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Concise Total Syntheses of Variolin B and Deoxyvariolin B

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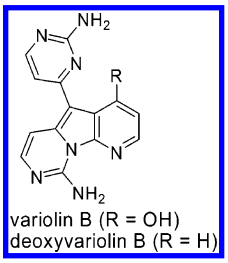

The total synthesis of the marine alkaloid variolin B has been achieved in 8 steps and 17% overall yield, starting from commercially available 4-chloro-2-methylthiopyrimidine. The key reaction involves the tandem deoxygenation and cyclization of a triarylmethanol using a combination of triethylsilane and trifluoroacetic acid. In addition, the deoxygenated analogue was prepared in 6 steps and 23% overall yield, starting from the same starting material.

Introduction

Marine organisms have provided a vast array of structurally diverse and biologically interesting structures.[1] However, to date, few marine natural products have become useful pharmaceutical drugs. One of the major reasons for this is the difficulty in obtaining adequate quantities of the marine organism, as secondary metabolites from marine organisms are usually produced in very low quantities and, therefore, large amounts of the organism are required.[2] Harvesting large quantities of marine organisms is difficult and expensive, and can also have a major ecological impact. As a consequence, chemical synthesis is playing an increasingly important role in providing supplies of marine natural products.

A recent example of this is variolin B (**1**), a novel marine alkaloid which was isolated from the rare, and difficult-to-access, Antarctic sponge *Kirkpatrickia variolosa* by the group of Blunt and Munro.[3] Preliminary investigations established that variolin B (**1**) displayed strong in vitro activity against the P388 (murine leukaemia) cell line (IC_{50} = 210 ng/mL), as well as moderate antiviral activity. Further investigations into variolin B's biological activity have been hampered by a lack of material. This has led to considerable interest in the synthesis of variolin B, with several groups reporting syntheses of the variolin core and/or fragments of the core.[4,5] In 2001, we reported[6] the first total synthesis of variolin B. Since then, two other total syntheses have been completed.[7] The majority of the synthetic approaches build up the tricyclic core of variolin B in a linear fashion from an heteroaryl component using conventional heterocyclic chemistry.[4,5a,5b,5d] In contrast, we have employed a highly convergent approach based on the recognition of a hidden symmetry element in

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(1) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1.

(2) Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765.

(3) (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1994**, *50*, 3987. (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993.

(4) Syntheses of fragments of the variolin core structure: (a) Álvarez, M.; Fernández, D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 249. (b) Álvarez, M.; Fernández, D.; Joule, J. A. *Synthesis* **1999**, 615. (c) Minguez, J. M.; Vaquero, J. J.; Alvarez-Builla, J.; Castaño, O.; André, J. L. *J. Org. Chem.* **1999**, *64*, 7788. (d) Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355. (e) Álvarez, M.; Fernández, D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 471.

(5) Syntheses of the variolin core structure (a) Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777. (b) Mendiola, J.; Minguez, J. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2000**, *2*, 3253. (c) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 311. (d) Álvarez, M.; Fernández, D.; Joule, J. A. *Tetrahedron Lett.* **2001**, *42*, 315. (e) Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2004**, *69*, 4974. (f) Fernandez, D.; Ahaidar, A.; Danelon, G.; Cironi, P.; Marfil, M.; Perez, O.; Cuevas, C.; Albericio, F.; Joule, J. A.; Alvarez, M. *Monatsh. Chem.* **2004**, *135*, 615. (g) Ahaidar, A.; Fernaindez, D.; Perez, O.; Cuevas, C.; Albericio, F.; Joule, J. A.; Alvarez, M. *ARKIVOC* (Gainesville, FL, United States), **2004**, *iv*, 74.

(6) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 8697.

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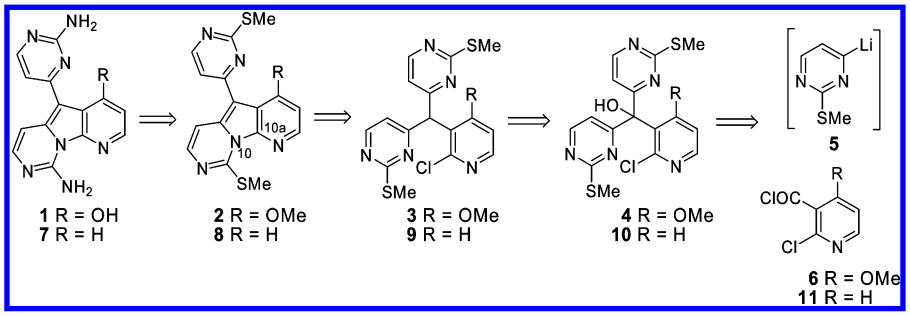
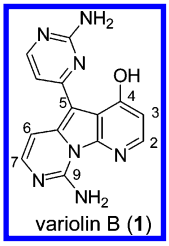
SCHEME 1



variolin B. In this paper, we present full details of our synthetic strategy and its application to the total synthesis of variolin B and the nonnatural analogue, deoxyvariolin B.

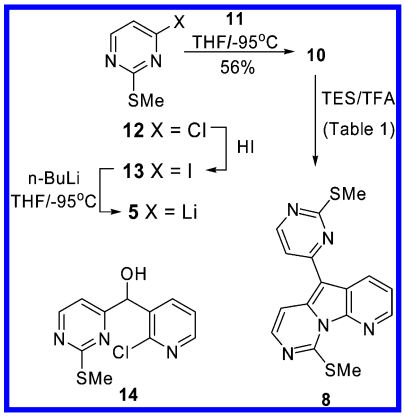


Results and Discussion

Our retrosynthetic strategy for variolin B (**1**) is outlined in Scheme 1, with the key compound being the core structure **2**, which contains the appropriate functionality to introduce the highly polar amino groups.[8] Examination of **2** reveals a hidden symmetry element, which leads to the disconnection of the N10−C10a bond indicated in Scheme 1. Thus, it was anticipated that cyclization of the symmetrical triarylmethane **3** would generate the desired core structure with appropriate functionality to allow elaboration to variolin B. Triarylmethane **3** should be obtained by deoxygenation of the alcohol **4**, which, in turn, could be rapidly constructed by reaction of the known[9] lithio species **5** (2 equiv) with acid chloride **6**. When this work was initiated, there were no reports on the preparation of the tricyclic core of the variolins, so it was decided to start with the commercially available acid chloride **11**, which would lead to the deoxy-analogue **7**. This would establish the feasibility of our approach and, if successful, would provide insights into the structure−activity relationships of variolin B.

Synthesis of the Deoxyvariolin Core 8. Lithio species **5** was generated by treatment of iodopyrimidine

SCHEME 2



13[10] with *n*-butyllithium at −95 °C as detailed by Undheim and co-workers.[9] The lithio species is extremely reactive, and we observed that warming above −95 °C led to decomposition of the reagent. However, when the bath temperature was maintained at −95 °C, **5** reacted with acid chloride **11** to form triarylmethanol **10** in an optimized yield of 56% (Scheme 2, left-hand side). A major contaminant is the biaryl alcohol **14**, which is not easily separated by chromatography. Therefore, the mixture was reacted with manganese dioxide, which allowed the contaminant to be readily removed. Three equivalents was required for complete consumption of the acid chloride, and slow addition of pre-cooled (−95 °C) reagents[11] was vital to minimize decomposition of the lithio species.[12]

Deoxygenation of triarylmethanol **10** was attempted using a variety of methods. Deoxygenation via the Barton ester[13] was complicated by difficulties in obtaining the required xanthate cleanly. Numerous methods were screened for the direct conversion of the tertiary alcohol **10** to the triarylmethane **9**. These included $NaCNBH_3$/

(7) (a) Molina, P.; Fresneda, P. M.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2002**, *43*, 1005. (b) Molina, P.; Fresneda, P. M.; Delgado, S. *J. Org. Chem.* **2003**, *68*, 489. (c) Ahaidar, A.; Fernández, D.; Perez, O.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Álvarez, M. *Tetrahedron Lett*. **2003**, *44*, 6191 (d) Ahaidar, A.; Fernández, D.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Álvarez, M. *J. Org. Chem.* **2003**, *68*, 10020.

(8) Converting a thiomethyl group into a amino group is a common procedure. For a recent example, see: Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 855.

(9) Lithio species **5** is generated by iodine−lithium exchange of 4-iodo-2-methylthiopyrimidine (**13**) using n-BuLi in THF at −95 °C. See ref 5c and Majeed, A. J.; Antonsen, Ø.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993.

(10) Iodide **13** is readily prepared by stirring chloride **12** in 55% aqueous HI solution. See the Supporting Information and the references in footnote 9 for further details.

(11) It was found that when a specialized piece of glassware first described by Suzuki and Noyori was used, efficient control over the internal temperature could be achieved. Addition of the n-BuLi through the spiral port ensures that the n-BuLi solution is efficiently pre-cooled to −95 °C before it reacts with the iodide. See: Suzuki, M.; Noyori, R. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994; pp 201−206.

