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Application of Selective Palladium-Mediated Functionalization of the Pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine Heterocyclic System for the Total Synthesis of Variolin B and Deoxyvariolin B

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Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

Keywords: Cross-coupling / Total synthesis / Natural products / Heterocycles

The reaction of protected 3-bromo-2-(bromomethyl)-4-methoxypyrrolo[2,3-*b*]pyridine and tosylmethyl isocyanide (TosMIC) afforded a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine derivative in good yield. This compound was transformed through installation of the pyrimidine moiety in the C5 position, hydrolysis, and decarboxylation in an advanced intermediate for the total or formal synthesis of the natural alkaloid variolin B. Reaction of 3-bromo-2-(bromomethyl)-4-chloropyrrolo[2,3-*b*]pyridine with *N*-tosylmethyl dichloroformimide as a synthetic TosMIC equivalent afforded trihalosubstituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine. This compound was used in a new total synthesis of the alkaloid variolin B by selective and sequential C–N, C–C, and C–O palladium-mediated functionalization at the C9, C5, and C4 positions of the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system. A formal synthesis of deoxyvariolin B is also described by using the same synthetic strategy.

Introduction

In 1994, Munro and Blunt reported the isolation and structure of the variolins, a family of alkaloids isolated from the Antarctic sponge *Kirtpatrickia varialosa*[1] (**1**–**3**, Figure 1). In addition to being one of the rare examples of a natural product containing the pyrrolo[1,2-*c*]pyrimidine system [the other example is the alkaloid hinckdentine (**4**)[2] isolated from the bryozoan *Hincksinoflustra denticulata*[3]], it was claimed that variolins have antiproliferative activity against P388 murine leukemia cells.[1] An in vitro screening also showed variolin B to be highly active as an antiviral agent (*Herpes simplex* Type I, *polio* Type I).

Three total syntheses of variolin B have been reported to date. The first total synthesis was reported by Morris.[4] In this convergent synthesis the tricyclic system is formed from pre-existing pyridine and pyrimidine rings by using the possibilities offered by a highly symmetrical key intermediate. The two other total syntheses of variolin B were reported by Molina[5] and Alvarez,[6] respectively, and in these cases the tricyclic core was obtained in a linear route starting from 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine).

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

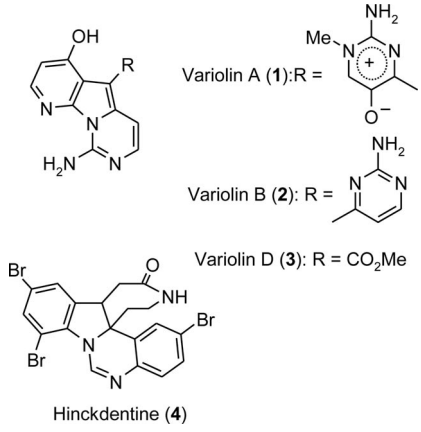

Figure 1. Structures of variolins and hinckdentine.

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In addition, some of these approaches have also been employed for the synthesis of deoxyvariolin B[7] and some variolin B derivatives and analogs in the search for compounds with improved cytotoxic activity.[8] In this context, the three reported methods employed in the synthesis of the core nucleus scarcely explored the introduction of chemical diversity at the C4 position (oxygen functionality), with the Morris synthesis having the best potential to introduce alkyl- and arylamino substituents at C9 and the Alvarez synthesis for aryls and heteroaryls at C5.

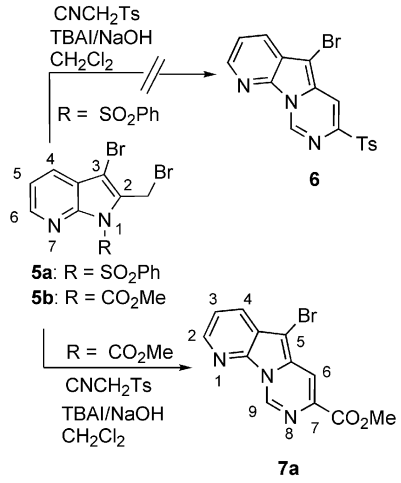
Our synthetic strategy for variolin B was based on our initial studies on azolopyrimidine syntheses,[9] which allowed the development of a new route for the construction of the heterocyclic core of variolins from an appropriately substituted 7-azaindole through its reaction with tosylmethyl isocyanide (TosMIC).[10] Herein we describe in detail our synthetic studies towards the synthesis of variolins, which have led to a conceptually different convergent approach to variolin B and deoxyvariolin B.[11] Our approach is well suited not only for the synthesis of the natural alkaloid but also for the eventual structural modification of the natural product by using sequential palladium-mediated C–N, C–C, and C–O coupling reactions for the installation of key structural substituents on a trihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, which is a key intermediate.

Results and Discussion

Our initial studies towards the synthesis of variolin B were started as an extension of the reaction of TosMIC with azole carboxaldehydes[9] to develop an easy and straightforward route to the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system, the core heterocycle of variolins. However, this initial approach was abandoned when it was found that the required starting azaindole was not able to produce the desired tricyclic system.[10b]

The failure of this initial strategy led us to examine the reaction of an *N*-protected 2-bromomethylazaindole and TosMIC under basic conditions on the assumption that the product of the nucleophilic substitution would be stable enough for further transformation into the corresponding pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine derivative after deprotection. Some attempts with *N*-phenylsulfonyl-protected 3-bromo-2-bromomethyl-7-azaindole **5a** (Scheme 1) were unsuccessful to obtain the desired tricyclic intermediate **6**.

The alternative protection of the azaindole derivative as the methyl carbamate afforded the *N*-protected bromomethyl compound **5b**. This derivative cleanly reacted with TosMIC under phase-transfer (PTC) conditions (TBAI/NaOH/CH_2Cl_2) to afford the unexpected methyl 5-bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylate (**7a**) in 65% yield. The mechanism proposed[10] to account for the formation of **7a** involves initial nucleophilic substitution of TosMIC on the bromomethylpyrrole followed by intramolecular transfer of the methoxycarbonyl protecting group. Subsequent attack of the pyrrole nitrogen



Scheme 1. Reaction of some *N*-protected 2-bromomethylazaindoles and TosMIC under basic conditions.

on the isocyanide group would lead to cyclization and 1,2-elimination of *p*-toluenesulfinic acid to afford **7a**. This unexpected result was clearly very convenient because our initial strategy to variolins could be easily adapted to achieve a key tricyclic intermediate (Figure 2) by the simple introduction of an oxygenated functionality at C4 in the starting azaindole. Thus, our retrosynthetic strategy to synthesize variolin B is shown in Figure 2.

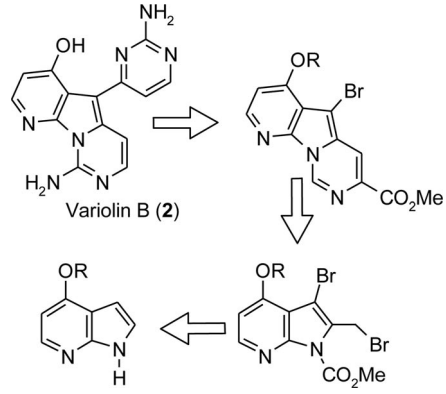
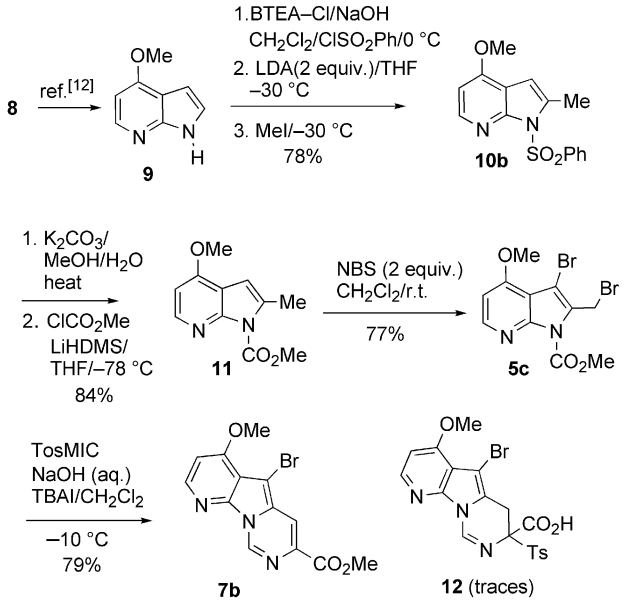


Figure 2. Retrosynthetic analysis for variolin B.

The total synthesis of **2** started from 7-azaindole (**8**; Scheme 2), which was transformed into 4-methoxy-7-azaindole (**9**) by following a literature procedure via 4-chloro-7-azaindole.[12] Subsequent steps to **5c** were a modified route regarding those optimized for the preparation of **5b** and began with the initial deprotection of **10b** and subsequent protection as the *N*-methoxycarbonyl carbamate to supply **11**.

