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Preparing Functional Bis(indole) Pyrazine by Stepwise Cross-coupling Reactions: An Efficient Method to Construct the Skeleton of Dragmacidin D

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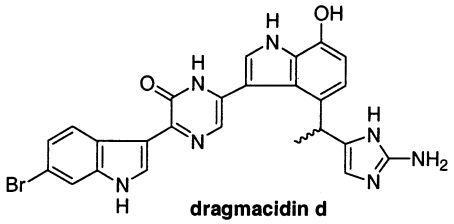
A direct approach for selective construction of properly substituted bis(indole) pyrazine, the skeleton of a marine alkaloid dragmacidin D, has been developed. The key steps involved the regioselective introduction of two indole units, using the palladium(0)-catalyzed Suzuki and the Stille cross-coupling reactions sequentially.

The structure uniqueness and biological importance of certain bis(indole) secondary metabolites, containing either an imidazole- or a pyrazine-derived spacer unit, have driven the search for even more efficient synthetic routes to these compounds.[1] Dragmacidin D, a novel secondary metabolite, was isolated from a deep-water marine sponge of the genus *Spongosorites* by Wright in 1992[2] and Capon in 1995.[3] Structurally, it varied from the previously reported dragmacidins.[4] To the best of our knowledge, this was the first of the marine derived bis(indole) compound to have alkyl substitution on C-4 of an indole ring, the first to incorporate the 2-aminoimidazole functionality which has been reported previously in the Agealasidae,[5] Axinellidae,[5] and Verongidae[6] sponges, and the first to have the 2(1*H*)-pyrazinone spacer. Dragmacidin D exhibited a broad spectrum of biological activity. It inhibited the growth of the feline leukemia virus, the opportunistic fungal pathogens *Cryptococcus neoformans* and *Candida albicans*, and the P388 and A549 tumor cell lines. Further biological studies indicated that dragmacidin D and its co-metabolite dragmacidin E have been identified as potent inhibitors of serine-threonine protein phosphatases, while dragmacidin D was a selective inhibitor of PP1.[7] In particular, dragmacidin D was found to selectively inhibit neural nitric oxide synthase (bNOS) in the presence of inducible NOS (iNOS).[8] This ability may be useful in a variety of therapeutic areas including the treatment of Alzheimer's, Parkinson's, and Huntington's diseases.[9]



dragmacidin d

Its unique structure and wide range of biological and pharmacological activities have attracted much attention and prompted many research groups to undertake the synthetic study.[10] The first successful construction of the bis(indol-3-yl)-2(1*H*) pyrazinone ring system in dragmacidin D has been achieved via the condensation of two indolyl glycine derived units, followed by the selective reduction and intramolecular cyclization by our group,[11] and then the intramolecular condensation of the oxotryptamine with ketoamide under heating condition by Horne.[12] In prior work, we have reported the enantioselective synthesis of the 2-aminoimidazole segment of dragmacidin D.[13] As a continuing study, we wish to report an efficient synthesis of functional bis(indole) pyrazine **1**, the skeleton of dragmacidin D, by the sequential implementation of palladium(0)-catalyzed Suzuki and Stille cross-coupling reactions that are exquisitely selective.

