

A Strategy for the Total Synthesis of Dragmacidin E. Construction of the Core Ring System

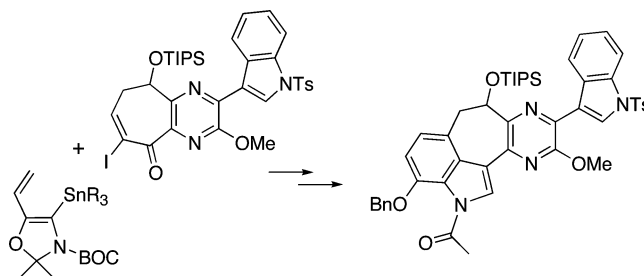
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ABSTRACT



The construction of the dragmacidin core ring system by a route that features the application of a new indole annelation reaction sequence is described.

Dragmacidins D, E, and F are an intriguing collection of bisindole alkaloids isolated from marine sponges.¹ They are structurally more complex than the dragmacidin A, B, and C congeners² that lack the guanidinium functionality and possess a piperazine linker instead of a pyrazinone between the two indole moieties (Figure 1). It has been suggested that dragmacidin D is the biosynthetic precursor to both dragmacidins E and F via bond formation between C(5'') and C(5'')^{1a} or C(4'') and C(6'')^{1b}, respectively. Moreover, dragmacidins D and E displayed antibiotic activity against *E. coli* (MIC = 9 and 12 μ M, respectively) and *C. albicus* (MIC = 11 and 20 μ M, respectively). In addition, dragmacidins D and E have been reported to be potent inhibitors of serine–threonine protein phosphatases,^{1a} biological targets of potential therapeutic value.³ However, in a subsequent

review,³ the protein phosphatase (PP1 and PP2a) inhibitory activity was claimed to be quite low, although no experimental evidence was provided. The promising biological activity coupled with the challenging architecture of these natural products has stimulated effort directed toward their total synthesis.⁴ The Stoltz group is the front runner in this endeavor and has reported the first and only syntheses of dragmacidins D and F.^{4f–h} The Feldman group has recently disclosed an approach to dragmacidin E that features the early, stereoselective construction of the cycloheptannelated indole substructure.⁴ⁱ

We became interested in the synthesis of dragmacidin E following the development of a method in our laboratories

(1) (a) 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. (b) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Fomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743.

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

(3) McCluskey, A.; Sim, A. T. R.; Sakoff, J. A. *J. Med. Chem.* **2002**, *45*, 1151.

(4) (a) Jiang, B.; Gu, X.-H. *Bioorg. Med. Chem.* **2000**, *8*, 363. (b) Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559. (c) Yang, C.-G.; Wang, J.; Jiang, B. *Tetrahedron Lett.* **2002**, *43*, 1063. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941. (e) Yang, C.-G.; Liu, G.; Jiang, B. *J. Org. Chem.* **2002**, *67*, 9392. (f) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (g) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (h) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970. (i) Feldman, K. S.; Ngermeesri, P. *Org. Lett.* **2005**, *7*, 5449.

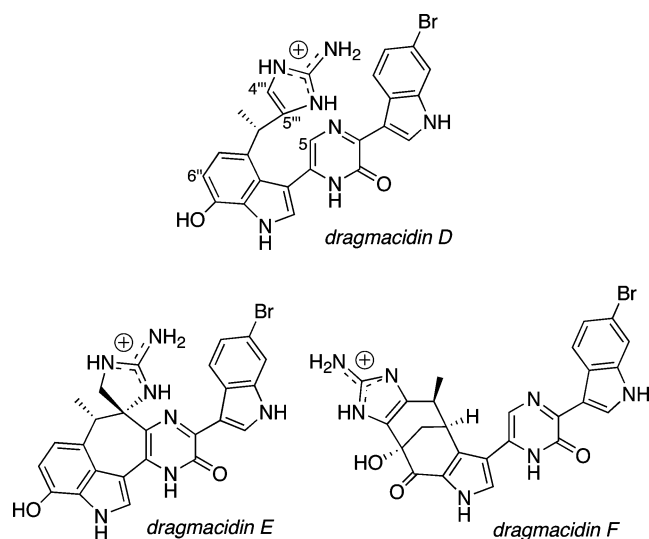
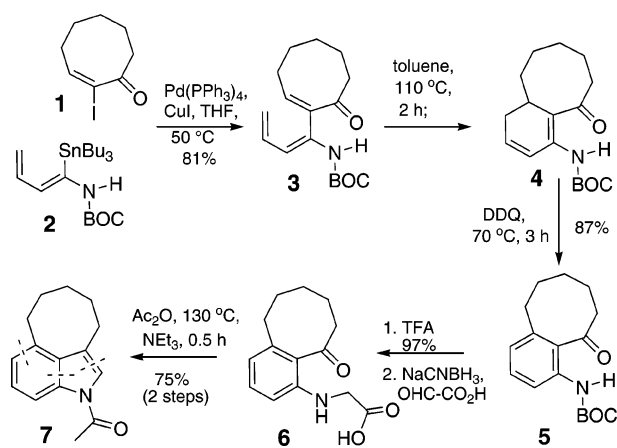


