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Reaction of Bromomethylazoles and Tosylmethyl Isocyanide. A Novel Heterocyclization Method for the Synthesis of the Core of Marine Alkaloids Variolins and Related Azolopyrimidines

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A novel and efficient synthesis of the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system, the heterocyclic core of the variolin family of marine alkaloids, is described. The route involves the reaction of 3-bromo-2-(bromomethyl)pyrrolo[2,3-*b*]pyridine and tosylmethyl isocyanide (TosMIC) under phase-transfer conditions. This unprecedented reaction was also used to synthesize a series of new methoxycarbonyl azolopyrimidines by reaction of TosMIC with bromomethylindoles, bromomethylbenzimidazole, and bromomethylpyrazole. Hydrolysis and decarboxylation of 5-bromo-7-methoxycarbonylpyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine obtained by this heterocyclization process and installation of the pyrimidine moiety in the C5 position open an alternative approach to complete a total synthesis of variolin B.

Introduction

We previously reported a novel synthesis of pyrrolo-[1,2-*c*]pyrimidine and some derivatives based on the reaction of tosylmethyl isocyanide (TosMIC) with 2-pyrrole carboxaldehydes.[1] This method provided a simple and efficient route to the target system, which could be obtained in 40% overall yield (compared to 1% for the previously reported procedure[2]).

This heterocyclic system, although rare in nature, is present in the marine alkaloid hinckdentine (**1**)—some analogues of which have cataleptogenic activity.[3,4] The ring system is also present in the variolins, a family of alkaloids isolated from the antarctic sponge *Kirkpatrickia varialosa*, which have antitumor and antiviral activity[5] (Figure 1).

These latter alkaloids, particularly variolin B (**3**), have attracted the attention of several groups that have been involved in the total synthesis of this alkaloid. All of the approaches described to date involve the construction of the pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidine as one of the key steps of the synthetic strategy. The first total synthesis of variolin B was reported by Morris,[6] who prepared the highly functionalized core **8** in three steps from the commercially available 2-methylthiopyrimidine (**5**) (Scheme 1). Molina[7] completed the synthesis of the tricyclic system using a sequential approach. In this total synthesis the 4-methoxypyridine (**6**) was converted into the appropriate 7-azaindole by an indole synthesis involving a nitrene insertion process. Subsequent formation of the pyrimidine ring was achieved by a carbodiimide-mediated cyclization process. In the most recently reported total synthesis, Alvarez[8] prepared the tricyclic system from 4-methoxy-7-azaindole (**7**), which is functionalized with an appropriate aminoethyl side chain, followed by formation of the third ring with concomitant

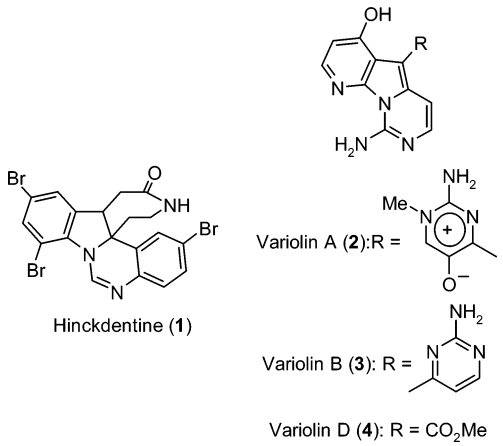

FIGURE 1. Structure of hinckdentine and variolins.

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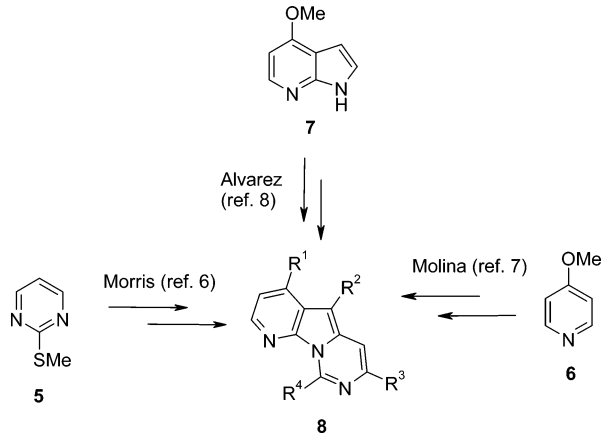
SCHEME 1. Synthetic Strategies for the Tricyclic Core of Variolin B



introduction of a protected amino group. Two syntheses of deoxyvariolin B[9] and several patents that focus on the preparation of analogues of variolin B[10] are also based on these methodologies for the construction of the pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system.

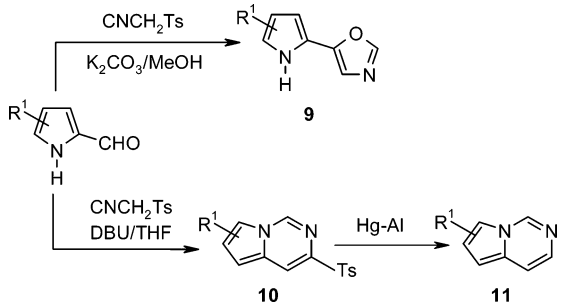
In the work described here we present a detailed account of our studies on the synthesis of the heterocyclic core of variolins.[11] Our synthetic approach, which is complementary to the efforts described to date, employs a 2-bromomethyl-7-azaindole for the construction of the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system through an unprecedented reaction with TosMIC.[12] The method has been extended to different bromomethyl substituted azoles and has allowed the preparation of a novel series of heterocyclic systems.

Results and Discussion

Although the cyclocondensation reaction between aldehydes and TosMIC has proven to be particularly useful in oxazole synthesis,[13] we found that in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) the pyrrole NH competes with the oxygen to furnish 3-tosylpyrrolo[1,2-*c*]pyrimidines (**10**) in yields of up to 60% (Scheme 2). This method allowed the synthesis of pyrrolo[1,2-*c*]pyrimidine (**11**, $R^1 = H$) with a significant reduction in the number of steps and constitutes the best reported procedure to date for the synthesis of pyrrolo[1,2-*c*]pyrimidines.[1,14]

Given the ease of formation of the pyrrolo[1,2-*c*]-pyrimidine nucleus, we envisaged a simple and straightforward strategy for the synthesis of the pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system **14**. The synthesis would depend on an efficient condensation of

SCHEME 2



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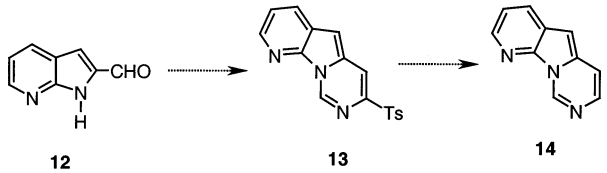

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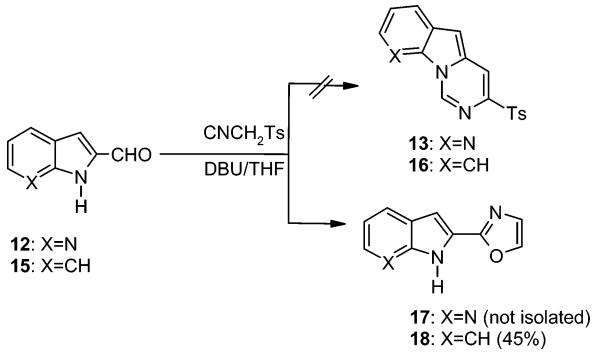

7-azaindole-2-carboxaldehyde (**12**) with TosMIC to afford the expected 3-tosylpyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (**13**), which could subsequently be converted into the desired variolin core by an apparently simple desulfonylation (Scheme 3).

The 7-azaindole-2-carboxaldehyde **12** was prepared by a literature procedure.[15] However, all attempts to prepare the tricyclic compound **13** only afforded complex reaction mixtures in which the oxazole derivative **17** could be detected but could not be isolated presumably due to its instability. When the 2-indolecarboxaldehyde (**15**)[16] was tested, the resulting undesired oxazole **18**[16] was also the dominant product, despite the fact that indole **15** is a far more electron-rich system than its 7-aza analogue **12** (Scheme 4).

The results described above seem to preclude the use of our initial approach to tricycle **14**, and so we decided to examine the reaction of an *N*-protected 2-bromomethylazaindole with TosMIC under basic conditions in the hope that the product of the nucleophilic substitution would be sufficiently stable for further transformation into the corresponding pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine derivative after deprotection.