(12) This reaction can also be carried out more simply using Barbier-type conditions—*n*-butyllithium was added dropwise to a mixture of iodide **13** and acid chloride **11** in THF at −95 °C. See the Experimental Section for full details.

(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

TABLE 1. Optimization of the Reaction Conditions for the Synthesis of 8 from 10

entry	equiv of TES	equiv of TFA	yield of **8** (%)
1	2.0	8.3	15
2	4.0	8.2	18
3	8.0	8.2	22
4	8.1	4.3	34
5	7.8	2.0	33

ZnI_2,[14] Pd−C/$AlCl_3$/cyclohexene,[15] P/I_2/HI,[16] H_2/Pd−C, $LiAlH_4$/ $AlCl_3$,[17] $NaBH_4$/TFA,[18] and H_2/Adams' catalyst/TFA[19]—all of which resulted in either no reaction or the formation of complex mixtures. It appeared that the π-deficient rings of the pyrimidines were undergoing reduction in preference to hydrogenolysis of the C−O bond. This impasse was finally resolved by using a combination of triethylsilane (TES) with trifluoroacetic acid (TFA) (Scheme 2 and Table 1).[20]

An initial attempt using 1.2 equiv of TES in refluxing TFA produced a mixture of several products. While the desired triarylmethane **9** was not among these (as ^{1}H NMR spectroscopy clearly showed the presence of two nonidentical pyrimidine rings in each product), we were pleased to find that one of the products was, in fact, the variolin core structure **8**, albeit in ~5% yield. The other products isolated from the TES/TFA reaction were identified as **15**, **16** and **17** (Scheme 3). These products had not been deoxygenated, suggesting that they were the result of acid-promoted reactions. Indeed, when triarylmethanol **10** was refluxed in neat TFA, the compounds **15**, **16**, and **17** were formed in the ratio of 14:1:4.

While one might conclude that upon deoxygenation of **10**, the triarylmethane **9** cyclizes under the reaction conditions to afford the tricyclic core **8**, the presence of compounds **15** and **16** led us to consider an alternate mechanism whereby cyclization of **10** might precede deoxygenation (Scheme 3). In this process, the initially formed species is **18**, which would be a common intermediate for all three cyclized products **8**, **15** and **16**. Reduction of **18** with TES, followed by elimination of water would afford the desired product **8**, while acid-catalyzed rearrangements would lead to the formation of **15** and **16** as detailed in Scheme 3. Compound **17**, which still contains a chlorine atom, cannot arise from **18** but presumably forms by rearrangement of **10** in a process similar to that shown for **16**.[21]

We reasoned, therefore, that decreasing the amount of TFA and increasing the amount of TES in the reaction should minimize the formation of side-products **15**−17 and lead to greater yields of the desired variolin core **8**. Indeed, this was the case, with **8** being isolated in 34% yield under optimized conditions (see Table 1). While this yield was modest, it should be noted that we have gained access to the tricyclic core of variolin B in just three steps from commercially available materials.

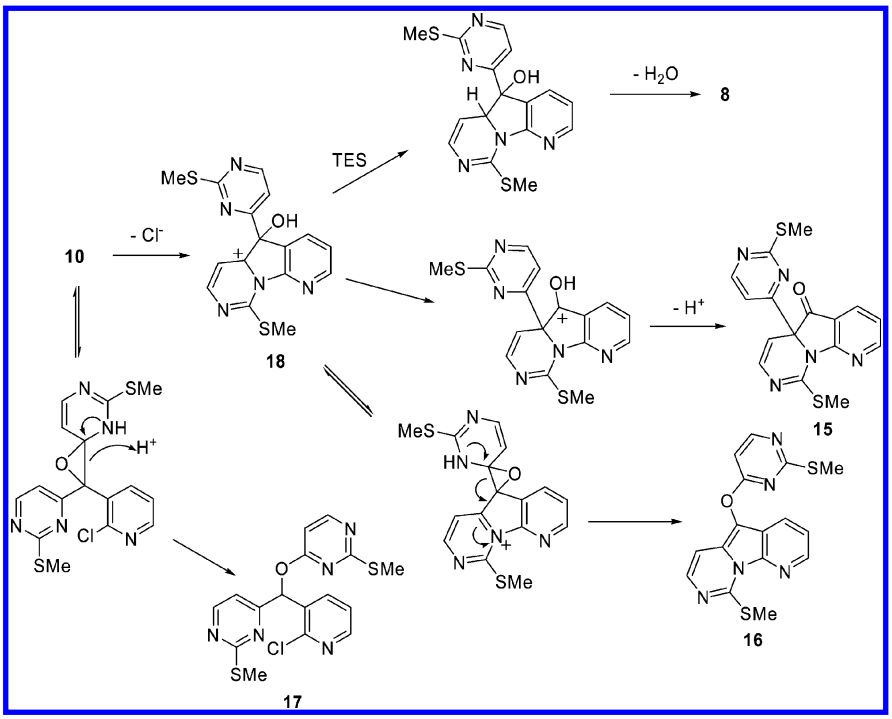
Synthesis of the Variolin Core 2. Our attention turned to the application of this methodology to the synthesis of the oxygen-containing core structure **2**. Using the conditions established for the synthesis of triarylmethanol **10**, the double-addition of lithio species **5** to acid chloride **6**[22] was examined (Scheme 4). Unfortunately, triarylmethanol **4** was isolated in only 14% yield. Prolonged reaction at −95 °C offered no improvement to the yield; it appeared that decomposition of the lithio species predominated over addition to the hindered carbonyl group of **6**. As the equivalent Grignard reagent is reported to be stable at 0 °C,[23] we hoped that it might react more readily with the acid chloride **6**. However, despite attempting this reaction under a variety of conditions, **4** was never observed in the product mixture.

As the instability of **5** was hampering our efforts at producing **4**, it was decided to prepare **4** by the reaction of the 3-lithiopyridine derived from **21** with the symmetrical ketone **20** as detailed in Scheme 4. The symmetrical ketone **20** was readily available by reaction of lithio species **5** with 0.5 equiv of diethyl carbonate at −95 °C. The 3-lithiopyridine had previously been prepared by reaction of 2-chloro-4-methoxypyridine (**21**)[24] with either LDA or LTMP at −78 °C, but significant amounts of starting material were recovered in both cases.[23b,c] Comins and LaMunyon have shown that LDA is too weak a base for the complete deprotonation of 2-, 3-, and 4-methoxypyridines.[25] Consequently, we decided to examine the lithiation of **21** with butyllithium reagents, even though it has been reported that attempts to use the stronger alkyllithium bases (*n*-, *s*- or *t*-BuLi) failed due to competing substitution or halogen−metal exchange.[23c] While the use of *t*-BuLi at −78 °C resulted in nucleophilic attack at the pyridine ring, the use of *n*-BuLi resulted in an efficient lithiation at −95 °C.[26] Reaction of the generated lithio species with the ketone **20** at −78 °C resulted in the desired triarylmethanol **4** being obtained in 76% yield, constituting a significant improvement on the former approach.

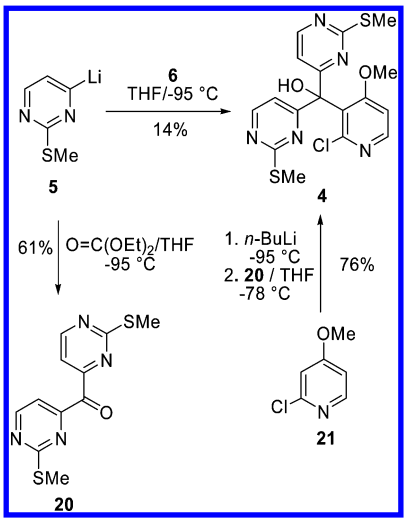
Reaction of **4** with TES/TFA, under the optimized conditions used on **10**, resulted in the formation of tricyclic core **2** in a disappointing yield of 9% yield (Scheme 5 and Table 2, entry 1). The major product of the reaction was compound **22,** isolated in 54% yield. Careful optimization of the reaction conditions allowed

(14) Lau, C. K.; Dufresne, C.; Bélanger, P. C.; Piétré, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038.
(15) Olah, G. A.; Prakash, G. K. S. *Synthesis* **1978**, 397.
(16) Lee, W. Y.; Park, C. H.; Kim, Y. D. *J. Org. Chem.* **1992**, *57*, 4074.
(17) Brewster, J. H.; Osman, S. F.; Bayer, H. O.; Hopps, H. B. *J. Org. Chem.* **1964**, *29*, 121.
(18) Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172.
(19) Peterson, P. E.; Casey, C. *J. Org. Chem.* **1964**, *29*, 2325.
(20) For a review of ionic hydrogenation see Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.
(21) It is interesting to note that **17** could not be converted into **16**. Exposure of **17** to TFA at reflux did not lead to cyclization.
(22) Acid chloride **6** was generated in 97% yield from 2-chloro-4-methoxynicotinic acid (**19**) by reaction with oxalyl chloride. Acid **19** was obtained in 4 steps from commercially available materials by modifying a synthesis of the bromo-analogue described by Kasum, B.; Prager, R. H. *Aust. J. Chem.* **1983**, *36*, 1455. See the Supporting Information for more details.
(23) Leprêtre, A.; Turck, A.; Plé, N.; Knochel, P.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 265.
(24) 2-Chloro-4-methoxypyridine (**21**) was produced in three steps and 48% overall yield from 4-nitropyridine-*N*-oxide. Details are provided in the Supporting Information. See also (a) Talik, Z. *Roczniki Chem.* **1962**, *36*, 1313. *Chem. Abstr.* **1963**, *59*, 6358b (b) Walters, M. A.; Shay, J. *Tetrahedron Lett.* **1995**, *36*, 7575. and (c) Connon, S. J.; Hegarty, A. F. *Tetrahedron Lett.* **2001**, *42*, 735.
(25) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
(26) Quenching with MeOD after 1 h of reaction at −78 °C gave the C3-deuterated pyridine in ~84% yield (judging by ^{1}H NMR spectroscopy), together with some starting material (~7%) and a small amount of addition product (~9%). When the lithiation was repeated at −95 °C, the addition product was virtually eliminated.