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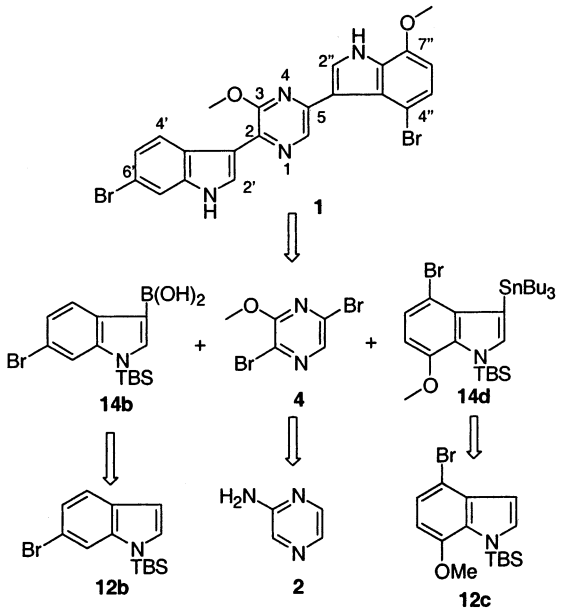
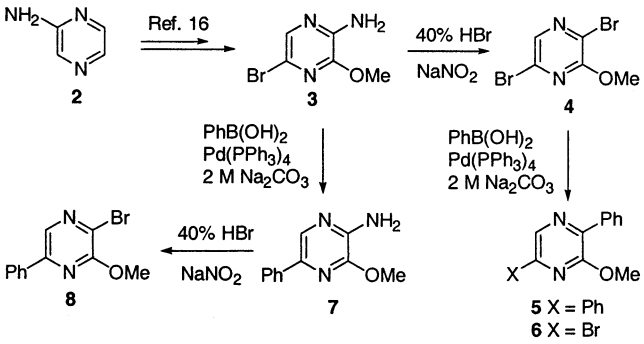


FIGURE 1. Retrosynthetic approach.

SCHEME 1. Synthesis of Bromide Pyrazine



The use of palladium complex chemistry has been extensively explored for the synthesis and functionalization of indoles.[14] Retrosynthetically, the functional bis(indole) pyrazine **1** was envisioned to arise by a stepwise, regioselective introduction of the indole fragments **14b** and **14d** to the 2- and 5-positions of the pyrazine **4** by a palladium(0)-catalyzed cross-coupling reaction. The synthetic route we were looking for had to fulfill the requirement of special regioselectivity. As illustrated in Figure 1, one of the partners, dibromopyrazine **4**, could be easily prepared from the commercially available 2-aminopyrazine **2**. The indole building blocks **14b** and **14d** could be readily obtained from the corresponding indoles **12b** and **12c** according to a known procedure.[15] 4,7-Disubstituted indole **12c** was easily available from *m*-cresol according to our prior report.[13]

As shown in Scheme 1, the synthesis was started with 2-amino-5-bromo-3-methoxylpyrazine **3** prepared from commercially available 2-aminopyrazine **2** as described in the literature.[16] Then the diazotization of compound **3** afforded intermediate diazonium compound which was converted to the corresponding bromo analogue directly to give the desired fragment 2,5-dibromo-3-methoxylpyrazine **4** in moderate yield.[17]

To evaluate the reaction scope of dibromopyrazine **4**, both the reactivity and the regioselectivity of Suzuki chemistry were first investigated. Thus, treatment of **4** with an excess of phenylboronic acid and 10 mol % of tetrakis(triphenylphosphine)palladium in the presence of aqueous sodium carbonate in refluxing benzene−methanol under argon atmosphere for 4 h produced the corresponding diphenylpyrazine **5** in 94% yield. As expected, treatment of compound **4** with an equivalent amount of phenylboronic acid under the above condition solely yielded **6** in high yield. The regioselectivity of the Suzuki cross-coupling reaction was determined by the following procedure. The reaction of monobrominated pyrazine **3** and phenylboronic acid highly afforded compound **7**, which was subjected to the diazotization bromination sequence to give brominated phenylpyrazine **8** in moderate yield. The ^{1}H NMR experiment indicated that compounds **6** and **8** were not the same, which demonstrated that the cross-coupling reaction of dibromopyrazine **4** could be steadily achieved by stepwise and in complete selectivity under the standard Suzuki conditions.

