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Synthesis of Marine Sponge Bisindole Alkaloids Dihydrohamacanthins

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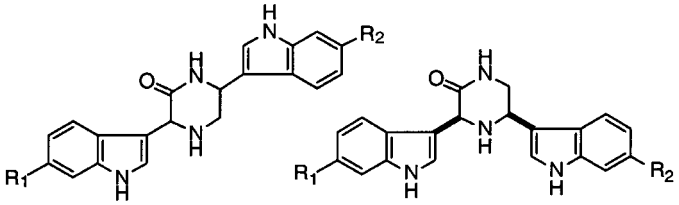
ABSTRACT



A convergent synthesis of the marine sponge bisindole alkaloids dihydrohamacanthins is described. The synthesis centers on the construction of 3,5- and 3,6-linked pyrazinones and their reduction to the requisite piperazinones with sodium cyanoborohydride.

Over the past decade, a number of bisindole metabolites containing either an imidazole- or piperazine-derived spacer have been isolated from various genera of sponges.[1] Metabolites within this family illicit a myriad of biological responses that include cytoxic and antitumor activities. Recently, a bioassay guided fractionation of the Mediterranean sponge *Rhaphisia lacazei* produced *cis*-3,4-dihydrohamacanthin A (**1a**), *trans*-3,4-dihydrohamacanthins A (**1b**−**3b**), and *cis*-3,4-dihydrohamacanthins B (**5**−**7**).[2] These metabolites are the first reported examples of bis(indolyl)-piperazinones and are closely related to hamacathin A and B, which are the 3,4-dehydro analogues ($R_1 = R_2 =$ Br).[3,4] Further biological testing of dihydrohamacanthins was not possible because of the limited quantity of material obtained from the isolation procedure. Herein we outline a short and general approach to synthesis of 3,5- and 3,6-linked bis-(indolyl)piperazinones **3a,b**, **4a,b**, **6**, and **8** from a common precursor, oxotryptamine **9**.

We recently reported the total synthesis of bisindole alkaloids topsentin and nortopsentin (imidazole-derived spacer) and dragmacidin (piperazine-dervied spacer) from oxotryptamine **9**.[5,6] Although the self-dimerization of α-aminoketones such as **9** is well-proven,[7] its potential use in a mixed cyclocondensation reaction would offer a novel and attractive entry to the unsymmetrical piperazinone spacer unit found in dihydrohamacanthins. We felt that the amine salt of **9** would retard the self-condensation pathway, thus allowing for potential condensation with other substrates.

Scheme 1 outlines the synthesis of dihydrohamacanthin A (**4a** and **4b**) utilizing this approach. Heating oxotryptamine **9**[5] with ketoamide **10** in the presence of 1.2 equiv of methanesulfonic acid afforded 3,6-bis(indol-3-yl)-2(1*H*)-pyrazinone (**11**)[8] in 30% yield. Reduction of pyrazinone **11**

(1) For a review, see: Faulkner, D. J. *J. Nat. Prod. Rep.* **2001**, *18*, 1 and references therein.
(2) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447.
(3) For isolation, see: Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1994**, *57*, 1437.
(4) For a synthesis of the (−)-antipode of hamacanthin A, see: (a) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865.
(5) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121.
(6) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3185.
(7) Sato, N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Boulton, A. J., Eds.; Pergamon: New York, 1996; Vol. 2, p 266.
(8) A 10-step synthesis of pyrazinone **11** has been recently reported; see: Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559.

