The First Total Synthesis of Dragmacidin D

Neil K. Garg, Richmond Sarpong, and Brian M. Stoltz*

*Contribution from The Arnold and Mabel Beckman Laboratories of Chemical Synthesis,
Division of Chemistry and Chemical Engineering, California Institute of Technology,
1200 East California Boulevard, MC 164-30, Pasadena, California 91125*

Received July 23, 2002

Abstract: The first total synthesis of the biologically significant bis-indole alkaloid dragmacidin D (**5**) has been achieved. Thermal and electronic modulation provides the key for a series of palladium-catalyzed Suzuki cross-coupling reactions that furnished the core structure of the complex guanidine- and aminoimidazole-containing dragmacidins. Following this crucial sequence, a succession of meticulously controlled final events was developed leading to the completion of the natural product.

Introduction

Biologically active molecules isolated from marine organisms constitute an ever-growing subset of all natural products collected, and among them are some of the most potent antitumor and cytotoxic agents yet discovered.[1] The dragmacidins (Figure 1, **1**−**7**) represent an emerging class of bioactive marine natural products obtained by an exhaustive set of protocols from a number of deep water sponges including *Dragmacidon*, *Halicortex*, *Spongosorites*, and *Hexadella*, and the tunicate *Didemnum candidum*.[2,3] The initial four dragmacidins identified contained a piperazine linker (Figure 1, **1**−**4**) and displayed modest antifungal, antiviral, and cytotoxic activities. Recently, the structurally more complex aminoimidazole- and guanidine-containing pyrazinone dragmacidins D (**5**), E (**6**), and F (**7**) were isolated and shown to possess a wide range of interesting biological properties as well.

In particular, dragmacidin D (**5**) is a potent inhibitor of serine-threonine protein phosphatases (PP), and preliminary evidence suggests that dragmacidin D is a selective inhibitor of PP1 versus PP2A.[3b] It is also an in vivo nonsteroidal antiinflammatory agent as shown by its potent inhibition of resiniferitoxin-induced inflammation in mouse ear models.[4] Additionally, dragmacidin D was found to selectively inhibit neural nitric oxide synthase (bNOS) in the presence of inducible NOS (iNOS).[5] Endogenous nitric oxide (NO), produced via NOS-mediated metabolism of
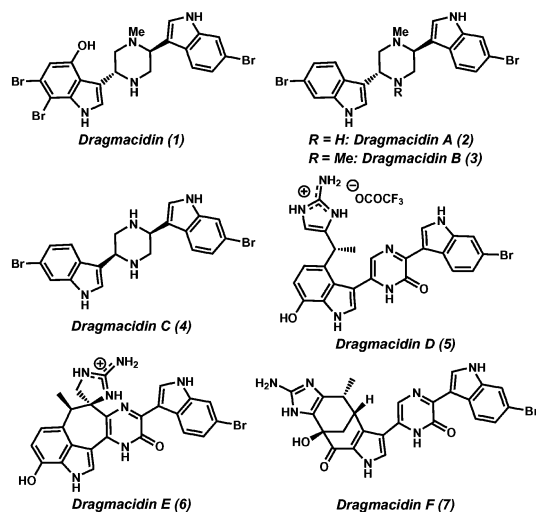

Figure 1. The dragmacidin alkaloids.

L-arginine, is known to play a role in a variety of regulatory functions such as the control of blood pressure, antibacterial activity, gastric motility, and neurotransmission.[6] Alternatively, the overproduction of nitric oxide by certain NOS isozymes has been implicated in a host of inflammatory diseases, such as arthritis[7] and asthma,[8] as well as some neurodegenerative disorders. Therefore, the ability to selectively inhibit the brain NOS isozyme (bNOS) may be useful in a variety of therapeutic areas including the treatment of Alzheimer's, Parkinson's, and Huntington's diseases.[9]

* To whom correspondence should be addressed. E-mail: stoltz@caltech.edu.

(1) (a) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48.

(2) (a) Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L., Jr.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116−3118. (b) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715−720. (c) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564−569.

(3) (a) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772−4775. (b) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carroll, A. R. *J. Nat. Prod.* **1998**, *61*, 660−662. (c) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743−3748.

(4) Jacobs, R. S.; Pomponi, S.; Gunasekera, S.; Wright, A. PCT Int. Appl. WO 9818466, May 7, 1998.

(5) Longley, R. E.; Isbrucker, R. A.; Wright, A. E. U.S. Patent 6,087,363, July 7, 2000.

