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Total synthesis of (±)-hyrtiazepine

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ABSTRACT

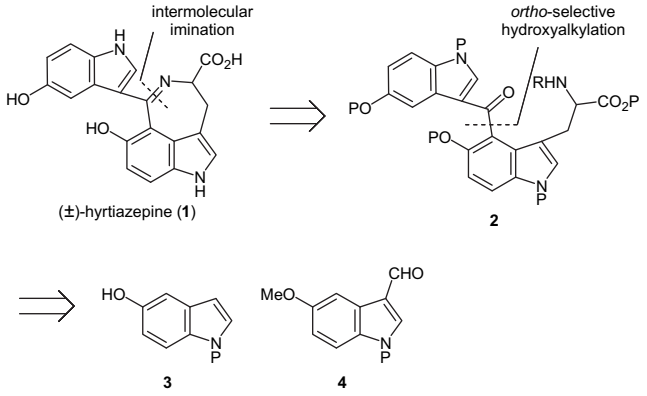
The total synthesis of the azepinoindole alkaloid, (±)-hyrtiazepine, was achieved. Construction of the azepinoindole core structure was carried out by C-4 selective α-hydroxyalkylation of 5-hydroxyindole, introduction of serine at C-3 of the indole moiety, and intramolecular imination.

1. Introduction

Hyrtiazepine (**1**), an azepinoindole alkaloid, was initially isolated from the marine sponge *Hyrtios erectus* by Bourguet-Kondracki and co-workers in 2006.[1] The unique heterocyclic structure of **1**, which includes two 5-hydroxyindoles and a seven-membered ring thought to be a significant structure in medicinal chemistry, has prompted us to investigate its total synthesis. To our knowledge, the total synthesis of **1** has not been achieved by any group so far. The *ortho* selective α-hydroxyalkylation reaction reported by Nagata and Aoki in 1979[2] is one of the versatile C–C bond forming reactions and its aromatic version is the most useful method for the preparation of 2-(α-hydroxyalkyl)phenols.[3] Although the low regioselectivity for the addition of a carbon unit is usually encountered by phenol derivatives used as substrates, in the case of 5-hydroxyindole derivatives, a selectivity at C-4 position of the indole is known.[3b] The selectivity is dependent on the stability of the intermediate, similar to the Claisen rearrangement observed in the case of 5-hydroxyindole.[4] Therefore, we attempted the first total synthesis of hyrtiazepine (**1**) from 5-hydroxyindole by using the *ortho* selective α-hydroxyalkylation reaction. Herein we report the total synthesis of (±)-hyrtiazepine (**1**).

2. Results and discussion

The retrosynthesis is shown in Scheme 1. Construction of the azepinoindole core structure was achieved by *ortho* selective



Scheme 1. Retrosynthesis of (±)-hyrtiazepine (**1**).

α-hydroxyalkylation, followed by intramolecular imination.[5] We envisioned that the application of this strategy would produce the azepinoindole core of **1** effectively. We examined the α-hydroxyalkylation of 5-hydroxyindoles **8a** and **b** with 3-methoxycarbaldehydes **10a** and **b**. These substrates for α-hydroxyalkylation were prepared from commercially available 5-hydroxyindole (**5**) and 3-methoxyindolecarbaldehyde (**9**), respectively (Scheme 2). *N*-Benzyl 5-hydroxyindole **8a** was prepared according to the literature.[6] On the other hand, *N*-tosyl 5-hydroxyindole **8b**[7] was prepared as follows. After silylation of the hydroxyl group with TBSCl in DMF and tosylation of **6** with TsCl in THF, resulting **7** was converted into **8b** with 6 N HCl aq in THF in 78% yield from **5**. Indolecarbaldehydes

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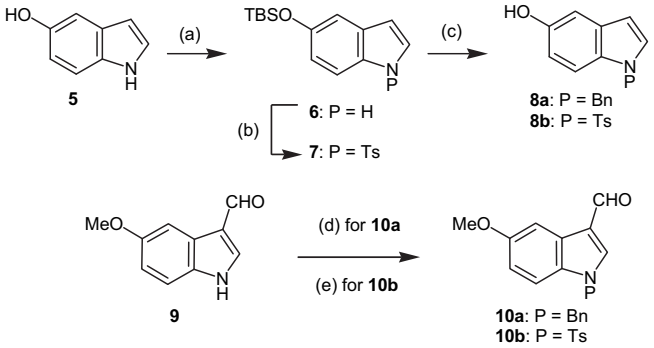
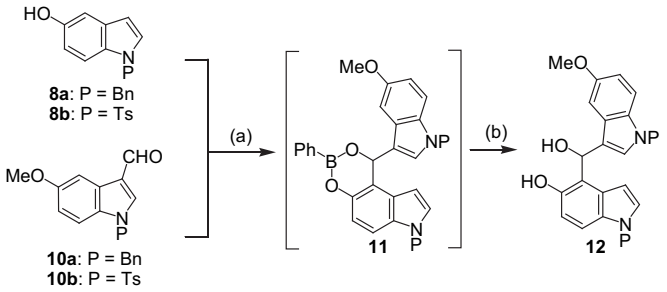


Scheme 2. Preparation of *N*-Ts 5-hydroxyindole **8b** and carbaldehydes **10a** and **b**. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 0.5 h; (b) TsCl, NaH, THF, rt, 2 h (96%); (d) 6 N HCl aq, THF, reflux, 2 h (78% from **5**); (d) BnBr, K_2CO_3, DMF, rt, 24 h (96%); (e) TsCl, NaH, THF, rt, 3 h (94%).