The bromination of **11** in dichloromethane with the use of NBS (2 equiv.; optimized reactions conditions) gave **5c** in 77% yield. Azaindole derivative **5c** reacted with TosMIC in a two-phase system (NaOH/CH_2Cl_2) in the presence of TBAI as a phase-transfer catalyst to afford key tricyclic compound **7b** in an initial 61% yield, which was improved to 79% by conducting the reaction at low temperature



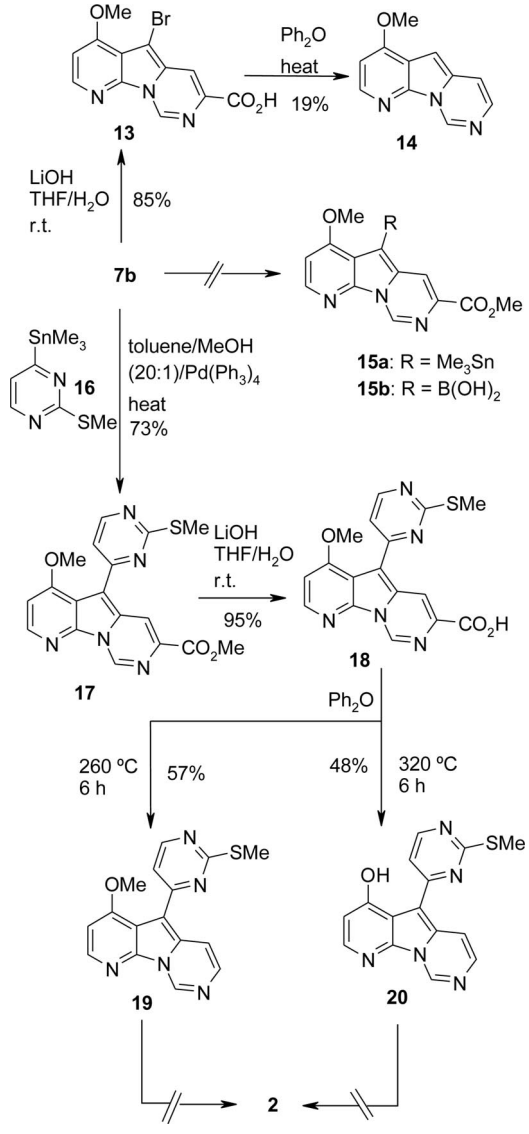
Scheme 2. Optimized synthesis of key tricyclic compound **7b** from azaindole **8**.

(–10 °C) and by only partial purification by column chromatography (the compound is extremely polar) for isolation of the product. It is noteworthy that in the course of our experiments to improve the initial yield we were able to detect compound **12**. The structure of this acid strongly supports the previously proposed mechanism to rationalize the formation of the tricyclic methoxycarbonyl esters from the bicyclic precursors.

Transformation of key intermediate **7b** into the natural alkaloid required the removal of the methoxycarbonyl group at C7, the functionalization of the pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine system at C9 and C5, and the deprotection of the oxygen functionality. Removal of the protecting and ester groups and the introduction of the pyrimidine moiety at C5 seemed feasible on the basis of published results and our own studies.[13] However, direct introduction of the amino substituent at C9 of a pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine was unprecedented.

Consequently, our efforts were focused on exploring the feasibility of the amination reaction on C9. Previous studies on model compounds[10b] showed that the C9 position can be selectively metalated but that the metalated intermediate was highly reactive, producing a mixture of dimeric compounds. This situation precluded the possibility of achieving appropriate functionalization of this position through a precursor with an amino group. It was also reported in same work that the ester group could be removed from the model compound by hydrolysis followed by thermal decarboxylation,[13] although small amounts of the debrominated compound were also formed. In this work, additional studies on similar models showed that some primary amines were able to produce a nucleophilic attack on both the ester group and the C9 position of the tricyclic derivatives. However, no satisfactory results were obtained in the presence of ammonia.

These and further studies on model compounds allowed us to prepare two advanced intermediates, **19** and **20**, by following the synthetic route shown in Scheme 3. Removal of the ester group in **7b** required hydrolysis of the methyl ester, which was attempted under different conditions. The best yield was obtained by using LiOH in aqueous THF. On the basis of our previous results, decarboxylation of highly insoluble acid **13** was achieved by prolonged heating in diphenyl ether, but under these conditions, debromination was also promoted and **14** was isolated as the major product. Other attempts to promote decarboxylation resulted in either no reaction (Cu/quinoline) or extensive decomposition (KOH/MeOH, NaOH/toluene). Adsorption of compound **13** on silica gel and heating under microwave irradiation led to recovery of unaltered starting material at low power and decomposition at high power or after prolonged irradiation times.



Scheme 3. Synthesis of advanced intermediates **19** and **20**.

We envisaged that if the pyrimidine ring was incorporated at C5 before decarboxylation, the desired compound should be obtainable without going through intermediate **13**. On the basis of this analysis, we attempted to transform **7b** into the corresponding 5-trialkylstannylderivative **15a** by treatment with *t*BuLi followed by chlorotrimethylstannane in the hope that the behavior of the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system would resemble that of 3-bromo-7-azaindoles, which were transformed into the corresponding stannanes by Alvarez and co-workers by using these standard conditions.[14] However, compound **7b** did not react and all attempts resulted in recovery of the starting material or formation of homocoupling products. Similar results were obtained on attempting to convert **7b** into the corresponding boronic acid derivative **15b** to be used as a partner in a Suzuki–Miyaura coupling.[15]

To achieve the biaryl connection between **7b** and the pyrimidine moieties we turned our attention to pyrimidinylstannane **16**, which was first reported by Undheim and coworkers[16] and later employed by the Alvarez group (65%) in the synthesis of deoxyvariolin B.[7] In our hands, **16** was prepared in 90% yield by simple slow addition of the stannane (Sn_2Me_6) to 4-iodo-2-methylthiopyrimidine. The coupling reaction between **7b** and **16** proceeded in acceptable yields (53%) when tetrakis(triphenylphosphane)palladium(0) was used as the catalyst in toluene. Under more polar conditions, the yield was improved and **17** was obtained in 73% yield, the optimum value, in a mixture of toluene/MeOH (20:1).

Coupled compound **17** was selectively hydrolyzed to acid **18** and subsequent decarboxylation in refluxing Ph_2O provided, as predicted, desired intermediate **19** or **20** in acceptable yields depending on the heating conditions. These intermediates could be used in a formal or in a new total of synthesis of variolin B. Unfortunately, extensive studies showed that neither **19** nor **20** could be transformed into a previously reported intermediate or the natural alkaloid because all attempts to incorporate the amino group in the C9 position failed.

In spite of the disappointing results obtained from these studies, we envisaged that the strategy for building the tricyclic system might still serve for the synthesis of variolin if we were able to find a reagent suitable for the heterocyclization reaction to give the pyrimidine nucleus and for the incorporation of some functionality at C9 that could be transformed into the amino group. Such an intermediate would have general structure **21**, and as a result, our reagents of choice were the TosMIC synthetic equivalent represented by tosylmethylimines **22**,[17] with the general structure represented in Figure 3. Thus, of the different possibilities for **22** (Y = Cl, Br, OMe, SMe) our choices were **22a** (Y = Cl) and **22b** (Y = Br), as any of these *N*-tosylmethyl dihaloformimides would enable a conceptually different approach to variolin B on the basis of the synthesis of a trihalo-substituted pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]-pyrimidine. This approach is well suited not only for the synthesis of this alkaloid but also for the eventual structural modification of the natural product by using sequential palladium-mediated C–N, C–C, and C–O coupling reactions for the installation of key structural substituents.

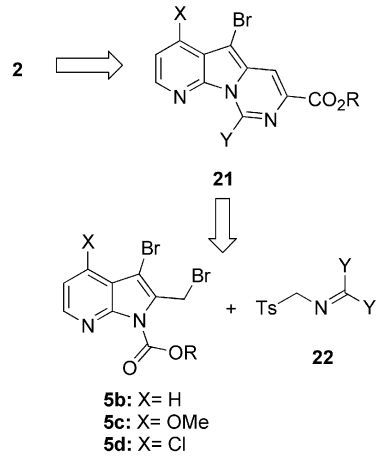
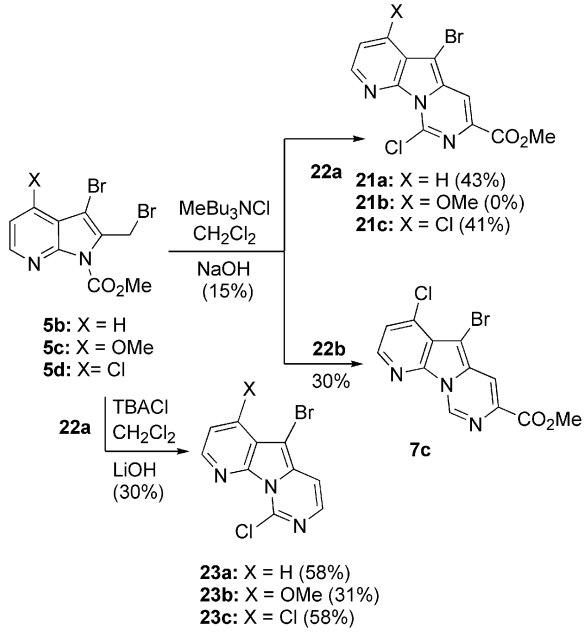


Figure 3. Retrosynthetic analysis for variolin B.

