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The formal total synthesis of dragmacidin B, *trans*-dragmacidin C, and *cis*- and *trans*-dihydrohamacanthins A

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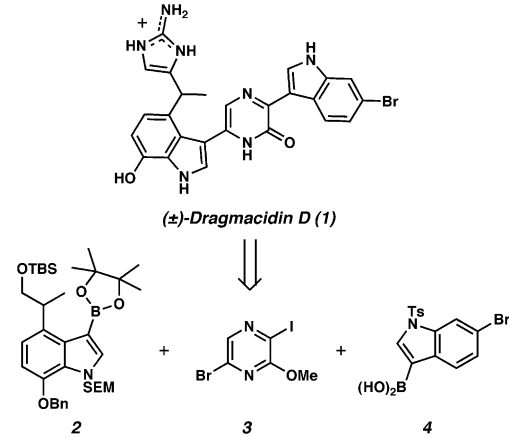
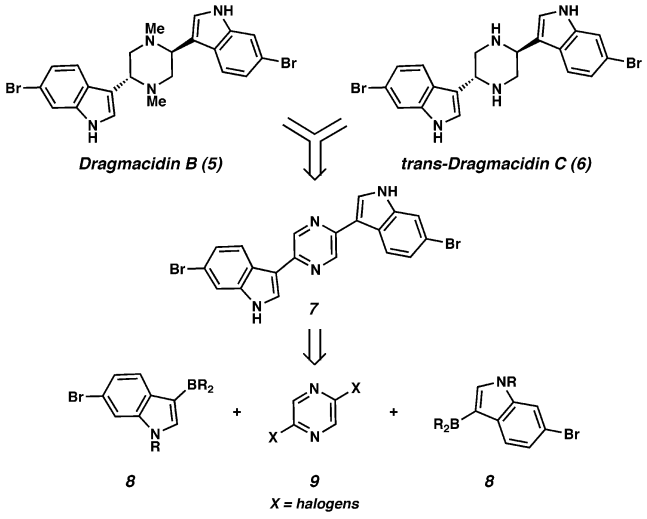
Abstract—A facile formal total synthesis of dragmacidin B, *trans*-dragmacidin C, and *cis*- and *trans*-dihydrohamacanthins A is presented. Our approach to these bis(indole) alkaloids involves a one-pot, four-step cross-coupling/deprotection sequence where complete halogen selectivity is observed. A related approach to access the dihydrohamacanthins is also described.

Over the past several decades, biologically active natural products isolated from marine organisms have served as promising leads in the area of drug discovery.[1] The dragmacidin family of bis(indole) alkaloids represents an emerging class of cytotoxic natural products obtained from deep-water marine sponges.[2] In 2002, we described the total synthesis of dragmacidin D (**1**, Scheme 1).[3] Our route to **1** featured a series of thermally controlled, halogen-selective Suzuki cross-couplings of **2**, **3**, and **4** to construct the bis(indole)pyrazine framework of the natural product. Importantly, the 6-bromoindole moiety could be maintained throughout these reactions. Herein, we report an extension of this approach to achieve the formal total synthesis of several related bis(indole) alkaloids.



Scheme 1.

A retrosynthetic strategy for the preparation of dragmacidin B (**5**) and *trans*-dragmacidin C (**6**) is shown below in Scheme 2. Based on conditions reported by Horne, each of the bis(indole) alkaloids can be accessed from unsaturated derivative **7** in a single step.[4] Pyrazine **7**,



Scheme 2.

Keywords: Suzuki; Heterocycles; Bis(indole); Dragmacidin; Palladium.
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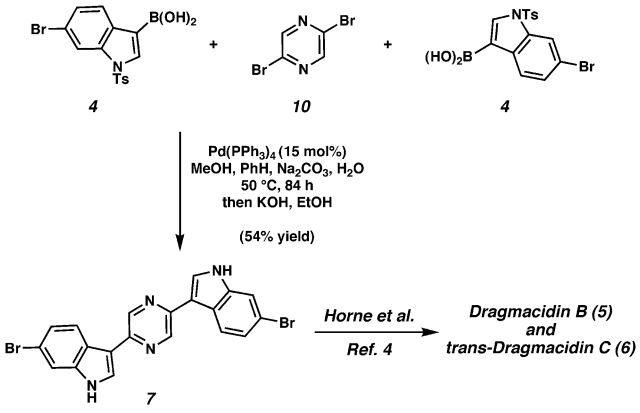
in turn, would be obtained from two halogen-selective Suzuki cross-coupling reactions of boronic acid **8** with a dihalogenated pyrazine (**9**). We anticipated that the boronic acid fragment employed in our synthesis of dragmacidin D (i.e., **4**) could be utilized as a surrogate for **8** in order to achieve our current goals. However, the success of our plan would depend highly on the choice of halogens for pyrazine **9**.

