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Synthetic studies on dragmacidin D: synthesis of the left-hand fragment

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ABSTRACT

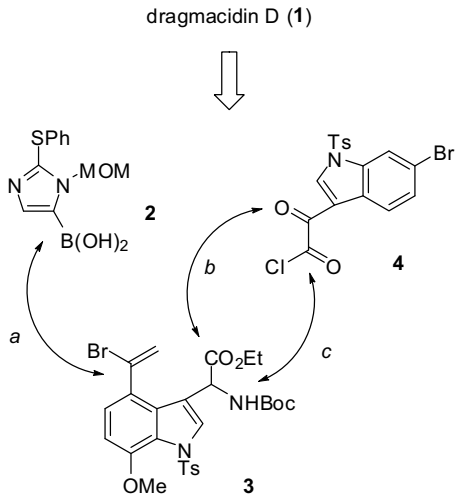
We report a synthesis of a left-hand fragment of bis(indole)-class marine alkaloid, dragmacidin D. The synthesis features Suzuki–Miyaura reaction for the coupling of imidazolyl boronic acid and (4-indolyl)vinyl bromide.

Dragmacidin D (**1**) is a bis(indole) alkaloid, isolated first from a deep-water marine sponge of the genus *Spongosorites* by Wright et al. in 1992.[1] With other dragmacidins,[2,3] **1** receives considerable attention because of the diverse biological spectrum of activities such as potent inhibition of serine-threonine protein phosphatases (PP1)[3] and brain nitric oxide synthase (bNOS)[4] (Fig. 1).

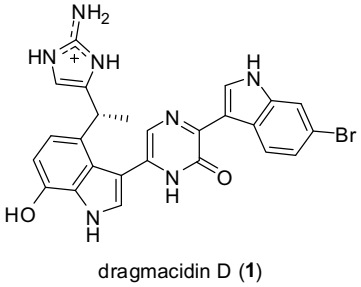
Structurally, dragmacidin D (**1**) contains two indoles with pyrazinone spacer between them. Among dragmacidin family, the characteristic features of **1** are the presence of guanidine functionality and a stereogenic center at a benzylic position.

As for the chemical synthesis of **1**, Jiang and co-workers have reported some synthetic studies,[5,6] and Stoltz's group has accomplished the first total synthesis in 2002.[7] Prompted by the intriguing biological activities, we also started our own program directed toward the total synthesis of **1**, aiming for the development of a route amenable to the analogue preparation.

Our synthetic strategy is shown in Scheme 1. Three advanced intermediates **2**–**4** have retrosynthetically emerged as key fragments, which would be assembled sequentially. It should be emphasized here that the intermediates **2**–**4** may have structural variants as branching points for diverted synthesis of analogues.[8] Coupling reaction of the intermediates **2** and **3** is of significance, since Suzuki–Miyaura reaction[9] between imidazolyl boronic acid and vinyl bromide (arrow *a*) was planned to be used for this purpose.[10] As shown by arrows *b* and *c*, it was envisioned that the central pyrazinone ring would be constructed by successive reactions between indole side chains.[11] In this Letter, we report syntheses and coupling of fragments **2** and **3** toward the suitably protected left-hand fragment **17**.



Scheme 1. Synthetic plan for dragmacidin D (**1**) amenable to analogue synthesis.



dragmacidin D (**1**)

Figure 1. Structure of dragmacidin D (**1**).

Synthesis of imidazolyl boronic acid fragment **2** is shown in Scheme 2. Here, imidazole derivative **5**, prepared from imidazole in two steps (MOM protection and SPh group introduction),[12] was used as a starting material. Deprotonation of **5** followed by the addition of trimethyl borate gave the boronic acid **2** after acidic work-up. The reaction was highly regioselective,[13] giving rise to the desired **2** as a sole product in 50% yield.

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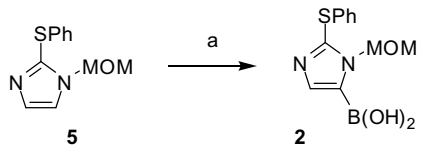
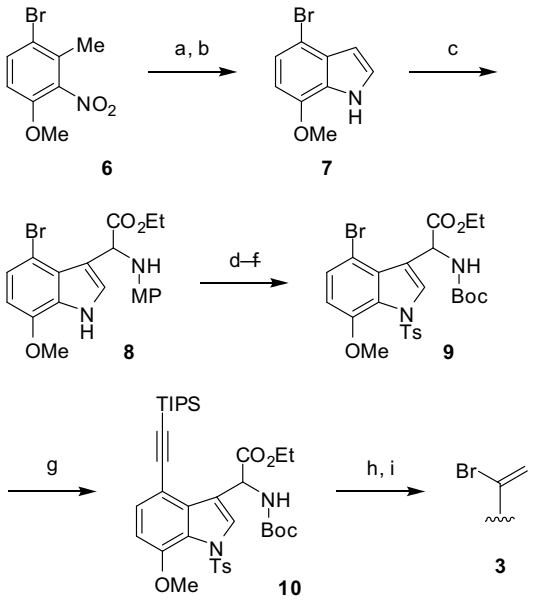


