Total Synthesis of Marine Bisindole Alkaloid (+)-*cis*-Dihydrohamacanthin B

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Abstract: The total synthesis of the marine bisindole alkaloid (+)-*cis*-dihydrohamacanthin B was achieved from optically pure (*R*)-indolylglycinol.

Key words: bromoindole, indolylglycinol, oxazolidin-2-one, pyrazine, Staudinger reduction

A growing number of bromoindole alkaloids are being discovered from a variety of marine invertebrates, including bryozoans, coelenterates, sponges and tunicates. Adding to their interest is the fact that they display a wide range of biological activity.[1] The bisindole dihydropyrazinone alkaloids, hamacanthin A (**1a**) and B (**1b**), found in the marine sponges, *Hamacantha*, *Rhaphisia* and *Spongosorites*, indicate significant antimicrobial activity against *Candida albicans*, *Cryptococcus neoformans* and *Bacillus subtilis*.[2a] Also, **1a** and **1b** show potent antibacterial activity against methicillin-resistant strains via inhibition of sortase A (Srt A) activity.[2b,c] Recently, dihydrohamacanthin A (**2a**,**b**) and B (**2c**) (Figure 1) have been isolated from the marine sponges, *Rhaphisia lacazei* and *Spongosorites* sp.[3] These compounds show moderate to significant cytotoxicity to several cancer cell lines.[3b]

Since only small quantities of dihydrohamacanthins **2** were available from nature, efficient methods for the total synthesis of these compounds have been required to provide these alkaloids and the related compounds for launching a thorough biological investigation.

The total synthesis of racemic hamacanthins **1**, *cis*- and *trans*-dihydrohamacanthins A (**2a**,**b**) have been accomplished by several groups and us.[4] However, there are few example of the total synthesis of optical active alkaloids, namely, (+)-hamacanthin A (**1a**), (–)-antipodes of *cis*- and *trans*-dihydrohamacanthins A (**2a**,**b**), from indolylglycinol,[5a] and (–)-antipode of **1a** and (+)-hamacanthin B (**1b**) from (*S*)-indolylethanediol.[5b,c] Recently, we have synthesized (+)-hamacanthin A (**1a**) and B (**1b**), and (–)-antipode of *cis*-dihydrohamacanthin B (**2c**) from azide (*S*,*R*)-**3** via (*S*)-**4**, and revealed that the natural **2c** has (+)-(3*S*,5*R*)-configuration (Scheme 1).[6] Herein we describe the first asymmetric total synthesis of natural *cis*-(+)-dihydrohamacanthin B (**2c**) via (*R*)-indolylglycinol **4**.

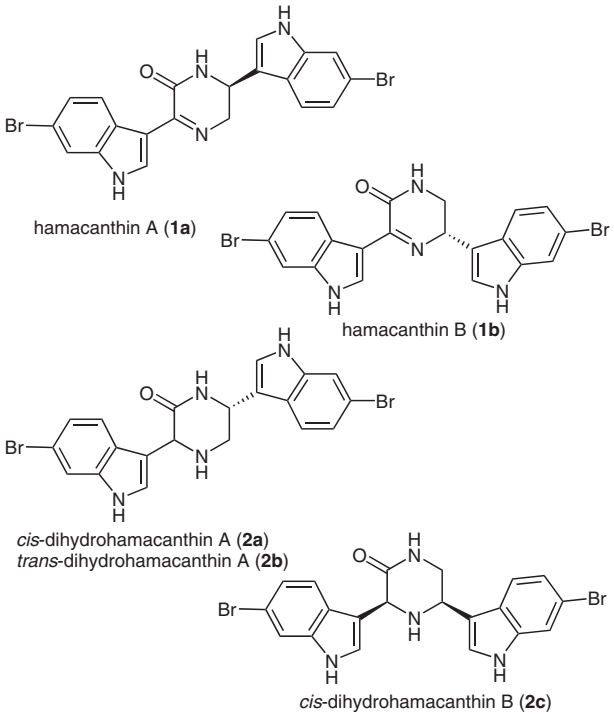
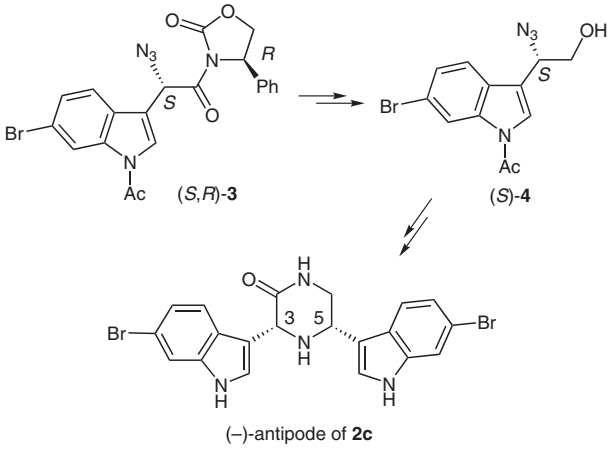


Figure 1 Bisindole dihydropyrazinone alkaloids **1a**,**b** and **2a–c**



Scheme 1 Total synthesis of antipode of *cis*-dihydrohamacanthin B (**2c**)

For the synthesis of natural *cis*-(+)-dihydrohamacanthin B (**2c**), we attempted two routes to (*R*)-indolylglycinol **4** from azides (*R*,*R*)-**5** or (*R*,*S*)-**3**, as the diastereomer and enantiomer of (*S*,*R*)-**3**, respectively (Scheme 2).[7]

