Pergamon

Tetrahedron Letters 42 (2001) 315–317

TETRAHEDRON LETTERS

Synthesis of deoxyvariolin B

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Received 20 September 2000; accepted 30 October 2000

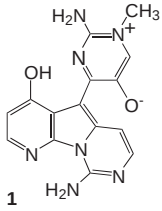
Abstract—A synthesis of deoxyvariolin B (**5**) is described. The tricyclic pyridopyrrolopyrimidone (**11**) was prepared from 7-azaindole via lithiation at C-2, introduction of an aminoethyl side-chain, then closure of the third ring. A heteroaryl palladium(0)-catalysed coupling reaction was used to introduce a pyrimidine substituent at C-5.

Variolin A (**1**), variolin B (**2**), variolin D (**3**) and *N*-3′-methyl-3′,4′,5′,6′-tetrahydrovariolin B (**4**) comprise a group of marine heterocyclic substances isolated from the Antarctic sponge *Kirkpatrickia varialosa* in 1994.[1,2] They have a common tricyclic skeleton, a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, which has no precedents in either terrestrial or marine natural products. There have been three previous reports[3–5] of the construction of this system. Two of these [4,5] describe different ways for the preparation of the core tricycle of the variolins, but in each case with an ester group at C-7; in neither study was an appropriate substituent introduced at C-5.

An important feature of these compounds is significant bioactivity:[1] variolin B is the most active, having cytotoxic activity against the P388 cell line, and also being effective against *Herpes simplex*; it was inactive against a range of other microorganisms. Variolin A also showed important cytotoxic activity against the P388 cell line. *N*-3′-Methyl-3′,4′,5′,6′-tetrahydrovariolin B inhibited the growth of *Sacharomyces cerevisiae* and showed in vitro activity against the HCT 116 cell line. Variolin D was inactive in all the assays. The differential activity of these alkaloids is believed to show the biological importance of the heterocyclic rings at C-5 in **1**, **2**, and **4**, as opposed to the 5-methoxycarbonyl substituent in variolin D **3**.

For the synthesis of deoxyvariolin B **5**, a pyridopyrrolopyrimidine tricycle **11** was constructed from 7-azaindole, with a subsequent palladium(0)-catalysed heteroaryl coupling of a 5-iodo derivative of **11** for the introduction of a pyrimidine as the 5-substituent.

The introduction of a protected aminoethyl chain at the 2-position of 7-azaindole[6] was achieved by reaction of a 2-lithio-derivative with 2-phthalimidoacetaldehyde **6**.[7] Although lithiation of 1-phenylsulfonyl-7-azaindole had previously been described,[8] we found that the method described by Katritzky[9] for indole 2-lithiation was also suitable for 7-azaindole, gave superior results, and additionally avoided *N*-protection and *N*-deprotection steps. Thus, 2-lithiation of 7-azaindole-1-carboxylic acid lithium salt, formed in situ, giving **7**, then reaction with aldehyde **6** afforded the alcohol **8** in 44% yield. Protection of the alcohol as a tetrahydropyranyl ether gave a diastereomeric mixture which was used without attempting separation (both stereogenic centres are lost later in the synthesis). Hydrazinolysis of the phthalimide protecting group yielded the amine **9** quantitatively, and this was converted into tetrahydropyrimi-



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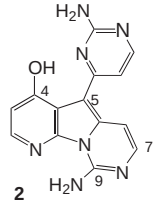

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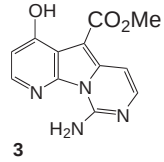

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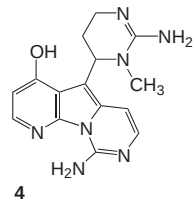

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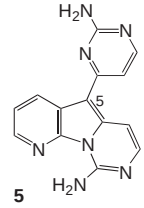

