JOC Article

Carbodiimide-Mediated Preparation of the Tricyclic Pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine Ring System and Its Application to the Synthesis of the Potent Antitumoral Marine Alkaloid Variolin B and Analog

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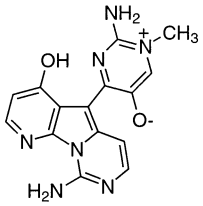
A total synthesis of the marine alkaloid variolin B has been completed in 13 steps in an overall yield of 6.5% from 3-formyl-4-methoxypyridine. Our approach is based on the sequential formation of the 7-azaindole ring, the tricyclic pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine ring system, and finally installation of the 2-aminopyrimidine ring at C5. The required 7-azaindole ring appropriately substituted is formed by a modified indole synthesis involving a nitrene insertion process (two steps). Formation of the annelated pyrimidine ring is achieved by two routes both involving a carbodiimide-mediated cyclization process, which allow incorporation of the amine functionality at C9 of the core tricyclic (six steps). Installation of the northeast 2-aminopyrimidine ring at C5 is performed using the Bredereck protocol (three steps). Ultimate, thermal decarboxylation with concomitant *O*-methyl deprotection and further *N*-benzyl deprotection by the action of triflic acid completed the synthesis of the target natural product variolin B.

Introduction

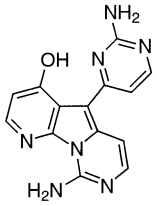
Marine organisms are among the most promising sources of new biologically active molecules.[1] Certain secondary metabolites are nontraditional guanidine-based alkaloids[2] that possess a broad spectrum of powerful biological activities. The guanidine moiety is frequently found in the guise of a 2-aminoimidazole ring[3] or a 2-aminopyrimidine ring,[4] which represent an emerging structural class of marine alkaloids based upon their high degree of biological activity. In 1994, Blunt and Munro reported the isolation and structural elucidation of the variolins a new class of marine alkaloids from the rare, difficult to access Antartic sponge *Kirkpatrickia variolosa*.[5]

This new class of alkaloids are interesting from both the structural and biological points of view. All the variolins have a common pyridopyrrolopyrimidine core, strictly a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, with either a heterocyclic or methoxycarbonyl group attached at C5, which has no precedents in either terrestrial or marine natural products. Variolins can also be considered as guanidine-based alkaloids in which the guanidine moiety is found in the guise of a 2-aminopyrimidine ring.

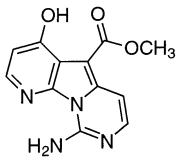
An important feature of variolins is significant bioactivity; variolin B is the most active, having citotoxic activity against the P388 murine leukemia cells, and also being effective against *Herpes simples* type I, it is inactive against a range of other microorganisms.[5a] Variolin A also showed important cytotoxic activity against the P388 cell line. *N*-3'-Methyl-3′,4′,5′,6′-tetrahydrovariolin B inhibited the grow of *Sacharomyces cerevisiae* and showed in vitro activity against the HCT 116 cell line. The differential biological activity of these alkaloids is believed to show the importance of the 2-aminopyrimidine ring at C5.



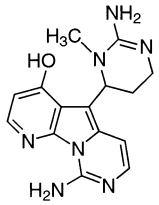
Variolin A



Variolin B



Variolin D



N-3′-methyl-3′,4′,5′,6′-tetrahydrovariolin B

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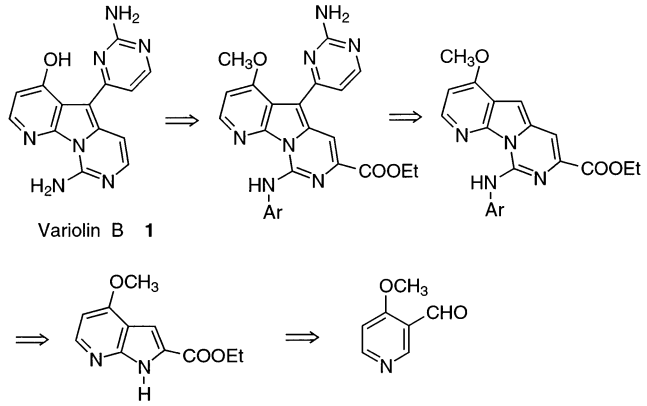
SCHEME 1



Consequently, owing to the intriguing structure of these alkaloids, significant bioactivity, and also its low natural occurrence, the elaboration of the central tricyclic core has stimulated interest in the scientific community and attracted assorted synthetic efforts. Recently, the first total synthesis of the architecturally sophisticated alkaloid variolin B has been reported;[6] this synthesis starts from commercially available 4-iodo-2-methylthiopyrimidine involving as a key step a tandem deoxygenation/cyclization of an appropriate triheteroaryl methanol using a combination of triethylsilane and trifluoroacetic acid. This work prompted us to report as a preliminary communication[7] a new synthesis of variolin B using our experience in the field of iminophosphorane. In view of our interest in the synthesis of natural marine alkaloids as lead compounds to new and more biologically active agents, we present now the full account of a general synthetic method for building the central heterocyclic moiety presents in variolins, which is essential for making this family of compounds and a wide variety of analogues readily available.

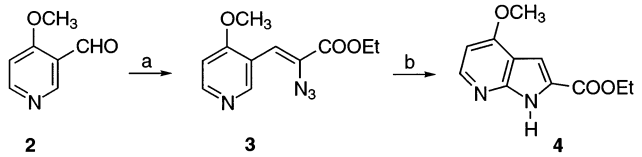
Our approach to the synthesis of variolin B is depicted in the retrosynthetic analysis shown in Scheme 1. The key steps were: (a) the synthesis of an appropriately functionalized 2,4-disubstituted-7-azaindole, (b) construction of the central core pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine ring that typify this compound by two different routes involving a carbodiimide-mediated pyrimido annelation process, and (c) installation of the 2-aminopyrimidine ring at C5.

Critical to the success of this strategy was the formation of a 4-methoxy-7-azaindole equipped with appropriate functionalization at C2 for subsequent manipulation to generate the fused pyrimidine ring.

Results and Discussion

Limited general synthetic pathways exist in the literature for the preparation of 7-azaindoles; they involve classical methods such as Fisher, Madelung, and Reissert procedures, which despite their synthetic value, generally suffer from harsh reaction conditions and modest yields.[8] The intramolecular inverse electron demand Diels−Alder reaction of appropriately substituted 1,2,4-triazines[9] and direct *ortho*-lithiation of aminopyridine derivatives[10] have been also used for the preparation of substituted 7-azaindoles. Recently, palladium-catalyzed heteroannelations of 2-amino-3-iodopyridine derivatives with internal alkynes based on modified synthetic procedures for indoles[11] have been useful for the preparation of 2, 3-disubstituted 7-azaindole derivatives.[12] Moreover, functionalization at the 2-, 3-, and 6-position of the 7-azaindole derivatives through palladium-mediated coupling reactions has been reported.[13] Nevertheless, reports on the functionalization at the 4-position are very limited in the literature and only has briefly been reported the preparation of 4-C-substituted-7-azaindoles through palladium-catalyzed Suzuki, Sonogashira, and Heck coupling reactions.[13d]

SCHEME 2[a]



[a] Reagents and conditions: (a) N_3CH_2COOEt, NaEtO, EtOH, −15 °C (61%); (b) *o*-xylene, reflux (67%).

The first facet of the synthesis, the preparation of the appropriately 2,4-disubstituted-7-azaindole, was accomplished by taking advantage of a modified Hemetsberger indole synthesis which has been successfully applied for the synthesis of a number of indole alkaloids.[14] For this purpose the required 3-formyl-4-methoxypyridine **2** was prepared in 77% yield following the Comins protocol[15] by *ortho*-lithiation of 4-methoxypyridine with mesityllithium as the metalating base followed by reaction with *N*,*N*-dimethylformamide. Condensation of **2** with ethyl azidoacetate in the presence of NaEtO at −15 °C provided the vinyl azide **3** in 61% yield. When compound **3** was exposed to heat in *o*-xylene at reflux temperature for a short period of time, indolization took place by a nitrene insertion process to give the key intermediate 2-ethoxycarbonyl-4-methoxy-7-azaindole **4** in 67% yield. (Scheme 2).

Before our first synthesis of the pyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine ring[16] bearing suitable functionalities

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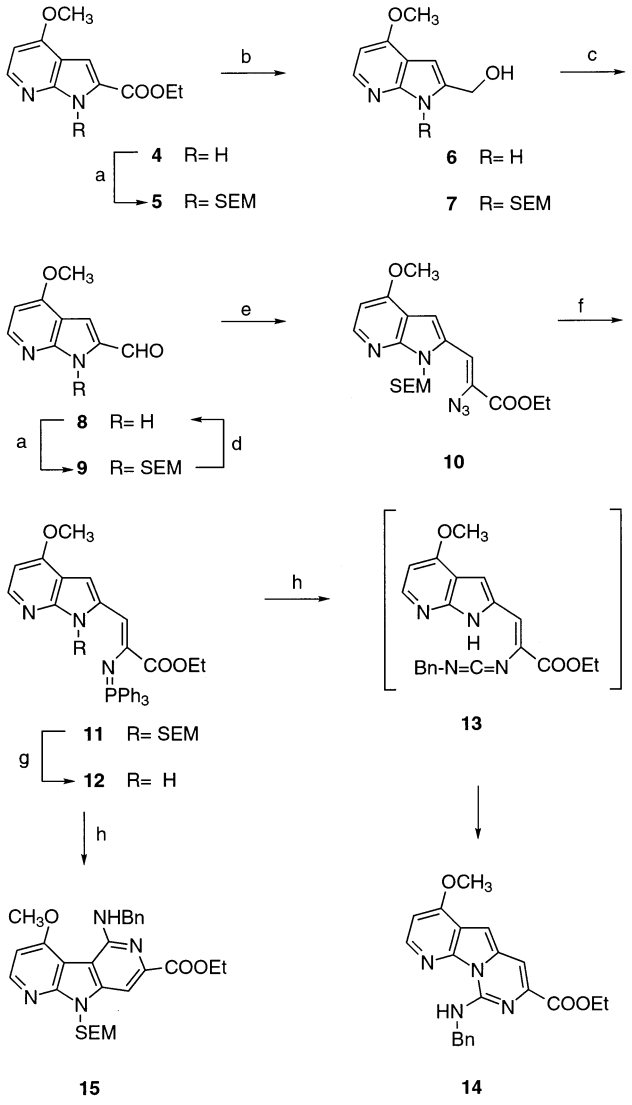
(15) Comins, D. L.; La Munyon, D. H. *Tetrahedron Lett.* **1988**, 773.

for the preparation of the natural product, there was only one report dealing with the preparation of a thiofunctionalized derivative of this ring system.[17] Almost at the same time of our approach three syntheses appeared employing different solutions to the challenging problem of constructing the core tricyclic of variolin B. The first one involves the reaction of *N*-methoxycarbonyl-2-bromomethyl-4-methoxy-7-azaindole with tosylmethyl isocyanide (TOSMIC) to give the target tricyclic ring although without any kind of substituent introduced at C9.[18] The second way is based on the introduction of an aminomethyl side-chain at C2 of the 7-azaindole ring followed by closure and aromatization to give the tricyclic ring bearing an oxo functionality at C9.[19] The third way involves the deoxygenation and concomitant cyclization of a bis(2-methylthiopyrimidyl)pyridylmethanol using the combination of triethylsilane and trifluoroacetic acid.[20] In the two latter approaches the amine functionality at C9 required is absent but elements of its eventual formation are present.