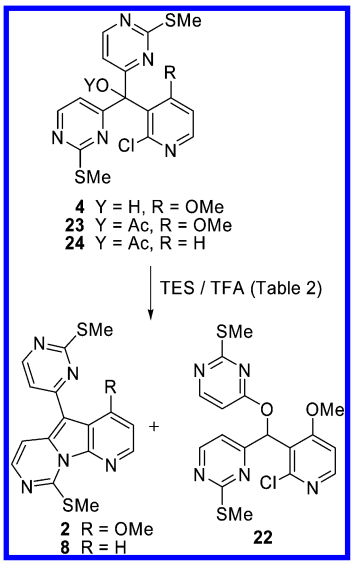
SCHEME 3



SCHEME 4



SCHEME 5



the yield of **2** to be improved to 47% (entry 2). Interestingly, no products analogous to **15** and **16** were observed in this reaction. Ether **22** is presumably formed in a manner similar to the deoxy-equivalent **17** (Scheme 3) whereby the hydroxyl group attacks one of the pyrimidine rings and the C−C bond breaks to relieve the strain of the resulting epoxide. It was reasoned that if this side reaction could be blocked, higher yields of **2** could be obtained. To test this hypothesis, it was decided to protect the hydroxyl group as the acetate **23**. Acetylation of **4** proved to be a slow reaction, with poor conversion. However, if the reaction to form **4** was quenched with acetyl chloride, acetate **23** was generated in 78% yield. When **23** was treated with TES and TFA under essentially the same conditions that were used for alcohol **4**, the variolin core **2** was formed as the sole product in 75% yield, without any trace of **22** (Entry 3). This modification was also applicable in the deoxy-series, with the cyclization of the acetate **24**[27] affording **8** in 69% yield, with no trace of the side-products **15**−**17** (Entry 4).

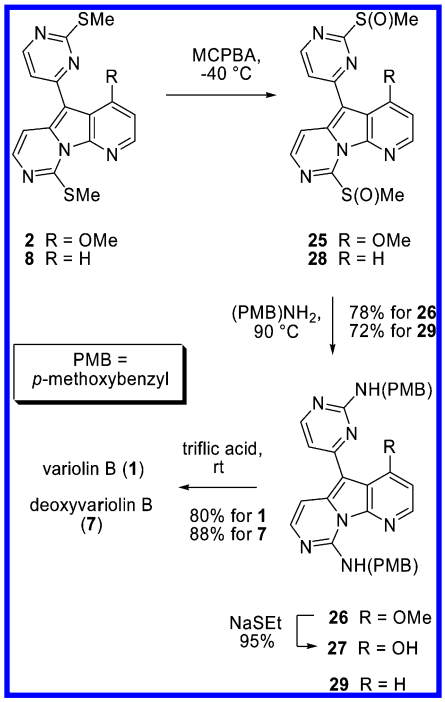
Synthesis of Variolin B (1) and Deoxyvariolin B (7). Having developed a concise route to the variolin core, deprotection of the methoxy group of **2** and substitution of the thiomethyl groups with ammonia would complete the synthesis of variolin B (Scheme 6). The use of boron tribromide failed to remove the methoxy protecting group, producing complexes that precipitated out of solution. Heating **2** with sodium ethanethiolate in DMF

(27) The acetate **24** was synthesized using the Barbier-type reaction, followed by an acetyl chloride quench. Despite the crude material looking clean by NMR spectroscopy, the purified acetate **24** was obtained in only 50% yield. However, if the crude reaction mixture was submitted directly to the cyclization conditions, **8** could be obtained in 50% overall yield (based on acid chloride **11**).

TABLE 2. Synthesis of Core Structures 2 and 8 Using TES/TFA

entry	substrate	conditions	% yield 2/8	% yield 22
1	**4**	8 equiv TES/4 equiv TFA/70°C	9	54
2	**4**	8 equiv TES/2 equiv TFA/$ClCH_2CH_2Cl$/100°C	47	28
3	**23**	8 equiv TES/2 equiv TFA/$ClCH_2CH_2Cl$/100°C	75	0
4	**24**	8 equiv TES/2 equiv TFA/1$ClCH_2CH_2Cl$/100°C	69	n/a

SCHEME 6



at 95 °C did result in deprotection, but partial displacement of the thiomethyl groups by sodium ethanethiolate had also occurred. It was decided, therefore, to carry out the methoxy deprotection after the amino groups had been introduced.

Oxidation of **2** with 2 equiv of MCPBA at −40 °C gave predominantly the bis-sulfoxide **25** as a 1:1 mixture of diastereomers. While substitution of the sulfoxides with ammonia would take us one step closer to the target, we felt the use of a protected amine would give a more easily handled product. Thus, heating the crude oxidized mixture in neat *p*-methoxybenzylamine resulted in clean substitution of both sulfoxide groups to afford bis-amine **26**, in 78% yield for the two steps. Removal of the methoxy group was now revisited and treatment with an excess of sodium ethanethiolate in DMF at 55 °C cleanly produced the pyridinol **27** in 95% yield, without affecting the *p*-methoxybenzyl groups.

DDQ oxidation failed to effect the deprotection of the p-methoxybenzyl groups, while the use of TFA[28] led to removal of only the *p*-methoxybenzyl group on the pendant pyrimidine ring. However, standing **27** in neat triflic acid at room-temperature resulted in the removal of both protecting groups. After neutralization, the crude material was purified by flash chromatography on reversed-phase silica to give variolin B (**1**) as its trifluoroacetate salt. The free base was obtained by neutralization of the salt, with concentrated aqueous ammonia solution, in 80% yield from **27**. Synthetic variolin B was compared to a natural sample provided by Blunt and Munro and exhibited identical spectroscopic properties to those reported for the natural material.[3] It was equally potent in the P388 assay as the natural product.

The deoxygenated analogue **7** was readily generated from core structure **8** using a similar sequence to that used for variolin B (Scheme 6).[29] Of note is that this analogue was found to have essentially the same activity in the P388 assay (IC50 = 157 ng/mL) as variolin B, which indicates that the hydroxyl group is not essential to the biological activity of variolin B.

In summary, variolin B has been produced in 8 steps and 17% overall yield, starting from the commercially available pyrimidine **12**. Highlights of our synthesis include the tandem deoxygenation/cyclization to form the core variolin skeleton and the straightforward functional group manipulation required to introduce the necessary functionality of variolin B. The analogue deoxyvariolin B (**7**) was prepared in 6 steps, in 23% overall yield, and was found to be as biologically active as the natural product. This synthetic strategy is readily amenable to the production of analogues and will provide material to allow further investigation of the biological properties.

Experimental Section[30]

(2-Chloropyridin-3-yl)bis-[2-(methylsulfanyl)pyrimidin-4-yl]methanol (10). The reaction vessel[11] was charged with iodide **13** (5.00 g, 19.8 mmol) and freshly distilled THF (270 mL), and cooled to −95 °C (MeOH/liquid N_2). A solution of *n*-BuLi in hexanes (1.57 M, 12.6 mL, 19.8 mmol) was carefully added to the stirred solution over 20 min, while maintaining the temperature at −95 °C. After 20 min, a solution of acid chloride **11** (1.17 g, 6.67 mmol) in THF (10 mL) was added to the dark mixture over 5 min. After 3.5 h at −95 °C, the reaction was quenched with methanol (1 mL) and allowed to warm overnight. Excess THF was removed in vacuo, and the residue was taken up in water/EtOAc. After separation of the layers, the aqueous layer was re-extracted with EtOAc (x2). The organic layers were combined and washed with saturated brine solution. After drying with $MgSO_4$ and concentration, the crude material was purified by flash chromatography on silica, eluting with 25−50% EtOAc/hexanes, to afford triarylmethanol **10** (1.24 g, ~93% pure by ^1H NMR spectroscopy) in addition to a number of other side products, one of which was the secondary alcohol **14**. Fractions which contained mixtures of **10** and **14** were subjected to oxidation by MnO_2 (2 g) in refluxing benzene (12 mL). Filtration through Celite (rinsing with boiling EtOAc) and concentration in vacuo gave a mixture, which was readily separated by chromatography on silica, eluting with 25−50% EtOAc/hexanes, to yield a further 343 mg of **10** (~95% pure by ^1H NMR spectroscopy). Thus, **10**

(28) Smith, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.