Three bromomethylpyridopyrroles (**5b**–**d**) were chosen as model substrates to test the heterocyclization reaction. Compounds **5d** (X = Cl) and **5b** (X = H) should afford the corresponding advanced precursors for variolin B and its deoxy analog, respectively (Scheme 4). On the other hand, methyl 2-bromomethyl-4-methoxypyrrolo[2,3-*b*]pyridin-1-yl carboxylate (**5c**; X = OMe) was also chosen as a starting azaindole, 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 was not feasible from **5d**.



Scheme 4. Synthesis of the di- or trihalo-functionalized pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines.

The reaction of **5b**–**d** with **22a**,**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 intermediates **21a**,**c**, albeit in moderate yields. Derivative **21b** could not be ob-

tained under these conditions. Moreover, *N*-tosylmethyl dibromoformimide (**22b**) was prone to bromine loss to regenerate TosMIC, which reacted with **5d** to give the previously described[10b] methyl 5-bromo-4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-7-yl carboxylate (**7c**) in 30% yield.

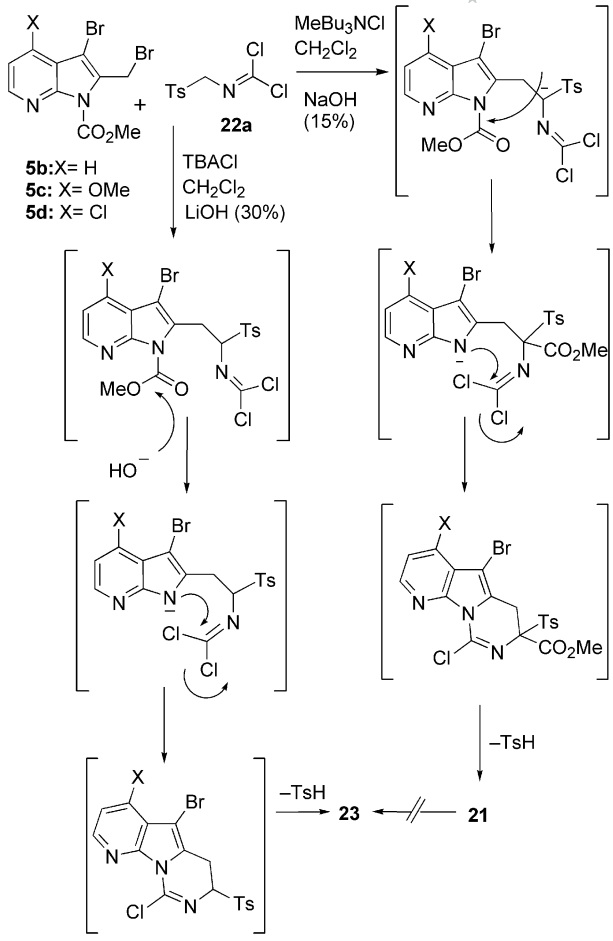
In the search for the optimal conditions it was observed that compound **21a** was not formed on using more concentrated NaOH (30%), and unexpected compound **23a** was isolated in 5% yield. This result was very convenient in terms of our ultimate goal, the total synthesis of variolin, as it circumvents the need to remove the methoxycarbonyl group. Consequently, we studied this heterocyclization process further to find a set of appropriate conditions to obtain **23a**–**c** in a synthetically useful yield. The best results were obtained for **23a** (58% yield) under phase-transfer conditions in the two-phase system LiOH (30%)/CH_2Cl_2, with tetrabutylammonium chloride (TBACl) as the catalyst at room temperature.[18] The use of a less lipophilic base such as NaOH and/or other phase-transfer catalysts did not improve the yield. Under these optimal conditions, compounds **23b** and **23c** were obtained in 31 and 58% yield, respectively.

The mechanistic proposal for the formation of compounds **21** and **23** is shown in Scheme 5. Although the formation of **21** can be explained by a mechanism similar to that proposed for the reaction between **5b** and TosMIC (Scheme 1),[10a] the first step in the formation of **23** is also likely to involve the nucleophilic substitution of **22a** on the corresponding bromomethylpyrrole (**5b**, X = H; **5c**, X = OMe; **5d**, X = Cl). Subsequent deprotection of the azolic pyrrole under phase-transfer conditions, cyclization by attack of the pyrrole nitrogen on the chloroimine, and 1,2-elimination of *p*-toluenesulfinic acid would afford tricyclic derivatives **23** Support for this mechanism was provided by the unsuccessful attempts to transform **21** into **23** under the reaction conditions described (Scheme 5).

At this stage, the completion of the synthesis of variolin B would involve either of the intermediates **23b** or **23c** obtained from **5c** or **5d**, respectively. Compound **23b** has the advantage of the presence of the methoxy substituent at the C4 position but the drawback associated with the lower yield in which it was obtained when compared to **23c** (31 vs. 58%). The approach from **23c** (X = Cl) offered not only the potential synthesis of the alkaloid but also the versatility required for eventual structural modification of the natural product at the C4 position.

As a result, trihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **23c** was the intermediate chosen for the installation of the key structural substituents on the variolin core system through a conceptually different approach based on sequential palladium-mediated C–N, C–C, and C–O coupling reactions (Figure 4).

Prior to undertaking the total synthesis of variolin B, dihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **23a** was employed as a model compound to explore the introduction of the aminopyrimidine moiety at C5 and the amino substituent at C9. It is worth noting that the successful introduction of these two substituents would lead to a



Scheme 5. Proposed mechanism for the formation of compounds **21** and **23**.

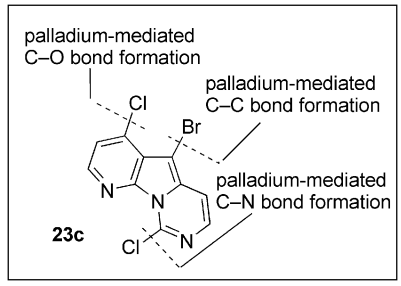
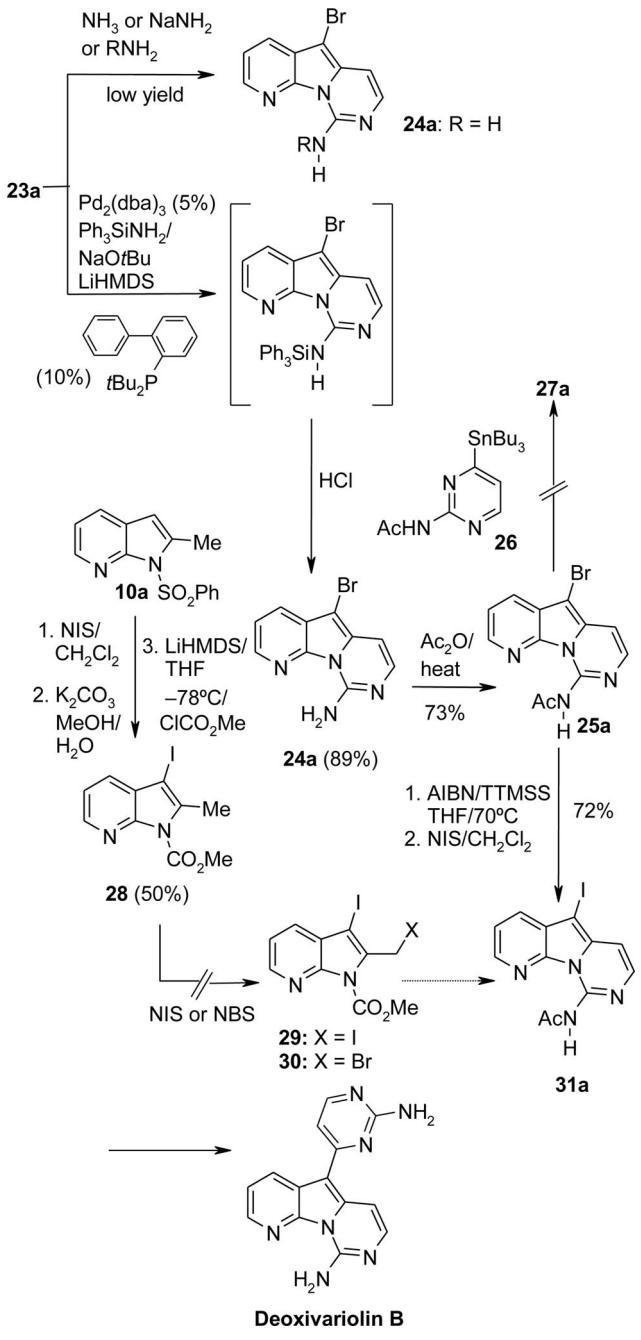


Figure 4. Functionalization of a trihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine through palladium-mediated reactions.

new total or formal synthesis of deoxyvariolin B. Functionalization at the C5 position with the appropriate pyrimidinyl moiety by using the palladium methodology was previously shown to be successful for pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine derivative **7b** (Scheme 3). As a consequence, we focused on exploring the conversion of **23a** into amino derivative **24a** (Scheme 6) by simple nucleophilic displacement of the chloride substituent in the C9 position. Different experiments were carried out in the presence of ammonium hydroxide, sodium amide, and some aliphatic amines, but this substitution reaction proved to be inappro-

priate for our purposes, with substitution products formed in very low yields. Consequently, we turned our attention to the palladium-promoted C–N bond formation developed by Buchwald and Hartwig.[19]



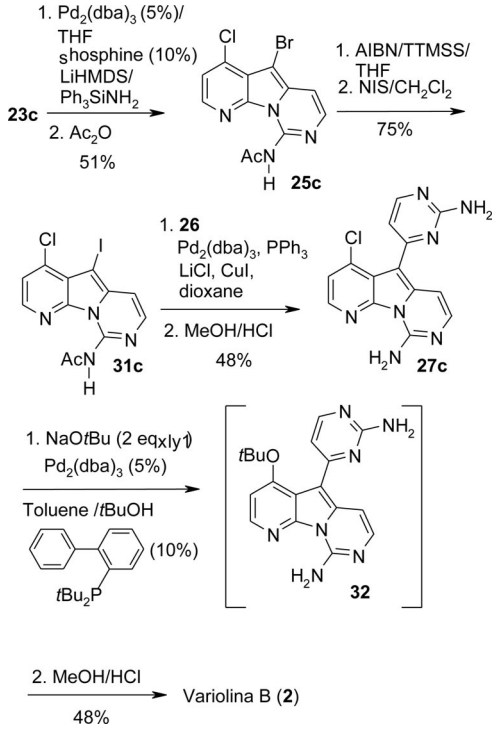
Scheme 6. Formal synthesis of deoxivariolin B.

