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Total Syntheses of Variolin B and Deoxyvariolin B[1]

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Two alternative synthetic routes have been developed for the preparation of variolin B and deoxyvariolin B. The strategy is based on the preparation of the core tricyclic ring common to all variolins, pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, followed by a palladium-catalyzed cross-coupling reaction to give the tetracyclic system.

Variolins **1**−**4** (Figure 1) comprise a group of marine heterocyclic substances isolated from the Antarctic sponge *Kirkpatrickia variolosa*.[2,3] They have a common tricyclic ring skeleton, which has no precedents in either terrestrial or marine natural products, namely a pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine; in each case the nucleus carries a substituent at position 5. Pharmacological evaluation of these compounds showed important antiviral and antiproliferative activity against P388 leukaemia cells.[2,3] Variolin B (**2**) is the most active of the family, oxidation or reduction of the isolated D ring as in variolin A (**1**) or *N*-3′-methyl-3′,4′,5′,6′-tetrahydrovariolin B (**3**), respectively, reduces the activity. The biological importance of the aminopyrimidine substituent at C5 is corroborated by the lack of activity of variolin D (**4**) in which C5 carries only a methoxycarbonyl group.

Herein, total syntheses of variolin B and deoxyvariolin B based on novel strategies are presented.[4] Our approach for the synthesis of both the natural product and non-natural analogues is based on the construction of the tricyclic pyridopyrrolopyrimidine core starting with a 7-azaindole **5** followed by the introduction of the C5 substituent, the D ring, by a palladium-catalyzed cross-coupling reaction. We used two alternative procedures for the construction of the aminopyrimidine ring C, assembling first a 2-aminoethyl-substituted 7-azaindole, **8**. For the preparation of deoxyvariolin B the cyclization of **8a** was achieved by using triphosgene [$(Cl_3CO)_2CO$] to give tetrahydropyrimidinone **9a**. The use of an intermediate of this type required the transformation of the tetrahydropyrimidone unit into a 2-aminopyrimidine unit. To avoid the need for this transformation, a more convergent strategy was used subsequently for the synthesis of variolin B, thus, by employing *N*-tosyldichloromethanimine ($TsN{=}CCl_2$) as a cyclization reagent, compound **8b** could be converted in one step into the protected aminodihydropyrimidine **14** (Scheme 1) requiring only deprotections and a dehydration to form **16**.

In our preliminary studies aimed at the preparation of the tricyclic compound **11a**, we attempted the cyclization of **13** anticipating intramolecular electrophilic attack at the α position of the π-rich five-membered ring. However, with use of a variety of conditions,[5] with different acids, no traces of the desired tricycle **11a** could be detected. The 1-substituted 7-azaindole **13** was obtained by reaction of 7-azaindole with aminoacetaldehyde dimethyl acetal, triphosgene, and diisopropylethylamine (DIPEA), following a protocol with minor modifications described for the preparation of simpler unsymmetrically substituted ureas.[6]

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(5) Conditions: (a) dry HCl in benzene at reflux temperature, (b) aq 2 N HCl in benzene at reflux, (c) BBr_3 in benzene at room temperature and reflux, (d) concentrated H_2SO_4 at 100 °C, (e) TFA at reflux, (f) MsOH at 100 °C.

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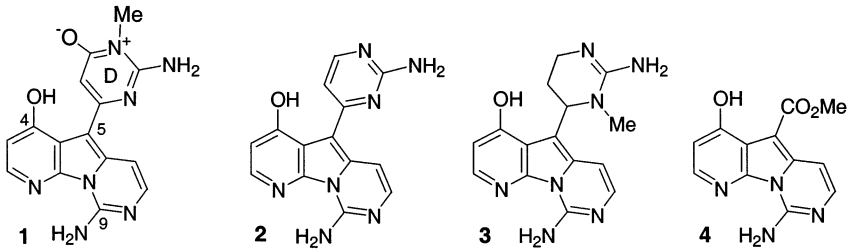
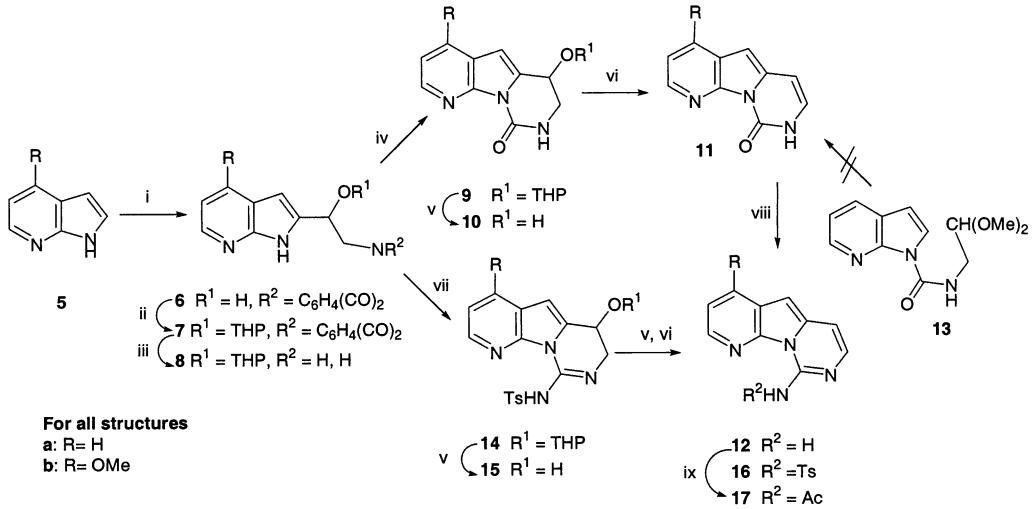


FIGURE 1. Structures of variolins **1**−**4**.

SCHEME 1. Preparation of 9-Aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines 12, 16, and 17[a]



[a] Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C to rt, (b) CO_2, −78 °C, (c) *t*-BuLi, THF, −78 °C, (d) 2-phthalimidoacetaldehyde, THF, −78 °C to rt; (ii) DHP, HCl, benzene, $CHCl_3$, △; (iii) $NH_2NH_2 \cdot H_2O$, EtOH, △; (iv) $(Cl_3CO)_2CO$, DIPEA, CH_2Cl_2, rt; (v) 4 N HCl, CH_2Cl_2; (vi) MsCl, TEA, CH_2Cl_2, 0 °C; (vii) $TsN{=}C(Cl)_2$, DIPEA, CH_2Cl_2; (viii) (a) TMSCl, HMDSA, 2,6-lutidine, (b) NH_3, 150 °C, 60 psi; (ix) Ac_2O, THF, rt.

Results and Discusion

Preparation of 9-Aminopyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidines 12, 16, and 17. Commercially available 7-azaindole **5a** was converted into a 2-lithiated species with use of the device first described by Katritzky for indole,[7] in which the nitrogen is blocked by successive reactions with *n*-BuLi, then CO_2, generating NCO_2Li, and then, without isolation, in situ *C*-lithiation is achieved with *t*-BuLi. Reaction of the lithiated species with 2-phthalimidoacetaldehyde[8] gave the alcohol **6a** in 44% yield, with characteristic signals in its ^{1}H NMR spectrum for the three protons of the aminoethanol chain constituting an ABX system at δ 3.88, 4.00, and 5.06 ppm. For the next step, protection of the hydroxyl group was necessary to avoid the competitive formation of an oxazolidinone during the preparation of the tricyclic system. We chose to use a tetrahydropyranyl ether as the protecting group since it offered the advantages of being orthogonal[9] to the phthalimide protecting group, and also having sufficient stability to survive the conditions needed for the cyclization. Furthermore, we anticipated that the acidic conditions for its removal might also lead to dehydration and thus the formation of pyrimidinone **11** in a one-pot deprotection/dehydration. Elimination of the phthaloyl protecting group by hydrazinolysis gave **8a**.

The tetrahydropyrimidine **9a** was obtained as a 1:1 diastereomeric mixture in 76% yield by reaction of **8a** and triphosgene and DIPEA in CH_2Cl_2 at room temperature for a short time. A strong absorption at ν 1716 cm^{-1} in the IR spectrum of the product confirmed the cyclization to **9a**. The diastereomeric mixture, without separation, was quantitatively *O*-deprotected with aq 4 N HCl in chloroform, but disappointingly without dehydration. The very polar **10a** was isolated and characterized as its hydrochloride, and used as such for further synthetic steps.

Several conditions were tested for dehydration of **10a** under acidic conditions,[10] but all attempts, rather surprisingly, led to the recovery of the benzylic alcohol. The required 1,2-elimination of water was finally achieved by mesylation of the alcohol **10a** with MsCl and triethylamine (TEA) at 0 °C, giving the pyrimidinone **11a** in a high yield. The two coupled doublets at δ 6.50 and 6.79 ppm with a coupling constant of 7.4 Hz for the protons at C6 and C7, replacing the ABX system of the precursor tetrahydropyrimidine, confirmed the structure of **11a**.

The 9-aminopyrimidine system of compound **12a** required the conversion of the carbonyl group of **11a** into a leaving group for displacement with ammonia. The

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(10) Conditions: (a) concentrated H_2SO_4 at room temperature, (b) TsOH in $CHCl_3$ at reflux, (c) dry HCl in benzene with a Dean−Stark separator.

preparation of the corresponding chloropyrimidine from **11a** with use of $POCl_3$ at room temperature or reflux, using $POCl_3$ and PCl_5 in a solvent ($CHCl_3$) or without a solvent, at varying temperatures and for various times, was unsuccessful—starting material **11a** was quantitatively recovered in the milder conditions and only decomposition products were produced at reflux, for example, in $POCl_3$ for 2 h. The functional group interconversion was finally achieved in a 30% yield for the two steps by transformation of the pyrimidinone ring into the *O*-trimethylsilylpyrimidine by reaction with hexamethyldisilazane (HMDSA), followed by a reaction with ammonia at 150 °C and 60 psi in a Parr reactor following a procedure reported by Vorbrüggen for the preparation of 4-amino-2-pyrimidinones.[11] In the *O*-silylation step, we used 2,6-lutidine as a cosolvent because **11a** was not soluble in HMDSA. Significant differences in the ^{1}H NMR spectra of **11a** and **12a** confirmed the transformation, thus the chemical shifts for the protons at C6 and C7 of **12a** were further downfield, at δ 6.72 and 7.30 ppm, and the coupling constant was reduced to 6.6 Hz, both features in agreement with the formation of a fully aromatic ring.

Following a comparable sequence, the pyrimidinone **11b** was obtained from 4-methoxy-7-azaindole **5b**[12] via intermediates **6b**, **7b**, **8b**, **9b**, and **10b**. However, the transformation of pyrimidinone **11b** into the aminopyrimidine **12b**, using the conditions developed for the deoxy-series, afforded a mixture of **12b** and recovered **11b** in yields of 22% and 15%, respectively, for the two-step sequence. Increasing the temperature and pressure for the nucleophilic substitution step resulted only in a more complex mixture, due probably to competitive and/or additional substitution of the C4 methoxy group.

The greater reactivity of **11b** in comparison with **11a** made it necessary to develop an alternative procedure to avoid the pyrimidinone → amino-pyrimidine transformation in the methoxy series. Since it was the aim to introduce a carbon and a nitrogen, directly, just as a carbon and an oxygen had been introduced in the formation of **9** using a phosgene synthon, we considered the use of a nitrogen analogue of phosgene, $O{=}CCl_2$, namely *N*-tosyldichloromethanimine[13] ($TsN{=}CCl_2$). An examination of the literature showed that this reagent had been used in several situations for cyclizations producing five-membered rings, where 1,4-related bis-nucleophiles had been reacted to give five-membered rings carrying TsHN on the carbon between the two nucleophilic atoms; examples include closures with two nitrogens,[14] a nitrogen and an oxygen,[15] and a nitrogen and a carbon.[16] There are no examples of six-membered-ring formation by reaction of $TsN{=}CCl_2$ with a 1,5-diamine; however, the comparable reagent $TsN{=}C(SMe)_2$ has been used to construct six-membered *N*-tosylguanidines.[17]

We were delighted to find that the reaction of $TsN{=}CCl_2$ with **8a** and with **8b** led to the formation of 9-tosylamino dihydropyrimidines **14a** and **14b**. Reaction of **8a** with $TsN{=}CCl_2$ and DIPEA in dichloromethane at room temperature afforded **14a** (60%), which was then *O*-deprotected to **15a** and dehydrated to **16a** (74% for the two steps) by using the conditions described above. Similarly, in the methoxy series, **8b** was converted into **16b** in 44% yield for the three steps.

