Enantioselective Synthesis for the (−)-Antipode of the Pyrazinone Marine Alkaloid, Hamacanthin A

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A short enantioselective total synthesis for the (−)-antipode of the antifungal marine alkaloid, hamacanthin A, (6*R*)-3,6-bis(6-bromoindol-3-yl)-5,6-dihydro-2(1*H*)-pyrazinone, is described. This synthesis proceeds through the coupling of 3-indolyl-α-oxoacetyl chloride and 3-indolyl azidoethylamine, followed by intramolecular aza-Wittig type cyclization. A concise and useful approach for the synthesis of (1*R*)-1-(indol-3-yl)-2-azidoethylamine using the Sharpless asymmetric dihydroxylation reaction followed by stereospecific azidation is also presented.

Introduction

Marine organisms are among the most promising sources of a great variety of new biologically active molecules. Over the past few years, a large number of marine natural products containing the indole nucleus have been isolated. Certain bis(indole) secondary metabolites, containing either an imidazole- or piperazine-derived spacer unit, exhibit a broad spectrum of powerful biological activities.[1] A new family of natural Hamacanthins isolated from a deep-water marine sponge has become larger each year.[2,3] Hamacanthin A, the first member of this family isolated from *Hamacantha sp*, has been reported to show significant antimicrobial activity against *Candida albicans* and *Cryptococcus neoformans*.[4] On the basis of NMR spectroscopy, its structure was elucidated to be 3,6-bis(6-bromoindol-3-yl)-5,6-dihydro-2(1*H*)-pyrazinone, but the absolute configuration has not been assigned.[2]

Recently, several methods have been developed to synthesize racemic, naturally occurring bis(indole) alkaloids by constructing the central heterocyclic moiety between the indole residues via the condensation of two suitable indolyl precursors[5] as a key step. For example, synthesis of the racemic dragmacidin family, which has a piperazine-derived spacer unit linking two indole rings in a trans relationship,[6] has been accomplished via the successful construction of the piperazine ring system.[7] However, to the best of our knowledge, there have been few reports on the efficient synthesis of optically active natural bis(indole) alkaloids.[8] In view of our interest in the synthesis of natural marine bis(indole) alkaloids as lead compounds to new and more biologically active agents, the formulation of a concise and general enantioselective synthetic method for building the central chiral heterocyclic moiety, and to determine the absolute configurations of the optically active bis(indole) alkaloids, is essential. In this report, we describe the first enantioselective total synthesis of the (−)-antipode of hamacanthin A (**1**) as a typical example of a novel and general method for the synthesis of optically active 3,6-bis(indol-3-yl)-5,6-dihydro-2(1*H*)-pyrazinone derivatives.

Results and Discussion

Retrosynthetically, a convergent route toward the (−)-antipode of hamacanthin A (**1**) was simple disconnection of the double bond, as illustrated in Figure 1. We found that coupling of 3-indolyl-α-oxoacetyl chloride **3** and 3-indolyl-azidoethylamine **4**, followed by intramolecular aza-Wittig-type cyclization, could lead to the desired product. Since the absolute configuration of hamacanthin A has not been assigned, we chose to synthesize the (*R*)-enantiomer. The required (*R*)-3-indolyl azidoethylamine **4** should be derived from (*S*)-indolyl ethanediol **5**, which was generated by asymmetric dihydroxylation of vinyl indole **6**.

The known 6-bromoindole **7** was prepared via Batcho−Leimgruber indole synthesis from commercially available 4-bromo-2-nitrotoluene by reaction with dimethylformamide dimethyl acetal followed by reduction of the inter-

(1) For a review, see: Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1 and references therein.

(2) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Nat. Prod*. **1994**, *57*, 1437.

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

(4) For further interesting biological properties of hamacanthin A described in the patent literature, see: *Chem. Abstr*. **1996**, *124*, 76517y; *Chem. Abstr*. **1998**, *129*, 587d; *Chem. Abstr*. **2000**, *133*, 99589y.

(5) For the synthesis of indolylglycines, see: (a) Clark, B. P.; Harris, J. R. *Synth. Commun*. **1997**, *27*, 4223. (b) Johannsen, M. *Chem. Commun*. **1999**, 2233. (c) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett*. **2001**, *42*, 2545.

(6) For other related bis(indole) natural alkaloids, see: (a) 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) Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L.; Wright, A.; Koehn, F. *J. Org. Chem*. **1988**, *53*, 3116. (c) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem*. **1992**, *57*, 4772. (d) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carrol, A. R. *J. Nat. Prod*. **1998**, *61*, 660. (e) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743.