Our initial results showed that **23a** can be converted selectively into 9-aminopyrido[3′,3′:4,5]pyrrolo[1,2-*c*]pyrimidine (**24a**) by using triphenylsilylamine (Ph_3SiNH_2) as an ammonia equivalent in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) by using 2 mol-% of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and 4 mol-% of (2-biphenyl)di-*tert*-butylphosphane followed by treatment of the reaction mixture with acid. The best yield (89%) was obtained by using a slight excess of LiHMDS (1.2 equiv.) and Ph_3SiNH_2 (1.2 equiv.) in THF at room temperature (16 h) or under reflux (12 h). Prior to the reaction of **24a** with pyrimidinyl stannane **26**, prepared according to the procedure reported by Alvarez and co-workers[6a] it was necessary to protect the amino group and this was achieved by using acetic anhydride under reflux. Protected derivative **25a** was obtained in 73% yield and this could not be improved by using other conditions due to the formation of the diacetylated byproduct, which proved difficult to isolate and purify. Compound **25a** could not be prepared directly from **23a** by using a palladium- or copper-catalyzed amidation reaction under standard reaction conditions.[20]

The coupling reaction between **25a** and **26** was attempted under the conditions reported previously[6a] [$Pd_2(dba)_3$/PPh_3/LiCl/CuI, dioxane, heat] but these were not appropriate for the coupling reaction, and starting material **25a** was recovered unaltered and extensive decomposition of **26** occurred. A broad study was undertaken to find a suitable set of conditions for the synthesis of **27a**, including the use of electronically rich and bulky phosphanes [PCy_3, P*t*Bu_3, (2-biphenyl)di-*tert*-butylphosphane], more polar solvents (DMSO, DMF), and other fluoride sources (CsF, TBAF). However, all attempts proved unsuccessful and the deacetylated product and/or the starting material were recovered. This failure led us to consider the use of diiodo or bromoiodo azaindoles **29** and **30**, respectively (Scheme 6) as partners in the coupling reaction on the assumption that the higher reactivity would lead to success in the coupling process.

After some experimentation, it was found that **30** could not be prepared through the procedure used for the synthesis of **5c** (Scheme 2), as the attempted radical halogenation of intermediate **28** failed with NIS and *ipso*-substitution compound **5b** was formed when NBS was employed as a brominating agent.[21] Therefore, we chose a debromination–iodination strategy to obtain the desired intermediate.[22] Thus, under the conditions shown in Scheme 6, desired intermediate **31a** was obtained in 72% yield from **25a**. As this intermediate is the same as that obtained by Alvarez and co-workers in their synthesis of deoxyvariolin B,[6a] we had achieved a formal synthesis of this variolin B analog.

The total synthesis of variolin B was continued by transforming trihalo-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **23c** into the C9-aminated derivative with lithium bis(trimethylsilyl)amide/triphenylsilylamine (LiHMDS/Ph_3SiNH_2) as the ammonia source in the presence of $Pd_2(dba)_3$. This process gave **25c** after protection of the amino group (Scheme 7). As the attempted C–C coupling reaction between **25c** and **26** did not give the expected coupling product it was also necessary to prepare the corresponding iodo derivative **31c** by the same debromination–iodination process used on **25a**. Fortunately, **31c** reacted with the pyrimidyl stannyl reagent **26** to afford the expected coupling product **27c**, after deprotection of both amino groups.



Scheme 7. Total synthesis of variolin B (**2**).

Having obtained compound **27c**, we turned our attention to the introduction of the oxygen functionality in the C4 position. It was reported that diamino derivative **27c** could be transformed into the C4 methoxy derivative by reaction with sodium methoxide in MeOH/THF. However, this transformation required heating at 90 °C for 40 h and the best yield was 41 %.[8c] Consequently, we decided to explore the functionalization of the C4 position under milder conditions through a palladium-promoted C–O coupling reaction. Although this reaction has rarely been used in heterocyclic chemistry, several examples are known in which it has been applied to aryl halides by using Ni or Pd as catalysts.[23] Thus, before attempting the C–O functionalization on **27c** we tested the feasibility of this unprecedented heterocyclic reaction on a commercially available 2-methyl-4-chloroquinoline model. Furthermore, our choice of nucleophilic partner for the coupling reaction was sodium *tert*-butoxide (NaO*t*Bu) because the *tert*-butyl group could be more easily removed than the methyl group to generate the required hydroxy substituent at C4.

The best results for the model substrate (65% yield) were obtained by irradiating the reaction mixture in a microwave oven with a reaction time of 2 min at 300 W power by using a mixture of toluene/*t*BuOH as solvent, $Pd_2(dba)_3$ (5 mol-%), and (2-biphenyl)di-*tert*-butylphosphane (10 mol-%).[11] It is noteworthy that experiments with a Ni catalyst and other alkoxides failed to improve this yield. Compound **27c** was subjected to the optimized conditions found for the C–O coupling reaction on the model quinoline substrate to afford *tert*-butoxy derivative **32**, which was converted without isolation into variolin B in 48% yield by removal of the *tert*-butyl group under acidic conditions (Scheme 7).

Conclusions

In summary, we have developed a new heterocyclization method for constructing the tricyclic pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine system, the core heterocyclic nucleus of variolin alkaloids, by reaction of appropriate bromomethylazaindole derivatives with tosylmethyl isocyanide (TosMIC) or tosylmethylimines (TosMIC synthetic equivalent). The advanced intermediate obtained in the reaction with TosMIC could not be transformed into the natural alkaloid due to a problem associated with the introduction of the C9 amino functionality. In contrast, the approach based on the reaction of bromomethylazaindoles and *N*-tosylmethyl dichloroformimide as the key step allowed the synthesis of dihalo- and trihalopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine derivatives, which were transformed into a previously reported advanced intermediate in the total synthesis of deoxyvariolin B and into the natural product variolin B by three successive palladium-promoted cross-coupling reactions. We are currently investigating the behavior of variolin B and some analogs obtained by these strategies as selective DNA binders.

Experimental Section

General Remarks: All reactions were carried under an atmosphere of argon and by using solvents that were dried by routine procedures. Column chromatography was performed by using silica gel (60 F_{254}, 70–200 μm) as the stationary phase. IR spectra were determined on KBr pellets. NMR spectra were obtained at 200, 300, or 500 MHz (^{1}H) and 50, 75, or 125 MHz (^{13}C). Chemical shifts are reported in ppm relative to tetramethylsilane. Microwave experiments were performed in sealed reaction vessels using a microwave oven CEM-Discovery (IR monitoring temperature). Compounds **9**[12] and **22a/b**[17] were synthesized according to previously reported procedures. The following compounds have been described previously: 4-methoxy-1-(phenylsulfonyl)pyrrolo[2,3-*b*]-pyridine,[24] 3-iodo-2-methyl-1-(phenylsulfonyl)pyrrolo[2,3-*b*]pyridine,[25] **2**,[4a] *N*-(pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide,[6a] **31a**,[6a] **27c**,[8d] **7b**,[10a] **7c**,[10b] and **10a**.[10b]

4-Methoxy-1-(phenylsulfonyl)pyrrolo[2,3-*b*]pyridine:[24] To a solution of azole **9**[12] (7.52 g, 50.85 mmol) and benzyltriethylammonium chloride (TEBACl, 0.30 g, 1.32 mmol) in CH_2Cl_2 (100 mL) was added powdered NaOH (6.35 g, 159 mmol). The solution was cooled to 0 °C and benzenesulfonyl chloride (7.14 mL, 55.93 mmol) was added dropwise. The mixture was stirred at 0 °C for 4 h and then warmed to room temperature. The resulting mixture was filtered through Celite and washed with CH_2Cl_2, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (silica gel; hexane/EtOAc, 7:3) to yield the product (11.57 g, 79%) as a white powder. M.p. 149–151 °C. IR (KBr): $\tilde{\nu}$ = 1581, 1493, 1367, 1297, 1143 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OMe), 6.59 (d, J = 5.6 Hz, 1 H), 6.64 (d, $^3J_{H,H}$ = 3.8 Hz, 1 H, 3-H), 7.50–7.40 (m, 3 H), 7.54 (d, $^3J_{H,H}$ = 3.8 Hz, 1 H, 2-H), 8.16–8.11 (m, 2 H), 8.28 (d, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 100.8, 102.7, 112.8, 123.9, 127.7, 128.9, 133.8, 138.2, 146.9, 148.7, 159.7 ppm. MS (EI): *m*/*z* (%) = 288 (31) [M]$^+$, 224 (75), 223 (67), 147 (57), 117 (91), 77 (100). $C_{14}H_{12}N_2O_3S$ (288.33): calcd. C 58.32, H 4.20, N 9.72; found C 58.34, H 4.21, N 9.71.