With the desired reactivity and regioselectivity of dibromopyrazine **4** in mind, we then focused our attention on the study of the coupling of **4** with indol-3-ylboronic acid (Scheme 2). Similarly, a high yield of coupling product **10b** was obtained by reaction of *N*-tosyl indol-3-ylboronic acid **9b**[18] and 2,5-dibromo-3-methoxylpyrazine **4**. However, all efforts toward the critical second introduction of the tosyl protective indole unit to the intermediate **10b** failed. Neither treatment of dibromopyrazine **4** with an excess of the electron-deficient indolylboronic acid **9b** directly nor treatment of compound **10b** with another equivalent amount of **9b** gave the desired bis(indole) pyrazine. No improvement was obtained by employing a stronger base such as $Ba(OH)_2$,[19] or a higher reaction temperature, or a more active palladium catalyst bearing the bidentate ligand (dppf),[20] or the recent efficient method developed by Fu.[21] On the other hand, coupling of bromide indolylpyrazine **10b** with phenylboronic acid under the above Suzuki condition afforded the desired product **11** in 80% yield. We then considered the more active indolylboronic acid bearing an electron-donating protective group, and decided to use the *tert*-butyldimethylsilyl (TBDMS) moiety as the protective group. According to the literature reported, the required *N*-(*tert*-butyldimethylsilyl)indol-3-ylboronic acids **14a**−**c** were prepared from the corresponding 3-bromoindoles **13a**−**c** by halogen−metal exchange with *t*-BuLi at −78 °C, followed by transmetalation of the

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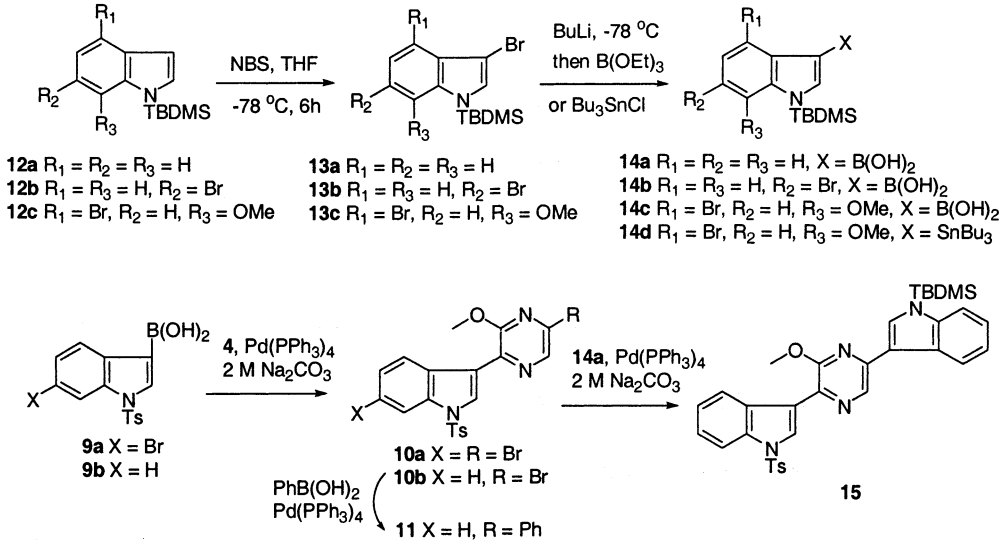
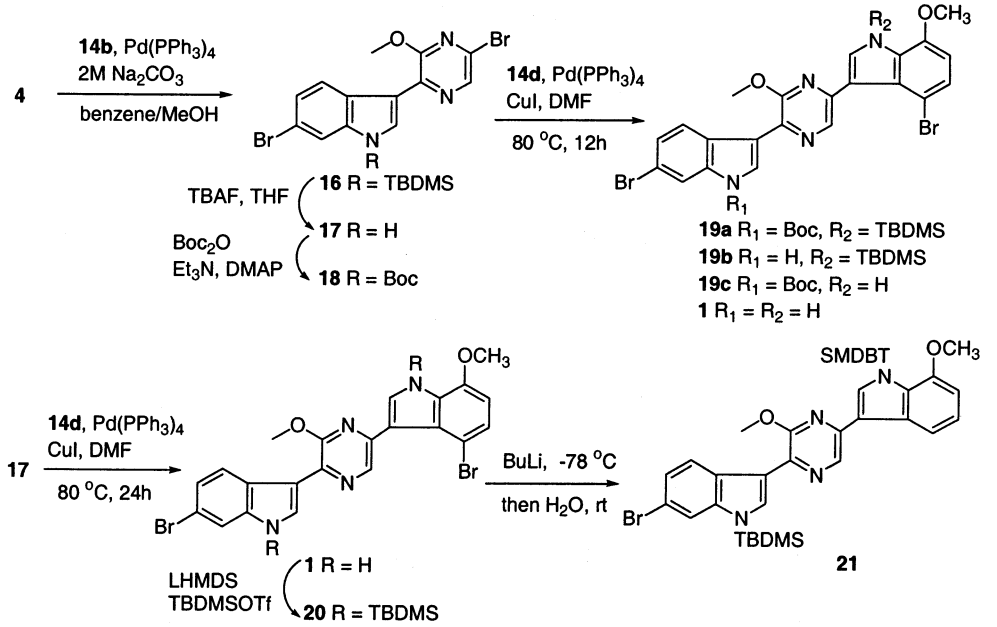
SCHEME 2. Synthesis of Indole Reagents 14 and Bis(indole) Pyrazine 15