Scheme 2. Synthesis of the imidazolyl boronic acid fragment **2**. Reagents and conditions: (a) *n*-BuLi, $B(OMe)_3$, THF, −78 °C rt, 1.5 h, then hydrochloric acid (1 M), 50%; MOM = methoxymethyl.

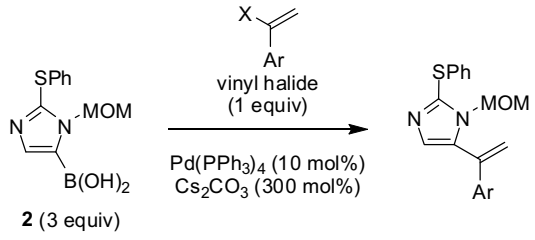
4-Bromo-7-methoxy-1*H*-indole (**7**), used for the synthesis of indole fragment **3**, was prepared in 73% by Batcho–Leimgruber indole synthesis[14] with slight modification of a reported procedure[6] using zinc metal in AcOH, in place of Raney-Ni and hydrazine (Scheme 3). The amino ester side chain was introduced to **7** by three-component, Mannich-type Friedel–Crafts reaction in the presence of $MgSO_4$ to provide **8** in 76% yield.[15] Protecting group manipulation was then carried out on **8** (*N*-tosylation, MP-deprotection, and *N*-Boc formation) to give **9** in 22% overall yield. For the preparation of vinyl halide **3**, acetylene group was initially introduced to **9** employing Sonogashira cross-coupling reaction.[16] Thus, when **9** was reacted with TIPS-acetylene in the presence of $Pd(PPh_3)_4$ (10 mol %), CuI (5 mol %), and triethylamine at 100 °C, **10** was cleanly obtained in 47% yield. Unreacted **9** was recovered in 50% yield and reused. TIPS group of **10** was removed by Bu_4NF (88% yield), and treatment with HBr·AcOH gave the desired indole fragment **3** in 100% yield, ready for coupling with the imidazolyl fragment **2**.

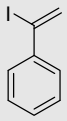
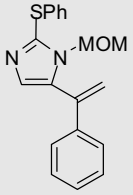
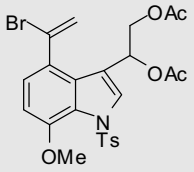
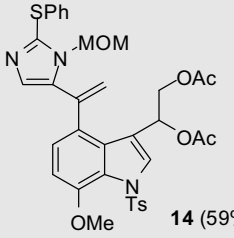
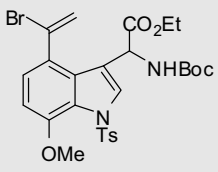
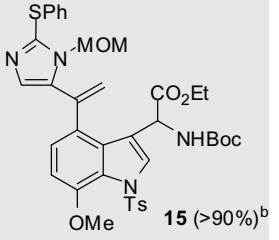
Suzuki–Miyaura cross-coupling reaction[9] of imidazolyl boronic acid **2** with three vinyl halides, including **3**, was next examined (Table 1). Here, 3 equiv of boronic acid **2** was used. As shown in run 1, 1-(1-iodovinyl)benzene (**11**)[17] was employed first under standard conditions ($Pd(PPh_3)_4$, aqueous Cs_2CO_3, THF, rt), and the coupling product **12** was found to be obtained only in unsatisfactory yield (30%). The reaction with (4-indolyl)vinyl bromide **13**, which is analogous to **3** but had been prepared independently,[18] was found to be sluggish at rt. However, at elevated temperature, cross-coupling product **14** was obtained in 59% yield after deacetylation (run 2). Since hydrolytic protodeboronation of **2** was observed as an undesired side reaction in runs 1 and 2, addition of water was supposed to be inconvenient for this coupling. We, therefore, determined to use non-aqueous conditions for the coupling reaction between **2** and **3** in run 3. Thus, when NaOEt (150 mol %)[19] was used in combination with $Pd(PPh_3)_4$ (10 mol %) and Cs_2CO_3 (300 mol %) in 1,4-dioxane at 100 °C, we gratifyingly found that the desired product **15** was obtained in >90% yield from ^1H NMR analysis,[20] and was cleanly isolated in 74% yield after reduction of the ethyl ester (compound **16**, see Scheme 4). As expected, no protodeboronation was observed in this reaction.[10]