4-Methoxy-2-methyl-1-(phenylsulfonyl)pyrrolo[2,3-*b*]pyridine (10b): 4-Methoxy-1-(phenylsulfonyl)pyrrolo[2,3-*b*]pyridine (7.81 g, 27.13 mmol) was dissolved in THF (290 mL) under an argon atmosphere, and the solution was cooled to –30 °C. Then, LDA (2 M in THF, 27.1 mL, 54.2 mmol) was added dropwise, and the mixture was stirred at –30 °C for 40 min. After this time, methyl iodide (10.13 mL, 162 mmol) was added, and the mixture warmed to room temperature and stirred at room temperature for 6 h. The reaction mixture was quenched with NH_4Cl, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; hexane/EtOAc, 7:3) to give **10b** (8.11 g, 99%) as a yellow powder. M.p. 99–101 °C. IR (KBr): $\tilde{\nu}$ = 1562, 1452, 1375, 1292, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.69 (d, $^4J_{H,H}$ = 0.9 Hz, 3 H, Me), 3.91 (s, 3 H, OMe), 6.36 (q, $^4J_{H,H}$ = 0.9 Hz, 1 H, 3-H), 6.60 (d, J = 5.7 Hz, 1 H), 7.57–7.42 (m, 3 H), 8.12–8.10 (m, 2 H), 8.25 (d, J = 5.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 55.4, 101.1, 102.9, 111.6, 127.4, 128.8, 133.6, 135.9, 139.3, 145.6, 150.8, 158.5 ppm. MS (EI): *m*/*z* (%) = 302 (11) $[M]^+$, 238 (34), 161 (100), 131 (58), 77 (74). $C_{15}H_{14}N_2O_3S$ (302.35): calcd. C 59.59, H 4.67, N 9.27; found C 59.59, H 4.67, N 9.24.

4-Methoxy-2-methylpyrrolo[2,3-*b*]pyridine: To a solution of 1-(phenylsulfonyl) derivative **10b** (3.02 g, 10 mmol) in MeOH/H_2O (3:1, 170 mL) was added K_2CO_3 (6.90 g, 50 mmol), and the mixture was heated to reflux for 16 h. Afterward, the solution was allowed to cool to room temperature. Methanol was removed in vacuo, and the resulting suspension was partitioned between water and ethyl acetate. Organic layers were combined and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure to give a crude product, which was purified by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) to yield the product (1.60 g, 99%) as a white powder. M.p. 207–209 °C. IR (KBr): $\tilde{\nu}$ = 1602, 1334, 1298, 1269 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.38 (s, 3 H, Me), 3.95 (s, 3 H, OMe), 6.15 (s, 1 H, 3-H), 6.57 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, 5-H), 7.92 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, 6-H), 11.50 (br. s, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 13.5, 56.0, 96.4, 98.7, 103.4, 124.1, 135.4, 143.7, 145.2 ppm. MS (EI): *m*/*z* (%) = 162 (100) $[M]^+$, 147 (49), 119 (56). $C_9H_{10}N_2O$ (162.19): calcd. C 66.65, H 6.21, N 17.27; found C 66.63, H 6.24, N 17.26.

Methyl 4-Methoxy-2-methylpyrrolo[2,3-*b*]pyridine-1-carboxylate (11): LiHMDS (1 M in THF, 8.4 mmol, 8.4 mL) was added to a solution of 4-methoxy-2-methylpyrrolo[2,3-*b*]pyridine (1.234 g, 7.62 mmol) in dry THF (25 mL) under an atmosphere of argon at –78 °C, and the mixture was stirred at the same temperature for 20 min. Then, the mixture was warmed to room temperature over a period of 2 h. The mixture was cooled again to –78 °C, methyl chloroformate (0.7 mL, 8.4 mmol) was added dropwise, stirring was continued for 2 h at –78 °C, and then the reaction was warmed to room temperature, stirring at the same temperature until the starting material had been consumed (as monitored by TLC, 12 h). The mixture was treated with NH_4Cl and extracted with EtOAc, and the combined layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by chromatography (silica gel; EtOAc) to yield **11** (1.41 g, 84%) as a white solid. M.p. 88–90 °C. IR (KBr): $\tilde{\nu}$ = 3368, 1736, 1569, 1442, 1288, 1080 1269 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, Me), 3.86 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 6.28 (s, 1 H, 3-H), 6.55 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, 5-H), 8.20 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5, 53.8, 55.3, 100.7, 102.0, 111.9, 124.1, 136.0, 145.3, 146.9, 158.3 ppm. MS (EI): *m*/*z* (%) = 220 (77) $[M]^+$, 205 (53), 161 (97), 133 (100). $C_{11}H_{12}N_2O_3$ (220.23): calcd. C 59.99, H 5.49, N 12.72; found C 60.00, H 5.49, N 12.73.

Methyl 3-Bromo-2-bromomethyl-4-methoxypyrrolo[2,3-*b*]pyridine-1-carboxylate (5c): Powdered NBS (7.12 g, 40 mmol) was added to a solution of *N*-methyl carbamate protected **11** (4.40 g, 20 mmol) in CH_2Cl_2 (200 mL), and the mixture was stirred at room temperature until the starting material had been consumed (as monitored by TLC, 48 h). The solvent was evaporated under reduced pressure, and the residue was purified by chromatography (silica gel; CH_2Cl_2/acetone, 98:2) to yield **5c** (5.82 g, 77%) as a yellow solid. M.p. 171–172 °C. IR (KBr): $\tilde{\nu}$ = 1739, 1578, 1449, 1394, 1295, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OMe), 4.12 (s, 3 H, OMe), 5.02 (s, 2 H, CH_2), 6.67 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 5-H), 8.36 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.0, 54.8, 55.8, 98.1, 101.6, 110.1, 131.6, 148.2, 148.5, 150.2, 160.4 ppm. MS (EI): *m*/*z* (%) = 381, 379, 377 (53, 100, 50) $[M]^+$. $C_{11}H_{10}Br_2N_2O_3$ (378.02): calcd. C 34.95, H 2.67, N 7.41; found C 35.01, H 2.67, N 7.43.

Methyl 5-Bromo-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylate (7b): A mixture of **5c** (0.378 g, 1 mmol), TosMIC (0.220 g, 1.1 mmol), and TBAI (0.080 g, 0.2 mmol) in CH_2Cl_2 (7 mL) and sodium hydroxide (15% in H_2O, 7 mL) was stirred at –10 °C for 17 h. Then, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure, providing a crude that was treated with acetone and filtered to afford **7b** (0.250 g). The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) to give other 0.015 g of **7b** as a bright yellow powder. Yield: 79%. M.p. 256–257 °C. IR (KBr): $\tilde{\nu}$ = 1711, 1568, 1468, 1437, 1352, 1324, 1294, 1225, 1013 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OMe), 4.07 (s, 3 H, OMe), 6.86 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 3-H), 8.23 (d, J = 1.5 Hz, 1 H), 8.42 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 2-H), 9.44 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.0, 56.1, 82.7, 102.0, 112.3, 116.4, 128.9, 135.5, 137.7, 141.2, 147.0, 160.8, 165.0 ppm. MS (EI): *m*/*z* (%) = 337, 335 (100, 97) $[M]^+$, 322, 320 (46, 45), 320 (45), 57 (93). $C_{13}H_{10}BrN_3O_3$ (336.15): calcd. C 46.45, H 3.00, N 12.50; found C 46.41, H 3.02, N 12.51.

5-Bromo-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylic Acid (13): To a solution of ester **7b** (0.336 g, 1.0 mmol) in THF/H_2O (4:1, 5 mL) was added LiOH·H_2O (63 mg, 1.5 mmol), and the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was concentrated, water was added, and the aqueous solution was neutralized with 1 N HCl. The solid thus obtained was filtered and washed with water and Et_2O/hexane to afford **13** (0.274 g, 85%) as a yellow powder that was used without further purification. M.p. >260 °C. IR (KBr): $\tilde{\nu}$ = 3630, 3449, 1719, 1570, 1435, 1324, 1285, 1224, 1014 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 4.06 (s, 3 H, OMe), 7.18 (d, $^3J_{H,H}$ = 5.6 Hz 1 H, 3-H), 7.99 (s, 1 H), 8.50 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, 2-H), 9.53 (s, 1 H) ppm. MS (EI): *m*/*z* (%) = 323, 321 (100, 99) $[M]^+$, 279, 277 (76, 81), 264, 262 (69, 69).