It was essential to have a good experimental procedure to remove the tosyl protecting group—although many protocols for achieveing *N*-detosylation exist, no generally applicable method has emerged. Using **16a**, several of the reported experimental conditions were tested for the detosylation: treatment with aqueous HBr,[18] HBr and AcOH in phenol at reflux temperature,[19] aqueous HI, HF,[20] Mg and NH_4Cl in EtOH,[21] Red-Al in toluene at different temperatures,[22] and NaOH in MeOH or DCM all failed to bring about *N*-tosyl deprotection. Only with Na in liquid ammonia[23,24] was **12a** obtained, but then only in a 38% yield; Na-naphthalene[25] in THF at −78 °C gave the *N*-deprotected **12a** in a 25% yield. A much better result was obtained by using a reductive photolysis of the tosyl group, thus irradiation with a high-pressure Hg lamp with a Pyrex filter, $NaBH_4$ as a reducing agent, and 1,4-dimethoxybenzene as an electron source[26] allowed the removal of the *N*-tosyl group from **16a** in a 64% yield.

Introduction of Ring D. Now came the introduction of ring D by a palladium-catalyzed cross-coupling reaction, the procedure that had allowed us to prepare simpler 3-aryl- and 3-heteroaryl-7-azaindoles[27] and 5-arylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones.[28] Thus, from **12a** via the *N*-acetylated derivative **17a**,[29] the 5-iodo derivative **18a** was produced in good yield (93%) with use of *N*-iodosuccinimide (NIS) at low temperature in chloroform for a short time. The regiochemistry of the iodination of **17a** was evidenced by the absence of a ^{1}H NMR C5 singlet signal (δ 6.53 ppm in **17a**) and by the presence in the aromatic region of an ABC system for the pyridine and an AB system for the pyrimidine protons.

The coupling of **18a** with **19**,[30] using a combination of $Pd_2(dba)_3$ (18%), PPh_3 (40%), LiCl, and CuI at reflux

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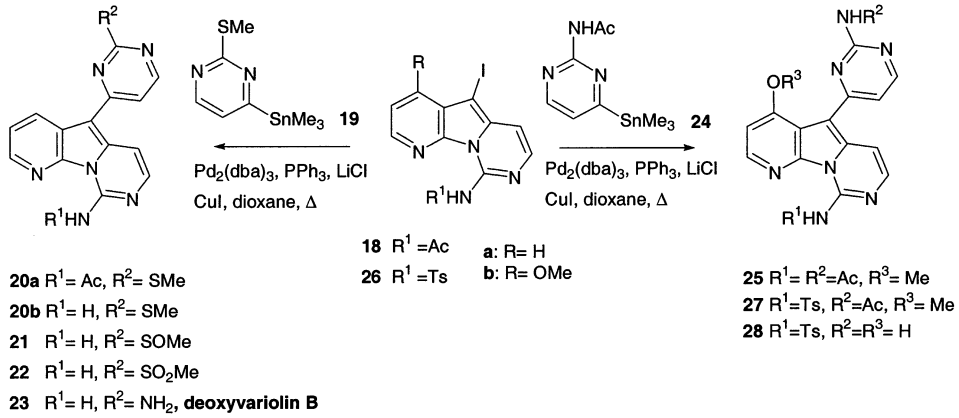
(29) Protection of the 9-amino group was important because the iodination of **12a** gave an unidentified iodinated product that decomposed during attempted purification, presumably the result of iodine attack at the primary amine.

SCHEME 2. Palladium-Catalyzed Cross-Coupling Reactions for the Introduction of D Ring



temperature of dioxane, gave a mixture of the anticipated acetamide **20a** and its corresponding amine **20b**.[31] For convenience, the product mixture was not routinely separated but converted completely into the amine with dry HCl in methanol, yielding **20b** in a 45% yield for the two steps. The introduction of the new pyrimidine ring was proved by the ^{1}H NMR spectrum in which there was a new AB system at δ 7.33 and 8.48 ppm with a coupling constant of 5.4, and also by the three-hydrogen singlet at δ 2.68 ppm of the methylthio substituent.

For the transformation of **20b** into deoxyvariolin B there only remained the substitution of the methylthio group with an amino group. For that purpose **20b** was *S*-oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to sulfone **22**. The sulfoxide **21** could be obtained in a 90% yield by treatment of **20b** with 1.8 equiv of *m*-CPBA at 0 °C during 30 min in CH_2Cl_2. Oxidation of **21** to **22** also proceeded in good yield with *m*-CPBA. The substitution of the methanesulfonyl group of **22** was effected with ammonium hydroxide in dioxane at reflux, giving deoxyvariolin B **23** in excellent yield.

Finally, in the methoxy series, **18b** was prepared from **12b** in the same way, and with similar yields as those found for the deoxy compounds. To make a more convergent synthesis, by removing the necessity for the MeS $\rightarrow$ NH_2 interconversion, the tin derivative **24** was prepared from 4-chloro-2-aminopyrimidine[32] by *N*-protection then halogen metal interchange by reaction with hexamethylditin catalyzed by $Pd(PPh_3)_4$.

The coupling reaction in the same conditions as before between the iodo derivative **18a** and the tin derivative **24** followed by treatment with aq HCl gave deoxyvariolin B **23** in a 54% yield for the two steps. Using for the coupling reaction the iodo compound **18b** and the tin derivative **24** gave only a 40% yield of the expected fully protected variolin B, **25**; however, using the tosyl derivative **26b** and the organometallic **24** afforded **27**, a fully protected variolin B, in a satisfying 75% yield. Simultaneous deprotection of the methoxy and 3′*N*-acetyl groups was achieved by treatment of **27** with an aqueous solution of hydrobromic acid at reflux for 10 min to give the *N*-tosyl variolin B **28** in a 60% yield. Application of the photochemical *N*-detosylation procedure used for deoxyvariolin, but with $H_2NNH_2 \cdot H_2O$ as a reducing agent instead of $NaBH_4$, then gave variolin B **2** in a 30% yield.

The synthetic product had identical spectroscopic data with those described for the natural alkaloid and showed identical TLC and HPLC behavior as a sample of the natural product supplied by Pharma Mar.

In conclusion, we have developed a novel synthetic route from an azaindole for the preparation of deoxyvariolin B via a pyrimidone functionalized C ring and for variolin B via a protected aminopyrimidine. This approach is flexible for the preparation of analogues differing in the ring D with use of other aryl or heteroaryl organometallics for the coupling reaction with the iodo compounds **18** or **26**. Using pyridine-ring-substituted 7-azaindoles as starting materials will provide opportunities for further diversity, producing variants with substituents in the A ring.

Experimental Section

2-(1-Hydroxy-2-phthalimidoethyl)-7-azaindole (6a). To a cooled (−78 °C) solution of 7-azaindole **5a** (7.6 g, 64 mmol) in dry THF (150 mL) was added *n*-BuLi (44 mL, 1.6 M in hexane) and the mixture was stirred for 10 min. Dry CO_2 was bubbled through the mixture for 40 min. The solvent was evaporated and the residue was dissolved in fresh dry THF (400 mL). The solution was cooled at −78 °C and *t*-BuLi (42 mL, 1.7 M in hexane) was added. The mixture was stirred for 20 min then a solution of 2-phthalimidoacetaldehyde (14 g, 71 mmol) in THF (400 mL) was added slowly. After 1.5 h the reaction was quenched with saturated aq NH_4Cl (100 mL) and the organic solvent evaporated. The mixture was dissolved in CH_2Cl_2 and washed with water, then the organic solution was dried and evaporated. The crude product was purified by flash column chromatography, where elution with CH_2Cl_2/acetone (95/5) gave 7-azaindole **5a** (3.8 g, 50%) and with CH_2Cl_2/MeOH (98/2) afforded **6a** (8.7 g, 44%) as a white solid. Mp 231−232 °C (CH_2Cl_2/MeOH). IR (KBr) ν 3200 (m, NH),1760 (s, C=O), 1704 (s, NCO), 1427 (m, C−N), 1395 (m, C−O). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.88 (dd, J = 13.6 and 6.0 Hz, 1H, H2′), 4.00 (dd, J = 13.6 and 7.8 Hz, 1H, H2′), 5.06 (ddd, J = 7.8, 6.0, and 5.2 Hz, 1H, H1′), 5.83 (d, J = 5.2 Hz, 1H, OH), 6.34 (d, J = 1.8 Hz, 1H, H3), 6.99 (dd, J = 8.0 and 4.8 Hz, 1H, H5), 7.81−7.88 (m, 4H, Phth), 7.89 (dd, J = 8.0 and 1.4 Hz, 1H, H4), 8.14 (dd, J = 4.8 and 1.4 Hz, 1H, H6), 11.75 (br s, 1H, NH). ^{13}C NMR (DMSO d_6, 75 MHz) δ 43.6 (t, C2′), 64.4 (d, C1′), 96.8 (d, C3), 115.4 (d, C5), 119.8 (s, C3a), 123.0 (d, Phth-β), 127.6 (d, C4), 131.6 (s, Phth-ipso), 134.3 (d, Phth-α), 140.8 (s, C2), 142.1 (d, C6), 148.6 (s, C7a), 167.7 (s, Phth-CO). MS (EI) *m*/*z* 308 (6), 307 (M^+, 25), 244 (8), 160 (43), 147 (100),

(30) Majeed, A. J.; Antonsen, Φ.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993−1006. The preparation of **19** was improved—see Experimental Section.

(31) Acetamide **20a** and amine **20b** could be separated by column chromatography. See Experimental Section.

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119 (52). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C (66.44), H (4.26), N (13.67). Found: C (65.11), H (4.26), N (13.37).

2-(1-Hydroxy-2-phthalimidoethyl)-4-methoxy-7-azaindole (6b). To a cooled (−78 °C) solution of 4-methoxy-7-azaindole **5b**[12] (3.55 g, 24 mmol) in THF (75 mL) was added *n*-BuLi (16.5 mL, 1.6 M in hexane) and the mixture was stirred for 10 min. Dry CO_2 was bubbled through the mixture for 40 min. The solvent was evaporated and the residue was dissolved in fresh dry THF (175 mL). The solution was cooled at −78 °C and *t*-BuLi (15.5 mL, 1.7 M in hexane) was added. The mixture was stirred for 20 min. A solution of 2-phthalimidoacetaldehyde (5 g, 26 mmol) in THF (100 mL) was added slowly. After 1.5 h the reaction was quenched with saturated aq NH_4Cl (50 mL) and the organic solvent evaporated. The residue was dissolved in CH_2Cl_2 and washed with water, then the solution was dried and evaporated to leave material that was purified by flash column chromatography. Elution with CH_2Cl_2/acetone (95/5) gave **5b** (2.06 g, 58%) and with CH_2Cl_2/MeOH (98/2) gave **6b** (3.68 g, 43%) as a white solid. Mp 225−226 °C (from CH_2Cl_2/MeOH). IR (KBr) ν 3500 (s, NH/OH), 1702 (s, C═O), 1594 (m), 1395 (m). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.88 (s, 3H, Me), 3.86 (dd, J = 13.8 and 6.0 Hz, 1H, H2′), 3.95 (dd, J = 13.8 and 7.8 Hz, 1H, H2′), 5.00 (ddd, J = 7.8, 6.0, and 5.1 Hz, 1H, H1′), 5.73 (d, J = 5.1 Hz, 1H, OH), 6.30 (d, J = 1.8 Hz, 1H, H3), 6.58 (d, J = 5.4 Hz, 1H, H5), 7.83 (m, 4H, Phth), 8.02 (d, J = 5.4 Hz, 1H, H6), 11.65 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 43.6 (t, C2′), 55.3 (q, Me), 64.2 (d, C1′), 94.0 (d, C5), 97.8 (d, C3), 109.5 (s, C3a), 123.0 (d, Phth-β), 131.6 (s, Phth-ipso), 134.3 (d, Phth-α), 138.1 (s, C2), 144.2 (d, C6), 150.3 (s, C7a), 158.5 (s, C4), 167.7 (s, Phth-CO). MS (EI) *m*/*z* 338 (4), 337 (M^+, 20), 319 (44), 177 (100). Anal. Calcd for $C_{18}H_{15}N_3O_4 \cdot {}^1/_4H_2O$: C (63.25), H (4.57), N (12.29). Found: C (63.32), H (4.54), N (12.07).