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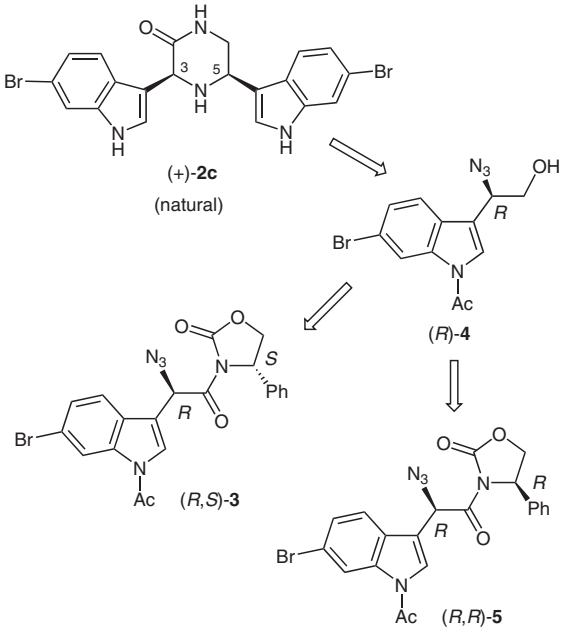
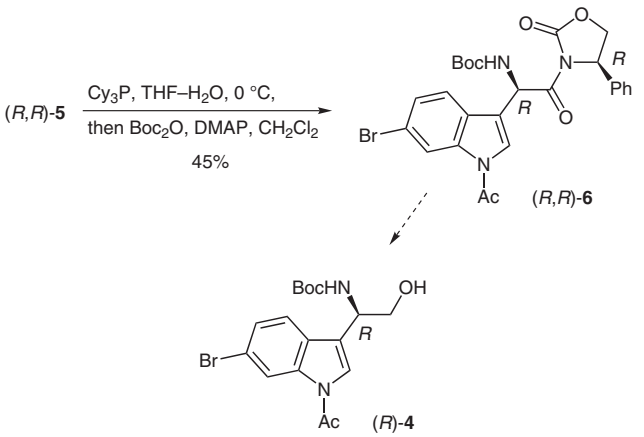


Scheme 2 Synthetic plan for natural *cis*-dihydrohamacanthin B (**2c**)

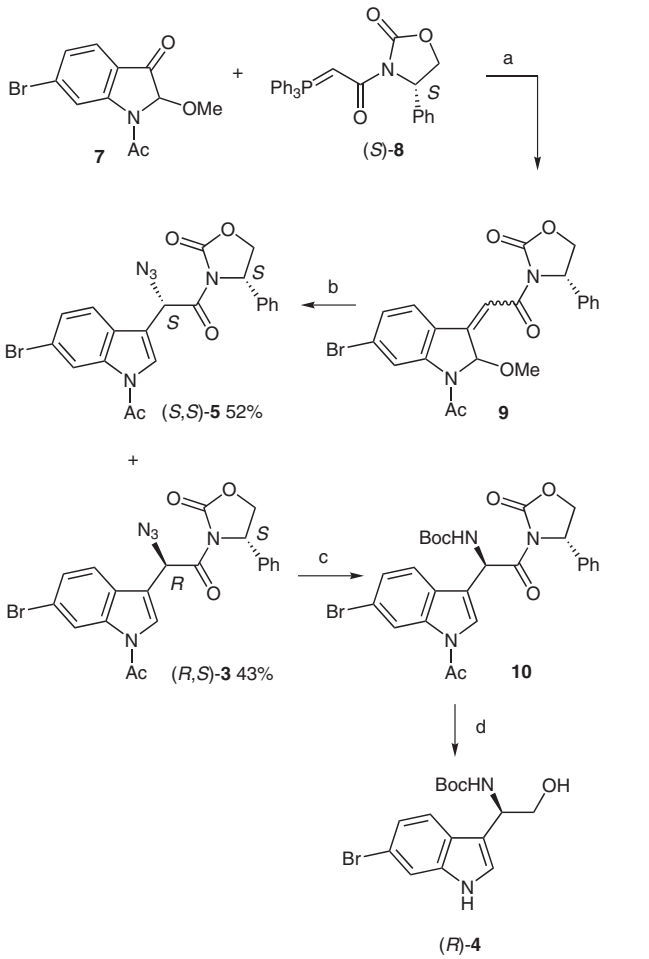
According to the previously reported Staudinger reduction of (*S*,*R*)-**3** with *n*-Bu_3P/HCl–H_2O,[6] (*R*,*R*)-**5** was similarly treated resulting in a complex mixture. Further attempts of this reaction using Ph_3P, *n*-Bu_3P and *t*-Bu_3P under several conditions other than tricyclohexyl phosphine (Cy_3P) were failed.[8,9] Thus, the reduction of (*R*,*R*)-**5** with Cy_3P/H_2O followed by treatment with $(Boc)_2O$ produced (*R*,*R*)-**6** in 45% yield (Scheme 3). But several attempts to effect reductive elimination of the oxazolidinone moiety of (*R*,*R*)-**6** to (*R*)-**4** were unsuccessful. Since compared with the ready conversion of (*S*,*R*)-**3** to (*S*)-**4** (Scheme 1),[6] this conversion of diastereomeric (*R*,*R*)-**5** to (*R*)-**4** was troublesome, we decided to investigate another access to (*R*)-**4** from enantiomeric (*R*,*S*)-**3** (Scheme 2).

