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Palladium-mediated C–N, C–C, and C–O functionalization of azolopyrimidines: a new total synthesis of variolin B

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Abstract

A new total synthesis of the alkaloid variolin B is achieved by a selective and sequential palladium-mediated functionalization of a trihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine. This intermediate is obtained by a new heterocyclization reaction between an appropriate bromomethyl azaindole and *N*-tosylmethyl dichloroformimide. The methodology may be effective for the synthesis of some analogs by substitution on the relatively unexplored C4 and C9 positions of the alkaloid.

Keywords: Variolin B; Total synthesis; Palladium-mediated C–N, C–C and C–O; Pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine; *N*-tosylmethyl dichloroformimide

Variolin B is a member of a family of marine alkaloids isolated from an extremely rare Antarctic sponge, *Kirkpatrickia varialosa*.[1] The potent antitumoral activity found for variolin B and some analogs and the fact that the natural compound is no longer available from its natural source have led to several groups to develop the total syntheses of the natural alkaloid.[1,2] From the three reported total syntheses, those of Molina[3] and Alvarez[4] used a similar strategy to build up the tricyclic heterocyclic core, with the pyrimidine ring being constructed by an annelation method on the 7-azaindole system. In the strategy described by Morris[5] the tricyclic system is formed from pre-existent pyridine and pyrimidine rings using the possibilities offered by a highly symmetrical key intermediate.

Regarding the functionality present in the alkaloid, the three total syntheses incorporate the oxygen substituent on the pyridine ring in some of the starting compounds. However, the amino functionality at C9 is introduced in relatively early stages in the approaches of Molina and Alvarez, but in the Morris synthesis this group is incorporated in an advanced intermediate. The pyrimidine substituent at C5 is the last substituent to be introduced in both the Alvarez and the Molina routes—albeit using different strategies—while in the Morris approach this heterocyclic substituent can be viewed as a starting material.

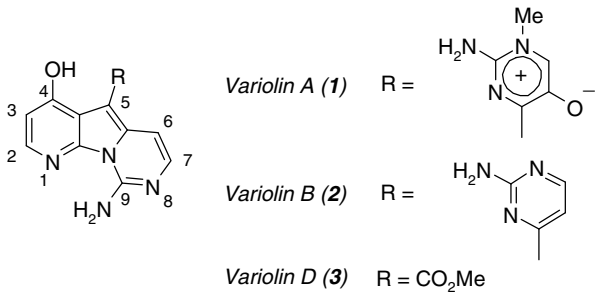

Fig. 1. Structure of the variolin alkaloid family.

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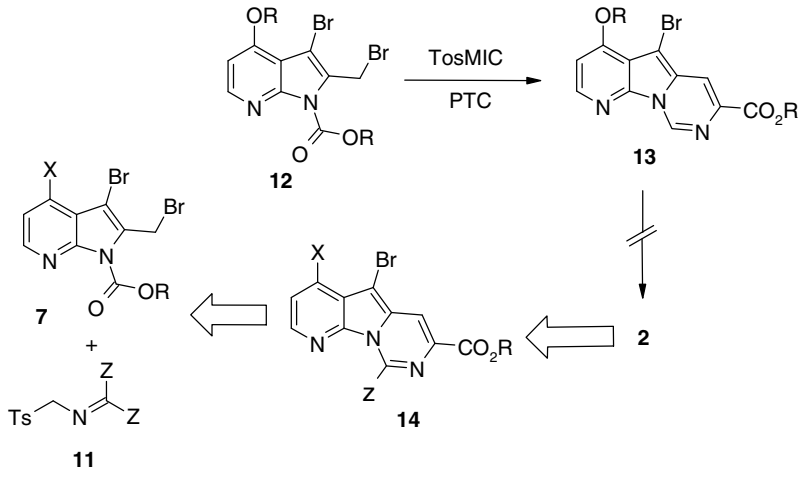
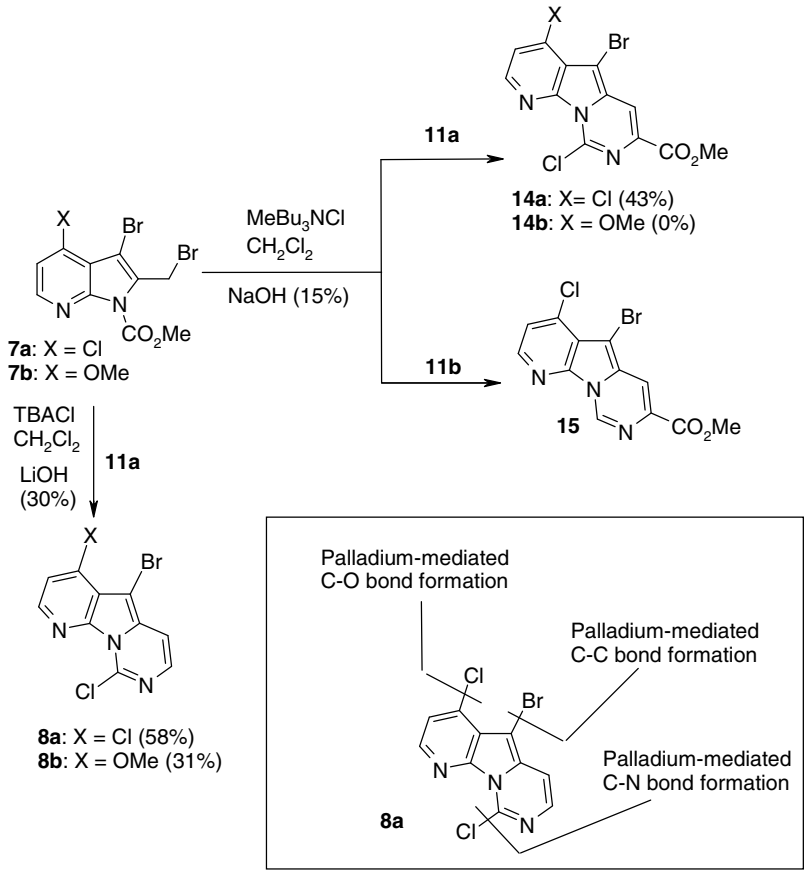


