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Asymmetric aminohydroxylation of vinyl indoles: a short enantioselective synthesis of the bisindole alkaloids dihydrohamacanthin A and dragmacidin A

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Abstract—A useful approach for the direct enantioselective synthesis of (*S*)-*N*-Boc-protected α-indol-3-ylglycinols from vinyl indoles using the Sharpless asymmetric aminohydroxylation reaction, with enantioselectivities of up to 94% and isolated yields of up to 65%, is described. Expeditious enantioselective syntheses of hamacanthin A and dragmacidin A have been achieved using the corresponding *N*-Boc-protected α-6-bromo-indol-3-ylglycinol as the key intermediate. Furthermore, the absolute stereochemistry of *cis*- and *trans*-dihydrohamacanthin A has been determined through the enantioselective total synthesis of the unnatural enantiomers.

1. Introduction

The biological importance of certain bisindole secondary metabolites, containing either an imidazole- or piperazine-derived spacer unit, drives the search for ever more efficient synthetic routes to these compounds.[1] To our knowledge, the successful construction of the piperazine ring system in the dragmacidin family[2] has been achieved via diborane reduction of diketopiperazine intermediates,[3] or selective reduction and reductive methylation with sodium cyanoborohydride.[4] However, the absolute configurations of this class of optically active bisindole alkaloids have not been determined to date.[5] We felt that a direct preparation of enantiopure α-indol-3-ylglycinol would offer a facile entry to this bisindole series. Moreover, this chiral synthon is found in a number of indole-related natural products,[6] and its efficient synthesis should find many useful applications. Previously, we have successfully prepared (*R*)-3-indolyl azidoethylamine using the Sharpless asymmetric dihydroxylation reaction followed by stereospecific azidation.[7] Although that synthesis was highly concise and ensured rapid access to reasonable amounts of material, the unsolved problem associated with the selective reduction of the azido to the amino group still remained irksome and prompted us to investigate a fresh approach. Herein, we describe a novel and practical enantioselective preparation of enantiomerically pure α-indol-3-yl-amino alcohols using Sharpless asymmetric aminohydroxylation reaction (Sharpless AA). In addition, a short enantioselective synthesis of hamacanthins A and dragmacidin A has been achieved using the corresponding (*S*)-1-(indol-3-yl)-2-azidoethylamine as key intermediate. The antipodes of the *cis*- and *trans*-dihydrohamacanthin A were also synthesized and their absolute configuration was determined.

Retrosynthetically, the common intermediate leading to the total synthesis of hamacanthin A, *cis*- or *trans*-3,4-dihydrohamacanthin A and dragmacidin A would be compound **18**. As shown in Fig. 1, hamacanthin A **2** could be considered to be the product of deprotection of compound **18**, and *cis*- or *trans*-3,4-dihydrohamacanthin A **3** or **4** would be derived from the partial reduction of compound **18**, while dragmacidin A **1** could be viewed as the complete reduction product of compound **18**. We felt that a successful enantioselective route to the key intermediate **18** would open the door to the synthesis of bisindolyl dihydropyrazinone-type marine alkaloids and their analogues.

The convergent route toward intermediate **18** is illustrated in Fig. 2. Compared with our earlier reports,[7] the new synthetic strategy requires a practical and general method for the synthesis of enantiopure α-indol-3-ylgly-

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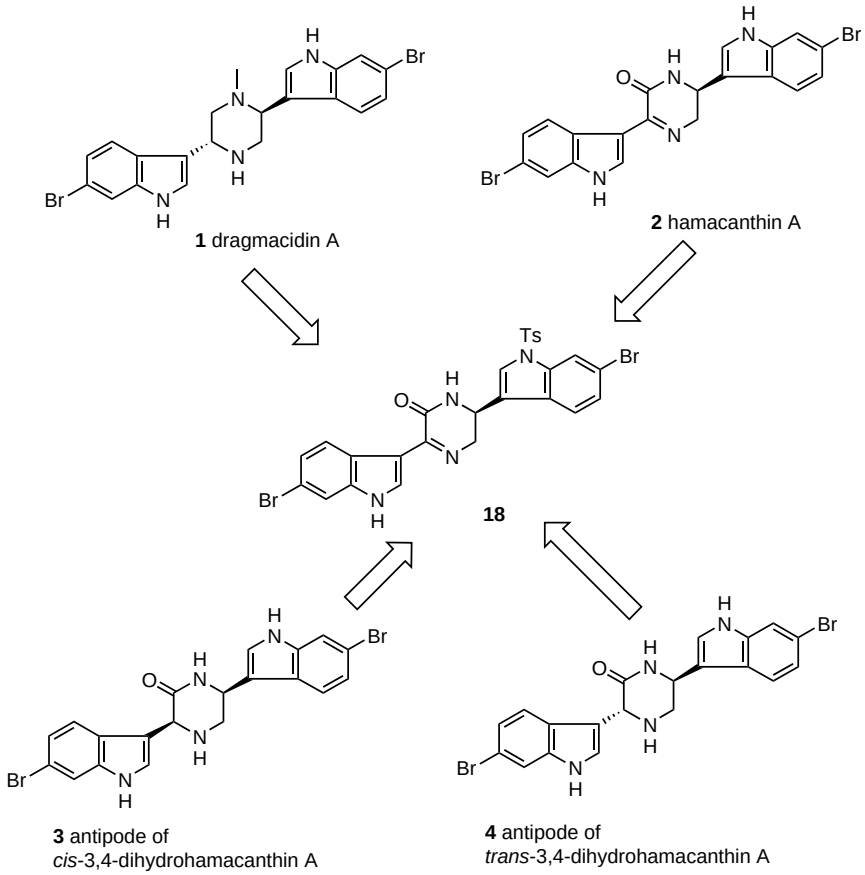


Figure 1.

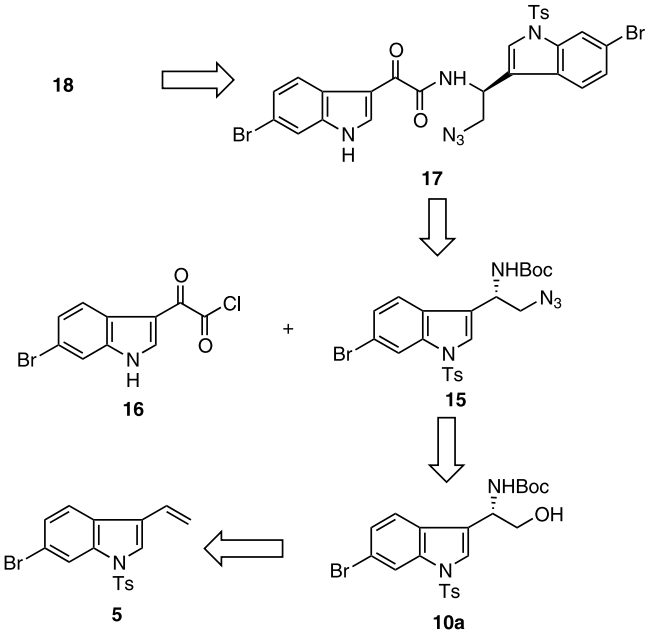


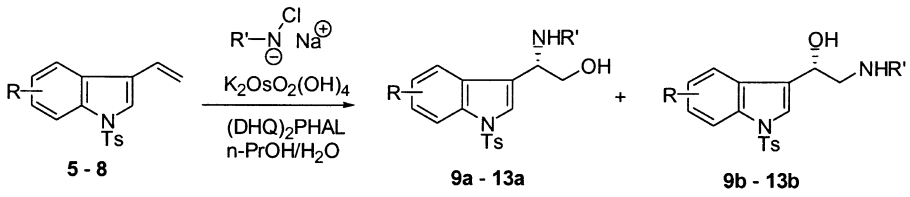
Figure 2.

cinol **10a**, which would be obtained by conversion of vinyl indole **5** using the Sharpless AA procedure.

2. Results and discussion

The catalytic asymmetric aminohydroxylation (AA) reaction provides chiral α-aryl amino alcohols by applying the carbamate AA process with a wide range of substituted styrenes.[8] However, to the best of our knowledge, there are few reports on the Sharpless AA reactions of vinyl indole substrates. Initially, this reaction emerged as a process in which Cbz carbamate was used as the nitrogen/oxidant at room temperature, unfortunately, only moderate enantioselectivity (80% e.e.) was obtained even though the reaction was carried out at low temperature (0°C) (entry 1, Table 1). Gratifyingly, AA of the vinyl 6-bromoindole **5** using Boc carbamate as the nitrogen/oxidant proved to be more successful at 0°C. Thus, the vinyl 6-bromoindole **5** was converted to (*S*)-indolylglycinol **10a** (65%, 94% e.e.) using the complementary $(DHQ)_2PHAL$ catalyst, as well as its regioisomer **10b** (13%, 17% e.e.) (entry 2). Notably, the enantioselectivities and regioselectivities were greatly affected by the substituents of the indole ring (entries 3–5). The vinyl indole **6** was subjected to this process to give **11a** (86% e.e.) and its regioisomer **11b** (42% e.e.) in a ratio of 7:3 with a total yield of 65%. Moderate enantioselectivities, poor regioselectivities and low yields were obtained when the indole was substituted at the 5-position, either with the electron-donating methoxy group (entry 4) and the electron-withdrawing bromo substituent (entry 5).