Preparation of the azide (*R*,*S*)-**3** was performed by our reported method[6] as shown in Scheme 4.



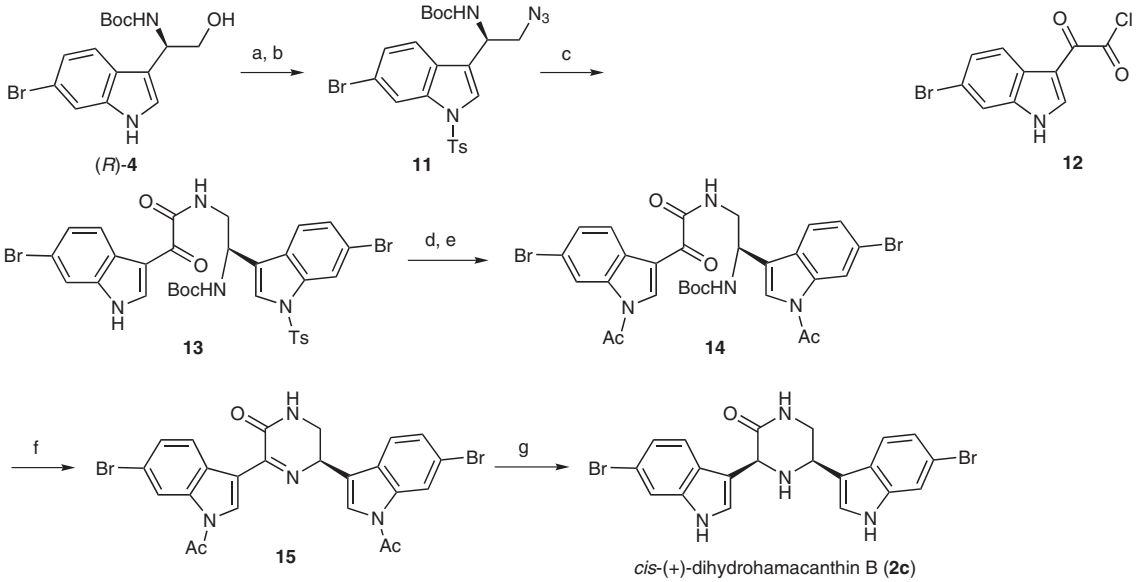
Scheme 3 Attempted preparation of indolylglycinol (*R*)-**4** from azide (*R*,*R*)-**5**

Reaction of readily available indolin-3-one **7**[10] with the optically active ylide **8**[11] in refluxing benzene smoothly proceeded with Wittig olefination to give a diastereomeric mixture of *N*-(3-indolylideneacetyl)oxazolidinone **9** in high yield. When the mixture of **9** was treated with $TMSN_3$ in the presence of methanesulfonic acid, (*S*,*S*)-**5** and (*R*,*S*)-**3** were obtained in 52% and 43% yields, respectively.[12] Azide (*R*,*S*)-**3** was smoothly reduced with *n*-Bu_3P in the presence of 10% HCl at 0 °C to the resulting amine, which was treated with Boc_2O to give oxazolidinylindolylglycine **10** in 58% yield. The reductive removal of the oxazolidinone moiety from **10** with sodium borohydride[13] followed by hydrolysis with LiOH afforded (*R*)-(–)-indolylglycinol **4** in 83% yield without epimerization.[14]



Scheme 4 *Reagents and conditions*: (a) benzene, reflux, 8 h, 96%; (b) $TMSN_3$, $MeSO_3H$, 4 Å MS, CH_2Cl_2, 0 °C to r.t., 1 h; (c) *n*-Bu_3P, 10% HCl, THF, 0 °C to r.t., 12 h, then Boc_2O, DMAP, CH_2Cl_2, r.t., 3 d, 58%; (d) $NaBH_4$, THF–H_2O, r.t., 30 min, then aq 10% LiOH, r.t., 30 min, 83%.

Treatment of (*R*)-(–)-**4** with tosyl chloride at –20 °C provided *N*,*O*-ditosylate, which was displaced with NaN_3 at 80 °C leading to aminoazide **11** in 73% yield in two steps (Scheme 5). Reduction of azide **11** with Ph_3P/H_2O followed by condensation with 6-bromoindole-3-yl-α-oxoacetyl chloride (**12**) afforded amide **13** in 72% yield. After detosylation of **13** with 10% KOH in refluxing



Scheme 5 *Reagents and conditions*: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, –20 °C, 20 h, 92%; (b) NaN_3, DMF, 80 °C, 1 h, 79%; (c) Ph_3P, H_2O, THF, reflux, 1 h, then **12**, Et_3N, THF, 0 °C to r.t., 1 h, 72%, (d) 10% KOH, EtOH, reflux, 1 h, 76%; (e) Ac_2O, DMAP, THF, r.t., 12 h, 80%; (f) HCO_2H, CH_2Cl_2, r.t., 16 h, then EtOH, reflux, 1 h, 71%; (g) $NaBH_3CN$, MeOH, r.t., 1 d, 67%.

EtOH, the indole nitrogens were protected by acetylation to give *N*-(2-aminoethyl)-2-oxoethanamide **14** in 60% yield (2 steps). Removal of the Boc group in **14** followed by refluxing in ethanol provided 3,5-bisindolylpyrazinone **15** in 71% yield. Finally, stereoselective reduction of **15** with sodium cyanoborohydride gave only (3*S*,5*R*)-*cis*-dihydrohamacanthin B (**2c**) in 67% yield, whose relative configuration was determined by its NOE experiment (Figure 2). The spectral data and specific rotation of synthetic **2c** were completely identical to those of the natural product.