In our first approach, the pyrimido annelation reaction, which allows incorporation of the amine functionality is accomplished by taking advantage of our developed tandem aza Wittig/heterocumulene-mediated ring closure applied to fused pyrimidines.[21] To this end, we required the 2-formyl-4-methoxy-7-azaindole **8**, which was prepared from **4**, by the following sequence: reduction with $LiAlH_4$/THF gave **6** in 93% yield, which in turn was converted into **8** in 60% yield by reaction with MnO_2. However, from the reaction of **8** with ethyl azidoacetate under basic conditions, only numerous intractable decomposition products were formed. Therefore, we decided to protect the 7-azaindole ring prior to condensation with ethyl azidoacetate. Although, the *N*-SEM-protected 2-formyl-4-methoxy-7-azaindole **9** was obtained in 93% yield from **8** using standar conditions, the best results for the preparation of this compound were obtained by the following three-step sequence: (a) *N*-SEM protection of **4** provided **5** in 94% yield, (b) reduction with $LiAlH_4$/THF at reflux temperature gave **7** in 93% yield, and (c) oxidation with MnO_2 in CH_2Cl_2 at room temperature afforded **9** in 86% yield.

Condensation of the *N*-SEM-protected 7-azaindole **9** with ethyl azidoacetate under the same conditions used for the preparation of **3** furnished the vinyl azide **10** in 85% yield. The Staudinger reaction of **10** with triphenylphosphine in dry CH_2Cl_2 at room temperature gave the expected iminophosphorane derivative **11** in 82% yield. Treatment of **11** with tetrabutylammonium fluoride (TBAF)$-SiO_2$ under microwave heating for 1 min proved advantageous and cleanly removed the SEM group to give **12** in 70% yield, without affecting the iminophosphorane group. The use of TBAF/THF as deprotecting agent resulted even after an extended reaction time in a low yield of **12** with a considerable amount of the product

SCHEME 3[a]



[a] Reagents and conditions: (a) SEM-Cl, NaH, DMF (**5**, 94%), (**9**, 93%); (b) $LiAlH_4$, THF, reflux (**6**, 93%), (**7**, 93%); (c) MnO_2, CH_2Cl_2, rt (**8**, 60%; **9**, 86%); (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2 (95%); (e) N_3CH_2COOEt, NaEtO, EtOH, −15 °C (85%) (f) Ph_3P, CH_2Cl_2, rt (82%); (g) TBAF$-SiO_2$, THF, MW (70%); (h) BnNCO, THF, 50 °C (**14**, 97%); (**15**, 90%).

derived from the hydrolytic cleavage of the iminophosphorane moiety. Iminophosphorane **12** was more appropriately prepared by changing the reaction sequence. Thus sequential treatment of the azide **10** with $BF_3{\cdot}Et_2O$ and triphenylphosphine allowed the one-flask conversion of **10** into **12** in 88% yield.

Aza-Wittig reaction of iminophosphorane **12** with benzyl isocyanate in dry THF at 50 °C proceeded uneventfully to afford directly the desired pyrimido annelation product **14** in almost quantitative yields, thus completing the tricyclic pyridopyrrolopyrimidine ring bearing oxo and nitrogen functionalities placed at suitable positions for the preparation of the target molecule (Scheme 3).

The regioselective cyclization of the non isolable intermediate carbodiimide **13** to afford the angular fused pyrimidine **14** instead of the linear tricyclic compound deserves some comments. We have previously reported

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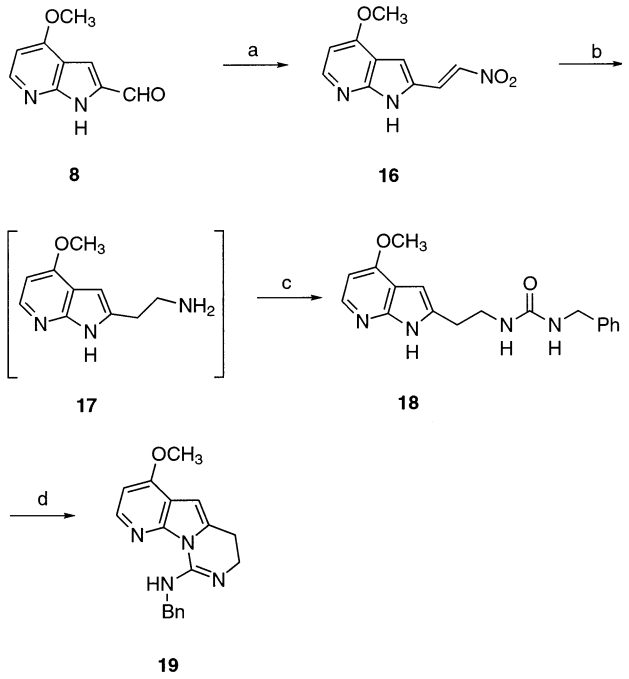
that β-(indol-2-yl)vinyl heterocumulenes under thermal conditions undergo electrocyclic ring-closure to give γ-carbolines,[22] whereas when the indole ring is substituted at C3, heterocyclization reaction takes place by nucleophilic attack of the amino group on the central carbon of the heterocumulene moiety to give pyrimido-[1,6-*a*]indoles.[23] In the present case the preferential formation of the intramolecular amination product **14** with respect to the electrocyclic ring-closure product could be explained by the lower reactivity of α-vinyl-7-azaindoles than the same indole derivatives in electrocyclic process due to decrease of the energy level of the HOMO of the diene.[13c] The linear tricyclic compound **15** was obtained in 90% yield by treatment of the *N*-SEM-protected 7-azaindole **11** with benzyl isocyanate.

The second approach to prepare the tricyclic core of variolins without the undesired ester group at C7 is based on our finding that carbodiimides resulting from the aza Wittig reaction of the iminophosphorane derived from 2-(2-azidoethyl)indole and isocyanates undergo regioselective intramolecular cyclization under acid ($SnCl_4$), basic (KHMDS) and thermal conditions (160° C) to give dihydropyrimido[3,4-*a*]indoles.[24] The starting material of choice was the 2-formyl-4-methoxy-7-azaindole **8** prepared from **9** in 95% yield by *N*-SEM deprotection with $BF_3{\cdot}Et_2O$. Condensation of **8** with nitromethane under Henry conditions led to the 2-nitrovinyl-7-azaindole **16** in 80% yield. When compound **16** was submitted to react with $LiAlH_4$ the 2-(2-aminoethyl)-7-azaindole **17** was obtained as a solid. However, its purification was tedious and the isolated solid was found to be sunlight unstable, for these reasons compound **17** was used without isolation for the next step. The direct conversion of **16** into the urea derivative **18** was achieved in 60% yield by sequential treatment with $LiAlH_4$ and benzyl isocyanate. Dehydration of **18** and concomitant cyclization of the resulting carbodiimide to give **19** was accomplished in 90% yield under mild conditions by using the Appel reagent ($CCl_4/PPh_3/Et_3N$). The fact that the cyclization of the intermediate carbodiimide takes place under mild conditions (DCM, 50 °C) is in clear contrast with the results found for related carbodiimides in the indole series, which need drastic conditions. All attempts to promote the aromatization of the dihydropyrimidine ring in **19** failed and only complex mixtures were obtained (Scheme 4).

The next task was the installation of the 2-aminopyrimidine ring at C5, which was effected along the lines previously employed in our meridianins (3-aminopyrimidylindoles) synthesis,[25] using an acetyl side chain as C2 moiety for the construction of the 2-aminopyrimidine ring.[26] Acylation of compound **19** proved to be more problematic than we have anticipated, because the tricyclic pyridopyrrolodihydropyrimidine ring did not survive under the conditions employed for acylation of the 7-azaindole.[25] We then decided to switch our plans, one could envisage that the introduction of a bromine at

SCHEME 4[a]



[a] Reagents and conditions: (a) CH_3NO_2, NH4AcO, EtOH, 75 °C (80%); (b) $LiAlH_4$, THF, 0 °C to rt; (c) $PhCH_2NCO$, CH_2Cl_2, rt (60%); (d) $CCl_4/Ph_3P/Et_3N$, CH_2Cl_2, 50 °C (90%).

C5 in the tricyclic ring would provide the site for the formation of the acetyl appendage. Since, bromination of 7-azaindole has precedent to proceed at C3,[27] we were reasonably optimistic about the chances of success for the regioselective bromination at C5 of compound **19**.

The bromination reaction was carried out under classical conditions (Br_2, pyridine, 0 °C or NBS at −60 °C), thus allowing the predictable and exclusive incorporation of the bromine atom at C5 of the tricyclic ring, as evidenced by the disappearance of H-5 triplet at δ 6.31 ppm with $J = 1.2$ Hz in the ^{1}H NMR spectrum of **19**, to give **20** in 70% yield. The replacement of the bromine atom in **20** by the acetyl functionality to give **21** was achieved in 65% yield by coupling with (α-ethoxyvinyl)-tributyltin[28] in the presence of dichlorobis (triphenylphosphine)palladium (II).[29] Oxidative conversion of the dihydroheterocyclic compound **21** to the corresponding heteroaromatic **22** was achieved either by using bromotrichloromethane in combination with DBU[30] or DDQ in dichloromethane at room temperature, albeit in very disapointing yield (32−40%).

