
Alejandro Baeza a, Javier Mendiola b, Carolina Burgos a,*, Julio Alvarez-Builla a, Juan J. Vaquero a, *

a Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain
b Centro de Investigación Lilly, Avenida de la Industria 30, 28108 Alcobendas, Madrid, Spain

Received 25 January 2008; revised 4 April 2008; accepted 9 April 2008
Available online 12 April 2008

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 Molina3 and Alvarez4 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 Morris5 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.
However, the reported methods employed in the synthesis of this nucleus scarcely explored the introduction of chemical diversity at C4 position (oxygen functionality), 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 1. Approach and retrosynthesis for variolin B.

azaindole 12 and tosylmethylisocyanide (TosMIC) under phase transfer conditions. 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 tosylmethyl-imines 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 multi-gram scale by improving the literature procedure (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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Phosphine</th>
<th>Conditions</th>
<th>17 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Toluene, 110 °C</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Pd2dba3 (10%)</td>
<td>BINAP</td>
<td>Toluene, 110 °C</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Pd2dba3 (10%)</td>
<td>tBu2P</td>
<td>Toluene, 110 °C, 20 h</td>
<td>Traces</td>
</tr>
<tr>
<td>4</td>
<td>Pd2dba3 (10%)</td>
<td>tBu2P</td>
<td>Toluene, 150 °C, sealed vessel, 20 h</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Ni(cod)2 (10%)</td>
<td>tBu2P</td>
<td>Toluene, 150 °C, sealed vessel, 20 h</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Pd2dba3 (5%)</td>
<td>tBu2P</td>
<td>Toluene, 150 °C, MW, 150 W, 5 min</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>Pd2dba3 (5%)</td>
<td>tBu2P</td>
<td>Toluene/t-BuOH, 150 °C, MW, 150 W, 5 min</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>Pd2dba3 (5%)</td>
<td>tBu2P</td>
<td>Toluene/t-BuOH, 150 °C, MW, 300 W, 2 min</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>Pd2dba3 (5%)</td>
<td>tBu2P</td>
<td>MeCN, 150 °C, MW, 300 W, 2 min</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Pd2dba3 (5%)</td>
<td>dpff</td>
<td>Toluene/t-BuOH, 150 °C, MW, 300 W, 2 min</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>Pd2dba3 (5%)</td>
<td>BINAP</td>
<td>Toluene/t-BuOH, 150 °C, MW, 300 W, 2 min</td>
<td>41</td>
</tr>
</tbody>
</table>
Initial results showed that the reaction of 7a,b and 11a,b failed under different homogeneous conditions [DBU/CH₂Cl₂, NEt₃/CH₂Cl₂, i-Pr₂NEt, 14% NaOH], and phase-transfer catalysis (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 15.²

In the search for the optimal PTC conditions, a number of catalysts for the reaction of 7a,b and 11a,b 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 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 (NaO₄-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) [Pd₂(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 reaction with a commercially available 2-methyl-4-chloroquinoline model 16 (Scheme 3).

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. 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. 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 (NaO₄-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) [Pd₂(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 reaction with a commercially available 2-methyl-4-chloroquinoline model 16 (Scheme 3).

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. 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. 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 (NaO₄-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) [Pd₂(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 reaction with a commercially available 2-methyl-4-chloroquinoline model 16 (Scheme 3).
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 (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/triphenylsilyleamine (LiHMDS/Ph$_3$SiNH$_2$) 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, 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. 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-buty 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.

Acknowledgments

The authors acknowledge financial support from the Spanish Ministerio de Educación y Ciencia (project CTQ2005/011060/BQU), Comunidad de Madrid (CAM), and Universidad de Alcalá (UAH) (project CCG-UAH/SAL-0660) and a grant from the Ministerio de Educación y Ciencia (A.B.).

Supplementary data


References and notes


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