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Total Syntheses of Brominated Marine Sponge Alkaloids

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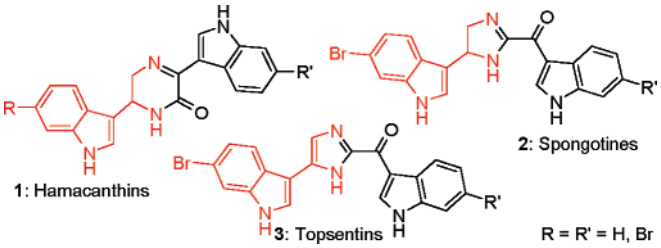
ABSTRACT



Total syntheses of six brominated marine sponge bis(indole) alkaloids of the hamacanthin, spongotine, and topsentin classes are described. Retrosynthetic analysis shows that their structures all include the 1-(6′-bromoindol-3′-yl)-1,2-diaminoethane unit 13a. This key moiety has been prepared from brominated indolic *N*-hydroxylamine 5b via synthetic intermediate 8b.

Natural products of marine origin still continue to fascinate organic chemists due to the wide diversity of their structural features and biologists for their potent biological properties.[1] Many of these compounds are implicated in chemical defense against predators or biofouling[2] and possess a panel of biological properties.[3] In particular, compounds belonging to the bis(indole) alkaloids class, such as hamacanthins **1**,[4−6] spongotines **2**,[4,5,7] topsentins **3**,[4,5,8] nortopsentins,[4] and dragmacidins,[4] isolated from marine sponges, have received a lot of attention because some of them exhibit various potent bioactivities such as cytotoxic, antiviral, antitumor, and anti-inflammatory activities.[5,6b,9] These properties have made them attractive targets for biomedical purposes.[10]

In this context, we noticed that hamacanthins **1**, spongotines **2**, and topsentins **3** include the 1-(indol-3′-yl)-1,2-diaminoethane unit **13** (Figure 1), a common key moeity that

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(5) In a recent article, Jung et al. described the structural elucidation and/or biological activities of all natural products described herein except **3b**. See: Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Cho, H. Y.; Jung, J. H. *J. Nat. Prod.* **2007**, *70*, 2.

(6) (a) For the first isolation of (*S*)-(+)-hamacanthin **1a**, see: Gunasekera, S. P.; Mccarthy, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1994**, *57*, 1437. (b) For the first isolation of (*R*)-(−)-hamacanthins **1b** and **1c**, see: Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Ya Sim, C.; Sik Im, K.; Jung, J. H. *J. Nat. Prod.* **2005**, *68*, 711. (c) For the first isolation of (*S*)-(+)-hamacanthin **1d**, see ref 5.

(7) (a) For the first isolation of the (−)-spongotine A **2a**, see: Tsujii, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446. (b) For the first isolation of the (−)-spongotine C **2b**, see ref 5.

(8) (a) For the first isolation of topsentin **3a**, see: Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod.* **1999**, *62*, 647. (b) For the first isolation of topsentin **3b**, see ref 6b.

(9) Oh, K.-B.; Mar, W.; Kim, S.; Kim, J.-Y.; Lee, T.-H.; Kim, J.-G.; Shin, D.; Sim, C. J.; Shin, J. *Biol. Pharm. Bull.* **2006**, *29*, 570.

(10) For patent literature, see: (a) Gunasekera, S. P.; Cross, S. S.; Kashman, Y.; Lui, M. S. Eur. Patent 272 810, 1988; *Chem. Abstr.* **1988**, *109*, 129417q. (b) Gunasekera, S. P.; Cross, S. S. Eur. Patent 304 157, 1989; *Chem. Abstr.* **1989**, *111*, 160196g. (c) Gunasekera, S. P.; Cross, S. S.; Kashman, Y.; Lui, M. S.; Rinehart, K. L.; Tsujii, S. U.S. Patent 4 866 084, 1989; *Chem. Abstr.* **1990**, *112*, 185775d. (d) Sun, H. H.; Sakemi, S.; Gunasekera, S.; Kashman, Y.; Lui, M.; Burres, N.; McCarthy, P. U.S. Patent 4 970 226, 1990; *Chem. Abstr.* **1991**, *115*, 35701z. (e) McConnell, O. J.; Saucy, G.; Jacobs, R. U.S. Patent 5 290 777, 1994; *Chem. Abstr.* **1994**, *120*, 236178m. (f) Wright, A. E.; Mattern, R.; Jacobs, R. S. Patent WO 2000002857, 2000.