10a[8] and **b** were prepared by benzylation and tosylation in 96% and 94% yields, respectively.

Next, the *ortho* selective α-hydroxyalkylation of **8a** and **b** with **10a** and **b** was examined (Table 1). In the case of *N*-benzyl protected indoles, desired borate **11** or phenol **12** was not produced by the α-hydroxyalkylation (runs 1–3). In contrast, in the case of the tosyl moiety as the protecting group in indole, desired **12** was obtained in 77% yield from **8b** (run 4). We thought that the complex mixtures (runs 1–3) were produced by the activation at C-3 position of the indole moiety by the benzyl group. The assignment of **12** was determined from the HMBC correlations of both the aromatic protons (H-6 and 2′) with a carbon (C-8) and the proton (H-8) with carbons (C-4, 5, and 3′) (Fig. 1).

Table 1
ortho Selective α-hydroxyalkylation of 5-hydroxyindoles **8** and indolecarbaldehydes **10**



Run	5-OH-indole	Carbaldehyde	Results
1	**8a**	**10a**	Complex mixtures
2	**8a**	**10b**	Complex mixtures
3	**8b**	**10a**	Complex mixtures
4	**8b**	**10b**	77%

Reagents and conditions: (a) $PhB(OH)_2$, $EtCO_2H$, toluene, reflux, 24 h; (b) 30% H_2O_2 aq, THF, 0 °C, 0.5 h.

Substrate **19** for intramolecular imination[5] was prepared as follows (Scheme 3). After the phenolic hydroxyl group in **12** was alkylated with MeI in DMF to afford alcohol **13** in 75% yield, the second hydroxyl group was oxidized with IBX[9] in DMSO to obtain ketone **14** in 86% yield. After one tosyl group in **14** was removed with KOH in MeOH at room temperature in 92% yield and resulting **15** was alkylated with BnBr in 98% yield, the remaining tosyl group in **16** was removed in 84% yield. Finally, after carboxylic acid **18** was obtained by the addition of serine under acidic conditions in 82% yield,[10] **18** was converted into methyl ester **19** in 88% yield.[11]

We tried to perform the intramolecular imination under acidic conditions (Table 2).[5] Complex mixtures were obtained with TFA in

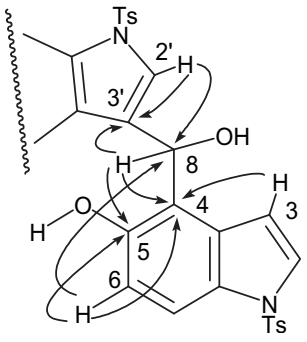
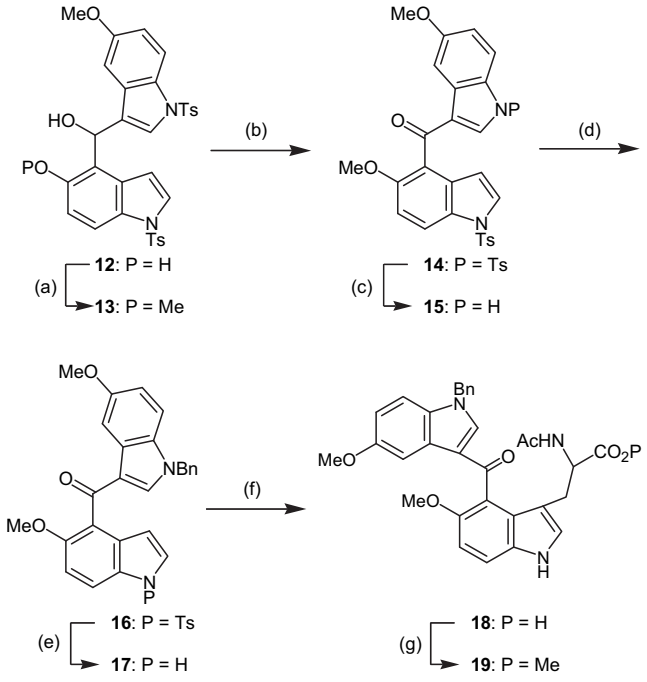
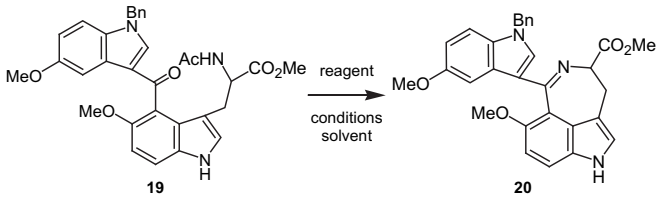


Fig. 1. Selected HMBC correlations of phenol **12**.



Scheme 3. Preparation of methyl ester **19**. Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt, 2 h (75%); (b) IBX, DMSO, rt, 2 h (86%); (c) KOH, MeOH, rt, 0.5 h (92%); (d) BnBr, K_2CO_3, DMF, rt, 2 h (98%); (e) KOH, MeOH, reflux, 3 h (84%); (f) serine, Ac_2O, AcOH, 80 °C, 2 h (82%); (g) MeI, K_2CO_3, DMF, rt, 0.5 h (88%).