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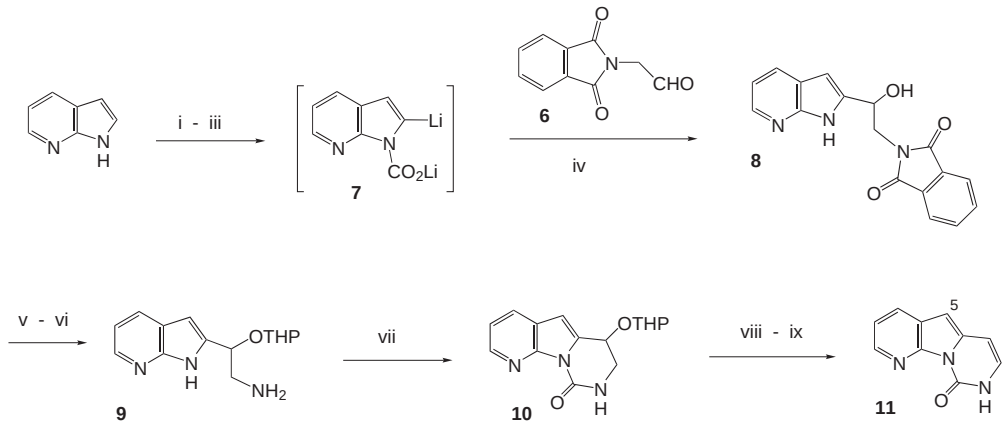
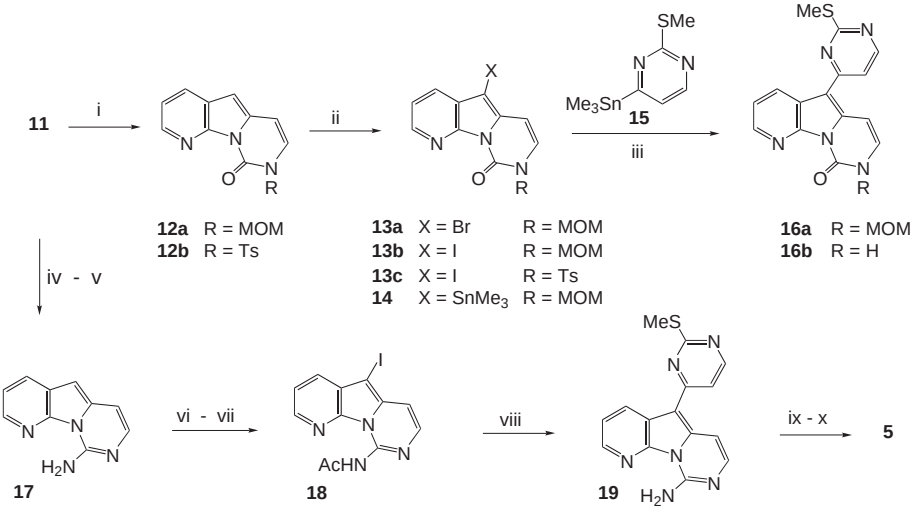


Scheme 1. *Reagents*: (i) *n*-BuLi, THF, −78°C to rt; (ii) CO_2, −78°C; (iii) *t*-BuLi, THF, −78°C; (iv) **6**, THF, −78°C to rt (44%); (v) DHP, HCl, benzene, $CHCl_3$, Δ (87%); (vi) $NH_2NH_2{\cdot}H_2O$, EtOH, Δ (100%); (vii) $(Cl_3CO)_2CO$, DIPEA, CH_2Cl_2, rt (76%); (viii) 4N HCl, CH_2Cl_2 (100%); (ix) MsCl, TEA, CH_2Cl_2, 0°C (95%).

done **10** in 76% yield on treatment with triphosgene in CH_2Cl_2 with diisopropyl ethylamine (DIPEA) as base. Removal of the protecting group then dehydration via the mesylate gave dihydropyrimidone **11**,[10] in six operational steps from 7-azaindole (Scheme 1). Ring closure to the azaindole nitrogen, and not to the azaindole C-3, was confirmed by the ^{1}H NMR spectrum of **11** which had a singlet signal at δ 6.60 for the 5-hydrogen.