4-Methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (14): From acid **13** (0322 g, 1.0 mmol) and without further purification, the resulting yellow powder was suspended in Ph_2O (5 mL), and the mixture was heated at 260 °C and stirred for 4 h at this temperature. The residue was washed with hexane/EtOAc (1:1) to yield compound **14** (38 mg, 19%), which was isolated as an orange powder. M.p. 178–181 °C. IR (KBr): $\tilde{\nu}$ = 2922, 1571, 1308, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.05 (s, 3 H, OMe), 6.61 (s, 1 H), 6.81 (d, J = 5.4 Hz, 1 H), 7.23 (d, J = 6.9 Hz, 1 H), 7.53 (d, J = 6.9 Hz, 1 H), 8.35 (d, J = 5.4 Hz, 1 H), 9.49 (s, 1 H) ppm. MS (EI): *m*/*z* (%) = 199 (100) $[M]^+$, 184 (68). $C_{11}H_9N_3O$ (199.21): calcd. C 66.32, H 4.55, N 21.09; found C 66.58, H 5.78, N 20.98.

Methyl 5-(2′-Methylthiopyrimidin-4-yl)-4-methoxypyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine-7-carboxylate (17): To a suspension of **7b** (50 mg, 0.149 mmol) in toluene/MeOH (20:1, 1 mL) was added stannane **16** (48 mg, 0.164 mmol) and $Pd(PPh_3)_4$ (1.7 mg, 0.0015 mmol), and the reaction mixture was heated to reflux for 14 h. Then, the reaction mixture was filtered through Celite, washed with CH_2Cl_2, and concentrated under reduced pressure, and the residue was treated with Et_2O. The solid obtained was filtered to afford **17** (41.1 mg, 73%) as a bright yellow powder. M.p. 217–218 °C. IR (KBr): $\tilde{\nu}$ = 3561, 1735, 1570, 1439, 1346, 1328 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, Me), 4.01 (s, 3 H, OMe), 4.07 (s, 3 H, OMe), 6.96 (d, J = 5.5 Hz, 1 H), 7.56 (d, J = 5.3 Hz, 1 H), 8.49 (d, J = 5.5 Hz, 1 H), 8.52 (d, J = 5.3 Hz, 1 H), 9.17 (d, J = 1.3 Hz, 1 H), 9.65 (d, J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 53.1, 55.9, 102.8, 111.3, 117.0, 118.9, 128.3, 132.3, 137.6, 138.1, 142.8, 146.8, 156.4, 160.2, 160.8, 164.8, 171.8 ppm. MS (EI): m/z (%) = 381 (100) $[M]^+$, 351 (37), 321 (18), 291 (24), 276 (9). $C_{18}H_{15}N_5O_3S$ (381.42): calcd. C 56.68, H 3.96, N 18.36; found C 56.69, H 3.96, N 18.37.

5-(2′-Methylthiopyrimidin-4-yl)-4-methoxypyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine-7-carboxylic Acid (18): To a solution of ester **17** (57 mg, 0.149 mmol) in THF/H_2O (4:1, 5 mL) was added $LiOH·H_2O$ (9.2 mg, 0.22 mmol), and the reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was concentrated, water was added, and the aqueous solution was neutralized with 1 N HCl. The solid thus obtained was filtered and washed with water and Et_2O/hexane to afford **18** (52 mg, 95%) as a brown powder that was used without further purification. M.p. >250 °C. IR (KBr): $\tilde{\nu}$ = 3415, 1719, 1567, 1442, 1344, 1103, 1016 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.62 (s, 3 H, Me), 4.05 (s, 3 H, OMe), 7.29 (d, J = 5.9 Hz, 1 H), 7.70 (d, J = 5.4 Hz, 1 H), 8.57 (d, J = 5.9 Hz, 1 H), 8.62 (d, J = 5.4 Hz, 1 H), 9.03 (s, 1 H), 9.72 (s, 1 H), 13.40 (br. s, 1 H, OH) ppm.

5-(2′-Methylthiopyrimidin-4-yl)-4-methoxypyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (19): A suspension of acid **18** (37 mg, 0.1 mmol) in Ph_2O (0.5 mL) was heated at 260 °C for 6 h. Then the reaction mixture was filtered through silica gel by using Ph_2O as solvent. The crude product was purified by column chromatography (CH_2Cl_2/acetone, 95:5) to afford **19** (18.5 mg, 57%) as a yellow powder. M.p. 170–172 °C. IR (KBr): $\tilde{\nu}$ = 3423, 1561, 1439, 1358 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, Me), 4.05 (s, 3 H, OMe), 6.93 (d, J = 5.5 Hz, 1 H), 7.51 (d, J = 5.5 Hz, 1 H), 7.81 (d, J = 6.8 Hz, 1 H), 8.24 (dd, J = 6.8, 1.6 Hz, 1 H), 8.41 (d, J = 5.5 Hz, 1 H), 8.47 (d, J = 5.5 Hz, 1 H), 9.63 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 55.7, 102.7, 109.0, 111.8, 114.1, 116.9, 133.8, 138.4, 139.8, 141.9, 145.1, 146.6, 155.8, 157.4, 160.3 ppm. MS (EI): m/z (%) = 323 (100) $[M]^+$, 290 (43), 251 (25). $C_{16}H_{13}N_5OS$ (323.38): calcd. C 59.43, H 4.05, N 21.66; found C 59.45, H 4.06, N 21.65.

4-Hydroxy-5-(2′-methylthiopyrimidin-4-yl)pyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (20): A suspension of acid **18** (37 mg, 0.1 mmol) in Ph_2O (0.5 mL), following the same procedure described for **19** and after heating at 320 °C for 6 h, **20** (15 mg, 48%) was obtained as a yellow powder. M.p. 159–160 °C. IR (KBr): $\tilde{\nu}$ = 3378, 2924, 1582, 1442, 1311 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, Me), 6.93 (d, J = 5.4 Hz, 1 H), 7.40 (d, J = 5.4 Hz, 1 H), 7.71 (d, J = 6.9 Hz, 1 H), 7.96 (d, J = 6.9 Hz, 1 H), 8.29 (d, J = 5.4 Hz, 1 H), 8.50 (d, J = 5.4 Hz, 1 H), 9.69 (s, 1 H), 14.44 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 101.9, 109.0, 110.8, 111.7, 112.2, 133.6, 137.9, 139.6, 141.7, 143.1, 146.4, 157.2, 158.6, 160.3 ppm. MS (API, ESI+): m/z = 310 $[M + 1]^+$, 308 $[M - 1]^+$. $C_{15}H_{11}N_5OS$ (309.35): calcd. C 58.24, H 3.58, N 22.64; found C 58.26, H 3.54, N 22.65.

General Procedure for the Preparation of Methyl Pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine Carboxylates 21a,c: To a mixture of the corresponding bromoazole **5b** or **5d** (1.0 mmol) was added *N*-tosylmethyl dichloroformimide (**22a**; 0.210 g, 1.1 mmol), the phase-transfer catalyst in CH_2Cl_2 (0.1 mmol in 10 mL), and NaOH (15% in H_2O, 10 mL), and the reaction mixture was stirred at room temperature for 5 h. Then, water (10 mL) was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **21a**,**c**, which was purified by chromatography on silica gel to yield the pure compounds.

Methyl 5-Bromo-9-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylate (21a): Starting from **5b** (0.348 mg, 1.0 mmol), **22a** (1.1 mmol), and Bu_3NMeCl (24 mg), and after purification by chromatography (CH_2Cl_2/hexane, 95:5), **21a** (146 mg, 43%) was obtained as a yellow powder. M.p. 185–187 °C. IR (KBr): $\tilde{\nu}$ = 1721, 1561, 1441, 1395, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OMe), 7.58 (dd, J = 8.2, 4.6 Hz, 1 H), 8.16 (d, J = 8.2 Hz, 1 H), 8.24 (s, 1 H, 6-H), 8.70 (d, J = 4.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 53.2, 84.9, 97.1, 121.8, 128.6, 132.0, 135.2, 136.9, 138.4, 147.7, 164.5 ppm. MS (DIP-CI, NH_3): m/z (%) = 344, 342, 340 (25, 100, 80) $[M + 1]^+$. $C_{12}H_7BrClN_3O_2$ (340.57): calcd. C 42.32, H 2.07, N 12.34; found C 42.14, H 2.12, N 12.30.

Methyl 5-Bromo-4,9-dichloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylate (21c): Starting from **5d** (0.383 g, 1.0 mmol), **22a** (1.1 mmol), and Bu_3NMeCl (24 mg), and after purification by chromatography (CH_2Cl_2/hexane, 95:5), **21c** (154 mg, 43%) was obtained as a yellow powder. M.p. >250 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1725, 1634, 1557, 1466, 1372, 1185 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OMe), 7.45 (d, $^3J_{H,H}$ = 4.8 Hz, 1 H, 3-H), 8.27 (s, 1 H, 6-H), 8.41 (d, $^3J_{H,H}$ = 4.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.9, 89.1, 102.3, 114.3, 121.9, 122.3, 129.0, 131.1, 132.7, 137.4, 146.3, 167.9; 3 ppm. MS (DIP-CI, NH_3): m/z (%) = 378, 376, 374 (7, 14, 9) $[M + 1]^+$, 318 (83), 279 (32), 102 (93), 86 (100). $C_{12}H_6BrCl_2N_3O_2$ (375.01): calcd. C 38.43, H 1.61, N 11.21; found C 38.29, H 1.70, N 11.18.