On the other hand, the reaction of compound **14** with *N*,*N*-dimethylacetamide in the presence of $POCl_3$ allowed the direct introduction of the acetyl group at C5 to give **23** in 90% yield, which was converted into **22** in somewhat better yield: ester hydrolysis provided the acid **24** in quantitative yield which under thermal treatment

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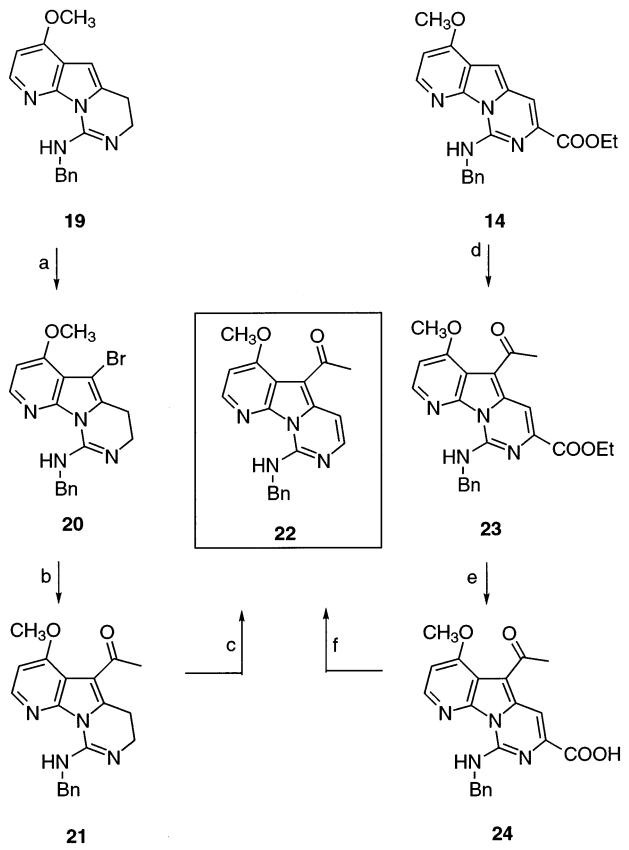
SCHEME 5[a]



[a] Reagents and conditions: (a) Br_2 pyridine, 0 °C (50%); NBS, THF, CH_2Cl_2 (70%); (b) α-(ethoxyvinyl)tributyltin, DMF, $PdCl_2(PPh_3)_2$, 70 °C; acetone, 1 M HCl, rt (65%); (c) i: DBU, $CBrCl_3$ (32%); ii: DDQ, CH_2Cl_2 (40%); (d) DMA, $POCl_3$ (90%); (e) LiOH, THF-H_2O (100%); (f) Ph_2O, 250 °C (50%).

underwent decarboxylation to give **22** in moderate yield (50%). (Scheme 5)

The acetyl derivatives **22** and **23** were reacted with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) in dimethylformamide at 110 °C to give the enaminones **25** and **26** in moderate yields (45%). Switching to the more reactive *N*,*N*-dimethylformamide di-*tert*-butylacetal (DMF-DtBA) produced the best yields at lower reaction temperature. Thus, when compounds **22** and **23** were treated with DMF-DtBA in DMF at 80°C the enaminones **25** and **26** was obtained in 85−70% yield.

Conversion of **25** to **27**, which involves the formation of the substituted 2-aminopyrimidine ring, was achieved in 90% yield by treatment with guanidine hydrochloride in 2-methoxyethanol in the presence of anhydrous potassium carbonate. Under the same reaction conditions, enaminone **26** underwent ring-closure and concomitant ester hydrolysis to give **28** in 93% yield. It must be mentioned that a previous work[19] related on the synthesis of deoxyvariolin B, the introduction of the 2-aminopyrimidine ring at C5 of the tricyclic core was achieved in four steps in 36% overall yield, by heteroaryl palladium (0)-catalyzed coupling followed by oxidation with MCPBA and further treatment with ammonium hydroxide. In the present approach, using the Bredereck protocol,[26] this chemical operation is performed in three steps in 56% overall yield.

All that remained for realization of the final goal were decarboxylation and *O*- and *N*-deprotection. To remove the *O*-methyl group, compound **27** was treated with an excess of sodium methanethiolate[31] in dry DMF to give **29** in 85% yield. Decarboxylation of **28**, essential to our objective of preparing variolin B, proved to be difficult. After several trials with various reagents and conditions (Cu/quinoline, Δ; $Cu_2Cr_2O_5$/BaO, Δ, and Barton radical decarboxylation procedure[32]), we were unable to accomplish this transformation. This series of frustrating results was finally broken by using only thermal conditions. Thus when compound **28** was heated in diphenyl ether at 280 °C for 5 h, a 1:1 mixture of the desired decarboxylation product **27** and, much to our surprise, decarboxylation/*O*-methyl deprotection product **29** was obtained. Traces of water present in compound **28** are apparently enough to inhibit the *O*-methyl deprotection since when this reaction was carried out under rigorous anhydrous conditions, compound **29** was obtained as the only reaction product. Thus, when acid **28**, previously dried over anhydrous magnesium sulfate, was heated in dry diphenyl ether under the same reaction conditions under nitrogen, compound **29** was obtained in 67% yield. Despite the moderate yield and considering that this conversion concatenates two transformations, the yield must be considered as good.

To the best of our knowledge, this serendipitously thermal *O*-methyl deprotection is unprecedented, and we are currently exploring the scope and applicability of this deprotection method. Finally, the *N*-benzyl protecting group was removed by treatment of **29** in neat triflic acid at 50 °C to give the variolin B **1** in 74% yield, whose spectra are in excellent agreement with those reported for natural **1** (Scheme 6).

The convenience of the above synthetic pathway to variolin B makes this approach very attractive for the preparation of structurally related compounds. Thus, the key intermediate **14** was converted into **35** a regioisomer of variolin B by a six-step sequence in an overall yield of 28%. Hydrolysis of compound **14** provided the acid **30** in 95% yield, which in turn was converted into the 3-acetyl derivative **31** in 62% yield by the action of methyllithium at −15 °C. Formation of enaminone **32** (84% yield) followed by formation of the 2-aminopyrimidine ring afforded **33** in 90% yield. The *O*-methyl deprotection gave **34** in 83% yield, which by *N*-benzyl deprotection under acid conditions yielded **35** in 75% yield (Scheme 7). From these results, it is important to point out that the introduction of the 2-aminopyrimidine ring at C7 takes place under milder reaction conditions and higher yield than at C5.

Conclusions

A total synthesis of the marine alkaloid variolin B has been achieved in 13 steps in an overall yield of 6.5%. The required 2-ethoxycarbonyl-4-methoxy-7-azaindole was formed from 3-formyl-4-methoxypyridine by condensation with ethyl azidoacetate followed by thermal treatment

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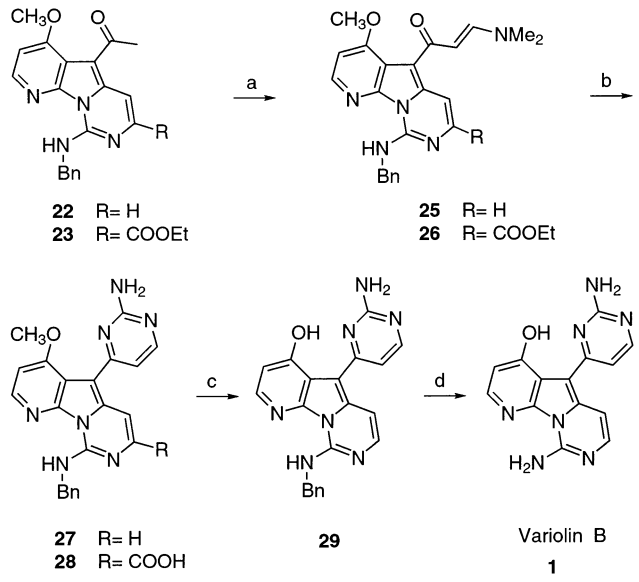
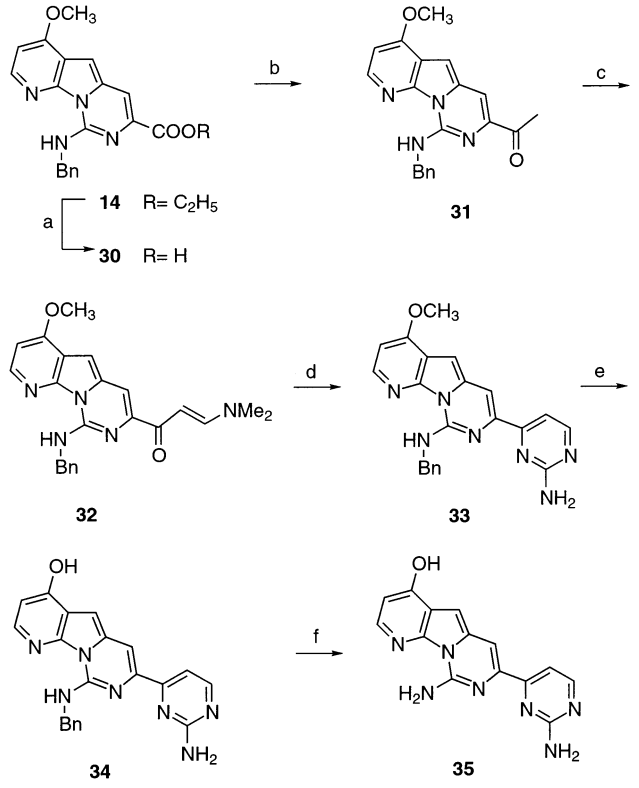
(32) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun*. **1983**, 939. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (c) Crich, D. *Aldrichimica Acta* **1987**, *20*, 35.

SCHEME 6[a]



[a] Reagents and conditions: (a) DMF-DtBA, DMF, 70−80 °C (**25**, 85%), (**26**, 70%); (b) $H_2N(C{=}NH)NH_2{\cdot}HCl$, K_2CO_3, 2-methoxyethanol, reflux (27, 90%), (28, 93%); (c) i: NaMeS, DMF, 80 °C (85%); ii: Ph_2O, 280 °C, 4 h (67%); (d) triflic acid, 50 °C (74%).

SCHEME 7[a]



[a] Reagents and conditions: (a) LiOH, THF−H_2O (95%); (b) MeLi, THF, −15 °C (62%); (c) DMF-DtBA, DMF, 80 °C (84%); (d) $H_2N(C{=}NH)NH_2{\cdot}HCl$, K_2CO_3, 2-methoxyethanol, 110 °C (90%); (e) NaMeS, DMF, 80 °C (83%); (f) triflic acid, rt (75%).

(two steps). Formation of the core tricyclic was achieved by two routes; both of them involve initial *N*-SEM protection of the 7-azaindole and reduction followed by oxidation to give 2-formyl-7-azaindole. The first one involves condensation with ethyl azidoacetate and *N*-SEM deprotection, Staudinger reaction with triphenylphosphine and then aza-Wittig reaction of the iminophosphorane with benzylisocyanate (six steps). The second route is based on the formation of a fused dihydropyrimidine ring by condensation with nitromethane, reduction, and condensation with benzyl isocyanate followed by dehydration and concomitant cyclization of the resulting carbodiimide. These pyrimido annelation processes allow the direct introduction of the amine functionality at C9 of the tricyclic ring system. Installation of the 2-aminopyrimidine ring involves regioselective acylation at C5 of the tricyclic ring, followed by condensation of the resulting acetyl derivative with DMF-DtBA and cyclization by reaction with guanidine (three steps). Eventually, thermal decarboxylation with concomitant *O*-methyl deprotection followed by *N*-benzyl deprotection affords the target variolin B, that was found to be identical in all respects with the natural product.

Experimental Section

General Methods. All reactions were carried under N_2 and using solvents that were dried by routine procedures. Column chromatography was performed with the use of silica gel (60 Ac.c 70−200 μm, SDS) as the stationary phase. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were determined as Nujol emulsions or films. NMR spectra were obtained at 200, 300, or 400 MHz (^{1}H) and 50, 75, or 100 MHz (^{13}C). Chemical shifts are reported in ppm relative to trimethylchlorosilane. Reactions under microwave irradiation were carried out in a microwave reactor (2.45 GHz, adjustable power within the range 0−300 W with a simple mode focused system) fitted with a rotational system and a IR detector of temperature. The microwave oven is monitored by a computer that allows the temperature of the reaction mixture to be adjusted.