Figure 1. Selected members of the dragmacidin family of natural products.

that is especially useful for constructing indoles that are bridged at the C(3) and C(4) positions (Scheme 1).⁵ For example, we discovered that the Stille coupling reaction of 2-iodoenone **1** with the stannane **2** gave a trienecarbamate **3** that underwent a smooth 6π -electrocyclic ring closure to cyclohexadiene **4** and oxidation in the same pot with DDQ to afford the protected aniline **5**. Removal of the Boc group with TFA was uneventful, and a reductive amination of the resultant aniline with glyoxylic acid provided acid **6**.

Scheme 1



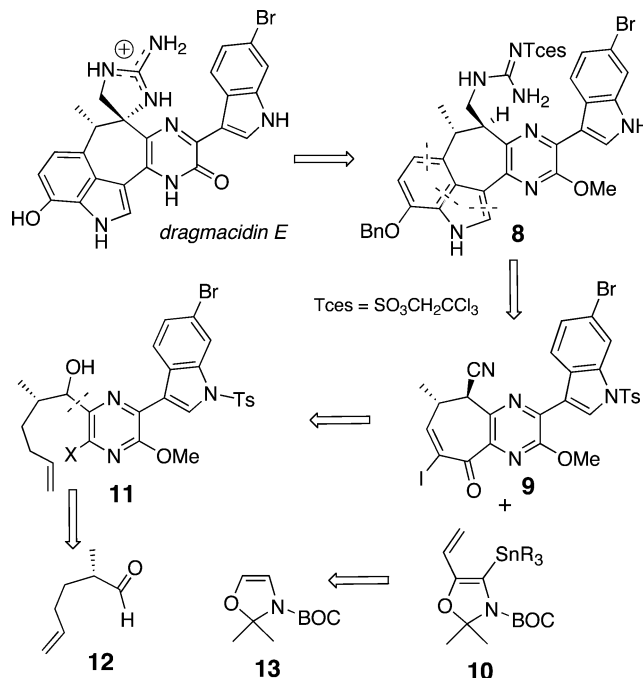
Completion of the indole annelation sequence was accomplished by heating acid **6** in acetic anhydride, which effected cyclization to the *N*-acetylindole **7**, presumably via a münchnone intermediate.⁶

A retrosynthetic analysis for the synthesis of dragmacidin E that takes advantage of this methodology is outlined in

(5) (a) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946. (b) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643.

Scheme 2. Thus, we planned to introduce the potentially problematic guanidine functionality at the end of the synthesis via the DuBois rhodium-mediated intramolecular C–H amination reaction of the *N*-trichloroethoxysulfonyl guanidine **8**.⁷ In the key disconnection, the indole **8** could

Scheme 2



be elaborated from the 2-iodoenone **9** and stannane **10** by the previously discussed reaction sequence. A number of schemes for the preparation of the cycloheptenone **9** could be envisaged, one of which involves an intramolecular Heck reaction of the halopyrazine **11**. It seemed likely that the haloindole substituent would tolerate this transformation based on the well-precedented superior reactivity of pyrazinyl halides toward oxidative addition.^{4e–h} Finally, the pyrazine **11** could be assembled by addition of the appropriate metalated pyrazine⁸ to the readily available, optically pure aldehyde **12**.⁹

To quickly validate this synthesis plan, we elected to initially prepare the core ring system without the methyl, bromo, and guanidine functionalities, and accordingly, the preparation of 2-iodoenone **20** (Scheme 3) became our