(29) It has also been prepared by Álvarez and Joule's group, using 7-azaindole as starting material. See refs 5d and 7d for details.

(30) General procedures are detailed in the Supporting Information.

was obtained as an orange foam (1.58 g, ~93% pure, 56% yield). An analytical sample was obtained by flash chromatography on reversed phase silica, eluting with 75% MeOH/water, to give an off-white solid. Mp: 54−58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 6H, SCH_3), 6.33 (s, 1H, OH), 7.17 (dd, J = 4.9, 7.8 Hz, 1H, H-5), 7.23 (dd, J = 2.0, 7.8 Hz, 1H, H-4), 7.40 (d, J = 5.1 Hz, 2H, H-5′), 8.38 (dd, J = 2.0, 4.9 Hz, 1H, H-6), 8.56 (d, J = 5.1 Hz, 2H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (SCH$_3$), 79.4 (Ar$_3$$C$OH), 114.8 (C-5′), 121.7 (C-5), 136.8 (C-3), 138.9 (C-4), 149.1 (C-6), 151.5 (C-2), 158.0 (C-6′), 168.8 (C-4′), 171.8 (C-2′). IR ($CDCl_3$): υ_{max} 3381, 1549. MS (EI): *m/z* (rel intensity) 391/393 (59/25), 356 (100), 266/268 (71/29), 125 (68), 45 (53). HRMS (EI): Calcd for $C_{16}H_{14}{}^{35}ClN_5O^{32}S_2$ (M^+) 391.0328, found 391.0332.

Synthesis of 10 via Barbier-Type Conditions. Iodide **13** (1.576 g, 6.3 mmol) was dissolved in THF (17 mL) and transferred via cannula to a pre-cooled solution of the acid chloride **11** (0.500 g, 2.8 mmol) in THF (8 mL) at −96 °C. A solution of *n*-BuLi in hexanes (1.7 M, 3.68 mL, 6.3 mmol) was then added dropwise over 10 min with vigorous stirring. The dark red/brown solution was stirred at −96 °C for a further 2h; then methanol (400 μL) was added over 1 min. The deep red solution was stirred at room temperature for 2 h, then diluted with CH_2Cl_2 (75 mL), washed with sat. aq. $NaHCO_3$ solution (100 mL), brine (100 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. This crude material was dissolved in benzene (15 mL), MnO_2 (1 g) added, and the black suspension was stirred at reflux for 2 h. This was then filtered through a Celite plug and concentrated in vacuo. The red/brown residues were purified by flash chromatography on silica, eluting with 50% EtOAc/hexanes, to give the triarylmethanol **10** as an orange solid (0.521 g, ~95% pure, 40% yield).

(2-Chloropyridin-3-yl)bis-[2-(methylsulfanyl)pyrimidin-4-yl]methyl acetate (24). The reaction vessel[11] was charged with a solution of iodide **13** (3.296 g, 13.1 mmol) in freshly distilled THF (40 mL), and cooled to −95 °C (MeOH/liquid N_2). A solution of acid chloride **11** (1.043 g, 5.9 mmol) in THF (10 mL) was transferred to the reaction vessel via cannula. A solution of n-BuLi in hexanes (1.6 M, 8.17 mL, 13.1 mmol) was then added dropwise over 20 min with vigorous stirring. The dark red/brown solution was stirred at −96 °C for a further 2h, then acetyl chloride (2.11 mL, 29.6 mmol) was added over 5 min. The deep red solution was stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ solution (200 mL), brine (150 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. This crude material was purified by repeated flash chromatography on silica, eluting with 1:1 EtOAc/hexanes, to give the acetate **24** as an orange solid (1.300 g, 98% pure, 50% yield). Mp: 58−61 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, COCH_3), 2.39 (s, 6H, SCH_3), 7.26 (dd, J = 4.9, 7.8 Hz, 1H, H-5), 7.30 (d, J = 4.9 Hz, 2H, H-5′), 7.89 (dd, J = 1.7, 8.1 Hz, 1H, H-4), 8.39 (dd, J = 2.0, 4.9 Hz, 1H, H-6), 8.51 (d, J = 4.8 Hz, 2H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (SCH$_3$), 21.3 (COCH$_3$), 85.9 (C(Ar)$_3$OAc), 114.7 (C-5′), 121.1 (C-5), 134.0 (C-3), 141.3 (C-4), 149.2 (C-6), 150.3 (C-2), 157.4 (C-6′), 166.1 (C-4′), 168.6 (COCH$_3$), 172.6 (C-2′). IR (KBr): υ_{max} 1757, 1549, 1400, 1348, 1207, 1086, 1061, 903. HRMS (ESI): Calcd for $C_{18}H_{17}{}^{35}ClN_5O_2{}^{32}S_2$ (MH^+) 434.0512, found 434.0512.

9-(Methylsulfanyl)-5-[2-(methylsulfanyl)pyrimidin-4-yl]pyrido[3′,2′:4,5]pyr rolo[1,2-*c*]pyrimidine (8).

1. Preparation from Triarylmethanol 10

Triarylmethanol **10** (97% pure, 497 mg, 1.23 mmol) was heated with TFA (0.41 mL, 5.3 mmol) and TES (1.65 mL, 10.3 mmol) in a sealed Young's tube at 75 °C for 66 h. After concentration of excess reagents in vacuo, the residue was dissolved in CH_2Cl_2 (65 mL) and neutralized with 5% aqueous $NaHCO_3$ solution (40 mL). After extraction with CH_2Cl_2 the extracts were worked up in the usual manner. Analysis of the ^{1}H NMR spectrum of the crude mixture revealed the presence of the title compound, and lesser amounts of **16** and **17**, in addition to several unidentified products. Repeated flash chromatography on silica, eluting with 37−70% EtOAc/ hexanes, gave the variolin core **8** as a yellow solid (143 mg, 34%). Mp: 210−211 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (s, 3H, 2′-SCH_3), 2.74 (s, 3H, 9-SCH_3), 7.36 (d, J = 5.1 Hz, 1H, H-5′), 7.52 (dd, J = 4.5, 8.2 Hz, 1H, H-3), 7.83 (d, J = 6.8 Hz, 1H, H-7), 8.07 (d, J = 6.8 Hz, 1H, H-6), 8.52 (d, J = 5.1 Hz, 1H, H-6′), 8.61 (dd, J = 1.5, 4.5 Hz, 1H, H-2), 8.65 (dd, J = 1.5, 8.2 Hz, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (2′−SCH$_3$), 14.9 (9-SCH$_3$), 101.4 (C-5), 108.3 (C-6), 112.9 (C-5′), 120.7 (C-4a), 120.8 (C-3), 128.0 (C-4), 137.5 (C-5a), 139.9 (C-7), 141.8 (C-2), 143.0 (C-10a), 155.1 (C-9), 156.6 (C-6′), 160.9 (C-4′), 172.4 (C-2′). MS (EI): *m/z* (rel intensity) 339 (100), 306 (10), 220 (14), 133 (12). HRMS (EI): Calcd for $C_{16}H_{13}N_5{}^{32}S_2$ (M^+) 339.0612, found 339.0617.

Other compounds isolated from this reaction are as follows:

9-(Methylsulfanyl)-5-[2-(methylsulfanyl)pyrimidin-4-yloxy]pyrido[3′,2′:4,5] pyrrolo[1,2-*c*]pyrimidine (16). This could be further purified by reversed phase preparative HPLC, eluting with 85% CH_3CN/water + 0.05% TFA, to give a yellow solid. Mp: 205−207 °C, sweats at 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, 2′-SCH_3), 2.72 (s, 3H, 9-SCH_3), 6.62 (d, J = 5.4 Hz, 1H, H-5′), 6.96 (d, J = 6.6 Hz, 1H, H-6), 7.39 (dd, J = 4.8, 8.2 Hz, 1H, H-3), 7.49 (d, J = 6.6 Hz, 1H, H-7), 7.85 (dd, J = 1.5, 8.2 Hz, 1H, H-4), 8.39 (d, J = 5.4 Hz, 1H, H-6′), 8.56 (dd, J = 1.5, 4.8 Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (2′∠SCH_3), 14.6 (9-SCH$_3$), 102.2 (C-5′), 104.8 (C-6), 115.6 (C-4a), 119.0 (C-5), 119.7 (C-3), 125.4 (C-4), 126.2 (C-5a), 135.4 (C-7), 139.0 (C-10a), 141.5 (C-2), 153.5 (C-9), 158.8 (C-6′), 168.5 (C-4′), 173.2 (C-2′). MS (EI): *m/z* (rel intensity) 355 (94), 308 (17), 230 (100), 143 (19), 113 (18), 73 (15). HRMS (EI): Calcd for $C_{16}H_{13}N_5O^{32}S_2$ (M^+) 355.0562, found 355.0559.