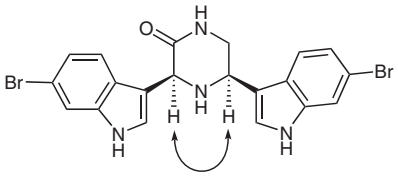


Figure 2 NOE experiment of (+)-dihydrohamacanthin B (**2c**)

In summary, we have achieved a total synthesis of natural *cis*-dihydrohamacanthin B (**2c**) from indoline-3-one **7** in 2.6% overall yield for 11 steps via optically pure (*R*)-indolylglycinol **4**.

All melting points are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. Optical rotations were obtained on a JASCO DIP-140 digital polarimeter. Optical purities were determined on a HPLC (JASCO UV-975) instrument equipped with AD (Daisel Chemical Ind., Ltd., Chiralpak), OD (Daisel Chemical Ind., Ltd., Chiralcel) or Finepak SIL-5 column (JASCO Corporation). IR spectra were recorded on a Shimadzu FTIR-8400s spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-AL300 (300 MHz), JEOL JMN-GSX 400 (400 MHz) or JEOL JNM-LA 500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. *J* values are given in Hertz. Mass spectra were recorded on a JEOL JMS-DX 302 or JEOL JMS 700 instrument with a direct inlet system. Elemental analyses were obtained using a PerkinElmer Model 240B elemental analyzer. Column chromatography was carried out on a silica gel (Kanto Chemical Co. Inc., 230–400 mesh and Merck, 230–400 mesh).

(5″*S*)-(*Z*)-1-Acetyl-6-bromo-2-methoxy-3-{2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethylidene}indoline (9)

A solution of indolin-3-one **7** (7.0 g, 25 mmol) and (*S*)-**8** (17 g, 37 mmol) in benzene (200 mL) was refluxed for 8 h. After removal of the solvent, the residue was chromatographed on a column of silica gel with EtOAc–hexane (1:2) as eluent to give indoline **9** (11 g, 96%) as a yellowish solid; mp 215–217 °C. Major *Z*-isomer was assigned and minor *E*-isomer was inseparable.

IR ($CHCl_3$): 1778, 1681, 1628 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3CO), 2.92 (s, 3 H, CH_3O), 4.30 (dd, *J* = 8.7, 3.3 Hz, 1 H, C*H*H), 4.75 (t, *J* = 8.7 Hz, 1 H, C*H*H), 5.55 (dd, *J* = 8.7, 3.3 Hz, 1 H, C*H*CH_2), 6.65 (d, *J* = 1.8 Hz, 1 H, C*H*OMe), 7.25–7.43 (m, 6 H, ArH), 7.48 (d, *J* = 6.6 Hz, 1 H, ArH), 7.86 (d, *J* = 1.8 Hz, 1 H, CH), 8.52 (br, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 50.2, 57.6, 70.2, 87.9, 111.6, 119.9, 122.2, 124.8, 125.4, 127.2, 127.7, 128.5, 129.0, 138.4, 145.9, 148.4, 153.5, 162.4, 169.6.

MS (EI, 70 eV): *m*/*z* (%) = 472 (M + 2, 58), 470 (M^+, 56), 430 (20), 428 (20), 309 (33), 307 (33), 267 (99), 265 (100), 252 (30), 250 (31), 240 (46), 238 (49).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{19}BrN_2O_5$: 470.0477; found: 470.0472.

1-Acetyl-6-bromo-3-{1′-azido-2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethyl}indoles [(1′*R*,5″*S*)-3 and (1′*S*,5″*S*)-5]

Under N_2, $MeSO_3H$ (1.4 mL, 11 mmol) was added to a mixture of indoline **9** (0.5 g, 1.1 mmol), $TMSN_3$ (1.4 mL, 11 mmol) and 4 Å MS (0.5 g) in anhyd CH_2Cl_2 (50 mL) at 0 °C. After stirring at r.t. for 1 h, the resulting mixture was filtered on Celite to remove 4 Å MS. The filtrate was washed with H_2O (900 mL) and aq sat. $NaHCO_3$ (900 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica

gel with EtOAc–hexane (1:3) as eluent to afford azide (*S*,*S*)-**5** (0.27 g, 52%) and (*R*,*S*)-**3** (0.22 g, 43%) as white solids.

(1′*R*,5″*S*)-3
Mp 145–148 °C; $[\alpha]_D^{20}$ –120.9 (*c* 0.28, $CHCl_3$).

IR ($CHCl_3$): 2108, 1782, 1717 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 4.28 (dd, *J* = 8.9, 4.0 Hz, 1 H, C*H*H), 4.76 (t, *J* = 8.9 Hz, 1 H, C*H*H), 5.52 (dd, *J* = 8.9, 4.0 Hz, 1 H, C*H*CH_2), 6.40 (s, 1 H, C*H*CO), 6.99 (s, 1 H, ArH), 7.09 (d, *J* = 7.3 Hz, 2 H, ArH), 7.21–7.38 (m, 5 H, ArH), 8.65 (d, *J* = 1.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 56.4, 57.5, 70.1, 113.7, 119.4, 119.7, 120.2, 125.0, 126.0, 126.4, 127.2, 128.78, 128.84, 136.0, 137.2, 152.3, 167.7, 167.8.