General Procedure for the Preparation of Azolopyrimidines 23a–c: A mixture of bromomethylazole **5b**–**d** (2.8 mmol), *N*-tosylmethyl dichloroformimide (**22a**; 0.821 g, 3.1 mmol), TBACl (80 mg, 0.28 mmol) in CH_2Cl_2 (30 mL), and 30% LiOH (30 mL) was stirred at room temperature for 5 h. The reaction mixture was poured into water (20 mL), the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a crude product, which was purified by chromatography on silica gel to yield pure compounds **23a**–**c**.

5-Bromo-4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (23a): Chromatography: hexane/EtOAc (8:2). Yield: 58%; yellow solid. M.p. >250 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3066, 1616, 1587, 1495, 1388, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, J = 6.4 Hz, 1 H), 7.51 (d, J = 6.4 Hz, 1 H), 7.52 (dd, J = 8.0, 4.6 Hz, 1 H), 8.10 (dd, J = 8.0, 1.5 Hz, 1 H), 8.61 (dd, J = 4.6, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 82.5, 110.3, 121.3, 122.2, 127.1, 129.5, 134.0, 136.3, 139.3, 143.5 ppm. MS (DIP-CI, NH_3): m/z (%) = 286, 284, 282 (25, 100, 80) $[M + 1]^+$. $C_{10}H_5BrClN_3$ (282.53): calcd. C 42.51, H 1.78, N 14.87; found C 42.39, H 1.72, N 14.98.

5-Bromo-9-chloro-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (23b): Chromatography: CH_2Cl_2/acetone (95:5). Yield: 31%; yellow solid. M.p. 250 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1609, 1566, 1492,

1296, 1001, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.06 (s, 3 H, OMe), 6.85 (d, J = 5.5 Hz, 1 H), 7.26 (d, J = 6.4 Hz, 1 H), 7.45 (d, J = 6.4 Hz, 1 H), 8.45 (d, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9, 79.9, 101.8, 110.8, 112.3, 130.1, 132.7, 135.3, 139.9, 144.9, 159.9 ppm. MS (DIP-CI, NH_3): m/z (%) = 316, 314, 312 (25, 100, 80) $[M + 1]^+$. $C_{11}H_7BrClN_3O$ (312.55): calcd. C 42.27, H 2.26, N 13.44; found C 42.17, H 2.11, N 13.51.

5-Bromo-4,9-dichloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (23c): Chromatography: hexane/EtOAc (8:2). Yield: 58%; yellow solid. M.p. > 250 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3070, 1634, 1553, 1475, 1268, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 6.6 Hz, 1 H), 7.50 (d, J = 5.1 Hz, 1 H), 7.58 (d, J = 6.6 Hz, 1 H), 8.45 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 80.8, 110.6, 122.1, 128.9, 130.0, 133.5, 135.1, 135.9, 136.8, 142.5 ppm. MS (APCI): m/z (%) = 322, 320, 318, 316 (8, 46, 100, 61) $[M + 1]^+$. $C_{10}H_4BrCl_2N_3$ (316.97): calcd. C 37.89, H 1.27, N 13.26; found C 37.80, H 1.31, N 13.28.

5-Bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-amine (24a): To a mixture of **23a** (0.282 g, 1.0 mmol), triphenylsilylamine (0.330 g, 1.2 mmol), $Pd_2(dba)_3$ (18 mg,0.02 mmol), and (2-biphenyl)di-*tert*-butylphosphane (12 mg, 0.04 mmol) in dry THF (10 mL) was added LiHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol) under an atmosphere of dry argon. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) provided **24a** (0.234 g, 89%) as an orange powder. M.p. 205–207 °C. IR (KBr): $\tilde{\nu}$ = 3317, 1659, 1613, 1571, 1390, 1121, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.72 (d, J = 6.7 Hz, 1 H), 7.42 (dd, J = 8.1, 4.4 Hz, 1 H), 7.43 (d, J = 6.7 Hz 1 H), 8.02 (dd, J = 8.1, 1.5 Hz, 1 H), 8.34 (dd, J = 4.4, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.6, 100.2, 120.0, 126.0, 128.3, 129.2, 130.1, 133.5, 135.6, 140.2 ppm. MS (DIP-CI, NH_3): m/z (%) = 265, 263 (94, 100) $[M + 1]^+$, 184 (12). $C_{10}H_7BrN_4$ (263.10): calcd. C 45.65, H 2.68, N 21.30; found C 45.51, H 2.58, N 21.48.

***N*-(5-Bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide (25a):** A suspension of **24a** (0.263 g, 1.0 mmol) in acetic anhydride (15 mL) was heated under reflux for 30 min. Then, the solvent was eliminated under reduced pressure to yield a dark oil, which was treated with a saturated $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography (silica gel; CH_2Cl_2/acetone, 95:5) provided **25a** (0.223 g, 73%) as an orange solid. M.p. 202–203 °C. IR (KBr): $\tilde{\nu}$ = 3016, 1700, 1619, 1574, 1398, 1007, 944 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, Me), 7.00 (d, J = 6.6 Hz, 1 H), 7.46 (dd, J = 8.1, 4.8 Hz, 1 H), 7.59 (d, J = 6.6 Hz, 1 H), 8.04 (dd, J = 8.1, 1.5 Hz, 1 H), 8.42 (dd, J = 4.8, 1.5 Hz, 1 H), 12.59 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 80.1, 100.5, 105.6, 120.7, 122.6, 127.4, 134.1, 138.3; 141.1, 142.7, 170.5 ppm. MS (DIP-CI, NH_3): m/z (%) = 307, 305 (100, 100) $[M + 1]^+$, 263 (22). $C_{12}H_9BrN_4O$ (305.14): calcd. C 47.24, H 2.97, N 18.36; found C 47.29, H 3.02, N 18.31.

***N*-(Pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide:**[6a] A solution of TTMSS (49 mg, 0.2 mmol), AIBN (33 mg, 0.2 mmol), and **25a** (31 mg, 0.1 mmol) in dry THF (1.5 mL) was slowly added (3 h) to an additional dry THF (2 mL) at 70–80 °C (bath temperature). The resulting reaction mixture was stirred for 12 h at this temperature. Evaporation of the solvent under reduced pressure and purification by chromatography (silica gel; CH_2Cl_2/acetone, 95:5) provided the debrominated derivative (18 mg, 80%) as a yellow powder. M.p. 158–160 °C (ref.[6a] 160–161 °C).

3-Iodo-2-methyl-1-(phenylsulfonyl)pyrrolo[2,3-*b*]pyridine:[25] To a solution of **10a**[10b] (1.0 g, 3.67 mmol) in CH_2Cl_2 (20 mL) was added NIS (1.65 g, 7.36 mmol), and the mixture was stirred at room temperature for 48 h. Then, the solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel; hexane/EtOAc, 8:2) to afford the product (1.34 g, 92%) of as a white powder. M.p. 147–148 °C. IR (KBr): $\tilde{\nu}$ = 1578, 1547, 1449, 1368, 1259, 1176 1005 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.82 (s, 3 H, Me), 7.19 (dd, J = 7.7, 4.8 Hz, 1 H), 7.44–7.58 (m, 4 H), 8.13 (d, J = 7.1 Hz, 2 H), 8.37 (dd, J = 4.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 68.6, 119.9, 124.7, 127.9, 129.3, 129.5, 134.3, 138.7, 139.2, 145.2, 148.5 ppm. MS (DIP-CI, NH_3): m/z (%) = 399 (100) $[M + 1]^+$, 277 (7), 258 (8). $C_{14}H_{11}IN_2O_2S$ (398.22): calcd. C 42.23, H 2.78, N 7.03; found C 41.52, H 2.79, N 6.98.

3-Iodo-2-methylpyrrolo[2,3-*b*]pyridine: To a solution of 1-benzenesulfonyl-3-iodo-2-methylpyrrolo[2,3-*b*]pyridine (3.98 g, 10 mmol) in MeOH (130 mL) and water (43 mL) was added K_2CO_3 (6.91 g, 50 mmol), and the suspension was heated at reflux for 10 h. Then, the reaction mixture was concentrated under reduced pressure, diluted with water (20 mL), and extracted with EtOAc. The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography (silica gel; hexane/EtOAc, 8:2) provided the product (1.80 g, 70%) as a white powder. M.p. 169–171 °C. IR (KBr): $\tilde{\nu}$ = 1608, 1586, 1401, 1277, 1046 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, Me), 7.09 (dd, J = 7.7, 4.8 Hz, 1 H), 7.62 (d, J = 7.7 Hz, 1 H), 8.21 (d, J = 4.8 Hz, 1 H), 10.41 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.9, 56.1, 116.6, 124.6, 128.6, 138.5, 141.8, 149.0 ppm. MS (APCI): m/z (%) = 259 (100) $[M + 1]^+$, 133 (11). $C_8H_7IN_2$ (258.06): calcd. C 37.23, H 2.73, N 10.86; found C 37.20, H 2.71, N 10.84.