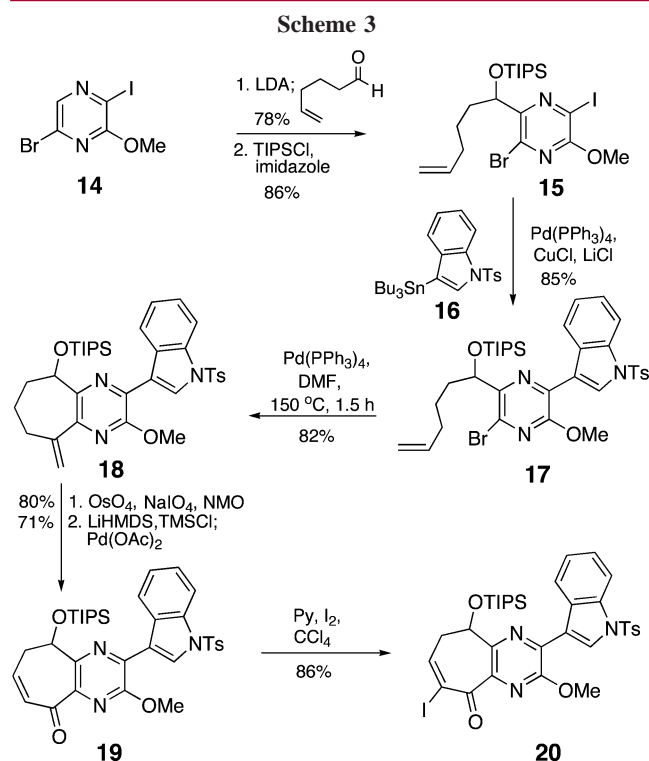
(6) To the best of our knowledge, only two indoles had been synthesized from aryl ketones/aldehydes by this type of cyclization, prior to our own work. Indole: (a) Glud, W. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 421. (b) Tighineanu, E.; Chiraleu, F.; Răileanu, D. *Tetrahedron* **1980**, *36*, 1385. 5-Methoxyindole: Blaikie, K. G.; Perkin, W. H., Jr. *J. Chem. Soc., Trans.* **1924**, *125*, 296. We thank a referee for pointing out the latter example.

(7) Kim, M.; Mulcahy, J. V.; Espino, C. G.; DuBois, J. *Org. Lett.* **2006**, *8*, 1073.

(8) (a) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301. (b) Turck, A.; Plé, N.; Dognon, D.; Harmoy, C.; Quéguiner, G. *J. Heterocycl. Chem.* **1994**, *31*, 1449. (c) Toudic, F.; Turck, A.; Plé, N.; Quéguiner, G. J.; Darabantu, M.; Lequeux, T.; Pommelet, J. C. *J. Heterocycl. Chem.* **2003**, *40*, 855.

(9) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888.

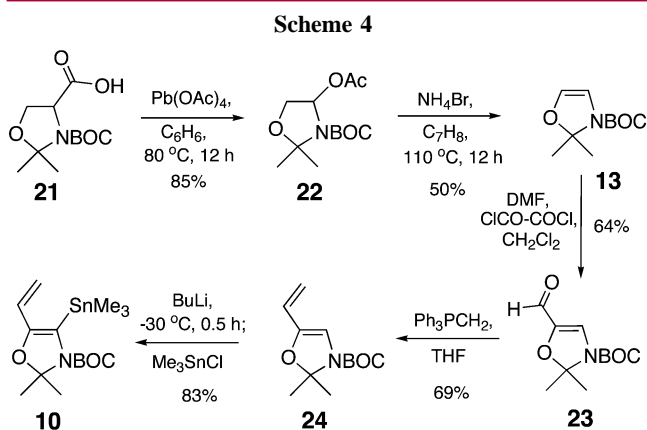
immediate goal. To that end, the easily accessible pyrazine **14**^{4f} was metalated by employing a procedure used for related halopyrazines⁸ and added to 5-hexenal to afford an alcohol