Table 1. Asymmetric aminohydroxylation of vinyl indoles



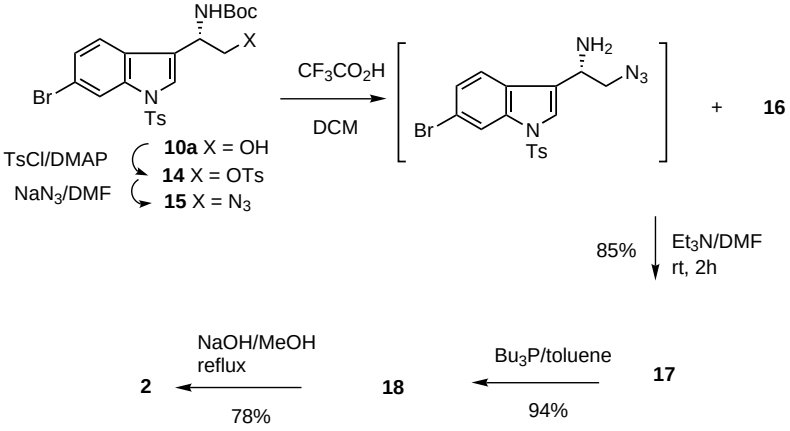
5 - 8 9a - 13a 9b - 13b

Entry	Vinyl indole	R′	Product	Yield (%)[a]	E.e. (%)[c]
1	X = 6-Br **5**	Cbz	**9a**	39 (59)[b]	80 (80)
			9b	31 (22)	24 (28)
2	**5**	Boc	**10a**	65	94
			10b	13	17
3	X = H **6**	Boc	**11a**	46	86
			11b	19	42
4	X = 5-OMe **7**	Boc	**12a**	25	75
			12b	25	3
5	X = 5-Br **8**	Boc	**13a**	34	69
			13b	22	12

[a] Isolated yields.
[b] The value in the brackets is the result of reaction carried out at 0°C.
[c] Determined by HPLC using a chiral column with an isopropanol/hexane eluent.

Having successfully constructed the desired functionality, we turned to a short synthesis of hamacanthin A, as shown in Scheme 1. Conversion of α-6-bromoindol-3-ylglycinol **10a** to the corresponding tosylate offered **14** in 86% yield. Displacement of the tosylate **14** with NaN_3 in DMF gave the desired azide **15** in 88% yield. After the same transformation as our earlier studies for the synthesis of the (−)-antipode of hamacanthin A,[7] hamacanthin A **2** was obtained with a specific rotation of +82. Comparison with naturally isolated hamacanthin A,[6a] which has a specific rotation of +84, revealed that natural hamacanthin A has (*S*)-configuration.

Starting from intermediate **18**, the synthesis of the (−)-antipodes of *cis*- and *trans*-3,4-dihydrohamacanthin A **3** and **4** was performed using $NaBH_4$-mediated reduction and L-Selectride® deprotection procedures. Thus, treatment of compound **18** with excess $NaBH_4$ in methanol at room temperature gave the imine reduction products **19** and **20** in 62 and 36% yields, respectively. The *cis*-product **19** was the major product due to the steric factor of the substrate. The tosyl group used in indole protection can be removed with $LiAlH_4$,[9a] by alkaline hydrolysis[9a] or by a milder chemoselective method involving the use of excess Mg in methanol.[9b] However, we found that all of these known procedures were less successful for removal of the tosyl group in compounds **19** and **20**. Treatment of either **19** or **20** in the presence of NaOH in refluxing methanol afforded an inseparable mixture of *cis*- and *trans*-deprotection product **3** and **4** in an equilibrium ratio of 2:3, due to base-catalysed epimerization. Finally, upon treatment of **19** with L-Selectride® in refluxing THF for 8 hours, **3** was obtained in 87% yield with a specific rotation of −8. Comparison with naturally isolated *cis*-3,4-dihydrohamacanthin A,[6b] which has a positive specific rotation of +8.1, revealed that natural *cis*-3,4-dihydrohamacanthin A has (3*R*,6*R*)-configuration. The antipode of *trans*-3,4-dihydrohamacanthin A **4** was



Scheme 1.

obtained from **20** in the same manner with a specific rotation of −6, demonstrating that the natural *trans*-3,4-dihydrohamacanthin A has (3*S*,6*R*)-configuration. The ^{1}H and ^{13}C NMR chemical shifts and coupling constants of synthetic *cis*- and *trans*-3,4-dihydrohamacanthin A corresponded to those reported for *cis*- and *trans*-3,4-dihydrohamacanthin A isolated from nature, and their relative stereochemistry was confirmed by NOESY experiments (Scheme 2).

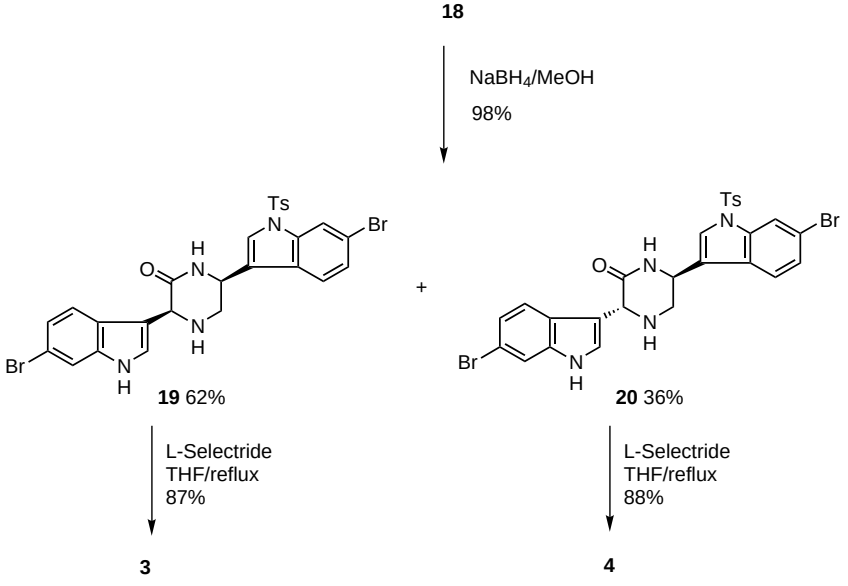
We finally turned our attention to the enantioselective total synthesis of dragmacidin A. Clearly, the installation of methyl substituent in the amide **18**, followed by L-Selectride®-induced deprotection of the tosyl group in the indole ring and reduction of the imine and amide could lead to the total enantioselective synthesis of the target molecule.

Indole **18** was selectively protected by treatment with $(Boc)_2O$ in the presence of DMAP as a catalyst to provide compound **22** in 82% yield along with the totally protected side product **21** in 14% yield.[10] Installation of the *N*-methyl group on the amide was effected in quantitative yield by treatment of **22** with excess methyl iodide using anhydrous potassium carbonate as base in refluxing acetone. The procedure involving the use of sodium hydride and methyl iodide in DMF proved less successful due to the presence of the strong base. The reduction of compound **23** using $NaBH_4$ (alone or in combination with a Lewis acid), or L-Selectride® at either room temperature or reflux were unsuccessful. (Treatment of **23** with L-Selectride® at room temperature removed the Boc protection of the indole ring to give **24**, and the removal of the tosyl group took place when the reaction was performed in refluxing THF.) CF_3CO_2H-mediated cleavage of the Boc group occurred smoothly to give compound **24** in 96% yield. Because of heavy steric control from the substrate, the reduction of **24** with $NaBH_4$ in methanol at room temperature gave the *cis*-isomer **25** as the major product in 82% yield along with the *trans*-product **26** in 17% yield. The relative configuration of compounds **25** and **26** were determined by NOESY experiments. Finally, the synthesis of dragmacidin A was completed by the efficient deprotection of the tosyl group in **26** with L-Selectride® to give **27** in 80% yield, followed by reduction of **27** with an excess borane in 42% yield (Scheme 3). The spectral data of the synthesised final product **1** were identical to those of the natural material, and its relative stereochemistry was confirmed by NOESY experiments.