(2-Chloropyridin-3-yl)-[2-(methylsulfanyl)pyrimidin-4-yl]-[2-(methylsulfan yl)pyrimidin-4-yloxy]methane (17). This could be further purified by flash chromatography on reversed phase silica, eluting with 80% MeOH/water, followed by flash chromatography on silica, eluting with 50% EtOAc/ hexanes, to give a viscous gum. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, 2″-SCH_3), 2.44 (s, 3H, 2′-SCH_3), 6.58 (d, J = 5.9 Hz, 1H, H-5″), 7.19 (d, J = 4.9 Hz, 1H, H-5′), 7.27 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 7.43 (s, 1H, Ar$_2$CHOAr), 7.84 (dd, J = 1.8, 7.6 Hz, 1H, H-4), 8.31 (d, J = 5.9 Hz, 1H, H-6″), 8.38 (dd, J = 1.8, 4.8 Hz, 1H, H-6), 8.54 (d, J = 4.9 Hz, 1H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91 (SCH$_3$), 13.93 (SCH$_3$), 74.3 (Ar$_2$$C$HOAr), 103.2 (C-5″), 113.4 (C-5′), 122.6 (C-5), 132.5 (C-3), 137.6 (C-4), 149.3 (C-6), 150.1 (C-2), 157.8 (C-6′), 158.0 (C-6″), 165.3 (C-4′), 166.8 (C-4″), 172.3 (C-2″), 172.9 (C-2′). MS (ES): *m/z* (rel intensity) 392/394 (100/40), 356 (19), 250/252 (39/18). HRMS (ES): Calcd for $C_{16}H_{15}{}^{35}ClN_5O^{32}S_2$ (MH^+) 392.0407, found 392.0409.

9-(Methylsulfanyl)-5a-[2-(methylsulfanyl)pyrimidin-4-yl]-5a*H*-pyrido[3′,2′: 4,5]pyrrolo[1,2-*c*]pyrimidin-5-one (15). Triarylmethanol **10** (500 mg, 1.28 mmol) was heated with TFA (0.82 mL, 11 mmol) at 80 °C for 10 h. After removal of excess TFA in vacuo, the residue was dissolved in CH_2Cl_2 (65 mL) and neutralized with 5% aqueous $NaHCO_3$ solution (40 mL). After extraction with CH_2Cl_2, the extracts were worked up as usual. ^{1}H NMR spectroscopic analysis of the crude material showed it to contain ketone **15** as the major product, together with lesser amounts of **16** and **17**. Flash chromatography on silica, eluting with 30−50% EtOAc/hexanes, followed by flash chromatography on reversed phase silica, eluting with 75% MeOH/water, gave **15** as a yellow solid (~95% pure by ^{1}H NMR, 70 mg, 15%). An analytical sample was obtained by reversed phase preparative HPLC, eluting with 75% CH_3CN/ water + 0.05% TFA, to give a yellow solid. This compound slowly decomposes over a matter of weeks at room temperature. Mp: 52−55 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H, 2′-SCH_3), 2.52 (s, 3H, 9-SCH_3), 5.96 (d, J = 6.6 Hz, 1H, H-6), 6.76 (d, J = 6.6 Hz, 1H, H-7), 7.12 (dd, J = 4.9, 7.4 Hz, 1H, H-3), 7.14 (d, J = 4.9 Hz, 1H, H-5′), 7.96 (dd, J = 1.6, 7.4

Hz, 1H, H-4), 8.47 (d, J = 4.9 Hz, 1H, H-6′), 8.66 (dd, J = 1.6, 4.9 Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.08 (SCH_3), 14.14 (SCH_3), 70.8 (C-5a), 107.1 (C-6), 112.66 (C-5′), 112.71 (C-4a), 118.8 (C-3), 134.6 (C-4), 136.9 (C-7), 154.6 (C-9), 156.2 (C-2), 158.1 (C-6′), 164.3 (C-10a), 165.4 (C-4′), 172.8 (C-2′), 193.2 (C-5). IR ($CDCl_3$): υ_{max} 1732, 1414. HRMS (ES): Calcd for $C_{16}H_{14}N_5O^{32}S_2$ (MH^+) 356.0640, found 356.0642.

2. Preparation from Acetate 24.

Triarylmethyl acetate **24** (745 mg, 1.72 mmol) was heated with TFA (0.264 mL, 3.43 mmol), TES (2.19 mL, 13.7 mmol) and 1,2-dichloroethane (4 mL) in a sealed Young's tube at 100 °C for 3 days. The orange solution was diluted with CH_2Cl_2 (350 mL), washed with sat. aq. $NaHCO_3$ solution, brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. This crude material was purified by repeated flash chromatography on silica, eluting with 37% EtOAc/hexanes, to give the variolin core **8** as a yellow microcrystalline solid (424 mg, 95% pure, 69%).

3. Preparation of 8 from Iodide 13.

The reaction vessel[11] was charged with a solution of the acid chloride **11** (1.004 g, 5.7 mmol) in THF (40 mL) and cooled to −95 °C (MeOH/liquid N_2). A solution of iodide **13** (3.164 g, 12.6 mmol) in freshly distilled THF (10 mL) was added via cannula. A solution of n-BuLi in hexanes (1.58 M, 7.94 mL, 12.6 mmol) was then added dropwise over 20 min with vigorous stirring. The dark red/brown solution was stirred at −96 °C for a further 2h then acetyl chloride (2.04 mL, 28.5 mmol) was added over 5 min. The deep red solution was stirred at room temp for 1 h, then diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ then brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. This crude material was then transferred to a Young's tube and left at 0.03 mmHg for 16 h to remove any 1-iodobutane. To this residue, was added 1,2-dichloroethane (10 mL), TFA (0.879 mL, 11.4 mmol) and TES (7.27 mL, 45.6 mmol), and the resulting dark red/brown solution incubated at 100 °C for 3 d. The dark brown solution was diluted with CH_2Cl_2 (400 mL), washed with sat. aq. $NaHCO_3$ solution, brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. This crude material was purified by flash chromatography on silica, eluting with 10% EtOAc/CH_2Cl_2, to give the variolin core as a yellow microcrystalline solid (985 mg, 98% pure, 50% yield over 2 steps).

9-(4-Methoxybenzylamino)-5-[2-(4-methoxybenzylamino)pyrimidin-4-yl]py rido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine (29). Under atmospheric conditions, a solution of m-CPBA (102 mg, 591 μmol) in chloroform (10 mL) was cooled to −55 °C (MeOH/N_2) and added dropwise, over 15 min, to a similarly cooled stirred solution of core structure **8** (100 mg, 295 μmol) in chloroform (10 mL). The solution was left to warm to room temperature over 1 h, then washed with sat. aq. $NaHCO_3$ solution (25 mL), brine (25 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to leave a yellow solid. This crude material, which was used without purification, was predominantly a mixture of diastereomeric bis-sulfoxides **28** with the following spectroscopic characteristics. ^{1}H NMR (500 MHz, $CDCl_3$): (as most signals for the diastereoisomers coincide, they are all quoted as multiplets) δ 3.03 (m, 3H), 3.23 (m, 3H), 7.62−7.65 (m, 1H), 7.77 (m, 1H), 8.23 (m, 1H), 8.63 (m, 1H), 8.66−8.69 (m, 1H), 8.78−8.80 (m, 1H), 8.85 (m, 1H). The crude oxidized material (109 mg, 0.29 mmol) was heated with toluene (2 mL) and p-methoxybenzylamine (192 μL, 1.46 mmol) at 100 °C for 3 d. The solution was allowed to cool to room temperature, diluted with CH_2Cl_2 (20 mL), and washed with sat. aq. $NaHCO_3$ solution, brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material thus obtained was purified by repeated flash chromatography on neutralized silica, eluting with 0.5% MeOH/CH_2Cl_2 (0.1% TEA), to give the bis-amine **29** as an orange foam (109 mg, 72% over 2 steps). Mp: 54−60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.808 (s, 3H, OCH_3), 3.811 (s, 3H, OCH_3), 4.69 (d, J = 5.9 Hz, 2H, 2′-NHCH_2Ar), 4.89 (d, J = 5.4 Hz, 2H, 9-NHCH_2-Ar), 5.52 (br, 1H, 2′∠NH), 6.89−6.93 (m, 4H, PMB H-3″, PMB H-3‴), 6.98 (d, J = 5.4 Hz, 1H, H-5′), 7.33−7.42 (m, 6H, H-3, H-6, PMB H-2″, PMB H-2‴), 7.63 (d, J = 6.8 Hz, 1H, H-7), 8.27 (dd, J = 1.0, 5.2 Hz, 1H, H-2), 8.31 (d, J = 5.4 Hz, 1H, H-6′), 8.56 (br m, 1H, H-4), 10.36 (br t, J = 5.4 Hz, 1H, 9-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3 (9-NHCH_2Ar), 45.1 (2′-NHCH_2Ar), 55.3 (both OCH_3), 100.6 (C-5), 101.5 (C-6), 107.9 (C-5′), 113.9 (PMB C-3″ or PMB C-3‴), 114.0 (PMB C-3‴ or PMB C-3″), 120.0 (C-3), 121.9 (C-4a), 128.4 (C-4), 128.6 (PMB C-2‴), 128.8 (PMB C-2″), 130.3 (PMB C-1″), 131.4 (PMB C-1‴), 138.4 (C-5a), 139.5 (C-2), 143.0 (C-7), 143.4 (C-10a), 149.0 (C-9), 157.4 (C-6′), 158.7 (PMB C-4″ or PMB C-4‴), 158.9 (PMB C-4‴ or PMB C-4″), 162.1 (C-4′ or C-2′), 162.2 (C-2′ or C-4′). IR (KBr): υ_{max} 3240, 2959−2835 (series of weak bands), 1560, 1512. MS (EI): m/z (rel intensity) 517 (56), 397 (12), 382 (12), 121 (100). HRMS (EI): Calcd for $C_{30}H_{27}N_7O_2$ (M^+) 517.2226, found 517.2242.