The route started from commercially available 7-azaindole **7a** (Scheme 5). Treatment of **7a** with phenylsul-

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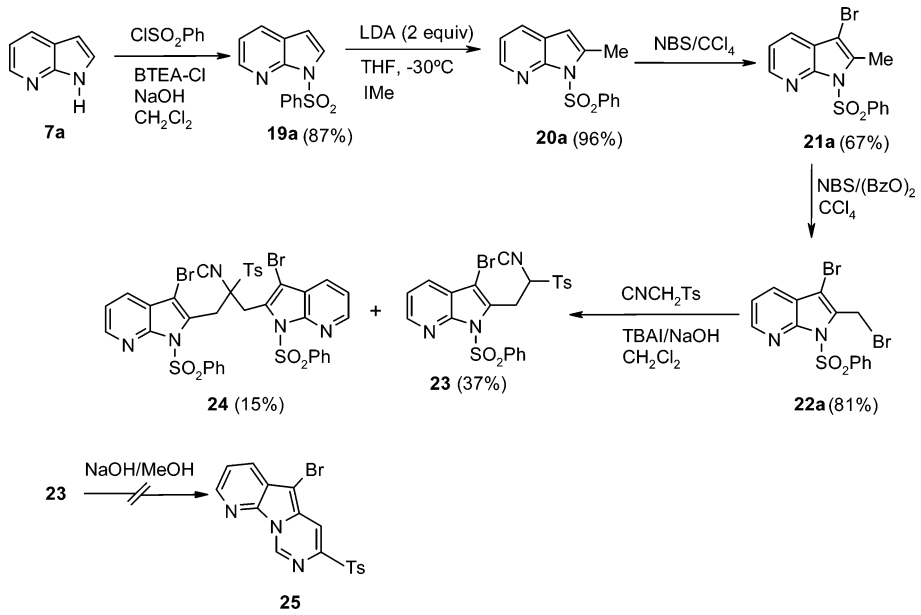
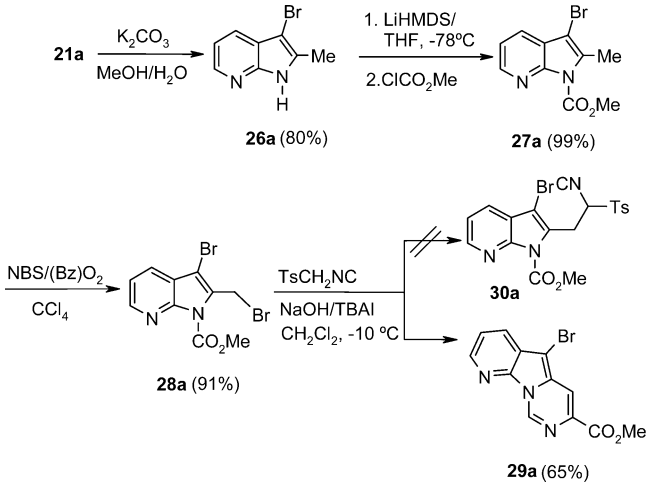
SCHEME 5



fonyl chloride produced the protected azaindole **19a** in 87% yield.[15] This compound was then methylated (LDA/THF/MeI) to give **20a** in 96% yield.[15] The attempted selective bromination of **20a** under radical conditions [NBS/$(BzO)_2$ or NBS/AIBN] afforded in all cases variable mixtures of the desired 2-bromomethyl-7-azaindole, 3-bromo-2-methyl-7-azaindole, and 3-bromo-2-bromomethyl-7-azaindole depending of the conditions. A change in the protecting group of the 7-azaindole (Boc and CO_2Me) afforded similar results. We therefore decided to promote a sequential electrophilic and radical bromination to obtain the dibromo compound **22a** and use this azaindole derivative as a good model to test the reaction with TosMIC. The electrophilic bromination of **20** (NBS/CCl_4, rt) afforded the 3-bromo-7-azaindole **21a** in 67% yield. Subsequent radical bromination of **21a** [NBS/$(BzO)_2$] gave the dibromo derivative **22a** in 81% yield. The reaction of **22a** with TosMIC under phase transfer conditions (TBAI/NaOH/CH_2Cl_2) to prevent the formation of the disubstituted compound[17] afforded the desired product **23**. Unfortunately the yield was only 37% in the best case and unreacted starting materials and the dialkylated derivative **24** (15%) were also isolated from the reaction mixture. Both, **23** and **24** are unstable compounds and all attempts to transform **23** into the tricyclic intermediate **25** failed under the conditions for deprotection because of decomposition of **23**. We therefore considered the protection of **7a** as a carbamate hoping that removal of such a protecting group under acidic conditions would preserve the stability of the product, 2-methyl-7-azaindole. However, the introduction of the methyl substituent on C-2 proved troublesome on both the *N*-Boc- and *N*-methyl carbamate 7-azaindoles with decomposition or deprotection observed during the attempted methylation under conditions similar to those employed for **20a**.

Finally, the desired intermediate **28a** was obtained by deprotection of **21a** followed by reaction with methoxycarbonyl chloride and subsequent radical bromination (Scheme 6). Having obtained azaindole **28a**, we proceeded to test its reaction with TosMIC under the phase transfer conditions employed to optimize the formation of **23**. Bromomethyl compound **28a** reacted cleanly, but **30a** was not formed under these reaction conditions. A new, yellow fluorescent product formed and was unambiguously identified as 5-bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylic acid methyl ester (**29a**, 65% yield) (Scheme 6).

SCHEME 6



This result was unexpected but was also very convenient in terms of our ultimate goal—the synthesis of the variolin core and variolins themselves. Indeed, the synthesis of the tricyclic compound **29a** could be easily adapted to prepare a key intermediate by simply introducing the hydroxy functionality at C-4 in the starting azaindole **7a**.

The mechanism proposed to account for the formation of **29a** involves initial nucleophilic substitution of TosMIC on the bromomethypyrrole followed by intramolecular transfer of the methoxycarbonyl protecting group. Subsequent attack of the pyrrole nitrogen on the isocyanide

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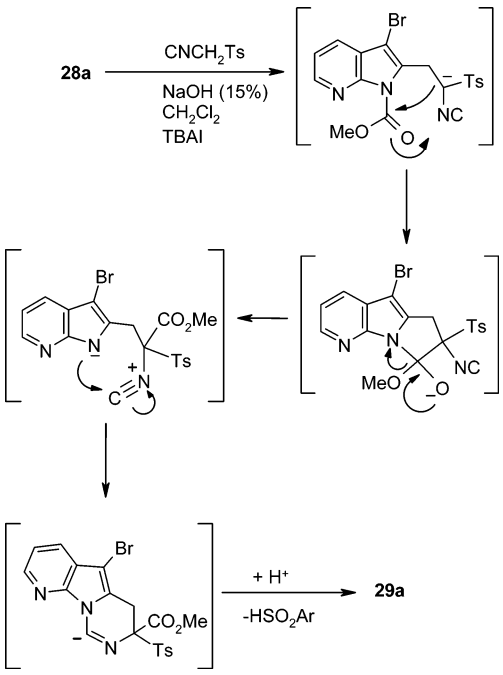
SCHEME 7



group would lead to cyclization and 1,2-elimination of *p*-toluenesulfinic acid would afford the azolopyrimidine derivative **29a** (Scheme 7).

The success of this unusual and unprecedented heterocyclization led us to study the general scope of this reaction. Therefore, in addition to the 7-azaindole **28a**, a range of different azoles were prepared in an attempt to explore the behavior of different heterocycles in this cyclization reaction. Two 7-azaindoles, three indoles, 3-methylpyrazole, benzimidazole, and imidazole were transformed into the bromomethylazoles **28b**−**h** by following the general procedure shown in Scheme 8. Each azaindole was protected as a benzenesulfonamide, methylated, brominated under electrophilic conditions, deprotected and finally protected as a carbamate to afford substituted azaindoles **27a**,**b**. Commercially available methyl indoles **7c**−**e** were transformed into **27c**−**e** by protection as methyl carbamates followed by electrophilic bromination. Radical bromination of indole and azaindole derivatives afforded the corresponding dibromocompounds **28a**−**e**. Commercially available pyrazole **7f**, benzimidazole **7g**, and imidazole **7h** were protected as methyl carbamates and brominated under radical conditions to give substrates **28f**,**g**,**i**.