Table 2
Intramolecular imination of methyl ester **19**



Run	Reagent	Solvent	Conditions	**20**
1	TFA	CH_2Cl_2	rt 12 h	Complex mixtures
2	6 N HCl	THF	Reflux 12 h	Complex mixtures
3	6 N HCl	MeOH	Reflux 12 h	24%
4	3 N HCl	MeOH	Reflux 24 h	40%

CH_2Cl_2 (run 1) and 6 N HCl aq in THF (run 2). However, desired azepinoindole **20** was obtained with 6 N HCl aq in MeOH under reflux in 24% yield (run 3). The assignment of **20** was determined from the HMBC correlations of both the aromatic proton (H-2′) and the methine proton (H-4) with a carbon (C-6) (Fig. 2). Finally, the

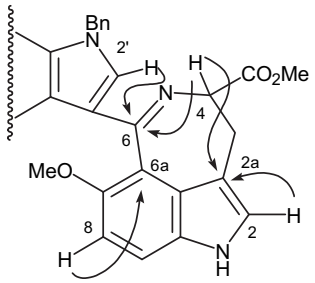
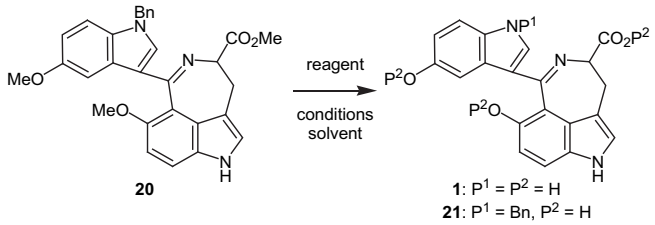


Fig. 2. Selected HMBC correlations of azepinoindole **20**.

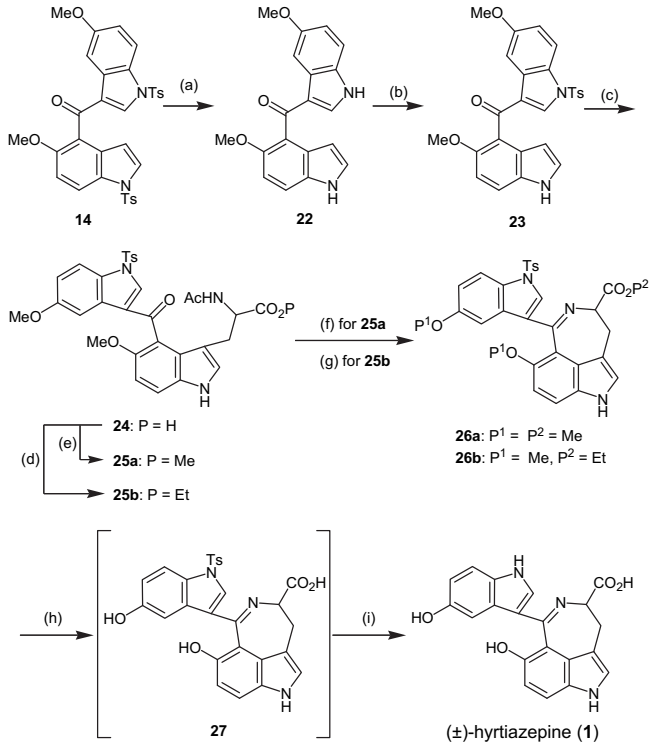
yield was improved to 40% yield by using 3 N HCl aq (run 4). Although we were able to construct the azepinoindole core, all protecting groups, particularly the benzyl group, were not removed by the trial based on deprotection of **20** with $AlCl_3$ and BBr_3 (Table 3).

Table 3
Trials for debenzylation of **20**



Run	Reagent	Solvent	Conditions	Results
1	$AlCl_3$	Toluene	Reflux 3 h	Complex mixtures
2	BBr_3	CH_2Cl_2	Reflux 2 h	**21**: 3%

Therefore, we exchanged the benzyl group with a tosyl group (Scheme 4). Since carbonyl group at C-3′ position activates tosyl group at N-1′ position, selective detosylation at N-1 position seems difficult. Therefore, after all the tosyl groups in **14** were removed in 92% yield, resulting **22** was retosylated to afford **23** in 85% yield. Then, carboxylic acid **24** was obtained in 68% yield using the same method as that for preparing **17**, and **24** was converted into methyl ester **25a** and ethyl ester **25b** in 82% and 81% yields, respectively.[11] Esters **25a** and **b** were examined for potential use in the intramolecular imination with 3 N HCl aq. Although methyl ester **25a** gave desired **26a** in low yield (23%) when MeOH was used as solvent similar to **19**, ethyl ester **25b** gave **26b** in 70% yield when EtOH was used as solvent. In the case of imination of **25a** in EtOH, ester exchange occurred. Finally, with the removal of methyl groups and ethyl ester in **26b** with BBr_3 in CH_2Cl_2 and the detosylation of **27** with K_2CO_3 in MeOH, the total synthesis of (±)-hyrtiazepine (**1**) was achieved in 6.1% yield from 5-hydroxyindole (**5**). The spectral data, including HMBC experiments (Fig. 3), were identical with those of the natural product.