Materials. The 3-formyl-4-methoxypyridine **2**,[15] ethyl azidoacetate[33] and α-(ethoxyvinyl)tributylltin[28] were synthesized according to already reported procedures.

Preparation of Ethyl α-Azido-*β*-(4-methoxypyrid-3-yl)-acrylate (3). A mixture of ethyl azidoacetate (4.15 g, 32 mmol) and 3-formyl-4-methoxypyridine **2** (1.1 g, 8.02 mmol) in anhydrous EtOH (50 mL) was added dropwise under N_2 at −15 °C to a well-stirred solution containing Na (0.74 g, 32.1 mmol) in anhydrous EtOH (30 mL). The mixture was stirred at that temperature for 72 h. The resultant solution was poured into aqueous 30% ammonium chloride (50 mL). The separated solid was washed with H_2O, air-dried, and recrystallized from EtOAc/*n*-hexane (1:1) to give **3** (1.21 g, 61% yield) as colorless needles: mp 106−108°C; IR (Nujol) ν: 2129 (N_3), 1710 (s), 1593 (s), 1287 (s), 1098 (s), 1028 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, 3H, J = 7.2 Hz), 3.92 (s, 3H,), 4.38 (q, 2H, J = 7.2 Hz), 6.81 (d, 1H, J = 5.7 Hz), 7.19 (s, 1H), 8.43 (d, 1H, J = 5.7 Hz), 9.25 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 55.5, 62.3, 105.8, 115.9, 118.8, 126.7, 151.3, 151.4, 162.7, 163.1. EIMS: *m*/*z* (%) 248 (M$^+$, 49), 220 (85), 192 (30), 174 (82), 147 (100), 132 (50), 119 (68), 117 (92), 107 (52), 90 (95). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.10; H, 4.70; N, 22.41.

Preparation of 2-Ethoxycarbonyl-4-methoxypyrrolo-[2,3-*b*]pyridine (4). A stirred solution of vinyl azide **3** (1.0 g, 4.03 mmol) in dry *o*-xylene (140 mL) was heated in a molten salts bath at 170 °C for 25 min. After cooling at −10 °C the precipitated white solid was collected by filtration, washed with Et_2O and recrystallized from CH_2Cl_2 to give **4** (0.59 g, 67% yield) as white needles; mp 216−217 °C; IR (Nujol) ν: 3416 (NH), 1723 (CO), 1583 (s), 1524 (s), 1345 (s) cm^{-1}. ^{1}H NMR

(33) Hemestsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194.

(300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, J = 6.9 Hz), 3.97 (s, 3H), 4.32 (q, 2H, J = 6.9 Hz), 6.71 (d, 1H, J = 5.7 Hz), 7.09 (s, 1H), 8.28 (d, 1H, J = 5.7 Hz), 12.45 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 55.5, 60.2, 98.3, 103.4, 109.7, 125.7, 148.4, 150.4, 160.4, 160.5. EIMS: *m*/*z* (%) 220 (M^+, 98), 221 (38), 192 (28), 175 (58), 174 (100), 145 (35). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.79; H, 5.64; N, 12.60.

Preparation of *N*-(Trimethylsilyl)ethoxymethyl-2-ethoxycarbonyl-4-methoxy pyrrolo[2,3-*b*]pyridine (5). To a suspension of sodium hydride (0.44 g, 11.1 mmol) in dry DMF (18 mL) was added dropwise under N_2 a solution of the 7-azaindole **4** (1.77 g, 8.03 mmol) in the same solvent (15 mL). The mixture was stirred at room temperature for 45 min. After this time, the solution was cooled at 0 °C, and 2-(trimethylsilyl)ethoxymethyl chloride (2 mL, 11.2 mmol) was slowly added. The solution was allowed to warm at room temperature and stirred for 12 h. Then, it was poured into H_2O (20 mL) and stirred for 30 min, and the precipitated solid was collected by filtration, air-dried, washed with Et_2O, and recrystallized from *n*-hexane to give **5** (2.7 g, 94% yield) as white prisms: mp 74−75 °C. IR (Nujol) ν: 1716 (CO), 1601 (s), 1571 (s), 1503 (s), 1332 (s), 1297 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.12 (s, 9H), 0.87 (t, 2H, J = 8.4 Hz), 1.39 (t, 3H, J = 7.2 Hz), 3.52 (t, 2H, J = 8.4 Hz), 3.98 (s, 3H), 4.36 (q, 2H, J = 7.2 Hz), 6.09 (s, 2H), 6.54 (d, 1H, J = 5.7 Hz), 7.37 (s, 1H), 8.33 (d, 1H, J = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −1.6, 14.2, 17.8, 55.6, 60.7, 66.0, 71.1, 98.8, 107.6, 109.5, 126.1, 148.7, 151.8, 161.1, 161.3. EIMS: *m*/*z* (%) 350 (M^+, 7), 351 (9), 307 (42), 277 (41), 249 (94), 232 (94), 219 (96), 204 (99), 174 (98), 161 (99), 148 (38), 72 (100). Anal. Calcd for $C_{17}H_{26}N_2O_4Si$: C, 58.26; H, 7.48; N, 7.99. Found: C, 58.10; H, 7.30; N, 7.81.

Preparation of 2-Hydroxymethylpyrrolo[2,3-*b*]pyridines (6 and 7). To a solution of the appropriate 7-azaindole **4** or **5** (4.85 mmol) in anhydrous THF (40 mL) was added $LiAlH_4$ (5.33 mL of a 1 M solution in THF, 5.33 mmol). The mixture was stirred at reflux temperature for 30 min. After cooling, it was poured into cool H_2O (20 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried ($MgSO_4$). After filtration, the filtrate was concentrated to dryness and the residue was chromatographed on a silica gel column with Et_2O as eluent.

6: (0.8 g, 93% yield); mp 213-215 °C (white prisms). IR (Nujol) ν: 3920 (s), 3356 (s), 1604 (s), 1546 (m), 1160(s), 1006 (s) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.92 (s, 3H), 4.56 (d, 2H, J = 5.7 Hz), 5.23 (t, 1H, J = 5.7 Hz), 6.29 (s, 1H), 6.60 (d, 1H, J = 5.4 Hz), 8.04 (d, 1H, J = 5.4 Hz), 11.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 56.8, 94.4, 97.8, 109.7, 138.4, 143.9, 150.4, 158.5. EIMS: *m*/*z* (%) 179 (M^+ + 1, 13), 178 (M^+, 100), 161 (98), 149 (25), 134(40), 118 (21), 105 (10). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.44; H, 5.82; N, 15.65.

7: (1.39 g, 93% yield); yellow oil. IR (film) ν: 3370 (m), 1612 (s), 1576 (s), 1548 (s), 1292 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.08 (s, 9H), 0.90 (t, 2H, J = 8.1 Hz), 3.27 (t, 1H, J = 6.3 Hz), 3.55 (t, 2H, J = 8.1 Hz), 4.0 (s, 3H), 4.79 (d, 2H, J = 6.3 Hz), 5.79 (s, 2H), 6.55 (d, 1H, J = 5.7 Hz), 6.56 (s, 1H), 8.19 (d, 1H, J = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −1.6, 17.8, 55.5, 57.2, 66.2, 70.3, 98.6, 98.7, 109.8, 137.3, 145.2, 151.0, 159.9. EIMS: *m*/*z* (%) 308 (M^+, 58), 309 (38), 290 (8), 265 (39), 249 (49), 235 (91), 232 (51), 205 (22), 189 (87), 177 (99), 159 (89), 144 (58), 43 (100). Anal. Calcd for $C_{15}H_{24}N_2O_3Si$: C, 58.41; H, 7.84; N, 9.08. Found: C, 58.30; H, 7.92; N, 8.92.

Preparation of 2-Formylpyrrolo[2,3-*b*]pyridines (8 and 9). To a solution of the appropriate 2-hydroxymethyl-7-azaindole **6** or **7** (6.48 mmol) in anhydrous CH_2Cl_2 (20 mL) was added active MnO_2 (2.81 g, 32.4 mmol). The mixture was stirred at room temperature for 72 h under N_2. Afterward, it was filtered over a Celite pad, which was washed with CH_2Cl_2 (2 × 10 mL) and Et_2O (2 × 10 mL). The combined filtrates were concentrated to dryness, and the resulting solid was recrystallized from Et_2O/*n*-hexane (1:1) to give the corresponding 2-formyl-7-azaindole derivative.

8: (0.68 g, 60% yield); mp 250−252 °C (white prisms). IR (Nujol) ν: 1672 (s), 1610 (m), 1584 (s) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.0 (s, 3H), 6.74 (d, 1H, J = 5.4 Hz), 7.33 (s, 1H), 8.34 (d, 1H, J = 5.4 Hz), 9.79 (s, 1H), 12.50 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 98.5, 109.5, 110.0, 134.3, 150.1, 151.2, 161.1, 182.3. EIMS: *m*/*z* (%) 177 (M^+ + 1, 29), 176 (M^+, 100), 161 (21), 147 (21), 133 (79), 119 (26), 105 (60). Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.14; H, 4.73; N, 15.71.

9: (1.7 g, 86% yield) mp 80−81 °C (white prisms). IR (Nujol) ν: 1680 (CO), 1661 (s), 1598 (s), 1569 (s), 1496 (s) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: −0.16 (s, 9H), 0.76 (t, 2H, J = 7.8 Hz), 3.47 (t, 2H, J = 7.8 Hz), 4.02 (s, 3H), 5.92 (s, 2H), 6.85 (d, 1H, J = 5.4 Hz), 7.54 (s, 1H), 8.42 (d, 1H, J = 5.4 Hz), 9.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: −1.5, 17.1, 56.1, 65.3, 70.7, 99.8, 109.4, 113.6, 133.5, 150.7, 151.8, 161.4, 183.0. EIMS: *m*/*z* (%) 306 (M^+, 29), 307 (27), 277 (23), 263 (46), 233 (55), 220 (29), 205 (53), 189 (99), 176 (38), 162 (100). Anal. Calcd for $C_{15}H_{22}N_2O_3Si$: C, 58.79; H, 7.24; N, 9.14. Found: C, 58.60; H, 7.03; N, 9.05.

This compound was also prepared from **8** in 93% yield, using the same method as described for the preparation of **5** from **4**.