MS (EI, 70 eV): *m*/*z* (%) = 483 (M + 2, 4), 481 (M^+, 4), 455 (49), 453 (46), 425 (42), 423 (39), 382 (36), 380 (39), 265 (32), 264 (32), 263 (29), 262 (27), 223 (96), 222 (67), 221 (100), 220 (54), 142 (39), 132 (76), 104 (53).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{16}BrN_5O_4$: 481.0385; found: 481.0381.

(1′*S*,5″*S*)-5
Mp 145–147 °C.

IR ($CHCl_3$): 2110, 1782, 1716 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, CH_3), 4.33 (dd, *J* = 9.0, 3.9 Hz, 1 H, C*H*H), 4.66 (t, *J* = 8.7 Hz, 1 H, C*H*H), 5.40 (dd, *J* = 8.4, 3.6 Hz, 1 H, C*H*CH_2), 6.45 (s, 1 H, C*H*CO), 7.33–7.48 (m, 6 H, ArH), 7.58 (s, 1 H, ArH), 7.64 (d, *J* = 8.4 Hz, 1 H, ArH), 8.68 (d, *J* = 1.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 56.6, 58.1, 70.4, 113.9, 119.6, 119.9, 120.8, 125.76, 125.80, 126.7, 127.4, 129.0, 129.3, 136.3, 137.7, 152.7, 167.5, 168.1.

MS (EI, 70 eV): *m*/*z* (%) = 483 (M + 2, 4), 481 (M^+, 4), 455 (41), 453 (40), 265 (30), 264 (24), 263 (30), 262 (20), 223 (95), 222 (51), 221 (100), 220 (39), 142 (32), 132 (33), 104 (40).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{16}BrN_5O_4$: 481.0385; found: 481.0388.

***tert*-Butyl (1*R*′,5*S*″)-*N*-{1-(1′-Acetyl-6′-bromoindol-3′-yl)-2-oxo-2-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)}ethylcarbamate (10)**
To a solution of azide (*R*,*S*)-**3** (2.0 g, 4.0 mmol) in THF (40 mL) and aq 10% HCl (1.5 mL), was added Bu_3P (2.0 mL, 8.1 mmol) was added dropwise at 0 °C. The stirred mixture was gradually warmed to r.t. over 12 h. After removal of the solvent, the residue was diluted with EtOAc (200 mL) and the EtOAc layer was washed with brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude amine. A solution of the crude amine, DMAP (50 mg, 0.404 mmol) and di-*tert*-butyl dicarbonate (4.6 mL, 20 mmol) in CH_2Cl_2 (40 mL) was stirred at r.t. for 3 d. After removal of the solvent, the residue was purified by column chromatography on silica gel with EtOAc–hexane (1:1) as eluent to afford indolylglycine **10** (1.3 g, 58%) as a colorless powder; mp 111–114 °C.

IR ($CHCl_3$): 3445, 3020, 1784, 1709 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-C_4H_9), 2.46 (s, 3 H, CH_3CO), 4.22 (dd, *J* = 9.0, 4.2 Hz, 1 H, CH*H*), 4.73 (t, *J* = 9.0 Hz, 1 H, C*H*H), 5.37 (br d, *J* = 8.4 Hz, 1 H, NH), 5.49 (dd, *J* = 9.0, 4.5 Hz, 1 H, C*H*CH_2), 6.79 (d, *J* = 8.1 Hz, 1 H, C*H*NHBoc), 6.98 (d, *J* = 7.5 Hz, 2 H, ArH), 7.10–7.29 (m, 6 H, ArH), 8.63 (s, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 28.2, 49.7, 57.5, 69.9, 80.3, 116.1, 119.2, 119.3, 120.3, 125.1, 125.8, 126.5, 126.9, 128.6, 135.9, 137.4, 152.1, 154.5, 168.0, 169.5.

MS (EI, 70 eV): *m*/*z* (%) = 557 (M + 2, 3), 555 (M^+, 3), 457 (15), 455 (15), 311 (36), 309 (35), 267 (100), 265 (93), 225 (77), 223 (88), 117 (36).

HRMS (EI): *m*/*z* calcd for $C_{26}H_{26}BrN_3O_6$: 555.1005; found: 555.1003.

***tert*-Butyl (*R*)-*N*-{1-(6′-Bromoindol-3′-yl)-2-hydroxy}ethylcarbamate [(*R*)-4]**
$NaBH_4$ (0.35 g, 9.2 mmol) in H_2O (2.0 mL) was added to a solution of indolylglycine **10** (1.4 g, 2.3 mmol) in THF (40 mL) at r.t. After stirring at the same temperature for 30 min, aq 10% LiOH (25 mL) was added. The mixture was stirred under the same conditions for 30 min. The resulting mixture was concentrated to give a residue, which was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on a column of silica gel with EtOAc–hexane (2:1) as eluent to provide indolylglycinol (*R*)-**4** (0.68 g, 83%) as colorless crystals; mp 161–162 °C; $[\alpha]_D^{20}$ –21.7 (*c* 0.86, $CHCl_3$).