SCHEME 3. Synthesis of Compound 1



resulting 3-lithioindole with $B(OEt)_3$.[15] It was noteworthy that BuLi achieved highly selective lithiation of the substituted 3-bromoindoles **13a**−**c** to give the corresponding 3-lithioindole as the single product instead of *t*-BuLi. With the electron-rich indol-3-ylboronic acids **14a**−**c** prepared by using the modified procedure in hand, we then examined the coupling of bromide indolylpyrazine **10b** with indolylboronic acid **14a** under the above Suzuki condition. Gratifyingly, the desired cross-coupling product **15** was readily obtained in 80% yield. Moreover, the electronic effect of the two indoles induced by protective groups would lead to the expected selectivity toward the assembly of the 2-aminoimidazole segment on the indole ring. This might provide a possible strategy to accomplish the final total synthesis.

After successfully constructing the bis(indole) pyrazine, we then started the synthetic study to the skeleton of dragmacidin D with properly substituted groups. Apparently, the introduction of the 6-bromoindole building block with an electron-withdrawing protective group such as Ts or Boc to the C-2 position of the dibromopyrazine **4** and then the 4,7-disubstituted indole unit with an electron-donating protective group such as TBDMS to the C-5 position of **4** sequentially finished the regioselective synthesis of the target molecule **1**. The coupling of *N*-tosyl-6-bromoindol-3-ylboronic acid **9a**[18] and dibromopyrazine **4** gave a very low yield of **10a** due to the less reactive indolylboronic acid **9a** (Scheme 2). Consequently, as illustrated in Scheme 3, the coupling of the more active boronic acid **14b** with dibromopyrazine **4** produced the expected 3-pyrazinylindole **16** in good yield. Considering that the different electronic effect of the protective group on the indole rings would be helpful for the final total synthesis of natural product, we decided to change the TBDMS protective group in **16** to an electron-withdrawing group such as Boc. The removal of the silyl moiety

from **16** was accomplished with tetrabutylammonium fluoride in THF at room temperature to give 3-pyrazinylindole **17** in over 95% yield.[22] Then indole **17** was readily protected by treatment with Boc_2O in the presence of DMAP as a catalyst to provide compound **18** in 96% yield.[23] Unfortunately, the introduction of the 4,7-disubstituted indole building block to **18** was unsuccessful under Suzuki conditions, because the 4,7-disubstituted indolylboronic acid **14c** was very unstable and easily converted to the corresponding indole **12c**. For this reason, it was necessary to study the tin-based palladium(0)-catalyzed coupling process as a route to the introduction of the 4,7-disubstituted indole unit.[24] Therefore, the required 3-tributylstannylindole **14d** was prepared by reaction of the 3-lithioindole derivative with tributyltin chloride. Stille coupling of the crude 3-tributylstannylindole **14d** with 3-pyrazinylindole **18** in the presence of a cocatalyst of tetrakis(triphenylphosphine)-palladium and copper(I) iodide in heating DMF for 12 h resulted in four partially deprotected products **19a**−**c** and **1** in 61% total yield along with unconverted starting material **18**.[25] This indicated that both the Boc and the TBDMS protective groups on the indole rings were unstable under Stille conditions due to the basic property.