(6) (a) Fukuto, J. M.; Chaudhuri, G. *Annu. Rev. Pharmacol. Toxicol.* **1995**, *35*, 165−194. (b) Yun, H. Y.; Dawson, V. L.; Dawson, T. M. *Crit. Rev. Neurobiol.* **1996**, *10*, 291−316.

(7) Amin, A. R.; Attur, M.; Abramson, S. B. *Curr. Opin. Rheumatol.* **1999**, *11*, 202−209.

(8) (a) Baraldi, E.; Dario, C.; Ongaro, R.; Scollo, M. *Am. J. Respir. Crit. Care Med.* **1999**, *159*, 1284−1288. (b) Sanders, S. P. *Proc. Soc. Exp. Biol. Med.* **1999**, *220*, 123−132. (c) Stirling, R. G.; Kharitonov, S. A.; Campbell, D.; Robinson, D. S.; Durham, S. R.; Chung, K. F.; Barnes, P. J. *Thorax* **1998**, *53*, 1030−1034.

(9) (a) Molina, J. A.; Jimenez-Jimenez, F. J.; Orti-Pareja, M.; Navarro, J. A. *Drugs Aging* **1998**, *12*, 251−259. (b) Thorns, V.; Hansen, L.; Masliah, E. *Exp. Neurol.* **1998**, *150*, 14−20.
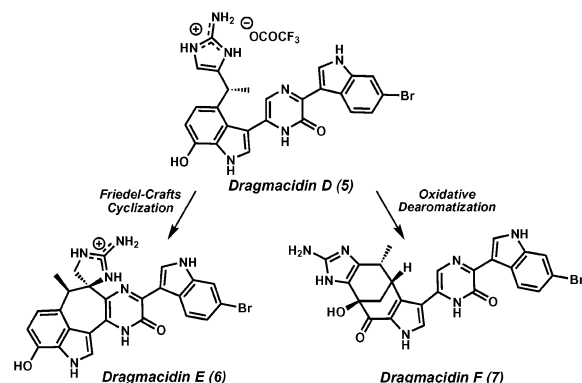
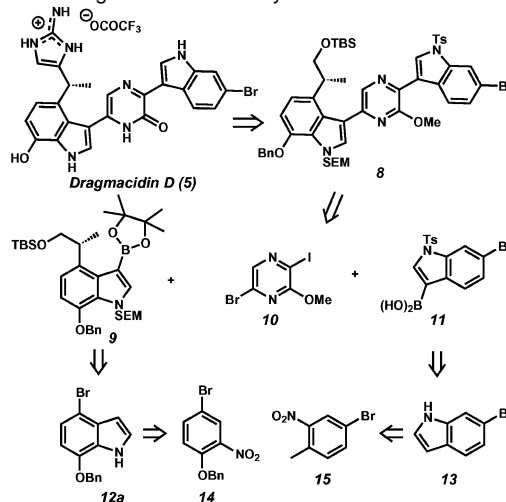**Figure 2.** The potential biosynthetic relationship of dragmacidins D, E, and F.

Given the biological relevance of the dragmacidins, especially the pyrazinone-containing dragmacidins D, E, and F, it is surprising that relatively little synthetic chemistry has been published regarding these structures.[10] Moreover, due to the general difficulty in isolating the dragmacidins, nature is an impractical source for obtaining the large quantities of material necessary for advanced biological testing and analogue synthesis. Herein, we outline an efficient synthesis of the common core structure of dragmacidins D, E, and F, which we have prepared by the implementation of sequential temperature-modulated Suzuki cross-coupling reactions that are exquisitely selective. Additionally, we have elaborated this core by a delicate series of highly specific transformations to accomplish the first total synthesis of dragmacidin D (**5**).

Results and Discussion

Synthetic Planning. Our synthetic planning in the area of the dragmacidins began with the recognition that the complex dragmacidins D, E, and F are likely biosynthetically related.[11] Of the possible biosynthetic scenarios, most probable is the notion that dragmacidins E and F are derived by cyclization of either dragmacidin D or a closely related congener (Figure 2). For example, Friedel–Crafts type cyclization could result in the conversion of D to E (i.e., **5** → **6**), while an oxidative dearomatization with concomitant cyclization could facilitate the formation of the unique polycyclic framework present in dragmacidin F (i.e., **5** → **7**). Therefore, the identification of dragmacidin D as a suitable *biosynthetic* precursor to dragmacidins E and F led to its designation by us as a reasonable first *synthetic* target in this class of complex alkaloids.