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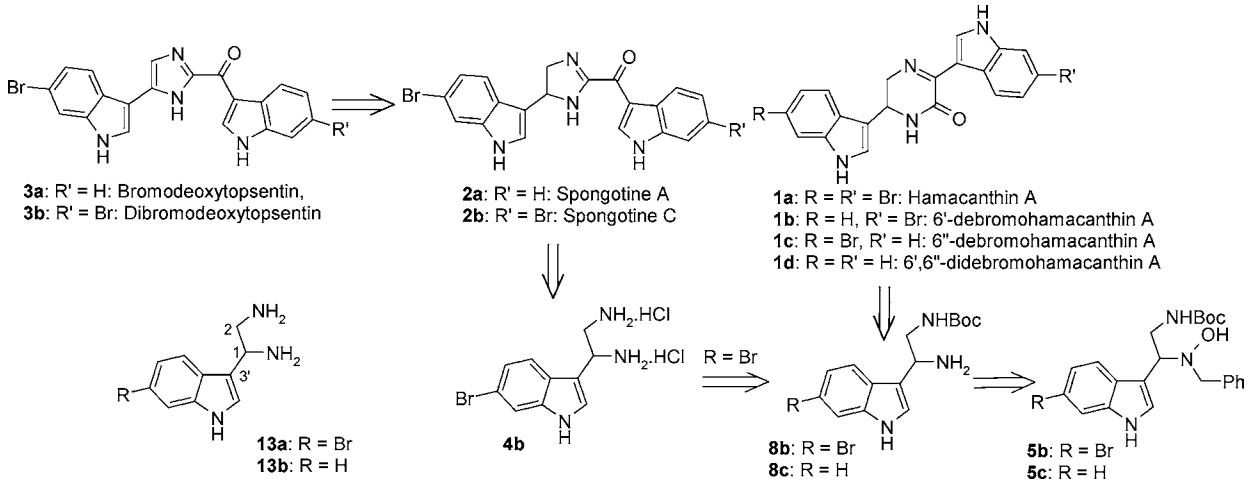
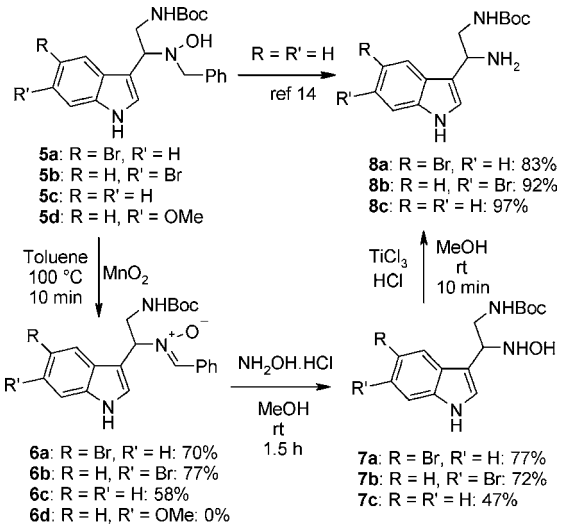


Figure 1. Retrosynthetic analysis and structures of synthesized bis(indole) alkaloids.

could be elaborated by a reaction of α-amino nitrones with the appropriate indolic core.[11] However, the few reported total syntheses of these alkaloids[12,13] **1** and **3** do not use precursors containing this indolic 1,2-diaminoethane moiety. Moreover, the synthesis of spongotines **2** was not described until our recent report[14] describing the total synthesis of two (±)-spongotines **2** and three topsentins **3** from nonbrominated *N*-hydroxylamine **5c** (R = H). However, this strategy could not be applied to the brominated bis(indole) alkaloids because debromination occurred during the debenzylation step. We consequently sought a strategy compatible with the bromoindolyl moiety.

In this paper, we wish to report the recent developments of our methodology which allow access to building blocks **4b** and **8b** from brominated *N*-hydroxylamine **5b**[11] and its application to the total syntheses of (±)-hamacanthins **1a**,**c**, (±)-spongotines **2a**,**b**, and topsentins **3a**,**b**. This new methodology has been applied to the 6-bromoindolyl, 5-bromoindolyl, and indolyl series as shown in Scheme 1. The synthesis of (±)-hamacanthins **1b** and **1d** (R ≠ Br) from indolic *N*-hydroxylamine **5c** is also reported. To the best of our knowledge, we describe herein the first total syntheses of all these alkaloids except (±)-hamacanthin **1a** and topsentin **3a**.[12,13]

Scheme 1



First, the indolic *N*-hydroxylamines **5a**−**c** have been oxidized to nitrones **6a**−**c** by using manganese dioxide[15] at 100 °C during 10 min in toluene. The nitrones **6a**−**c** are obtained with 70%, 77%, and 58% yields, respectively. We observed that the more activated the indolic core was, the lower the yield was. In particular, we got 0% yield with **5d** (complete degradation of the reaction mixture). We then performed the hydroxyaminolysis of indolic nitrones **6a**−**c** with hydroxylamine hydrochloride in MeOH at room temperature. Primary *N*-hydroxylamines **7a**−**c** have been obtained in good yields. Finally, these *N*-hydroxylamines **7a**−**c**

(11) For the preparation of indolic *N*-hydroxylamines, see: (a) Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallée, Y. *Tetrahedron* **2000**, *56*, 791. (b) Denis, J.-N.; Mauger, H.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 8515.