Deoxyvariolin B (7). Bis-amine **29** (180 mg, 0.35 mmol) was dissolved in triflic acid (2 mL) and the deep orange/red solution stirred at room temp for 2.5 h. The solution was cooled to 0 °C, and aq NH_3 was added dropwise until a yellow precipitate had formed. Sat. aq. $NaHCO_3$ was added carefully until bubbling ceased. The suspension was filtered and the yellow/green solid washed with H_2O. The crude material was dissolved in THF (40 mL), Merck DIOL (40 μm APD) (1.5 g) added and the suspension slowly diluted with hexanes (60 mL) with vigorous swirling, which led to coating of the DIOL with the product. The suspension was loaded onto a DIOL column (8.5 g) and flash chromatography, eluting with 2% MeOH/CH_2Cl_2, gave deoxyvariolin B (**7**) as a yellow microcrystalline solid (84 mg, 88%).Mp: dec at ∼220−240 °C (lit.[5d] 160−162 °C). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 6.51 (s, 2H, 2′∠NH_2), 7.05 (d, J = 5.4 Hz, 1H, H-5′), 7.57 (dd, J = 4.8, 8.2 Hz, 1H, H-3), 7.62 (d, J = 6.3 Hz, 1H, H-7), 7.67 (d, J = 6.3 Hz, 1H, H-6), 8.22 (d, J = 5.4 Hz, 1H, H-6′), 8.44 (dd, J = 1.5, 4.8 Hz, 1H, H-2), 8.5 (br, 1H, 9-NH), 8.90 (dd, J = 1.5, 8.2 Hz, 1H, H-4), 9.4 (br, 1H, 9-NH). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 99.6 (C-5), 101.9 (C-6), 107.1 (C-5′), 121.0 (C-3), 121.7 (C-4a), 129.4 (C-4), 138.3 (C-5a), 140.3 (C-2), 143.0 (C-10a), 144.0 (C-7), 149.9 (C-9), 158.2 (C-6′), 161.6 (C-4′), 163.6 (C-2′). IR (KBr): υ_{max} 3304, 3142−2849 (series of weak bands), 1647, 1574, 1514, 1472, 1456, 1269. MS (EI): m/z (rel intensity) 277 (100), 236 (54). HRMS (EI): Calcd for $C_{14}H_{11}N_7$ (M^+) 277.1076, found 277.1072.

2-Chloro-4-methoxynicotinoyl chloride (6). Carboxylic acid **19**[22] (1.27 g, 6.77 mmol), oxalyl chloride (2.4 mL, 28 mmol) and DMF (3 drops) were stirred in CH_2Cl_2 at room temperature for 19 h, with a $CaCl_2$ drying tube used to exclude atmospheric moisture. After concentration in vacuo, the crude product was purified by Kugelrohr distillation (150 °C, 0.07 mmHg) to give acid chloride **6** as a white crystalline solid (1.36 g, 97%). Mp: 66−69 °C, sweats at 62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H, OCH_3), 6.89 (d, J = 5.9 Hz, 1H, H-5), 8.36 (d, J = 5.9 Hz, 1H, H-6). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.8 (OCH_3), 106.4 (C-5), 123.9 (C-3), 146.1 (C-2), 152.1 (C-6), 162.9 (C-4), 164.3 (C=O). IR ($CDCl_3$): 1792, 1578, 1302, 1047. MS (EI): m/z (rel intensity) 170/172 (100/34), 112/114 (27/9). HRMS (EI): Calcd for C7H5^{35}ClNO2 (M^+ − Cl) 170.0009, found 170.0007.

Bis-[2-(methylsulfanyl)pyrimidin-4-yl]methanone (20). The reactor was charged with iodide **13** (3.90 g, 15.5 mmol) and distilled THF (47 mL), and cooled to −97 °C (MeOH/N2). A solution of n-BuLi in hexanes (1.55 M, 10.0 mL, 15.5 mmol) was slowly added to the stirred solution over 21 min, while maintaining the temperature at −97 °C. After 30 min, a solution of diethyl carbonate (0.94 mL, 7.8 mmol) in THF (4 mL) was added over about 3 min. After 15 min at −97 °C, the reaction was allowed to warm to −35 °C over 2 h, and then to room temperature. The reaction mixture was shaken with sat. aq. NH_4Cl solution, extracted with EtOAc, and subjected to standard workup. The crude material was partially purified by Kugelrohr distillation (160 °C, 0.03 mmHg after removing more volatile components), then subsequently by flash chromatography on silica, eluting with 25, 30 and then 50% EtOAc/

hexanes, to give ketone **20** as a pale yellow solid (1.14 g, 53%). Mp: 106−107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (s, 6H, SCH_3), 7.54 (d, J = 4.9 Hz, 2H, H-5), 8.79 (d, J = 4.9 Hz, 2H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (SCH$_3$), 114.9 (C-5), 158.8 (C-6), 159.2 (C-4), 173.2 (C-2), 190.7 (*C*=O). IR (KBr): 1695, 1564, 1553, 1420, 1356, 1319. MS (EI): *m/z* (rel intensity) 278 (100), 214 (23), 125 (76). HRMS (EI): Calcd for $C_{10}H_{10}N_4O^{32}S_2$ (M^+) 278.0296, found 278.0289.

(2-Chloro-4-methoxypyridin-3-yl)bis-[2-(methylsulfanyl)pyrimidin-4-methanol (4).

1. Preparation by Reaction of 5 with 6.

The reaction vessel[11] was charged with iodide **13** (4.44 g, 17.6 mmol) and freshly distilled THF (180 mL), and cooled to −95 °C (MeOH/N_2). A solution of *n*-BuLi in hexanes (1.55 M, 11.4 mL, 17.7 mmol) was added dropwise to the stirred solution over 19 min, while maintaining the temperature at −95 °C. After 30 min, a solution of acid chloride **6** (1.21 g, 5.86 mmol) in THF (9 mL) was added to the dark mixture over 7 min. The reaction was stirred for 4.5 h at −95 °C, quenched with MeOD (1.2 mL) and allowed to warm to room temperature. Excess THF was removed in vacuo, and the residue was taken up in water/EtOAc and extracted with EtOAc (x4). The extracts were washed with brine and dried over MgSO4. Partial concentration of the EtOAc solution gave a precipitate, which was removed by filtration and washed with EtOAc. Concentration of the filtrate and washings gave the crude material. Flash chromatography on silica, eluting with 55−80% EtOAc/ hexanes, gave triarylmethanol **4** as a tan solid (383 mg, 14% yield, ~93% pure by ^{1}H NMR spectroscopy). Mp: 135−137 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (s, 6H, SCH_3), 3.43 (s, 3H, OCH_3), 6.55 (s, 1H, OH), 6.76 (d, J = 5.4 Hz, 1H, H-5), 7.39 (d, J = 5.4 Hz, 2H, H-5′), 8.25 (d, J = 5.4 Hz, 1H, H-6), 8.46 (d, J = 5.4 Hz, 2H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (SCH$_3$), 55.8 (OCH$_3$), 78.0 (Ar3COH), 107.1 (C-5), 113.7 (C-5′), 124.8 (C-3), 149.8 (C-6), 152.3 (C-2), 157.2 (C-6′), 165.9 (C-4), 171.0 (C-4′), 171.1 (C-2′). IR ($CDCl_3$): 3344 (br), 1576, 1551, 1348, 1209, 1043. MS (EI): *m/z* (rel intensity) 421/423 (65/29), 387 (19), 370 (21), 369 (21), 342 (38), 338 (57), 296 (44), 268 (60), 260 (100), 125 (98), 112 (22). HRMS (EI): Calcd for $C_{17}H_{16}{}^{35}ClN_5O_2{}^{32}S_2$ (M^+) 421.0434, found 421.0448.