Although the structure of dragmacidin D appears deceptively simple, closer consideration reveals several synthetic challenges,

---

(10) Although some elegant synthetic work directed at the piperazine-containing dragmacidins has appeared, reports directed toward those members possessing guanidine-functionalized indoles around a pyrazinone core have been limited. For synthetic work aimed at the piperazine-containing dragmacidins, see: (a) Jiang, B.; Smallheer, J. M.; Amaral-Ly, C.; Wuonola, M. A. *J. Org. Chem.* **1994**, *59*, 6823–6827. (b) Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett.* **1994**, *35*, 371–374. (c) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027–3029. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3185–3187. (e) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383–394. (f) Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245–4248. For studies specifically targeting dragmacidins D, E, or F, see: (g) Jiang, B.; Gu, X.-H. *Bioorg. Med. Chem.* **2000**, *8*, 363–371. (h) Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559–1568. (i) Yakushijin, K.; Horne, D. A. PCT Int. Appl. WO 0194310 A1, December 13, 2001. (j) Yang, C.-G.; Wang, J.; Jiang, B. *Tetrahedron Lett.* **2002**, *43*, 1063–1066. (k) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941–943.
(11) For a brief discussion, see refs 3b and 3c.

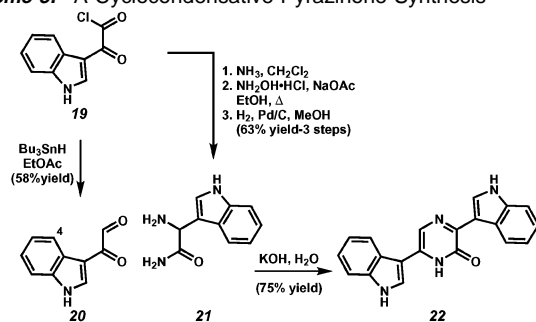**Scheme 1.** Dragmacidin D Retrosynthetic Plan

Scheme 2. Alternate Dragmacidin D Retrosynthesis
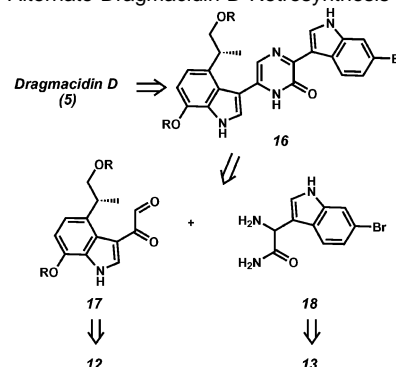
for example: (A) the seven nitrogen atoms present in the compact structure, (B) the four differentially substituted heterocycles, (C) the nontrivial nature of the substitution patterns on the 3,6-disubstituted and 3,4,7-trisubstituted indoles, and (D) the highly polar and reactive nature of the aminoimidazolium subunit and of potential precursors to the natural product. Presented in Scheme 1 is our retrosynthetic strategy for the synthesis of dragmacidin D. As a key strategic maneuver, we chose to introduce the aminoimidazolium functionality of dragmacidin D at a late stage in the synthesis to facilitate the handling of key intermediates. Thus, disconnection of the natural product (**5**) provides silyl ether **8** (Scheme 1), which was envisioned to arise by a stepwise, palladium-catalyzed three-component coupling of fragments **9** + **10** + **11**. Critical to the success of this plan was the capacity to utilize metallo-bromoindole **11** directly in the cross-coupling sequence, thereby defining a strategic challenge that would limit the options available for protecting groups as well as end-game scenarios. The indole building blocks **12** and **13** were readily available from simple aromatic starting materials **14** and **15**.

An Initial Cyclocondensation Digression. In addition to the strategy described above, we considered an alternative method to construct the bis-indole framework wherein disconnection of the pyrazinone **16** directly revealed two fragments, keto aldehyde **17** and aminoamide **18** (Scheme 2). These functionalized indoles were likewise available from the parent indoles **12** and **13**. Aside from the obvious advantage of increased convergence, this approach avoided selectivity issues with regard

Scheme 3. A Cyclocondensative Pyrazinone Synthesis

Scheme 4. Preparation of the 3,4,7-Trifunctionalized Indole Subunit


to halide/organometallic couplings alluded to in the transition-metal approach described above.

