A Facile Synthesis of Dragmacidin B and 2,5-Bis(6'-bromo-3'-indolyl)piperazine

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ABSTRACT



A short synthesis of dragmacidin B (1), 2,5-bis(6'-bromo-3'-indolyl)piperazine (2), and corresponding didebromo analogues 8 and 9 is described. The key steps involve the dimerization of oxotryptamines 4 and 11 to give bis(indolyl)pyrazines 5 and 12, which upon selective reduction and reductive methylation with sodium cyanoborohydride afforded the requisite piperazine natural products.

Marine sponges produce a number of bioactive bisindole metabolites containing either an imidazole or piperazine derived spacer unit.¹ The 2,5-bis(3'-indolyl)piperazine alkaloids, dragmacidin B (1)² (from the sponge, *Hexadella* sp.) and 2,5-bis(6'-brono-3'-indolyl)piperazine (2)³ (from the tunicate, *Didemnum candidum*), are representative of a group of bisindole metabolites containing a piperazine linker.⁴ Despite the broad range of biological activity exerted by the class of bis(indolyl)piperazines, which includes cytoxicity,

(1) Faulkner, D. J. Nat. Prod. Rep. 2000, 17, 7 and previous reports in this series.

(2) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715. Although originally named dragmacidon B, this metabolite also has been referred to as dragmacidin B.^{5a} We prefer the use of dragmacidin B because of its structural similarity to dragmacidin, the first isolated bisindole piperazine metabolite.^{4a}

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only two reports have described the successful construction of the piperazine ring system.⁵ In both reports, access to the substituted piperazines was achieved via diborane reduction of diketopiperazine intermediates.



Biosynthetically, dragmacidin B and the related bisindole imidazole, topsentin A, are conceivably derived by the condensation of two tryptamine derivatives in either a headto-head (topsentins) or head-to-tail (dragmacidins) orientation. Recently, we reported a concise synthesis of topsentin A that proceeded through the facile preparation of oxotryptamine 4 and its head-to-head condensation in the presence of ammonia and air.⁶ In this communication, we describe a simple synthesis of dragmacidin B (1), 2,5-bis-(6'-bromo-3'-indolyl)piperazine (2), and debromo analogues 8 and 9 via head-to-tail dimerizations of oxotryptamines 4 and 11. In addition, we disclose a useful method for the preparation of substituted piperazines from pyrazines via selective reduction and reductive methylation with sodium cyanoborohydride.

Our approach to the piperazine ring system begins with acyl cyanide 3 (Scheme 1). Hydrogenation over Pd/C gave



oxotryptamine 4 in excellent yield.⁶ There is ample literature precedent suggesting that α -amino ketones such as 4 can undergo dimerization to pyrazines.⁷ Upon heating 4 in a xylene/EtOH (4:1) solution under a sealed atmosphere of argon followed by exposure to air and filtration, pyrazine 5 was obtained in good yield as a yellow solid. The success of this result prompted us to pursue the dimerization of hydroxy tryptamine 6, which in principle would lead directly to the desired piperazine ring system. Reduction of acyl

cyanide 3 with LAH⁸ gave the expected amino alcohol 6.9Heating 6 under analogous conditions (e.g., 4 to 5) produced a complicated mixture of products, none of which appeared to contain a piperazine ring. Instead, symmetrical dimer 7 and indole were isolated as the principle components but only in modest amounts. These results suggest that a retrotype aldol mechanism is operative under these conditions that precludes the desired dimerization event. Biosynthetically, it is interesting to speculate that a related type of degradative process may be occurring during the formation of 4- and 6-bromo-substituted indole metabolites that lack substituents at the 3-position.¹⁰

Next, reduction of the pyrazine ring in 5 to the requisite piperazine system was investigated (Scheme 2). In relevant



indole chemistry, Gribble and co-workers have shown that indoles can be readily reduced to indolines using borohydrides and carboxylic acids.¹¹ By adopting this set of reaction conditions, pyrazine 5 underwent clean conversion to piperazine 8 using NaBH₃CN in acetic acid. Only the thermodynamically more stable trans diequatorial isomer was detected. Using formic acid as solvent, piperazine 5 underwent reductive methylation to afford dimethyl piperazine 9 in satisfactory yield. In both cases, reduction of the indole double bond was not observed. These results suggest that the initial reduction of pyrazine to piperazine prevents reduction of the indole double bond, possibly through steric factors.12

With the synthetic approach and methodology in hand for the debromo dragmacidin analogues 8 and 9, our attention turned to the natural products, dragmacidin B (1) and 2,5bis(6'-bromo-3'-indolyl)piperazine (2) (Scheme 3). Both substituted piperazines 1 and 2 contain a 6-bromoindole

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⁽⁸⁾ Burger, A.; Hornbaker, E. D. J. Am. Chem. Soc. 1952, 74, 5514. (9) All new compounds gave satisfactory spectral data (1H and 13C NMR and HRMS).

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moiety. Accordingly, the introduction of bromine directly to the 6-position of oxotryptamine **4** was viewed as the most direct approach in our synthetic scheme. This approach is based on the successful incorporation of bromine to 3-cy-anoindole, which produced 6-bromo-3-cyanoindole as the major product.⁶ In the present case, however, bromination (23 °C, 12 h) of oxotryptamine **4** produced an isomeric

mixture of 5- and 6-substituted indole derivatives **10** and **11** in an approximate 2:1 ratio, respectively. Bromoindoles **10** and **11** can be separated by flash chromatography. Condensation of **11** under thermal conditions gave pyrazine **12** in good yield. Selective reduction of the pyrazine ring using NaBH₃CN in formic or acetic acid (23 °C, 24 h) afforded dragmacidin B (1) and 2,5-bis(6'-bromo-3'-indolyl)piperazine (2), respectively. Spectral data for synthetic **1** and **2** were consistent with those reported for the corresponding natural material.

In summary, a short synthesis of bis(indolyl)piperazine natural products 1 and 2 has been achieved. The synthesis is highly convergent and highlights a useful preparation of piperazines from pyrazines under convenient reaction conditions.

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Supporting Information Available: ¹H and ¹³C NMR spectra for compounds 5-12, dragmacidin B (1), and 2,5-bis(6'-bromo-3'-indolyl)piperazine (2). This material is available free of charge via the Internet at http://pubs.acs.org.

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