2-(2-Amino-1-hydroxyethyl)-7-azaindole. To a solution of **6a** (250 mg, 0.80 mmol) in EtOH (25 mL) was added NH_2-$NH_2 \cdot H_2O$ (40 μL, 0.80 mmol). The solution was refluxed for 2.5 h then the solvent was removed under vacuum. The residue was dissolved in 2 N NaOH (10 mL) and the solution continuously extracted with CH_2Cl_2 to give the title compound (140 mg, 100%) as a white solid. IR (film) ν 3200 (s, NH/OH), 1593 (m, C═N), 1422 (m, C−N), 1286 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.91 (br s, 2H, CH_2), 4.74 (br s, 1H, CH), 6.15 (s, 1H, H3), 6.90 (dd, J = 8.0 and 4.8 Hz, 1H, H5), 7.72 (dd, J = 8.0 and 1.4 Hz, 1H, H4), 8.05 (dd, J = 4.8 and 1.4 Hz, 1H, H6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1 (t, CH_2), 68.9 (d, CH), 96.8 (d, C3), 115.6 (d, C5), 121.1 (s, C4a), 128.8 (d, C4), 140.9 (s, C2), 141.6 (d, C6), 147.8 (s, C7a). MS (EI) *m*/*z* 177 (M^+, 1), 148 (100), 119 (67).

2-[2-Oxo-1,3-oxazolidin-5-yl]-7-azaindole. A solution of triphosgene (32 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added at room temperature to a solution of 2-(2-amino-1-hydroxyethyl)-7-azaindole (50 mg, 0.27 mmol) and DIPEA (107 μL, 0.60 mmol) in CH_2Cl_2 (5 mL). After being stirred for 1 h the mixture was quenched with saturated aq NH_4Cl (10 mL), the organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined and dried organic solutions were evaporated and the residue was purified by flash column chromatography, elution with CH_2Cl_2/MeOH (98/2) giving the title compound (13 mg, 25%) and elution with CH_2Cl_2/MeOH (9/1) giving **10a** (11 mg, 20%). Spectroscopic data for 2-[2-oxo-1,3-oxazolidin-5-yl]-7-azaindole: IR (film) ν 3244 (m, NH), 1740 (s, C═O), 1298 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.97 (dd, J = 10.5 and 4.8 Hz, 1H, H4′), 4.48 (dd, J = 10.5 and 8.7 Hz, 1H, H4′), 6.18 (dd, J = 8.7 and 4.8 Hz, 1H, H5′), 6.80 (s, 1H, H3), 7.25 (dd, J = 7.8 and 4.5 Hz, 1H, H3), 7.88 (dd, J = 7.8 and 1.5 Hz, 1H, H4), 8.48 (dd, J = 4.5 and 1.5 Hz, 1H, H4), 11.80 (br s, 1H, NH). MS (EI) *m*/*z* 203 (M^+, 4), 180 (100).

2-[2-Phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (7a). To a solution of **6a** (10.2 g, 33 mmol) in $CHCl_3$ (1 L) were added 6 N HCl in dry benzene (180 mL) and then 2,3-dihydropyran (46 mL, 330 mmol). The mixture was refluxed for 7 h. After cooling the mixture was washed with saturated aq $NaHCO_3$, dried, and evaporated and the residue was purified by flash column chromatography, elution with CH_2Cl_2/MeOH (97/3) giving **7a** (10.8 g, 87%), a diastereomeric mixture (NMR, 1:1), as a white solid. IR (film) ν 1717 (s, C═O), 1390 (m, C−O), 1026 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30−1.80 (m, 6H, H3″, H4″, and H5″), 3.25−3.45 (m, 2H, H2′), 3.80, 3.98, 4.22 and 4.38 (m, dd, J = 14.0 and 4.4 Hz, dd, J = 14.8 and 2.0 Hz, and dd, J = 14.0 and 9.4 Hz, 2H, H6″), 4.58 and 4.72 (dd, J = 3.2 and 2.8 Hz, and dd, J = 3.4 and 3.0 Hz, 1H, H2″), 5.30 and 5.39 (dd, J = 8.4 and 5.2 Hz, and dd, J = 9.2 and 4.0 Hz, 1H, H1′), 6.47 and 6.51 (d, J = 1.8 Hz, and d, J = 1.8 Hz, 1H, H3), 7.08 and 7.15 (dd, J = 8.2 and 4.8 Hz, and dd, J = 8.2 and 5.2 Hz, 1H, H5), 7.69 (m, 2H, Phth-β), 7.86 (m, 2H, Phth-α), 7.86 (m, 1H, H4), 8.43 and 8.63 (dd, J = 4.8 and 1.6 Hz, and dd, J = 5.0 and 1.7 Hz, 1H, H7), 10.8 and 12.5 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.8 and 19.9 (t), 25.0 and 25.2 (t), 30.2 and 30.8 (t), 41.6 and 42.8 (t, C6″), 61.8 and 63.6 (t, C2′), 69.3 and 71.7 (d, C1′), 95.5 and 97.9 (d, C2″), 100.3 and 100.8 (d, C3), 115.9 (d, C5), 120.6 and 120.7 (s, C3a), 123.2 and 123.4 (d, Phth-β), 128.7 and 128.8 (d, C4), 131.8 and 132.0 (s, Phth-ipso), 133.9 and 134.0 (d, Phth-α), 136.5 and 137.8 (s, C2), 143.1 (d, C6), 148.7 and 149.2 (s, C7a), 168.1 (s, Phth-CO). MS (EI) *m*/*z* 391 (M^+,1), 307 (9), 147 (38), 85 (100). Anal. Calcd for $C_{22}H_{21}N_3O_4 \cdot {}^1/_2H_2O$: C (65.99), H (5.54), N (10.49). Found: C (66.02), H (5.80), N (10.28).

4-Methoxy-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (7b). Following the same procedure as for **7a**, from **6b** (3.8 g, 11 mmol) in $CHCl_3$ (350 mL), 6 N HCl in benzene (35 mL) and 2,3-dihydropyran (10 mL, 110 mmol), **7b** (3.07 g, 65%) was obtained as a diastereomeric mixture (NMR, 1:1). IR (film) ν 1714 (s, C═O), 1392 (m, C−O), 1026 (m, C−O). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30−1.80 (m, 6H, H3″, H4″, and H5″), 3.25−3.45 (m, 2H, H2′), 3.99 and 4.01 (s, 3H, OMe), 3.96, 4.08, 4.28 and 4.39 (dd, J = 13.5 and 3.9 Hz, dd, J = 13.8 and 4.6 Hz, dd, J = 13.8 and 8.5 Hz, and dd, J = 13.5 and 9.6 Hz, 2H, H6″), 4.57 and 4.73 (br t, J = 3.2 Hz, and br t, J = 3.4 Hz, 1H, H2″), 5.25 and 5.33 (dd, J = 6.9 and 2.4 Hz, and dd, J = 9.9 and 4.1 Hz, 1H, H1′), 6.54 and 6.58 (br s and br s, 1H, H3), 6.56 and 6.62 (d, J = 5.7 Hz, and d, J = 5.7 Hz, 1H, H5), 7.68 (m, 2H, Phth-β), 7.83 (m, 2H, Phth-α), 8.38 and 8.57 (d, J = 5.7 Hz, and d, J = 5.7 Hz, 1H, H7), 11.7 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.9 and 19.5 (t), 25.0 and 25.3 (t), 30.2 and 30.7 (t), 42.0 and 43.0 (t, C6″), 55.4 (q, MeO), 61.7 and 62.9 (t, C2′), 69.4 and 71.5 (d, C1′), 94.4 and 95.3 (d, C2″), 97.7 (d, C5), 97.8 and 100.1 (d, C3), 110.5 (s, C3a), 123.1 and 123.2 (d, Phth-β), 132.1 and 132.1 (s, Phth-ipso), 133.8 and 133.9 (d, Phth-α), 134.0 and 135.2 (s, C2), 144.9 and 145.1 (d, C6), 150.6 and 151.1 (s, C7a), 159.8 (s, C4), 168.1 (s, Phth-CO). MS (EI) *m*/*z* 422 (2), 421 (M^+, 4), 337 (15), 177 (100). *M* calculated for $C_{23}H_{23}N_3O_5$ 421.1637; HRMS found (M^+) 421.1625.

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (8a). To a solution of **7a** (10.2 g, 26 mmol) in EtOH (630 mL) was added $NH_2NH_2 \cdot H_2O$ (1.53 mL, 31 mmol). The mixture was refluxed for 3 h, then the solvent was evaporated and the residue dissolved in CH_2Cl_2 and washed with saturated aq $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic solutions were evaporated to obtain **8a** (6.72 g, 100%), a light orange solid, as a diastereomeric mixture (NMR, 1:1). IR (film) ν 3200 (m, NH), 1421 (m, C−N), 1022 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.90 (m, 6H, H3″, H4″, and H5″), 3.20 (m, 2H, H2′), 3.48 and 3.90 (m, 1H, H6″), 4.60 and 4.85 (br t, J = 3.5 Hz, and m, 1H, H2″), 4.85 and 4.97 (m and br t, J = 5.7 Hz, 1H, H1′), 6.32 and 6.43 (s, 1H, H3), 7.03 and 7.07 (dd, J = 6.6 and 4.8 Hz, and dd, J = 6.6 and 5.0 Hz, 1H, H5), 7.85 and 7.90 (dd, J = 6.6 and 1.4 Hz, 1H, H4), 8.29 and 8.36 (dd, J = 4.8 and 1.4 Hz, and dd, J = 5.0 and 1.4 Hz, 1H, H7), 10.9 and 12.5 (br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7 and 20.0 (t), 25.1 and 25.3 (t), 30.6 and 30.9 (t), 45.3 and 47.3 (t, C6″), 62.9

and 63.5 (t, C2′), 73.4 and 75.5 (d, C1′), 96.1 and 97.3 (d, C2″), 99.8 and 99.9 (d, C3), 115.6 (d, C5), 120.7 (s, C3a), 128.4 and 128.5 (d, C4), 138.3 and 139.0 (s, C2), 142.2 and 142.3 (d, C6), 148.5 and 149.0 (s, C7a). MS (CI, CH_4) *m*/*z* 263 (15), 262 (M^+, 100). M + H calculated for $C_{14}H_{19}N_3O_2$ + H 262.1555; HRMS found $(M + H)^+$ 262.1557.