The appeal of the cyclocondensation approach was heightened by the success of a simple model system that constituted one of our first experiments in this area. Synthesis of the unfunctionalized keto aldehyde **20** and aminoamide **21** was straightforward from the well-known product of the reaction of indole with oxalyl chloride (i.e., **19**).[12] Modified Rosenmund reduction of acid chloride **19** by the action of Bu$_3$SnH produced aldehyde **20** in modest yield.[13] Alternatively, treatment of **19** with ammonia, followed by oximation of the resulting ketoamide, and reduction with H$_2$ over Pd/C in MeOH produced aminoamide **21**. In the key cyclocondensation experiment, simply heating keto aldehyde **20** and aminoamide **21** in aq KOH at 70 °C led to the formation of pyrazinone **22** in 75% yield (Scheme 3).

With this result in hand, we investigated the synthesis and cyclocondensation of a number of highly functionalized systems more closely aligned with the target molecule (i.e., **5**). Our enthusiasm for this direct cyclocondensative coupling approach was quickly diminished, however, as all attempts to synthesize more advanced pyrazinones produced none of the desired dragmacidin framework. For example, attempted coupling of keto aldehydes **23a**−**c** with aminoamide **18** under a variety of basic and acidic conditions provided only traces (if any) of the pyrazinone products (eq 1). It became clear that cyclocondensation approaches to the dragmacidins that involved substitution at the C(4) position of indoles of the type **23** would not be feasible in our hands.[14]


R^1 = CH$_2$OBn, R^2 = CH$_3$: **23a**
R^1 = CH$_2$OBn, R^2 = H: **23b**
R^1 = CO$_2$CH$_3$, R^2 = CH$_3$: **23c**
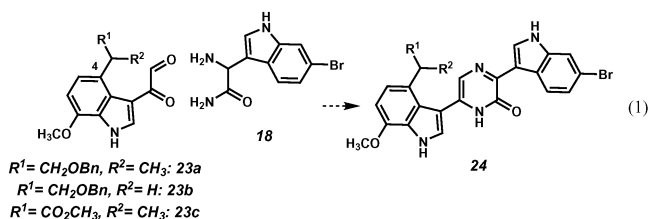
Synthesis of the Building Blocks. With the difficulties of the cyclocondensation approach clearly illuminated, we investigated our initial palladium coupling approach to dragmacidin D. As a starting point for the synthesis, the parent 4,7-disubstituted indole was accessed by employing the Bartoli
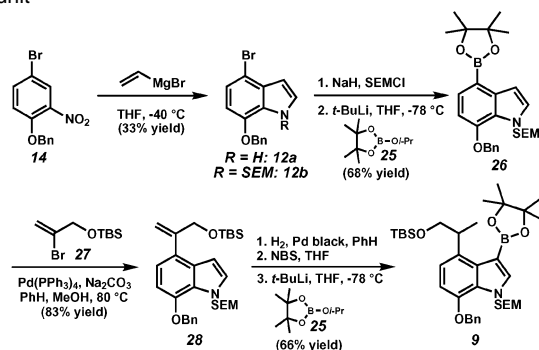
reaction (Scheme 4).[15] Thus, treatment of nitroaromatic **14** with 3.5 equiv of vinyl Grignard reagent produced the benzyloxy indole **12a** directly in modest yield. Following initial protection of the indole nitrogen by a 2-(trimethylsilyl)ethoxymethyl (SEM) group,[16] halogen−metal exchange and trapping by dioxaborolane reagent **25** produced metalloindole **26**.[17] Suzuki coupling of indole **26** and vinyl bromide **27**[18] provided ether **28**.[19] Final conversion of ether **28** to coupling fragment **9** was accomplished using a sequence involving selective hydrogenation of the terminal olefin,[20] bromination at the C(3) position,[21] and halogen−metal exchange/trapping with dioxaborolane **25** (66% yield, three steps).

The differentially substituted pyrazine core structure (e.g., **10**, Scheme 5) was readily available by iodination of known aminopyrazine **29**[22] via the in situ prepared diazonium salt.[23] Preparation of the bromoindole boronic acid derivative **11** from the parent **13**[24] proceeded by protection of the indole nitrogen,[25]

(14) Although there is clearly an electronic difference between indoles **20**, **21** and **23a**−**c**, **18**, respectively, the steric component of C(4) substitution appears to be the determining factor as illustrated by the reaction of **i** and **18** to produce the desired pyrazinone **ii** in good yield.
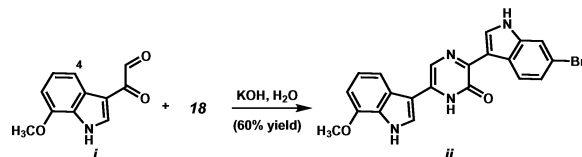

