2 (q); 93.9 (s); 94.1 (s); 102.5 (d, C3); 107.8 (d, C6); 117.3 (d, C5′); 129.0 (d, Ts); 129.5 (d, Ts); 136.3 (s); 136.5 (s); 140.1 (d, C7); 141.9 (s); 142.9 (d, C6′); 143.5 (s); 144.9 (s); 156.9 (d, 2); 158.5 (s); 160.4 (s); 162.0 (s).

17. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 9H, $SnMe_3$); 2.53 (s, 3H, Me); 7.13 (d, $J=4.8$ Hz, 1H, H5); 7.98 (bs, 1H, NH); 8.35 (d, $J=4.8$ Hz, 1H, H6); ^{13}C NMR ($CDCl_3$, 75 MHz) 9.5 (q, 3Me), 25.3 (q, Me), 124.4 (d, C5); 130.3 (q, C4); 154.7 (d, C6); 155.4 (s); 186.4 (s). MS (EI) m/z 300 ($^{120}SnM^{+}$, 1), 285 (^{120}SnM–Me, 34) 270 (^{120}SnM–2Me, 1), 255 (^{120}SnM–3Me, 6), 244 (^{120}SnM–3Me–Ac, 30), 136 (M–$SnMe_3$, 100).
18. ^{1}H NMR ($CDCl_3$–CD_3OD, 400 MHz) δ 2.40 (s, 3H, Me); 6.81 (d, $J=7.0$ Hz, 1H, H-6); 7.05–7.09 (m, 2H, H-3 and H-5′); 7.28 (d, $J=8.0$ Hz, 2H, Ts); 7.71 (d, $J=6.2$ Hz, 1H, H-6′); 8.03 (d, $J=8.0$ Hz, 2H, Ts); 8.09 (d, $J=7.0$ Hz, 1H, H-7); 8.29 (d, $J=5.6$ Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$–CD_3OD, 100 MHz) 20.1 (q); 101.8 (d, C3); 103.9 (s); 105.0 (s); 106.0 (d, C6); 110.1 (d, C5′); 123.5 (s); 128.0 (d, Ts); 128.9 (d, Ts); 129.3 (d, C7); 134.3 (d, C6′); 138.3 (s); 139.0 (s); 142.9 (s); 143.1 (s); 156.2 (s); 159.0 (s); 160.7 (d, C2).
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