Table 1 shows the various bromomethylazoles **28a**−**i** prepared according to the conditions detailed in Scheme 8. All these substrates were then reacted with TosMIC under the same conditions as for **28a** and these reactions produced the corresponding azolopyrimidines **29b**−**i**. The results summarized in Table 1 indicate that the heterocyclization process proceeded in moderate or good yields -the only exception being the bromomethylimidazole **28i** (Table 1, entry 8), which decomposed extensively under phase transfer conditions. A range of different homogeneous conditions were tested for this substrate but only in THF/Et_3N were traces of the imidazopyrimidine **29i** detected.

In all cases, the isolated yield seems to be closely related to the resistance of the substrate to deprotection under the phase transfer conditions. For example, in **28b** the heterocyclization process clearly competes with deprotection atom and the deprotected compound is isolated as the main reaction product. On the other hand, in the reaction of **28a** significant amounts of the deprotected compound were not observed. This difference in yield is associated with the presence of the electron-withdrawing substituent (4-choro) in **28b** which presumably favors the deprotection of this substrate. A similar effect of the electron-withdrawing group on the yield is observed on comparing substrates **28c** and **28e**. In the cases of benzimidazole and pyrazole, their more electron-deficient nature when compared with indole would account for the lower yields of **29f** and **29g** when compared with **29c**. With some of these substrates, we also observed that the temperature of the reaction has a significant effect on the deprotection and azolopyrimidine yield. For example, at room temperature **29a** is isolated in only 40−45% yield. However, in the case of bromomethylindoles **28c**−**e** (Table 1, entries 3−5) the temperature had little effect on the yield of the reaction (**29c**−**e**).

Although this heterocyclization method allowed the preparation of different bicyclic and tricyclic heterocycles, it seems limited to azole chemistry. For example, the attempted reaction of TosMIC with *N*-Boc-protected 2-bromomethylpyrrolidine[18] resulted in the formation of complex reaction mixtures. We also proved that the use of a bulkier carbamate such as Boc in those substrates that gave low or moderate yields of the azolopyrimidine did not improve the yields. As an example, the *N*-Boc-protected benzimidazole **28h** afforded the tricyclic derivative **29h** in 40% yield.

The method described above is very advantageous in the context of our synthetic interest in variolins and can give the heterocyclic core of these alkaloids in a cascade process. However, any attempt at the total synthesis of such a compound would involve the appropriately substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine heterocycle, the removal of the methyl ester group, the functionalization of the C5 position bearing the bromine atom with an appropriate pyrimidine ring, and the introduction of the amino group in C9 position. For this purpose, the tricyclic derivatives **29a** was considered a good model to test all these heterocyclic transformations.

First, we studied the formation of the corresponding carboxylic acid **31a** from **29a** and the subsequent decarboxylation reaction. The ester hydrolysis was carried out under three different sets of basic conditions: K_2CO_3/MeOH−H_2O, KOH/MeOH, and LiOH/THF−H_2O. The pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine substrate (**29a**) was hydrolyzed under all the conditions tested, but it decomposes to a great extent in KOH/MeOH. With either K_2CO_3 or LiOH at room temperature, **31a** was obtained in excellent yield (Scheme 9).

Initial attempts to promote decarboxylation of the highly insoluble acid **31a** under standard conditions resulted in either no reaction (Cu/quinoline) or extensive decomposition (KOH/MeOH, NaOH/toluene). When the substrate was adsorbed on silica gel and heated under microwave irradiation **31a** was recovered unaltered at

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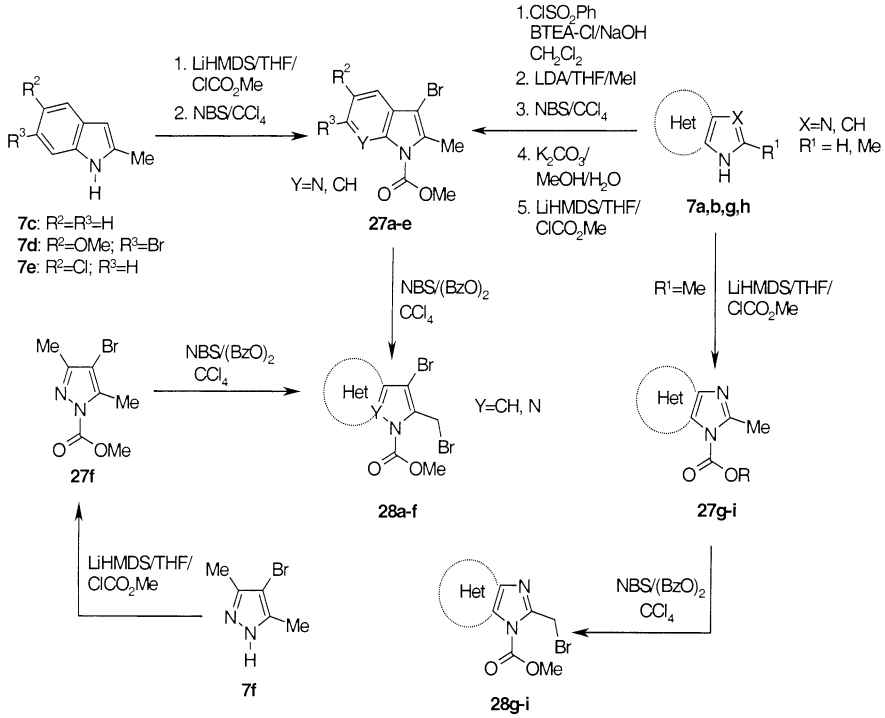
SCHEME 8



low power and decomposition was observed upon increasing the power or irradiation time. On the basis of our previous results in the synthesis of pyrrolo[1,2-*a*]pyrimidines,[1,14] decarboxylation was finally achieved by heating (12 h) in diphenyl ether (250 °C). However, under these conditions the yields were moderate or low (23−35%). Longer reaction times resulted in lower yields due to decomposition and formation of debrominated products. Similar results were found with the pyrimido[1,6-*a*]indole **29c** although in this case better yields were obtained. This likely reflects the greater stability of **29c** and **31c** to basic conditions and heating.

Our strategy for the introduction of the pyrimidine moiety in the C5 position initially focused on the preparation of a boronic acid or stannane from **29a** and a subsequent Suzuki or Stille reaction. However, all our efforts to prepare the organometallics failed, likely by the instability of the organolithium intermediate and/or the organometallics themselves. We therefore considered the coupling of **29a** and an appropriate stannane or boronic acid to achieve the required C5 substitution on this pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine. We proved that **29a** reacted with (3-methylthiopyrimidinyl)trimethyltin[19] in the presence of $Pd(PPh_3)_4$ producing the cross-coupling product **33** in a 63% yield when the reaction was carried out in toluene/MeOH (20:1).

Finally, we turned our attention to the C9 position. Based on our earlier studies on the reactivity of the pyrrolo[1,2-c]pyrimidine,[14] we attempted the metalation of this position and subsequent quenching with a source of electrophilic bromine. After many experiments we were unable to obtain the desired 1-bromo derivative **34** using different lithium bases (LDA, *t*-BuLi, and LHMDS) and 1,2-dibromoethane or 1,2-dibromotetrachlorethane in THF at −78 °C. The only compounds isolated from this attempted functionalization of the C9 position were dimers **35** and **36**. The mixture **35/36** is slowly oxidized on standing or with NBS, yielding **36** in a 64% yield.

Conclusions

Variolins are a class of marine alkaloids characterized by a highly functionalized pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine system. The heterocyclic core of these alkaloids has been prepared by reaction of 3-bromo-2-bromomethylpyrrolo[2,3-*b*]pyridine and tosylmethyl isocyanide (TosMIC). This efficient and novel reaction was also used to synthesize a new series of methoxycarbonylazolopyrimidines. The 5-bromo-7-methoxycarbonylpyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine obtained by this heterocyclization process was subjected to hydrolysis and decarboxylation and functionalized at the C5 position with an appropriately substituted pyrimidine ring. These heterocyclic transformations are key elements to complete a formal or total synthesis of variolin B, a target that is currently one of our goals.

Experimental Section

General Methods. All reactions were carried under Ar and using solvents that were dried by routine procedures. Column chromatography was performed using silica gel (60 F_{254}, 70−200 μm) as the stationary phase. All melting points are uncorrected. IR spectra were determined on films. NMR spectra were obtained at 200, 300, or 500 MHz (^{1}H) and 50 or 75 MHz (^{13}C). Chemical shifts are reported in ppm relative to tetramethylsilane. The 8-chloropyrrolo[2,3-*b*]pyridine **7b**, 7-azaindole-2-carboxaldehyde **12**, and 2-methyl-1-phenylsulfonylpyrrolo[2,3-*b*]piridine **20a** was synthesized according to the previously reported procedures.