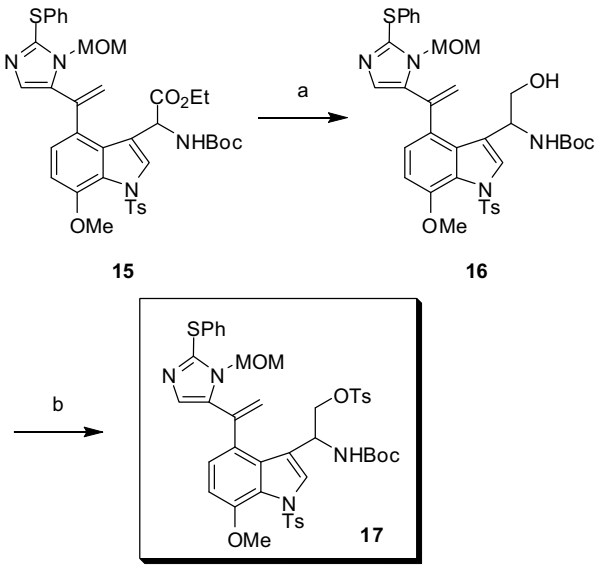
Scheme 3. Synthesis of the (4-indolyl)vinyl bromide fragment **3**. Reagents and conditions: (a) $HC(OMe)_2$–NMe_2, pyrrolidine, DMF, 110 °C, 4.5 h; (b) Zn, AcOH, 85 °C, 1.5 h, 73% (two steps); (c) 4-methoxyaniline, ethyl glyoxalate, $MgSO_4$, CH_2Cl_2, rt, 10 h, 76%; (d) TsCl, triethylamine, 4-dimethylaminopyridine, THF, 65 °C, 24 h, 60%; (e) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, −15 °C, 15 min, 62%; (f) Boc_2O, CH_2Cl_2, rt, 2 h, 60%; (g) (triisopropylsilyl)acetylene, $Pd(PPh_3)_4$ 10 mol %), CuI (5 mol %), 1,4-dioxane/triethylamine (1:1), 100 °C, 10 h, 47% (50% recovery); (h) Bu_4NF, THF, H_2O, 0 °C, 30 min, 88%; (i) HBr·AcOH, THF, 0 °C, 0.5 h, 100%; Boc = *tert*-butoxycarbonyl, MP = 4-methoxyphenyl, TIPS = triisopropylsilyl, Ts = 4-tolylsulfonyl.

Table 1
Suzuki–Miyaura cross-coupling reaction of imidazolyl boronic acid **2** with vinyl halides



Run	Vinyl halide	Additive and reaction conditions	Product (isolated yield)
1	 **11**	THF/H_2O (10:1), rt, 10 h	 **12** (30%)
2	 **13**	1,4-dioxane/ H_2O (10:1), 95 °C, 4 h	 **14** (59%)[a]
3	 **3**	NaOEt (150 mol %), 1,4-dioxane, 100 °C, 2.5 h	 **15** (>90%)[b]

[a] Yield determined after removal of two acetyl groups (K_2CO_3, MeOH, rt).
[b] After reduction of ethyl ester, the cross-coupling product was cleanly isolated in 74% yield (two steps), see text, Ref. 20, and Scheme 4.



Scheme 4. Synthesis of the left-hand fragment of dragmacidin D (**1**). Reagents and conditions: (a) $LiBH_4$, THF, 40 °C, 1 h, 74% (two steps from **3**); (b) TsCl, triethylamine, 4-dimethylaminopyridine, CH_2Cl_2, rt, 1 h, 92%.

Finally, the coupling product **15**, thus obtained successfully, was converted into the left-hand domain of dragmacidin D (**1**). Thus, the ester **15** was reduced with $LiBH_4$, giving rise to alcohol **16** in 74% yield for two steps (from **3**), which in turn was tosylated to provide the desired left-hand fragment **17** in 92% yield, ready for coupling with the second indole fragment **4**.

In summary, we have established the route to two fragments **2** and **3** as advanced intermediates for the diverted synthesis of dragmacidin D (**1**) and analogues. Furthermore, Suzuki–Miyaura reaction for the coupling of these fragments has been successfully demonstrated, leading to the suitably protected left-hand fragment of **1**. Coupling of **17** with the second indole fragment **4** toward the total synthesis is currently underway in our laboratory and will be reported in due course.

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20. The yield was evaluated from ^1H NMR spectrum, since the coupling product **15** was contaminated with small quantities of reactants, which could not be completely removed by chromatographic purification.