(15) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129−2132. (b) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, *5*, 657−663.
(16) (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630−633. (b) Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530−535.
(17) Belletete, M.; Beaupre, S.; Bouchard, J.; Blondin, P.; Leclerc, M.; Durocher, G. *J. Phys. Chem. B* **2000**, *104*, 9118−9125.
(18) Li, K.; Du, W.; Que, N. L. S.; Liu, H.-W. *J. Am. Chem. Soc.* **1996**, *118*, 8763−8764.
(19) For general reviews on Suzuki couplings, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.
(20) (a) Maki, S.; Okawa, M.; Matsui, R.; Hirano, T.; Niwa, H. *Synlett* **2001**, *10*, 1590−1592. (b) In the presence of minor impurities and/or solutions of benzene that were not presaturated with H$_2$, the reaction produced a major byproduct identified as enol ether **iii**.
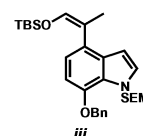
(21) (a) Ayer, W. A.; Craw, P. A.; Ma, Y.-T.; Miao, S. *Tetrahedron* **1992**, *48*, 2919−2924. (b) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10−11.
(22) Barlin, G. B. *Aust. J. Chem.* **1983**, *36*, 983−992.
(23) Zhu, Z.; Moore, J. S. *J. Org. Chem.* **2000**, *65*, 116−123.
(24) Prepared from **15** by a modified Leimgruber−Batcho synthesis, see: Schumacher, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935−942.

(12) (a) Kharasch, M. S.; Kane, S. S.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, *62*, 2242−2243. (b) Hashem, M. A.; Sultana, I.; Hai, M. A. *Indian J. Chem., Sect. B* **1999**, *38*, 789−794.
(13) (a) Vereshchagin, A. L.; Bryanskii, O. V.; Semenov, A. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, *19*, 40−42. (b) Kuivila, H. G. *J. Org. Chem.* **1960**, *25*, 284−285.

**Scheme 5.** Synthesis of the Pyrazine and Bromoindole Fragments

Pyrazine Fragment

Bromoindole Fragment
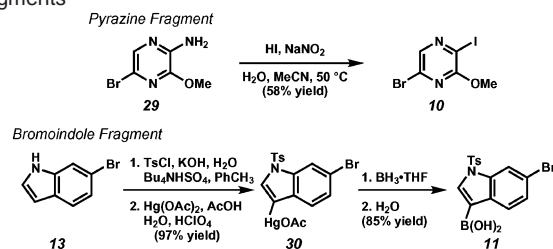
treatment with Hg(OAc)$_2$, and reaction of the resulting orga-nomercurial **30** with BH$_3$·THF followed by hydrolytic workup (Scheme 5, 82% overall yield from **13**).[26]

Fragment Coupling. Having efficient means to access the desired building blocks for the preparation of the dragmacidin D skeleton in hand, we turned our attention toward experiments that would delineate suitable conditions for coupling. We initially surveyed a variety of coupling reactions involving model indoles and various halogenated pyrazine derivatives to gauge the relative reactivity of such systems as well as the suitability of the protective groups on the indole nitrogen. It was quickly established that halogenated pyrazines are highly reactive toward palladium-mediated couplings to metalated indoles. Furthermore, particularly useful for the proposed synthesis of dragmacidin D is the fact that the oxidative addition of palladium(0) to pyrazinyl halides is more facile than that to simple aromatic halides, as has been established in the literature.[27] For example, coupling of borylated indoles **31a** and **31b** with readily available chloropyrazine **32**[28] proceeded smoothly at 80 °C under standard Suzuki conditions (eq 2). Under identical conditions, simple aryl chlorides do not readily participate in such couplings.[29] Ad-ditionally, treatment of chloroiodopyrazine **34** with 2 equiv of indole **31a** at 23 °C produced indolopyrazine **35a** exclusively, while raising the temperature to 80 °C resulted in the formation of the bis-indolopyrazine **36** (eq 3). Again these results were in good accord with expectations derived from literature observa-tions. A more surprising development was observed upon treatment of pyrazine **34** with an excess of silylated boronic ester **31b** (2.3 equiv) at 80 °C. Under these conditions, exclusively monocoupled product was obtained as a mixture of silylated and desilylated compounds (eq 4, **35b** and **35c**). Clearly, this dichotomy points to a remote electronic effect of the indole protecting group for the activation of the intermediate chloroindolopyrazine (**35**) toward coupling. Thus, our choice of a tosyl protective group for the bromoindole fragment proved fortuitous. Furthermore, to maximize position selectivity in the couplings leading to dragmacidin D, chloroiodopyrazine **34** gave way to bromoiodopyrazine **10** as the optimal synthetic linchpin.