Scheme 4. Preparation of (±)-hyrtiazepine (**1**). Reagents and conditions: (a) KOH, THF, MeOH, reflux, 0.5 h (92%); (b) TsCl, NEt_3, CH_2Cl_2, rt, 2 h (85%); (c) serine, Ac_2O, AcOH, 80 °C, 2 h (68%); (d) MeI, K_2CO_3, DMF, rt, 2 h (81%); (e) EtI, K_2CO_3, DMF, rt, 2 h (82%); (f) 3 N HCl aq, MeOH, reflux, 20 h (23%); (g) 3 N HCl aq, EtOH, reflux, 20 h (70%); (h) BBr_3, CH_2Cl_2, reflux, 3 h; (i) K_2CO_3, MeOH, reflux, 4 h (52% from **26b**).

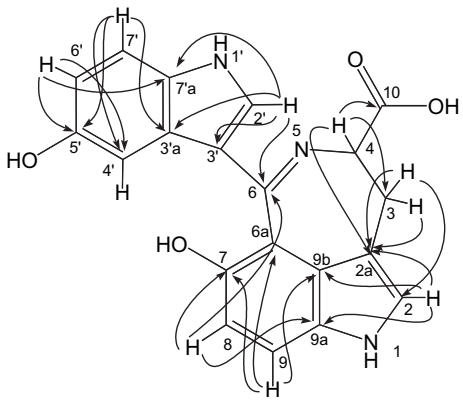


Fig. 3. HMBC correlations of (±)-hyrtiazepine (**1**).

3. Conclusion

We have achieved the first total synthesis of (±)-hyrtiazepine (**1**) by the *ortho* selective α-hydroxyalkylation of *N*-tosyl 5-hydroxyindole **8b** with *N*-tosyl 3-methoxyindolecarbaldehyde **10b** and the intramolecular imination of **25b** in 22 steps from **5** and 20 steps from **9** in 6.1%, and 7.4% overall yields, respectively. Moreover, it is suggested that the *ortho* selective α-hydroxyalkylation has high selectivity for the C-4 position of 5-hydroxyindole derivatives and is useful for the synthesis of 5-hydroxyindole derivatives, similar to the Claisen rearrangement. Thus, our synthetic method could provide an efficient route to various natural products having the 5-hydroxyindole core.

4. Experimental section

4.1. General

All melting points were measured on a Yanaco MP-500D and are uncorrected. IR spectra were recorded on a JASCO FT/IR-6300 spectrophotometer; ATR=attenuated total reflectance system. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated, on a JEOL JNM-ECP 400 and a Bruker 400 MHz with tetramethylsilane (TMS) as the internal reference. ESIMS was recorded on a JEOL JMS-T100LC mass spectrometer. TLC Silica gel 60 F_{254} TLC plates (Merck No. 5715) and NH plates (Fuji Silysia Chemical Ltd., No. TO 80817) were used and for column chromatography, spherical silica gel 60 (particle size 63–210 μm, Kanto Chemical, No. 37565-84 for neutral) and NH silica gel (Fuji Silysia Chemical Ltd.,

particle size 100–200 mesh, No. IO61280 and 200–350 mesh, No. HU80502) were used.

*4.1.1. 1-Benzyl-5-methoxy-3-1H-indole-carbaldehyde (**10a**).* Under Ar, to a mixture of K_2CO_3 (332 mg, 2.40 mmol) and **9** (194 mg, 1.11 mmol) in DMF (2 mL), benzyl bromide (0.2 mL, 1.68 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=1:1) to give **10a** as a colorless powder (283 mg, 96%). Mp: 96–97 °C. IR (ATR, cm^{-1}): 1649. ^1H NMR (400 MHz) δ: 3.90 (3H, s), 5.33 (2H, s), 6.94 (1H, dd, *J*=8.8, 2.4 Hz), 7.16–7.19 (2H, m), 7.21 (1H, d, *J*=8.8 Hz), 7.32–7.39 (3H, m), 7.67 (1H, s), 7.82 (1H, d, *J*=2.4 Hz), 9.97 (1H, s). HRESIMS: *m*/*z* 266.1195 (calcd for $C_{17}H_{16}NO_2$: 266.1181).

*4.1.2. 5-Methoxy-1-(toluene-4-sulfonyl)-3-1H-indole-carbaldehyde (**10b**).* Under Ar, after a mixture of NaH (115 mg, 2.88 mmol, 60% in mineral oil) and **9** (160 mg, 0.92 mmol) in THF (3 mL) was stirred at room temperature for 10 min, *p*-toluenesulfonyl chloride (353 mg, 1.85 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=5:1) to give **10b** as a colorless powder (283 mg, 94%). Mp: 125–126 °C. IR (ATR, cm^{-1}): 1673, 1366, 1162. ^1H NMR (400 MHz) δ: 2.37 (3H, s), 3.84 (3H, s), 7.00 (1H, dd, *J*=8.7, 2.4 Hz), 7.28 (2H, d, *J*=8.7 Hz), 7.70 (1H, d, *J*=2.4 Hz), 7.82 (3H, d, *J*=8.7 Hz), 8.16 (1H, s), 10.1 (1H, s). ^{13}C NMR (100 MHz) δ: 21.7, 55.8, 104.0, 114.1, 116.2, 122.3, 127.2, 127.3, 129.7, 130.3, 134.4, 136.6, 146.1, 157.8, 185.5. HRESIMS: *m*/*z* 352.0596 (calcd for $C_{17}H_{15}NNaO_4S$: 352.0620).