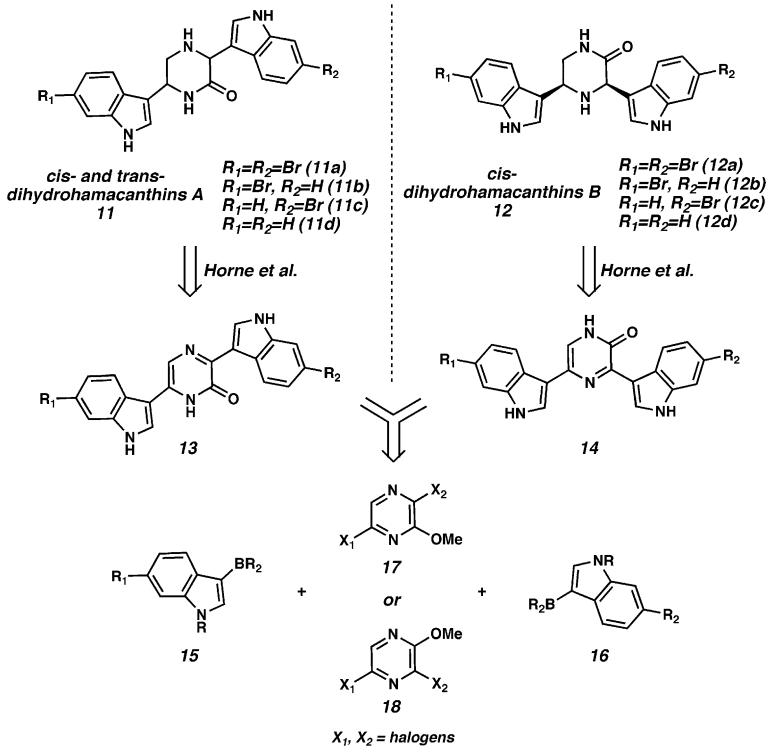
In order to probe the limits of our halogen-selective Suzuki cross-coupling methodology, we chose to use known dibromide **10**[5] as the critical pyrazine fragment (Scheme 3). In a one-pot, four-step transformation, an excess of 6-bromoindoloboronic acid (**4**) was exposed to dibromopyrazine **10** under our standard cross-coupling conditions. Following quenching with KOH/ethanol, the deprotected pyrazine product (**7**) was obtained in 54% yield.[6] Notably, although four bromides were introduced in the reaction mixture, only the two pyrazinyl bromides were reactive in the presence of Pd(0) at 50 °C. This rapid synthesis of bis(indole) pyrazine **7** constitutes a formal total synthesis of both dragmacidin B (**5**) and *trans*-dragmacidin C (**6**).[4,7,8]



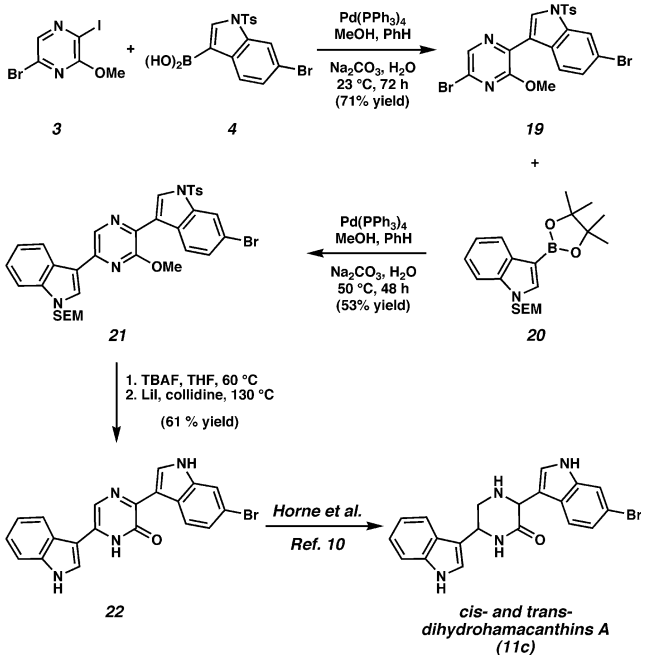
Scheme 3.