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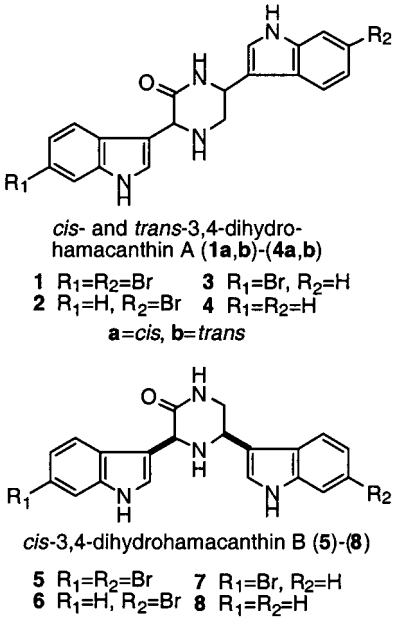
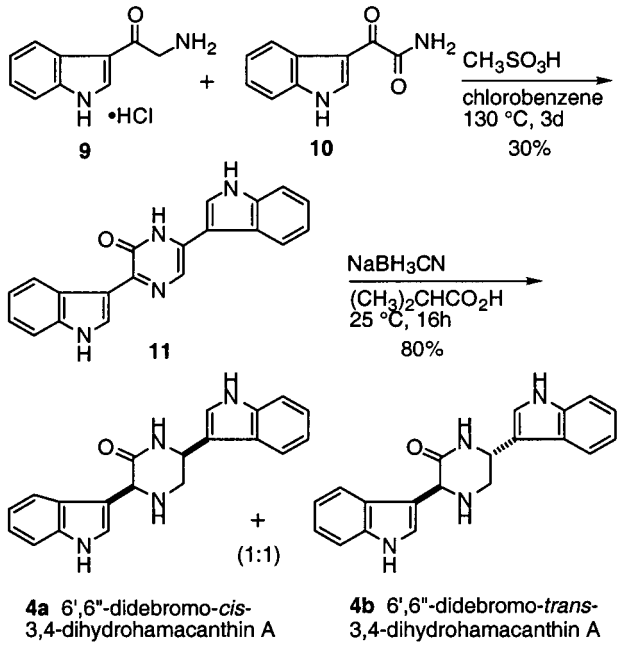


Figure 1.

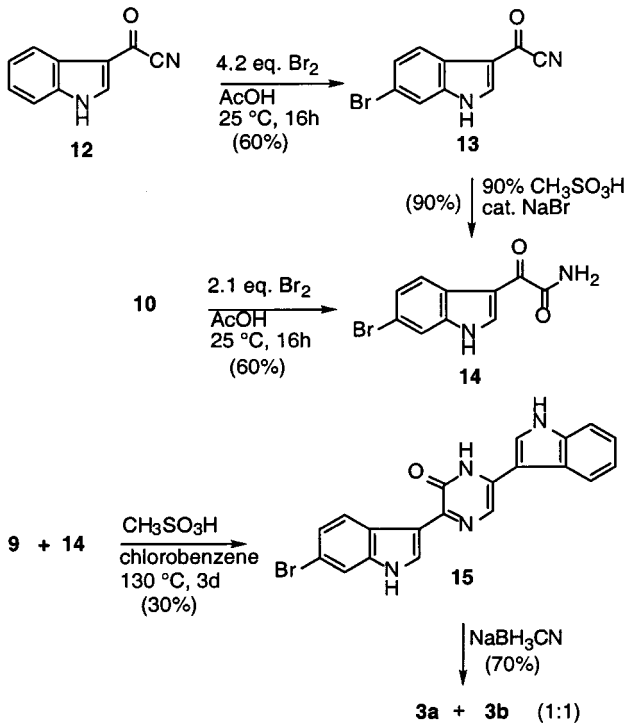
using sodium cyanoborohydride produced the desired piperazinones **4a** and **4b** as a 1:1 mixture of diastereomers that were separated by preparative thin layer chromatography. Although the yield for the condensation of **9** and **10** is modest, alternative methods for the preparation of 3,6-substituted piperazinones are lacking and the present method is short.

For the synthesis of *cis*- and *trans*-6″-debromo-3,4-dihydrohamacanthins A (**3a** and **3b**), bromoamide **14** was

