

Synthesis of Dragmacidin D via Direct C–H Couplings

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Supporting Information

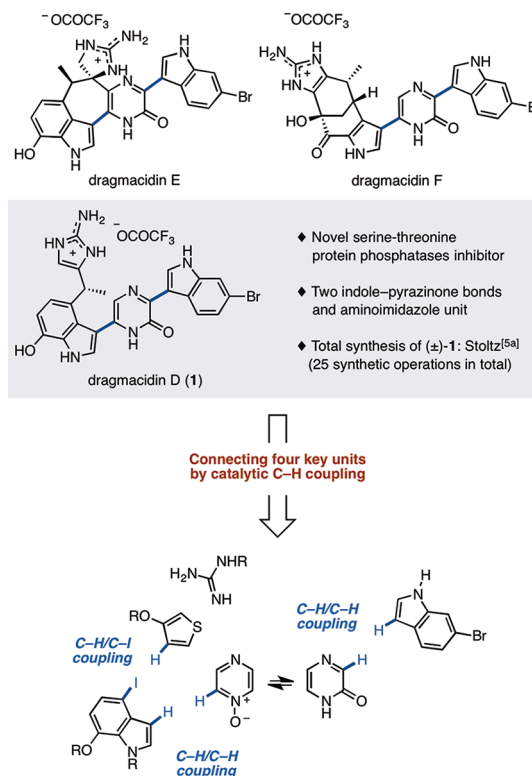
ABSTRACT: Dragmacidin D, an emerging biologically active marine natural product, has attracted attention as a lead compound for treating Parkinson's and Alzheimer's diseases. Prominent structural features of this compound are the two indole–pyrazinone bonds and the presence of a polar aminoimidazole unit. We have established a concise total synthesis of dragmacidin D using direct C–H coupling reactions. Methodological developments include (i) Pd-catalyzed thiophene–indole C–H/C–I coupling, (ii) Pd-catalyzed indole–pyrazine *N*-oxide C–H/C–H coupling, and (iii) acid-catalyzed indole–pyrazinone C–H/C–H coupling. These regioselective catalytic C–H couplings enabled us to rapidly assemble simple building blocks to construct the core structure of dragmacidin D in a step-economical fashion.

The search for natural products in marine and terrestrial environments has led to the discovery of a number of biologically active bis(indole) alkaloids, which include the family of dragmacidins. Dragmacidin D (**1**; Scheme 1), which has been found to serve as a potent inhibitor of serine–threonine protein phosphatases,¹ has received particular attention as a lead compound for treating Parkinson's, Alzheimer's, and Huntington's diseases.^{2,3} In addition to **1**, closely related dragmacidin E and F are also known within this family of natural products.⁴ These compounds exhibit prominent structural features such as two indole–pyrazinone bonds (shown in blue in Scheme 1) and an aminoimidazole moiety. Because of their unique chemical structures and promising biological activities, dragmacidins have been synthetic targets for many chemists.^{5,6} In 2002, Stoltz and co-workers reported the first, and only, synthesis of (±)-**1** using Pd-catalyzed Suzuki–Miyaura cross-coupling as a key reaction.^{5a} Herein, we report a concise total synthesis of **1** utilizing direct C–H couplings as step-economical unit-assembling reactions (Scheme 1).

As exemplified by the work of Stoltz, the cross-coupling reaction is one of the most reliable methods for carbon–carbon bond formations in total synthesis.⁷ However, several steps are required as both of the coupling partners (organometallics and organic halides) must be prefunctionalized prior to cross-coupling. Meanwhile, direct C–H functionalization has garnered significant attention from the synthetic community as an “ideal” method for carbon–carbon and carbon–heteroatom bond formation.^{8,9} Although the development of new reactions and catalysts continues to evolve at a rapid pace, successful applications of this method to the synthesis of complex natural products are still rare.^{10,11} Thus, as a part of our program focusing on synthesis-oriented methodology development in catalytic C–H coupling,¹² we set out to rapidly synthesize **1**.