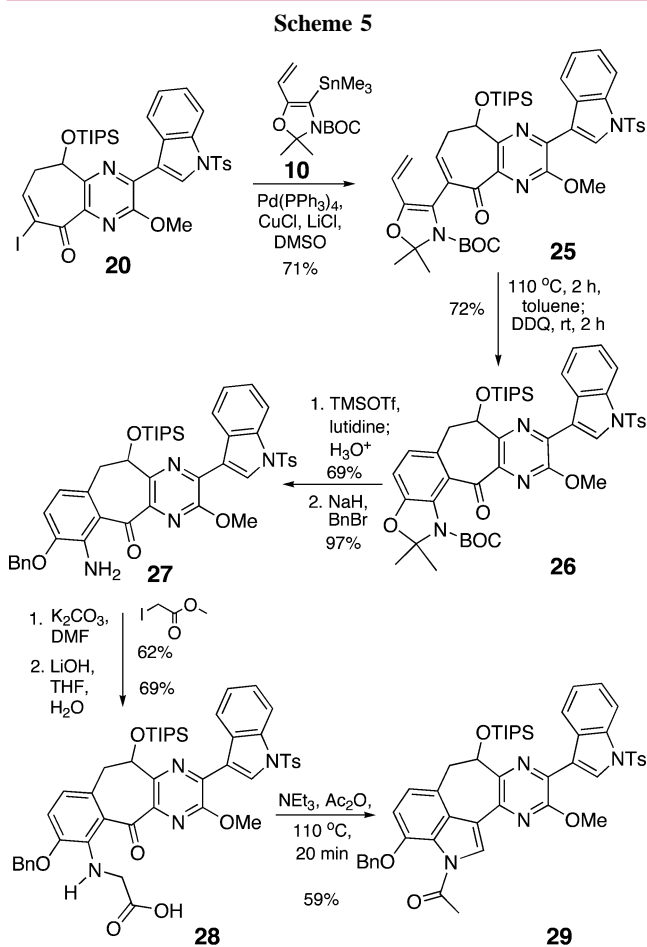
that was transformed to the TIPS ether **15**. Previous studies had shown that the chemoselective coupling of dihalopyrazines similar to **15** with indoloboronic acids analogous to stannane **16** proceeds cleanly.^{4e–h} Our case was no exception, affording the fully substituted pyrazine **17** in good yield, under Stille coupling conditions developed by Corey.¹⁰

We were pleased to discover that the bromopyrazine **17** underwent a smooth cyclization to the cycloheptannelated pyrazine **18** upon subjection to standard Heck reaction conditions. Oxidative cleavage of the alkene moiety of pyrazine **18** followed by dehydrogenation of the resulting ketone following the Saegusa protocol afforded cycloheptenone **19** that was converted to the initial target, 2-iodoenone **20**, via treatment with iodine in pyridine.¹¹

We now turned our attention to the preparation of the dienylstannane **10** required for the indole annelation (Scheme 4). The known acid **21**¹² was converted to the oxazoline **13** following a route that had previously been reported for the analogous 2-*tert*-butyl oxazolidine.¹³ Thus, oxidative decarboxylation of acid **21** with lead tetraacetate gave oxazolidine **22**, which was subjected to ammonium bromide in order to promote the elimination of acetic acid and thereby furnish



enecarbamate **13**. Regioselective Vilsmeier–Haack formylation of enecarbamate **13**¹⁴ gave the vinylogous imide **23** that was converted to diene **24** using standard Wittig olefination conditions. Finally, metalation of the dienecarbamate **24** with butyllithium followed by stannylation of the resulting vinyl anion gave the desired stannane **10**.



(10) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(11) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Sennayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

(12) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2005**, *15*, 45.

The stage was now set for the execution of the indole annelation reaction sequence (Scheme 5). The Stille coupling

of the 2-iodoenone **20** with dienylstannane **10** proceeded smoothly to provide the trienecarbamate **25**. Heating trienecarbamate **25** in toluene promoted an electrocyclic closure that could be monitored by TLC. When the transformation to the corresponding cyclohexadiene was judged to be complete (2 h), the temperature was lowered (rt) and 2 equiv of DDQ was added to effect aromatization to the benzoxazolidine **26**. Although we were able to successfully remove the Boc protecting group from carbamate **26**, all attempts to subsequently append the acetic acid side chain to the resulting benzoxazoline via reductive amination or alkylation protocols failed. Accordingly, both the Boc group and *N,O*-acetal were removed to afford a hydroxy aniline whose hydroxyl

functionality was converted to the benzyl ether **27**. Alkylation of the aniline **27** with methyl iodoacetate provided the methyl ester (62%; aniline **27** was also recovered, 28%), which underwent saponification to give the desired anilinoacetic acid **28**. Acid **28** was then converted to the bisindole **29** using our standard conditions for ring closure.

In conclusion, we have prepared the core ring system of dragmacidin E by a route that features our 6π -electrocyclic ring-closure-based method for the construction of complexly substituted indoles. The incorporation of additional functionality that will permit the completion of the total synthesis is now warranted and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) (a) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 843. (b) Seebach, D.; Stucky, G. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 1351. (c) Lamatsch, B.; Seebach, D. *Helv. Chim. Acta* **1992**, 75, 1095. (d) Ghosez, L.; Yang, G.; Cagnon, J. R.; Bideau, F. L.; Marchand-Brynaert, J. *Tetrahedron* **2004**, 60, 7591.

(14) Seebach has shown that oxazolidines of this type prefer to undergo electrophilic addition at C(5), presumably due to the greater stability of an *N*-acyliminium ion vis-à-vis an oxonium generated by attack at C(4); see refs 13b and 13c.