Preparation of 3-Bromo-2-methyl-1-phenylsulfonylpyrrolo[2,3-*b*]pyridine (21a). To a solution of **20a** (7.14 g, 26.3

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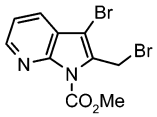
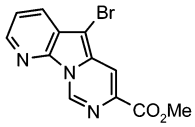
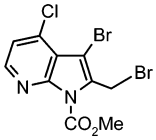
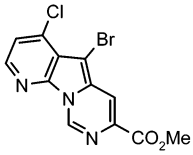
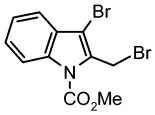
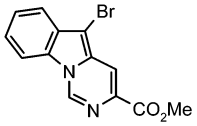
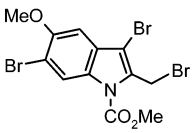
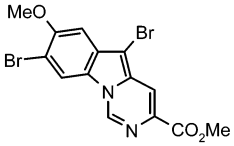
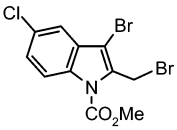
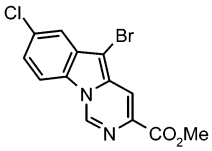
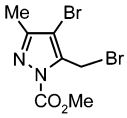
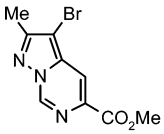
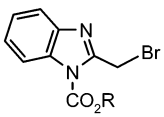
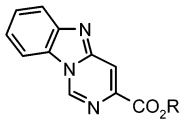
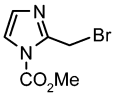
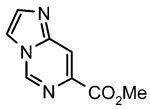
TABLE 1. Azolopyrimidines 29 from 2-Bromomethylazoles 28 and TosMIC

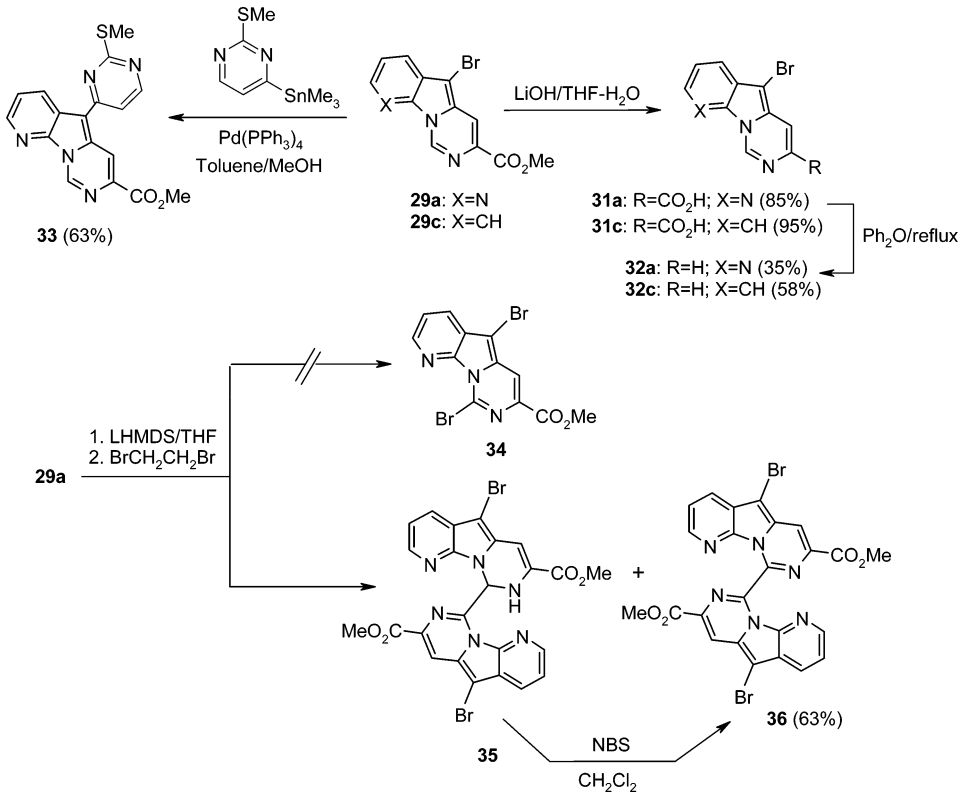
Entry	2-Bromomethyazoles (**28**)		Conditions[a]	Azolopyrimidines (**29**)		Yield (%)
1		**28a**	–10 ºC, 20 min		**29a**	65
2		**28b**	0 ºC, 2 h		**29b**	27
3		**28c**	r.t., 2 h		**29c**	89
4		**28d**	r.t., 2 h		**29d**	56
5		**28e**	r.t., 2 h		**29e**	58
6		**28f**	–10 ºC, 20 min		**29f**	44
7		**28g** (R=Me) **28h** (R=CMe$_3$)	–20 ºC, 2 h		**29g** **28h**	41 40
8		**28i**	–10 ºC, 2 h		**29i**	traces

[a] TosMIC (1.1 mmol), $Bu_4N^+I^-$ (0.2 mmol), CH_2Cl_2, aq NaOH.

mmol) in CCl_4 (250 mL) was added NBS (4.68 g, 26.3 mmol), and the mixture was stirred at room temperature for 12 h. Afterward, the succinimide was removed by filtration, the solution was concentrated to dryness, and the residue was chromatographed on a silica gel column using hexane/ethyl acetate (9:1) as eluent to give **21a** (6.18 g, 67% yield). Mp: 134−135 °C (white solid). IR (KBr) ν_{max}: 2902, 1638, 1583, 1561, 1375, 1183 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.75 (s, 3H); 7.20 (dd, 1H, J = 7.7, 4.8 Hz); 7.60−7.40 (m, 3H); 7.69 (dd, 1H, J = 7.7, 1.6 Hz); 8.18−8.10 (m, 2H); 8.42 (dd, 1H, J = 4.8, 1.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.3; 97.4; 119.5; 121.6; 127.2; 127.6; 129.0; 134.0; 135.3; 138.9; 144.9; 147.4. MS (EI) m/z (relative intensity): 352 (12); 350 (M^+, 12); 288 (22); 286 (22); 211 (31); 209 (32); 77 (100). Anal. Calcd for $C_{14}H_{11}BrN_2O_2S$: C, 47.88; H, 3.16; N, 7.98. Found: C, 47.84; H, 3.17; N, 7.95.

3-Bromo-2-bromomethyl-2-methyl-1-phenylsulfonylpyrrolo[2,3-*b*]pyridine (22a). A mixture of **21a** (0.70 g, 1.99 mmol), 4 mg of benzoyl peroxide, and NBS (2 mmol) in 20 mL of CCl_4 was heated at reflux temperature for 2.5 h. Then the reaction mixture was allowed to cool to room temperature and filtered and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using hexane/EtOAc (9:1) as eluent yielding 0.69 g of **22a** (81%) as a yellow solid. Mp: 149−150 °C. IR (KBr) ν_{max}: 1394, 1378, 1297, 1177, 1088 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.21 (s, 2H); 7.25 (dd, 1H, J = 7.9, 5.1 Hz); 7.52−7.47 (m, 2H); 7.61−7.57 (m, 1H); 7.78 (dd, 1H, J = 7.9, 1.5 Hz); 8.45−8.40 (m, 2H); 8.49

SCHEME 9



(dd, 1H, J = 5.1, 1.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.8; 101.0; 119.9; 120.8; 126.0; 128.5; 128.8; 128.9; 133.0; 134.4; 138.2; 146.7. EM (EI) m/z (relative intensity): 430 (M^+, 2); 351 (13); 349 (13); 141 (48); 77 (100). Anal. Calcd for $C_{14}H_{10}Br_2N_2O_2S$: C, 39.10; H, 2.34; N, 6.51. Found: C, 39.16; H, 2.32; N, 6.50.

Reaction of 22a with TosMIC. To a mixture of **22a** (340 mg, 0.79 mmol), TosMIC (154 mg, 0.79 mmol), and TBAI (58 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) a 30% aqueous solution of NaOH (15 mL) was added, and the resulting mixture was vigorously stirred at −10 °C for 2 h. Then the reaction mixture was diluted with water and extracted with CH_2Cl_2, the organic phase waswashed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel to provide 159 mg (37%) of **23** (hexane/EtOAc, 7:3) and 94 mg (15%) of **24** (hexane/EtOAc, 1:1).