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-4-methoxy-7-azaindole (8b). Following the same procedure as for **8a**, from **7b** (2.9 g, 10 mmol) in EtOH (100 mL) and $NH_2NH_2{\cdot}H_2O$ (420 μL, 15 mmol), after a reaction time of 3 h, **8b** (1.9 g, 95%) orange foam was obtained as a diastereomeric mixture (NMR, 1:1). IR (film) ν 3150 (m, NH), 1590 (m, C═C), 1329 (m, C−N), 1114 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.90 (m, 6H, H3″−H5″), 3.19 (m, 2H, H2′), 3.48 and 3.90 (m, 1H, H6″), 3.99 and 4.00 (s, 3H, MeO), 4.60 and 4.85 (m, 1H, H2″), 4.85 and 4.97 (m and br t, J = 5.7 Hz, 1H, H1′), 6.42 and 6.51 (s, 1H, H3), 6.51 and 6.55 (d, J = 5.4 Hz, 1H, H5), 8.23 and 8.30 (d, J = 5.4 Hz, 1H, H7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0 (t), 25.2 and 25.4 (t), 30.7 and 30.9 (t), 45.4 and 47.4 (t, C6″), 55.4 and 55.5 (q, MeO), 62.9 and 63.4 (t, C2′), 73.5 and 75.5 (d, C1′), 94.7 and 96.1 (d), 97.1 and 99.6 (d, C3), 97.6 (d, C5), 110.5 (s, C3a), 135.8 and 136.5 (s, C2), 144.3 and 144.4 (d, C6), 150.3 and 151.3 (s), 159.4 and 159.5 (s). MS (CI, CH_4) *m*/*z* 291 (M^+, 2), 262 (12), 190 (8), 177 (100). *M* calculated for $C_{15}H_{21}N_3O_3$ 291.1582; HRMS found M^+ 291.1571.

6,7,8,9-Tetrahydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (9a). A solution of **8a** (7.4 g, 28 mmol) and DIPEA (5 mL, 28 mmol) in CH_2Cl_2 (300 mL) was slowly added to a solution of triphosgene (2.82 g, 10 mmol) in CH_2Cl_2 (740 mL), and the mixture was stirred at room temperature for 30 min. The mixture was washed with saturated aq NH_4Cl and then with water, dried, and evaporated to give **9a** (6.06 g, 76%), a yellow foam, as a diastereomeric mixture (NMR, 1:1). IR (KBr) ν 3252 (m, NH), 1716 (s, C═O), 1407 (m, C−N), 1302 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.80 (m, 6H, H3′, H4′, and H5′), 3.45−4.00 (m, 2H, H7 and H6′), 3.90 (m, 2H, H7 and H6′), 4.71 and 4.94 (m, 1H, H2′), 5.04 and 5.10 (dd, J = 3.2 and 3.0 Hz, and t, J = 4.4 Hz, 1H, H6), 6.56 and 6.59 (s, 1H, H5), 6.79 and 7.00 (br s, 1H, NH), 7.20 and 7.22 (dd, J = 7.6 and 4.8 Hz, and dd, J = 8.0 and 4.8 Hz, 1H, H3), 7.89 and 7.93 (dd, J = 7.6 and 1.8 Hz, and dd, J = 8.0 and 1.8 Hz, 1H, H4), 8.54 and 8.57 (dd, J = 4.8 and 1.8 Hz, and dd, J = 4.8 and 1.4 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.9 and 19.3 (t, C4′), 25.3 and 25.4 (t, C5′), 30.1 and 30.4 (t, C3′), 43.5 and 45.3 (t, C6′), 62.2 and 62.6 (t, C7), 63.2 and 64.3 (d, C6), 95.7 and 96.7 (d, C2′), 102.3 and 103.7 (d, C5), 118.6 (d, C3), 121.3 and 121.7 (s, C4a), 129.1 and 129.2 (d, C4), 133.5 and 136.1 (s, C5a), 145.2 and 145.6 (d, C2), 148.0 and 148.1 (s, C10a), 149.8 and 150.2 (s, C9). MS (CI, CH_4) *m*/*z* 289 (6), 288 (M^+, 25), 204 (23), 85 (100). M + H calculated for $C_{15}H_{17}N_3O_3$ + H 288.1348; HRMS found $(M + H)^+$ 288.1352.

6,7,8,9-Tetrahydro-6-(2,3,5,6-tetrahydropyran-2-yl)-oxy-4-methoxy-pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidin-9-one (9b). Following the same procedure as for **9a**, **9b** was obtained from triphosgene (20 mg, 0.07 mmol) in CH_2Cl_2 (3 mL), **8b** (58 mg, 0.20 mmol), and DIPEA (34 μL, 0.20 mmol) in CH_2Cl_2 (3 mL), with a reaction time of 30 min at room temperature. The crude product was purified by flash column chromatography, elution with CH_2Cl_2/MeOH (98/2) giving **9b** yellow foam (40 mg, 63%) as a diastereomeric mixture (NMR, 1:1). IR (KBr) ν 3258 (m, NH), 1714 (s, C═O), 1566 (m, C═N), 1290 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.80 (m, 6H, H3′, H4′, and H5′), 3.45 and 3.95 (m, 2H, H6′), 3.65 and 3.75 (m, 2H, H7), 4.00 (s, 3H, MeO), 4.67 and 4.94 (m, 1H, H2′), 4.99 and 5.07 (m, 1H, H6), 6.20 and 6.30 (br s, 1H, NH), 6.65 and 6.66 (s, 1H, H5), 6.69 (d, J = 5.9 Hz, 1H, H3), 8.44 and 8.46 (d, J = 5.9 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.7 and 19.4 (t, C4′), 25.3 and 25.4 (t, C5′), 30.1 and 30.3 (t, C3′), 43.5 and 45.3 (t, C6′), 61.9 and 62.6 (t, C7), 62.9 and 63.9 (d, C6), 95.5 and 96.2 (d, C2′), 99.6, 100.6 and 101.1 (d, C3 and C5), 130.9 (s, C5a), 147.3 and 147.7 (d, C2), 149.9 and 150.3 (s, C10a or C4), 159.7 (s, C9). MS (EI) *m*/*z* 318 (2), 317 (M^+, 28), 233 (22), 217 (66), 216 (65), 177 (100), 85 (100). *M* calculated for $C_{16}H_{19}N_3O_4$ 317.1376; HRMS found (M^+) 317.1383.

6,7,8,9-Tetrahydro-6-hydroxypyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidin-9-one (10a). To a solution of **9a** (6 g, 21 mmol) in CH_2Cl_2 (400 mL) was added 4 N aq HCl (400 mL). After 45 min of stirring at room temperature the two layers were separated and the organic layer re-extracted with 4 N aq HCl. The combined aqueous solutions were filtered and evaporated to obtain **10a** hydrochloride (5 g, 100%) as a light orange solid. IR (KBr) ν 3500 (s, OH), 1721 (s, C═O), 1638 (m, C═C), 1503 (m, C═N). ^{1}H NMR (CD_3OD, 300 MHz) δ 3.61 (dd, J = 13.0 and 5.0 Hz, 1H, H7), 3.77 (dd, J = 13.0 and 4.0 Hz, 1H, H7), 5.23 (dd, J = 5.0 and 4.0 Hz, 1H, H6), 7.05 (s, 1H, H5), 7.86 (dd, J = 8.0 and 6.0 Hz, 1H, H3), 8.56 (dd, J = 6.0 and 1.2 Hz, 1H, H2), 8.86 (dd, J = 8.0 and 1.2 Hz, 1H, H4). ^{13}C NMR (CD_3OD, 75 MHz) δ 45.8 (t, C7), 59.6 (d, C6), 101.9 (d, C5), 119.0 (d, C3), 127.1 (s, C4a), 124.3 (d, C4), 137.4 (s, C5a), 139.4 (d, C2), 141.9 (s, C10a), 149.0 (s, C9). MS (CI, NH_3) *m*/*z* 205 (3), 204 (M^+, 4), 180 (100), 163 (50), 130 (90). *M* calculated for $C_{10}H_{10}N_3O_3$ 204.0773; HRMS found (M^+) 204.0772.

A solution of **10a** hydrochloride in saturated aq Na_2CO_3 was continuously extracted with CH_2Cl_2 to give the free base. IR (KBr) ν 3400 (m, NH/OH), 1707 (s, C═O), 1468 (m, C−N), 1408 (m, C−N), 1297 (m, C−O). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.27 (m, 1H, H7), 3.42 (m, 1H, H7), 4.90 (dd, J = 9.3 and 5.1 Hz, 1H, H6), 5.88 (d, J = 5.1 Hz, 1H, OH), 6.54 (s, 1H, H5), 7.21 (dd, J = 7.4 and 4.2 Hz, 1H, H3), 7.88 (br s, 1H, NH), 7.99 (br d, J = 7.4 Hz, 1H, H2), 8.30 (br d, J = 4.2 Hz, 1H, H4). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.0 (t, C7), 55.7 (d, C6), 95.4 (d, C5), 113.8 (d, C3), 116.7 (s, C4a), 124.2 (d, C4), 135.4 (s, C5a), 139.3 (d, C2), 142.9 (s, C10a), 143.8 (s, C9).

6,7,8,9-Tetrahydro-6-hydroxy-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (10b). To a solution of **9b** (25 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) was added 4 N aq HCl (5 mL) and the mixture was stirred at room temperature for 45 min. The organic layer was separated and re-extracted with 4 N aq HCl. The combined aqueous solutions were filtered and evaporated to obtain **10b** hydrochloride (20 mg, 95%) as a light orange solid. IR (film) ν 3244 (m, NH), 1718 (s, C═O), 1627 (s, NCO), 1505 (m, C═N), 1298 (m, C−O). ^{1}H NMR (CD_3OD, 200 MHz) δ 3.56 (dd, J = 13.6 and 4.8 Hz, 1H, H7), 3.71 (dd, J = 13.6 and 3.6 Hz, 1H, H7), 4.29 (s, 3H, MeO), 5.11 (dd, J = 4.8 and 3.6 Hz, 1H, H6), 6.91 (s, 1H, H5), 7.40 (d, J = 6.9 Hz, 1H, H3), 8.42 (d, J = 6.9 Hz, 1H, H2). ^{13}C NMR (CD_3OD, 75 MHz) δ 48.9 (t, C7), 60.5 (q, Me), 62.3 (d, C6), 101.7 (d, C5), 105.5 (d, C3), 117.4 (s, C4a), 137.0 (s, C5a), 140.6 (d, C2), 141.4 (s, C10a), 151.9 (s, C9), 169.0 (s, C4). MS (EI) *m*/*z* 234 (12), 233 (M^+, 77), 215 (17), 55 (100). *M* calculated for $C_{11}H_{11}N_3O_3$ 233.0800; HRMS found (M^+) 233.0813.

8,9-Dihydropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (11a). To a cooled solution of **10a** (1 g, 4.2 mmol) and TEA (1.74 mL, 13 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added MsCl (320 μL, 4.2 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C then the organic solution was washed with saturated aq NH_4Cl and with water. The organic solution was dried and evaporated to obtain **11a** (730 mg, 95%) as a white solid pure enough to use without further purification; mp 265−266 °C (from MeOH). IR (KBr) ν 3424 (m, NH), 1721 (s, C═O), 1691 (m, NCO), 1633 (m, C═C), 1408 (m, C═N), 1380 (m), 1303 (m). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.50 (d, J = 7.4 Hz, 1H, H6), 6.60 (s, 1H, H5), 6.97 (dd, J = 7.4 and 5.3 Hz, 1H, H7), 7.37 (dd, J = 8.0 and 4.7 Hz, 1H, H3), 8.08 (dd, J = 8.0 and 1.7 Hz, 1H, H4), 8.39 (dd, J = 4.7 and 1.7 Hz, 1H, H2), 10.81 (br d, J = 5.3 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 94.9 (d, C5), 98.0 (d, C6), 119.8 (d, C3), 123.1 (s, C4a), 127.5 (d, C4), 128.0 (d, C7), 137.0 (s, C5a), 142.5 (d, C2), 145.6 (s, C10a), 146.7 (s, C9). MS (EI) *m*/*z* 186 (18), 185 (M^+, 15), 157 (M − CO, 10). MS (CI, NH_3) *m*/*z* 204 (M + 18, 12),

187 (14), 186 (M + 1, 100), 109 (48). *M* calculated for $C_{10}H_7N_3O$ 185.0589; HRMS found (M^+) 185.0593.