2. Preparation by Reaction of 20 with 21.

2-Chloro-4-methoxypyridine (**21**) (0.633 g, 4.41 mmol) was dissolved in freshly distilled THF (18 mL). The flask was cooled to below −90 °C (acetone/N_2), and a solution of *n*-BuLi in hexanes (1.55 M, 2.9 mL, 4.5 mmol) was slowly added over 17 min to the stirred solution, keeping the temperature below −90 °C. The orange solution was then stirred at −78 °C for 1 h, by which time it had become a wine-red color. The reaction mixture was again cooled to below −90 °C, and a solution of ketone **20** (1.14 g, 4.09 mmol) in THF (10 mL) was added over 11 min while maintaining the temperature below −90 °C. The dark mixture was then stirred at −78 °C for 3.5 h, quenched with methanol and allowed to warm to room temperature. The reaction mixture was shaken with sat. aq. NH_4Cl solution, extracted with EtOAc and subjected to standard workup. Flash chromatography on silica, eluting with 80% EtOAc/hexanes, gave triarylmethanol **4** as a pale yellow solid (1.32 g, 76%).

(2-Chloro-4-methoxypyridin-3-yl)bis-[2-(methylsulfanyl)pyrimidin-4-yl]me thyl acetate (23). 2-Chloro-4-methoxypyridine (**21**)[23] (0.141 g, 0.980 mmol) was dissolved in freshly distilled THF (4 mL). The flask was cooled to below −90 °C and a solution of *n*-BuLi in hexanes (1.6M, 0.61 mL, 0.98 mmol) was added over 2 min to the stirred solution. The orange solution was then stirred at −78 °C for 1 h, by which time it had become a wine-red color. The reaction mixture was again cooled to below −90 °C and a solution of ketone **20** (271 mg, 0.974 mmol) in THF (2.2 mL) was added over 2 min. The dark mixture was stirred at −78 °C for 3 h, whereupon freshly distilled acetyl chloride (0.30 mL, 4.2 mmol) was added. After warming to room temperature overnight, the reaction mixture was shaken with sat. aq. NaHCO3 solution, extracted with EtOAc, and subjected to standard workup. Flash chromatography on silica, eluting with 80% EtOAc/hexanes, gave acetate **23** (308 mg, 68%). Mp: 151−154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, OCOCH_3), 2.39 (s, 6H, SCH_3), 3.49 (s, 3H, OCH_3), 6.76 (d, J = 5.6 Hz, 1H, H-5), 7.18 (d, J = 5.4 Hz, 2H, H-5′), 8.23 (d, J = 5.6 Hz, 1H, H-6), 8.39 (d, J = 5.4 Hz, 2H, H-6′). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.0 (SCH$_3$), 21.4 (OCOCH$_3$), 55.9 (OCH$_3$), 84.5 (Ar3COAc), 107.0 (C-5), 114.8 (C-5′), 122.5 (C-3), 149.7 (C-6), 152.1 (C-2), 156.6 (C-6′), 166.3 (C-4), 168.16 (C-4′ or *C*=O), 168.22 (*C*=O or C-4′), 171.7 (C-2′). IR (KBr): 1755, 1572, 1549, 1346, 1207, 1038. MS (EI): *m/z* (rel intensity) 463(2), 428 (51), 423/421 (61/27), 420 (55), 404 (24), 370 (37), 369 (100), 268 (32), 125 (48), 83 (31). HRMS (EI): Calcd for $C_{19}H_{18}N_5O_3{}^{32}S_2$ (M^+ − Cl) 428.0851, found 428.0860.

Formation of Variolin Core 2.

1. Preparation from Triarylmethanol 4.

A mixture of triarylmethanol **4** (100 mg, 0.237 mmol) and TFA (37μL, 0.48 mmol) was dissolved in 1,2-dichloroethane (0.5 mL). The resulting orange solution was transferred to a Young's tube, fitted with a rubber septum, containing TES (0.30 mL, 1.9 mmol). With a strong stream of argon flowing, the septum was replaced with a Teflon screw-cap, and the sealed reaction vessel was heated at 100 °C for 43 h. After cooling, the vessel was opened and the contents diluted with CH_2Cl_2 (12 mL). The solution was neutralized with 5% aq NaHCO3 solution (8 mL) and worked up with CH_2Cl_2 according to the standard procedure. Flash chromatography on silica, eluting with 48−75% EtOAc/hexanes, gave in order of elution: **a. 4-Methoxy-9-(methylsulfanyl)-5-[2-(methylsulfanyl)pyrimidin-4-yl]pyrido[3′,2′:4,5] pyrrolo[1,2-*c*]-pyrimidine (2)** as a yellow solid (41 mg, 47%). Mp: 192−194 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H, 2′-SCH_3), 2.70 (s, 3H, 9-SCH_3), 4.03 (s, 3H, OCH_3), 6.92 (d, J = 5.4 Hz, 1H, H-3), 7.40 (d, J = 5.4 Hz, 1H, H-5′), 7.71 (d, J = 6.8 Hz, 1H, H-7), 7.98 (d, J = 6.8 Hz, 1H, H-6), 8.48 (m, 2H, H-2, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (SCH$_3$), 14.9 (SCH$_3$), 55.6 (OCH$_3$), 101.9 (C-3), 102.5 (C-5), 108.5 (C-6), 110.8 (C-4a), 117.7 (C-5′), 135.9 (C-5a), 138.6 (C-7), 143.5 (C-2), 144.3 (C-10a), 154.2 (C-9), 155.6 (C-6′), 159.6 (C-4), 161.1 (C-4′), 171.2 (C-2′). IR ($CDCl_3$): 1570, 1468, 1285, 1013. MS (EI): *m/z* (rel intensity) 369 (100), 354 (13), 112 (10), 70 (10). HRMS (EI): Calcd for $C_{17}H_{15}N_5O^{32}S_2$ (M+) 369.0718, found 369.0720.

b. (2-Chloro-4-methoxypyridin-3-yl)-[2-(methylsulfanyl)pyrimidin-4-yl]-[2-(met hylsul-fanyl)pyrimidin-4-yloxy]methane (22) as a viscous gum (28 mg, 28%). Trituration with *n*-hexane gave an off-white solid. Mp: 113−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, 2′-SCH_3), 2.44 (s, 3H, 2″-SCH_3), 3.84 (s, 3H, OCH_3) 6.57 (d, J = 5.9 Hz, 1H, H-5″), 6.80 (d, J = 5.9 Hz, 1H, H-5), 7.17 (d, J = 4.9 Hz, 1H, H-5′), 7.79 (s, 1H, Ar2CHOAr), 8.27 (d, J = 5.9 Hz, 1H, H-6), 8.30 (d, J = 5.9 Hz, 1H, H-6″), 8.49 (d, J = 4.9 Hz, 1H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.88 (SCH$_3$), 13.90 (SCH$_3$), 56.2 (OCH$_3$), 71.8 (Ar2CHOAr), 103.5 (C-5″), 106.4 (C-5), 112.9 (C-5′), 120.8 (C-3), 150.7 (C-6), 152.5 (C-2), 157.1 (C-6′), 158.0 (C-6″), 166.0 (C-4), 167.1 (C-4′), 167.3 (C-4″), 172.1 (C-2′), 172.4 (C-2″). MS (EI): *m/z* (rel intensity) 421/423 (94/43), 387 (21), 374/376 (33/13), 296 (79), 280 (39), 246 (79), 212 (100), 184 (28), 147 (43), 125 (58), 112 (45), 104 (48), 77 (53), 76 (50), 70 (44). HRMS (EI): Calcd for $C_{17}H_{16}N_5O_2{}^{35}Cl{}^{32}S_2$ (M^+) 421.0434, found 421.0444.

2. Preparation from Acetate 23.

A mixture of acetate **23** (112 mg, 0.241 mmol) and TFA (37 μL, 0.48 mmol) was dissolved in 1,2-dichloroethane (0.5 mL). The resulting orange solution was transferred to a Young's tube, fitted with a rubber septum, containing TES (0.31 mL, 1.9 mmol). With a strong stream of argon flowing, the septum was replaced with a Teflon screw-cap, and the sealed reaction vessel was heated at 80 °C for 26 h. After cooling, the vessel was opened and the contents diluted with CH_2Cl_2 (15 mL). The solution was neutralized with 5% aq $NaHCO_3$ solution (8 mL) and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 and the organic extracts were worked

up according to the standard procedure. Flash chromatography on silica, eluting with 48% EtOAc/hexanes, gave core structure **2** (67 mg, 75%).

