Pergamon

Tetrahedron Letters 42 (2001) 8697–8699

TETRAHEDRON LETTERS

Total synthesis of variolin B

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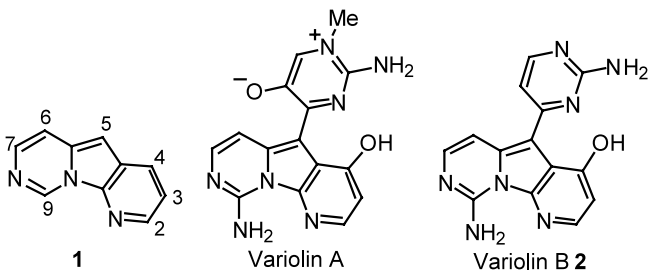
Received 28 August 2001; revised 25 September 2001; accepted 5 October 2001

Abstract—The total synthesis of the marine alkaloid variolin B has been achieved in eight steps, starting from commercially available 4-chloro-2-methylthiopyrimidine. The key reaction involves the tandem deoxygenation and cyclization of a triarylmethanol using a combination of triethylsilane and trifluoroacetic acid.

Marine organisms have provided a tremendous array of functionally diverse and biologically interesting structures.[1] In 1994, Blunt and Munro reported the structural elucidation of the variolins, a class of novel alkaloids isolated from the rare, difficult to access Antarctic sponge *Kirkpatricka varialosa*.[2,3] The variolins contain a fused pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core **1**, with either a heterocyclic aromatic ring or ester group attached at C5. Recently, variolin B (**2**) has attracted considerable interest as a synthetic target because of its potent anti-tumor activity, and because it is no longer possible to collect the original sponge source. A variety of strategies[4–7] have been developed to synthesize the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core of the variolins, with the majority of these syntheses employing conventional heterocyclic chemistry.



1 Variolin A Variolin B **2**

Our retrosynthetic strategy for variolin B **2** is outlined in Scheme 1, with the key compound being the core structure **3**, which contains the appropriate functionality to introduce the highly polar amines.[7] Examination of **3** reveals a hidden symmetry element, which leads to the disconnection indicated in Scheme 1. Our previous work[7] on the variolin core structure has indicated that **3** could be generated by a tandem deoxygenation/cyclization of triarylmethanol **4**. In this Letter, we present the successful application of this strategy to the first reported total synthesis of variolin B.

In our synthesis of the variolin core,[7] we prepared the necessary tertiary alcohol by reaction of 4-lithio-2-methylthiopyrimidine (**5**) with 2-chloronicotinoyl chloride. Adaptation of this strategy to the synthesis of triaryl alcohol **4** is detailed in Scheme 2. Acid chloride **6** was generated in 97% yield from the acid **7**[8] by reaction with oxalyl chloride. However, the addition of the lithio species **5**[9] to the acid chloride **6** proved to be a low yielding process, with the desired triaryl alcohol **4** being obtained in poor yields (5–15%). Extensive efforts to optimize this reaction were hampered by the instability of lithiated pyrimidine **5** above −95°C. The equivalent Grignard reagent is reported to be stable at 0°C,[10] but all attempts to react this reagent with acid chloride **6** failed to yield any trace of **4**. The unacceptably low yield of this reaction meant that an alternative approach to triaryl alcohol **4** had to be developed (Scheme 2).

Reaction of lithio species **5** with 0.5 equiv. of diethyl carbonate at −95°C gave the symmetric ketone **8** in 53% yield.† Addition of **8** to a solution of lithiated pyridine derivative **9**[11] in THF at −78°C resulted in the formation of the desired triaryl alcohol **4** in 76% yield.

With triaryl alcohol **4** available, attention could now be focused on the conversion of **4** into the core structure **3** using our tandem deoxygenation/cyclization protocol.[7]

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† Yields are for purified compounds. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.