8,9-Dihydro-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidin-9-one (11b). Following the same procedure as for **11a**, from **10b** (113 mg, 0.42 mmol), TEA (195 μL, 1.25 mmol), and MsCl (32 μL, 0.42 mmol) in CH_2Cl_2 (20 mL) with a reaction time of 30 min, **11b** (74 mg, 85%) was obtained as a white solid requiring no further purification. IR (KBr) *ν* 3380 (m, NH), 1721 (s, C═O), 1693 (m, NCO), 1633 (m, C═C), 1500 (m, C═N), 1294 (m, C−O). ^{1}H NMR (DMSO-d_6, 500 MHz) *δ* 3.98 (s, 3H, Me), 6.44 (d, *J* = 7.5 Hz, 1H, H6), 6.54 (s, 1H, H5), 6.89 (dd, *J* = 7.5 and 2.0 Hz, 1H, H7), 6.96 (d, *J* = 5.5 Hz, 1H, H3), 8.26 (d, *J* = 5.5 Hz, 1H, H2). ^{13}C NMR (DMSO-d_6, 75 MHz) *δ* 55.5 (q, Me), 92.6 (d, C5), 98.9 (d, C6), 101.0 (d, C3), 124.7 (d, C7), 114.0 (s, C4a), 134.1 (s, C5a), 144.9 (d, C2), 146.5 (s, C9), 147.7 (s, C10a), 159.1 (s, C4). MS (EI) *m*/*z* 216 (17), 215 (M^+, 100), 214 (11), 200 (59), 172 (48). *M* calculated for $C_{11}H_9N_3O_2$ 215.0694; HRMS found (M^+) 215.0690.

9-Aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (12a). TMSCl (400 μL, 2.70 mmol) was added to a solution of **11a** (500 mg, 2.70 mmol) in 2,6-lutidine (40 mL) and HMDSA (60 mL) and the mixture was refluxed for 15 h. TMSTf (100 μL, 0.27 mmol) was added and NH_3 was bubbled through the mixture for 15 min at 0 °C. The mixture was enclosed in a sealed steel reactor and heated at 150 °C for 8 h. (60 psi). The solvent was evaporated and the crude product purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (98/2) gave **12a** (150 mg, 30%) as a light yellow solid. Mp 214−215 °C dec (from CH_2Cl_2/hexane). IR (KBr) *ν* 3452 (m, NH), 3304 (m, NH), 1654 (m, C═C), 1618 (m, C═C), 1570 (m, C═N), 1403 (m, C−N). ^{1}H NMR (DMSO-d_6, 300 MHz) *δ* 6.49 (s, 1H, H5), 6.72 (d, *J* = 6.6 Hz, 1H, H6), 6.80 (br s, 1H, NH), 7.30 (d, *J* = 6.6 Hz, 1H, H7), 7.42 (dd, *J* = 7.8 and 4.6 Hz, 1H, H3), 8.14 (dd, *J* = 7.8 and 1.5 Hz, 1H, H4), 8.33 (dd, *J* = 4.6 and 1.5 Hz, 1H, H2), 8.60 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) *δ* 88.8 (d, C5), 101.0 (d, C6), 119.6 (d, C3), 122.9 (s, C4a), 127.5 (d, C4), 136.8 (s, C5a), 138.9 (d, C2), 139.4 (d, C7), 141.8 (s, C10a), 148.8 (s, C9). MS (EI) *m*/*z* 185(15), 184 (M^+, 100), 183 (7). *M* calculated for $C_{10}H_8N_4$ 184.0749; HRMS found (M^+) 184.0747.

9-Amino-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (12b). Following the same procedure as for **12a**, **11b** (60 mg, 0.27 mmol) was reacted with HMDSA (30 mL), 2,6-lutidine (15 mL), and TMSCl (36 μL, 0.27 mmol) at reflux for 15 h. TMSTf (12 μL, 0.06 mmol) was added and NH_3 was bubbled through the mixture for 15 min at 0 °C then the mixture heated at 150 °C for 8 h in a sealed steel reactor (60 psi). The solvent was evaporated and the crude material purified by flash column chromatography, eluting with CH_2Cl_2/MeOH (99/1) giving **12b** (13 mg, 22%) and with CH_2Cl_2/MeOH (95/5) giving **11b** (9 mg, 15%). Data for **12b**: ^{1}H NMR ($CDCl_3$ + CD_3OD, 300 MHz) *δ* 4.01 (s, 3H, OMe), 6.45 (s, 1H, H5), 6.61 (d, *J* = 6.6 Hz, 1H, H6), 6.75 (d, *J* = 5.6 Hz, 1H, H3), 7.14 (d, *J* = 6.6 Hz, 1H, H7), 8.18 (d, *J* = 5.6 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$ + CD_3OD, 75 MHz) *δ* 55.6 (q, Me), 87.5 (d, C5), 100.6 (d, C6), 102.2 (d, C3), 114.3 (s, C4a), 134.4 (s, C5a), 136.0 (d, C2), 141.7 (d, C7), 142.8 (s, C10a), 149.0 (s, C9), 158.8 (s, C4). MS (EI) *m*/*z* 215 (7), 214 (M^+, 36), 213 (6), 199 (36), 57 (100). (ES+) *m*/*z* 216 (20), 215 (M + 1, 100).

1-[*N*-(2,2-Dimethoxyethyl)carbamoyl]-7-azaindole (13). To a cooled solution of triphosgene (503 mg, 1.7 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added slowly (1 h) 7-azaindole **5a** (500 mg, 4.2 mmol) in CH_2Cl_2 (10 mL). A solution of aminoacetaldehyde dimethyl acetal (508 μL, 4.7 mmol) and DIPEA (1.6 mL, 9.3 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred for 10 min at room temperature. The solution was washed twice with a 0.25 M HCl solution, and twice with a saturated $NaHCO_3$ solution, dried, and evaporated, and the residue was purified by flash column chromatography. Elution with hexane/CH_2Cl_2 (1/1) gave **13** (483 mg, 46%) as a white solid. IR (film) *ν* 3200 (m, NH), 1710 (s, C═O), 1556 (m), 1418 (m, C−N), 1271 (m, C−O). ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 3.47 (s, 6H, 2 × OMe), 3.68 (t, *J* = 5.7 Hz, 2H, CH_2), 4.61 (t, *J* = 5.7 Hz, 1H, CH), 6.53 (d, *J* = 4.2 Hz, 1H, H3), 7.19 (dd, *J* = 8.2 and 5.2 Hz, 1H, H5), 7.94 (dd, *J* = 8.2 and 1.4 Hz, 1H, H4), 7.99 (d, *J* = 4.2 Hz, 1H, H2), 8.31 (dd, *J* = 5.2 and 1.4 Hz, 1H, H6), 9.90 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50 MHz) *δ* 41.9 (t, CH_2), 54.4 (q, OMe), 102.8 (d, CH), 103.0 (d, C3), 117.9 (d, C5), 123.4 (s, C3a), 126.1 (d, C2), 129.8 (d, C4), 142.4 (d, C6), 146.6 (s, C7a), 151.7 (s, CO). MS (EI) *m*/*z* 249 (M^+, 1), 234 (1), 218 (3), 174 (4), 118 (46). Anal. Calcd for $C_{12}H_{15}N_3O_3$: C (57.82), H (6.07), N (16.86). Found: C (57.46), H (6.75), N (16.63).

6,7-Dihydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (14a). A solution of **8a** (1.0 g, 3.83 mmol) and DIPEA (2 mL, 11.5 mmol) in CH_2Cl_2 (50 mL) was added slowly to a solution of TsN═CCl_2[13] (1.15 g, 4.6 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 90 min and was washed with H_2O. The organic solution was dried and evaporated to give a crude product that was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (99/1) gave **14a** (1.18 g, 71%) as a pale orange solid. IR (film) *ν* 3312 (m, NH),1634 (s, C═N), 1589 (s, C═N), 1472 (s, SO_2), 1134 (s, SO_2). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.50−1.85 (m, 6H, H3′, H4′, and H5′), 2.37 (s, 3H, Me), 3.40−3.85 (m, 4H, H6′ and H7), 4.67 and 4.90 (2dd, *J* = 3.9 and 3.3 Hz and 3.0 and 2.4 Hz, 1H, H2′), 5.00−5.07 (m, 1H, H6), 6.59 and 6.61 (2s, 1H, H5), 7.20 (dd, *J* = 7.8 and 4.8 Hz, 1H, H3), 7.26 (d, *J* = 8.4 Hz, 2H, Ts), 7.85 and 7.84 (2dd, *J* = 7.8 and 1.5 Hz, 1H, H4), 8.12 (d, *J* = 8.4 Hz, 2H, Ts), 8.40 (br s, 1H, NH), 8.51 and 8.50 (2dd, *J* = 4.8 and 1.5 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 18.7, 19.1 (t), 21.5 (q), 25.2, 25.3 (t), 29.9, 30.2 (d), 43.1 and 44.7 (t), 62.2 and 63.7 (t), 62.5 (d), 95.6 and 96.8 (d), 104.0 and 105.5 (d), 119.2 (d), 121.5 (s), 126.4 (d), 129.2 (d), 131.9 (s), 133.7 (s), 140.0 (s), 142.5 (s), 145.5 and 145.8 (d), 148.1 (s). MS (CI) *m*/*z* 0.441 (M + 1, 2), 440 (M, 1), 339 (M − OTHP, 5), 185 (54), 85 (100). M + H calculated for $C_{22}H_{25}N_4O_4S$ + H 441.1596; HRMS found $(M + H)^+$ 441.1591.

6,7-Dihydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxy-4-methoxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (14b). A solution of **8b** (1.0 g, 3.44 mmol) and DIPEA (1.9 mL, 10.9 mmol) in CH_2Cl_2 (50 mL) was slowly added to a solution of TsN═CCl_2 (952 mg, 3.78 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 30 min then washed with H_2O. The organic solution was dried and evaporated to give material that was purified by flash column chromatography, eluting with CH_2Cl_2/MeOH (99/1) giving **14b** (1.05 g, 65%) as a pale orange solid. IR (KBr) *ν* 3312 (m, NH), 1625 (s, C═N), 1587 (s, SO_2), 1293 (s, SO_2). ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 1.18−1.82 (m, 6H, H3′, H4′, and H5′), 2.38 (s, 3H, CMe), 3.40−3.60 (m, 2H, H6′), 3.64−3.80 (m, 2H, H-7), 3.97 (s, 3H, OMe), 4.41 and 4.90 (2dd, *J* = 3.2 and 3.4 Hz and 2.6 and 1.9 Hz, 1H, H2′), 4.90−5.05 (m, 1H, H6), 6.67 and 6.69 (2s, 1H, H5), 7.26 (d, *J* = 8.4 Hz, 2H, Ts), 8.10 (d, *J* = 8.4 Hz, 2H, Ts), 8.40 (d, *J* = 2.8 Hz, 1H, H3), 8.42 (d, *J* = 2.8 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 18.6, 19.3 (t), 21.6 (q), 25.2, 25.3 (t), 30.0, 30.2 (d), 43.3 and 44.9 (t), 55.6 (q), 61.9 and 62.3 (t), 62.7 and 63.5 (d), 95.5 and 96.4 (d), 101.3 and 101.4 (d), 102.9 (d), 111.9 (s), 126.2 (s), 126.4 (d), 129.2 (d), 129.3 (s), 132.2 (s), 142.5 (s), 147.6 and 150.0 (d), 159.7 (s). MS (CI) *m*/*z* 471 (M + 1, 3), 369 (M − OTHP, 11), 214 (25), 198 (89). M + H calculated for $C_{23}H_{27}N_4O_5S$ + H 471.1702; HRMS found $(M + H)^+$ 471.1699.