With regard to the union of building blocks **9**, **10**, and **11**, we have found that room-temperature Suzuki coupling of dihalopyrazine **10** and indole **11** proceeds selectively to the coupled indolopyrazine **37** (see Scheme 6). In the critical second

(2)

(3)

(4)
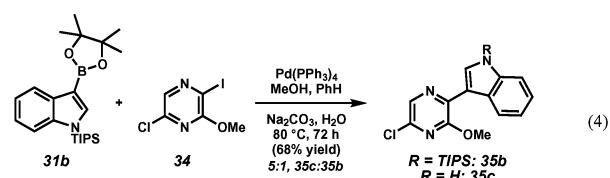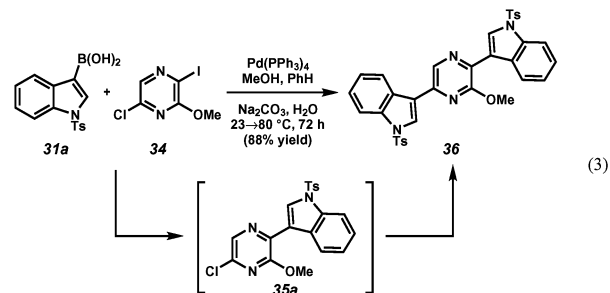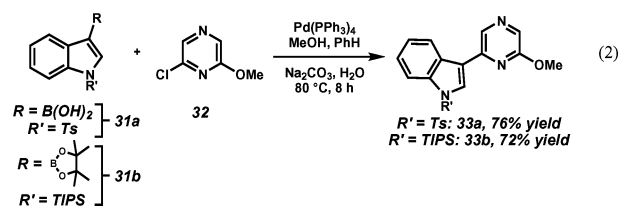
Suzuki coupling of dibromide **37** with metallo-indole **9**, we were delighted to find that under carefully controlled conditions (50 °C, 72 h), the desired bis-indole alkoxy pyrazine **8** was formed in good yield and with complete selectivity for coupling of the pyrazinyl bromide in the presence of the indolyl bromide. As predicted from the model studies above (eqs 2–4), precise temperature control is needed for this sequence of coupling reactions, particularly in the reaction of **9** + **37** → **8**. At temperatures approaching 80 °C, coupling of the bromoindole unit becomes competitive with the desired mode of coupling. Thus, it was particularly important to perform the reaction at the lowest possible temperature (50 °C), to maximize selectivity in this sequence.

Scheme 6. Sequential Selective Suzuki Couplings
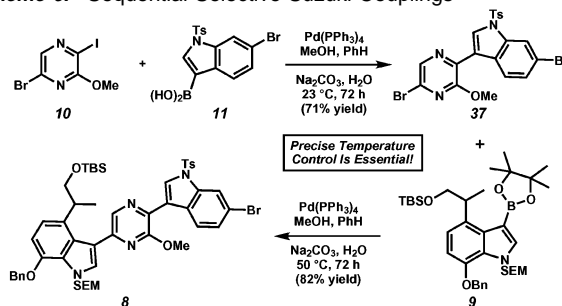
End-Game Strategy 1. With the suitably elaborated bis-indolopyrazine core structure available from the Suzuki chem-istry, we initiated our final approach to dragmacidin D. Selective cleavage of the silyl ether in **8** was accomplished by the action of HF·pyridine,[30] and the resulting primary alcohol was oxidized to carboxylic acid **38a** (Scheme 7). Arndt–Eistert homologation to α-bromo ketone **39** was initially problematic and furnished essentially none of the desired product (ca. 10% yield). Instead,

(25) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; McPhail, A. T. *J. Org. Chem.* **1988**, *53*, 3170−3178.
(26) Zheng, Q.; Yang, Y.; Martin, A. R. *Heterocycles* **1994**, *37*, 1761−1772.
(27) For an excellent discussion of the cross-coupling chemistry of pyrazines, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000; pp 355−373.
(28) Turck, A.; Plé, N.; Dognon, D.; Harmoy, C.; Quéguiner, G. *J. Heterocycl. Chem.* **1994**, *31*, 1449−1454.
(29) For a discussion, see: Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(30) For the cleavage of silyl ethers with HF·pyridine, see: Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, *6*, 453−461.