We had to give up the protective group strategy and turned to the construction of the skeleton of dragmacidin D first. After the Stille coupling time was prolonged to 24 h, the properly substituted bis(indolyl) pyrazine **1** was available as a single product in 92% yield from the reaction of compound **17** with **14d**. Next, we examined the possibility of the introduction of the 2-aminoimidazole segment at the C-4″ position of the disubstituted indole ring in compound **1**. Total silylation of **1** by treatment with TBDMS triflate in the presence of LHMDS yielded the required **20** in high yield.[26] To our delight, the lithiation of **20** with BuLi occurred regioselectively to give the expected compound **21** as a single product in 70% isolated yield.

In summary, the above reaction sequence provided at least two places where we could plan to bring in the 2-aminoimidazole chain in order to accomplish a total synthesis. One would be the coupling of intermediate **17** with a proper indole building block bearing an alkyl substitution at the 4-position, the other would be at the 4″-position in fragment **20**. The strategy developed here to build the skeleton of dragmacidin D by critically selective introduction of two indole units, using Suzuki and Stille cross-coupling reactions sequentially, combined with the flexible route for the preparation of the 2-aminoimidazole segment may be applicable to the final asymmetric total synthesis of bis(indole) marine alkaloid dragmacidin D.

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Experimental Section

General Procedure.[27] The assignment of compound **1** was supported by an X-ray crystallographic structure determination.

2,5-Dibromo-3-methoxylpyrazine (4). A mixture of 2-amino-5-bromo-3-methoxylpyrazine **3** (1.02 g, 5 mmol) in 20 mL of 40% hydrobromic acid was stirred at room temperature for 1 h. Under cooling in a brine-ice bath, to this mixture was added 4 mL of water containing $NaNO_2$ (1.04 g, 15 mmol). The addition was completed within 20 min with continuous stirring. The whole was slowly allowed to reach room temperature, left standing for 1 h at 50 °C, and partially neutralized with saturated sodium bicarbonate solution. The resulting solution was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine successively, dried (Na_2SO_4), and concentrated under vacuum. Purification by flash chromatography (silica, hexane/AcOEt 20:1) gave compound **4** (648 mg, 54%) as a light yellow solid. Mp 122−123 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.08 (s, 3H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 138.0, 135.1, 127.7, 56.0; EIMS *m*/*z* (%) 268 (M^+, 100), 267/269 (38), 266/270 (55). Anal. Calcd for $C_5H_4Br_2N_2O$: C, 22.39; H, 1.49; N, 10.45. Found: C, 22.64; H, 1.58; N, 10.69.

General Procedure: Palladium(0)-Catalyzed Suzuki Coupling Reaction of Bromopyrazine with Indol-3-ylboronic Acid. A mixture of indol-3-ylboronic acid, bromopyrazine, aqueous sodium carbonate (2 M), and tetrakis-(triphenylphosphine)palladium (10 mol %) in benzene and methanol (v/v 4:1) was refluxed under an argon atmosphere. The reaction was monitored with TLC. When the reaction was completed, anhydrous sodium sulfate was added. The mixture was filtered and the filtrate was evaporated under vacuum. The residue was subjected to flash column chromatography (eluted with ethyl acetate/hexane) to give cross-coupling products.

5-Bromo-3-methoxyl-2-(*N*-tosylindol-3-yl)pyrazine (10b). Pyrazine **10b** (390 mg, 85%) was obtained as a white solid from **4** (268 mg, 1.0 mmol), **9b** (380 mg, 1.2 mmol), aqueous sodium carbonate (1.0 mL, 2 M), and tetrakis(triphenylphosphine)-palladium (116 mg, 0.1 mmol) by the general procedure with chromatography. Mp 201−202 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 4.20 (s, 3H), 7.23 (d, J = 8.4 Hz, 2H), 7.35 (m, 2H), 7.82 (d, J = 8.4 Hz, 2H), 8.01 (m, 1H), 8.35 (s, 1H), 8.50 (s, 1H), 8.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 145.3, 137.2, 134.9, 134.8, 132.1, 130.0, 129.1, 129.0, 126.9, 125.3, 124.0, 123.6, 115.9, 113.2, 55.0, 21.6; EIMS *m*/*z* (%) 457/459 (M^+, 34), 302/304 (100); HRMS calcd for $C_{20}H_{16}BrN_3O_3S$ 457.0097, found 457.0099.