(7) (a) Jiang, B.; Smallheer, J. M.; Amaral-Ly, C.; Wuonola, M. A. *J. Org. Chem*. **1994**, *59*, 6823. (b) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett*. **2000**, *2*, 3027. (c) Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett*. **1994**, *35*, 371. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett*. **2000**, *2*, 3185.

(8) For a review, see: Gu, X.-H.; Jiang, B. *Chin. J. Org. Chem*. **2000**, *20*, 168.

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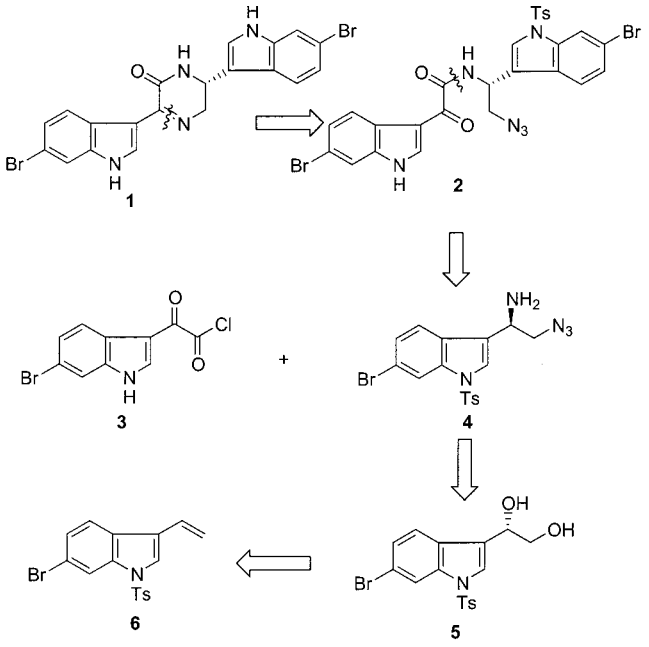
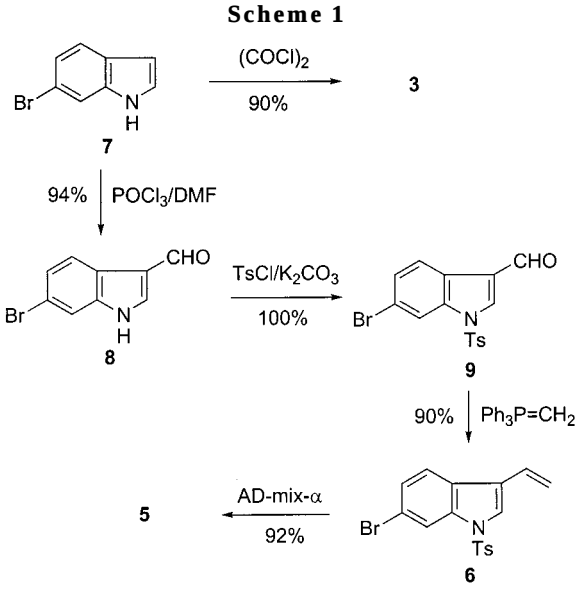


Figure 1.

mediate enamine with hydrazine hydrate in the presence of Raney-Ni as a catalyst.[9] 3-Indolyl-α-oxoacetyl chloride **3** was prepared in 90% yield by heating 6-bromoindole **7** with oxalyl chloride in ether for 10 h.[10a] The requisite vinyl indole **6** was prepared from 6-bromoindole **7** in high yield by Vilsmeier−Haack reaction with phosphorus oxychloride/dimethylformamide,[7a,10] followed by Wittig olefination of the *N*-tosyl-indole-3-carbaldehyde **9**[11] with methylenetriphenylphosphorane under typical Wittig conditions.[12] Osmium tetraoxide-catalyzed asymmetric dihydroxylation (Sharpless AD reaction) has been well studied for the construction of a chiral vicinal diol using cinchona alkaloid as a chiral ligand and potassium ferricyanide as a co-oxidant. The advantage of the Sharpless AD reaction is that the newly generated chiral carbon center can be predicted based on the hydroquinidine and hydroquinine chiral ligands in the AD-mixture reagents.[13] Extension of this methodology to the asymmetric oxidation of vinyl indole **6** was very successful. Thus, compound **6** was subjected to AD-mix-α in *tert*-butyl alcohol/water (1:1) for 10 h at 0 °C to give (*S*)-1-(indol-3-yl)-1,2-ethanediol **5** in 92% yield with 99% ee. The enantiomeric excess was determined by HPLC using a chiral OD column with an eluent of 2-propanol/hexane (2/8) (Scheme 1).