(12) For the synthesis of (±)- and (*S*)-(+)-hamacanthins A **1a**, see: (a) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron*: *Asymmetry* **2002**, *13*, 383. (b) Kouko, T.; Matsumura, K.; Kawasaki, T. *Tetrahedron* **2005**, *61*, 2309. (c) Kawasaki, T.; Kouko, T.; Totsuka, H.; Hiramatsu, K. *Tetrahedron Lett.* **2003**, *44*, 8849. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121. For the synthesis of non-natural (*R*)-(−)-hamacanthin A, see: Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865.

(13) For the synthesis of topsentin A (**3**, R = R′ = H), see: (a) Braekman, J. C.; Daloze, D.; Stoller, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 809. (b) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycl. Commun.* **1996**, *2*, 189. (c) Achab, S. *Tetrahedron Lett.* **1996**, *37*, 5503. (d) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887. For the synthesis of topsentin **3a**, see ref 13c.

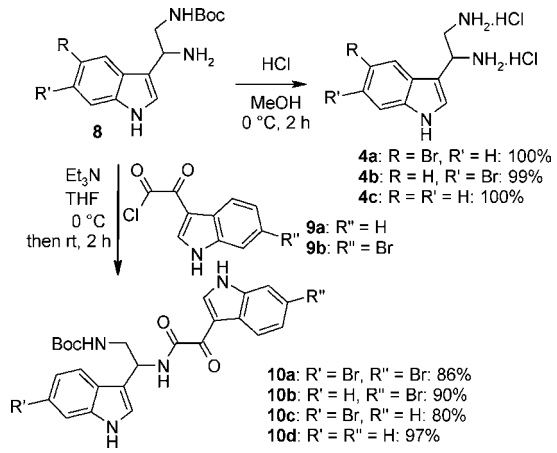
(14) Guinchard, X.; Vallée, Y.; Denis, J.-N. *J. Org. Chem.* **2007**, *72*, 3972.

(15) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503.

have been reduced with 2 equiv of titanium trichloride in MeOH[16] to afford the corresponding monoprotected diamines **8a**−**c** in 83−97% yields. The benzyl group has consequently been removed in a three-step sequence via a strategy of oxidation−hydroxyaminolysis−reduction, providing the free amines **8a**, **8b**, and **8c** in 45%, 51%, and 26% overall yields, respectively.

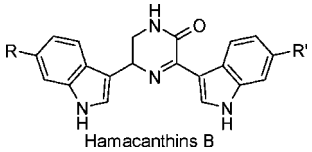
Amines **8a**−**c** have been deprotected with a 8% solution of hydrochloric acid in dry MeOH[14,17] affording quantitatively the corresponding indolic 1,2-diamine salts **4a**−**c** (Scheme 2). These salts are stable and could be stored at

Scheme 2



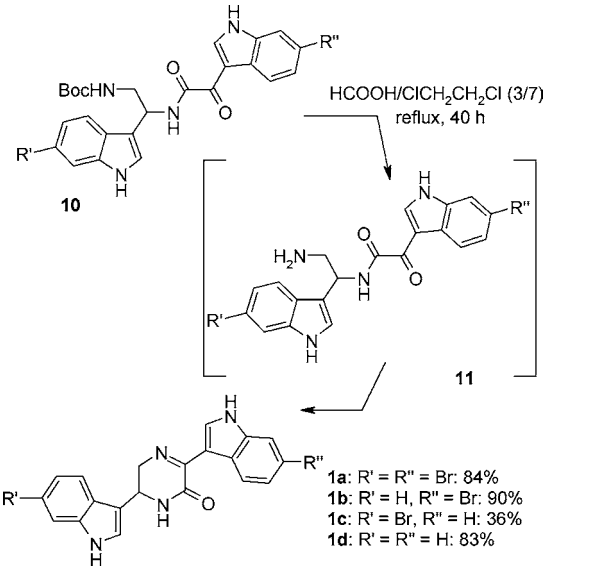
0 °C over long periods without any degradation. However, when we tried to obtain the basic 5- and 6-bromoindolic 1,2-diamino compounds by basic treatment of **4a** and **4b**, respectively, degradation occurred quickly. On the other hand, amines **8b**,**c** have been reacted with α-ketoacid chlorides **9**, prepared from the corresponding indoles,[18] providing the amides **10a**−**d** in excellent yields.