Scheme 1. Approach and retrosynthesis for variolin B.

However, the reported methods employed in the synthesis of this nucleus scarcely explored the introduction of chemical diversity at C4 position (oxygen functionality),[2c,d] with the Morris synthesis having the best potential to introduce alkyl- and aryl-amino substituents at C9 and the Alvarez synthesis for aryls and heteroaryls at C5 (Fig. 1).

In this Letter we wish to disclose a conceptually different approach to variolin B that is based on the synthesis of a trihalo-substituted pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine (heterocyclic core of variolins). This makes the approach well suited not only for the synthesis of this alkaloid but also for the eventual structural modification of the natural product using sequential palladium-mediated C–N, C–C, and C–O coupling reactions for the installation of key-structural substituents.

Our initial strategy for the synthesis of the heterocyclic core of variolin B was based on an unprecedented reaction between a protected 4-alkoxy-3-bromo-2-bromomethyl-7-



Scheme 2. Synthesis of the trihalo-functionalized pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **8a**.

azaindole **12** and tosylmethylisocyanide (TosMIC) under phase transfer conditions.[6] This allowed the efficient preparation of the appropriately substituted pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine carboxylate[7] (Scheme 1).

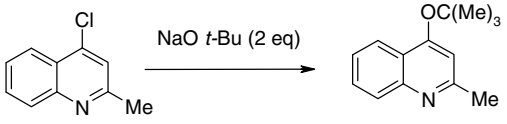
However, from the resulting intermediate **13** the total synthesis of variolin B could not be achieved because all attempts to carry out the amination at the C9 position failed.

We envisaged that this strategy for building up the tricyclic system might serve for variolin synthesis if we were able to find a reagent suitable for the heterocyclization reaction leading to the pyrimidine nucleus and for the incorporation of some functionality at C9 that could be transformed into the amino group. As this intermediate should have the general structure **14**, our reagents of choice were tosylmethylimines **11** with the structure represented in Scheme 1.

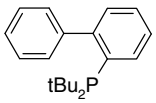
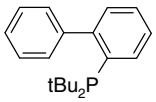
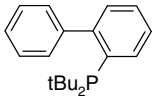
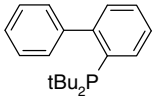
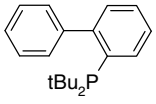
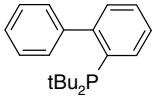
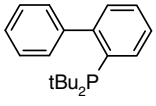
As noted above, our original strategy was to construct a trihalo-functionalized pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine that could be used for variolin B through sequential palladium-catalyzed coupling reactions. Thus, from the different possibilities for **11** (Z = Cl, Br, OMe, SMe) our choices were **11a** (Z = Cl) and **11b** (Z = Br). These *N*-tosylmethyl dihaloformimides were prepared on a multigram scale by improving the literature procedure[8] (see Supplementary data).

Two 4-substituted 3-bromo-2-bromomethylpyrrolo-[2,3-*b*]pyridin-1-yl methyl carboxylates (**7a**: X = Cl; **7b**: X = OMe)[7] were also chosen as starting azaindoles for the reaction with **11a,b**, as we envisaged that a methoxy group in the C4 position of the tricycle would prove very convenient for the synthetic strategy if variolin B were not feasible from **7a**.