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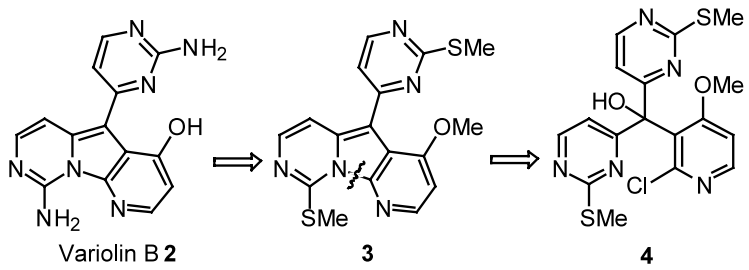
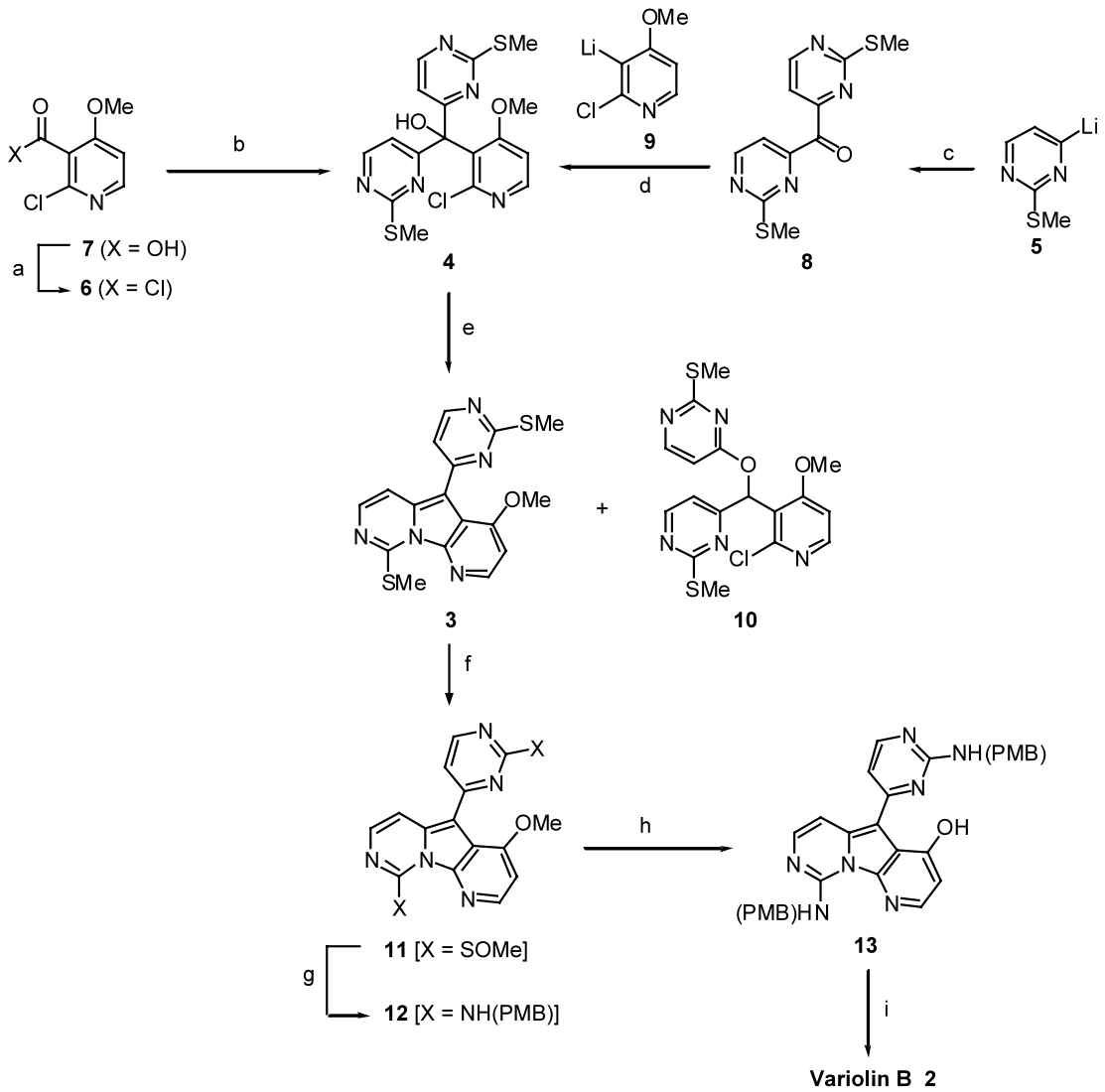
PII: S0040-4039(01)01881-0



Scheme 1. Retrosynthetic strategy for the synthesis of **2**.



Scheme 2. (a) $(COCl)_2$/cat. DMF/CH_2Cl_2 (97%); (b) 3 equiv. **5**/THF/−95°C (5–15%); (c) 0.5 equiv. $(EtO)_2CO$/THF/−95°C–rt (53%); (d) THF/−78°C (76%); (e) 8 equiv. Et_3SiH/2 equiv. TFA/1,2-dichloroethane/100°C (47%); (f) 2 equiv. *m*-CPBA/$CHCl_3$/−35°C; (g) 10 equiv. *p*-methoxybenzylamine/85°C (78% from **3**); (h) 10 equiv. NaSEt/DMF/55°C (95%); (i) TfOH/rt [PMB = *p*-methoxybenzyl].

Reaction of **4** under our previously reported conditions [8 equiv. triethylsilane (TES) and 4 equiv. trifluoroacetic acid (TFA)/70°C] afforded the desired core structure **3** in a disappointing 10% yield. The major product from this reaction was ether **10** (54% yield), which may arise from attack of the hydroxyl group onto one of the pyrimidine rings and subsequent C–C bond cleavage. Careful optimization of this reaction established that the best conditions involved carrying out the reaction in a sealed tube at 100°C with 8

equiv. of TES and 2 equiv. of TFA, with 1,2-dichloroethane as solvent. With these adjustments, **3** was isolated in a much improved 47% yield.

Oxidation of **3** with 2 equiv. of *m*-chloroperbenzoic acid in chloroform at −35°C proceeded smoothly to give the disulfoxide **11**, which was heated in the presence of *p*-methoxybenzylamine at 85°C to give the bisprotected-amine **12** in 78% yield for the two steps, starting from **3**. To remove the methoxy protecting group, **12** was treated with an excess of sodium ethanethiolate in dry DMF at 55°C for 7 h to give the pyridinol **13** in 95% yield.

Finally, the *p*-methoxybenzyl protecting groups on the amines were quantitatively removed by stirring **13** in neat triflic acid at room temperature. After neutralization with aqueous ammonia solution, the crude material was purified using reverse-phase silica flash chromatography (eluting with 70% methanol/water with 0.5% TFA added) to give variolin B **2** as the conveniently handled trifluoroacetate salt.[2] To obtain the sparingly soluble free base, the salt was neutralized with concentrated ammonia solution to give material that was identical in all respects with the natural product.

In summary, the first total synthesis of variolin B has been completed in eight steps from commercially available materials. Highlights of our synthesis include the tandem deoxygenation/cyclization to form the core variolin skeleton and the straightforward functional group manipulation required to introduce the necessary functionality of variolin B. This synthetic strategy is readily amenable to the production of analogs and will provide material to allow further investigation of the biological properties.

Acknowledgements

We thank PharmaMar SA, Tres Cantos for financial assistance, Professors M. H. G. Munro and J. W. Blunt for their support of this work, Professors P. J. Steel and A. J. Phillips for helpful discussions and Mr. Bruce Clark for mass spectrometry experiments.

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