Methyl 3-Iodo-2-methylpyrrolo[2,3-*b*]pyridine-1-carboxylate (28): LiHMDS (1 M in THF, 8.4 mL, 8.4 mmol) was added to a solution of methyl 3-iodo-2-methylpyrrolo[2,3-*b*]-pyridine (1.97 g, 7.62 mmol) in dry THF (25 mL) under an atmosphere of argon at –78 °C. The reaction mixture was stirred at this temperature for 20 min, and it was then warmed to room temperature over a period of 2 h. When the reaction mixture turned red it was cooled again to –78 °C and methyl chloroformate (0.7 mL, 8.4 mmol) was added dropwise and stirring was continued for 1 h at –78 °C. Then the reaction was warmed to room temperature and stirred for a further 4 h. The mixture was quenched with NH_4Cl and extracted with EtOAc, and the combined organic layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) to give **28** (1.98 g, 82%) as a white powder. M.p. 118–119 °C. IR (KBr): $\tilde{\nu}$ = 1741, 1576, 1556, 1449, 1397, 1255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, Me), 4.10 (s, 3 H, MeO), 7.23 (dd, J = 7.9, 4.8 Hz, 1 H), 7.63 (dd, J = 7.9, 1.5 Hz 1 H), 8.39 (dd, J = 4.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 54.6, 68.1, 118.9, 119.8, 124.9, 129.35, 139.5, 145.2, 148.4 ppm. MS (DIP-CI, NH_3): m/z (%) = 317 (100) $[M + 1]^+$; 282 (9). $C_{10}H_9IN_2O_2$ (316.10): calcd. C 38.00, H 2.87, N 8.66; found C 38.12, H 2.73, N 8.68.

***N*-(5-Iodopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide (31a):**[6a] To a cold solution (0 °C) of *N*-(pyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidin-9-yl)acetamide (23 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added NIS (25 mg, 0.11 mmol), and the mixture was stirred at this temperature for 1 h. Removal of the solvent under

reduced pressure and purification by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) provided iodo derivative **31a** (32 mg, 90%) as a yellow powder. M.p. 160–161 °C (ref.[6a] 163–164 °C).

***N*-(5-Bromo-4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl) amine:** A solution of LiHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol) was added dropwise to a mixture of azolopyrimidine **23c** (0.317 g, 1.0 mmol), triphenylsilylamine (0.330 g, 1.2 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), and (2-biphenyl)di-*tert*-butylphosphane (12 mg, 0.04 mmol) in dry THF (10 mL) under an atmosphere of dry argon. The resulting mixture was stirred at room temperature for 16 h and then poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give a crude product, which was purified by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) to yield the pure compound (21 mg, 71%) as an orange solid. M.p. 189–190 °C. IR (KBr): $\tilde{\nu}$ = 3311, 1658, 1475, 1377 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, J = 6.8 Hz, 1 H), 7.37 (d, J = 5.3 Hz, 1 H), 7.47 (d, J = 6.8 Hz, 1 H), 8.16 (d, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.4, 100.7, 121.3, 126.6, 128.1, 129.2, 130.2, 135.2, 139.6, 140.9 ppm. MS (DIP-CI, NH_3): m/z (%) = 301, 299, 297 (33, 100, 71) $[M + 1]^+$, 219 (19). $C_{10}H_6BrClN_4$ (297.54): calcd. C 40.37, H 2.03, N 18.83; found C 40.32, H 2.08, N 18.89.

***N*-(5-Bromo-4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)-acetamide (25c):** A suspension of *N*-(5-bromo-4-chloropyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)amine (0.297 g, 1 mmol) in acetic anhydride (15 mL) was heated to reflux for 30 min. Afterward, the mixture was allowed to cool to room temperature. The solvent was removed in vacuo, and the resulting oil was basified with a saturated solution of $NaHCO_3$ in water and extracted with CH_2Cl_2. The organic layers were combined and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure to give a crude product, which was purified by chromatography (silica gel; CH_2Cl_2/acetone, 95:5) to yield pure compound **25c**. Yield: 72%; orange solid. M.p. 230–233 °C. IR (KBr): $\tilde{\nu}$ = 3018, 1708, 1640, 1532, 1345, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3 H, Me), 7.07 (d, J = 6.6 Hz, 1 H), 7.46 (d, J = 5.3 Hz, 1 H), 7.64 (d, J = 6.6 Hz, 1 H), 8.28 (d, J = 5.3 Hz, 1 H), 12.56 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 78.0, 105.1, 118.3, 120.9, 134.5, 135.6, 138.7, 139.8, 140.6, 141.7, 169.8 ppm. MS (DIP-CI, NH_3): m/z (%) = 343, 341, 339 (21, 100, 80) $[M + 1]^+$, 299 (38). $C_{12}H_8BrClN_4O$ (339.58): calcd. C 42.44, H 2.37, N 16.50; found C 42.39, H 2.48, N 16.53.

***N*-(4-Chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide:** A solution of TTMSS (49 mg, 0.2 mmol), AIBN (33 mg, 0.2 mmol), and **25c** (34 mg, 0.1 mmol) in THF (1.5 mL) was added dropwise with the use of a syringe pump over the course of 3 h to an additional amount of THF (2 mL) at 80 °C (bath temperature). Stirring was maintained at the same temperature for a further 12 h. The solution was concentrated, and the crude mixture was purified by chromatography (silica gel; CH_2Cl_2/acetone, 95:5) to yield the pure product. Yield: 83%; yellow solid. M.p. 150 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3153, 1710, 1588, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, Me), 6.67 (s, 1 H, 5-H), 7.02 (d, J = 6.6 Hz, 1 H), 7.45 (d, J = 5.3 Hz, 1 H), 7.57 (d, J = 6.6 Hz, 1 H), 8.31 (d, J = 5.3 Hz, 1 H), 12.80 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7, 89.5, 107.7, 120.0, 122.8, 126.6, 129.1, 135.9, 137.0, 140.2, 169.6 ppm. MS (DIP-CI, NH_3): m/z (%) = 263, 261 (32, 100) $[M + 1]^+$. $C_{12}H_9ClN_4O$ (260.68): calcd. C 55.29, H 3.48, N 21.49; found C 55.38, H 3.31, N 21.41.

***N*-(4-Chloro-5-iodopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)-acetamide (31c):** To a cold solution (0 °C) of *N*-(4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-yl)acetamide (26 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added NIS (25 mg, 0.11 mmol), and the mixture was stirred at this temperature for 1 h. Removal of the solvent under reduced pressure and purification by chromatography (silica gel; CH_2Cl_2/acetone, 9:1) yielded pure **31c**. Yield: 90%; yellow solid. M.p. 157–159 °C. IR (KBr): $\tilde{\nu}$ = 3021, 1678, 1561, 1325, 1192 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3 H, Me), 7.05 (d, J = 6.7 Hz,1 H), 7.44 (d, J = 5.3 Hz, 1 H), 7.65 (d, J = 6.7 Hz,1 H), 8.27 (d, J = 5.3 Hz, 1 H), 12.64 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 46.5, 108.0, 120.5, 121.7, 136.9, 138.5, 138.8, 140.2, 140.5, 142.9, 170.6 ppm. MS (ESI): m/z (%) = 389, 387 (99, 100) $[M + 1]^+$. $C_{12}H_8ClIN_4O$ (386.58): calcd. C 37.28, H 2.09, N 14.49; found C 36.92, H 2.01, N 14.87.

5-(2-Aminopirimidin-4-yl)-4-hydroxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidin-9-amine (2):[4a] A solution of **31c** (39 mg, 0.1 mmol), stannane **26** (60 mg, 0.2 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol), PPh_3 (3 mg, 0.012 mmol), LiCl (12 mg, 0.3 mmol), and CuI (1 mg, 0.006 mmol) in dioxane (1 mL) was heated at reflux for 1.5 h. The solvent was eliminated under reduced pressure, and the residue was treated with hydrogen chloride–methanol solution (5 mL) and heated again to reflux for 1 h. Then, the reaction mixture was concentrated under reduced pressure, and the residue was treated with CH_2Cl_2 (1 mL). The organic phase was extracted with HCl (4 N), and the two phases were separated. The aqueous phase was basified with powdered Na_2CO_3 and extracted with CH_2Cl_2, and the combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) to provide diamine **27c** (15 mg, 48%) as a yellow powder, which was used in the next step.[8d] A solution of **27c** (16 mg, 0.05 mmol), $Pd_2(dba)_3$ (2.5 mg, 0.0025 mmol), di-*tert*-butylphenylphosphane (1 mg, 0.005 mmol), and NaO*t*Bu (10 mg, 0.1 mmol) in toluene/*t*BuOH (5:1, 2 mL) in a sealed reaction vessel and under a dry argon atmosphere was irradiated in a microwave oven (CEM-Discovery) at 150 °C and 300 W (IR monitoring temperature) for 2 min. The solvent was evaporated, and the residue was dissolved in hydrogen chloride–methanol solution (2 mL) at room temperature for 30 min. Then, the reaction mixture was basified with 30% aqueous NH_4OH, saturated with solid NaCl, extracted with CH_2Cl_2, and dried (Na_2SO_4). After evaporation of CH_2Cl_2, the residue was purified by chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) to yield pure **2** (48%). Yellow solid. M.p. >300 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.79 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 3-H), 7.00 (br. s, 2 H, NH_2), 7.13 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 5′-H), 7.24 (d, $^3J_{H,H}$ = 6.7 Hz, 1 H, 6-H), 7.63 (d, $^3J_{H,H}$ = 6.7 Hz, 1 H, 7-H), 8.15 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 2-H), 8.26 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 6′-H), 8.50 (br. s, 1 H), 9.70 (br. s, 1 H), 16.04 (s, 1 H) ppm.

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