Our initial blueprint for the synthesis of **1** is shown in Scheme 1. The most direct way to install the two indole moieties

Scheme 1. Dragmacidin D (**1**), E, and F, and Our C–H Coupling Strategy for a Concise Total Synthesis of **1**

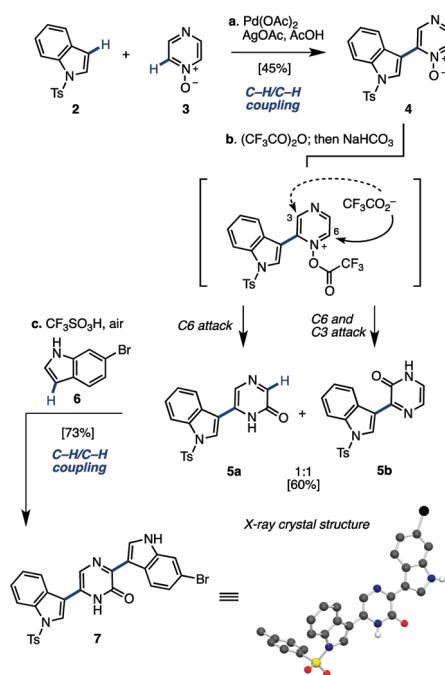


on the pyrazinone core is a C–H/C–H cross-coupling reaction. To enhance reactivity and to control regioselectivity in this coupling, we planned to capitalize on the tautomeric switch between pyrazinone and pyrazine *N*-oxide. Whereas pyrazine *N*-oxide could be coupled with indole at the most acidic carbon α to the N–O moiety using Pd catalysts,¹³ the installation of indole on the opposite carbon could be achieved in the pyrazinone form by way of an oxidative Friedel–Crafts-type reaction. This sequence was designed so that the oxidation state of the central pyrazinone moiety of **1** remains unaltered throughout the synthesis. We also envisioned that a thiophene moiety with an oxygen substituent at C3-position could be utilized as a four-carbon unit of the aminoimidazole side chain of **1**. Thus, an indole–thiophene bond disconnection was conceived, resulting in the necessity of inventing a C4-selective coupling reaction onto such a thiophene ring.

We began our study by investigating two sequential C–H/C–H couplings to access the bis(indolyl)pyrazinone unit using

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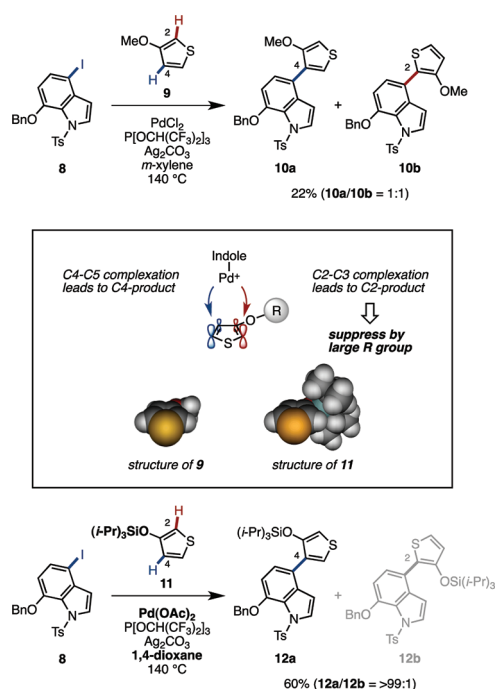
Scheme 2. Construction of Bis(indolyl)pyrazinone Unit via Two Sequential C–H/C–H Couplings^a

^a Reagents and conditions: (a) **2** (1.0 equiv), **3** (4.0 equiv), Pd(OAc)₂ (10 mol %), AgOAc (3.0 equiv), AcOH (1.0 equiv), 1,4-dioxane, 120 °C, 16 h, 45% (65% of unreacted **3** was recovered); (b) (CF₃CO)₂O (4.0 equiv), DMF, 23 °C, 12 h, 60% (**5a/5b** = 1:1); (c) CF₃SO₃H (0.5 equiv), **6** (2.0 equiv), 80 °C, air, 73% from **5a**.

model substrates (Scheme 2). As our first step, we recently reported that a C–H/C–H coupling reaction of indoles (or pyrroles) and azine *N*-oxides can be catalyzed by the combination of Pd(OAc)₂/2,6-lutidine/AgOAc.^{13a} By modifying our original conditions, regioselective and reasonably efficient coupling of *N*-tosylindole (**2**) and pyrazine *N*-oxide (**3**) was achieved. Thus, the treatment of **2** (1.0 equiv) and **3** (4.0 equiv) in the presence of Pd(OAc)₂ (10 mol %), AgOAc (3.0 equiv), and AcOH (1.0 equiv) in 1,4-dioxane at 120 °C afforded the target coupling product **4** in 45% yield (75% yield based on recovered starting material) with 65% of unreacted **3** recovered.¹⁴ Upon treatment of *N*-oxide **4** with (CF₃CO)₂O,¹⁵ a formal rearrangement occurred to give two regioisomers of pyrazinones **5a** and **5b** in 60% yield (**5a/5b** = 1:1).¹⁶ Subsequently, we found that a C–H/C–H coupling reaction between **5a** and 6-bromoindole (**6**) could be achieved with CF₃SO₃H (0.5 equiv) in DMF under air. The desired coupling product **7** was obtained from **5a** in good yield, whereas the regioisomer **5b**¹⁷ did not react with **6** at all. The molecular structure of **7** was determined by single-crystal X-ray diffraction analysis (Scheme 2). The precise mechanism of this C–H/C–H coupling is unclear at present, but we presume that the reaction proceeds by a Friedel–Crafts-type addition followed by oxidation.¹⁸