Preparation of α-Azido-β[(1-(trimethylsilyl)ethoxymethyl)-4-methoxy-pyrrolo[2,3-*b*]pyrid-2-yl]propenic Acid Ethyl Ester (10). This compound was prepared from **9** and ethyl azidoacetate in 85% yields using the same method as described for **3**. The titled compound was purified by chromatography on a silica gel column using CH_2Cl_2/EtOAc (9:1) as eluent: mp 106−108 °C (yellow prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 2127 (s), 1709 (s), 1597 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.10 (s, 9H), 0.87 (t, 2H, J = 8.1 Hz), 1.38 (t, 3H, J = 7.2 Hz), 3.51 (t, 2H, J = 8.1 Hz), 4.00 (s, 3H), 4.36 (q, 2H, J = 7.2 Hz), 5.76 (s, 2H), 6.52 (d, 1H, J = 5.4 Hz), 7.15 (s, 1H), 7.53 (s, 1H), 8.21 (d, 1H, J = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −1.4, 14.2, 17.6, 55.6, 62.2, 65.8, 70.2, 98.7, 104.6, 111.0, 112.6, 125.7, 130.7, 146.9, 150.8, 160.2, 163.1. EIMS: *m*/*z* (%) 417 (M^+, 2), 389 (41), 359 (7), 344 (11), 331 (20), 273 (37), 258 (40), 249 (25), 226 (41), 199 (34), 175 (32), 73 (100). Anal. Calcd for $C_{19}H_{27}N_5O_4Si$: C, 54.65; H, 6.52; N, 16.77. Found: C, 54.46; H, 6.71; N, 16.59.

Preparation of the *N*-Protected Iminophosphorane (11). To a solution of the azide **9** (1.03 g, 2.46 mmol) in anhydrous CH_2Cl_2 (15 mL) was added a solution of triphenylphosphine (0.64 g, 2.46 mmol) in the same solvent (15 mL) dropwise under N_2. The resultant solution was stirred at room temperature for 24 h. Afterward, the solution was concentrated to dryness and the residue was chromatographed on a silica gel column using Et_2O/*n*-hexane (8:2) as eluent to give **11** (1.31 g, 82% yield); mp 103−104 °C (yellow prisms from Et_2O). IR (Nujol) ν: 1698 (s), 1566 (s), 1500 (s), 1462 (s), 1434 (s), 1379 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.07 (s, 9H), 0.95 (t, 2H, J = 8.0 Hz), 1.00 (t, 3H, J = 6.9 Hz), 3.61 (t, 2H, J = 8.0 Hz), 3.89 (q, 2H, J = 6.9 Hz), 3.93 (s, 3H), 5.80 (s, 2H), 6.47 (d, 1H, J = 5.5 Hz), 7.00 (d, 1H, J_{HP} = 7.5 Hz), 7.39−7.48 (m, 9H), 7.73−7.80 (m, 7H), 8.09 (d, 1H, J = 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −1.4, 14.0, 17.7, 55.4, 60.8, 65.4, 70.0, 98.8, 100.6, 104.3 (d, ^3J = 20.7 Hz), 111.4, 128.1 (d, ^3J = 12.1 Hz), 130.9 (d, ^4J = 2.2 Hz), 132.4 (d, ^2J = 9.8 Hz), 132.8 (d, ^1J = 102.7 Hz), 136.5, 137.8, 143.8, 150.8, 158.9, 167.0 (d, ^3J = 7.5 Hz). ^{31}P NMR (125 MHz, $CDCl_3$) δ: 9.4. EIMS: *m*/*z* (%) 652 (M^+, 88), 653 (15), 550 (53), 535 (9), 522 (50), 277 (28), 262 (100), 183 (97), 152 (20), 108 (42), 73 (91). Anal. Calcd for $C_{37}H_{42}N_3O_4PSi$: C, 68.18; H, 6.49; N, 6.45. Found: C, 68.31; H, 6.64; N, 6.28.

Preparation of Iminophosphorane (12). Method A. A mixture of *N*-protected iminophosphorane **11** (0.15 g, 0.23 mmol) and TBAF−SiO_2 (4 g, 1 mmol F^-/g SiO_2) was placed in a cylindrical quart tube. The tube was introduced into microwave reactor (2.45 GHz, adjustable power with the range

0−300 W) and irradiated at 90% power for 90 s. After cooling, the solid mixture was chromatographed on a silica gel column using Et_2O/*n*-hexane (7:3) as eluent to give **12** (84 mg, 70% yield) as yellow prisms: mp 195−196 °C (CH_2Cl_2/Et_2O). IR (Nujol) ν: 3302 (m), 1686 (s), 1608 (m), 1559 (m), 1457 (s), 1382 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.02 (t, 3H, J = 7.2 Hz), 3.88 (q, 2H, J = 7.2 Hz), 3.97 (s, 3H), 6.45 (d, 1H, J = 5.4 Hz), 6.48 (d, 1H, J = 1.8 Hz), 6.80 (d, 1H, J_{HP} = 7.8 Hz), 7.44−7.54 (m, 9H), 7.70−7.80 (m, 6H), 8.07 (d, 1H, J = 5.4 Hz), 11.78 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 55.4, 61.0, 97.1, 97.6, 107.7 (d, ^3J = 20.7 Hz), 111.2, 128.5 (d, ^3J = 12.2 Hz), 131.3 (d, ^4J = 2.3 Hz), 132.1 (d, ^2J = 9.8 Hz), 132.4 (d, ^4J = 103.2 Hz), 135.8, 136.3, 144,4, 149.8, 158.6, 167.1 (d, ^3J = 7.5 Hz). ^{31}P NMR (125 MHz, $CDCl_3$) δ: 12.6. EIMS: *m*/*z* (%) 522 (M^+ + 1, 28), 521 (M^+, 78), 464 (15), 277 (12), 262 (91), 237 (51), 201 (31), 186 (81), 183 (100), 152 (15), 108 (37), 77 (91). Anal. Calcd for $C_{31}H_{28}N_3O_3P$: C, 71.39; H, 5.41; N, 8.06. Found: C, 71.19; H, 5.59; N, 7.85.

Method B. To a solution cooled at 0 °C of vinyl azide **10** (1.45 g, 3.42 mmol) in anhydrous CH_2Cl_2 (60 mL) was added dropwise $BF_3{\cdot}Et_2O$ (1.49 mL, 12.14 mmol) under N_2. The resultant solution was allowed to warm to room temperature and stirred for 3 h protected from the sunlight. Afterward, an aqueous 5% solution of NaOH was added until basic pH, and stirring was continued for additional 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness at room temperature under reduced pressure. The crude *N*-deprotected azide was dissolved in anhydrous CH_2Cl_2 (60 mL), and a solution of triphenylphosphine (0.90 g, 3.47 mmol) in the same solvent (10 mL) was added under N_2. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed off under reduced pressure, and the residue was chromatographed on a silica gel column using Et_2O as eluent to give **12** (1.59 g, 88% yield).

Preparation of 9-Benzylamino-7-ethoxycarbonyl-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (14). To a solution of iminophosphorane **12** (0.8 g, 1.54 mmol) in anhydrous THF (25 mL) was added benzyl isocyanate (0.24 g, 1.84 mmol) dropwise under N_2. The reaction mixture was stirred at 50 °C for 24 h. The solvent was removed off under reduced pressure, and the residue was chromatographed on a silica gel column with CH_2Cl_2 as eluent to give **14** (0.55 g, 97% yield); mp 167−169 °C (yellow needles from CH_2Cl_2/Et_2O); IR (Nujol) ν: 3269 (m), 1730 (s), 1713 (s), 1699 (s), 1615 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (t, 3H, J = 7.2 Hz), 4.03 (s, 3H), 4.41 (q, 2H, J = 7.2 Hz), 5.02 (q, 2H, J = 5.4 Hz), 6.72 (s, 1H), 6.73 (d, 1H, J = 6.0 Hz), 7.28−7.31 (m, 1H), 7.36 (tm, 2H, J = 7.2 Hz), 7.55 (dm, 2H, J = 7.2 Hz), 7.61 (s, 1H), 8.19 (d, 1H, J = 6.0 Hz), 10.0 (t, 1H, J = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 45.0, 55.7, 61.2, 91.3, 100.3, 106.5, 114.4, 127.3, 128.0, 128.5, 134.3, 137.1, 138.7, 142.7, 143.9, 147.9, 159.2, 165.8. EIMS: *m*/*z* (%) 377 (M^+ + 1, 17), 376 (M^+, 40), 347 (7), 302 (28), 205 (22), 149 (72), 105 (20), 57 (100). Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.82; H, 5.54; N, 14.70.

Preparation of 5-Benzylamino-7-ethoxycarbonyl-4-methoxy-9-[(trimethylsilyl)ethoxymethyl]pyrido-[3′,2′:4,5]pyrrolo[3,2-*c*]pyridine (15). To a solution of iminophosphorane **11** (0.1 g, 0.15 mmol) in anhydrous THF (7 mL) was added benzyl isocyanate (19 μL, 0.15 mmol) dropwise under N_2. The reaction mixture was stirred at 50 °C for 24 h. The solvent was removed off under reduced pressure and the residue was chromatographed on a silica gel column with Et_2O/*n*-hexane (7:3) as eluent to give **15** (70 mg, 90% yield); IR (Nujol) ν: 3398 (s), 1736 (s), 1707 (s), 1604 (s), 1089 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: −0.094 (s, 9H), 0.91 (t, 2H, J = 8.1 Hz), 1.46 (t, 3H, J = 7.2 Hz), 3.57 (t, 2H, J = 8.1 Hz), 3.77 (s, 3H), 4.46 (q, 2H, J = 7.2 Hz), 4.87 (d, 2H, J = 4.8 Hz), 5.81 (s, 2H), 6.62 (d, 1H, J = 5.7 Hz), 7.27−7.3 (m, 1H), 7.35−7.40 (m, 2H), 7.47−7.52 (m, 3H), 7.72 (s, 1H), 8.29 (d, 1H, J = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −1.6, 14.3, 17.6, 45.8, 55.5, 61.1, 66.2, 70.4, 99.1, 99.8, 103.6, 104.0, 127.1, 128.1, 128.4, 139.7, 143.4, 143.7, 150.8, 152.9, 159.1, 166,1. EIMS: *m*/*z* (%) 508 (M^+ + 2, 27), 506 (M^+,100), 476 (15), 447 (15), 402 (21), 389 (53), 376 (36), 342 (26), 301 (31), 268 (33), 106 (31), 91 (56). Anal. Calcd for $C_{27}H_{34}N_4O_4Si$: C, 64.00; H, 6.76; N, 11.06. Found: C, 63.89; H, 6.64; N, 11.17

Preparation of 4-Methoxy-2-(2-nitrovinyl)-7-pyrrolo-[2,3-*b*]pyridine (16). To a solution of NH_4AcO (0.197 g, 2.55 mmol) in anhydrous EtOH (22 mL) were added compound **8** (0.45 g, 2.55 mmol) and nitromethane (3.1 g, 51 mmol) at room temperature under N_2. The reaction mixture was stirred at 75 °C for 2 h and then allowed to cool to 0 °C. After dilution with Et_2O (20 mL), the precipitate solid was separated by filtration and washed with H_2O (5 mL) and Et_2O (2 × 5 mL). The filtrated and the combined organic layers were concentrated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column using MeOH (9.5:0.5) as eluent and further recrystallized from EtOH to give **16** (0.45 g, 80% yield); mp > 300 °C. IR (Nujol) ν: 3089 (m), 1629 (s), 1589 (s), 1468 (s), 1147 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.95 (s, 3H), 6.68 (d, 1H, J = 5.4 Hz), 7.21 (s, 1H), 8.07 (m, 2H), 8.24 (d, 1H, J = 5.4 Hz), 12.22 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.8, 98.8, 109.6, 111.1, 127.7, 129.9, 135.3, 149.4, 152.2, 160.1. EIMS: *m*/*z* (%) 220 (M^+ + 1, 15), 219 (M^+, 100), 189 (7), 172 (53), 158 (32), 148 (16), 129 (25). Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.45; N, 14.54. Found: C, 54.85; H, 4.34; N, 14.68.