Table 1
Optimization of the C–O coupling reaction on 2-methyl-4-chloroquinoline (**16**)



16 **17**

Entry	Catalyst	Phosphine	Conditions	**17** Yield (%)
1	—	—	Toluene, 110 °C	NR
2	$Pd_2(dba)_3$ (10%)	BINAP	Toluene, 110 °C	NR
3	$Pd_2(dba)_3$ (10%)		Toluene, 110 °C, 20 h	Traces
4	$Pd_2(dba)_3$ (10%)		Toluene, 150 °C, sealed vessel, 20 h	43
5	$Ni(cod)_2$ (10%)		Toluene, 150 °C, sealed vessel, 20 h	NR
6	$Pd_2(dba)_3$ (5%)		Toluene, 150 °C, MW, 150 W, 5 min	34
7	$Pd_2(dba)_3$ (5%)		Toluene/*t*-BuOH, 150 °C, MW, 150 W, 5 min	64
8	$Pd_2(dba)_3$ (5%)		Toluene/*t*-BuOH, 150 °C, MW, 300 W, 2 min	65
9	$Pd_2(dba)_3$ (5%)		MeCN, 150 °C, MW, 300 W, 2 min	13
10	$Pd_2(dba)_3$ (5%)	dppf	Toluene/*t*-BuOH, 150 °C, MW, 300 W, 2 min	12
11	$Pd_2(dba)_3$ (5%)	BINAP	Toluene/*t*-BuOH, 150 °C, MW, 300 W, 2 min	41

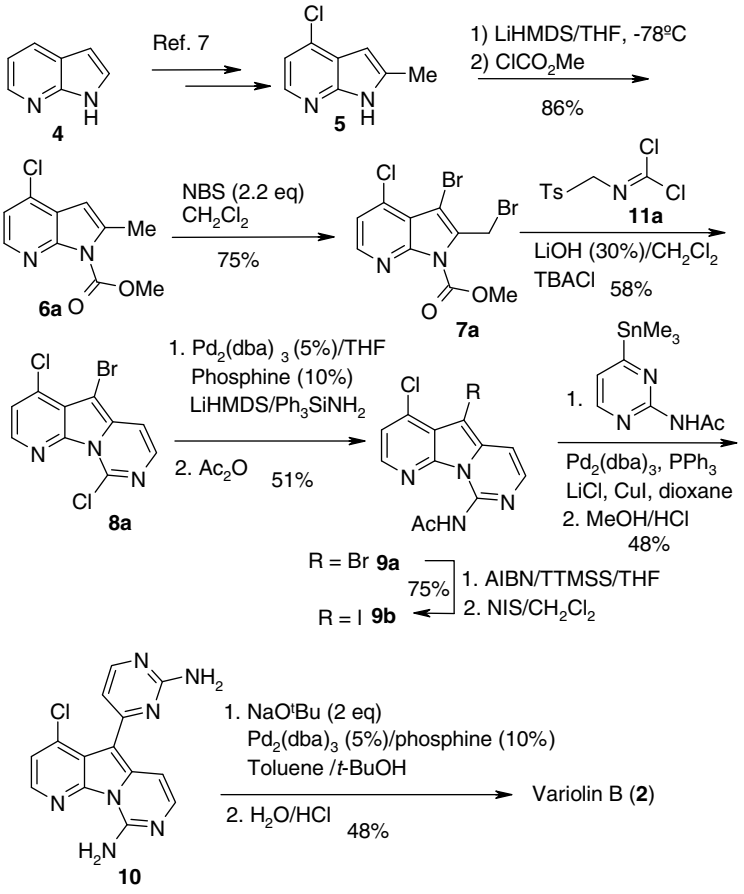
Initial results showed that the reaction of **7a,b** and **11a,b** failed under different homogeneous conditions [DBU/CH_2Cl_2, NEt_3/CH_2Cl_2, *i*-Pr_2NEt, 14% NaOH], and phase-transfer catalyst (PTC) conditions were necessary to obtain intermediate **14a** (X = Cl, Scheme 2). Moreover, *N*-tosylmethyl dibromoformimide **11b** was prone to lose bromine to regenerate TosMIC, which reacted with **7a** to give the previously described 5-bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-7-yl methyl carboxylate **15**.[7]

In the search for the optimal PTC conditions, a number of catalysts for the reaction of **7a,b** and **11a** were screened. In a precedent report,[9] it was found that compound **14a** was not formed on using higher concentrations of NaOH (30%) and the unexpected compound **8a** was isolated instead. This result was very convenient since it circumvents the need to remove the methoxycarbonyl group from **14a**. Therefore, we concentrated our efforts on finding a set of appropriate conditions to obtain **8a**, with the optimized conditions shown in Scheme 2. It is worth noting that, under the optimal conditions found for **8a**, pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **8b** (X = OMe) is obtained in only 31% yield (Scheme 2).