Although the regioselectivity problem in the pyrazinone formation remained unsolved, we nevertheless moved on to the greater challenge of synthesizing dragsmacidin D (**1**). The synthesis begins with iodoindole derivative **8**, which was easily synthesized in three steps from commercially available 7-benzyloxyindole.¹⁹ At first, the coupling of iodoindole **8** and 3-methoxythiophene (**9**) was conducted using our original thiophene arylation

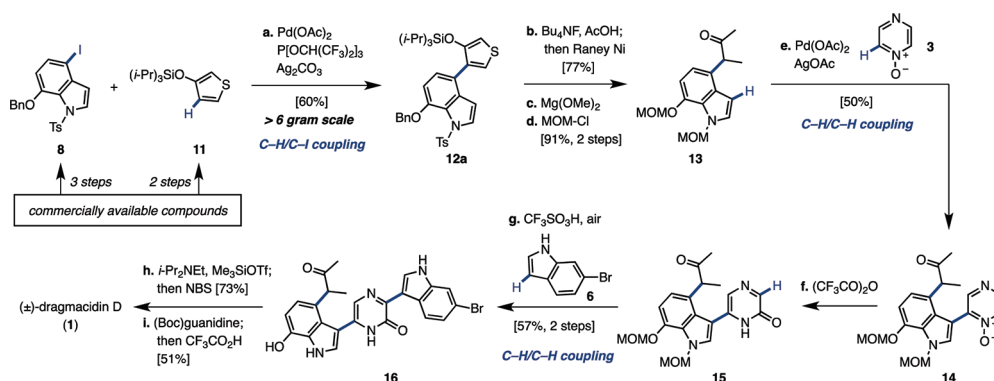
Scheme 3. C4-Selective Indolation of Thiophene Having Oxygen Substituent at C3 Position



conditions,²⁰ employing PdCl₂ (10 mol %), P[OCH(CF₃)₂]₃ (20 mol %), and Ag₂CO₃ (1.0 equiv) in *m*-xylene at 140 °C (Scheme 3). Unfortunately, however, these conditions afforded an equimolar and inseparable mixture of desired C4-arylated product **10a** and undesired C2-arylated product **10b** in 22% combined yield.

As the C2-position is the most electronically reactive position in **9** (α to the sulfur atom and *ortho* to the methoxy group), complete suppression of C2-arylated product is a formidable task. On the basis of our mechanistic analyses,^{20b} the complexation of C2–C3 and C4–C5 π -bonds to palladium species would lead to the formation of C2- and C4-arylated products, respectively (Scheme 3). An important ramification of this mechanistic picture is that the suppression of C2–C3 complexation might be achieved by a large substituent at the C3 position of the thiophene ring, thereby increasing the C4-regioselectivity in the thiophene indolation. However, the replacement of the methoxy group of **9** with benzoate, pivalate, and phenoxy groups gave mixtures of regioisomers in low yield. Upon further investigation, we found that when the 3-triisopropylsilyloxy-substituted thiophene **11** (prepared in two steps from commercially available 3-thienylboronic acid)¹⁹ was used as a substrate, C4-arylated product **12a** was obtained in 23% yield with virtually complete regioselectivity. The effective shielding of C2–C3 π -bond by triisopropylsilyl group can be easily understood by the space-filling models (Scheme 3). Encouraged by this finding, we further screened the conditions and found that the use of Pd(OAc)₂ as a catalyst and 1,4-dioxane as a solvent increased the yield of **12a** to a 60%, maintaining perfect regioselectivity (Scheme 3). Gratifyingly, more than 6 g of **12a** was prepared under these conditions.²¹

With a critical hurdle overcome, we subsequently moved forward to the synthesis of **1** (Scheme 4). Removal of the triisopropylsilyl group from **12a** with Bu₄NF/AcOH, followed by treatment with Raney Ni, allowed the concomitant reduction of thiophene and