The primary hydroxyl group of **5** was selectively protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in CH_2Cl_2 in 94% yield. Several methods have been reported for converting a secondary alcohol to an azide group.[14] Initially, we tried to convert the secondary alcohol in **10** into the corresponding mesylate or tosylate, followed by nucleophilic attack by an azide ion to prepare azido compound **11**. However, when **10** was reacted with methanesulfonyl chloride or tosyl chloride, only the starting material was recovered due to steric hindrance of the secondary alcohol. Fortunately, we found that the Mitsunobu procedure[15] worked well for our desired transformation. Thus, compound **10** was treated with diphenylphosphoryl azide (DPPA), triphenylphosphine, and diethylazodicarboxylate (DEAD) at −20 °C to lead to (*R*)-azidoindole **11** in 87% yield with an inversion of configuration. Cleavage of the *tert*-butyldimethyl silyl ether using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave indolyl azido alcohol **12** in 98% yield. While the azido group in **12** was reduced to an amino group using $LiAlH_4$ at 0 °C followed by protection of the resulting amino alcohol with $(Boc)_2O$, we found that $LiAlH_4$ not only reduced the azido group, but also induced partial debromination of the 6-bromo substituent in the indole ring. After tosylation of the alcohol, a mixture of 6-bromoindolyl aminoethanol **13a** and indolyl aminoethanol **13b** in a ratio of 4:1 was isolated in 70% yield in three steps. Displacement of the tosylate group in **13a** with sodium azide in DMF gave the desired (*R*)-indolyl azidoethylamine **14** in 88% yield (Scheme 2).

Scheme 1



With indolyl azidoethylamine **14** and 3-indolyl-α-oxoacetyl chloride **3** in hand, we then turned to build the central 5,6-dihydropyrazinone ring in hamacanthin A (Scheme 3). Removal of the Boc group in **14** with CF_3-COOH in dichloromethane followed by coupling of the resulting free azidoamine **4** with 3-indolyl-α-oxoacetyl chloride **3** immediately gave bis(indolyl) azido-ketone **2** in 74% yield. Subsequent formation of the central chiral pyrazinone ring was performed through a Staudinger-aza Wittig sequence.[16] Reaction of the azido group in **2**

(9) (a) Maehr, H.; Smallheer, J. M. *J. Org. Chem.* **1981**, *46*, 1752. (b) Dellar, G.; Djura, P.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1679. (c) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1984**, *63*, 214.

(10) (a) Da Settimo, A.; Saettone, M. F.; Nannipieri, E.; Barili, P. *Gazz. Chim. Ital.* **1967**, *97*, 1304. (b) Schmidt, U.; Wild, J. *Liebigs Ann. Chem.* **1985**, 1882.

(11) Gulati, D.; Chauhan, P. M. S.; Pratap, R.; Bhakuni, D. S. *Indian. J. Chem. Sect. B* **1994**, *33*, 10.

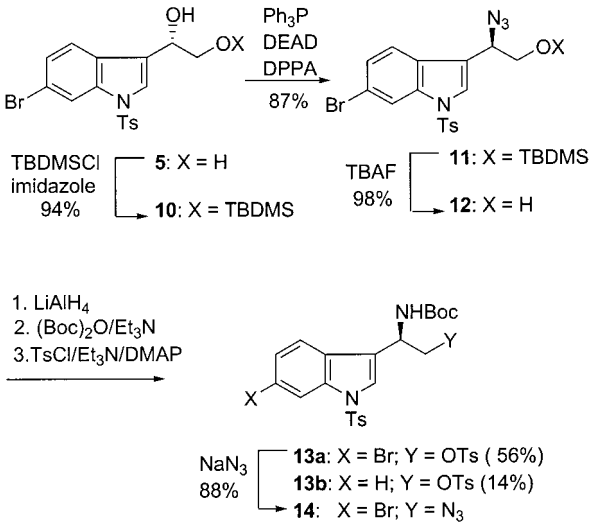
(12) (a) Bergamasco, R.; Porter, Q. N.; Yap, C. *Aust. J. Chem.* **1977**, *30*, 1531. (b) Pindur, U.; Pfeuffer, L. *Monatsh. Chem.* **1989**, *120*, 157.

(13) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Turpin, J. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 6563.