Preparation of the Urea Derivative (18). To a suspension of the nitrovinyl compound **16** (0.5 g, 2.28 mmol) in anhydrous THF (50 mL) was added $LiAlH_4$ (5.69 mL of a 1 M solution in THF, 5.69 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 2 h. Afterward, 5% aqueous solution of NaOH (40 mL) was added, and stirring was continued for additional 15 min. The mixture was extracted with EtOAc (4 × 20 mL), and the combined organic layers were washed with H_2O (2 × 10 mL), and dried ($MgSO_4$). After filtration, the solution was concentrated to dryness to give the crude amine **17**, which was used in the next step without purification. To a solution of the amine **17** in anhydrous CH_2Cl_2 (25 mL) was added benzyl isocyanate (0.35 g, 2.61 mmol) dropwise at 0 °C under N_2. Then, the mixture was stirred at room temperature for 4 h. The solvent was removed off under reduced pressure, and the residue was purified by column chromatography on a silica gel column using CH_2Cl_2/EtOH (9:1) as eluent to give **18** (0.44 g, 60% yield); mp 234−235 °C. IR (Nujol) ν: 3323 (m), 3139 (m), 3096 (m), 1581 (s), 1515 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.83 (t, 2H, J = 6.0 Hz), 3.40 (m, 2H), 3.92 (s, 3H), 4.21 (d, 2H, J = 5.4 Hz), 6.01 (brs, 1H), 6.20 (s, 1H), 6.39 (brs, 1H), 6.59 (d, 1H, J = 5.2 Hz), 7.21−7.29 (m, 5H), 8.01 (d, 1H, J = 5.2 Hz), 11.44 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 28.9, 38.8, 42.9, 55.2, 94.7, 97.8, 110.1, 126.5, 126.9, 128.1, 136.0, 140.8, 143.4 150.4, 158.0. EIMS: *m*/*z* (%) 325 (M^+ + 1, 9), 324 (M^+, 100), 217 (21), 174 (100), 161 (39), 147 (27), 106 (22), 91 (28). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.52; H, 6.08; N, 17.38.

Preparation of 9-Benzylamino-4-methoxypyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]-6,7-dihydropyrimidine (19). To a solution of urea **18** (0.15 g, 0.46 mmol) in anhydrous CH_2Cl_2 (25 mL), triphenylphosphine (0.24 g, 0.92 mmol), triethylamine (0.14 g, 1.38 mmol), and CCl_4 (0.36 g, 2.31 mmol) were added at room temperature under N_2. The reaction mixture was heated at reflux temperature for 24 h. After cooling, the solvent was removed under high vacuum and the residue was chromatographed on a silica gel column using EtOAc/MeOH (8:2) as eluent to give **19** (0.13 g, 90% yield); mp 119−121 °C (yellow prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3299 (m), 1658 (s), 1605 (m), 1561 (s), 1291 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.95 (td, 2H, J = 6.6, 1.2 Hz), 3.63 (t, 2H, J = 6.6 Hz), 3.96 (s, 3H),, 4.69 (d, 2, J = 4.8 Hz), 6.31 (t, 1H, J = 1.2 Hz), 6.56 (d, 1H, J = 5.7 Hz), 7.23−7.28 (m, 1H), 7.32−7.37 (m, 2H),

7.45−7.48 (m, 2H), 8.03 (d, 1H, J = 5.7 Hz), 8.82 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.1, 42.0, 45.2, 55.6, 95.9, 100.3, 111.4, 127.1, 127.6, 128.5, 134.3, 138.5, 143.9, 146.8, 148.2, 159.4. EIMS: m/z (%) 307 (M^+ + 1, 36), 306 (M^+, 100), 176 (50), 161 (73), 91 (61). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.42; H, 5.83; N, 18.37.

Preparation of 9-Benzylamino-5-bromo-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-6,7-dihydropyrimidine (20). Method A. To a solution of compound **19** (0.19 g, 0.62 mmol) in anhydrous pyridine (6 mL) was added bromine (32 μL, 0.62 mmol) slowly at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h and then poured into ice−water and stirred for 20 min. After this time, the mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using EtOAc/MeOH (8:2) as eluent to give **21** (0.12 g, 50% yield); mp 129−130 °C (white prisms from CH_2Cl_2/Et_2O). mp 129−130 °C (white prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3258 (m), 1661 (s), 1604 (m), 1555 (s) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.81 (t, 2H, J = 6.7 Hz), 3.55 (t, 2H, J = 6.7 Hz), 3.90 (s, 3H), 4.57 (d, 2, J = 5.4 Hz), 6.51 (d, 1H, J = 5.6 Hz), 7.18−7.38 (m, 5H), 7.97 (d, 1H, J = 5.6 Hz), 8.60 (t, 1H, J = 5.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.2, 42.0, 45.0, 55.6, 85.8, 100.2, 109.4, 127.0, 127.4, 128.5, 133.0, 139.0, 144.4, 145.5, 146.8, 159.9. EIMS: m/z (%) 386 (M^+ + 2, 90), 384 (M^+, 91), 305 (M^+-Br, 49), 256 (19), 241 (40), 239 (43), 91 (100). Anal. Calcd for $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54. Found: C, 56.00; H, 4.35; N, 14.64.

Method B. To a solution of compound **19** (0.3 g, 0.98 mmol) in THF/CH_2Cl_2 (1:1) (50 mL), NBS (0.183 g, 1.03 mmol) was added in three portions at −20 °C under N_2. The reaction mixture was stirred at −20 °C for 24 h and then poured into ice−water. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using AcOEt/MeOH (8:2) as eluent to give **21** (0.26 g, 70% yield).

Preparation of 9-Benzylamino-5-acetyl-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-6,7-dihydropyrimidine (21). A mixture of the bromo compound **20** (0.238 g, 3.1 mmol), (α-ethoxyvinyl)tributyltin (0.79 g, 2.19 mmol), and dichlorobis-(triphenylphosphine)palladium (II) (0.087 g, 0.123 mmol) in anhydrous DMF (15 mL) was stirred at 70 °C for 30 h under N_2. After cooling, the mixture was poured into H_2O (15 mL) and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using AcOEt/MeOH (8:2) as eluent to give as mixture of **21** and the vinyl ether. A solution of this mixture in acetone/1 M HCl (4:1) (37.5 mL) was stirred at room temperature for 48 h. Afterward, H_2O (30 mL) and K_2CO_3 were added until pH = 7 and extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using AcOEt/MeOH (8:2) as eluent to give **21** (0.14 g, 65%); mp 137−138 °C (white prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3330 (m), 1669 (s), 1596 (s), 1574 (m), 1531 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.66 (s, 3H), 3.20 (t, 2H, J = 6.8 Hz), 3.60 (t, 2H, J = 6.8 Hz), 4.01 (s, 3H), 4.66 (d, 2, J = 4.8 Hz), 6.71 (d, 1H, J = 5.6 Hz), 7.26−7.30 (m, 1H), 7.36 (t, 2H, J = 7.5 Hz), 7.44 (d, 2H, J = 7.5 Hz), 8.11 (d, 1H, J = 5.6 Hz), 9.01 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 32.0, 41.6, 45.0, 55.5, 101.1, 108.3, 113.5, 127.0, 127.4, 128.5, 138.8, 141.0, 144.5, 145.3, 147.8, 159.7, 196.9. EIMS: m/z (%) 349 (M^+ + 1, 21), 348 (M^+, 100), 305 (60), 203 (55), 91 (90). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 70.15; H, 5.91; N, 16.17.

Preparation of 9-Benzylamino-5-acetyl-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (22). Method A. To a solution of compound **24** in anhydrous Ph_2O (15 mL) was heated in a molten salts bath at 250 °C for 24 h under N_2. After cooling, the solution was chromatographed on a silica gel column first with CH_2Cl_2 as eluent to separate the Ph_2O and then with CH_2Cl_2/EtOAc (7:3) to give **22** (44 mg, 50% yield); mp 150−151 °C (orange prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3208 (m), 1621 (s), 1595 (s), 1463 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.74 (s, 3H), 4.07 (s, 3H), 4.94 (d, 2H, J = 5.6 Hz), 6.87 (d, 1H, J = 5.6 Hz), 7.30−7.33 (m, 1H), 7.39 (t, 2H, J = 7.4 Hz), 7.47 (d, 2H, J = 7.4 Hz), 7.65 (d, 1H, J = 6.4 Hz), 7.74 (d, 1H, J = 6.4 Hz), 8.171 (d, 1H, J = 5.6 Hz), 10.61 (t, 1H, J = 5.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.3, 44.8, 55.6, 102.3, 102.4, 104.5, 111.2, 127.3, 127.4, 128.7, 138.2, 140.9, 141.8, 144.6, 144.9, 148.1, 159.1, 195.2. EIMS: m/z (%) 347 (M^+ + 1, 30), 346 (M^+, 100), 331 (54), 198 (62), 91 (71). Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.24; H, 5.38; N, 16.29.

Method B. To a solution of dihydropyrimidine derivative **21** (40 mg, 0.115 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DDQ (29 mg, 0.126 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 24 h. Afterward, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column first with EtOAc/*n*-hexane (6:4) as eluent and then EtOAc/MeOH (8:2) to give **22** (12 mg, 48%) and compound **21** (15 mg).

Method C. To a solution of dihydropyrimidine derivative **21** (50 mg, 0.143 mmol) in anhydrous CH_2Cl_2 (8 mL) were slowly added DBU (42 μL, 0.43 mmol) and $CBrCl_3$ (86 μL, 0.272 mmol) at room temperature under N_2. The reaction mixture was stirred at room temperature for 24 h. Afterward, aqueous saturated solution of NH_4Cl was added and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using EtOAc/*n*-hexane (8:2) as eluent to give **22** (16 mg, 32%).