3-Methoxyl-5-phenyl-2-(*N*-tosylindol-3-yl)pyrazine (11). **11** (71 mg, 80%) was obtained as a yellow solid from **10b** (92 mg, 0.2 mmol), phenylboronic acid (31 mg, 0.25 mmol), aqueous sodium carbonate (0.3 mL, 2 M), and tetrakis(triphenylphosphine)palladium (25 mg, 0.025 mmol) by the general procedure with chromatography. Mp 147−149 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 4.25 (s, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.32−7.50 (m, 5H), 7.82 (d, J = 8.2 Hz, 2H), 8.03 (dd, J = 7.2 and 1.5 Hz, 1H), 8.08 (d, J = 7.2 Hz, 2H), 8.56 (s, 1H), 8.76 (s, 1H), 8.77 (dd, J = 7.0 and 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 145.5, 145.2, 137.2, 136.3, 135.2, 135.0, 132.2, 130.0, 129.5, 129.4, 128.9, 128.8, 127.0, 126.6, 125.1, 124.0, 123.9, 117.0, 113.3, 53.8, 21.6; EIMS *m*/*z* (%) 455 (M^+, 84), 300 (100). Anal. Calcd for $C_{26}H_{21}N_3O_3S$: C, 68.57; H, 4.62; N, 9.23. Found: C, 68.26; H, 4.86; N, 8.97.

***N-tert*-Butyldimethylsilyl-3,4-dibromo-7-methoxylindole (13c).** Under a dry ice-acetone bath, freshly recrystallized NBS (660 mg, 3.7 mmol) was added to a solution of 4-bromo-7-methoxylindole **12c** (1.2 g, 3.53 mmol) in anhydrous THF (15 mL). The mixture was stirred for 6 h at this temperature, allowed to warm to room temperature, and

(27) For detailed information, see: Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865.

diluted with ether. The organic phase was washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (silica, hexane) afforded compound **13c** (980 mg, 66%). Mp 123−125 °C (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 3.87 (s, 3H), 0.87 (s, 9H), 0.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 133.5, 131.5, 127.3, 125.7, 104.2, 103.5, 92.6, 54.3, 26.7, 19.6, −1.3; EIMS m/z (%) 419 (M^+, 55), 417/421 (M^+, 28), 347 (100); HRMS calcd for $C_{15}H_{21}Br_2NOSi$ 416.9761, found 416.9760.

3-Methoxyl-2-(*N*-tosylindol-3-yl)-5-(*N*-*tert*-butyldimethylsilylindol-3-yl)pyrazine (15). 15 (98 mg, 80%) was obtained as a yellow solid from **10b** (92 mg, 0.2 mmol), **14a** (70 mg, 0.25 mmol), aqueous sodium carbonate (0.3 mL, 2 M), and tetrakis(triphenylphosphine)palladium (25 mg, 0.025 mmol) by the general procedure with chromatography. Mp 220−222 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 6H), 0.98 (s, 9H), 2.30 (s, 3H), 4.32 (s, 3H), 7.20 (d, J = 8.2 Hz, 2H), 7.24−7.38 (m, 4H), 7.56 (m, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.82 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 8.50 (m, 1H), 8.52 (s, 1H), 8.72 (s, 1H), 8.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 145.0, 144.6, 142.2, 135.2, 135.0, 134.2, 132.0, 131.3, 129.9, 129.7, 128.7, 127.9, 126.9, 124.9, 123.8, 123.7, 122.4, 121.5, 121.1, 117.4, 116.2, 114.3, 113.2, 53.9, 26.3, 21.5, 19.3, −3.4; EIMS m/z (%) 608 (M^+, 30). Anal. Calcd for $C_{34}H_{36}N_4O_3SSi$: C, 67.10; H, 5.92; N, 9.21. Found: C, 67.11; H, 6.11; N, 8.97.