3-Bromo-2-(2′-isocyanyl-2′-tosylethyl)-1-phenylsulfonylpyrrolo[2,3-*b*]pyridine (23). Unstable pale yellow solid. Mp: 160−163 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.49 (s, 3H); 3.91 (dd, 1H, J = 14.4 Hz, J = 11.1 Hz); 4.08 (dd, 1H, J = 14.4 Hz, J = 3.7 Hz); 5.41 (dd, 1H, J = 11.1 Hz, J = 3.7 Hz); 7.27 (dd, 1H, J = 8.1, 4.8 Hz); 7.29−7.27 (m, 1H); 7.59−7.44 (m, 3H); 7.62−7.55 (m, 1H); 7.78 (dd, 1H, J = 8.1, 1.6 Hz); 7.97 (d, 2H, J = 8.2 Hz); 8.09 (d, 2H, J = 7.3 Hz); 8.48 (dd, 1H, J = 4.8, 1.6 Hz).

1,3-Bis(3-bromo-1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-2-yl)-2-isocyanyl-2-tosylpropane (24). Brown powder. Unstable at room temperature. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3H); 4.27 (d, 2H, J = 15.5 Hz); 4.48 (d, 2H, J = 15.5 Hz); 7.16 (dd, 2H, J = 8.0, 4.7 Hz); 7.47−7.30 (m, 8H); 7.70 (dd, 2H, J = 8.0, 1.4 Hz); 7.89 (d, 4H, J = 8.2 Hz); 8.12 (m, 2H); 8.39 (dd, 2H, J = 4.7, 1.4 Hz).

General Procedures for the Preparation of 27a−h. Protection of Pyrrolo[2,3-*b*]pyridines 7a,b as *N*-Benzenesulfonamide. To a solution of the azole **7a,b**[20] (5.0 mmol) and benzyltriethylammoniun chloride (0.13 mmol) in CH_2Cl_2 (10 mL) was added powdered NaOH (15.62 mmol). The solution was cooled to 0 °C, and phenylsulfonyl chloride (6.25 mmol) was added dropwise. The mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature. The resulting mixture was filtered over Celite and washed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel. *N*-Phenylsulfonyl azaindoles were isolated using hexane/EtOAc as eluent.

Methylation of Pyrrolo[2,3-*b*]pyridines. *N*-Phenylsulfonyl azaindoles (5.0 mmol) were dissolved in THF (25 mL) under an argon atmosphere, and the solution was cooled to −30 °C. Then LDA (10.0 mmol, 2 M, THF) was added dropwise and the mixture stirred at −30 °C for 40 min. After this time, methyl iodide (30 mmol) was added, and the mixture was allowed to warm to room temperature and stirred at room temperature for 3−16 h. The reaction mixture was quenched with NH_4Cl, extracted with CH_2Cl_2, and dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using variable mixtures of hexane,EtOAc as eluent to give the corresponding methyl *N*-phenylsulfonyl azaindoles.

Electrophilic Bromination. General Procedure. A mixture of the azole (5 mmol) and NBS (5 mmol) was stirred in CCl_4 (50 mL) at room temperature for 12 h. Then the succinimide was filtered off and washed with CCl_4, and the combined organic phases wereevaporated under reduced pressure. The residue was chromatographed on silica gel using hexane/EtOAc as eluent to give pure brominated compounds.

Deprotection of Pyrrolo[2,3-*b*]pyridines. To a solution of the *N*-phenylsulfonyl azaindole (2.15 mmol) in MeOH/H_2O (170 mL, 3:1 v/v) was added K_2CO_3 (6.45 mmol) and the mixture heated to reflux temperature. The resultant solution was stirred for 7 h at reflux temperature. Afterward, the solution was allowed to cool to room temperature. Methanol was removed in vacuo, and the resulting suspension was partioned between water and ethyl acetate. Organic layers were combined and dried (Na_2SO_4). After filtration, the filtrate

(20) Clark, B. A. J.; Patrick, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2270.

was concentrated to dryness and the residue was chromatographed on a silica gel column using hexane/EtOAc (1:1) as eluent.

Protection as *N*-Methylcarbamates. General Procedure for Azoles 27a−g,i. LiHMDS in THF (2.61 mmol, 2.6 mL, 1 M) was added to a solution of the azole (2.35 mmol) in dry THF (8 mL) under argon at −78 °C, and the mixture was allowed to warm to room temperature over a period of 2 h. The mixture was cooled again to −78 °C, methyl chloroformate (0.22 mL, 2.61 mmol) was added dropwise, stirring was continued for 2 h at −78 °C, and then the reaction was allowed to warm to room temperature. The mixture was treated with NH_4Cl, extracted with ethyl acetate, and the combined layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the crude product was chromatographed on a silica gel column using hexane/EtOAc as eluent.

3-Bromo-1-methoxycarbonyl-2-methylpyrrolo[2,3-*b*]pyridine (27a). Chromatography hexane/EtOAc 6:4 (0.56 g, 89% yield). Mp: 114−115 °C (white solid). IR (KBr) ν_{max}: 1732, 1564, 1446, 1394, 1314, 1257 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.66 (s, 3H); 4.10 (s, 3H); 7.23 (dd, 1H, J = 7.7, 4.6 Hz); 7.76 (dd, 1H, J = 7.7, 1.5 Hz); 8.43 (dd, 1H, J = 4.6, 1.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.4; 54.0; 96.6; 119.0; 121.4; 127.7; 135.4; 144.5; 146.7; 150.8. MS (EI) *m*/*z* (relative intensity): 271 (98); 269 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.77; N, 10.41. Found: C, 44.61; H, 3.36; N, 10.38.

3-Bromo-4-chloro-1-methoxycarbonyl-2-methylpyrrolo-[2,3-*b*]pyridine (27b). Chromatography hexane/EtOAc 8:2 (0.55 g, 77% yield). Mp: 146−148 °C (white solid). IR (KBr) ν_{max}: 1734, 1575, 1550, 1440, 1376, 1285, 1190 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.62 (s, 3H); 4.19 (s, 3H); 7.20 (d, 1H, J = 5.3 Hz); 8.24 (d, 1H, J = 5.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.5; 54.5; 94.2; 115.9; 120.5; 128.8; 137.0; 141.3; 142.2; 144.8 MS (EI) *m*/*z* (relative intensity): 305 (18); 303 (M^++1, 18); 167 (100). Anal. Calcd for $C_{10}H_8BrClN_2O_2$: C, 39.57; H, 2.66; N, 9.23. Found: C, 39.51; H, 2.68; N, 9.24.

3-Bromo-1-methoxycarbonyl-2-methylindole (27c). Chromatography hexane/EtOAc 9:1 (0.48 g, 92% yield). Mp: 75−77 °C (lit.[21] mp 75−76 °C). ^1H NMR δ: 2.65 (s, 3H); 4.09 (s, 3H); 7.28−7.34 (m, 2H); 7.43 (m, 1H); 8.08 (m, 1H).

3,6-Dibromo-5-methoxy-1-methoxycarbonylcarbonyl-2-methylindole (27d). Chromatography hexane/EtOAc 9:1 (0.67 g, 76%). Mp: 136−137 °C (white solid). IR (KBr) ν_{max}: 1736, 1464, 1435, 1365, 1210, 1109 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.53 (s, 3H); 3.88 (s, 3H); 3.96 (s, 3H); 6.81 (s, 1H); 8.19 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.7; 53.7; 56.1; 99.2; 99.7; 108.5; 119.6; 128.1; 128.4; 135.0; 151.0; 152.1. MS (EI) *m*/*z* (relative intensity): 379 (42); 377 (M^+, 86); 375 (43); 63 (32); 59 (100). Anal. Calcd for $C_{12}H_{11}Br_2NO_3$: C, 38.23; H, 2.94; N, 3.71. Found: C, 38.30; H, 2.97; N, 3.68.

5-Chloro-1-methoxycarbonyl-2-methylindole (27e). Chromatography hexane/EtOAc 8:2 (0.42 g, 59%). Mp: 49−50 °C (white solid). IR (KBr) ν_{max}: 1738, 1459, 1371, 1317, 1210, 1094, 1069 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.59 (s, 3H); 4.04 (s, 3H); 6.25 (s, 1H); 7.16 (dd, 1H, J = 8.9, 2.1 Hz); 7.37 (d, 1H, J = 2.1 Hz); 7.97 (d, 1H, J = 8.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.6; 53.4; 107.6; 116.3; 118.9; 123.1; 128.2; 130.6; 134.5; 139.0; 152.0. MS (EI) *m*/*z* (relative intensity): 226 (34); 224 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.00; H, 4.50; N, 6.28.