*4.1.3. 5-(tert-Butyl-dimethyl-silanyloxy)-1H-indole (**6**).* Under Ar, a mixture of **5** (2.98 g, 22.4 mmol), imidazole (3.36 g, 49.3 mmol), and *tert*-butyldimethylsilyl chloride (3.57 g, 23.7 mmol) in DMF (20 mL) was stirred at room temperature for 0.5 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=0:1 to 10:1) to give **6** as a colorless oil (5.54 g, quant.). IR (ATR, cm^{-1}): 3416. ^1H NMR (400 MHz) δ: 0.21 (6H, s), 1.02 (9H, s), 6.45 (1H, ddd, *J*=3.2, 2.1, 0.8 Hz), 6.78 (1H, dd, *J*=8.8, 2.5 Hz), 7.08 (1H, d, *J*=2.5 Hz), 7.17 (1H, dd, *J*=2.6, 2.6 Hz), 7.24 (1H, dd, *J*=8.8, 0.8 Hz). ^{13}C NMR (100 MHz) δ: −4.43, 18.2, 25.8, 102.2, 110.1, 111.2, 116.3, 124.8, 128.5, 131.4, 149.3. HRESIMS: *m*/*z* 286.1011 (calcd for $C_{14}H_{21}KNO_1Si$: 286.1030).

*4.1.4. 5-(tert-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-1H-indole (**7**).* Under Ar, a mixture of **5** (5.20 g, 39.1 mmol), imidazole (4.98 g, 73.1 mmol), and *tert*-butyldimethylsilyl chloride (8.51 g, 56.5 mmol) in DMF (30 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was added to a mixture of NaH (3.01 g, 75.3 mmol, 60% in mineral oil) in THF (40 mL). After the mixture was stirred at room temperature for 10 min, *p*-toluenesulfonyl chloride (14.0 g, 73.4 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (*n*-hexane/AcOEt=5:1) to give **7** as colorless needles (15.1 g, 96% from **5**). Mp: 94–96 °C. IR (ATR, cm^{-1}): 1366, 1149. ^1H NMR (400 MHz) δ: 0.19 (6H, s), 0.99 (9H, s), 2.34 (3H, s), 6.54 (1H, d, *J*=3.8 Hz), 6.84 (1H, dd, *J*=8.8, 2.4 Hz), 6.93 (1H, d, *J*=2.4 Hz), 7.22 (1H, d, *J*=8.0 Hz), 7.50 (1H, d, *J*=3.8 Hz), 7.73 (2H, d, *J*=8.0 Hz), 7.83 (1H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz) δ: −4.5, 18.2, 21.5, 25.7, 28.8 (CH_3), 109.0, 111.1, 114.1, 118.1, 126.8, 127.1, 129.8, 130.0, 131.9, 135.3, 144.8, 152.0. HRESIMS: *m*/*z* 402.1535 (calcd for $C_{21}H_{28}NO_3SSi$: 402.1559).

*4.1.5. 1-(Toluene-4-sulfonyl)-1H-indole-5-ol (**8b**).* Under Ar, a mixture of **5** (1.01 g, 7.59 mmol), imidazole (1.02 g, 15.0 mmol), and *tert*-butyldimethylsilyl chloride (1.70 g, 11.3 mmol) in DMF (5 mL) was stirred at room temperature for 0.5 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was added to a mixture of NaH (604 mg, 15.1 mmol, 60% in mineral oil) in THF (10 mL). After the mixture was stirred at room temperature for 10 min, *p*-toluenesulfonyl chloride (2.88 g, 15.1 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. A solution of the residue in THF (10 mL) and 6 N HCl aq (20 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt, washed with satd $NaHCO_3$ aq and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=5:1 to 1:1) to give **8b** as a colorless solid (1.69 g, 78% from **5**). Mp: 160–161 °C. IR (ATR, cm^{-1}): 3391, 1369, 1144. ^1H NMR (400 MHz) δ: 2.34 (3H, s), 4.72 (1H, br s), 6.54 (1H, d, *J*=3.6 Hz), 6.84 (1H, dd, *J*=8.8, 2.4 Hz), 6.92 (1H, d, *J*=2.4 Hz), 7.21 (2H, d, *J*=8.2 Hz), 7.52 (1H, d, *J*=3.6 Hz), 7.73 (2H, d, *J*=8.2 Hz), 7.85 (1H, d, *J*=8.8 Hz). HRESIMS: *m*/*z* 326.0224 (calcd for $C_{15}H_{13}KNO_3S$: 326.0253).