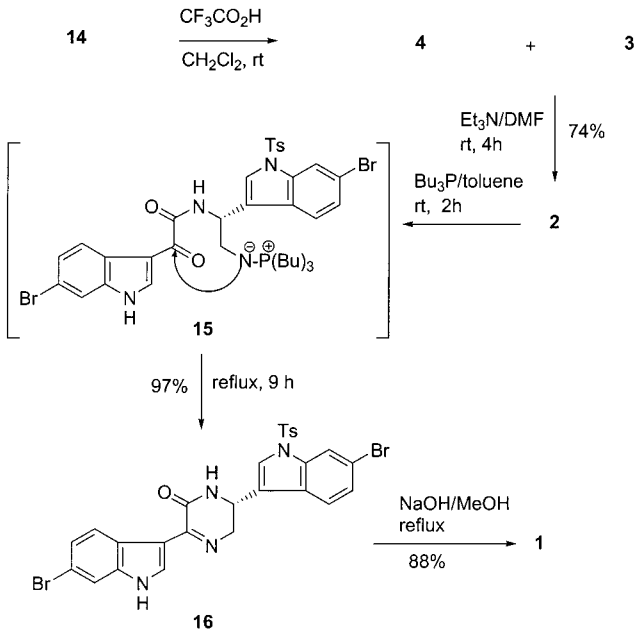
(14) (a) For a review, see: Lohray, B. B. *Synthesis* **1992**, 1035. (b) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339. (c) Pearson, A. J.; Heo, J.-N. *Tetrahedron Lett.* **2000**, *41*, 5991. (d) Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310.

(15) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 2



Scheme 3



with tributylphosphine in toluene at ambient temperature first gave the corresponding iminophosphorane **15**, which directly cyclized to afford the expected central 5,6-dihydropyrazinone **16** in 97% yield. Upon treatment of compound **16** with sodium hydroxide in refluxing methanol to remove the tosyl group,[17] the expected (−)-antipode of hamacanthin A (**1**) was obtained in 88% yield with a specific rotation of −79 (*c* 0.20, CH_3OH). Comparison with naturally isolated hamacanthin A, which has a positive specific rotation of +84 (*c* 0.1, CH_3OH), revealed that natural hamacanthin A has an *S*-configuration.

Experimental Section

General. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin-Elmer 341MC instrument. Infrared (IR) spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-300 or INOVA-600 instrument. The chemical photoshifts are expressed in ppm and coupling constants are given in Hz. Low-resolution mass spectra were obtained on a VG-Quattro or HP-5969A spectrometer, and high-resolution mass spectra were recorded on a Finnigan MAT-95 spectrometer. Microanalyses were carried out at a Heraeus Rapid-CHNO instrument. All moisture-sensitive reactions were done under an argon atmosphere in oven dried (150 °C) glassware. Flash chromatography was performed using silica gel H (10−40 μm). Standard reagents and solvents were purified according to known procedures.[18]

6-Bromo-3-indolyl-α-oxoacetyl Chloride (3).[10a] 6-Bromoindole **7** (3.92 g, 20 mmol) in anhydrous ether (60 mL) was refluxed with oxalyl chloride (3.81 g, 30 mmol) for 10 h. After cooling to room temperature, hexane (50 mL) was added. The solid was filtered off, washed with hexane several times, and then dried under vacuum to give compound **3** (5.2 g, 90%) as a yellow solid. mp 221 °C dec; IR (KBr) 3204, 1787, 1626 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.63 (br s, 1H), 8.48 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H); EIMS *m/e* (relative intensity) 287/285 (4/3).

***N*-Tosyl-6-bromoindole-3-carbaldehyde (9).** A mixture of 6-bromoindole-3-carbaldehyde **8**[7a,10] (3.05 g, 13.6 mmol), tosyl chloride (4.75 g, 25 mmol), and anhydrous potassium carbonate (5.52 g, 40 mmol) in anhydrous 2-butanone (100 mL) was refluxed for 3 h. After filtration of the reaction mixture without cooling, the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica, Hex/AcOEt 6:1 and 2:1) to afford compound **9** (5.14 g, 100%) as a white solid. mp 146−147 °C (lit.[11] 115 °C); IR (KBr) 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.06 (s, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 8.12 (d, J = 10.7 Hz, 1H), 7.85 (d, J = 8.6 Hz, 2H), 7.48 (dd, J = 8.6 and 1.7 Hz, 1H), 7.33 (dd, J = 8.6 and 0.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.0, 146.5, 136.3, 135.8, 134.1, 130.5, 128.5, 127.2, 125.1, 123.7, 122.0, 120.1, 116.4, 21.7; EIMS *m/e* (relative intensity) 379/377 (63/61), 155 (70). Anal. Calcd for $C_{16}H_{12}BrNO_3S+H_2O$: C, 48.48; H, 3.54; N, 3.54. Found: C, 48.50; H, 3.30; N, 3.51.