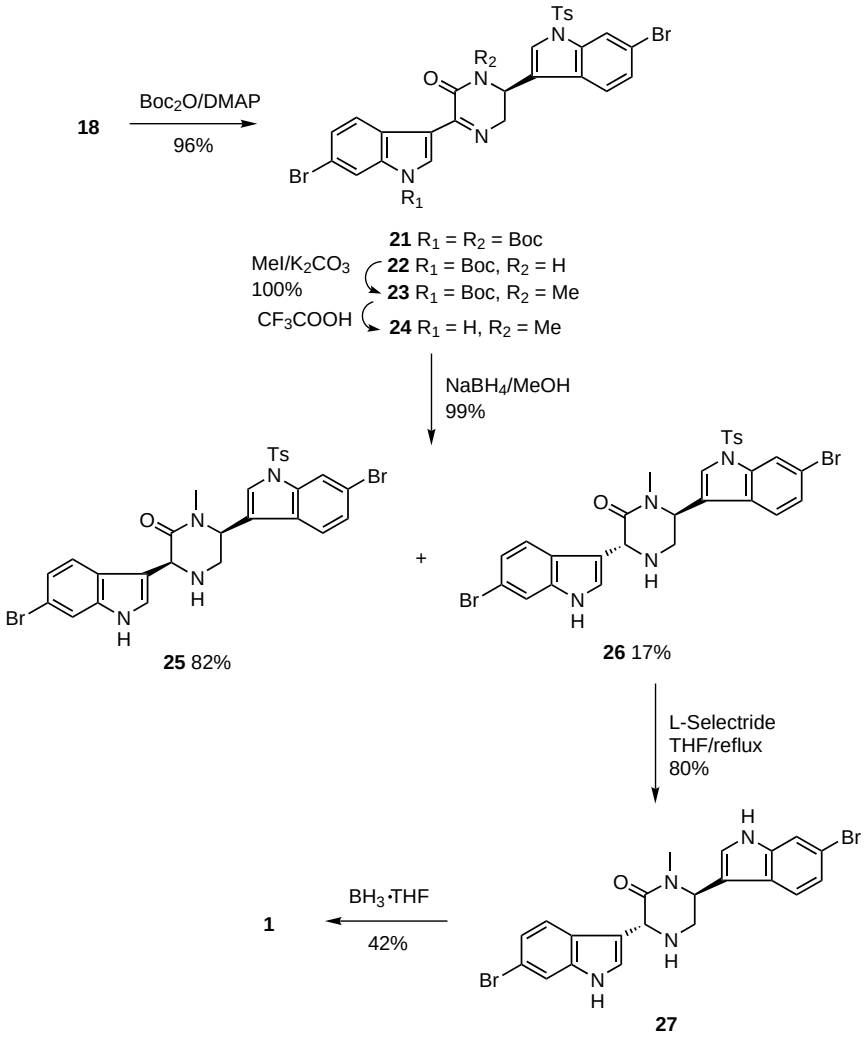
While the route outlined in Scheme 3 gave access to the enantioselective synthesis of dragmacidin A **1**, a remaining problem is how to transform the *cis*-product **25** to its *trans*-isomer **26**. As shown in Scheme 4, treatment of **25** with an organic base, such as Et_3N or DBU,[11] proved less successful. The use of inorganic bases, such as NaOH and K_2CO_3, in refluxing methanol directly gave a mixture of the desired **27** and **28** in an equilibrium ratio of 3:2, which could be easily separated by standard silica chromatography. Even though use of the weaker base $NaHCO_3$ also gave the same result.

3. Conclusion

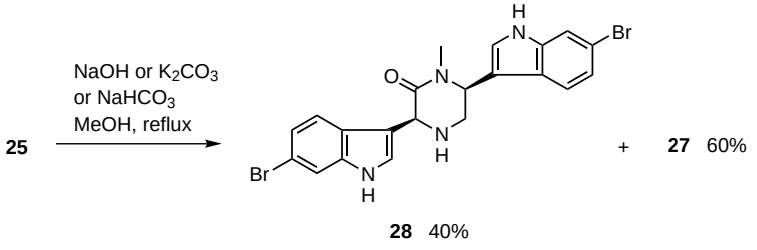
In conclusion, we have developed a new direct approach to the synthesis of enantiomerically pure 2-azido-1-(indol-3-yl)ethylamine **10a**, using the Sharpless asymmetric aminohydroxylation reaction followed by stereospecific azidation. This key intermediate proved very useful in the total synthesis of natural bisindole alkaloids containing piperizanone or piperizine moiety between the indole rings. Consequently, this work completed a highly efficient enantioselective synthesis of hamacanthin A **2** from 6-bromoindole in nine steps, employing **10a** as the key intermediate. Its dihydro derivatives, antipodes of *cis*- and *trans*-3,4-dihydrohamacanthin A **3** and **4** were also synthesized, and their



Scheme 2.



Scheme 3.



Scheme 4.

absolute stereochemistries were determined by comparison of the optical rotation. Moreover, the first enantioselective total synthesis of dragmacidin A **1**, leading to the determination of its absolute stereochemistry, was described.

4. Experimental

4.1. General

Anhydrous reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 341MC instrument. Infrared (IR) spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 300 or 400 MHz instrument and were referenced to tetramethylsilane (TMS) at 0.00 ppm. The chemical photo shifts 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. Flash chromatography was performed using silica gel H (10–40 μm). Standard reagents and solvents were purified according to known procedures.[12] The enantiomeric excess was determined by HPLC using a chiral column with an eluent of isopropanol/hexane.

4.2. General procedure for the preparation of vinylindoles 5[7]–8

To a suspension of methyltriphenylphosphonium bromide (1.4 equiv.) in THF was added *n*-butyllithium (1.2 equiv.) dropwise at −78°C under vigorous stirring. The mixture was then kept in an ice-water bath for 20 min and a solution of *N*-tosyl-indole-3-carbaldehyde in THF 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 was added to quench the reaction. The water layer was extracted with ether and the combined 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 **5**[7]–**8** as white solids.

4.2.1. *N*-Tosyl-3-vinylindole 6. Yield: 86%; mp 107°C (CH_2Cl_2/hexane) (lit.[13] 84–86°C); IR (KBr) 3120, 1635, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, $J=7.8$ Hz, 1H), 7.77 (d, $J=8.5$ Hz, 2H), 7.72 (d, $J=8.4$ Hz, 1H), 7.61 (s, 1H), 7.36–7.24 (m, 2H), 7.21 (d, $J=8.1$ Hz, 2H), 6.77 (dd, $J=17.8$ and 11.5 Hz, 1H), 5.79 (d, $J=17.8$ Hz, 1H), 5.34 (d, $J=11.5$ Hz, 1H), 2.33 (s, 3H); EIMS m/z: 297.

4.2.2. 5-Methoxyl-*N*-tosyl-3-vinylindole 7. Yield: 82%; mp 115°C (CH_2Cl_2/hexane); IR (KBr) 2959, 1633, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (dd, $J=6.8$ and 0.6 Hz, 1H), 7.73 (dd, $J=8.3$ and 1.7 Hz, 2H), 7.56 (s, 1H), 7.19 (dd, $J=8.6$ and 0.6 Hz, 2H), 7.15 (d, $J=2.2$ Hz, 1H), 6.94 (dd, $J=9.0$ and 2.5 Hz, 1H), 6.73 (ddd, $J=17.8$ and 11.3 and 0.6 Hz, 1H), 5.74 (dd, $J=17.8$ and 0.6 Hz, 1H), 5.32 (dd, $J=11.3$ and 0.6 Hz, 1H), 3.82 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 144.7, 134.7, 129.9, 129.7, 129.6, 127.2, 126.4, 124.5, 120.7, 114.8, 114.3, 113.3, 102.9, 55.4, 21.2; EIMS m/z: 327. Anal. calcd for $C_{18}H_{17}NO_3S$: C, 66.05; H, 5.20; N, 4.28. Found: C, 66.11; H, 5.30; N, 4.01%.

4.2.3. 5-Bromo-*N*-tosyl-3-vinylindole 8. Yield: 90%; mp 133°C (CH_2Cl_2/hexane); IR (KBr) 3141, 1630, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (dd, $J=5.6$ and 0.5 Hz, 1H), 7.85 (d, $J=0.7$ Hz, 1H), 7.74 (dd, $J=8.3$ and 1.7 Hz, 2H), 7.59 (s, 1H), 7.42 (dd, $J=8.8$ and 1.7 Hz, 1H), 7.23 (dd, $J=8.3$ and 0.7 Hz, 2H), 6.70 (ddd, $J=17.8$ and 11.2 and 0.7 Hz, 1H), 5.75 (dd, $J=17.8$ and 0.7 Hz, 1H), 5.36 (dd, $J=11.2$ and 0.7 Hz, 1H), 2.35 (s, 3H); EIMS m/z: 375/377. 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%.