Scheme 4. Synthesis of Dragmacidin D (**1**)^a

^a Reagents and conditions: (a) **8** (1.0 equiv), **11** (3.0 equiv), Pd(OAc)₂ (10 mol %), P[OCH(CF₃)₂]₃ (20 mol %), Ag₂CO₃ (1.0 equiv), 1,4-dioxane, 140 °C, 16 h, 60% (86% of unreacted **11** was recovered); (b) Bu₄NF (1.1 equiv), AcOH (1.1 equiv), THF, 23 °C, 10 min; then Raney Ni, 23 °C, 30 min, 77%; (c) Mg(OMe)₂, MeOH, 23 °C, 30 min, 95%; (d) methoxymethyl chloride (2.0 equiv), NaH (2.0 equiv), DMF/THF = 1:2, 0–23 °C, 15 min, 96%; (e) **3** (4.0 equiv), Pd(OAc)₂ (10 mol %), AgOAc (3.0 equiv), 1,4-dioxane, 120 °C, 16 h, 50% (one recycle); (f) (CF₃CO)₂O (4.0 equiv), DMF/THF = 1:1, 23 °C, 16 h; (g) **6** (1.2 equiv), CF₃SO₃H (0.5 equiv), DMF, air, 80 °C, 3 h, 57% (2 steps); (h) *i*-Pr₂NEt (10 equiv), Me₃SiOTf (10 equiv), CH₂Cl₂, 23 °C, 30 min; then *N*-bromosuccinimide (10 equiv), 0 °C, 1 h, 73%; (i) Boc-guanidine (3.0 equiv), THF, 55 °C, 16 h; then CF₃CO₂H/CH₂Cl₂, 23 °C, 20 min, 51%.

debenzylation to afford the corresponding methyl ketone in a one-pot process (77% yield). After the protecting group exchange from tosyl to methoxymethyl (MOM), the thus-obtained bis-MOM-protected indole **13** was then primed for the Pd-catalyzed C–H/C–H coupling reaction with pyrazine *N*-oxide (**3**). Although the yield of this reaction was not superb, a 50% yield was achieved by recycling **13**.¹⁹ Despite its moderate yield, the reaction furnished the coupling product **14** regioselectively. Treatment of **14** with (CF₃CO)₂O then furnished pyrazinone **15**. Notably, the ratio of the desired **15** over the undesired regioisomeric pyrazinone was 5:1. The increase in selectivity compared to that of the model study might be due to the presence of a sterically demanding side chain at the 4-position of the indole core, blocking the C3 attack of trifluoroacetate ion to the pyrazine core (Scheme 2). An oxidative C–H/C–H coupling reaction of pyrazinone **15** and 6-bromoindole (**6**) under the influence of CF₃SO₃H afforded the corresponding coupling product **16** with simultaneous removal of the two MOM groups.

During these studies, we found that a solution of bis(indolyl)-pyrazinone **16** is very sensitive to light, even though **16** is stable in a solid form. Therefore, the subsequent reactions were conducted in the dark using a small amount of **16**. The final transformation from **16** to dragmacidin D (**1**) necessitated the following two steps;^{22,23} (i) treatment with *i*-Pr₂NEt/Me₃SiOTf and then *N*-bromosuccinimide, and (ii) aminoimidazole formation from the resultant α -bromoketone and (Boc)guanidine, followed by deprotection of the Boc group using CF₃CO₂H and purification via reverse-phase preparative liquid chromatography. The ¹H and ¹³C NMR spectra of the synthetic sample of (±)-**1** were in complete agreement with those previously reported.^{1a,5a} As such, the total synthesis of (±)-**1** has been accomplished in a total of 15 synthetic operations.

In conclusion, a concise total synthesis of dragmacidin D (**1**) has been achieved using three direct C–H coupling reactions, Pd-catalyzed regioselective thiophene–indole C–H/C–I coupling (**8**+**11**), Pd-catalyzed regioselective indole–pyrazine *N*-oxide C–H/C–H coupling (**3**+**13**), and acid-catalyzed indole–pyrazinone C–H/C–H coupling (**6**+**15**), as step-economical unit-assembling reactions. With an efficient synthetic platform en-

route to **1** in hand, asymmetric synthesis of **1** and the feasibility to transform **1** into dragmacidin E and F^{5b} are currently ongoing in our laboratory.²⁴ As exemplified by the present work, assembling simple building blocks with least prefunctionalization by means of C–H coupling is what we consider to be an ideal approach to rapidly increase molecular complexity in organic synthesis.¹⁰ In addition to executing such complex molecule syntheses, we concomitantly continue our synthesis-oriented catalyst development campaign along this line. Such endeavors will surely unlock opportunities for markedly different connection/disconnection strategy in the construction of organic molecules.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, and spectral data for all compounds, including scanned image of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (24) For a bio-inspired divergent total synthesis of structurally related natural products, see: Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14710 and references therein.