***N*-Tosyl-6-bromo-3-vinylindole (6).** To a suspension of methyltriphenylphosphonium bromide (4 g, 11.2 mmol) in anhydrous THF (20 mL) was added dropwise *n*-butyllithium (2.5 M in hexane, 4 mL) at −78 °C under vigorous stirring. The mixture was then kept in an ice−water bath for 20 min, and a solution of **9** (3.1 g, 8.20 mmol) in THF (40 mL) was added to the clear solution. After further stirring for 20 min at this temperature, the reaction mixture was allowed to reach ambient temperature, and water (30 mL) was added to quench the reaction. The water layer was extracted with ether, and the organic phase was washed with brine and dried with sodium sulfate. The solvent was removed, and the residue was subjected to flash chromatography (silica, Hex/AcOEt 10:1) to give **6** (2.8 g, 90%) as a white solid. mp 142−143 °C; IR (KBr) 3134, 1596, 1544 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, J = 3.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.38 (dd, J = 8.5 and 1.7 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 6.72 (dd, J = 17.8 and 11.3 Hz, 1H), 5.75 (dd, J = 17.8 and 0.6 Hz, 1H), 5.35 (dd, J = 11.3 and 1.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 136.1, 134.8, 130.0, 129.7, 127.8, 127.0, 126.8, 124.3, 121.5, 120.7, 118.6, 116.7, 115.8, 21.5; EIMS *m/e* (relative intensity) 377/375 (71/68), 155 (19). Anal. Calcd for $C_{17}H_{14}BrNO_2S$: C, 54.25; H, 3.72; N, 3.72. Found: C, 54.47; H, 3.80; N, 3.48.

(*S*)-1-(*N*-Tosyl-6-bromoindol-3-yl)-1,2-ethanediol (5). A solution of AD-mix-α (12 g) in *tert*-butyl alcohol/water (100 mL, 1:1) was stirred vigorously at room temperature for 1 h. After the reaction mixture was chilled with an ice−water bath, compound **6** (3.0 g, 8.0 mmol) was added. Stirring was continued over 10 h at 0 °C. The resulting mixture was allowed

(16) (a) For a review, see: Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (b) Sugimori, T.; Okawa, T.; Eguchi, S.; Yashima, E.; Okamoto, Y. *Chem. Lett.* **1997**, 869. (c) Fresneda, P. M.; Molina, P.; Sanz, M. A. *Synlett* **2000**, 1190. (d) Kamal, A.; Laxman, E.; Reddy, P. S. M. M. *Tetrahedron Lett.* **2000**, *41*, 8631.

(17) (a) Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 4003. (b) Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783.

(18) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

to warm to room temperature for 3 h, quenched by the addition of sodium sulfite (9 g), and stirred for an additional 2 h. The aqueous layer was exacted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water and brine successively, dried over anhydrous sodium sulfate, filtered, and concentrated to give a syrupy residue which was purified by flash chromatography (silica, Hex/AcOEt 1:2) to give **5** (3.0 g, 92%) as a white solid in 99% ee. mp 65 °C; $[\alpha]^{20}_D = +43.0$ (*c* 1.47, $CHCl_3$); IR (KBr) 3352 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, $J = 1.6$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.33 (dd, $J = 8.5$ and 1.7 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 5.02 (m, 1H), 3.84 (m, 2H), 2.72 (d, $J = 3.9$ Hz, 1H), 2.36 (s, 3H), 2.18 (t, $J = 5.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 135.8, 134.6, 130.0, 127.6, 127.8, 126.8, 126.6, 123.8, 121.8, 121.2, 118.6, 116.6, 68.3, 66.4, 21.5; EIMS *m/e* (relative intensity) 411/409 (8/8), 155 (62). Anal. Calcd for $C_{17}H_{16}BrNO_4S$: C, 49.76; H, 3.90; N, 3.41. Found: C, 49.38; H, 4.20; N, 3.28.

(1*S*)-1-(*N*-Tosyl-6-bromoindol-3-yl)-2-[(*tert*-butyldimethylsilyl)oxy]-1-ethanol (10). To a solution of 1,2-ethanediol **5** (2.68 g, 6.5 mmol) in 50 mL of dichloromethane at 0 °C was added imidazole (1.33 g, 19.5 mmol), followed by *tert*-butyldimethylsilyl chloride (1.18 g, 7.8 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 12 h. After removal of the solvent under reduced pressure, the residue was purified by chromatography (silica, Hex/AcOEt 6:1). The desired compound **10** (3.2 g, 94%) was obtained as a syrup. $[\alpha]^{20}_D = +38.8$ (*c* 1.10, $CHCl_3$); IR (KBr) 3612 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (dd, $J = 2.0$ and 0.6 Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 0.9$ Hz, 1H), 7.48 (dd, $J = 8.5$ and 0.5 Hz, 1H), 7.34 (ddd, $J = 8.5$, 1.7 and 0.6 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 4.94 (m, 1H), 3.86 (dd, $J = 10.1$ and 3.7 Hz, 1H), 3.73 (dd, $J = 10.1$ and 7.9 Hz, 1H), 2.89 (d, $J = 3.2$ Hz, 1H), 2.36 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.4, 135.9, 135.1, 130.1, 128.1, 126.9, 126.6, 123.9, 121.7, 121.5, 118.5, 116.8, 68.3, 67.1, 25.9, 21.6, 18.3, −5.3; EIMS *m/e* (relative intensity) 524/522 (1/1), 155 (8). Anal. Calcd for $C_{23}H_{30}BrNO_4SSi$: C, 52.67; H, 5.72; N, 2.67. Found: C, 53.04; H, 5.77; N, 2.66.