*4.1.6. 4-{Hydroxy-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-methyl}-1-(toluene-4-sulfonyl)-1H-indol-5-ol (**12**).* A solution of **8b** (324 mg, 1.13 mmol), **10b** (540 mg, 1.64 mmol), benzeneboronic acid (287 mg, 2.35 mmol), and propanoic acid (0.02 mL, 0.27 mmol) in toluene (10 mL) was refluxed with azeotropic removal of water using a Dean–Stark type separator for 24 h. After evaporation of the solvent, the residue was dissolved with CH_2Cl_2. The organic layer was washed with satd $NaHCO_3$ aq, water and brine, dried over Na_2SO_4, and evaporated in vacuo. A mixture of the residue and 30% H_2O_2 aq (3 mL) in THF (5 mL) was stirred at 0 °C for 0.5 h. The reaction mixture was poured into ice/water and extracted with CH_2Cl_2. The organic layer was washed with sodium hydrogen sulfite solution and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=2:1 to 1:1) to give **12** as a yellow powder (534 mg, 77% from **8b**). Mp: 115–118 °C. IR (ATR, cm^{-1}): 3372, 1361, 1164. ^1H NMR (400 MHz) δ: 2.32 (3H, s), 2.33 (3H, s), 3.34 (1H, br d, *J*=2.8 Hz), 3.65 (3H, s), 6.37 (1H, d, *J*=3.6 Hz), 6.45 (1H, d, *J*=2.8 Hz), 6.87 (1H, dd, *J*=9.1, 2.5 Hz), 6.91 (1H, d, *J*=9.2 Hz), 7.00 (1H, d, *J*=2.5 Hz), 7.14 (2H, br d, *J*=8.3 Hz), 7.207 (1H, s), 7.212 (2H, br d, *J*=8.3 Hz), 7.40 (1H, d, *J*=3.6 Hz), 7.58 (2H, d, *J*=8.4 Hz), 7.71 (2H, d, *J*=8.4 Hz), 7.78 (1H, d, *J*=9.1 Hz), 7.82 (1H, d, *J*=9.2 Hz), 7.91 (1H, s). ^{13}C NMR (100 MHz) δ: 21.62, 21.66, 55.6, 60.5, 68.1, 102.6, 106.4, 114.3, 114.6, 114.8, 115.2, 115.9, 123.3, 125.6, 126.8, 127.1, 129.1, 129.3, 129.8, 129.9, 130.1, 130.4, 134.9, 135.2, 145.1, 145.2, 152.2, 156.6. HRESIMS: *m*/*z* 639.1250 (calcd for $C_{32}H_{28}N_2NaO_7S_2$: 639.1236).

*4.1.7. [5-Methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indol-4-yl]-methanol (**13**).* Under Ar, to a suspension of **12** (501 mg, 0.81 mmol) and K_2CO_3 (346 mg, 2.50 mmol) in DMF (5 mL) was added methyl iodide (0.07 mL, 1.12 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (*n*-hexane/AcOEt=5:1 to 1:1) to give **13** as a colorless powder (386 mg, 75%). Mp: 166–168 °C. IR (ATR, cm^{-1}): 3126, 1363, 1170. ^1H NMR (400 MHz) δ: 2.31 (6H, s), 3.47 (1H,

br s), 3.61 (3H, s), 3.79 (3H, s), 6.44 (1H, d, *J*=7.2 Hz), 6.72 (1H, d, *J*=3.6 Hz), 6.85 (1H, dd, *J*=9.0, 2.4 Hz), 6.92 (1H, d, *J*=2.4 Hz), 6.98 (1H, d, *J*=9.2 Hz), 7.12 (2H, br d, *J*=7.6 Hz), 7.18 (1H, s), 7.19 (2H, br d, *J*=7.6 Hz), 7.48 (1H, d, *J*=3.6 Hz), 7.60 (2H, d, *J*=8.4 Hz), 7.72 (2H, d, *J*=8.4 Hz), 7.82 (1H, d, *J*=9.0 Hz), 7.93 (1H, d, *J*=9.2 Hz). ^{13}C NMR (100 MHz) δ: 21.61, 21.64, 55.5, 56.6, 65.3, 102.9, 108.1, 109.8, 114.0, 114.1, 114.7, 121.1, 124.3, 125.8, 126.77, 126.78, 127.6, 129.8, 130.1, 130.36, 130.41, 130.42, 130.5, 135.2, 144.9, 145.2, 153.3, 156.4. HRESIMS: *m*/*z* 653.1384 (calcd for $C_{33}H_{30}N_2NaO_7S_2$: 653.1392).

*4.1.8. [5-Methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indol-4-yl]-methanone (**14**).* To a solution of **13** (1.20 g, 1.91 mmol) in DMSO (10 mL) was added IBX (859 mg, 3.01 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and filtered through a Celite pad. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with satd $NaHCO_3$ aq and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/acetone=1:1 to 1:3) to give **14** (1.0 g, 86%) as a colorless powder. Mp: 198–200 °C. IR (ATR, cm^{-1}): 1644, 1368, 1173. ^{1}H NMR (400 MHz) δ: 2.37 (6H, s), 3.77 (3H, s), 3.85 (3H, s), 6.49 (1H, d, *J*=4.0 Hz), 6.99 (1H, dd, *J*=9.2, 2.5 Hz), 7.06 (1H, d, *J*=9.2 Hz), 7.25 (2H, d, *J*=8.0 Hz), 7.27 (2H, d, *J*=8.0 Hz), 7.55 (1H, d, *J*=4.0 Hz), 7.70 (2H, d, *J*=7.2 Hz), 7.71 (1H, s), 7.77 (2H, d, *J*=7.2 Hz), 7.82 (1H, d, *J*=9.2 Hz), 7.86 (1H, *J*=2.5 Hz), 8.09 (1H, d, *J*=9.2 Hz). ^{13}C NMR (100 MHz) δ: 21.70, 21.72, 55.8, 56.9, 104.6, 108.1, 110.2, 114.1, 115.7, 116.3, 121.1, 121.9, 126.9, 127.2, 128.5, 128.9, 129.6, 130.08, 130.12, 130.2, 130.8, 134.7, 135.2, 135.8, 145.4, 145.9, 153.4, 157.8, 189.7. HRESIMS: *m*/*z* 629.1420 (calcd for $C_{33}H_{29}N_2O_7S_2$: 629.1416).