IR ($CHCl_3$): 3472, 3441, 3331, 3019, 1703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *t*-C_4H_9), 2.57 (br, 1 H, OH), 3.98 (br s, 2 H, CH_2), 5.09 (br s, 2 H, C*H*CH_2, N*H*Boc), 7.12 (d, *J* = 2.7 Hz, 1 H, ArH), 7.23 (dd, *J* = 8.7, 1.8 Hz, 1 H, ArH), 7.49 (d, *J* = 1.5 Hz, 1 H, ArH), 7.50 (d, *J* = 8.7 Hz, 1 H, ArH), 8.30 (br, 1 H, indol-NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 50.1, 65.8, 79.9, 114.0, 114.2, 115.8, 120.0, 122.3, 122.9, 124.4, 136.9, 155.9.

MS (EI, 70e V): *m*/*z* (%) = 356 (M + 2, 6), 354 (M^+, 7), 325 (23), 323 (24), 269 (98), 267 (100), 239 (16), 237(15), 225 (32), 223 (41), 210 (49), 208 (48), 130 (14), 129 (28), 117 (20).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}BrN_2O_3$: 354.0579; found: 354.0578.

***tert*-Butyl (*R*)-*N*-2-Azido-1-(6′-bromo-1′-tosylindol-3′-yl)ethylcarbamate (11)**
Under N_2, a solution of indolylglycinol (*R*)-**4** (94 mg, 0.27 mmol), *p*-toluenesulfonyl chloride (0.51 g, 2.7 mmol), DMAP (32 mg, 0.27 mmol) and Et_3N (0.37 mL, 2.7 mmol) in anhyd CH_2Cl_2 (4.0 mL) was stirred at –20 °C for 20 h. The resulting mixture was washed with H_2O and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel with EtOAc–hexane (1:3) as eluent to afford the intermediate *N*,*O*-ditosylate (0.16 g, 92%) as a colorless powder.

***N*,*O*-Ditosylate**
Mp 190 °C; $[\alpha]_D^{20}$ +10.6 (*c* 0.94, $CHCl_3$).

IR ($CHCl_3$): 1360, 1240 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-C_4H_9), 2.36 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 4.24 (dd, *J* = 9.9, 3.6 Hz, 1 H, C*H*H), 4.36 (dd, *J* = 9.9, 4.2 Hz, 1 H, C*H*H), 5.03 (br s, 1 H, C*H*NH), 5.12 (br, 1 H, CHN*H*), 7.13–7.29 (m, 6 H, ArH), 7.43 (d, *J* = 0.9 Hz, 1 H, ArH), 7.54 (d, *J* = 6.6 Hz, 2 H, ArH), 7.75 (d, *J* = 6.6 Hz, 2 H, ArH), 8.10 (d, *J* = 1.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 21.6, 28.5, 47.1, 71.0, 79.6, 116.9, 118.5, 120.8, 122.0, 125.8, 127.1, 127.6, 128.2, 128.7, 130.3, 130.6, 130.9, 133.2, 135.4, 136.2, 145.6, 146.6.

HRMS (FAB): *m*/*z* calcd for $C_{29}H_{31}BrN_2O_7S_2$: 662.0756; found: 662.0755.

Under N_2, a suspension of the above *N*,*O*-ditosylate (0.16 g, 0.25 mmol) and NaN_3 (0.16 g, 2.5 mmol) in anhyd DMF (2.0 mL) was stirred at 80 °C for 1 h. After removal of the solvent, the residue was diluted with EtOAc (20 mL). The mixture was washed with H_2O (10 mL) and brine (5 mL), and then dried ($MgSO_4$). The organic layer

was concentrated and the residue was purified by column chromatography on silica gel with EtOAc–hexane (1:2) as eluent to afford *N*-Boc-aminoazide **11** (0.10 g, 79%) as a colorless powder.

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Mp 167–170 °C; $[\alpha]_D^{20}$ –5.4 (*c* 0.92, $CHCl_3$).

IR ($CHCl_3$): 3439, 2108, 1709 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.40 (s, 9 H, *t*-C_4H_9), 2.35 (s, 3 H, CH_3), 3.76–3.86 (m, 2 H, CH_2), 5.16 (dd, *J* = 13.6, 7.2 Hz, 1 H, C*H*CH_2), 6.63 (br, 1 H, NHBoc), 7.39 (d, *J* = 8.0 Hz, 2 H, ArH), 7.44 (dd, *J* = 8.4, 2.0 Hz, 1 H, ArH), 7.68 (d, *J* = 8.0 Hz, 1 H, ArH), 7.80 (d, *J* = 1.2 Hz, 1 H, ArH), 7.87 (d, *J* = 8.0 Hz, 2 H, ArH), 8.14 (d, *J* = 1.6 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 21.5, 28.5, 47.7, 54.4, 79.5, 116.9, 118.7, 122.3, 122.5, 125.4, 127.2, 127.5, 129.1, 130.9, 135.4, 136.3, 146.5, 155.5.

MS (EI, 70 eV): *m*/*z* (%) = 535 (M + 2, 1), 533 (M^+, 1), 479 (19), 477 (18), 451 (23), 449 (23), 423 (100), 421 (96), 379 (35), 378 (19), 377 (36), 376 (12), 296 (35), 294 (35), 155 (33), 91 (45), 57 (40).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{24}BrN_5O_4S$: 533.0732; found: 533.0725.