Preparation of 5-Acetyl-9-benzylamino-7-ethoxycarbonyl-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (23). To a solution of $POCl_3$ (1.78 mL, 19.1 mmol) in anhydrous $CHCl_3$ (5 mL) was added DMA (1.98 mL, 21.3 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 25 min. Then, a solution of compound **14** (0.4 g, 1.06 mmol) in $CHCl_3$ (6 mL) was added, and the reaction mixture was heated at 70 °C for 30 h. After cooling, the mixture was poured into a saturated solution of NaOAc in H_2O (159 mL) and then extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using EtOAc/CH_2Cl_2 (1:20) as eluent to give **23** (0.33 g, 90% yield) along with starting material (0.13 g); mp 223−225 °C. IR (Nujol) ν: 3229 (m), 1734 (s), 1715 (s), 1632 (m), 1607 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J = 7.2 Hz), 2.65 (s, 3H), 3.97 (s, 3H), 4.35 (q, 2H, J = 7.2 Hz), 4.92 (d, 2H, J = 5.4 Hz), 6.76 (d, 1H, J = 5.7 Hz), 7.21 (m, 1H), 7.29 (tm, 2H, J = 6.9 Hz), 7.44 (dm, 2H, J = 6.9 Hz), 8.11 (d, 1H, J = 5.7 Hz), 8.26 (s, 1H), 10.37 (t, 1H, J = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 32.3, 45.1, 55.7, 61.5, 102.3, 105.7, 107.8, 111.5, 127.4, 128.0, 128.6, 138.1, 139.1, 142.2, 143.1, 144.3, 148.0, 159.4, 165.1, 195.3. EIMS: m/z (%) 418 (M^+, 100), 403 (18), 389 (21), 344 (51), 91 (55). Anal. Calcd for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 65.92; H, 5.39; N, 13.31.

Preparation of 5-Acetyl-9-benzylamino-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylic Acid (24). To a solution of ester **23** (0.44 g, 1.05 mmol) in THF/H_2O (4:1) (175 mL) was added LiOH·H_2O (0.154 g, 3.67 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 2 h. Then, the THF was removed under

reduced pressure, and 1 N solution of HCl (10 mL) was added until acid pH. The separated solid was washed with H_2O (3 × 5 mL) dissolved in CH_2Cl_2 (150 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was recrystallyzed from CH_2Cl_2/Et_2O to give **24** (0.41 g, 100%); mp 231−232 °C (yellows needles). IR (Nujol) ν: 3209 (m), 1765 (s), 1733 (m), 1646 (m), 1632 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 4.04 (s, 3H), 4.93 (d, 2H, J = 5.5 Hz), 7.14 (d, 1H, J = 5.7 Hz), 7.24−7.37 (m, 3H), 7.49 (d, 2H, J = 7.2 Hz), 8.09 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 10.37 (t, 1H, J = 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.1, 44.0, 56.1, 103.3, 104.4, 106.7, 110.6, 127.2, 127.6, 128.5, 138.4, 138.5, 142.2, 143.6, 143.7, 147.6, 159.1, 165.7, 194.1. EIMS: m/z (%) 391 (M^+ + 1, 40), 390 (M^+, 100), 346 (40), 344 (50), 331 (21), 91 (71). Anal. Calcd for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.72; H, 4.51; N, 14.49.

Preparation of Enaminones 25 and 26. A mixture of the appropriate acetyl derivative **22** or **23** (1.6 mmol), *N*,*N*-dimethylformamide-di-*tert*-butylacetal (2.56 g, 12.6 mmol), and anhydrous DMF (33 mL) was stirred at 70−80 °C for 16−24 h under N_2. After cooling, the solution was poured into H_2O (100 mL) and then extracted with EtOAc (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using CH_2Cl_2/MeOH (9.5:0.5) as eluent for **25** and CH_2Cl_2/MeOH (9:1) for **26**.

25: (0.40 g, 85% yield) mp.166−167 °C; IR (Nujol) ν: 3223 (m), 1639 (m), 1577 (m), 1534 (m), 1460 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.97 (brs, 6H), 4.01 (s, 3H), 4.91 (d, 2H, J = 5.4 Hz), 5.81 (d, 1H, J = 12.6 Hz), 6.81 (d, 1H, J = 5.7 Hz), 7.27−7.38 (m, 4H), 7.45 (d, 2H, J = 6.9 Hz), 7.53 (d, 2H, J = 6.6 Hz), 7.66 (d, 2H, J = 12.6 Hz), 8.13 (d, 1H, J = 5.7 Hz), 10.47 (t, 1H, J = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 44.7, 55.5, 99.3, 101.8, 102.4, 106.0, 111.8, 127.2, 127.3, 128.6, 138.1, 138.4, 141.3, 141.4, 144.3, 148.6, 152.2, 159.4, 185.6. EIMS: m/z (%) 403 (M^+ + 2, 6), 402 (M^+ + 1, 37), 401 (M^+, 100), 385 (19), 384 (60), 304 (72), 198 (22), 91 (96). Anal. Calcd for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.44. Found: C, 68.70; H, 5.87; N, 17.57.

26: (0.53 g, 70% yield)mp 203−205 °C (orange prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 1783 (s), 1644 (s), 1619 (m), 1580 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, 3H, J = 7.2 Hz), 2.99 (brs, 6H), 4.02 (s, 3H), 4.40 (q, 2H, J = 7.2 Hz),, 5.02 (d, 2H, J = 5.4 Hz), 5.77 (d, 1H, J = 12.9 Hz), 6.82 (d, 1H, J = 5.7 Hz), 7.28−7.39 (m, 3H), 7.52 (m, 2H), 7.67 (d, 2H, J = 12.9 Hz), 8.19 (s, 1H), 8.20 (d, 1H, J = 5.7 Hz), 10.35 (t, 1H, J = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 37.2, 44.9, 45.0, 55.5, 61.2, 99.4, 101.6, 106.4, 109.9, 111.8, 127.3, 127.9, 128.5, 136.2, 138.4, 139.2, 142.8, 144.1, 147.1, 152.7, 159.9, 165.6, 185.2. EIMS: m/z (%) 474 (M^+ + 1, 37), 473 (M^+, 73), 456 (54), 376 (74), 301 (100), 186 (55), 98 (71), 91 (85). Anal. Calcd for $C_{26}H_{27}N_5O_4$: C, 65.95; H, 5.75; N, 14.79. Found: C, 65.80; H, 5.84; N, 14.61.

Preparation of Compounds 27 and 28. General Procedure. A mixture of the enaminone **25** or **26** (0.062 mmol), guanidine hydrochloride (18 mg, 0.186 mmol), anhydrous K_2CO_3 (30 mg, 0.217 mmol), and dry 2-methoxyethanol (7 mL) was heated at reflux temperature for 24 h under N_2. After cooling, the solvent was removed under high vacuum and the residue was chromatographed on a silica gel column using EtAcO/MeOH (8:2) as eluent for **27** and CH_2Cl_2/MeOH (8:2) for **28**.

27: (22 mg, 90% yield) mp 237−238 °C (yellow prisms). IR (Nujol) ν: 3456 (m), 3317 (m), 3190 (m), 1719(m), 1603 (s), 1575 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 4.87 (d, 2H, J = 5.5 Hz), 5.06 (s, 2H), 6.76 (d, 1H, J = 5.7 Hz), 6.98 (d, 1H, J = 5.4 Hz), 7.22−7.32 (m, 3H), 7.39 (d, 2H, J = 6.6 Hz), 7.40 (d, 1H, J = 6.6 Hz), 7.49 (d, 1H, J = 6.6 Hz), 8.11 (d, 1H, J = 5.7 Hz), 8.17 (d, 1H, J = 5.4 Hz), 10.40 (t, 1H, J = 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.8, 55.5, 101.2, 101.5, 101.6, 111.1, 113.2, 127.3, 127.4, 128.7, 137.0, 138.5, 141.5, 141.6, 144.6, 148.8, 156.3, 159.5, 162.4, 162.7. EIMS: m/z (%) 399 (M^+ + 2, 7), 398 (M^+ + 1, 42), 399 (M^+, 100), 382 (25), 266 (46), 91 (47). Anal. Calcd for $C_{22}H_{19}N_7O$: C, 66.49; H, 4.82; N, 24.67. Found: C, 66.40; H, 4.92; N, 24.78.

28. (27 mg, 93% yield) mp 200 °C (decomposes)(orange prisms). IR (Nujol) ν: 3350 (m), 1656 (s), 1108 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.99 (s, 3H), 4.97 (d, 2H, J = 5.4 Hz), 6.47 (s, 2H, NH_2), 6.83 (d, 1H, J = 5.7 Hz), 7.13 (d, 1H, J = 5.5 Hz), 7.25−7.38 (m, 3H), 7.49 (d, 2H, J = 7.2 Hz), 7.99 (s, 1H), 8.20 (d, 1H, J = 5.7 Hz), 8.31 (d, 1H, J = 5.5 Hz), 10.23 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.1, 55.9, 102.3, 103.4, 103.6, 111.1, 111.8, 127.1, 127.5, 128.5, 135.2, 138.8, 142.7, 143.5, 143.8, 147.4, 156.6, 159.4, 160.9, 163.1, 168.4. EIMS: m/z (%) 442 (M^+ + 1, 45), 441 (M^+, 75), 426 (48), 395 (54), 381 (72), 304 (31), 277 (34), 265 (48), 196 (28), 91 (100). Anal. Calcd for $C_{23}H_{19}N_7O_3$: C, 62.58; H, 4.34; N, 22.21. Found: C, 62.40; H, 4.45; N, 22.33.

Preparation of 9-Benzylamino-variolin B (29). Method A. To a solution of compound **27** (21 mg, 0.053 mmol) in anhydrous DMF (7 mL) was added NaMeS (37 mg, 0.53 mmol) at 80 °C under N_2. The reaction mixture was stirred at 80 °C for 3 h. After cooling, the mixture was poured into a saturated solution of NH_4Cl (100 mL), and 1 N HCl (4 mL) was added until pH = 4−5. The resultant mixture was extracted with EtOAc (5 × 30 mL), the combined organic extracts were washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using CH_2Cl_2/MeOH (9.5:0.5) as eluent to give **29** (17 mg, 85% yield); mp 298−300 °C (oranges prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3416 (m), 3308 (m), 3157 (m), 1657 (s), 1570 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 4.88 (d, 2H, J = 6.0 Hz), 6.79 (d, 1H, J = 5.6 Hz), 7.01 (brs, 2H), 7.13 (d, 1H, J = 5.4 Hz), 7.24 (d, 1H, J = 6.6 Hz), 7.25 (m, 1H), 7.35 (m, 2H), 7.43 (m, 2H), 7.65 (d, 1H, J = 6.6 Hz), 8.13 (d, 1H, J = 5.6 Hz), 8.27 (d, 1H, J = 5.4 Hz), 10.82 (brs, 1H), 16.05 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.9, 99.9, 100.6, 106.0, 107.4, 110.9, 127.1, 127.2, 128.5, 136.7, 138.7, 143.0, 143.7, 144.9, 149.2, 158.2, 159.9, 160.0, 161.3. EIMS: m/z (%) 385 (M^+ + 2, 12), 383 (M^+, 100), 306 (12), 292 (25), 278 (50), 252 (35), 210 (25), 91 (52). Anal. Calcd for $C_{21}H_{17}N_7O$: C, 65.79; H, 4.47; N, 25.57. Found: C, 65.60; H, 4.38; N, 25.45.

