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Synthesis of Dragmacidin D via Direct C−H Couplings

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Supporting Information

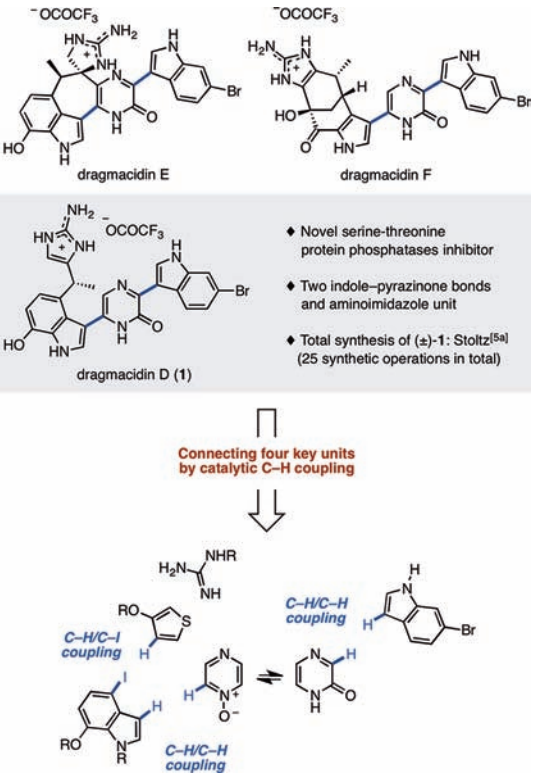
ABSTRACT: Dragmacidin D, an emerging biologically active marine natural product, has attracted attention as a lead compound for treating Parkinson's and Alzheimer's diseases. Prominent structural features of this compound are the two indole−pyrazinone bonds and the presence of a polar aminoimidazole 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. Becase of their unique chemical structures and promising biological activities, dragmacidins have been synthetic targets for many chemists.[5,6] In 2002, Stoltz and coworkers 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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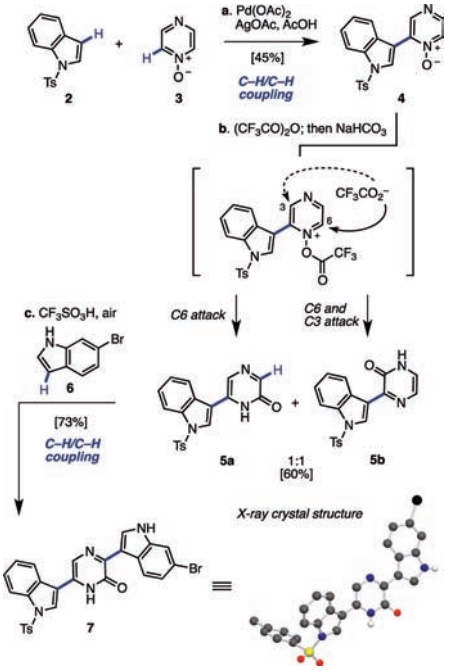
Scheme 2. Construction of Bis(indolyl)pyrazinone Unit via Two Sequential C−H/C−H Couplings[a]

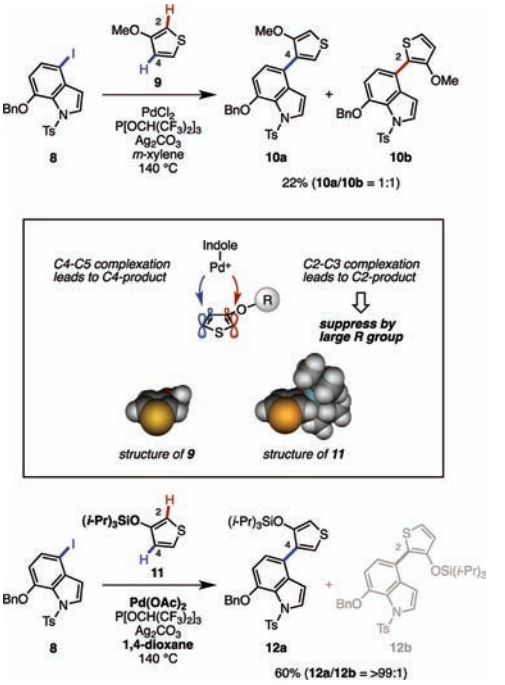


[a] Reagents and conditions: (a) **2** (1.0 equiv), **3** (4.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), AcOH (1.0 equiv), 1,4-dioxane, 120 °C, 16 h, 45% (65% of unreacted **3** was recovered); (b) $(CF_3CO)_2O$ (4.0 equiv), DMF, 23 °C, 12 h, 60% (**5a**/**5b** = 1:1); (c) CF_3SO_3H (0.5 equiv), **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 $(CF_3CO)_2O$,[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 CF_3SO_3H (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 dragmacidin 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 $PdCl_2$ (10 mol %), $P[OCH(CF_3)_2]_3$ (20 mol %), and Ag_2CO_3 (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 Bu_4NF/AcOH, followed by treatment with Raney Ni, allowed the concomitant reduction of thiophene and