5-Bromo-3-methoxyl-2-(*N*-*tert*-butyldimethylsilyl-6-bromoindol-3-yl)pyrazine (16). Pyrazine **16** (466 mg, 52%) was obtained as a white solid from **4** (536 mg, 2.0 mmol), crude **14b** (890 mg, 2.5 mmol), aqueous sodium carbonate (2.0 mL, 2 M), and tetrakis(triphenylphosphine)palladium (232 mg, 0.2 mmol) by the general procedure with chromatography. Mp 207−208 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 6H), 0.98 (s, 9H), 4.14 (s, 3H), 7.35 (dd, J = 8.6 and 1.2 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 8.11 (s, 1H), 8.32 (s, 1H), 8.56 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 142.3, 139.0, 137.2, 135.8, 130.0, 128.4, 124.5, 124.1, 116.7, 113.1, 54.7, 26.3, 19.4, −3.8; EIMS m/z (%) 497 (M^+, 100), 495/499 (53). Anal. Calcd for $C_{19}H_{23}Br_2N_3OSi$: C, 45.88; H, 4.63; N, 8.45. Found: C, 46.21; H, 4.68; N, 8.27.

5-Bromo-3-methoxyl-2-(6-bromoindol-3-yl)pyrazine (17). To a solution of compound **16** (398 mg, 0.8 mmol) in THF (15 mL) was added tetrabutylammonium fluoride (1 M in THF, 2.0 mL, 2.0 mmol). After the mixture was stirred for 1 h at ambient temperature, water was added to quench the reaction and the resulting mixture was extracted with ether. The organic phase was dried over sodium sulfate and concentrated under vacuum. Purification by flash chromatography (silica, hexane/AcOEt 2:1) afforded compound **17** (292 mg, 95%). Mp 219−220 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.09 (s, 3H), 7.29 (dd, J = 8.6 and 1.6 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 8.40 (s, 1H), 8.50 (d, J = 8.6 Hz, 1H), 11.83 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0, 139.2, 137.3, 136.5, 130.7, 128.7, 124.8, 124.0, 123.3, 115.0, 114.4, 109.3, 54.6; EIMS m/z (%) 383 (M^+, 100), 381/385 (M^+, 51). Anal. Calcd for $C_{13}H_9Br_2N_3O$: C, 40.73; H, 2.35; N, 10.97. Found: C, 41.01; H, 2.38; N, 10.93.

3-Methoxyl-2-(6-bromoindol-3-yl)-5-(4-bromo-7-methoxylindol-3-yl)pyrazine (1). A mixture of compound **17** (308 mg, 0.80 mmol), crude 3-tributylstannylindole **14d** (480 mg, 0.95 mmol), tetrakis(triphenylphosphine)palladium (116 mg, 0.1 mmol), and copper(I) iodide (30 mg) in DMF (5 mL) was heated (80−90 °C of the bath) and stirred for 24 h. After the mixture was cooled to room temperature, the system was diluted with the addition of AcOEt and washed with saturated aqueous potassium fluoride. The organic phase was washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (silica, eluted with ethyl acetate/hexane) afforded compound **1** (386 mg, 92%) as a yellow solid. Mp 230−232 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.01 (s, 3H), 4.18 (s, 3H), 6.75 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5 and 1.7 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 8.37 (d, J = 2.6 Hz, 1H), 8.47 (s, 1H), 8.70 (d, J = 8.4 Hz, 1H), 11.79 (br s, 1H), 12.06 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.4, 146.1, 140.9, 137.3, 137.2, 136.0, 129.8, 127.8, 127.6, 125.1, 124.3, 123.0, 114.8, 114.4, 114.3, 110.4, 103.9, 103.5, 55.6, 53.6; EIMS m/z (%) 529 (M^+, 100); HRMS calcd for $C_{22}H_{16}Br_2N_4O_2$ 525.9643, found 525.9646.