*4.1.9. (5-Methoxy-1H-indol-3-yl)-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indol-4-yl]-methanone (**15**).* To a solution of **14** (3.13 g, 4.98 mmol) in THF (40 mL) and MeOH (20 mL) was added KOH (1.09 g, 19.4 mmol), and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was poured into satd NH_4Cl aq and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=3:1 to 0:1) to give **15** (2.11 g, 92%) as a colorless amorphous solid. Mp: 201–203 °C. IR (ATR, cm^{-1}): 3137, 1591, 1369, 1139. ^{1}H NMR (400 MHz) δ: 2.35 (3H, s), 3.69 (3H, s), 3.81 (3H, s), 6.44 (1H, d, *J*=3.6 Hz), 6.86 (1H, dd, *J*=8.8, 2.6 Hz), 6.98 (1H, d, *J*=9.2 Hz), 7.19 (1H, d, *J*=8.8 Hz), 7.22 (2H, d, *J*=7.2 Hz), 7.25 (1H, d, *J*=2.6 Hz), 7.46 (1H, d, *J*=3.6 Hz), 7.72 (2H, d, *J*=7.2 Hz), 7.85 (1H, d, *J*=3.2 Hz), 7.98 (1H, d, *J*=9.2 Hz), 9.21 (1H, br s). ^{13}C NMR (100 MHz) δ: 21.7, 55.8, 57.0, 103.6, 108.2, 110.2, 112.5, 114.4, 115.1, 118.6, 122.6, 126.4, 126.9, 128.0, 129.8, 130.1, 130.5, 131.5, 135.1, 135.9, 145.3, 153.0, 156.6, 189.5. HRESIMS: *m*/*z* 475.1307 (calcd for $C_{26}H_{23}N_2O_5S$: 475.1328).

*4.1.10. (1-Benzyl-5-methoxy-1H-indol-3-yl)-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indol-4-yl]-methanone (**16**).* Under Ar, to a suspension of **15** (1.91 g, 4.14 mmol) and K_2CO_3 (2.06 g, 14.9 mmol) in DMF (15 mL) was added benzyl bromide (1.00 mL, 8.36 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=2:1) to give **16** (2.29 g, 98%) as a colorless powder. Mp: 200–202 °C. IR (ATR, cm^{-1}): 1615, 1369, 1167. ^{1}H NMR (400 MHz) δ: 2.37 (3H, s), 3.76 (3H, s), 3.87 (3H, s), 5.22 (2H, s), 6.54 (1H, dd, *J*=3.6, 0.8 Hz), 6.90 (1H, dd, *J*=8.8, 2.4 Hz), 7.03 (1H, d, *J*=8.8 Hz), 7.04–7.09 (2H, m), 7.15 (1H, d, *J*=8.8 Hz), 7.24 (2H, d, *J*=8.4 Hz), 7.27–7.32 (4H, m), 7.51 (1H, d, *J*=3.6 Hz), 7.74 (2H, d, *J*=8.4 Hz), 7.90 (1H, br s), 8.01 (1H, dd, *J*=8.8, 0.8 Hz). ^{13}C NMR (100 MHz) δ: 21.6, 51.0, 55.8, 56.9, 103.9, 108.4, 110.1, 111.2, 114.1, 115.0, 117.3, 122.6, 126.7, 126.8, 127.5, 127.9, 128.1, 128.9, 129.8, 129.9, 130.6, 132.0, 135.0, 135.7, 138.5, 145.1, 152.9, 156.7, 188.5. HRESIMS: *m*/*z* 565.1798 (calcd for $C_{33}H_{29}N_2O_5S$: 565.1797).

*4.1.11. (1-Benzyl-5-methoxy-1H-indol-3-yl)-(5-methoxy-1H-indol-4-yl)-methanone (**17**).* To a solution of **16** (2.29 g, 4.06 mmol) in THF (10 mL) and MeOH (10 mL) was added KOH (1.01 g, 18.0 mmol), and the mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into satd NH_4Cl aq and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=1:1) to give **17** (1.40 g, 84%) as a colorless powder. Mp: 173–175 °C. IR (ATR, cm^{-1}): 3320, 1585. ^{1}H NMR (400 MHz) δ: 3.79 (3H, s), 3.91 (3H, s), 5.22 (2H, s), 6.44 (1H, ddd, *J*=3.0, 2.2, 1.0 Hz), 6.89 (1H, dd, *J*=8.8, 2.5 Hz), 6.99 (1H, d, *J*=8.8 Hz), 7.07 (1H, dd, *J*=7.6, 1.6 Hz), 7.13 (1H, d, *J*=8.8 Hz), 7.18 (1H, dd, *J*=3.0, 3.0 Hz), 7.25–7.31 (3H, m), 7.40 (1H, dd, *J*=8.8, 1.0 Hz), 7.45 (1H, s), 8.02 (1H, d, *J*=2.5 Hz), 8.20 (1H, br s). ^{13}C NMR (100 MHz) δ: 51.1, 55.9, 58.1, 102.2, 104.1, 109.7, 111.2, 112.5, 114.0, 117.7, 122.2, 126.0, 126.8, 127.6, 127.8, 128.1, 129.0, 131.8, 132.1, 136.1, 138.9, 150.9, 156.6, 190.3. HRESIMS: *m*/*z* 411.1683 (calcd for $C_{26}H_{23}N_2O_3$: 411.1709).