Amides **10** were then refluxed during 40 h in a 3/7 mixture of HCOOH/1,2-dichloroethane to afford hamacanthins **1a**−**d** in good yields (Scheme 3). Deprotection by formic acid generates in situ the primary amines **11a**−**d**, which cyclized by reaction with the carbonyl to provide the expected hamacanthins **1**. This transformation has surprisingly shown total chemoselectivity toward hamacanthins of A series **1a**−**d** contrary to what was reported in similar synthetic strategies.[12c,d] No traces of any hamacanthin of B series were detected.



These syntheses of hamacanthins **1a**−**d** take advantage of the orthogonality of the benzyl and Boc protecting groups

Scheme 3



in the starting indolic *N*-hydroxylamines **5b**,**c**, which can be eliminated in different conditions.

The salt **4b** was reacted with *S*-methylthioimidate salts[14] **12a** and **12b** in MeOH in the presence of triethylamine. The desired natural spongotines **2a** and **2b** were obtained in 76% and 64% yields, respectively. As recently reported,[5] broading and/or doubling of ^{1}H NMR signals of compounds **2a** and **2b** were observed in neutral DMSO-d_6 solution due to slow interconversion of α-keto imidazoline tautomers and/or rotamers. The ^{1}H NMR spectrum of spongotine A **2a** with TFA in DMSO-d_6 solution is in agreement with the one described in this paper.[5]

Finally, oxidation of these imidazoline derivatives **2a**,**b** with IBX in DMSO[19] afforded the natural bromodeoxytopsentin **3a** and dibromodeoxytopsentin **3b** with 78% and 90% yields, respectively. Spectroscopic data for **3a** and **3b** are in agreement with those previously reported in the literature.[8,20] As expected, mixtures of slowly interconverting tautomers were observed in ^{1}H and ^{13}C NMR in neutral solution (CD_3COCD_3). We observed a splitting of all signals that could be suppressed by addition of 1% of CF_3COOD into the deuterated solvent.

In summary, we have developed the first synthesis of the original indolic 1,2-diamino derivatives **4a**,**b** and **8a**,**b**, brominated on either position 5 or 6 of the indole core from the corresponding indolic *N*-benzyl-*N*-hydroxylamines **5a**,**b**. The indolic 1,2-diamino compounds **8b**,**c** have then been

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(18) (a) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (b) Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G.; Armstrong, M. D. *J. Org. Chem.* **1958**, *23*, 1171. (c) Hashem, M. A.; Sultana, I.; Hai, M. A. *Indian J. Chem., Sect. B* **1999**, *38*, 789.

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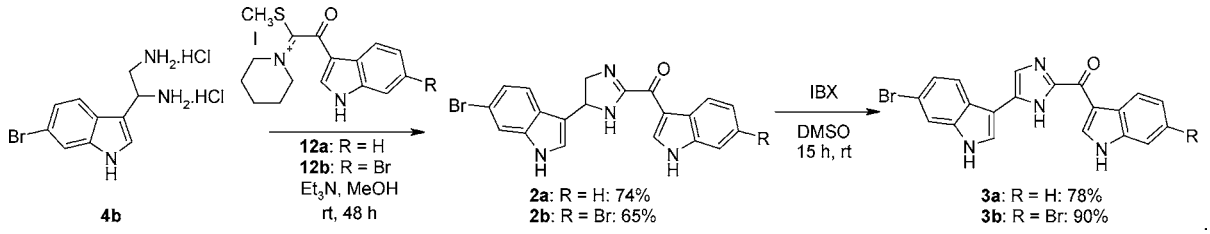
(20) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447.

Scheme 4



engaged as building blocks in the total synthesis of (±)-hamacanthins **1a**−**d** (obtained in 37%, 23%, 15%, and 21% overall yields, respectively, in five steps from *N*-hydroxylamines **5b**,**c**), (±)-spongotines **2a**,**b** (obtained in 38% and 33% overall yields, respectively, in five steps from *N*-hydroxylamine **5b**), and topsentins **3a**,**b** (both obtained in 29% overall yield in six steps from *N*-hydroxylamine **5b**). To the best of our knowledge, these are the first described total syntheses of (±)-hamacanthins **1b**−**d**, (±)-spongotines **2a**,**b**, and topsentin **3b**. This strategy is versatile and allows access to a large number of indolic alkaloids bearing different subsituents. Moreover, this strategy is smooth enough to avoid protecting groups on the nitrogen atom of the indolic cores.

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Supporting Information Available: Experimental procedures and characterization data for all products, ^{1}H NMR and/or ^{13}C NMR spectra of all new compounds, hamacanthins **1a**−**d**, spongotines **2a**,**b**, and topsentins **3a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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