(*R*)-2-(6″-Bromoindol-3″-yl)-{*N*-2′-(6‴-bromo-1‴-tosylindol-3‴-yl)-2′-(*tert*-butoxycarbonylamino)ethyl}-2-oxoethanamide (13)

A solution of *N*-Boc-aminoazide **11** (0.54 g, 1.0 mmol), Ph_3P (0.56 g, 2.1 mmol) and H_2O (0.37 mL) in THF (10 mL) was heated under reflux for 1 h. After removal of the solvent, a solution of **12** (0.45 g, 1.6 mmol) in anhyd THF (20 mL) was added to a solution of the residue in Et_3N (0.22 mL, 1.6 mmol) in anhyd THF (20 mL) under N_2 at 0 °C. The mixture was stirred at r.t. for 1 h and concentrated under reduced pressure. The residue was diluted with EtOAc (30 mL) and the EtOAc layer was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was chromatographed on a column of silica gel with EtOAc–hexane (1:2) as eluent to provide amide **13** (0.55 g, 72%) as a colorless powder; mp 240–243 °C; $[\alpha]_D^{20}$ +2.53 (*c* 0.66, acetone).

IR (KBr): 3458, 3343, 1674, 1633 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.36 (s, 9 H, *t*-C_4H_9), 2.20 (s, 3 H, CH_3), 3.71 (ddd, *J* = 19.6, 7.2, 6.0 Hz, 1 H, C*H*H), 4.03 (dt, *J* = 19.6, 7.2 Hz, 1 H, C*H*H), 5.31 (d, *J* = 7.6 Hz, 1 H, C*H*CH_2), 6.57 (br, 1 H, N*H*Boc), 7.21 (d, *J* = 7.6 Hz, 2 H, ArH), 7.42 (dt, *J* = 8.4, 1.6 Hz, 2 H, ArH), 7.72–7.86 (m, 5 H, ArH), 8.1 (s, 1 H, ArH), 8.25 (d, *J* = 8.4 Hz, 1 H, N*H*CH_2), 8.41 (br, 1 H, ArH), 9.05 (d, *J* = 1.2 Hz, 1 H, ArH), 11.37 (br, 1 H, indole-NH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 21.3, 28.5, 43.2, 47.6, 79.3, 113.4, 115.9, 116.9, 117.2, 118.5, 122.4, 123.1, 123.9, 125.1, 126.3, 126.5, 127.1, 127.4, 129.6, 130.8, 135.4, 136.5, 138.0, 140.0, 146.2, 155.9, 163.4, 181.3.

HRMS (FAB): *m*/*z* calcd for: $C_{32}H_{31}Br_2N_4O_6S$: 757.0331; found: 757.0321.

(*R*)-2-(1″-Acetyl-6″-bromoindol-3″-yl)-{*N*-2′-(1‴-acetyl-6‴-bromoindol-3‴-yl)-2′-(*tert*-butoxycarbonylamino)ethyl}-2-oxoethanamide (14)

A solution of amide (0.55 g, 0.72 mmol) and 10% KOH (48 mL) in EtOH (65 mL) was refluxed for 1 h. The resulting mixture was concentrated under reduced and the residue was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$), and evaporated. The crude product obtained was purified by column chromatography on silica gel with EtOAc–hexane (1:1) as eluent to afford the intermediate detosylated oxoethanamide (0.36 g, 76%) as a colorless powder.

Detosylated Oxoethanamide

Mp 234–236 °C; $[\alpha]_D^{20}$ –10.1 (*c* 0.63, acetone).

IR (KBr): 3375, 1674, 1632 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.37 (s, 9 H, *t*-C_4H_9), 3.71–3.80 (m, 1 H, C*H*H), 3.87–3.95 (m, 1 H, C*H*H), 5.33 (br, 1 H, C*H*CH_2), 6.32 (br, 1 H, N*H*Boc), 7.18 (dd, *J* = 8.7, 2.4 Hz, 1 H, ArH), 7.40 (dd, *J* = 8.7, 1.8 Hz, 1 H, ArH), 7.44 (d, *J* = 1.5 Hz, 1 H, ArH), 7.61 (d, *J* = 1.5 Hz, 1 H, ArH), 7.72 (d, *J* = 8.7 Hz, 1 H, ArH), 7.77 (d, *J* = 1.5 Hz, 1 H, ArH), 8.24 (d, *J* = 8.4 Hz, 1 H, ArH), 9.05 (d, *J* = 3.0 Hz, 1 H, ArH), 10.3 (br, 1 H, indole-NH), 11.32 (br, 1 H, indole-NH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 28.6, 44.4, 48.2, 78.8, 113.4, 114.9, 115.3, 115.8, 116.2, 117.1, 121.2, 122.6, 123.8, 123.9, 126.1, 126.2, 126.5, 137.9, 138.3, 139.9, 156.2, 163.4, 181.6.

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{25}Br_2N_4O_4$: 603.0243; found: 603.0236.

A solution of the above detosylated oxoethanamide (0.30 g, 0.50 mmol), Ac_2O (0.23 mL, 2.5 mmol), and DMAP (61 mg, 0.50 mmol) in anhyd THF (5 mL) was stirred at r.t. under N_2 for 12 h. The resulting mixture was evaporated and the residue was chromatographed on a column of silica gel with EtOAc–hexane (1:2) as eluent to afford acetate **14** (0.27 g, 80%) as a colorless powder.

14

Mp 224–227 °C; $[\alpha]_D^{20}$ +4.17 (*c* 0.12, DMSO).