These halogen-selective Suzuki couplings also have great potential for assembling a related family of natural products, the dihydrohamacanthins (Scheme 4).[9] In this scenario, the desired alkaloids (**11** and **12**) would be obtained from their pyrazinone counterparts (**13** and **14**), using the method established by Horne and co-workers.[10] Intermediates **13** and **14**, in turn, would arise via cross-coupling chemistry using indole fragments **15** and **16**, as well as pyrazine fragments **17** and **18**, in a manner similar to that describe above. Halogen-selective cross-couplings will be crucial to prepare all of the halogenation patterns present in this series of natural products (**11a–d**, **12a–d**).

To demonstrate the feasibility of this approach, we prepared one of the dihydrohamacanthin natural products (**11c**, Scheme 5). In the first Suzuki coupling, dihalopyrazine **3** and bromoindole **4** were treated with Pd(0) at 23 °C to afford coupled indolopyrazine **19**.[3] Dibromide **19**, in turn, was subjected to boronic ester **20** in the presence of Pd(0) at 50 °C to produce bis(indole)pyrazine **21** in 53% yield. In both cases, complete halogen-selectivity was observed. Subsequent removal of all protecting groups furnished pyrazinone **22**,[11] which has previously



Scheme 4.



Scheme 5.

been converted to the natural product (**11c**) in a single step.[10,12]

In summary, we have completed the formal total synthesis of dragmacidin B and *trans*-dragmacidin C. Our route features a one-pot, four-step halogen-selective cross-coupling/deprotection sequence to construct the bis(indole) scaffold of our targets. In addition, we have applied this methodology to the formal synthesis of a dihydrohamacanthin natural product.

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6. A vial charged with dibromopyrazine **10** (15.1 mg, 0.0635 mmol), boronic acid **4** (75 mg, 0.190 mmol), and tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.0095 mmol), was evacuated and purged with N_2. Deoxygenated benzene (1.2 mL), deoxygenated methanol (250 μL), and deoxygenated 2 M aq Na_2CO_3 (105 μL) were then added. The reaction mixture was sparged with argon for 3 min. The vial was then sealed, heated to 50 °C for 84 h, and cooled to 23 °C. EtOH (7 mL) and KOH (500 mg) were added. The reaction mixture was heated to 50 °C for 20 h, cooled to 23 °C, then quenched by pouring into 10% (w/v) aq citric acid (20 mL). EtOAc (30 mL) was added, and the layers were partitioned. The aqueous phase was further extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:1 CH_2Cl_2/MeOH eluent), then further purified by preparative thin layer chromatography (2:1 EtOAc/hexanes eluent) to afford known bis(indole) **7**[4] (16 mg, 54% yield) as a yellow powder.
7. Treatment of **7** with $NaBH_3CN$ in formic acid leads to the formation of dragmacidin B (**5**), while the analogous reaction conducted in acetic acid results in production of *trans*-dragmacidin C (**6**)[4].
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11. A reaction tube charged with indolopyrazine **19** (125 mg, 0.335 mmol), boronic ester **20** (90 mg, 0.168 mmol), and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.030 mmol), was evacuated and purged with N_2. Deoxygenated benzene (3.5 mL), deoxygenated methanol (690 μL), and deoxygenated 2 M aq Na_2CO_3 (180 μL) were then added. The reaction mixture was sparged with argon for 2 min. The tube was then sealed, heated to 50 °C for 48 h, cooled to 23 °C, and quenched by the addition of Na_2SO_4 (200 mg). The reaction mixture was filtered over a plug of SiO_2 (CH_2Cl_2 eluent) and the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 CH_2Cl_2/hexanes eluent), to afford bis(indole) **21** (62 mg, 53% yield), which was used immediately in the subsequent reaction. Bis(indole) **21** (30 mg, 0.043 mmol) was dissolved in 1.0 M TBAF in THF (1 mL, 1 mmol) and heated to 65 °C for 16 h. After cooling to 23 °C, the solvent was removed under reduced pressure and CH_2Cl_2 (5 mL) was added. The organic layer was washed with H_2O (2 × 1 mL) and brine (1 mL), concentrated to dryness, then purified by flash chromatography (CH_2Cl_2 eluent) to give the intermediate bis-*N*-deprotected product (16 mg, 89% yield). A mixture of this intermediate (1.5 mg, 0.0034 mmol), LiI (100 mg, 0.75 mmol), and collidine (1 mL) was heated to

130 °C for 4 days. After cooling to 23 °C, the reaction mixture was diluted with EtOAc (5 mL), washed with H_2O (3×5 mL), and brine (2 mL), then dried by passage over a plug of SiO_2 (EtOAc eluent). The solvent was removed under reduced pressure to afford known pyrazone **22**[10] (1.0 mg, 69% yield).

12. Reduction of **22** with $NaBH_3CN$ leads to the production of a **11c**.