Scheme 1



Scheme 2



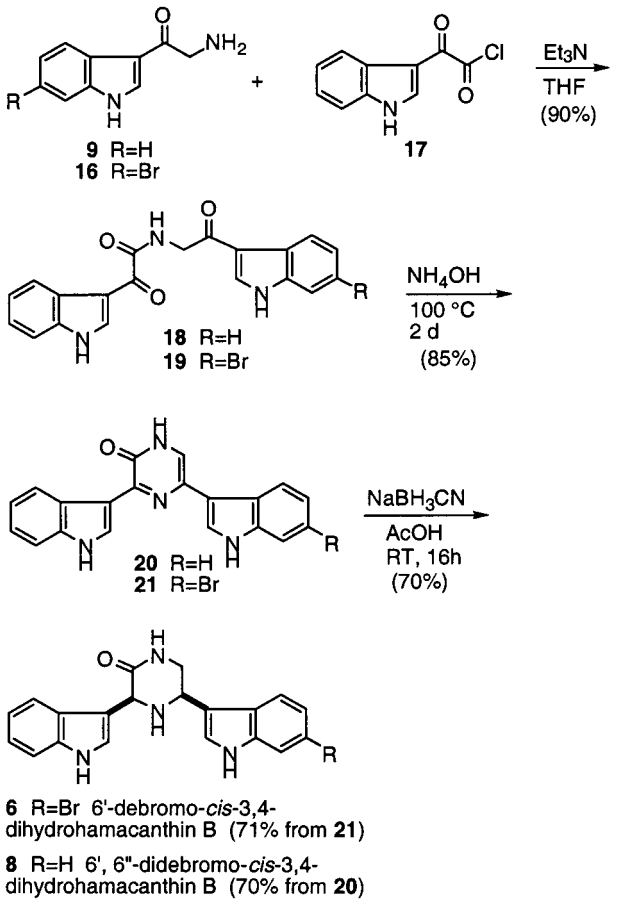
prepared by two different routes (Scheme 2). Treatment of **12** with excess bromine in acetic acid produced 6-bromoindole **13** in 60% yield after flash chromatography. Acid-facilitated hydrolysis[9] of the nitrile produced in high yield ketoamide **14**. Alternatively, **14** can be obtained directly from bromination of **10** and flash chromatography of the reaction mixture. Condensation of **9** and **14** under analogous conditions produced the desired bis(indolyl)pyrazinone **15** in modest yield.

Similarly, reduction of the pyrazinone with sodium cyanoborohydride gave dihydrohamacanthin A (**3a** and **3b**) without affecting the aromatic bromide substituent. All spectral data of synthetic **3b** were in satisfactory agreement with data reported for the natural product.[2] This cyclocondensation/reduction sequence represents a novel approach to 3,6-linked piperazinone construction as it relates to the synthesis of 3,6-linked bis(indolyl)piperazinones natural products, dihydrohamacanthins A.

Scheme 3 outlines the synthesis of *cis*-3,4-dihydrohamacanthin B (**6** and **8**). The approach is based on the preparation and reduction of 3,5-linked pyrazinones. In constrast to a dearth of existing methodolgy for the preparation of 3,6-linked pyrazinones, prior methodology for the general construction of 3,5-linked pyrazinones has been established by Bradbury[10] and involves the condensation of α-ketoamides such as **18** and **19** with ammonia. This approach has been utilized by Jiang for the prepartion of

(9) Photis, J. M. *Tetrahedron Lett.* **1980**, *21*, 3539.
(10) Bradbury, R. H.; Griffiths, D.; Rivett, J. E. *Heterocycles* **1990**, *31*, 1647.

Scheme 3



debromopyrazinone **20**.[8] Acylation of oxotryptamine **9** or 6-bromooxotryptamine **16**[6] with indole oxalyl chloride **17** afforded amides **18** and **19**, respectively. Using a modified Bradbury procedure, heating **18** or **19** in aqueous ammonia produced pyrazinones **20** and **21** in good yields. Reduction of these pyrazinones with sodium cyanoborohydride proceeded stereoselectively to give, exclusively, *cis*-3,5-linked piperazinones **6** and **8**. All spectral data for synthetic **6** were in satisfactory agreement with data reported for the natural product.[2]

In summary, we have developed a short route to 3,5- and 3,6-linked brominated and nonbrominated bis(indolyl)piperazinone natural products that is based on a new method of pyrazinone construction and reduction. The 2(1*H*)-pyrazinone spacer seen in **11** and **15** is also found in the related marine natural products dragmacidins,[11] as well as metabolites from microbial sources.[12]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **6**, **8**, **11**, **13**−**15**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772. (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. (c) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743.

(12) Vining, L. C. In *CRC Handbook of Microbiology*; Laskin, A. I., Lechevalier, H. A., Eds.; CRC Press: Boca Raton, FL, 1984; Vol. 5, pp 623−626.