4.3. Procedure for the benzyl carbamate-based AA

A solution of benzyl carbamate (470 mg, 3.1 mmol) in *n*-PrOH (4 mL) was treated with a freshly prepared aqueous solution of NaOH (122 mg, 3.05 mmol in 7.5 mL water), followed by the addition of freshly prepared *tert*-butyl hypochlorite (0.35 mL, 3.05 mmol). After 5 min a solution of $(DHQ)_2PHAL$ (48 mg, 0.12 mmol dissolved in 4 mL of *n*-PrOH) was added. A suspension of vinyl indole **5** (376 mg, 1 mmol) in *n*-PrOH (7 mL) was then added, followed by $K_2OsO_2(OH)_4$ (14.8 mg, 0.08 mmol). The mixture was stirred for 3 h at room temperature. The reaction mixture was cooled in an ice-bath, and the reaction was quenched with saturated aqueous sodium sulfite (15 mL). After stirring was continued for 1 h at room temperature, the two-phase mixture was separated, and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash chromatography (silica, hex/EtOAc, 2:1) to provide **9a** (321 mg, 59%) as a colorless solid and regioisomer **9b** as a colorless syrup (119 mg, 22%).

4.3.1. Phenylmethyl (1*S*)-*N*-[1-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 9a. Mp 173°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+29$ (*c* 0.59, $CHCl_3$); IR (KBr) 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, $J=1.6$ Hz, 1H), 7.74 (d, $J=8.4$ Hz, 2H), 7.56 (d, $J=0.9$ Hz, 1H), 7.39–7.24 (m, 9H), 5.31 (m, 1H), 5.12 (s, 2H), 5.07 (m, 1H), 3.98 (br, 2H), 2.36 (s, 3H), 2.14 (br, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.8, 145.8, 137.1, 134.9, 133.9, 130.4, 128.6, 128.3, 127.8, 127.7, 126.8, 126.7, 126.3, 124.6, 122.3, 122.1, 117.5, 115.5, 65.4, 63.2, 49.4, 21.0; EIMS m/z: 542/544. Anal. calcd for $C_{25}H_{23}BrN_2O_5S$: C, 55.25; H, 4.24; N, 5.16. Found: C, 55.38; H, 4.30; N, 5.12%.

4.3.2. Phenylmethyl (1*S*)-*N*-[2-[6-bromo-1-(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 9b. Syrup; $[\alpha]_D^{20}=+8$ (*c* 0.53, $CHCl_3$); IR (KBr) 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, $J=1.4$ Hz, 1H), 7.75 (d, $J=8.4$ Hz, 2H), 7.54 (s, 1H), 7.48–7.22 (m, 9H), 5.12 (m, 4H), 4.65 (br, 1H), 3.65 (m, 1H), 3.38 (m, 1H), 2.89 (br, 1H), 2.35 (s, 3H). Anal. calcd for $C_{25}H_{23}BrN_2O_5S$: C, 55.25; H, 4.24; N, 5.16. Found: C, 55.34; H, 4.31; N, 5.10%.

4.4. General procedure for the *tert*-butyl carbamate-based AA

A solution of *tert*-butyl carbamate (364 mg, 3.1 mmol) in *n*-PrOH (4 mL) was added NaOH (122 mg, 3.05 mmol in 7.5 mL water) and freshly prepared *tert*-BuOCl (0.35 mL, 3.05 mmol). After 5 min of stirring, the solution was cooled with an ice-water bath and a solution of $(DHQ)_2PHAL$ (48 mg, 0.12 mmol dissolved in 4 mL of *n*-PrOH) was added. A suspension of vinyl indole **5**–**8** (1 mmol) in 7 mL of *n*-PrOH was then

added followed by $K_2OsO_2(OH)_4$ (14.8 mg, 0.08 mmol). The reaction mixture was stirred for 3 h at this temperature and quenched with saturated aqueous sodium sulfite (15 mL). After stirring was continued for 1 h at room temperature, the two phase was separated, and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated to afford the crude product, which was purified by flash chromatography (silica, hex/EtOAc, 4:1) to provide **10a**–**13a** and **10b**–**13b**.

4.4.1. 1,1-Dimethylethyl (1*S*)-*N*-[1-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 10a. Mp 80–82°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+47$ (*c* 0.38, $CHCl_3$); IR (KBr) 3405, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, $J=1.4$ Hz, 1H), 7.76 (d, $J=8.4$ Hz, 2H), 7.54 (d, $J=0.8$ Hz, 1H), 7.43 (d, $J=8.4$ Hz, 1H), 7.33 (dd, $J=8.4$ and 1.7 Hz, 1H), 7.25 (d, $J=8.4$ Hz, 2H), 5.05 (m, 2H), 3.96 (m, 2H), 2.37 (s, 3H), 2.18 (br, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 145.4, 135.9, 134.9, 130.1, 128.0, 126.8, 126.7, 124.1, 121.0, 118.8, 116.8, 80.3, 64.8, 49.2, 28.3, 21.6; ESIMS *m*/*z*: 531.0/533.1. Anal. calcd for $C_{22}H_{25}BrN_2O_5S$: C, 51.87; H, 4.91; N, 5.50. Found: C, 52.07; H, 5.12; N, 5.31%.

4.4.2. 1,1-Dimethylethyl (1*S*)-*N*-[2-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 10b. Syrup; $[\alpha]_D^{20}=+9$ (*c* 0.30, $CHCl_3$); IR (KBr) 3419, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, $J=1.7$ Hz, 1H), 7.76 (d, $J=8.1$ Hz, 2H), 7.53 (s, 1H), 7.48 (d, $J=8.4$ Hz, 1H), 7.34 (dd, $J=8.4$ and 1.7 Hz, 1H), 7.25 (d, $J=8.4$ Hz, 2H), 5.03 (m, 1H), 4.94 (br, 1H), 3.59 (ddd, $J=13.82$ and 6.53 and 2.71 Hz, 1H), 3.33 (m, 1H), 2.36 (s, 3H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.1, 145.4, 136.0, 134.9, 130.1, 127.5, 127.0, 126.6, 123.6, 123.2, 121.4, 118.6, 116.8, 80.2, 68.1, 47.0, 28.3, 21.6; EIMS *m*/*z*: 509/511. Anal. calcd for $C_{22}H_{25}BrN_2O_5S$: C, 51.87; H, 4.91; N, 5.50. Found: C, 51.90; H, 5.11; N, 5.38%.

4.4.3. 1,1-Dimethylethyl (1*S*)-*N*-[1-[(4-methylphenyl)-sulfonyl-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 11a. Mp 74–75°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+38.6$ (*c* 1.25, $CHCl_3$); IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, $J=8.2$ Hz, 1H), 7.76 (dd, $J=8.4$ and 1.6 Hz, 2H), 7.56 (s, 1H), 7.55 (d, $J=6.9$ Hz, 1H), 7.36–7.20 (m, 4H), 5.13 (d, $J=7.8$ Hz, 1H), 5.06 (br, 1H), 3.96 (br, 2H), 2.34 (s, 3H), 145 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 144.8, 134.9, 134.7, 129.6, 128.9, 126.5, 124.7, 123.4, 123.1, 120.8, 119.5, 113.4, 79.8, 64.4, 49.1, 28.0, 21.2; ESIMS *m*/*z*: 453.1. Anal. calcd for $C_{22}H_{26}N_2O_5S$: C, 61.39; H, 6.05; N, 6.51. Found: C, 61.26; H, 6.25; N, 6.20%.

4.4.4. 1,1-Dimethylethyl (1*S*)-*N*-[2-[(4-methylphenyl)-sulfonyl-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 11b. Syrup; $[\alpha]_D^{20}=+11.8$ (*c* 1.20, $CHCl_3$); IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, $J=8.3$ Hz, 1H), 7.76 (dd, $J=8.4$ and 1.7 Hz, 2H), 7.60 (d, $J=7.8$ Hz, 1H), 7.58 (s, 1H), 7.32–7.25 (m, 2H), 7.21 (d, $J=8.4$ Hz, 2H), 5.06 (m, 1H), 4.95 (br, 1H), 3.62 (ddd, $J=14.33$ and 7.13 and 3.57 Hz, 1H), 3.36 (m, 1H), 3.29 (br, 1H), 2.33 (s, 3H), 145 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 144.9, 135.3, 135.0, 129.8, 128.6, 126.8, 124.8, 123.3, 123.2, 120.1, 113.6, 80.0, 68.0, 46.8, 28.3, 21.4; EIMS *m*/*z*: 430. Anal. calcd for $C_{22}H_{26}N_2O_5S$: C, 61.39; H, 6.05; N, 6.51. Found: C, 61.30; H, 5.97; N, 6.26%.

4.4.5. 1,1-Dimethylethyl (1*S*)-*N*-[1-[5-methoxyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 12a. Mp 69–71°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+22$ (*c* 0.85, $CHCl_3$); IR (KBr) 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, $J=8.9$ Hz, 1H), 7.72 (d, $J=8.2$ Hz, 2H), 7.51 (s, 1H), 7.20 (d, $J=8.0$ Hz, 2H), 6.98 (d, $J=2.1$ Hz, 1H), 6.93 (dd, $J=8.9$ and 2.1 Hz, 1H), 5.12 (br d, $J=7.6$ Hz, 1H), 5.02 (br, 1H), 3.95 (br s, 1H), 3.79 (s, 3H), 2.40 (s, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 155.9, 144.9, 135.0, 130.2, 129.8, 126.7, 124.2, 121.0, 114.6, 114.2, 102.0, 80.1, 64.8, 55.6, 49.1, 28.3, 21.5; ESIMS *m*/*z*: 483.2. Anal. calcd for $C_{23}H_{28}N_2O_6S$: C, 60.00; H, 6.09; N, 6.09. Found: C, 60.00; H, 5.77; N, 6.29%.