4-Methoxy-9-(4-methoxybenzylamino)-5-[2-(4-methoxybenzylamino)pyrim idin-4-yl]pyrido [3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (26). Core structure 2 (37 mg, 0.10 mmol) was dissolved in $CHCl_3$ (5 mL) under atmospheric conditions and cooled to −40 °C (CH_3CN/CO_2). A solution of *m*-CPBA in $CHCl_3$ (10 mg/mL) was similarly cooled and added dropwise to the solution of 2 until TLC analysis indicated the consumption of all starting material (after about 2 equiv of *m*-CPBA). The solution was warmed to room temperature and neutralized with sat. aq. NaHCO3 solution. This was extracted with CH_2Cl_2 and a standard workup gave a yellow solid which was predominantly a mixture of diastereomeric bis-sulfoxides 25. The crude mixture was used without purification; however, the bis-sulfoxides had the following spectroscopic characteristics: ^{1}H NMR (500 MHz, $CDCl_3$): (As most signals for the diastereoisomers coincide, they are all quoted as multiplets.) δ 3.02 (m, 3H), 3.19 (m, 3H), 4.12 (m, 3H), 7.00−7.01 (m, 1H), 7.98−7.99 (m, 1H), 8.12−8.14 (m, 1H), 8.48−8.49 (m, 1H), 8.64−8.67 (m, 1H), 8.79−8.81 (m, 1H).

The crude oxidized material **25** was heated with an excess of *p*-methoxybenzylamine (0.15 mL, 1.1 mmol) at 85 °C for 15 h. The red paste thus obtained was directly purified by flash chromatography on silica, eluting with 2.5−4% MeOH/CH_2Cl_2. This was chromatographed again on silica, eluting with 50% EtOAc/CH_2Cl_2 then 100% EtOAc, to give bis-amine **26** as a yellow-orange solid (43 mg, 78% over two steps). Mp: 74−77 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 6H, both PMB OC*H*$_3$), 3.99 (s, 3H, 4-OC*H*$_3$), 4.66 (d, J = 5.6 Hz, 2H, 2′-NHC*H*$_2$Ar), 4.85 (d, J = 5.5 Hz, 2H, 9-NHC*H*$_2$Ar), 5.51 (br, 1H, 2′∠N*H*PMB), 6.82 (d, J = 5.6 Hz, 1H, H-3), 6.89−6.91 (m, 4H, PMB H-3″, PMB H-3‴), 7.00 (d, J = 5.2 Hz, 1H, H-5′), 7.29 (br, 1H, H-6), 7.34 (d, J = 8.5 Hz, 2H, PMB H-2‴), 7.39 (d, J = 8.5 Hz, 2H, PMB H-2″), 7.43 (br d, J = 6.3 Hz, 1H, H-7), 8.16 (d, J = 5.6 Hz, 1H, H-2), 8.26 (d, J = 5.2 Hz, 1H, H-6′), 10.39 (br t, J = 5.5 Hz, 1H, 9-N*H*PMB). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3 (9-NH*C*H$_2$Ar), 44.9 (2′-NH*C*H$_2$Ar), 55.3 (both PMB O*C*H$_3$), 55.5 (4-O*C*H$_3$), 101.3 (C-5), 101.6 (C-3), 101.8 (C-6), 111.4 (C-4a), 112.2 (C-5′), 113.96 (PMB C-3‴ or PMB C-3″), 114.03 (PMB C-3″ or PMB C-3‴), 128.5 (PMB C-2‴), 128.8 (PMB C-2″), 130.5 (PMB C-1″), 131.4 (PMB C-1‴), 137.5 (C-5a), 141.5 (C-2), 141.9 (C-7), 144.7 (C-10a), 148.7 (C-9), 154.6 (br, C-6′), 158.7 (PMB C-4‴), 158.9 (PMB C-4″), 159.4 (C-4), 160.9 (C-2′), 162.6 (C-4′). IR (KBr): 3242, 2997−2833 (series of weak bands), 1570. MS (EI): *m/z* (rel intensity) 547 (65), 427 (14), 426 (9), 425 (12), 136 (38), 135 (53), 121 (100), 112 (21), 77 (24). HRMS (EI): Calcd for $C_{31}H_{29}N_7O_3$ (M^+) 547.2332, found 547.2334.

4-Hydroxy-9-(4-methoxybenzylamino)-5-[2-(4-methoxybenzylamino)pyrim idin-4-yl]pyrido [3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (27). A solution of sodium ethanethiolate (80%, 202 mg, 1.92 mmol) in dry DMF (2 mL) was added to a solution of bis-amine 26 (106 mg, 0.193 mmol) in DMF (2 mL), and the mixture was stirred at 55 °C for 7.5 h. After cooling, aq NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic extracts were washed three times with water to remove DMF and worked up as usual. Flash chromatography on silica, eluting with 4% MeOH/CH_2Cl_2, gave pyridinol 27 as a yellow solid (98 mg, 95%). Mp: 195−196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 3H, OC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 4.61 (d, J = 5.5 Hz, 2H, 2′-NHC*H*$_2$Ar), 4.85 (d, J = 5.5 Hz, 2H, 9-NHC*H*$_2$Ar), 5.35 (br, 1H, 2′∠N*H*PMB), 6.76 (d, J = 5.5 Hz, 1H, H-3), 6.88−6.92 (m, 4H, PMB H-3″, PMB H-3‴), 7.03 (d, J = 6.8 Hz, 1H, H-6), 7.06 (d, J = 5.7 Hz, 1H, H-5′), 7.32 (d, J = 8.4 Hz, 2H, PMB H-2‴), 7.40 (d, J = 8.4 Hz, 2H, PMB H-2″), 7.68 (d, J = 6.8 Hz, 1H, H-7), 8.05 (d, J = 5.5 Hz, 1H, H-2), 8.29 (d, J = 5.7 Hz, 1H, H-6′), 10.94 (br t, J = 5.5 Hz, 1H, 9-N*H*PMB), 15.7 (br, 1H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3 (9-NH*C*H$_2$Ar), 45.2 (2′-NH*C*H$_2$Ar), 55.3 (both O*C*H$_3$), 100.3 (C-6), 100.5 (C-5), 106.9 (C-5′), 107.5 (C-3), 111.4 (C-4a), 114.1 (PMB C-3″, PMB C-3‴), 128.8 (PMB C-2″), 129.2 (PMB C-2‴), 130.2 (PMB C-1″, PMB C-1‴), 137.5 (C-5a), 142.8 (C-2), 143.8 (C-7), 145.4 (C-10a), 149.7 (C-9), 158.6 (C-6′), 158.9 (PMB C-4″), 159.0 (PMB C-4‴), 159.5 (C-4′), 159.8 (C-4), 160.0 (C-2′). IR (KBr): ν_{max} 3223, 2820−2835 (series of weak bands), 1574. MS (EI): *m/z* (rel intensity) 533 (38), 413 (19), 412 (18), 411 (15), 121 (100). HRMS (EI): Calcd for $C_{30}H_{27}N_7O_3$ (M^+) 533.2175, found 533.2185.

Variolin B (1). Pyridinol **27** (31 mg, 0.058 mmol) was dissolved in neat TfOH (0.5 mL) under atmospheric conditions. The flask was stoppered, and the deep red solution was left at room temperature for 17 h. The reaction was cooled in ice and carefully quenched with ice−water (1 mL), followed by conc aq NH_3 solution (1 mL), which produced a bright yellow precipitate. After mixing thoroughly to ensure complete neutralization, the precipitate was filtered through a fine frit, washing with water and then MeOH/water (1:1). The solid was then suspended in MeOH/CH_2Cl_2 (a small amount of TFA was added to convert the free base to the more soluble salt form) and adsorbed onto a small amount of reversed phase silica for flash chromatography, eluting with 50% MeOH/water then 70% MeOH/water + 0.5% TFA. The bright yellow fractions were combined and concentrated *in vacuo* to give variolin B as its trifluoroacetate salt. The salt was neutralized by sonication with conc aq NH_3/MeOH to give the free base **1**. Concentration *in vacuo* (35 °C, 0.03 mmHg to remove ammonium trifluoroacetate) gave variolin B (**1**) as a brown-orange solid (13.6 mg, 80%). Mp: dec at ∼320 °C (lit[3a] 45 °C, dec). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 6.81 (d, J = 5.6 Hz, 1H, H-3), 6.97 (s, 2H, 2′∠N*H2*), 7.14 (d, J = 5.6 Hz, 1H, H-5′), 7.23 (d, J = 6.7 Hz, 1H, H-6), 7.63 (d, J = 6.7 Hz, H-7), 8.17 (d, J = 5.6 Hz, 1H, H-2), 8.27 (d, J = 5.6 Hz, 1H, H-6′), 8.45 (br, 1H, 9-N*H*), 9.79 (br, 1H, 9-N*H*), 16.05 (s, 1H, O*H*). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 99.6 (C-5), 100.3 (C-6), 106.0 (C-5′), 107.5 (C-3), 111.2 (C-4a), 137.1 (C-5a), 143.1 (C-2), 144.6 (C-7), 144.9 (C-10a), 150.3 (C-9), 158.3 (C-4′), 159.8 (C-4), 160.0 (C-6′), 161.4 (C-2′). IR (KBr): 3085, 1670, 1572, 1477, 1458, 1298. HRMS (ES): Calcd for $C_{14}H_{12}N_7O$ (MH^+) 294.1103, found 294.1096.

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Supporting Information Available: General experimental details, details of the preparation of **13**, **19**, and **21**, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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