4-Bromo-1-methoxycarbonyl-3,5-dimethylpyrazole (27f). Chromatography CH_2Cl_2/acetone 9:1 (0.53 g, 96%); mp 102−104 °C (white solid). IR (KBr) ν_{max} 1749, 1438, 1374, 1347, 1297, 1064 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.24 (s,3H); 2.50 (s,3H); 4.00 (s,3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9; 12.3; 53.9; 100.1; 141.3; 148.9; 150.4 MS (EI): *m*/*z* (relative intensity) 233 (M^+ + 1, 6); 189 (100); 187 (99). Anal. Calcd for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.89; N, 12.02. Found: C, 36.08; H, 3.87; N, 12.05.

(21) Nagarathnam, D. *Synthesis* **1992**, 743.

1-Methoxycarbonyl-2-methylbenzimidazole (27g). Chromatography CH_2Cl_2/acetone 9:1 (0.43 g, 96%). Mp: 122−124 °C (pale yellow solid). IR (KBr) ν_{max}: 1758, 1636, 1457, 1355, 1210 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.79 (s, 3H); 4.06 (s, 3H); 7.30−7.23 (m, 2H); 7.63 (dd, 1H, J = 7.1, 2.0 Hz); 7.85 (dd, 1H, J = 6.0, 2.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.1; 54.1; 108.8; 114.6; 119.1; 124.3; 132.6; 142.0; 150.9; 153.0. MS (EI) *m*/*z* (relative intensity): 191 (M^+ + 1, 100); 147 (18). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.32; N, 14.80.

2-Methyl-1-methoxycarbonylimidazole (27i). Chromatography CH_2Cl_2/acetone 9:1 (0.17 g, 51% yield, pale yellow oil). ^1H NMR (200 MHz, $CDCl_3$) δ: 2.49 (s, 3H); 3.84 (s, 3H); 6.67−6.69 (m, 1H); 7.17−7.19 (M, 1H). MS (EI) *m*/*z* (relative intensity): 82 (100), 81 (47), 54 (34). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.15; H, 5.37; N, 19.81.

2-Methyl-1-*tert*-butoxycarbonylbenzymidazole (27h). 2-Methylbenzimidazole (503 mg, 3.81 mmol) was dissolved in 20 mL of CH_2Cl_2, and triethyamine (0.5 mL, 3.81 mmol), (dimethylamino)pyridine (0.38 mmol), and Boc_2O (7.62 mmol) were added to the solution. Water (20 mL) was added, and the organic phase was washed with brine and dried (Na_2SO_4). The organic phase was filtered and concentrated under reduced pressure yielding 0.88 g of 2-methyl-*N*-*tert*-butoxycarbonylbenzymidazole. 99% yield. Mp: 275−278 °C dec (pale yellow solid). IR (KBr) ν_{max}: 1751, 1561, 1453, 1352, 1095, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 9H); 2.77 (s, 3H); 7.26−7.23 (m, 2H); 7.62−7.59 (m, 1H); 7.87−7.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.5; 27.1; 84.2; 113.7; 118.2; 122.9; 123.0; 131.9; 141.1; 147.9; 152.1. MS (ES) *m*/*z* (relative intensity) 233 (M + H^+, 100); 255 (M + Na^+, 42). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.20; H, 6.95; N, 12.05.

Radical Bromination. General Procedure for Azoles 28a−i. In a typical procedure, powdered NBS (1.78 g, 10 mmol) and benzoyl peroxide (20 mg) were added to a solution of the *N*-methyl carbamate protected azole (10 mmol) in CCl_4 (100 mL), and the mixture was stirred and heated at reflux temperature. The succinimide formed was filtered off, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column to yield pure compounds **28a−i** (yields are referred to the radical bromination step).

3-Bromo-2-bromomethyl-1-methoxycarbonylpyrrolo-[2,3-*b*]pyridine (28a). Chromatography hexane/EtOAc 9:1 (3.17 g, 91% yield). Mp: 147−148 °C (yellow solid). IR (KBr) ν_{max}: 1739, 1576, 1436, 1402, 1319, 1255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.05 (s, 3H); 4.97 (s, 2H); 7.20 (dd, 1H, J = 7.9, 4.8 Hz); 7.75 (dd, 1H, J = 7.9, 1.6 Hz); 8.45 (dd, 1H, J = 4.8, 1.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.5; 54.7; 100.4; 119.7; 121.0; 128.3; 133.8; 147.0; 147.3; 150.2. MS (EI) *m*/*z* (relative intensity): 351 (39); 349 (M^+ + 1, 80); 347 (41); 269 (99); 267 (100). Anal. Calcd for $C_{10}H_8Br_2N_2O_2$: C, 34.52; H, 2.32; N, 8.05. Found: C, 34.60; H, 2.32; N, 8.01.

3-Bromo-2-bromomethyl-4-chloro-1-methoxycarbonylpyrrolo[2,3-*b*]pyridine (28b). Chromatography hexane/EtOAc 8:2 (2.47 g, 65% yield). Mp: 160−161 °C (yellow solid). IR (KBr) ν_{max}: 1735, 1618, 1560, 1438, 1381, 1284 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.17 (s, 3H); 5.06 (s, 2H); 7.26 (d, 1H, J = 5.3 Hz); 8.37 (d, 1H, J = 5.3 Hz). MS (EI) *m*/*z* (relative intensity): 385 (32); 384 (11); 383 (M^+ + 1, 75); 305 (31); 303 (100); 301 (74). Anal. Calcd for $C_{10}H_7Br_2ClN_2O_2$: C, 31.41; H, 1.84; N, 7.32. Found: C, 31.32; H, 1.84; N, 7.34.

3-Bromo-2-bromomethyl-1-methoxycarbonylindole (28c). Chromatography hexane/EtOAc 95:5 (3.33 g, 96% yield). Mp 119−120 °C (lit.[21] mp 118−119 °C). ^1H NMR (300 MHz, $CDCl_3$) δ: 4.11 (s, 3H); 5.05 (s, 2H); 7.30−7.35 (m, 1H); 7.37−7.44 (m, 1H); 7.50−7.53 (m, 1H); 8.08−8.11 (m, 1H).

2-Bromomethyl-3,6-dibromo-5-methoxy-1-methoxycarbonylindole (28d). Chromatography hexane/EtOAc 98:2 (0.91 g, 20% yield). Mp: 175−176 °C (yellow solid). IR (KBr) ν_{max}:

1738, 1616, 1440, 1362, 1290, 1214 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.96 (s, 3H); 4.11 (s, 3H); 5.02 (s, 2H); 6.93 (s, 1H); 8.33 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.4; 54.1; 56.2; 100.3; 103.3; 111.0; 120.2; 127.7; 129.2; 133.1; 150.1; 152.6. MS (EI) *m/z* (relative intensity): 457 (8); 455 (M^+, 8), 378 (48), 376 (100), 374 (47), 59 (59). Anal. Calcd for $C_{12}H_{10}Br_3NO_3$: C, 31.61; H, 2.21; N, 3.07. Found: C, 31.59; H, 2.21; N, 3.08.

3-Bromo-2-bromomethyl-5-chloro-1-methoxycarbonylindole (28e). Chromatography hexane/EtOAc 95:5 (3.74 g, 98% yield). Mp: 138−139 °C (white solid). IR (KBr) ν_{max}: 2953, 1742, 1637, 1439, 1375, 1207, 1072 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.11 (s, 3H); 5.00 (s, 2H); 7.31 (dd, 1H, J = 9.0, 2.1 Hz); 7.47 (d, 1H, J = 2.1 Hz); 8.00 (d, 1H, J = 9.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.0; 54.4; 103.1; 117.1; 119.4; 126.9; 129.1; 129.9; 133.9; 134.2; 150.8. MS (EI) *m/z* (relative intensity): 381 (14); 304 (25); 303 (12); 302 (100); 300 (75); 132 (34); 127 (26); 59 (51). Anal. Calcd for $C_{11}H_8Br_2ClNO_2$: C, 34.64; H, 2.11; N, 3.67. Found: C, 34.70; H, 2.10; N, 3.68.