(1*R*)-1-(*N*-Tosyl-6-bromoindol-3-yl)-1-azido-2-[(*tert*-butyldimethylsilyl)oxy]ethane (11). To a solution of compound **10** (2.4 g, 4.58 mmol) in anhydrous THF (40 mL) were added triphenylphosphine (2.36 g, 9 mmol), diethyl azodicarboxylate (40% in toluene, 4.2 mL, 9 mmol), and diphenylphosphoryl azide (1.92 mL, 9 mmol) at −20 °C. The mixture was stirred for 8 h and then allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure, and the residue was directly subjected to flash chromatography (silica, Hex/AcOEt 20:1) to give intermediate **11** (2.19 g, 87%) as a syrup. $[\alpha]^{20}_D = -84.6$ (*c* 1.10, $CHCl_3$); IR (KBr) 2106 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, $J = 1.6$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 0.7$ Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.37 (dd, $J = 8.5$ and 1.7 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 4.63 (m, 1H), 3.99 (dd, $J = 10.5$ and 4.3 Hz, 1H), 3.93 (dd, $J = 10.5$ and 6.4 Hz, 1H), 2.36 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 135.7, 134.8, 130.1, 127.9, 126.84, 126.80, 125.0, 121.0, 118.8, 117.9, 116.8, 66.4, 59.3, 25.8, 21.6, 18.2, −5.5, −5.6; EIMS *m/e* (relative intensity) 522/520 (6/5), 155 (23). Anal. Calcd for $C_{23}H_{29}BrN_4O_3SSi$: C, 50.27; H, 5.28; N, 10.20. Found: C, 50.47; H, 5.20; N, 10.14.

(*R*)-2-Azido-2-(*N*-tosyl-6-bromoindol-3-yl)-1-ethanol (12). To a solution of compound **11** (2.2 g, 4.01 mmol) in THF (30 mL) was added tetrabutylammonium fluoride (1 M in THF, 8.0 mL, 8.0 mmol). After stirring for 1 h at ambient temperature, water (20 mL) was added to quench the reaction, and the resulting mixture was extracted with ether. The organic phase was dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica, Hex/AcOEt 2:1) afforded ethanol **12** (1.7 g, 98%) as a syrup. $[\alpha]^{20}_D = -125.4$ (*c* 0.585, $CHCl_3$); IR (KBr) 3340, 2105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, $J = 1.6$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.63 (s, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.38 (dd, $J = 8.5$ and 1.6 Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 2H), 4.82 (t, $J = 6.1$ Hz, 1H), 3.90 (t, $J = 6.1$ Hz, 2H), 2.37 (s, 3H), 1.99 (t, $J = 6.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 135.8, 134.5, 130.1, 127.5, 126.9, 126.8, 125.0, 121.0, 119.0, 117.5, 116.9, 65.0, 60.1, 21.6; EIMS *m/e* (relative intensity) 436/434 (36/37), 155 (42); HRE-IMS calcd for $C_{17}H_{15}BrN_4O_3S$: 434.0048; found: 434.0048. Anal. Calcd for $C_{17}H_{15}BrN_4O_3S$: C, 46.90; H, 3.45; N, 12.87. Found: C, 47.12; H, 3.80; N, 12.64.

(1*R*)-*N*-(*tert*-Butyloxycarbonyl)-1-(*N*-tosyl-6-bromoindol-3-yl)-2-[(4-methylphen-ylsulfonyl)oxy]ethylamine (13). To an ice-cooled suspension of $LiAlH_4$ (172 mg, 4.5 mmol) in freshly distilled THF (20 mL) under argon was injected a solution of compound **12** (394 mg, 0.91 mmol) in THF (8 mL). The reaction mixture was stirred for 1 h at this temperature, diluted with dry THF (10 mL), and quenched with ethanol (1 mL). The resulting mixture was filtered through a short silica column. The solvent was evaporated to furnish the crude amine, which was used in the next step without purification.