4.4.6. 1,1-Dimethylethyl (1*S*)-*N*-[2-[5-methoxyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 12b. Syrup; $[\alpha]_D^{20}=+2.5$ (*c* 1.675, $CHCl_3$); IR (KBr) 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (dd, $J=9.1$ and 0.6 Hz, 1H), 7.72 (dd, $J=8.5$ and 1.8 Hz, 2H), 7.52 (s, 1H), 7.20 (d, $J=8.0$ Hz, 2H), 7.04 (d, $J=2.4$ Hz, 1H), 6.92 (dd, $J=9.1$ and 2.4 Hz, 1H), 5.01 (br d, $J=4.2$ Hz, 1H), 4.95 (br, 1H), 3.80 (s, 3H), 3.60 (ddd, $J=13.75$ and 6.11 and 2.65 Hz, 1H), 3.37 (m, 1H), 3.28 (br, 1H), 2.33 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 156.3, 144.9, 135.0, 130.1, 129.8, 129.6, 126.7, 124.0, 123.3, 114.6, 113.8, 102.7, 80.0, 68.1, 55.7, 46.6, 28.3, 21.5; ESIMS *m*/*z*: 483.1. Anal. calcd for $C_{23}H_{28}N_2O_6S$: C, 60.00; H, 6.09; N, 6.09. Found: C, 60.10; H, 6.44; N, 5.77%.

4.4.7. 1,1-Dimethylethyl (1*S*)-*N*-[1-[5-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 13a. Mp 81–82°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+7.8$ (*c* 1.90, $CHCl_3$); IR (KBr) 1696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, $J=9.2$ Hz, 1H), 7.73 (d, $J=8.5$ Hz, 2H), 7.70 (d, $J=1.8$ Hz, 1H), 7.57 (s, 1H), 7.41 (dd, $J=9.2$ and 1.8 Hz, 1H), 7.23 (d, $J=8.5$ Hz, 2H), 5.16 (br d, $J=6.7$ Hz, 1H), 4.99 (br, 1H), 3.96 (br s, 2H), 2.28 (s, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 146.3, 135.6, 134.7, 131.7, 130.8, 128.7, 127.6, 125.6, 123.4, 121.2, 117.7, 115.8, 80.9, 65.1, 49.4, 28.5, 21.7; ESIMS *m*/*z*: 531.1/533.1. Anal. calcd for $C_{22}H_{25}N_2O_5BrS$: C, 51.87; H, 4.91; N, 5.50. Found: C, 52.11; H, 5.20; N, 5.21%.

4.4.8. 1,1-Dimethylethyl (1*S*)-*N*-[2-[5-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-hydroxy]ethylcarbamate 13b. Syrup; $[\alpha]_D^{20}=+4.8$ (*c* 1.50, $CHCl_3$); IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, $J=9.2$ Hz, 1H), 7.73 (d, $J=8.5$ Hz, 2H), 7.74 (s, 1H), 7.57 (s, 1H), 7.40 (dd, $J=9.2$ and 1.8 Hz, 1H), 7.22 (d, $J=8.0$ Hz, 2H), 5.02 (br s, 2H), 3.72 (br, 1H), 3.56 (ddd, $J=14.05$ and 6.72 and 3.66 Hz, 1H), 3.40

(m, 1H), 2.34 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 145.3, 134.8, 134.1, 130.4, 130.0, 127.8, 126.8, 124.5, 123.0, 122.7, 116.8, 115.2, 80.3, 68.2, 47.0, 28.3, 21.6; ESIMS m/z: 531.0/533.0. Anal. calcd for $C_{22}H_{25}N_2O_5BrS$: C, 51.87; H, 4.91; N, 5.50. Found: C, 52.01; H, 5.02; N, 5.20%.

4.4.9. 1,1-Dimethylethyl (1*S*)-*N*-[1-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-[(4-methylphenyl)sulfonyl]oxy]ethylcarbamate 14. A solution of **10a** (2.4 g, 4.74 mmol) in CH_2Cl_2 (60 mL) was treated with tosyl chloride (1.1 g, 5.8 mmol), Et_3N (1.01 g, 10 mmol) and DMAP (50 mg) for 5 h at room temperature. The mixture was washed with water and brine, and dried over anhydrous sodium sulfate overnight. After removal of the solvent, the residue was purified by flash chromatography (silica, hex/AcOEt, 6:1) to afford **14** as a white solid (2.7 g, 86%). Mp 190°C dec. (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+15$ (*c* 0.32, $CHCl_3$); IR (KBr) 3396, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 7.78 (d, $J=8.3$ Hz, 2H), 7.57 (d, $J=8.2$ Hz, 2H), 7.46 (s, 1H), 7.28 (m, 3H), 7.22 (s, 1H), 7.18 (d, $J=8.1$ Hz, 2H), 5.15 (br, 1H), 5.06 (br, 1H), 4.39 (dd, $J=10.1$ and 4.25 Hz, 1H), 4.26 (dd, $J=10.1$ and 3.73 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 1.45 (s, 9 H); ESIMS m/z: 685.1/687.1. Anal. calcd for $C_{29}H_{31}BrN_2O_7S_2$: C, 52.49; H, 4.68; N, 4.22. Found: C, 52.47; H, 4.75; N, 3.82%.

4.4.10. 1,1-Dimethylethyl (1*S*)-*N*-[1-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-2-azido]ethylcarbamate 15. To a solution of compound **14** (2.66 g, 4.02 mmol) in dry DMF (30 mL) was added sodium azide (975 mg, 15 mmol) at room temperature. The mixture was then stirred for 12 h at 80°C. After cooling to room temperature, the mixture was diluted with water (60 mL) and extracted with ethyl acetate (3×30 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 **15** as a white solid (1.8 g, 88%). Mp 174–176°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+4$ (*c* 1.67, $CHCl_3$); IR (KBr) 3341, 2103, 1691 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.03 (s, 1H), 7.87 (d, $J=8.2$ Hz, 2H), 7.82 (s, 1H), 7.67 (d, $J=8.4$ Hz, 1H), 7.58 (br d, $J=8.4$, 1H), 7.47 (d, $J=8.6$ Hz, 1H), 7.41 (d, $J=8.3$ Hz, 2H), 4.99 (m, 1H), 3.65 (d, $J=6.4$, 1H), 2.33 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.1, 145.8, 134.9, 133.8, 130.4, 128.0, 126.7, 126.5, 124.8, 121.9, 121.6, 117.7, 115.6, 78.4, 53.0, 46.5, 28.1, 21.0; ESIMS m/z: 556.1/558.1. Anal. calcd for $C_{22}H_{24}BrN_5O_4S$: C, 49.44; H, 4.49; N, 13.11. Found: C, 49.73; H, 4.49; N, 13.25%.

4.4.11. (*R*)-6-Bromo-*N*-[2-azido-1-[(6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]ethyl]-α-oxoindole-3-acetamide 17. To a stirred solution of compound **15** (1.76 g, 3.28 mmol) in CH_2Cl_2 (30 mL) in an ice-water bath under argon was added trifluoroacetic acid (12 mL, 15 mmol). The resulting solution was stirred at room temperature overnight and quenched by the addition of water (20 mL). The water phase was neutralized with aqueous 1N NaOH and extracted with CH_2Cl_2 (2×25 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 (1.7 mL, 12 mmol) in dry DMF (20 mL) cooled in an ice bath was added a solution of 6-bromo-3-indolyl-α-oxoacetyl chloride **16** (1.7 g, 5.9 mmol) in dry DMF (5 mL) dropwise. After 4 h, water (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3×20 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 **17** (1.9 g, 85%) as a light yellow solid. Mp 120–122°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+45$ (*c* 0.40, $CHCl_3$); IR (KBr) 3369, 2106, 1684, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (br s, 1H), 8.98 (d, $J=3.0$ Hz, 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 ($CDCl_3$, 75 MHz) δ 179.6, 161.8, 145.7, 138.6, 136.5, 135.6, 134.5, 130.2, 127.5, 127.0, 126.8, 126.7, 125.3, 124.3, 123.5, 120.6, 119.2, 119.1, 117.7, 116.7, 114.8, 113.1, 53.5, 45.2, 21.6; ESIMS m/z: 703.1. 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%.