Scheme 7. Studies toward the Synthesis of Dragmacidin D

Scheme 8. The Synthesis of Dragmacidin D
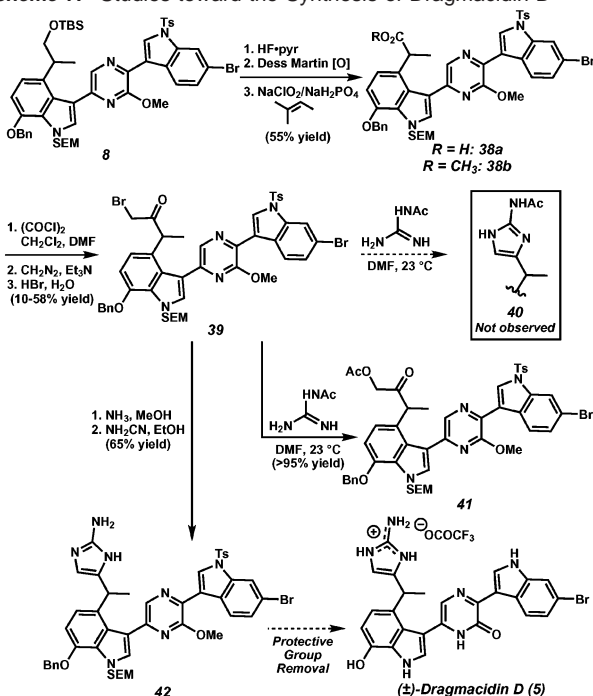
nearly a quantitative recovery of the corresponding methyl ester **38b** was obtained, pointing to rapid hydrolysis of the intermediate acid chloride and subsequent esterification by diazomethane. This result was particularly surprising given that model studies performed on analogous indolepropionic acid derivatives lacking substitution at the indole C(3) position proceeded without event. However, after careful and rigorous drying of the diazomethane over KOH followed by sodium metal,[31] we were able to obtain satisfactory yields of bromoketone **39** (58% yield). Again in stark contrast to model studies performed on simple derivatives, treatment of bromoketone **39** with acetylguanidine produced none of the desired aminoimidazole derivative **40**; rather, nearly a quantitative yield of acetoxyketone **41** was recovered.

Recognizing that substitution chemistry at the α-position of ketone **39** must occur to produce acetate **41**, we treated bromoketone **39** with a saturated $NH_3/MeOH$ solution to produce an aminoketone, which was converted to aminoimidazole **42** upon exposure to cyanamide in EtOH at 70 °C.[32] Although aminoimidazole **42** represented a protected form of the natural product **5**, all attempts to remove the four remaining protective groups resulted in nonspecific cleavage of the aminoimidazole moiety. Thus, compound **42** symbolized an unsatisfying dead-end for our synthesis.

Completion of the Total Synthesis. Unabated by our inability to transform **42** into **5**, we focused our attention on an end-game scenario that included the earlier deprotection of masked functionality and postponement of the aminoimidazole introduction. We also sought an alternative homologation protocol, as the Arndt−Eistert method had become our synthetic bottleneck. After extensive experimentation, our second-generation sequence was initiated by selective silyl ether cleavage of Suzuki adduct **8** and oxidation of the resulting primary alcohol
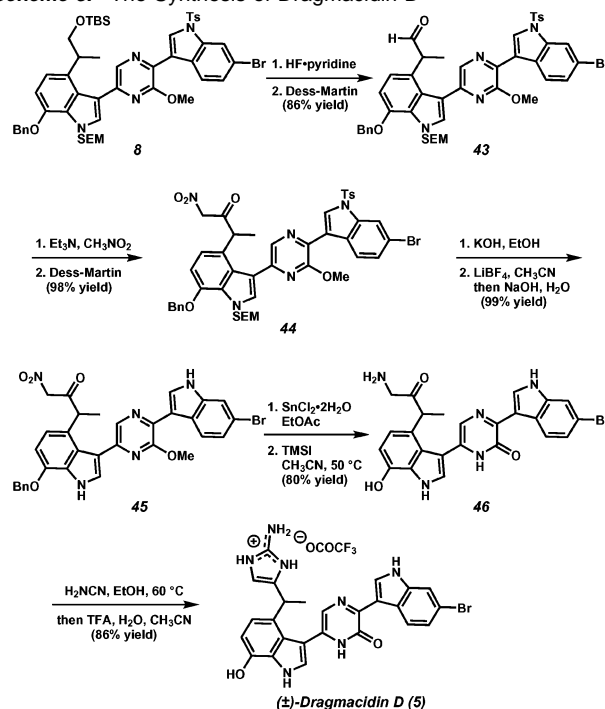
to aldehyde **43** using the Dess−Martin periodinane reagent (Scheme 8).[33,34] As an alternative to the problematic Arndt−Eistert homologation sequence discussed above, nitromethane addition[35] and subsequent oxidation to nitroketone **44** proceeded smoothly (98% yield, two steps). Importantly, this protocol provided a molecule (**44**) possessing the desired homologous carbon framework and delivered a nitrogen atom to the α-position of the ketone in two high yielding steps. With nitroketone **44** in hand, the cleavage of both indole nitrogen protective groups was readily accomplished. Scrupulously deoxygenated ethanolic KOH facilitated the removal of the N-tosyl group,[36] and $LiBF_4$ followed by aqueous NaOH effected complete hydrolysis of the SEM (i.e., **44** → **45**). Selective reduction of nitroketone **45** using stannous chloride[37] and removal of the benzyl and methyl ethers with iodotrimethylsilane revealed the fully deprotected aminoketone **46**.[38] Particularly noteworthy is that this sequence includes reduction of the nitro group to an amine and cleavage of the benzyl ether unit without the need for catalytic hydrogenative procedures or other methods that would have resulted in debromination of the indole C(6) position. Final installation of the aminoimidazolium unit with