To a mixture of the crude amine and Et_3N (0.21 mL, 1.5 mmol) in dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (327 mg, 1.5 mmol) in an ice-cooled bath. The reaction was stirred at 0 °C for 4 h and diluted with dichloromethane (10 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product (330 mg) dissolved in CH_2Cl_2 (15 mL) was reacted with tosyl chloride (127 mg, 0.67 mmol), Et_3N (0.15 mL, 1 mmol), and DMAP (15 mg) for 5 h at room temperature. The mixture was washed with water and brine and then dried (Na_2SO_4). After removal of the solvent, the crude product was purified by flash chromatography (silica, Hex/AcOEt 6:1) to afford compound **13a** (335 mg, 56% yield in three steps) and compound **13b** (74 mg, 14% yield).

Compound **13a**: $[\alpha]^{20}_D = -10.3$ (*c* 0.78, $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, $J = 1.6$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 0.8$ Hz, 1H), 7.26 (m, 2H), 7.17 (d, $J = 0.4$ Hz, 1H), 7.15 (d, $J = 8.5$ Hz, 2H), 5.12 (br, 1H), 5.04 (br, 1H), 4.36 (dd, $J = 10.0$ and 4.4 Hz, 1H), 4.24 (dd, $J = 10.0$ and 3.8 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H), 1.43 (s, 9H); ESIMS *m/e* 687.3 (M + Na). Anal. Calcd for $C_{29}H_{31}BrN_2O_7S_2$: C, 52.49; H, 4.68; N, 4.22. Found: C, 52.70; H, 4.84; N, 4.35.

Compound **13b**: IR (KBr) 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, $J = 8.3$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8.3$ Hz, 2H), 7.47 (s, 1H), 7.35−7.13 (m, 7H), 5.16 (br, 1H), 5.02 (br, 1H), 4.39 (dd, $J = 10.0$ and 4.5 Hz, 1H), 4.27 (dd, $J = 10.0$ and 4.1 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 1.43 (s, 9H); ESIMS *m/e* 607.4 (M + Na).

(1*R*)-*N*-(*tert*-Butyloxycarbonyl)-1-(*N*-tosyl-6-bromoindol-3-yl)-2-azidoethylamine (14). To a solution of compound **13a** (210 mg, 0.32 mmol) in dry DMF (6 mL) was added sodium azide (65 mg, 1 mmol) at room temperature. The mixture was then stirred for 12 h at 80 °C. After being cooled to room temperature, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water and brine and then dried (Na_2SO_4). After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica, Hex/AcOEt 4:1) to afford compound **14** (150 mg, 88%) as a white solid. mp 172−173 °C; $[\alpha]^{20}_D = -2.4$ (*c* 0.56, $CHCl_3$); IR (KBr) 2103, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, $J = 1.4$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 0.8$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 7.37 (dd, $J = 8.5$ and 1.5 Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 5.09 (br, 1H), 4.91 (br d, $J = 7.5$ Hz, 1H), 3.73 (m, 2H), 2.37 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.0, 145.6, 135.8, 134.9, 130.2, 127.8, 126.9, 124.1, 120.8, 120.6, 119.0, 116.9, 80.5, 54.1, 46.7, 29.7, 28.3, 21.6; EIMS *m/e* (relative intensity) 534 (0.6), 423/421 (100/96),155 (24). Anal. Calcd for $C_{22}H_{24}BrN_5O_4S$: C, 49.44; H, 4.49; N, 13.11. Found: C, 49.47; H, 4.56; N, 13.08.

(*R*)-6-Bromo-*N*-[(*N*-tosyl-6-bromoindol-3-yl)azidoethyl]-α-oxoindole-3-acetamide (2). To a stirred solution of compound **14** (114 mg, 0.213 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (0.8 mL, 10.3 mmol) in an ice−water bath under argon. The reaction solution was stirred at room-temperature overnight and quenched by the addition of water (10 mL). The water phase was neutralized with aqueous 1 N NaOH and extracted with CH_2Cl_2 (2 × 10 mL). The combined

organic layer was washed with saturated $NaHCO_3$ and brine successively and then dried over Na_2SO_4. The result was concentrated in vacuo to give a yellow oil, which was used in the next step without purification.