The completion of the synthesis of variolin B involved intermediate **8a**, from which the natural product might be obtained by three successive palladium-promoted cross-coupling reactions (Scheme 2). Functionalization in C5 and C9 using the palladium methodology was previously shown to be successful in this pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system.[4,9] As a result, the key step of this approach to variolin B was the formation of the C–O bond at the C4 position.

The C–O coupling reaction has rarely been used in heterocyclic chemistry, although several methods are known in which it has been applied to aryl halides using Ni or Pd as catalysts.[10] Thus, before attempting the C–O functionalization on **8a** we decided to test the feasibility of this unprecedented heterocyclic reaction on a commercially available 2-methyl-4-chloroquinoline model **16**. The reaction of **16** and sodium *tert*-butoxide (NaO*t*-Bu) was attempted in the presence of several catalysts and ligands at different temperatures. The results obtained are summarized in Table 1.

Initial experiments showed that in the absence of the palladium catalyst, the reaction failed (entry 1, Table 1) and only when the reaction was carried out in toluene in the presence of tris(dibenzylideneacetone) dipalladium (0) [$Pd_2(dba)_3$] at 150 °C in a sealed vessel for 20 h (entry 4) was **17** obtained in moderate yield (43%). Under similar conditions, catalyst bis(1,5-cyclooctadiene)nickel(0) [$Ni(cod)_2$] proved to be unsuccessful (entry 5). In order to find milder conditions that should be more appropriate for the variolin B synthesis, we attempted this coupling



Scheme 3. Total synthesis of variolin B.

reaction using microwave heating. The best results (65% yield) were obtained using a mixture of toluene/*t*-BuOH as solvent, $Pd_2(dba)_3$ (5 mol %) and (2-biphenyl)di-*t*-butylphosphine (10 mol %), with a reaction time of only 2 min at 300 W power (entry 8). Under these conditions, further experiments with other ligands and solvents failed to improve on this yield.

The overall synthesis of intermediate **8a** from 7-azaindole **4**, and its conversion into variolin B are shown in Scheme 3. The amination reaction at the C9 position was carried out with the system lithium bis(trimethylsilyl)amide/triphenylsilylamine ($LiHMDS/Ph_3SiNH_2$) as the ammonia source in the presence of $Pd_2(dba)_3$. This gave **9a** after protection of the amino group. According to previous reports for a related system,[4] the attempted C–C coupling reaction between **9a** and the appropriate *N*-(4-trimethylstannylpyrimidin-2-yl)acetamide did not give the expected coupling product **10** after a large number of experiments with different catalysts, ligands, and conditions-most of which resulted in the recovery of **9a** or its decomposition. To enhance the low reactivity of **9a**, it was transformed into the corresponding iodo-derivative by a debromination–iodination process to give **9b** in 75% yield. Fortunately, **9b** did react with the pyrimidyl stannyl compound to afford the expected coupling product **10**, after deprotection of both amino groups, albeit in moderate yield.[11] Finally, **10** was converted into variolin B by the introduction of the *t*-butoxy group in the C4 position using the same optimized conditions found for the C–O bond formation in **16** followed by the removal of the *t*-butyl protecting group under acid conditions.

In conclusion, we have developed a new convergent synthesis of variolin B starting from the commercially available 7-azaindole. From this, a trihalo pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine was obtained as the key intermediate by a new heterocyclization reaction between an appropriate bromomethyl azaindole and *N*-tosylmethyl dichloroformimide. From this intermediate, the natural product was obtained by three successive palladium-promoted cross-coupling reactions.

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Supplementary data

Experimental procedures and characterization data for compounds **5-11** and intermediates. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.063.

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11. Although the 3-iodo-2-methylpyrrolo[2,3-*b*]-pyridin-1-yl methyl carboxylate, an analogue of **6a** with iodo in C-3, could be prepared, all attempts to obtain the diiodo analogue of **7a** using NIS failed. Unexpectedly, the reaction of 3-iodo-2-methylpyrrolo[2,3-*b*]pyridin-1-yl methyl carboxylate with NBS afforded 3-bromo-2-bromomethylpyrrolo[2,3-*b*]pyridin-1-yl methyl carboxylate, likely by an *ipso*-substitution proccess in C-3 position.[12]
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