4-Bromo-5-bromomethyl-3-methyl-1-methoxycarbonylpyrazole (28f). Chromatography CH_2Cl_2 (2.93 g, 94% yield). Mp 75−76 °C (white solid). IR (KBr) ν_{max}: 1759, 1637, 1480, 1445, 1352, 1297, 1149 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3H); 4.10 (s, 3H); 4.79 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 12.6; 19.8; 55.2; 103.5; 140.9; 149.4; 151.7. MS (EI) *m/z* (relative intensity): 312 (M^+, 7); 310 (4); 233 (50); 231 (51); 65 (100), 63 (49). Anal. Calcd for $C_7H_8Br_2N_2O_2$: C, 26.95; H, 2.58; N, 8.98. Found: C, 27.01; H, 2.58; N, 8.98.

2-Bromomethyl-1-methoxycarbonylbenzimidazole (28g). Chromatography CH_2Cl_2 (1.39 g, 52% yield). Mp: 120−121 °C (pale yellow solid). IR (KBr) ν_{max}: 1756, 1605, 1539, 1453, 1357, 1320, 1292 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.14 (s, 3H); 4.94 (s, 2H); 7.38−7.24 (m, 2H); 7.74−7.71 (m, 1H); 7.79−7.89 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.7; 54.7; 115.0; 120.4; 124.9; 125.9; 132.7; 141.7; 150.1; 150.4 MS (EI) *m/z* (relative intensity): 271 (97); 269 (M^+ + 1, 100); 189 (99). Anal. Calcd for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.75; H, 3.38; N, 10.40.

2-Bromomethyl-1-*tert*-butoxycarbonylbenzymidazole (28h). Chromatography hexane/EtOAc (8:2) (1.18 g, 38% yield). Mp 76−77 °C (pale yellow solid). IR (KBr) ν_{max}: 1741, 1547, 1458, 1206, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.75 (s, 9H); 4.95 (s, 2H); 7.39−7.34 (m, 2H); 7.72 (dd, 1H, J = 7.2, 1.8 Hz); 7.97 (dd, 1H, J = 7.5, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.1; 26.9; 85.5; 114.2; 119.4; 123.7; 124.7; 132.3; 140.7; 147.0; 149.4. MS (ES) *m/z* (relative intensity): 311 (M^+, 98), 313 (M + 2, 100). Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.18; H, 4.85; N, 9.03.

2-Bromomethyl-1-methoxycarbonylimidazole (28i). Chromatography CH_2Cl_2 (0.24 g, 11% yield). Mp: 94−95 °C (white solid). IR (KBr) ν_{max}: 1772, 1430, 1295, 1190 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.03 (s, 3H); 4.82 (s, 2H); 6.96−6.98 (m, 1H); 7.40−7.42 (m, 1H). MS (EI) *m/z* (relative intensity): 220 (19); 218 (M^+, 20); 149 (24); 139 (27), 94 (100). Anal. Calcd for $C_6H_7BrN_2O_2$: C, 32.90; H, 3.22; N, 12.79. Found: C, 32.81; H, 3.21; N, 12.82.

General Procedure for the Reaction of 28a−h with TosMIC. Preparation of 29a−h. A mixture of the bromomethyl derivative **28** (1.0 mmol), TosMIC (0.22 g, 1.1 mmol), and TBAI (0.08 g, 0.2 mmol) in CH_2Cl_2 (7 mL) and aqueous sodium hydroxide solution (7 mL) was stirred at the temperature indicated in Table 1. After the appropriate reaction time (20 min to 2 h), the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, providing a crude that was chromatographed on silica gel to yield compounds **29a−h**.

5-Bromo-7-methoxycarbonylpyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidine (29a). Chromatography CH_2Cl_2/acetone 95:5 (0.20 g, 65% yield). Mp: 208−209 °C (yellow solid). IR (KBr) ν_{max}: 1732, 1637, 1618, 1567, 1523, 1439, 1286 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.04 (s, 3H); 7.57 (dd, 1H, J = 8.1, 4.6 Hz); 8.15 (dd, 1H, J = 8.1, 1.4 Hz); 8.26 (d, 1H, J = 1.2 Hz); 8.61 (dd, 1H, J = 4.6, 1.4 Hz); 9.55 (d, 1H, J = 1.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 53.1; 85.0; 116.0; 121.7; 122.0; 128.2; 130.3; 136.3; 138.0; 139.8; 145.1; 164.8. MS (EI) *m/z* (relative intensity): 306 (99); 304 (M^+,100); 249 (43); 248 (40); 247 (44); 246 (36). Anal. Calcd for $C_{12}H_8BrN_3O_2$: C, 47.08; H, 2.63; N, 13.73. Found: C, 47.13; H, 2.62; N, 13.76.

5-Bromo-4-chloro-7-methoxycarbonylpyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine (29b). Chromatography hexane/EtOAc 8:2 (0.09 g, 27% yield). Mp: 195−196 °C (yellow solid). IR (KBr) ν_{max}: 2924, 1713, 1444, 1356, 1260, 1098. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.06 (s, 3H); 7.55 (d, 1H, J = 5.0 Hz); 8.33 (s, 1H); 8.47 (d, 1H, J = 5.0 Hz); 9.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 53.2; 116.2; 121.1; 122.5; 123.9; 125.9; 128.2; 128.6; 130.0; 138.0; 144.6; 158.4. MS (EI) *m/z* (relative intensity) 344 (24); 342 (100); 341 (26); 340 (M^+ + 1, 77). Anal. Calcd for $C_{12}H_7BrClN_3O_2$: C, 42.32; H, 2.07; N, 12.34. Found: C, 42.25; H, 2.07; N, 12.37.

5-Bromo-3-methoxycarbonylpyrimido[1,6-*a*]indole (29c). Chromatography hexane/EtOAc 1:1 (0.27 g, 89% yield). Mp: 260−261 °C (yellow solid). IR (KBr) ν_{max}: 1729, 1456, 1372, 1217, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.02 (s, 3H); 7.59−7.52 (m, 2H); 7.82 (d, 1H; J = 7.6 Hz); 8.03 (d, 1H; J = 7.8 Hz); 8.25 (s, 1H); 9.14 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 53.0; 87.9; 111.0; 116.4; 120.1; 124.4; 126.0; 128.4; 129.0; 130.7; 135.8; 138.4; 165.2. MS (EI) *m/z* (relative intensity: 307 (96); 305 (M^+ + 1, 100); 254 (45); 226 (51). Anal. Calcd for $C_{13}H_9BrN_2O_2$: C, 51.17; H, 2.97; N, 9.18. Found: C, 51.09; H, 2.98; N, 9.17.

5,8-Dibromo-7-methoxy-3-methoxycarbonylpyrimido-[1,6-*a*]indole (29d). Chromatography CH_2Cl_2 (0.23 g, 56% yield). Mp: 279−280 °C (yellow solid). IR (KBr) ν_{max}: 1737, 1637, 1560, 1542, 1449 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.88 (s, 3H); 3.99 (s, 3H); 7.16 (s, 1H); 7.95 (s, 1H); 8.89 (s, 1H); 9.67 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 52.9; 56.6; 84.8; 98.8; 109.0; 113.8; 123.0; 128.4; 130.8; 134.9; 140.1; 153.7; 164.3. MS (EI) *m/z* (relative intensity): 417 (49); 415 (M^+ + 1, 100); 414 (40); 413 (50). Anal. Calcd for $C_{14}H_{10}Br_2N_2O_3$: C, 40.61; H, 2.43; N, 6.77. Found: C, 40.53; H, 2.43; N, 6.76.

5-Bromo-7-chloro-3-methoxycarbonylpyrimido[1,6-*a*]-indole (29e). Chromatography hexane/EtOAc 8:2 (0.20 g, 58% yield). Mp: 218−219 °C (yellow solid). IR (KBr) ν_{max}: 1731, 1655, 1446, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.08 (s, 3H); 7.48 (d, 1H; J = 9.0 Hz); 7.81 (s, 1H); 7.98 (d, 1H, J = 9.0 Hz); 8.24 (s, 1H); 9.12 (s, 1H). MS (EI) *m/z* (relative intensity): 343 (27); 342 (19); 341 (100); 340 (30); 339 (M^+ + 1, 77); 338 (16). Anal. Calcd for $C_{13}H_8BrClN_2O_2$: C, 45.98; H, 2.37; N, 8.25. Found: C, 46.03; H, 2.37; N, 8.23.