IR (KBr): 3348, 3304, 1730, 1701, 1676, 1647 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.40 (s, 9 H, *t*-C_4H_9), 2.68 (s, 3 H, CH_3), 2.83 (s, 3 H, CH_3), 3.57 (dt, *J* = 13.6, 6.6 Hz, 1 H, C*H*H), 3.78 (dt, *J* = 12.5, 6.6 Hz, 1 H, C*H*H), 5.26 (d, *J* = 6.6 Hz, 1 H, C*H*CH_2), 7.46 (d, *J* = 8.8 Hz, 1 H, N*H*Boc), 7.52 (d, *J* = 8.6 Hz, 1 H, ArH), 7.68 (dd, *J* = 8.6, 1.8 Hz, 1 H, ArH), 7.77 (d, *J* = 8.2 Hz, 1 H, ArH), 7.94 (s, 1 H, ArH), 8.24 (d, *J* = 8.6 Hz, 1 H, ArH), 8.54 (d, *J* = 1.6 Hz, 1 H, ArH), 8.59 (d, *J* = 1.6 Hz, 1 H, ArH), 9.05 (s, 1 H, ArH), 9.17 (br s, 1 H, N*H*CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.6, 23.7, 28.1, 43.1, 45.8, 78.1, 114.7, 117.3, 118.2, 118.40, 118.45, 120.8, 120.9, 122.8, 124.4, 125.9, 126.0, 127.8, 127.9, 135.3, 135.4, 138.5, 154.9, 162.1, 169.1, 169.9, 182.6.

HRMS (FAB): *m*/*z* calcd for $C_{29}H_{29}Br_2N_4O_6$: 687.0454; found: 687.0455.

(*R*)-3,5-Bis(1′-acetyl-6′-bromoindol-3′-yl)-5,6-dihydropyrazin-2(1*H*)-one (15)

A solution of **14** (0.18 g, 0.25 mmol) and HCO_2H (15 mL) in CH_2Cl_2 (15 mL) was stirred at r.t. for 16 h. After removal of the solvent and excess HCO_2H, the residue was diluted with EtOH (41 mL). The solution was refluxed for 1 h and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel with EtOAc–hexane (2:1) as eluent to afford 3,5-pyrazinone **15** (85 mg, 71%) as a colorless powder; mp >300 °C; $[\alpha]_D^{20}$ –176.5 (*c* 0.15, DMSO).

IR (KBr): 3445, 1707, 1695, 1585 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 3.57–3.66 (m, 2 H, CH_2), 5.34 (dd, *J* = 10.1, 5.5 Hz, 1 H, C*H*CH_2), 7.42 (d, *J* = 8.4 Hz, 1 H, ArH), 7.47 (d, *J* = 8.4 Hz, 1 H, ArH), 7.75 (d, *J* = 8.4 Hz, 1 H, ArH), 7.83 (s, 1 H, ArH), 8.27 (d, *J* = 8.4 Hz, 1 H, ArH), 8.52 (s, 1 H, ArH), 8.54 (s, 1 H, ArH), 8.78 (s, 1 H, ArH), 8.85 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.7, 23.8, 42.2, 53.8, 114.9, 117.4, 117.8, 118.0, 118.4, 120.3, 121.6, 124.1, 124.7, 125.9, 126.8, 126.9, 127.8, 132.6, 135.4, 135.8, 156.0, 156.3, 169.2, 169.5.

HRMS (FAB): *m*/*z* calcd for $C_{24}H_{19}Br_2N_4O_3$: 568.9824; found: 568.9824.

(3*R*,5*S*)-3,5-Bis(6′-bromoindol-3′-yl)piperazin-2-one [*cis*-Dihydrohamacanthin B, (2c)]

A solution of 3,5-pyrazinone **15** (56 mg, 0.098 mmol) and $NaCNBH_3$ (62 mg, 0.98 mmol) in MeOH (6 mL) was stirred at r.t. for 1 d. The excess of reducing agent in the resulting mixture was quenched with H_2O (2 mL). After removal of the solvent, the residue was extracted with EtOAc (5 × 8 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The crude product obtained was purified by column chromatography on silica gel with MeOH–CH_2Cl_2 (1:10) as eluent to afford *cis*-dihydrohamacanthin B (**2c**; 32 mg, 67%) as a yellow powder; mp 171–174 °C; $[\alpha]_D^{20}$ +89.7 (*c* 0.2, acetone).

IR ($CHCl_3$): 3281, 3265, 1645 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 3.50 (dt, *J* = 10.8, 3.6 Hz, 1 H, C*H*H), 3.70 (t, *J* = 10.8 Hz, 1 H, C*H*H), 4.63 (dd, *J* = 11.2, 3.6 Hz, 1 H, C*H*CH_2), 4.99 (s, 1 H, CHCO), 7.04 (d, *J* = 3.6 Hz, 1 H, N*H*-CO), 7.09 (dd, *J* = 8.4, 1.6 Hz, 1 H, ArH), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1 H, ArH), 7.32 (d, *J* = 2.0 Hz, 1 H, ArH), 7.35 (d, *J* = 2.4 Hz, 1 H, ArH), 7.47 (d, *J* = 1.6 Hz, 1 H, ArH), 7.54 (d, *J* = 1.6 Hz, 1 H, ArH), 7.76 (d, *J* = 8.0 Hz, 1 H, ArH), 7.79 (d, *J* = 8.4 Hz, 1 H, ArH), 10.2 (br, 1 H, indole-NH), 10.3 (br, 1 H, indole-NH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 49.9, 52.3, 58.9, 114.6, 114.8, 115.0, 115.2, 115.9, 116.2, 121.7, 122.1, 122.5, 122.7, 124.0, 125.6, 125.9, 126.8, 138.26, 138.34, 170.1.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{15}Br_2N_4O$: 484.9613; found: 484.9627.

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