6,7-Dihydro-6-hydroxy-9-tosylaminopyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine (15a). To a solution of **14a** (2 g, 4.54 mmol) in CH_2Cl_2 (50 mL) was added HCl (4 N, 50 mL) and the mixture was stirred for 90 min. The aqueous solution was basified with aq Na_2CO_3 to pH 9 and product extracted into CH_2Cl_2. The organic layer was dried and evaporated yielding **15a** (1.32 g, 82%) as a light yellow foam. IR (film) *ν* 3315 (m, NH), 1624 (s, C═N), 1589 (s, C═N), 1473 (s, SO_2), 1135 (s, SO_2). ^{1}H NMR (CD_3OD, 300 MHz) *δ* 2.35 (s, 3H, Me), 3.42−3.55 (m, 1H, H7), 3.70−3.84 (m, 1H, H7), 5.04 (m, 1H, H6), 6.55 (s, 1H, H5), 7.01 (dd, *J* = 5.2 and 3.2 Hz, H3), 7.24

(d, J = 8.6 Hz, 2H, Ts), 7.72 (br d, J = 5.2 Hz, H4), 8.04 (d, J = 8.6 Hz, 2H, Ts), 8.27 (dd, J = 3.2 and 1.0 Hz, H2), 8.42 (br , 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5 (q, Me), 45.8 (t, C7), 60.4 (d, C6), 103.7 (d, C5), 119.1 (d, C3), 126.5 (d, Ts), 129.2 (d, Ts), 129.4 (d, C4), 136.7 (s), 139.6 (s), 142.6 (s), 144.9 (d, C2), 148.5(s). MS (EI) m/z 356 (M^+, 3), 201 (M − Ts, 10). M calculated for $C_{17}H_{16}N_4O_3S$ 356.0943; HRMS found (M^+) 356.0956.

6,7-Dihydro-6-hydroxy-4-methoxy-9-tosylaminopyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (15b). To a solution of **14b** (8 g, 17 mmol) in CH_2Cl_2 (150 mL) was added HCl (4 N, 150 mL) and the mixture was stirred for 90 min. The aqueous solution was made basic with aq Na_2CO_3 to pH 9 and product extracted into CH_2Cl_2. The organic layer was dried and evaporated yielding **15b** (5.25 g, 80%) as a light yellow foam. IR (film) ν 3317 (s, OH), 1627 (m, C═N), 1294 (s, SO_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (s, 3H, Me), 3.35 (dm, J = 13.1 Hz, 1H, C7), 3.74 (dm, J = 13.1 Hz, 1H, C7), 5.00 (m, 1H, H6), 6.42 (d, J = 5.8 Hz, 1H, H3), 6.51 (s, 1H, H5), 7.23 (d, J = 8.2 Hz, 2H, Ts), 8.04 (d, J = 8.2 Hz, 2H, Ts), 8.09 (d, J = 5.8 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5 (q, Me), 44.9 (t, C7), 55.6 (q, OMe), 60.1 (d, C6), 100.1 (d, C5), 101.3 (d, C3), 112.2 (s), 126.6 (d, Ts), 129.3 (d, Ts), 134.3 (s), 139.5 (s), 142.7 (s), 146.7 (s), 148.6 (s), 148.7 (d, C2), 159.6 (s). MS (CI) m/z 387 (M + 1, 1), 386 (M, 1), 231 (M − Ts, 2), 216 (12). M calculated for $C_{18}H_{18}N_4O_4S$ 386.1049; HRMS found (M^+) 386.1096.

9-Tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (16a). As in the preparation of **11a**, but starting from **15a** (1.85 g, 5.19 mmol), TEA (1.44 mL, 0.92 mmol), and MsCl (1.32 mL, 5.30 mmol) in CH_2Cl_2 (80 mL), a crude product was obtained and purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (98/2) gave **16a** (1.22 g, 70%) as a yellow solid. IR (film) ν 3266 (m, NH), 1652 (s, C═N), 1573 (s, C═N), 1399 (s, SO_2), 1141 (s, SO_2). ^{1}H NMR (CD_3OD, 300 MHz) δ 2.37 (s, 3H, Me), 6.69 (s, 1H, H5), 6.74 (d, J = 7.5 Hz, 1H, H6), 7.04 (d, J = 7.5 Hz, 1H, H7), 7.31 (d, J = 8.4 Hz, 2H, Ts), 7.44 (dd, J = 7.8 and 4.8 Hz, 1H, H3), 8.00(d, J = 8.4 Hz, 2H, Ts), 8.14 (br d, J = 7.8 Hz, 1H, H4), 8.47 (dd, J = 4.8 and 1.5 Hz, 1H, H2). ^{13}C NMR (DMSO, 75 MHz) δ 21.1 (q, Me), 96.3 (d, C5), 101.6 (d, C6), 120.1 (s), 120.4 (d, C3), 123.6 (s), 126.1 (d, C4), 128.5 (d, C7), 129.48 (d, Ts), 129.54 (d, Ts), 134.5 (s), 138.4 (s), 142.5 (s), 143.0 (d, C2). MS (EI) m/z 338 (M^+, 19), 183 (67). M calculated for $C_{17}H_{14}N_4O_2S$ 338.0837; HRMS found (M^+) 338.0841.

4-Methoxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine (16b). In a way analogous to the synthesis of **11a**, but starting from **15b** (170 mg, 0.46 mmol), product **16b** was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (98/2) gave **16b** (126 mg, 78%) as a yellow solid. IR (film) ν 3266 (m, NH), 1293 (s, SO_2), 1603 (s, C═N). ^{1}H NMR (CD_3OD, 200 MHz) δ 2.38 (s, 3H, CMe), 4.08 (s, 3H, OMe), 6.68 (s, 1H, H5), 6.72 (d, J = 7.4 Hz, 1H, H6), 7.02 (d, J = 7.4 Hz, 1H, H7), 7.03(d, J = 5.4 Hz, 1H, H3), 7.31 (d, J = 8.2 Hz, 2H, Ar), 7.98 (d, J = 8.2 Hz, 2H, Ar), 8.35 (d, J = 5.4 Hz, 1H, H2), 11.05 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.8 (q, Me), 55.9 (q, OMe), 92.6 (d, C5), 102.1 (d, C6), 113.9 (s), 120.0 (s), 124.2 (d, C3), 126.0 (d, Ts), 129.3 (d, Ts), 132.6 (s), 142.2 (s), 144.0 (s), 145.1 (d, C7), 158.4 (d, C2). MS (EI) m/z 369 (7), 368 (M^+, 32), 303 (100), 213 (63), 198 (46). M calculated for $C_{18}H1_{16}N_4O_3S$ 368.0943; HRMS found (M^+) 368.0941.

9-Acetylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (17a). Acetic anhydride (200 μL, 2.04 mmol) was added to a solution of **12a** (250 mg, 1.36 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 20 h. The solvent was removed and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aq $NaHCO_3$. The organic layer was dried and evaporated. The crude was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (99/1) gave **17a** (225 mg, 75%) as a bright yellow solid. Mp 160−161 °C (CH_2Cl_2/hexane). IR (KBr) ν 3150 (m, NH), 1708 (s, C═O), 1626 (m, NCO). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H, CMe), 6.53 (s, 1H, H5), 6.97 (d, J = 6.6 Hz, 1H, H6), 7.41 (dd, J = 8.0 and 4.8 Hz, 1H, H3), 7.51 (d, J = 6.6 Hz, 1H, H7), 8.10 (dd, J = 8.0 and 1.5 Hz, 1H, H4), 8.41 (dd, J = 4.8 and 1.5 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.2 (q, Me), 90.5 (d, C5), 107.2 (d, C6), 119.6 (d, C3), 122.8 (s, C4a), 128.4 (d, C4), 136.0 (s, C5a), 136.5 (d, C2), 139.6 (d, C7), 141.3 (s, C10a), 142.3 (s, C9), 170.0 (s, CO). MS (EI) m/z 227 (3), 226 (M^+, 18), 184 (100). M calculated for $C_{12}H_{10}N_4O$ 226.0855; HRMS found (M^+) 226.0852. Anal. Calcd for $C_{12}H_{10}N_4O$: C (63.71), H (4.46), N (24.77). Found: C (63.65), H (4.59), N (24.80).

9-Acetylamino-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (17b). Acetic anhydride (5 μL, 0.05 mmol) was added to a solution of **12b** (8 mg, 0.04 mmol) in THF (1 mL) and the mixture was stirred at room temperature for 20 h. The solvent was removed and the residue was taken up in CH_2Cl_2. The solution was washed with saturated aq $NaHCO_3$, dried, and evaporated, giving **17b** (8.5 mg, 82%), which was used without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60 (s, 3H, Me), 4.07 (s, 3H, Me), 6.60 (s, 1H, H5), 6.82 (d, J = 5.7 Hz, 1H, H3), 6.96 (d, J = 6.6 Hz, 1H, H6), 7.47 (d, J = 6.6 Hz, 1H, H7), 8.29 (d, J = 5.7 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3 (q, Me), 55.8 (q, Me), 88.1 (d, C5), 100.7 (d, C6), 107.7 (d, C3), 114.1 (s, C4a), 134.5 (s, C5a), 135.9 (d, C2), 142.1 (d, C7), 159.5 (s, C4), 170.1 (s, CO). MS (ES+) m/z 258 (30), 257 (M + 1, 100). M calculated for $C_{13}H_{12}N_4O_2$ 256.0960; HRMS found (M^+) 256.0970.

9-Acetylamino-5-iodopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (18a). NIS (100 mg, 0.44 mmol) was added portionwise to a solution of **17a** (100 mg, 0.44 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After being stirred for 15 min, the solution was diluted with CH_2Cl_2 (50 mL) and washed twice with water. The organic layer was dried and evaporated to obtain **18a** (142 mg, 93%) as a bright yellow solid. Mp 163−164 °C dec (CH_2Cl_2/hexane). IR (KBr) ν 3050 (m, NH), 1694 (m, C═O), 1573 (m, C═N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.63 (s, 3H, CMe), 6.94 (d, J = 6.4 Hz, 1H, H6), 7.47 (dd, J = 8.2 and 4.8 Hz, 1H, H3), 7.61 (d, J = 6.4 Hz, 1H, H7), 7.93 (dd, J = 8.2 and 1.6 Hz, 1H, H4), 8.40 (dd, J = 4.8 and 1.6 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4 (q, Me), 46.7 (s, C5), 107.0 (d, C6), 120.6 (d, C3), 125.2 (s, C4a), 128.8 (d, C4), 136.9 (s, C5a), 138.6 (d, C7), 140.9 (d, C2), 141.5 (s, C10a), 142.7 (s, C9), 170.2 (s, CO). MS (EI) m/z 353 (3), 352 (M^+, 22), 310 (100). M calculated for $C_{12}H_9IN_4O$ 351.9821; HRMS found (M^+) 351.9821. Anal. Calcd for $C_{12}H_9IN_4O$: C (40.93), H (2.58), N (15.91). Found: C (40.91), H (2.64), N (15.79).

9-Acetylamino-5-iodo-4-methoxypyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (18b). NIS (6.5 mg, 0.03 mmol) was added portionwise to a solution of **17b** (8 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 15 min then diluted with CH_2Cl_2 (50 mL) and washed twice with water. The organic layer was dried and evaporated to obtain **18b** (8.4 mg, 71%) as a yellow gum. IR (film) ν 3261 (S, NH), 1694 (m, C═O), 1604 (m, C═N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.61 (s, 3H, Me), 4.08 (s, 3H, Me), 6.84 (d, J = 5.7 Hz, 1H, H3), 6.97 (d, J = 6.6 Hz, 1H, H6), 7.57 (d, J = 6.6 Hz, 1H, H7), 8.31 (d, J = 5.7 Hz, 1H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3 (q, Me), 55.8 (q, Me), 101.2 (d, C6), 107.7 (d, C3), 114.1 (s, C4a), 133.5 (s, C5a), 137.7 (d, C2), 142.5 (d, C7), 142.6 (s, C10a), 151.8 (s, C9), 170.4 (s, C4), 176.8 (s, CO). MS (ES+) m/z 384 (15), 383 (M + 1, 100), 192 (M + 2^{2+}, 50), 191 (M^{2+}, 22).