5-Bromo-2-methyl-5-methoxycarbonylpyrazolo[1,3-*c*]-pyrimidine (29f). Chromatography hexane/EtOAc 1:1 (0.12 g, 44% yield). Mp: 180−181 °C (white solid). IR (KBr) ν_{max}: 1724, 1616, 1532, 1470, 1337, 1277, 1204 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3H); 3.99 (s, 3H); 8.17 (s, 1H); 9.08 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 12.6; 53.1; 90.1; 114.3; 136.9; 138.5; 140.2; 155.0; 164.3. MS (EI) *m/z* (relative intensity): 272 (97); 270 (M^+ + 1, 100). Anal. Calcd for $C_9H_8BrN_3O_2$: C, 40.02; H, 2.99; N, 15.56. Found: C, 39.97; H, 3.00; N, 15.58.

3-Methoxycarbonylpyrimido[1,6-*a*]benzimidazole (29g). Chromatography EtOAc (0.09 g, 41% yield). Mp: 190−191 °C (white solid). IR (KBr) ν_{max}: 1735, 1638, 1513, 1458, 1243 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.05 (s, 3H); 7.70−7.51 (m, 2H); 8.10−8.01 (m, 2H); 8.43 (s, 1H); 9.39 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 53.3; 111.1; 115.9; 121.0; 124.2; 127.8; 139.0; 141.2; 145.2; 149.3; 151.1; 164.4.MS (EI) *m/z* (relative intensity): 227 (M^+, 100); 169 (93); 168 (75); 102 (63). Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.39; H, 4.00; N, 18.45.

3-*tert*-Butoxycarbonylpyrimido[2,3-*a*]benzymidazole (29h). Chromatography hexane/EtOAc 6:4 (0.11 g, 40% yield). Mp: 164−165 °C (pale yellow solid). IR (KBr) ν_{max}: 1729, 1519, 1251, 1097, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.64 (s, 9H); 7.38 (td, J = 8.2, 1.5 Hz); 7.50 (td, J = 8.2, 1.0

Hz); 7.88 (d, 1H, $J = 8.2$ Hz); 7.94 (d, 1H, $J = 8.2$ Hz); 8.21 (d, 1H, $J = 1.5$ Hz); 9.30 (d, 1H, $J = 1.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.4; 83.5; 111.5; 115.5; 121.1; 124.3; 128.7; 139.4; 143.3; 145.5; 147.0; 163.1; 176.4. MS (ES) *m*/*z* (relative intensity): 270 (M + 1, 100). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.92; H, 5.61; N, 15.59.

General Procedure for the Hydrolysis and Decarboxylation of 29a,c. To a solution of **29a**,**c** (1.0 mmol) in THF/H_2O (4:1 v/v) was added LiOH·H_2O (63 mg, 1.5 mmol), and the mixture was stirred at room temperature. Afterward, the THF was removed in vacuo, water was added (5 mL), and the solution was acidified with 1 N HCl (pH = 5). The yellow solid formed was filtered, washed with water, and dried in vacuo to give the corresponding acids **31a**,**c**. These acids, without further purification, were suspended in Ph_2O (5 mL), and the mixture was heated at 260 °C and stirred for 4 h at this temperature. The residue was chromatographed on a silica gel column using hexane/EtOAc 1:1 as eluent to yield compounds **32a**,**c**.

5-Bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (32a). Yield: 11.6 mg, 29%. Mp: 139−140 °C (pale brown solid). IR (KBr) ν_{max}: 3415, 3055, 1614, 1570, 1420, 1325, 1224, 1192 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (dd, 1H, $J = 6.7$, 1.5 Hz); 7.50 (dd, 1H, $J = 8.0$, 4.7 Hz); 7.68 (d, 1H, $J = 6.7$ Hz); 8.06 (dd, 1H, $J = 8.0$, 1.3 Hz); 8.49 (dd, 1H, $J = 4.7$, 1.3 Hz); 9.50 (d, 1H, $J = 1.5$ Hz). Anal. Calcd for $C_{10}H_6BrN_3$: C, 48.42; H, 2.44; N, 16.94. Found: C, 48.40; H, 2,41; N, 16.93.

5-Bromopyrimido[1,6-*a*]indole (32c). Yield: 44.4 mg, 55%. Mp: 149−150 °C (pale brown solid). IR (KBr) ν_{max}: 1606, 1452, 1352, 1214 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 (dd, 1H, $J = 6.6$, 1.4 Hz); 7.47−7.42 (m, 1H); 7.58−7.53 (m, 1H); 7.61 (d, 1H, $J = 6.8$ Hz); 7.78 (d, 1H, $J = 7.9$ Hz); 7.99 (d, 1H, $J = 8.4$ Hz); 9.14 (d, 1H, $J = 1.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 82.0; 110.3; 111.3; 119.0; 122.3; 125.2; 127.5; 128.6; 131.2; 136.2; 138.6. MS (EI) *m*/*z* (relative intensity): 249 (99); 247 (M$^+$, 100); 167 (52). Anal. Calcd for $C_{11}H_7BrN_2$: C, 53.49; H, 2.86; N, 11.33. Found: C, 53.47; H, 2.86; N, 11.34.

5-(2-Methylthiopyrimidin-4-yl)pyrido[3′,2′:4,5]pyrrolo[1,2-c]-pyrimidine-7-carboxylic Acid Methyl Ester (33). The ester 29a (50 mg, 0.163 mmol) was dissolved in 2 mL of toluene/MeOH (20/1) under argon. Pd(PPh_3)$_4$ (10%) and (2-methylthiopyrimidin-4-yl)trimethyltin (0.180 mmol) were added, and the mixture was heated at 110 °C. Afterward, the reaction mixture was filtered through Celite and washed with CH_2Cl_2, and the combined organic layers were concentrated under reduce pressure. The residue was chromatographed on silica gel (CH_2Cl_2/acetone 95:5) yielding 36 mg (63%) of the coupled compound. Mp: 235−236 °C (yellow solid). IR (KBr) ν_{max}: 3453, 1712, 1556, 1437, 1365, 1336, 1181. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.73 (s, 3H); 4.04 (s, 3H); 7.41 (d, 1H, $J = 5.4$ Hz); 7.60 (dd, 1H, $J = 8.2$, 4.4 Hz); 8.57 (d, 1H, $J = 5.4$ Hz); 8.72−8.62 (m, 2H); 9.23 (d, 1H, $J = 1.5$ Hz); 9.73 (d, 1H; $J = 1.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.4; 53.2; 105.7; 113.0; 118.3; 120.8; 122.4; 129.9; 133.7; 138.5; 141.4; 145.1; 157.3; 160.2; 164.7; 173.2. MS (ES) *m*/*z* (relative intensity): 351 (M$^+$, 100); 291 (75); 246 (41). Anal. Calcd for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 58.14; H, 3.71; N, 19.94.

Self-Condensation of 29a. Synthesis of 36. To a solution of **29a** (50 mg, 0.16 mmol) in dry THF (30 mL) was added 1 M LiHMDS in THF (0.17 mL, 0.17 mmol) under argon at −78 °C, and the solution was stirred at this temperature for 1 h. Then 1,2-dibromoethane (0.12 mL, 1.28 mmol) was added, and stirring was continued for 12 h at −78 °C. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2 (2 × 30 mL). The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure and the residue chromatographed on silica gel (hexane/EtOAc, 1:1) yielding 38 mg of a mixture of **35** and **36**. The mixture **35/36** was dissolved in 3 mL of CH_2Cl_2, NBS (14 mg, 0.08 mmol) was added, and the solution was stirred at room temperature for 4 h. Afterward, it was concentrated under reduced pressure and the dark orange residue was purified by chromatography on silica gel (hexane/EtOAc, 1:1) yielding 31 mg (64%) of the dimeric compound **36** as a orange solid. The same result was obtained when the reaction was carried out in the absence of 1,2-dibromoethane. Mp: 290−293 °C dec. IR (KBr) ν_{max}: 1725; 1565; 1436; 1413; 1235; 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99 (3H, s), 7.20 (1H, dd, $J = 8.05$, $J = 4.59$), 7.85 (1H, d, $J = 4.59$), 7.98 (1H, d, $J = 8.05$), 8.50 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.9; 85.97; 117.018; 120.94; 121.75; 127.65; 131.39; 136.03; 140.00; 141.98; 145.05; 164.80. MS (ES) *m*/*z* (relative intensity): 614 (M + 4$^+$, 18); 612 (M + 2$^+$, 37); 610 (M$^+$, 100). Anal. Calcd for $C_{24}H_{14}BrN_6O_4$: C, 47.24; H, 2.31; N, 13.77. Found: C, 46.98; H, 2.33; N, 13.73.

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Supporting Information Available: Complete experimental procedures for the synthesis and characterization data for all intermediate compounds shown in Schemes 8 and 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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