3-Methoxyl-2-(*N*-*tert*-butyldimethylsilyl-6-bromoindol-3-yl)-5-(*N*-*tert*-butyldimethylsilyl-4-bromo-7-methoxylindol-3-yl)pyrazine (20). To a solution of compound **1** (280 mg, 0.53 mmol) was added dropwise LHMDS (1 M, 1.8 mL, 1.8 mmol) under cooling in a dry ice−acetone bath. After this mixture was stirred for 10 min at this temperature, TBDMS triflate (0.47 mL, 2.5 mmol) was added to the reaction, and then the reaction system was allowed to reach room temperature. Two hours later, a buffer solution (pH 7) was added to the mixture and the mixture was extracted with ether. The organic layer was successively washed with 1 N aqueous hydrochloric acid, saturated sodium bicarbonate, and brine, and then dried over sodium sulfate and concentrated under vacuum. Purification by flash chromatography (silica, hexane) afforded **20** (350 mg, 88%) as a spumy solid. Mp 204−205 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.59 (s, 6H), 0.70 (s, 6H), 0.96 (s, 9H), 1.00 (s, 9H), 3.93 (s, 3H), 4.20 (s, 3H), 6.58 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.5 and 1.5 Hz, 1H), 7.46 (s, 1H), 7.68 (d, J = 1.5 Hz, 1H), 8.20 (s, 1H), 8.44 (s, 1H), 8.72 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 146.8, 142.3, 141.5, 137.7, 136.7, 135.3, 134.3, 132.5, 129.5, 128.8, 125.5, 124.2, 124.0, 117.6, 116.5, 115.7, 114.1, 104.9, 103.4, 54.3, 53.7, 26.8, 26.3, 19.6, 19.3, −1.3, −3.9; EIMS m/z (%) 756 (M^+, 22); HRMS calcd for $C_{34}H_{44}Br_2N_4O_2Si_2$ 754.1353, found 754.1336.

3-Methoxyl-2-(*N*-*tert*-butyldimethylsilyl-6-bromoindol-3-yl)-5-(*N*-*tert*-butyldimethylsilyl-7-methoxylindol-3-yl)pyrazine (21). To a solution of compound **20** (113 mg, 0.15 mmol) in dry THF (1 mL) was added dropwise BuLi (2 M, 80 μL, 0.16 mmol) at −78 °C. After continuous stirring for 30 min at this temperature, saturated ammonium chloride was added to quench the reaction. The mixture was diluted with ether, and the organic phase was washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (silica, hexane) gave compound **21** (70 mg, 70%) as a white solid. Mp 228−229 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.64 (s, 6H), 0.69 (s, 6H), 0.95 (s, 9H), 0.99 (s, 9H), 3.94 (s, 3H), 4.26 (s, 3H), 6.73 (d, J = 8.5 Hz, 1H), 7.21 (m, 1H), 7.35 (dd, J = 8.6 and 1.7 Hz, 1H), 7.66 (d, J = 1.4 Hz, 1H), 7.85 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.13 (s, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 147.2, 142.9, 142.3, 136.1, 134.6, 132.0, 130.8, 128.8, 124.2, 123.9, 121.7, 116.5, 116.3, 115.7, 114.3, 113.9, 102.7, 54.0, 53.6, 26.8, 26.3, 19.5, 19.3, −1.4, −3.9; EIMS m/z (%) 676 (M^+, 16), 531 (14); HRMS calcd for $C_{34}H_{45}BrN_4O_2Si_2$ 676.2288, found 676.2311.

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Supporting Information Available: X-ray analyst of compound **1**; experimental procedure and characterization data for compounds **5**−**8**, **10a**, **13a**−**b**, **14a**−**d**, **18**, **19b**; copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **10b**, **11**, **15**−**17**, **1**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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