2-Methanesulfanyl-4-trimethylstannylpyrimidine (19). TBAF (5 mL, 1 M in THF) was added dropwise to a solution of 4-iodo-2-methanesulfanylpyrimidine[38] (800 mg, 3.2 mmol), hexamethylditin (1 mL, 4.8 mmol), $Pd(OAc)_2$ (45 mg, 0.31 mmol), and PPh_3 (90 mg, 0.62 mmol) in THF (10 mL). The mixture was stirred at room temperature for 1.5 h. The solvent was removed under vacuum and the residue purified by neutral alumina column chromatography. Elution with hexane/AcOEt (99/1) yielded **19** (585 mg, 65%) as a colorless oil. IR (film) ν 1539 (m, C═N), 1402 (m), 1306 (m), 1196 (m). ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 0.34 (s, 9H, Me_3Sn), 2.54 (s, 3H, SMe), 7.08 (d, J = 4.5 Hz, 1H, H5), 8.26 (d, J = 4.5 Hz, 1H, H6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −9.5 (q, Me), 14.0 (q, Me), 124.5 (d, C5), 153.6 (d, C6), 171.4 (s, C2). MS (EI) *m*/*z* 291 ($^{120}SnM^+$, 50), 276 (^{120}SnM − Me, 100). *M* calculated for $C_8H_{14}N_2S^{120}Sn$ 290.9977; HRMS found (M^+) 290.9973.

9-Acetylamino-5-(2-methanesulfanylpyrimidin-4-yl)-pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (20a) and 9-Amino-5-(2-methanesulfanylpyrimidin-4-yl)pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (20b). A solution of **18a** (130 mg, 0.37 mmol), **19** (93 mg, 1.10 mmol), $Pd_2(dba)_3$ (76 mg, 0.07 mmol), PPh_3 (39 mg, 0.15 mmol), LiCl (47 mg, 1.10 mmol), and CuI (14 mg, 0.07 mmol) in dioxane (10 mL) was refluxed for 1.5 h. The organic solvent was removed and the resulting oil dissolved in CH_2Cl_2 and extracted four times with 4 N HCl, the aqueous solution was basified with solid Na_2CO_3, then the product was extracted with CH_2Cl_2. The extract was evaporated and the residue purified by flash column chromatography eluting with CH_2Cl_2/MeOH (99/1) giving **20a** (21 mg, 16%) as a yellow solid, mp 160−162 °C (from CH_2Cl_2/hexane). IR (KBr) ν 1704 (s, C═O), 1620 (m, C═C), 1556 (m), 1536 (m, C═N), 1517 (m), 1502 (m), 1476 (m, C−N), 1265 (m). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.67 (s, 3H, CMe), 2.69 (s, 3H, SMe), 7.36 (d, J = 5.2 Hz, 1H, H5′), 7.58 (dd, J = 8.2 and 4.8 Hz, 1H, H3), 7.83 (d, J = 6.6 Hz, 1H, H7), 7.93 (d, J = 6.6 Hz, 1H, H6), 8.52 (dd, J = 4.8 and 1.4 Hz, 1H, H2), 8.54 (d, J = 5.2 Hz, 1H, H6′), 8.77 (dd, J = 8.2 and 1.4 Hz, 1H, H4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (q, CMe), 26.4 (q, SMe), 104.5 (s, C5), 107.4 (d, C6), 113.0 (d, C5′), 121.1 (d, C3), 121.6 (s, C4a), 129.5 (d, C4), 137.7 (s, C5a), 141.0 (d, C2), 141.1 (d, C7), 142.5 (s, C10a), 143.3 (s, C9), 156.8 (d, C6′), 160.7 (s, C4′), 170.2 (s, C2′), 172.7 (s, CO). MS (EI) *m*/*z* 351 (M + 1, 3), 350 (M^+, 33), 308 (M − Ac, 100). *M* calculated for $C_{17}H_{14}N_6OS$ 350.0949; HRMS found (M^+) 350.0940. UV (MeOH) λ 255 (25 480), 400 (17 710). Elution with CH_2Cl_2/MeOH (95/5) gave **20b** (30 mg, 26%) as a yellow solid, mp 223−224 °C (from CH_2Cl_2/hexane). IR (KBr) ν 3390 (m, NH), 1632 (m, C═C), 1557 (m, C═N), 1517 (m), 1464 (m, C−N), 1265 (m). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 3H, Me), 7.33 (d, J = 5.4 Hz, 1H, H5′), 7.49 (dd, J = 8.4 and 4.8 Hz, 1H, H3), 7.58 (d, J = 6.6 Hz, 1H, H7), 7.68 (d, J = 6.6 Hz, 1H, H6), 8.40 (dd, J = 4.8 and 1.6 Hz, 1H, H2), 8.48 (d, J = 5.4 Hz, 1H, H6′), 8.73 (dd, J = 8.4 and 1.6 Hz, 1H, H4). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.4 (q, SMe), 100.3 (s, C5), 102.1 (d, C6), 112.6 (d, C5′), 120.7 (d, C3), 122.0 (s, C4a), 128.6 (d, C4), 138.7 (s, C5a), 140.3 (d, C2), 142.1 (s, C10a), 143.4 (d, C7), 149.8 (s, C9), 156.5 (d, C6′), 161.2 (s, C4′), 172.3 (s, C2′). MS (EI) *m*/*z* 309 (7), 308 (M^+, 33). *M* calculated for $C_{15}H_{12}N_6S$ 308.0844; HRMS found (M^+) 308.0839. UV (MeOH) λ_{max} 217 (16 324), 252 (21 415), 400 (11 692). A solution of **20a** (15 mg, 0.043 mmol) in 5 N HCl/MeOH (5 mL) was refluxed for 1 h. The solvent was removed and the residue dissolved in saturated aq Na_2CO_3. The solution was extracted with CH_2Cl_2. The organic solvent was evaporated giving **20b** (12 mg, 90%).

When the reaction was repeated and the HCl/MeOH treatment carried out before purification, **20b** (45%) was obtained as the only product.

9-Amino-5-(2-methanesulfinylpyrimidin-4-yl)pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (21). To a solution of **20** (20 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added *m*-CPBA (32 mg, 0.13 mmol). The mixture was stirred for 30 min then saturated aq $Na_2S_2O_3$ (1 mL) was added and the mixture was basified with saturated aq Na_2CO_3. The organic layer was separated and the aqueous layer re-extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give **21** (20 mg, 90%) as an orange foam. IR (film) ν 3388 (m, NH), 1635 (m, C═C), 1569 (m), 1519 (m, C═N), 1467 (m), 1267 (s, S═O). ^1H NMR ($CDCl_3$, 200 MHz) δ 3.03 (s, 3H, Me), 7.53 (dd, J = 8.2 and 4.8 Hz, 1H, H3), 7.63−7.78 (m, 3H, H7, H6, and H5′), 8.42 (dd, J = 4.8 and 1.4 Hz, 1H, H2), 8.73 (d, J = 5.4 Hz, 1H, H6′), 8.84 (dd, J = 8.2 and 1.4 Hz, 1H, H4). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.3 (q, Me), 99.5 (s, C5), 102.2 (d, C6), 116.5 (d, C5′), 121.3 (d, C3), 121.9 (s, C4a), 129.1 (d, C4), 140.0 (s, C5a), 140.8 (d, C2), 143.8 (s, C10a), 144.6 (d, C7), 150.0 (s, C9), 157.3 (d, C6′), 162.6 (s, C4′), 173.5 (s, C2′). MS (EI) *m*/*z* 324 (M^+, 47), 261 (100), MS (ES+) *m*/*z* 326 (20), 325 (M + 1, 100).

9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (22). Method A: To a solution of **21** (50 mg, 0.16 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (88 mg, 0.36 mmol) at room temperature. After the solution was stirred for 2 h, a saturated aq $Na_2S_2O_3$ solution (1 mL) was added and the mixture was basified with saturated aq Na_2CO_3. The organic layer was separated and the aqueous layer re-extracted with CH_2Cl_2. The combined, dried extracts were evaporated giving **22** (50 mg, 91%) as a light orange solid.

Method B: To a solution of **20b** (200 mg, 0.65 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (320 mg, 1.30 mmol). The mixture was stirred for 2 h at room temperature then saturated aq $Na_2S_2O_3$ solution was added (5 mL) and the mixture basified with saturated aq Na_2CO_3. The organic layer was separated and the aqueous layer re-extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give **22** (201 mg, 91%). Mp 118−189 °C (CH_2Cl_2/hexane). IR (film) ν 3340 (m, NH), 1569 (m, C═C), 1517 (m), 1462 (m), 1262 (s, SO_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 3H, Me), 7.56 (dd, J = 8.1 and 4.8 Hz, 1H, H3), 7.69 (d, J = 6.6 Hz, 1H, H7), 7.78 (d, J = 5.7 Hz, 1H, H5′), 7.80 (d, J = 6.6 Hz, 1H, H6), 8.44 (dd, J = 4.8 and 1.5 Hz, 1H, H2), 8.75 (d, J = 5.7 Hz, 1H, H6′), 8.84 (dd, J = 8.1 and 1.5 Hz, 1H, H4). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 39.8 (q, Me), 97.4 (s, C5), 101.0 (d, C6), 118.4 (d, C5′), 121.0 (s, C4a), 121.2 (d, C3), 128.6 (d, C4), 130.3 (s, C5a), 140.5 (d, C2), 143.3 (s, C10a), 146.8 (d, C7), 149.9 (s, C9), 157.5 (d, C6′), 161.5 (s, C4′), 165.2 (s, C2′). MS (CI, NH_3) *m*/*z* 342 (M + 2, 6), 341 (M + 1, 20), 340 (M^+, 100), 309 (M − O_2, 5), 263 (M − SO_2Me, 25). *M* calculated for $C_{15}H_{12}N_3O_2S$ 340.0742; HRMS found (M^+) 340.0740.

9-Amino-5-(2-aminopyrimidin-4-yl)pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (deoxyvariolin B, 23). Method A: A solution of **22** (25 mg, 0.04 mmol) in dioxane (3 mL) and 23% aq NH_3 (5 mL) was heated in a sealed steel vessel at 80 °C for 6 h. The mixture was cooled and the solvent removed leaving a residue that was dissolved in saturated aq Na_2CO_3 and extracted with CH_2Cl_2 several times. The organic extracts were dried and evaporated and the crude product thus obtained was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (97/3) gave **23** (18 mg, 90%) as a yellow solid.

Method B: A solution of **18a** (120 mg, 0.36 mmol), **24** (200 mg, 0.72 mmol), $Pd_2(dba)_3$ (75 mg, 0.06 mmol), PPh_3 (35 mg, 0.14 mmol), LiCl (42 mg, 1.10 mmol), and CuI (12 mg, 0.06 mmol) in dioxane (4 mL) was refluxed for 1.5 h. The organic solvent was removed and the oil dissolved in HCl/MeOH and the resulting solution refluxed for 1 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The organic solution was extracted with aq 4 N HCl four times then the combined aqueous extracts basified with solid Na_2CO_3 and extracted with CH_2Cl_2. After evaporation of the solvent the product was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (95/5) gave **23** (50 mg, 54%) as a yellow solid. Mp 160−162 °C (from CH_2Cl_2/hexane). IR (film) ν 3332 (m, NH), 1632 (m, C═C), 1574 (m, C═N), 1454 (m, C−N), 1262 (m). ^1H NMR (DMSO-d_6, 500 MHz) δ 6.55 (br s, 2H, 2′NH_2), 7.05 (d, J = 5.5 Hz, 1H, H5′), 7.57 (d, J = 8.0 and 4.4 Hz, 1H, H3), 7.62 (d, J = 6.6 Hz, 1H, H7), 7.68 (d, J = 6.6 Hz, 1H, H6), 8.21 (d, J = 5.5 Hz, 1H, H6′), 8.44 (dd, J = 4.4 and 1.4 Hz, 1H, H2), 8.55 (br s, 1H, 9NH), 8.91 (dd, J = 8.0 and 1.4 Hz, 1H, H4), 9.35 (br s, 1H, 9NH). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 99.5 (s, C5), 101.7 (d, C6), 106.8 (d, C5′), 120.7 (d, C3), 121.6 (s, C4a), 129.1 (d, C4), 138.2 (s, C5a), 140.1 (d, C2), 142.8 (s, C10a), 143.8 (d, C7), 149.7 (s, C9), 158.0 (d, C6′), 161.4 (s, C4′), 163.5 (s, C2′). MS (ES+) *m*/*z* 279 (20), 278 (M + 1, 100), 277 (M^+, 10). *M* calculated for $C_{15}H_{11}N_7$ 277.1075; HRMS found (M^+) 277.1071. UV (MeOH) λ_{max} 225 (36 010), 250 (34 126), 350 (20 942), 400 (26 481).