4.4.12. (*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl]-5,6-dihydro-1*H*-pyrazin-2-one 18. To a solution of compound **17** (1.84 g, 2.686 mmol) in dry toluene (100 mL) was added tributylphosphine (1.05 mL, 4.14 mmol). The mixture was stirred at room temperature for 20 min, and then heated under reflux for 6 h under an argon atmosphere. After removal of toluene, the residue was subjected to flash chromatography (silica, hex/AcOEt, 2:1 and 1:1) to afford compound **18** (1.6 g, 94%) as a yellow solid. Mp >300°C (CH_2Cl_2); $[\alpha]_D^{20}=-27$ (*c* 0.5, acetone); IR (KBr) 1672 cm^{-1}; ^{1}H 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/z: 638/640/642. Anal. calcd for $C_{27}H_{20}Br_2N_4O_3S$: C, 50.62; H, 3.12; N, 8.75. Found: C, 50.81; H, 3.20; N, 8.48%.

4.4.13. Hamacanthin A 2. A suspension of compound **18** (64 mg, 0.1 mmol) and NaOH (18 mg, 0.45 mmol) in absolute methanol (8 mL) was heated under reflux for 1 h. The solvent was evaporated in vacuo and 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 **2** (38 mg, 78%) as a yellow solid. Mp 270–271°C (AcOEt); $[\alpha]_D^{20}=+82$ (*c* 0.135, CH_3OH); IR (KBr) 3407, 1670 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.60 (br s, 1H), 11.17 (br d, $J=1.8$ Hz, 1H), 8.80 (br d, $J=1.9$ Hz, 1H), 8.43 (s, 1H), 8.30 (d, $J=8.6$ 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, $J=8.5$ and 5.4 Hz, 1H), 4.12 (dd, $J=16.3$ and 5.2 Hz, 1H), 4.07 (dd, $J=16.3$ and 8.6 Hz, 1H); ^1H NMR (acetone-d_6, 300 MHz) δ 8.55 (s, 1H), 8.44 (d, $J=8.5$ Hz, 1H), 7.74 (d, $J=8.5$ Hz, 1H), 7.67 (dd, $J=8.5$ and 1.4 Hz, 1H), 7.43 (s, 1H), 7.25 (dd, $J=8.6$ and 1.8 Hz, 1H), 7.20 (dd, $J=8.5$ and 1.8 Hz, 1H), 5.14 (dd, $J=9.3$ and 4.7 Hz, 1H), 4.27 (dd, $J=16.4$ and 5.0 Hz, 1H), 4.18 (dd, $J=16.5$ and 9.3 Hz, 1H); EIMS *m/z*: 486; HREIMS calcd for $C_{20}H_{14}{}^{79}Br_2N_4O$: 483.95604; found: 483.95344.

4.5. Reduction of compound 18

To a stirred suspension of **18** (192 mg, 0.3 mmol) in methanol (20 mL) cooled in an ice bath was added $NaBH_4$ (114 mg, 3 mmol). The mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of water (5 mL). After the solvent was removed, the residue was extracted with ethyl acetate (2×10 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (silica, AcOEt) to give **19** (120 mg, 62%) and **20** (70 mg, 36%) as yellow solids.

4.5.1. (3*S*,6*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-piperazin-2-one 19. Mp 164–165°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=-35$ (*c* 1.50, $CHCl_3$); IR (KBr) 3246, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.79 (br s, 1H), 8.07 (d, $J=1.5$ Hz, 1H), 7.78 (br s, 1H), 7.57 (s, 1H), 7.56 (d, $J=8.8$ Hz, 1H), 7.49 (d, $J=8.4$ Hz, 2H), 7.36 (d, $J=1.4$ Hz, 1H), 7.30 (dd, $J=8.4$ and 1.5 Hz, 1H), 7.24 (d, $J=8.4$ Hz, 2H), 7.13 (m, 2H), 6.82 (d, $J=8.1$ Hz, 2H), 4.98 (s, 1H), 4.90 (br d, $J=2.2$ Hz, 1H), 3.32 (dd, $J=13.2$ and 4.0 Hz, 1H), 3.04 (dd, $J=13.6$ and 5.5 Hz, 1H), 2.26 (br s, 1H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 145.5, 137.2, 136.1, 134.1, 130.0, 126.9, 126.6, 125.3, 124.6, 123.9, 123.0, 122.3, 120.9, 120.3, 118.9, 116.9, 115.8, 114.4, 113.3, 55.8, 50.5, 45.3, 21.4; ESIMS *m/z*: 640.9/643.0/645.0; HRESIMS calcd for $C_{27}H_{22}{}^{79}Br_2N_4O_3S$: 640.9852; found: 640.9863.

4.5.2. (3*R*,6*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-piperazin-2-one 20. Mp 184–185°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+16$ (*c* 0.42, $CHCl_3$); IR (KBr) 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.93 (br s, 1H), 8.13 (s, 1H), 7.77 (d, $J=8.4$ Hz, 2H), 7.57 (s, 1H), 7.62 (s, 1H), 7.47 (d, $J=8.4$ Hz, 1H), 7.41 (br s, 1H), 7.29 (s, 2H), 7.17 (d, $J=8.1$ Hz, 2H), 7.10 (dd, $J=8.4$ and 1.1 Hz, 1H), 7.05 (s, 1H), 6.69 (s, 1H), 4.92 (br s, 1H), 4.78 (s, 1H), 3.35 (dd, $J=12.1$ and 4.7 Hz, 1H), 2.98 (dd, $J=12.1$ and 9.1 Hz, 1H), 2.31 (s, 3H), 2.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 145.6, 137.3, 135.9, 134.6, 130.2, 127.0, 126.9, 125.2, 124.7, 124.0, 122.6, 121.1, 120.6, 118.9, 116.9, 115.5, 114.4, 112.6, 56.9, 51.2, 48.8, 21.6; ESIMS *m/z*: 641.0/643.0/645.0; HRESIMS calcd for $C_{27}H_{22}{}^{79}Br_2N_4O_3S$: 640.9852; found: 640.9859.

4.5.3. (3*S*,6*S*)-3,6-Bis(6-bromo-1*H*-indol-3-yl)piperazin-2-one 3. A solution of **19** (32 mg, 0.05 mmol) and L-Selectride® (1 M in THF, 1 mL, 1 mmol) in anhydrous THF (4 mL) was heated under reflux for 8 h. The reaction mixture was cooled to room temperature and quenched by careful addition of methanol. After concentration of the solution, the residue was purified by chromatography (silica, CH_2Cl_2/MeOH, 20:1) to afford compound **3** as a white solid (20 mg, 87%). Mp 146–147°C (CH_2Cl_2/MeOH); $[\alpha]_D^{20}=-8$ (*c* 0.17, CH_3OH); IR (KBr) 1653 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.13 (br s, 1H), 11.07 (br s, 1H), 8.06 (d, $J=1.6$ Hz, 1H), 7.68 (d, $J=8.6$ Hz, 1H), 7.55 (d, $J=1.6$ Hz, 1H), 7.54 (d, $J=1.6$ Hz, 1H), 7.50 (d, $J=8.6$ Hz, 1H), 7.34 (d, $J=2.3$ Hz, 1H), 7.30 (d, $J=2.0$ Hz, 1H), 7.08 (d, $J=0.8$ Hz, 1H), 7.06 (d, $J=1.2$ Hz, 1H), 4.89 (m, 1H), 4.72 (s, 1H), 3.10 (dd, $J=12.9$ and 4.3 Hz, 1H), 2.94 (dd, $J=12.9$ and 7.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.2, 137.3, 137.1, 125.7, 124.9, 124.3, 124.1, 121.7, 121.2, 121.0, 120.4, 115.6, 114.1, 113.9, 113.8, 113.6, 55.4, 50.2, 46.1; EIMS *m/z*: 490/488/486; HREIMS calcd for $C_{20}H_{16}{}^{79}Br_2N_4O$: 485.96908; found: 485.97106.

4.5.4. (3*R*,6*S*)-3,6-Bis(6-bromo-1*H*-indol-3-yl)piperazin-2-one 4. A solution of **20** (32 mg, 0.05 mmol) and L-Selectride® (1 M in THF, 1 mL, 1 mmol) in anhydrous THF (4 mL) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and quenched by careful addition of methanol. After concentration of the solution, the residue was purified by chromatography (silica, CH_2Cl_2/MeOH, 20:1) to give compound **4** as a white solid (21 mg, 88%). Mp 238°C dec. (CH_2Cl_2/MeOH); $[\alpha]_D^{20}=-6$ (*c* 0.275, CH_3OH/acetone=1:1); IR (KBr) 1653 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.16 (br d, $J=1.9$ Hz, 1H), 11.04 (br d, $J=1.9$ Hz, 1H), 7.95 (s, 1H), 7.62 (d, $J=3.8$ Hz, 1H), 7.60 (d, $J=3.6$ Hz, 1H), 7.56 (d, $J=1.6$ Hz, 1H), 7.53 (d, $J=1.6$ Hz, 1H), 7.36 (d, $J=2.2$ Hz, 1H), 7.32 (d, $J=2.2$ Hz, 1H), 7.13 (dd, $J=8.5$ and 1.9 Hz, 1H), 7.09 (dd, $J=8.5$ and 1.9 Hz, 1H), 4.98 (dd, $J=9.3$ and 4.4 Hz, 1H), 4.70 (s, 1H), 3.23 (dd, $J=12.4$ and 4.4 Hz, 1H), 2.98 (dd, $J=12.4$ and 9.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.1, 137.4, 137.1, 125.6, 125.2, 124.4, 124.1, 121.8, 121.4, 121.0, 120.7, 114.7, 114.4, 114.2, 113.9, 113.8, 113.6, 56.5, 50.8, 49.6; ESIMS *m/z*: 486.9/488.9/490.9; HRESIMS calcd for $C_{20}H_{16}{}^{79}Br_2N_4O$: 486.9764; found: 486.9771.