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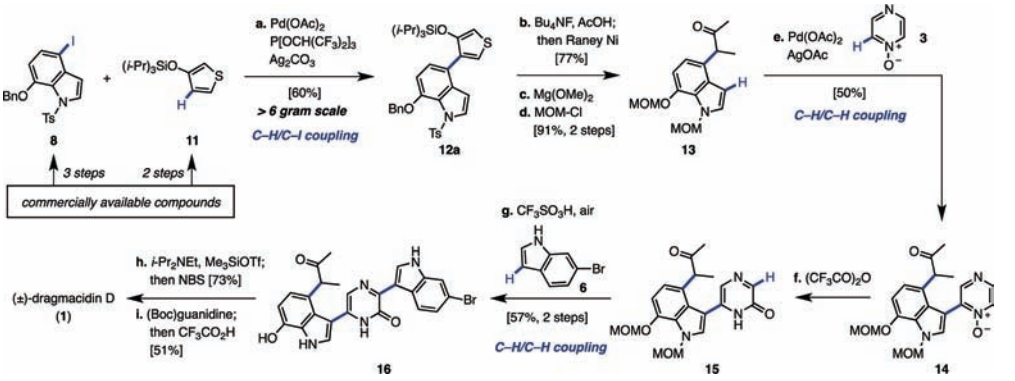
Scheme 4. Synthesis of Dragmacidin D (1)[a]



[a] Reagents and conditions: (a) **8** (1.0 equiv), **11** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), $P[OCH(CF_3)_2]_3$ (20 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 140 °C, 16 h, 60% (86% of unreacted **11** was recovered); (b) Bu_4NF (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) $(CF_3CO)_2O$ (4.0 equiv), DMF/THF =1:1, 23 °C, 16 h; (g) **6** (1.2 equiv), CF_3SO_3H (0.5 equiv), DMF, air, 80 °C, 3 h, 57% (2 steps); (h) *i*-Pr_2NEt (10 equiv), Me_3SiOTf (10 equiv), CH_2Cl_2, 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 CF_3CO_2H/CH_2Cl_2, 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 $(CF_3CO)_2O$ 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 CF_3SO_3H 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*-Pr_2NEt/Me_3SiOTf and then *N*-bromosuccinimide, and (ii) aminoimidazole formation from the resultant α-bromoketone and (Boc)guanidine, followed by deprotection of the Boc group using CF_3CO_2H and purification via reverse-phase preparative liquid chromatography. The ^1H and ^{13}C 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 ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) See the Supporting Information for possible mechanism.

(17) The structure of **5b** was confirmed by the X-ray crystal structure analysis after converting it to the corresponding *N*-methyl pyrazinone. See the Supporting Information for details.

(18) Although there has been no report using pyrazinone as substrate, the coupling of indole-quinoxalin-2-ones was previously reported. See,(a) Aoki, K.; Obata, T.; Yamazaki, Y.; Mori, Y.; Hirokawa, H.; Koseki, J.; Hattori, T.; Niitsu, K.; Takeda, S.; Aburada, M.; Miyamoto, K. *Chem. Pharm. Bull.* **2007**, *55*, 255. (b) Aoki, K.; Koseki, J.; Takeda, S.; Aburada, M.; Miyamoto, K. *Chem. Pharm. Bull.* **2007**, *55*, 922. (c) Han, Y.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron Lett.* **2010**, *51*, 2023.

(19) See the Supporting Information for details of this procedure.

(20) (a) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (b) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946.

(21) 86% of unreacted **11** was recovered after the reaction. When the reaction was conducted using an equimolar quantity of each coupling partner (**8** and **11**), the yield of **12a** decreased to 42%.

(22) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3578.

(23) No guanidination product was obtained when we used DMF instead of THF as a solvent.[5a]

(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.