2-Acetylamino-4-chloropyrimidine and 4-Chloro-2-diacetylaminopyrimidine. A solution of 2-amino-4-chloropyrimidine (500 mg, 3.9 mmol) in acetic anhydride (20 mL) was refluxed for 30 min. The solvent was removed under vacuum and the remaining oil was dissolved in saturated aq Na_2CO_3 and extracted with CH_2Cl_2. The organic solution was dried and evaporated to give an oil that was purified by flash column chromatography. Elution with CH_2Cl_2/hexane (2/1) gave 4-chloro-2-diacetylaminopyrimidine (122 mg, 16%) as a white solid. Mp 142−143 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.51 (s, 6H, 2Me), 7.04 (d, J = 5.2 Hz, 1H, H5), 8.47 (d, J = 5.2 Hz, 1H, H6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.3 (q, Me), 116.0 (d, C5), 157.5 (d, C6), 159.2 (s, C4), 161.8 (s, C2). MS (CI, CH_4) m/z 215 (^{37}ClM, 1), 214 (3), 213 (^{35}ClM, 1), 212 (5), 174 (32), 172 (^{35}ClM-Ac, 100). M + H calculated for $C_8H_8N_3O_2Cl$ + H 214.0383; HRMS found $(M + H)^+$ 214.0388. Elution with CH_2Cl_2 yielded 2-acetylamino-4-chloropyrimidine (270 mg, 45%) as a white solid. Mp 155−156 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.32 (s, 3H, Me), 7.45 (d, J = 5.3 Hz, 1H, H5), 8.76 (d, J = 5.3 Hz, 1H, H6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3 (q, Me), 121.2 (d, C5), 160.0 (s, C4), 163.1 (d, C6), 171.6 (s, C2). MS (EI) m/z 173 (^{37}ClM, 5), 171 (^{35}ClM, 16), 131 (32), 129 (100). M calculated for $C_6H_6N_3OCl$ 173.0170; HRMS found (M^+) 173.0163.

2-Acetylamino-4-trimethylstannylpyrimidine (24). A solution of 2-acetylamino-4-chloropyrimidine (170 mg, 1.0 mmol), hexamethylditin (400 μL, 1.8 mmol), and $Pd(PPh_3)_4$ (40 mg, 0.03 mmol) in dioxane (6 mL) was refluxed for 1 h. The solvent was removed under vacuum and the residue purified by neutral alumina column chromatography. Elution with hexane/AcOEt (7/3) gave **24** (240 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 9H, 3Me), 2.53 (s, 3H, Me), 7.13 (d, J = 4.8 Hz, 1H, H5), 8.35 (d, J = 4.8 Hz, 1H, H6), 8.81 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −9.5 (q, 3Me), 25.3 (q, Me), 124.4 (d, C5), 128.5 (s, C4), 154.7 (d, C6), 155.4 (s, C2), 186.4 (s, CO). MS (EI) m/z 300 (^{120}SnM$^+$, 1), 285 (34), 255 (^{120}SnM-3Me, 6), 244 (30), 136 (M − $SnMe_3$, 100). M calculated for $C_9H_{15}N_3OSn$ 301.0237; HRMS found (M^+) 301.0236.

9-Acetylamino-5-(2-acetylaminopyrimidin-4-yl)-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (25). A solution of **18b** (7 mg, 0.018 mmol), **24** (11 mg, 0.037 mmol), $Pd_2(dba)_3$ (4 mg, 0.004 mmol), PPh_3 (2 mg, 0.007 mmol), LiCl (2.5 mg, 0.055 mmol), and CuI (1 mg, 0.004 mmol) in dioxane (1 mL) was refluxed for 2 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The organic solution was extracted with 4 N HCl four times and the aqueous solution basified with solid Na_2CO_3 then extracted with CH_2Cl_2. After evaporation of the CH_2Cl_2 the residue was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (95/5) gave **25** (2 mg, 40%). IR (KBR) ν 3216 (m, NH), 1676 (s, C=O), 1580 (m, C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3H, Me), 2.60 (s, 3H, Me), 4.07 (s, 3H, Me), 6.97 (d, J = 5.4 Hz, 1H, H3), 7.26 (d, J = 6.6 Hz, 1H, H6), 7.48 (d, J = 5.4 Hz, 1H, H5′), 7.76 (d, J = 6.6 Hz, 1H, H7), 8.40 (d, J = 5.4 Hz, 1H, H2), 8.52 (d, J = 5.4 Hz, 1H, H6′). MS (ES+) m/z 392 (M + 1, 40), 350 (55). M calculated for $C_{19}H_{17}N_7O_3$ 391.1393; HRMS found (M^+) 391.1392.

5-Iodo-4-methoxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (26b). To a solution of **16b** (250 mg, 0.68 mmol) in CH_2Cl_2 (5 mL) cooled at −30 °C was added NIS (153 mg, 0.68 mmol) slowly and the mixture was stirred for 5 min at the same temperature. Then, the organic solution was washed with H_2O, dried, and evaporated yielding **26b** (319 mg, 95%) as a yellow solid, which was used without further purification. IR (film) ν 3259 (m, NH), 1604 (m, C=N), 1495 (s, SO_2), 1294 (s, SO_2). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.36 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.62 (d, J = 7.8 Hz, 1H, H6), 7.06 (d, J = 5.4 Hz, 1H, H3), 7.18 (d, J = 7.8 Hz, 1H, H7), 7.34 (d, J = 8.2 Hz, 2H, Ar), 8.02 (d, J = 8.2 Hz, 1H, Ar), 8.41 (d, J = 5.4 Hz, 1H, H2), 11.17 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.0 (q, Me), 56.1 (q, OMe), 81.2 (s, C5), 102.6 (d, C6), 113.9 (s), 126.1 (d, C3), 129.4 (4d, Ts), 134.0 (d, C7), 142.6 (s), 143.4 (s), 145.1(d, C2), 159.0 (s). MS (EI) m/z 495 (7), 494 (M^+, 31), 368 (12), 303 (58), 212 (100). M calculated for $C_{18}H_{15}N_4O_3SI$ 493.9909; HRMS found (M^+) 493.9890.

5-(2-Acetylaminopyrimidin-4-yl)-4-methoxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (27). A solution of **26b** (295 mg, 0.60 mmol), **24** (258 mg, 0.86 mmol), $Pd_2(dba)_3$ (120 mg, 0.13 mmol), PPh_3 (60 mg, 0.23 mmol), LiCl (74 mg, 1.8 mmol), and CuI (23 mg, 0.12 mmol) in dioxane (25 mL) was stirred at reflux temperature for 1 h. The solvent was then evaporated and the crude product dissolved in CH_2Cl_2. The organic solution was washed with aq 4 N HCl, and the aqueous solution was basified with solid $NaHCO_3$ and extracted with CH_2Cl_2. The organic solution was dried and evaporated giving a crude material that was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (99/1) gave **26b** (61.5 mg, 28%) and with CH_2Cl_2/MeOH (9/1) gave **27** (213 mg, 71%) as a yellow solid. IR (film) ν 3379 (s, NH), 1592 (s, C=O), 1519 (m, C=N), 1474 (s, SO_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, Me), 2.45 (s, 3H, Me), 4.05 (s, 3H, OMe), 6.92 (d, J = 5.2 Hz, 1H, H3), 7.30 (d, J = 8.4 Hz, 2H, Ts), 7.43 (d, J = 5.2 Hz, 1H, H5′), 7.56 (d, J = 6.8 Hz, 1H, H7), 7.95 (br s, 1H, H6), 8.13 (d, J = 8.4 Hz, 2H, Ts), 8.32 (d, J = 5.2 Hz, 1H, H6′), 8.49 (d, J = 5.2 Hz, 1H, H2), 8.69 (br s, 1H, NH), 13.28 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) 21.9 (q), 25.3 (q), 56.2 (q), 93.9 (s), 94.1 (s), 102.5 (d, C3), 107.8 (d, C6), 117.3 (d, C5′), 129.0 (d, Ts), 129.5 (d, Ts), 136.3 (s), 136.5 (s), 140.1 (d, C7), 141.9 (s), 142.9 (d, C6′), 143.5 (s), 144.9 (s), 156.9 (d, 2), 158.5 (s), 160.4 (s), 162.0 (s). MS (ES+) m/z 505 (33), 504 (M + 1, 100). M calculated for $C_{24}H_{22}N_7O_4S$ 504.1453; HRMS found (M^+) 504.1445.

5-(2-Aminopyrimidin-4-yl)-4-hydroxy-9-tosylaminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (28). A solution of **27** (200 mg, 0.4 mmol) in aq HBr (48%, 30 mL) was stirred at reflux for 20 min. After this time the solution was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give 220 mg of a yellow solid. Purification by flash column chromatography and elution with CH_2Cl_2/MeOH (95/5) gave **28** (107 mg, 60%) as a yellow solid. ^{1}H NMR ($CDCl_3$−CD_3OD, 400 MHz) δ 2.40 (s, 3H, Me), 6.81 (d, J = 7.0 Hz, 1H, H-6), 7.05−7.09 (m, 2H, H-3 and H-5′), 7.28 (d, J = 8.0 Hz, 2H, Ts), 7.71 (d, J = 6.2 Hz, 1H, H-6′), 8.03 (d, J = 8.0 Hz, 2H, Ts), 8.09 (d, J = 7.0 Hz, 1H, H-7), 8.29 (d, J = 5.6 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$−CD_3OD, 100 MHz) 20.1 (q), 101.8 (d, C3), 103.9 (s), 105.0 (s), 106.0 (d, C6), 110.1 (d, C5′), 123.5 (s), 128.0 (d, Ts), 128.9 (d, Ts), 129.3 (d, C7), 134.3 (d, C6′), 138.3 (s), 139.0 (s), 142.9 (s), 143.1 (s), 156.2 (s), 159.0 (s), 160.7 (d, C2). MS (ES+) m/z 448 (8), 447 (M^+, 78), 368 (10), 292 (100), 213 (68). M calculated for $C_{21}H_{18}N_7O_3S$ 448.1192; HRMS found (M^+) 448.1189.

5-(2-Aminopyrimidin-4-yl)-4-hydroxy-9-aminopyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (Variolin B, 2). A solution of **28** (100 mg, 0.22 mmol), 1,4-dimethoxybenzene (60 mg, 0.43 mmol), and $NH_2NH_2{\cdot}H_2O$ (0.45 mL, 9.27 mmol) in MeOH (80 mL) was irradiated under Ar with a high-pressure Hg lamp for 36 h. After that time the solvent was removed under vacuum and the residue was purified by preparative HPLC (Symetry C_8, μm, 30 × 100 mm, using a gradient of MeCN−H_2O between 25:72 and 55:45 during 30 min) to give variolin B **2** (19.7 mg, 30%). Analytical HPLC analysis was identical with a natural sample supplied by Pharma Mar, tr 6.2 min (Symetry C_8, gradient of MeCN−H_2O between 20:80 and 90:10 during 25 min).

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Supporting Information Available: General experimental details and ^{1}H and 13C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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