4.5.5. (6*S*)-3-[6-Bromo-1-(*tert*-butyloxycarbonyl)-1*H*-indol-3-yl]-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-5,6-dihydro-1*H*-pyrazin-2-one 22. To a stirred suspension of **18** (1.0 g, 1.56 mmol), DMAP (50 mg) and Et_3N (505 mg, 5 mmol) in EtOAc (80 mL) cooled in an ice bath was added a solution of $(Boc)_2O$ (341 mg, 1.56 mmol) in EtOAc (5 mL) dropwise. The mixture was stirred at this temperature for 2 h. The reaction mixture was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica, hex/AcOEt, 4:1) to afford **22** as a white solid (0.95 g, 82%) and compound **21** as a yellow solid (0.18 g, 14%). For **22**: mp 174–176°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=+94$ (*c* 0.64, $CHCl_3$); IR (KBr) 1745, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.42 (d, $J=1.6$ Hz, 1H), 8.26 (d, $J=8.6$ Hz, 1H), 8.14 (d, $J=1.4$ Hz, 1H), 7.61 (d, $J=8.4$ Hz, 2H), 7.52 (s, 1H), 7.44–7.35 (m, 3H), 6.96 (d, $J=8.2$ Hz, 2H), 6.91 (br s, 1H), 5.01 (m, 1H), 4.34 (dd, $J=16.8$ and 4.4 Hz, 1H), 4.14 (dd, $J=16.8$ and 8.7 Hz, 1H), 2.25 (s, 3H), 1.66 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 156.8, 148.9, 145.6, 136.0, 134.4, 132.4, 130.0, 127.2, 126.8, 126.7, 124.3, 120.5, 119.5, 119.2, 118.8, 118.1, 117.1, 114.5, 85.2, 53.1, 47.0, 28.0, 21.5; ESIMS *m*/*z*: 741.1/743.1. Anal. calcd for $C_{32}H_{28}Br_2N_4O_5S$: C, 51.89; H, 3.78; N, 7.57. Found: C, 52.22; H, 3.74; N, 7.36%.

4.5.6. 1,1-Dimethylethyl (6*S*)-3-[6-bromo-1-(*tert*-butyloxycarbonyl)-1*H*-indol-3-yl]-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-5,6-dihydro-2-oxo-1*H*-pyrazine-1-carboxylate 21. Mp 137–139°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=-70$ (*c* 0.68, $CHCl_3$); IR (KBr) 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.52 (d, $J=1.6$ Hz, 1H), 8.13 (m, 3H), 7.46–7.33 (m, 3H), 7.28–7.24 (m, 3H), 6.55 (d, $J=8.1$ Hz, 2H), 5.88 (br d, $J=4.7$ Hz, 1H), 4.58 (dd, $J=17.2$ and 1.6 Hz, 1H), 4.27 (dd, $J=17.2$ and 5.1 Hz, 1H), 2.16 (s, 3H), 1.72 (s, 9H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 155.0, 150.8, 148.9, 145.3, 136.1, 134.1, 132.4, 129.7, 127.2, 127.1, 126.9, 126.3, 124.6, 124.4, 120.4, 120.3, 119.1, 119.0, 118.1, 117.0, 113.9, 85.5, 85.1, 51.7, 49.7, 28.1, 27.8, 21.4; EIMS *m*/*z*: 640 (M−2×Boc). Anal. calcd for $C_{37}H_{36}Br_2N_4O_7S$: C, 52.86; H, 4.28; N, 6.67. Found: C, 53.25; H, 4.35; N, 6.37%.

4.5.7. (6*S*)-3-[6-Bromo-1-(*tert*-butyloxycarbonyl)-1*H*-indol-3-yl]-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-5,6-dihydro-1-methyl-1*H*-pyrazin-2-one 23. A mixture of compound **22** (807 mg, 1.09 mmol), anhydrous K_2CO_3 (1.5 g, 11 mmol) and MeI (1.56 g, 11 mmol) in anhydrous acetone (60 mL) was heated under reflux for 4 h. After removal of the solvent, water (20 mL) was added to the residue. The mixture was extracted with ether (2×40 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (silica, hex/AcOEt, 2:1) to give **23** as colorless needles (0.82 g, 100%). Mp 164–165°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=-26$ (*c* 0.55, $CHCl_3$); IR (KBr) 1747, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.89 (s, 1H), 8.42 (d, $J=1.6$ Hz, 1H), 8.16 (d, $J=1.4$ Hz, 1H), 8.12 (dd, $J=8.6$ and 2.7 Hz, 1H), 7.40–7.23 (m, 6H), 6.62 (d, $J=8.3$ Hz, 2H), 4.89 (m, 1H), 4.38 (dd, $J=16.7$ and 3.1 Hz, 1H), 4.22 (dd, $J=16.7$ and 5.4 Hz, 1H), 3.17 (s, 3H), 2.17 (s, 3H), 1.73 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.9, 149.0, 145.5, 136.5, 136.2, 134.1, 132.7, 129.9, 127.3, 127.2, 127.0, 126.7, 126.4, 124.6, 124.4, 120.3, 119.2, 118.8, 118.1, 117.3, 114.6, 85.2, 53.6, 51.5, 33.5, 28.1, 21.5. Anal. calcd for $C_{33}H_{30}Br_2N_4O_5S$: C, 52.52; H, 3.98; N, 7.43. Found: C, 52.64; H, 3.98; N, 7.08%.

4.5.8. (6*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-5,6-dihydro-1-methyl-1*H*-pyrazin-2-one 24. To a stirred solution of compound **23** (743 mg, 0.985 mmol) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (10 mL) in an ice-water bath under argon. The resulting solution was stirred at room temperature overnight and quenched by addition of water (20 mL). The water phase was neutralized with aqueous 1N NaOH and extracted with CH_2Cl_2 (2×20 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 purified by chromatography (silica, hex/AcOEt, 1:1) to afford **24** as a yellow solid (620 mg, 96%). Mp 132–134°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}=-115$ (*c* 0.74, $CHCl_3$); IR (KBr) 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.54 (br d, $J=1.9$ Hz, 1H), 8.14 (d, $J=8.5$ Hz, 1H), 8.13 (s, 1H), 7.59 (d, $J=1.6$ Hz, 1H), 7.38 (m, 2H), 7.28–7.22 (m, 4H), 6.49 (d, $J=8.4$ Hz, 2H), 4.88 (br, 1H), 4.33 (dd, $J=16.4$ and 3.2 Hz, 1H), 4.20 (dd, $J=16.4$ and 5.4 Hz, 1H), 3.18 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 157.3, 145.4, 137.0, 136.4, 133.8, 132.1, 129.8, 127.3, 127.0, 126.2, 125.1, 124.6, 124.5, 120.3, 119.4, 119.1, 117.2, 116.5, 114.1, 112.0, 53.7, 51.2, 33.5, 29.7, 21.4; EIMS *m*/*z*: 654; HREIMS calcd for $C_{28}H_{22}{}^{79}Br_2N_4O_3S$: 651.98191; found: 651.97992.

4.5.9. Sodium borohydride reduction of compound 24. To a stirred suspension of **24** (607 mg, 0.928 mmol) in methanol (30 mL) cooled in an ice bath was added $NaBH_4$ (350 mg, 9.28 mmol). The mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of water (10 mL). After the solvent was removed, the residue was extracted with ethyl acetate (2×20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (silica, AcOEt) to give **25** (500 mg, 82%) and **26** (100 mg, 17%) as yellow solids.