To a solution of the crude product and triethylamine (42 μL, 0.3 mmol) in dry DMF (5 mL) cooled in an ice bath was added a solution of 6-bromo-3-indolyl-α-oxoacetyl chloride **3** (63 mg, 0.22 mmol) in dry DMF (1 mL) dropwise. After 4 h, water (20 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water and brine successively, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (silica, Hex/AcOEt 2:1) gave compound **2** (107 mg, 74%) as a light yellow solid. mp 121 °C; $[\alpha]^{20}_D$ = −28.8 (*c* 0.51, $CHCl_3$); IR (KBr) 2106, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.02 (d, *J* = 3.0 Hz, 1H), 8.98 (br s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 1.3 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 0.7 Hz, 1H), 7.59 (d, *J* = 1.4 Hz, 1H), 7.45−7.26 (m, 5H), 5.48 (m, 1H), 3.85 (m, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 179.6, 161.5, 145.7, 138.5, 136.5, 135.8, 134.8, 130.3, 127.6, 127.1, 127.0, 126.9, 125.4, 124.4, 123.7, 120.6, 119.2, 119.1, 117.9, 116.9, 114.7, 113.3, 53.6, 45.1, 29.7, 21.6; ESIMS *m*/*e* 704.2 (M + Na). Anal. Calcd for $C_{27}H_{20}Br_2N_6O_4S$: C, 47.37; H, 2.92; N, 12.28. Found: C, 47.34; H, 3.20; N, 11.91.

(*R*)-3-(6-Bromoindol-3-yl)-6-(*N*-tosyl-6-bromoindol-3-yl)-5,6-dihydro-2(1*H*)-pyrazinone (16). To a solution of compound **2** (88 mg, 0.128 mmol) in dry toluene (4 mL) was added tributylphosphine (50 μL, 0.197 mmol). The mixture was stirred at room temperature for 2 h and then warmed to reflux for 9 h under an argon atmosphere. After the removal of toluene, the residue was subjected to flash chromatography (silica, Hex/AcOEt 2:1 and 1:1) to give compound **16** (79 mg, 97%) as a yellow solid. mp > 300 °C; $[\alpha]^{20}_D$ = +22 (*c* 0.325, acetone); IR (KBr) 1671 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.69 (br d, *J* = 2.6 Hz, 1H), 9.05 (br d, *J* = 3.0 Hz, 1H), 8.44 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 1.7 Hz, 1H), 7.60 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 8.5 and 1.7 Hz, 1H), 7.23 (dd, *J* = 8.6 and 1.8 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 2H), 5.05 (m, 1H), 4.14 (d, *J* = 5.6 Hz, 2H), 2.19 (s, 3H); ^1H NMR (acetone-d_6, 300 MHz) δ 8.58 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.64 (d, *J* = 0.9 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 8.5 and 1.7 Hz, 1H), 7.34 (s, 1H), 7.25 (dd, *J* = 8.6 and 1.8 Hz, 1H), 5.20 (m, 1H), 4.33 (dd, *J* = 16.5 and 5.9 Hz, 1H), 4.25 (dd, *J* = 16.5 and 5.2 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 158.96, 158.78, 146.9, 138.7, 137.3, 135.5, 134.0, 131.2, 129.2, 127.9, 127.8, 126.7, 126.4, 125.8, 124.9, 123.2, 123.1, 119.4, 117.6, 116.7, 115.6, 112.8, 53.4, 47.5, 21.7; EIMS *m*/*e* (relative intensity) 640 (18), 642/638 (10/10), 641/637 (9/9), 155 (17); HREIMS calcd for $C_{27}H_{20}{}^{79}Br^{81}BrN_4O_3S$: 639.9602; found: 639.9606. Anal. Calcd for $C_{27}H_{20}Br_2N_4O_3S$: C, 50.63; H, 3.13; N, 8.75. Found: C, 50.89; H, 3.31; N, 8.55.

(−)-Antipode of Hamacanthin A (1). A suspension of compound **16** (28 mg, 0.044 mmol) and NaOH (18 mg, 0.45 mmol) in 6 mL of absolute methanol was refluxed for 1 h. After the solvent was evaporated in vacuo, the residue was poured into water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water and brine successively, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (silica, Hex/AcOEt 2:3) gave compound **1** (18 mg, 88%) as a yellow solid. mp 275 °C; $[\alpha]^{20}_D$ = −79 (*c* 0.20, CH_3OH); IR (KBr) 1670 cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz) δ 11.61 (d, *J* = 2.1 Hz, 1H), 11.17 (br, 1H), 8.80 (br, 1H), 8.42 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.32 (s, 1H), 7.23 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.15 (dd, *J* = 8.5 and 1.8 Hz, 1H), 4.99 (dd, *J* = 8.4 and 5.1 Hz, 1H), 4.12 (dd, *J* = 16.2 and 4.8 Hz, 1H), 4.07 (dd, *J* = 16.2 and 9.0 Hz, 1H); EIMS *m*/*e* (relative intensity) 486 (100), 291/289 (11/9); HREIMS calcd for $C_{20}H_{14}{}^{79}Br_2N_4O$: 483.9560; found 483.9534.

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