(31) Arndt, F. *Org. Synth.* **1943**, Coll. Vol. *2*, 165.
(32) (a) Lancini, C. C.; Lazzari, E.; Sartori, C. *J. Antibiot.* **1968**, *21*, 387−392. (b) Howes, P. D.; Cleasby, A.; Evans, D. N.; Feilden, H.; Smith, P. W.; Sollis, S. L.; Taylor, N.; Wonacott, A. J. *Eur. J. Med. Chem.* **1999**, *34*, 225−234.

(33) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(34) (a) Aldehyde **43** was the last compound in the synthesis that was readily purified on preparative scale by silica gel flash chromatography. Although analytical scale purification beyond this point was enabled by reversed-phase HPLC or thin-layer chromatography on SiO_2, all preparative scale purification was conducted by reversed-phase C_{18} chromatography. Difficulties associated with the separation of similarly polar compounds by this method necessitated that all reactions in the sequence leading from **43** → **5** be high yielding. (b) The highly fluorescent nature (λ_{exc} = 365 nm) of many intermediates along the pathway from **8** → **5** facilitated the isolation of small amounts of compound in large quantities of solvent (i.e., ca. 1 mg/30−50 mL of solvent during reversed-phase chromatography). See the Supporting Information for details.
(35) (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945. (b) Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795−1805.
(36) Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670−5676.
(37) Sakowski, J.; Böhm, M.; Sattler, I.; Dahse, H.-M.; Schlitzer, M. *J. Med. Chem.* **2001**, *44*, 2886−2899.
(38) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495−496.

cyanamide followed by treatment with trifluoroacetic acid provided dragmacidin D (**5**) in 86% yield. Synthetic dragmacidin D was spectroscopically identical to samples obtained from natural sources (^{1}H NMR, ^{13}C NMR, IR, HRMS, UV).

Interestingly, the exact order of final synthetic events presented herein was essential for the completion of dragmacidin D. In particular, intermediates **44**−**46** were highly labile when treated under a variety of other conditions. For example, attempts to reduce nitroketone **44** or to remove the SEM group prior to detosylation resulted in substantial nonspecific decomposition. Likewise, efforts to deprotect **45** prior to nitro reduction led to the decomposition of the nitroketone moiety. Finally, reversing the order of the final two steps (i.e., aminoimidazole formation followed by treatment with TMSI) afforded only a low yield of dragmacidin D (ca. 5%).

Conclusion

In summary, we have completed the first total synthesis of the important bis-indole alkaloid dragmacidin D (**5**). The concise route that we have developed (longest linear sequence of 17 steps from **14**) relies on a key series of temperature-controlled selective Suzuki couplings and a meticulous sequence of final events leading to the completion of the natural product. Of particular note are the unique reactivity of 3,4,7-trisubstituted indoles and the steric and electronic subtleties associated with these systems. Specifically, the interplay of the indole C(3)−C(4) positions was observed in both the cyclocondensation approach and the end-game approaches to dragmacidin D. We are currently investigating the synthesis of a number of dragmacidin analogues, the development of an asymmetric route to dragmacidin D, and the extension of this chemistry toward the synthesis of dragmacidins E (**6**) and F (**7**) by both biomimetic and de novo synthetic routes. Results in these areas will be presented in due course.

Supporting Information Available: Full experimental details and characterization data for all synthetic intermediates, and spectral comparison for synthetic and natural **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA027822B