Method B. A degassed suspension of the variolinic acid **28** (0.13 g, 0.295 mmol) in dry Ph_2O (15 mL) was heated in a molten salts bath at 280 °C for 4 h under N_2. After cooling, to room temperature the solution was chromatographed on a silica gel column first with CH_2Cl_2 as eluent to separate the solvent and then with CH_2Cl_2/MeOH (9:1) to give **29** (76 mg, 67% yield).

Preparation of Variolin B (1). A solution of compound **29** (59 mg, 0.154 mmol) in triflic acid (3 mL) was stirred at 50 °C for 150 min under N_2. After cooling at 0 °C, MeOH (5 mL) was added and the resulting mixture was stirred at that temperature for 5 min. Afterward, a solution of 30% ammonium hydroxide was added until basic pH. The solvent was removed off at room temperature under reduced pressure until a yellow solid began to separate. The solid was collected by filtration and then washed with H_2O (3 × 5 mL) and Et_2O (2 × 5 mL) and air-dried to give crude variolin B (36 mg). The combined mother liquors and the filtrate were saturated with NaCl and then extracted with EtOAc (2 × 10 mL). The combined organic layers were concentrated to dryness to give a second crop of variolin B (8 mg). After purification by chromatography on a silica gel column using CH_2Cl_2/MeOH as eluent 9.5/0.5 and then 8.5/1.5, variolin B was obtained (33 mg, 74%) in a high state of purity. IR (Nujol) ν: 3290 (m), 3256 (m), 3102 (m), 1669 (m), 1573 (m), 1465 (s), 1385 (m), 1300 (m), 1271 (m), 1237 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 6.79 (d, 1H, J = 5.7 Hz, H-3), 6.99 (brs, 2H, NH_2−C-2′), 7.13 (d, 1H, J = 5.5 Hz, H-5′), 7.22 (d, 1H, J = 6.7 Hz, H-6), 7.63 (d, 1H, J = 6.7 Hz, H-7), 8.15 (d, 1H, J = 5.7 Hz, H-2), 8.26 (d, 1H, J = 5.5 Hz, H-6′), 8.5 (brs, 1H, NH−C-9), 9.7 (brs, 1H, NH−C-9), 16.03 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-

d_6) δ: 99.5 (C-5), 100.3 (C-6), 106.0 (C-5'), 107.4 (C-3), 111.1 (C-4a), 137,0 (C-5a), 143.1 (C-2), 144.5 (C-7), 144.9 (C-10a), 150.2 (C-9), 158.3 (C-2'), 159.8 (C-4), 160.0 (C-6'), 161.4 (C-4'). HREIMS $C_{14}H_{11}N_7O$ calcd 293.1025, found 293.1021.

Preparation of 9-Benzylamino-4-methoxypyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-7-carboxylic Acid (30). To a solution of ester **14** (0.5 g, 1.33 mmol) in THF/H_2O (4:1) (175 mL) was added LiOH·H_2O (0.195 g, 4.65 mmol) at room temperature. The resulting mixture was stirred at that temperature for 2 h. Afterward, the THF was removed under reduced pressure and a 1 N solution of HCl (12 mL) was added until acid pH. The separated solid was washed with H_2O (3 × 5 mL), dissolved in CH_2Cl_2 (150 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was recrystallyzed from CH_2Cl_2/Et_2O to give **30** (0.44 g, 95%); mp 231−232 °C (yellows needles). IR (Nujol) ν: 3253 (m), 1692 (s), 1610 (s), 1598 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 4.04 (s, 3H), 4.96 (d, 2H, J = 5.6 Hz), 6.84 (s, 1H), 7.04 (d, 1H, J = 5.7 Hz), 7.28−7.38 (m, 3H), 7.50 (m, 2H), 7.59 (s, 1H), 8.31 (d, 1H, J = 5.7 Hz), 9.90 (t, 1H, J = 5.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.8, 56.0, 91.3, 101.3, 105.8, 113.6, 127.12, 127.5, 128.5, 133.8, 136.6, 138.9, 143.1, 143.2, 147.1, 158.9, 166.0. EIMS: m/z (%) 350 (M^+ + 2, 13), 348 (M^+, 88), 303 (100), 289 (30), 213 (50), 186 (87), 171 (63), 91 (94). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.41; H, 4.63; N, 16.08. Found: C, 65.30; H, 4.51; N, 16.22.

Preparation of 7-Acetyl-9-benzylamino-4-methoxypyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (31). To a solution of acid **30** (0.5 g, 1.33 mmol) in anhydrous THF (15 mL) was added MeLi (0.72 mL, 1.148 mmol, 1.6M in ethyl ether) at −15 °C under N_2, and the resulting mixture was stirred at that temperature for 2 h. Afterward, the reaction mixture was poured into ice-H_2O (10 mL), and solid NH_4Cl was added until pH = 7 and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were concentrated to dryness, and the solvent was removed under reduced pressure. The remaining solid was chromatographed on a silica gel column using CH_2Cl_2/EtOAc (20:1) as eluent to give **31** (61 mg, 62% yields). IR (Nujol) ν: 3237 (m), 1683 (s), 1602 (s), 1503 (s), 1381 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.63 (s, 3H), 4.04 (s, 3H), 4.97 (d, 2H, J = 5.6 Hz), 6.73 (d, 1H, J = 5.4 Hz), 6.74 (s, 1H), 7.28−7.41 (m, 3H), 7.48 (s, 1H), 7.49−7.54 (m, 2H), 8.21 (d, 1H, J = 5.4 Hz), 10.02 (t, 1H, J = 5.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.6, 44.8, 55.7, 92.1, 100.3, 102.7, 114.5, 127.2, 127.7, 128.5, 134.6, 139.0, 142.6, 142.7, 143.8, 147.5, 159.2, 200.0. EIMS: m/z (%) 346 (M^+, 100), 331 (33), 256 (29), 213 (25), 91 (45). Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.22; H, 5.37; N, 16.29.

Enaminone 32. This compound was prepared from **31** using the same method as described for the preparation of **25** from **22**. The residue was chromatographed on a silica gel column using CH_2Cl_2/MeOH (9.5:0.5) as eluent to give **32** (59 mg, 84% yield); mp 240 °C (orange prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 3248 (m), 1645 (s), 1557 (m), 1380 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.94 (brs, 3H), 3.10 (brs, 3H), 4.03 (s, 3H), 5.99 (d, 2H, J = 5.6 Hz), 6.43 (d, 1H, J = 12.8 Hz), 6.68 (s, 1H), 6.72 (d, 1H, J = 5.4 Hz), 7.29−7.38 (m, 3H), 7.51−7.55 (m, 2H), 7.62 (s, 1H), 7.87 (d, 1H, J = 12.8 Hz), 8.16 (d, 1H, J = 5.4 Hz), 9.96 (t, 1H, J = 5.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 29.6, 37.3, 44.8, 55.6, 90.2, 92.4, 100.1, 102.0, 114.5, 127.0, 127.5, 128.5, 135.6, 139.3, 141.8, 143.8, 144.9, 147.1, 154.1, 158.9, 186.7. EIMS: m/z (%) 402 (M^+ + 1, 32), 401 (M^+, 100), 384 (45), 383 (37), 318 (59), 227 (45), 186 (30), 91 (56). Anal. Calcd for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.44. Found: C, 67.53; H, 5.01; N, 18.15.

Preparation of Compound 33. This compound was prepared from **32** using the same method as described for the preparation of **27** from **25**.

33: (90% yield) mp 222−224 °C (orange prisms from CH_2Cl_2/Et_2O). IR (Nujol) ν: 1615 (m), 1598 (m), 1463 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.02 (s, 3H), 5.01 (d, 2H, J = 5.7 Hz), 5.03 (brs, 2H), 6.66 (s, 1H), 6.72 (d, 1H, J = 5.6 Hz), 7.26 (m, 1H), 7.35 (d, 2H, J = 7.4 Hz), 7.50 (d, 2H, J = 7.4 Hz), 7.59 (d, 1H, J = 5.2 Hz), 7.85 (s, 1H), 8.15 (d, 1H, J = 5.6 Hz), 8.36 (d, 1H, J = 5.2 Hz), 10.00 (t, 1H, J = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.8, 55.7, 90.1, 100.3, 100.9, 108.4, 114.6, 127.2, 127.6, 128.6, 135.6, 139.1, 142.8, 142.9, 144.1, 147.7, 158.9, 159.1, 162.7, 164.1. EIMS: m/z (%) 399 (M^+ + 2, 4), 398 (M^+ + 1, 26), 397 (M^+, 100), 382 (25), 91 (40). Anal. Calcd for $C_{22}H_{19}N_7O$: C, 66.49; H, 4.82; N, 24.67. Found: C, 66.35; H, 4.97; N, 24.53.

Preparation of Compound 34. This compound was prepared from **33** using the same method as described for the preparation of **29** from **27**.

34: (83% yield). ^1H NMR (300 MHz, DMSO-d_6) δ: 4.96 (d, 2H, J = 5.8 Hz), 6.55 (brs, 2H), 6.81 (s, 1H), 6.82 (d, 1H, J = 5.4 Hz), 7.25 (m, 1H), 7.35 (t, 2H, J = 7.5 Hz), 7.39 (d, 1H, J = 5.1 Hz), 7.50 (d, 2H, J = 6.9 Hz), 7.78 (s, 1H), 8.13 (d, 1H, J = 5.4 Hz), 8.34 (d, 1H, J = 5.1 Hz), 10.02 (t, 1H, J = 5.8 Hz), 11.20 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.9, 90.2, 99.9, 105.1, 106.2, 113.7, 127.0, 127.4, 128.5, 134.2, 139.3, 142.3, 142.4, 144.9, 147.2, 157.6, 159.2, 162.5, 163.3. EIMS: m/z (%) 385 (M^+ + 2, 8), 384 (M^+ + 1, 42), 383 (M^+, 100), 277 (25), 91 (54). Anal. Calcd for $C_{21}H_{17}N_7O$: C, 65.79; H, 4.47; N, 25.57. Found: C, 65.63; H, 4.31; N, 25.66.

Preparation of Compound 35. This compound was prepared from **34** using the same method as described for the preparation of variolin B from **29**.

35: (75% yield). ^1H NMR (400 MHz, DMSO-d_6) δ: 6.54 (brs, 2H), 6.80 (s, 1H), 6.88 (d, 1H, J = 5.4 Hz), 7.36 (d, 1H, J = 5.0 Hz), 7.40 (brs, 1H), 7.77 (s, 1H), 8.15 (d, 1H, J = 5.4 Hz), 8.36 (d, 1H, J = 5.0 Hz), 8.6 (brs, 1H), 11.35 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 89.8, 99.7, 105.1, 106.0, 113.8, 134,2, 142.3, 142.9, 144.0, 148.1, 157.5, 159.2, 162.5, 163.4. EIMS: m/z (%) 294 (M^+ + 1, 24), 293 (M^+, 73), 207 (51), 90 (38), 83 (100). Anal. Calcd for $C_{14}H_{11}N_7O$: C, 57.33; H, 3.78; N, 33.43. Found: C, 57.25; H, 3.87; N, 33.55.

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