Based on our previous results in heteroaryl couplings of 3-halo- and 3-tributylstannyl-7-azaindoles[11] and on the halogenation of dihydropyrrolo[1,2-*c*]pyrimidin-1-ones,[12] the preparation and coupling of a tin derivative such as **14** was envisaged as a means for the introduction of a pyrimidine substituent at the five-position. *N*-Protection of **11** was achieved with methyl chloromethyl ether or with tosyl chloride using sodium hydride as base giving **12a** and **12b**, respectively. Halogenation of **12a** using *N*-bromosuccinimide (NBS) or iodine afforded **13a** (80%) and **13b** (62%), respectively, and iodination of **12b** with *N*-iodosuccinimide (NIS) gave **13c** (80%). The regioselectivity of halogenation was confirmed by comparisons of ^{1}H NMR spectra: the H-5 singlets at δ 6.41 ppm and 6.48 ppm present in the spectra of **12a** and **12b** were absent in the spectra of **13a**, **13b**, and **13c**. Treatment of **13a** with *n*-butyllithium followed by quenching with trimethyltin chloride[11] gave a complex mixture which could not be resolved. Treatment of **13b** with hexamethylditin and $Pd(PPh_3)_4$ hoping for iodine–tin interchange afforded a mixture of **14** and **12a** in a ratio of 7:3, but isolation of **14** by column chromatography failed. Accordingly, the coupling of the iodide **13b** with the pyrimidinyl-stannane **15**[13] was attempted.



Scheme 2. *Reagents*: (i) MOMCl, NaH, DMF, 0°C (87%) or TsCl, NaH, DMF, rt (40%); (ii) **13a** NBS, CH_2Cl_2, 0°C (80%); **13b** I_2, DMF, NaOH, rt (62%); **13c** NIS, $CHCl_3$, rt (80%); (iii) $Pd_2(dba)_3$, PPh_3, LiCl, CuI, dioxane, Δ **15** (→**16b** 10%); (iv) TMSCl, HMDSA, 2,6-lutidine; (v) NH_3, 150°C, 60 psi (30% two steps); (vi) Ac_2O, THF, rt (75%); (vii) NIS, $CHCl_3$, rt (95%); (viii) (a) $Pd_2(dba)_3$, PPh_3, LiCl, CuI, dioxane, Δ **15**; (b) HCl, MeOH, Δ (45% two steps); (ix) MCPBA, CH_2Cl_2, 0°C (90%); (x) aq. NH_4OH, dioxane, 80°C (90%).

Coupling between **13b** and **15** under a variety of experimental conditions always gave a mixture of **12a** and **16a** which it was impossible to separate. The situation was only marginally improved using **13c** instead of **13b** for although the deprotected tetracycle **16b** was obtained, the yield was only 10%.

Since, in any case, the carbonyl group in **11** would at some stage need to be transformed into an amino group, this step was now undertaken. *O*-Silylation of **11** with TMSCl and hexamethyldisilazane (HMDSA), followed by nucleophilic substitution with ammonia[14,15] gave amine **17**. *N*-Acetylation followed by regioselective iodination of the pyrrole ring proceeded in excellent yield giving **18** (Scheme 2).

The coupling between **18** and **15** using a combination of $Pd_2(dba)_3$, PPh_3, LiCl, and CuI gave a mixture of the anticipated acetamide and its corresponding amine and so the product mixture was not separated but immediately converted wholly into the amine, by methanolysis with dry HCl in methanol, yielding the amine **19** in 45% yield for the two steps. Deoxyvariolin B **5**[16] was prepared by substitution of the methylthio group of the newly introduced pyrimidine ring for an amino group, thus *S*-oxidation using *m*-chloroperbenzoic acid (MCPBA) followed by substitution of the resulting sulfone for an amino group using ammonium hydroxide afforded **5** in excellent yield.[17]

The flexible route to deoxyvariolin B **5** described here, will be applicable not only to the synthesis of variolin B itself, and the other variolins, with a 4-oxygenated-7-azaindole as starting point, but also to other analogues for the assessment of biological activities and the establishment of structure/activity relationships.

Acknowledgements

This work was supported by grants from the Ministerio de Educación y Cultura (PB97-0871 and 2FD97-0486) and the Comissionat per a Universitats i Recerca (Generalitat de Catalunya) (99-SGR00077 and 98XT-0049). The help rendered by Dr. J. L. Fernández Puentes, Dr. J. A. de la Fuente and Dra. M. D. García-Grávalos from the INSTITUTO BIOMAR S. A. is gratefully acknowledged.

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