4.5.10. (3*S*,6*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-1-methylpiperazin-2-one 25. Mp 152–153°C (AcOEt); $[\alpha]_D^{20}=-49$ (*c* 0.77, CH_3Cl); IR (KBr) 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.13 (s, 1H), 8.17 (d, $J=1.5$ Hz, 1H), 7.61 (d, $J=8.4$ Hz, 1H), 7.42–7.38 (m, 4H), 7.34 (d, $J=8.4$ Hz, 1H), 7.28 (d, $J=8.4$ Hz, 1H), 7.16 (dd, $J=8.4$ and 1.8 Hz, 1H), 7.11 (d, $J=1.8$ Hz, 1H), 6.79 (d, $J=8.4$ Hz, 2H), 4.98 (s, 1H), 4.73 (m, 1H), 3.46 (dd, $J=13.2$ and

4.0 Hz, 1H), 3.10 (dd, $J=13.2$ and 2.6 Hz, 1H), 3.03 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 145.6, 137.4, 136.4, 134.1, 130.0, 127.3, 126.9, 126.5, 125.5, 125.3, 123.6, 122.8, 121.6, 120.9, 120.2, 119.1, 117.2, 115.7, 114.4, 114.0, 56.9, 56.8, 46.8, 34.4, 21.4; EIMS m/z: 654; HREIMS calcd for $C_{28}H_{24}{}^{79}Br_2N_4O_3S$: 653.99359; found: 653.98942.

4.5.11. (3*R*,6*S*)-3-(6-Bromo-1*H*-indol-3-yl)-6-[6-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-1-methylpiperazin-2-one 26. Mp 244°C dec. (AcOEt); $[\alpha]_D^{20}=+12$ (c 0.20, CH_3OH/acetone = 1:1); IR (KBr) 1639 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.08 (br s, 1H), 8.04 (d, $J=1.6$ Hz, 1H), 7.91 (d, $J=8.2$ Hz, 2H), 7.90 (s, 1H), 7.63 (d, $J=8.5$ Hz, 1H), 7.58 (d, $J=8.5$ Hz, 1H), 7.53 (d, $J=1.4$ Hz, 1H), 7.46 (dd, $J=8.5$ and 1.4 Hz, 1H), 7.41 (d, $J=8.2$ Hz, 2H), 7.27 (d, $J=2.2$ Hz, 1H), 7.09 (dd, $J=8.5$ and 1.4 Hz, 1H), 4.97 (m, 1H), 4.87 (s, 1H), 3.28 (dd, $J=13.2$ and 5.0 Hz, 1H), 2.94 (dd, $J=13.2$ and 6.6 Hz, 1H), 2.64 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.3, 145.9, 137.1, 135.4, 133.6, 130.4, 127.8, 126.8, 126.1, 125.7, 125.0, 122.0, 121.6, 121.3, 121.2, 117.8, 115.9, 114.4, 113.8, 113.6, 56.2, 55.8, 46.8, 32.3, 21.0; EIMS m/z: 654; HREIMS calcd for $C_{28}H_{24}{}^{79}Br_2N_4O_3S$: 653.99358; found: 653.99420.

4.5.12. (3*R*,6*S*)-3,6-Bis(6-bromo-1*H*-indol-3-yl)-1-methylpiperazin-2-one 27. A solution of **26** (66 mg, 0.1 mmol) and L-Selectride® (1 M in THF, 1.5 mL, 1.5 mmol) in anhydrous THF (6 mL) was heated under reflux for 7 h. The reaction mixture was cooled to room temperature and quenched by careful addition of methanol. After concentration of the solution, the residue was purified by chromatography (silica, CH_2Cl_2/MeOH, 40:1) to give compound **27** as a white solid (40 mg, 80%). Mp 164–166°C (CH_2Cl_2/MeOH); $[\alpha]_D^{20}=-32$ (c 0.20, CH_3OH); IR (KBr) 1637 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 10.55 (br s, 1H), 10.32 (br s, 1H), 7.76 (d, $J=8.25$ Hz, 1H), 7.68 (d, $J=1.5$ Hz, 1H), 7.64 (d, $J=8.55$ Hz, 1H), 7.59 (d, $J=1.5$ Hz, 1H), 7.47 (d, $J=2.1$ Hz, 1H), 7.36 (d, $J=1.8$ Hz, 1H), 7.23 (dd, $J=8.55$ and 1.8 Hz, 1H), 7.14 (dd, $J=8.55$ and 1.8 Hz, 1H), 5.06 (dd, $J=7.0$ and 4.9 Hz, 1H), 5.00 (s, 1H), 3.47 (dd, $J=12.8$ and 4.6 Hz, 1H), 3.26 (dd, $J=12.8$ and 7.0 Hz, 1H), 2.84 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.0, 138.6, 138.3, 126.8, 125.4, 122.9, 122.6, 122.1, 120.9, 115.9, 115.4, 115.2, 115.0, 114.8, 114.5, 57.9, 57.7, 49.1, 32.5; ESIMS m/z: 500.9/502.9/504.9; HRESIMS calcd for $C_{21}H_{18}{}^{79}Br_2N_4O$: 500.9920; found: 500.9919.

4.5.13. Dragmacidin A 1. To an ice-cooled solution of compound **27** (30 mg, 0.06 mmol) in THF (2 mL) was added BH_3–THF (1.0 M in THF, 1.0 mL, 1.0 mmol), and the mixture was stirred at room temperature for 3 days. 1N HCl (0.5 mL) was added at 0°C, and the mixture was stirred for a further 2 h, condensed, and neutralized with $NaHCO_3$, then extracted with AcOEt (2×5 mL). The extract was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica, CH_2Cl_2/MeOH, 15:1) to give **1** (12 mg, 42%) as a viscous oil. $[\alpha]_D^{20}=+4$ (c 0.20, $CHCl_3$); IR (KBr) 3416, 2925, 2853, 1617, 1544, 1455 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 10.34 (br s, 1H), 10.34 (br s, 1H), 7.92 (d, $J=8.43$ Hz, 1H), 7.81 (d, $J=8.43$ Hz, 1H), 7.62 (d, $J=1.1$ Hz, 1H), 7.61 (d, $J=1.8$ Hz, 1H), 7.43 (d, $J=1.8$ Hz, 1H), 7.39 (d, $J=2.2$ Hz, 1H), 7.177 (dd, $J=8.5$ and 1.8 Hz, 1H), 7.175 (dd, $J=8.5$ and 1.8 Hz, 1H), 4.48 (dd, $J=10.6$ and 2.9 Hz, 1H), 3.48 (br d, $J=10.6$ Hz, 1H), 3.33 (dd, $J=11.7$ and 11.0 Hz, 1H), 3.19 (dd, $J=11.0$ and 2.6 Hz, 1H), 3.12 (dd, $J=11.7$ and 2.9 Hz, 1H), 2.44 (dd, $J=11.0$ and 10.6 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 138.4, 138.2, 126.4, 126.2, 124.6, 123.4, 122.3, 122.2, 122.1, 121.7, 118.1, 116.7, 115.0, 114.9, 114.7, 114.7, 64.0, 62.8, 54.3, 53.9, 43.9; HRESIMS calcd for $C_{21}H_{20}{}^{79}Br_2N_4$: 487.0127; found: 487.0127.

4.5.14. (3*S*,6*S*)-3,6-Bis(6-bromo-1*H*-indol-3-yl)-1-methylpiperazin-2-one 28. A mixture of **25** (66 mg, 0.1 mmol) and anhydrous K_2CO_3 in methanol (10 mL) was heated under reflux for 3 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, CH_2Cl_2/MeOH, 20:1) to give compound **28** as a white solid (20 mg, 40%) and **27** (30 mg, 60%). Mp 222–224°C (CH_2Cl_2/MeOH); $[\alpha]_D^{20}=-29$ (c 0.37, CH_3OH/acetone = 1:1); IR (KBr) 1637 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 10.43 (br s, 1H), 10.33 (br s, 1H), 7.83 (d, $J=8.5$ Hz, 1H), 7.60 (dd, $J=7.9$ and 1.8 Hz, 2H), 7.51 (d, $J=8.5$ Hz, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 4.95 (t, $J=5.2$ Hz, 1H), 4.93 (s, 1H), 3.37 (dd, $J=13.1$ and 4.9 Hz, 1H), 3.29 (dd, $J=13.1$ and 5.5 Hz, 1H), 2.86 (s, 3H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.22 (br s, 1H), 11.12 (br s, 1H), 7.69 (d, $J=8.5$ Hz, 1H), 7.56 (m, 2H), 7.50 (d, $J=8.2$ Hz, 1H), 7.47 (d, $J=8.5$ Hz, 1H), 7.36 (s, 1H), 7.32 (s, 1H), 7.14–7.06 (m, 3H), 4.86 (t, $J=5.1$ Hz, 1H), 4.81 (s, 1H), 3.19 (dd, $J=12.7$ and 4.4 Hz, 1H), 3.07 (dd, $J=12.9$ and 5.9 Hz, 1H), 2.76 (s, 3H), 2.29 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.1, 137.3, 137.2, 137.1, 137.0, 125.8, 124.9, 124.8, 124.7, 124.6, 121.9, 121.4, 121.1, 120.2, 114.2, 113.9, 113.6, 56.4, 56.3, 47.3, 32.6; EIMS m/z: 500; HREIMS calcd for $C_{21}H_{18}{}^{79}Br_2N_4O$: 499.98474; found: 499.98509.

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