*4.1.12. 2-Acetylamino-3-[4-(1-benzyl-5-methoxy-1H-indole-3-carbonyl)-5-methoxy-1H-indol-3-yl]-propionic acid (**18**).* Under Ar, to a mixture of **17** (1.09 g, 2.66 mmol) in AcOH (10 mL) and Ac_2O (1.00 mL, 10.6 mmol) was added L-serine (446 mg, 4.25 mmol) and the solution was stirred for 2 h at 80 °C. After cooling to room temperature, the reaction mixture was diluted with Et_2O and adjusted with 30% NaOH aq to pH 10. The partitioned water layer was ice-cooled and then, the organic layer was diluted with additional Et_2O and extracted with 10% NaOH aq. The combined water layer was acidified (pH 3) with 10% HCl aq and the water layer was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography ($CHCl_3$/MeOH=10:1) to give **18** (1.18 g, 82%) as a brownish powder. Mp: 146–149 °C. IR (ATR, cm^{-1}): 3254, 1716, 1619. ^{1}H NMR (400 MHz) δ: 1.82 (3H, s), 2.74 (1H, br s), 3.00 (1H, dd, *J*=14.8, 4.0 Hz), 3.57 (3H, s), 3.75 (3H, s), 3.91 (3H, br s), 4.56 (1H, br s), 5.22 (2H, s), 6.89 (1H, d, *J*=7.2 Hz), 6.96 (1H, d, *J*=8.8 Hz), 7.01 (1H, s), 7.06 (2H, d, *J*=6.0 Hz), 7.13 (1H, d, *J*=8.8 Hz), 7.23–7.31 (4H, m), 7.37 (1H, d, *J*=8.8 Hz), 7.70 (1H, br s), 8.63 (1H, br s). ^{13}C NMR (100 MHz, CD_3OD) δ: 21.0, 27.6, 50.4, 53.8, 54.8, 57.0, 103.8, 108.5, 109.6, 111.6, 112.5, 113.2, 118.2, 121.4, 124.7, 125.8, 126.8, 127.4, 127.6, 128.5, 132.5, 133.0, 136.5, 140.6, 150.0, 156.8, 171.7, 174.1, 193.6. HRESIMS: *m*/*z* 562.2003 (calcd for $C_{31}H_{29}N_3NaO_6$: 562.1954).

*4.1.13. 2-Acetylamino-3-[4-(1-benzyl-5-methoxy-1H-indole-3-carbonyl)-5-methoxy-1H-indol-3-yl]-propionic acid methyl ester (**19**).* Under Ar, to a suspension of **18** (1.15 g, 2.14 mmol) and K_2CO_3 (541 mg, 3.91 mmol) in DMF (10 mL) was added methyl iodide (0.26 mL, 4.18 mmol) and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was poured into 10% HCl aq and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (AcOEt only) to give **19** as a colorless powder (1.04 g, 88%). Mp: 111–114 °C. IR (ATR, cm^{-1}): 3271, 1738, 1658. ^{1}H NMR (400 MHz) δ: 1.82 (3H, s), 2.74 (1H, br s), 3.00 (1H, dd, *J*=14.8, 4.0 Hz), 3.57 (3H, s), 3.75 (3H, s), 3.91 (3H, br s), 4.56 (1H, br s), 5.22 (2H, s), 6.89 (1H, d, *J*=7.2 Hz), 6.96 (1H, d, *J*=8.8 Hz), 7.01 (1H, s), 7.06 (2H, d, *J*=6.0 Hz), 7.13 (1H, d, *J*=8.8 Hz), 7.23–7.31 (4H, m), 7.37 (1H, d, *J*=8.8 Hz), 7.70 (1H, br s), 8.08 (1H, br s), 8.63 (1H, br s). ^{13}C NMR (100 MHz) δ: 23.0, 27.3, 51.3, 52.2, 55.7, 56.0, 58.1, 104.3, 109.0, 110.7, 111.5, 112.8, 114.1, 118.9, 121.6, 125.5, 125.9, 126.9, 127.6, 128.3, 129.1, 132.4, 135.9, 139.4,

150.3, 157.0, 171.3, 172.7, 193.4. HRESIMS: *m*/*z* 554.2317 (calcd for $C_{32}H_{32}N_3O_6$: 554.2291).

*4.1.14. 6-(1-Benzyl-5-methoxy-1H-indol-3-yl)-7-methoxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid methyl ester (**20**).* A suspension of **19** (53.1 mg, 95.9 μM) in MeOH (2 mL) and 3 N HCl aq (1 mL) was refluxed for 24 h. After cooling to room temperature, the reaction mixture was poured into satd $NaHCO_3$ aq. The water layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (*n*-hexane/AcOEt=1:1) to give **20** (19.1 mg, 40%) as a yellow powder. Mp: 130–132 °C. IR (ATR, cm^{-1}): 3301, 1724, 1584. ^1H NMR (400 MHz) *δ*: 3.27 (1H, dd, *J*=15.2, 10.0 Hz), 3.45 (3H, s), 3.50 (1H, d, *J*=15.2 Hz), 3.85 (3H, s), 3.90 (3H, s), 4.75 (1H, d, *J*=10.0 Hz), 5.26 (2H, s), 6.82 (1H, dd, *J*=8.8, 2.5 Hz), 6.91 (1H, d, *J*=8.8 Hz), 7.05 (1H, s), 7.11 (2H, d, *J*=6.4 Hz), 7.12 (1H, d, *J*=8.8 Hz), 7.16 (1H, s), 7.22–7.30 (3H, m), 7.40 (1H, d, *J*=8.8 Hz), 7.73 (1H, d, *J*=2.5 Hz), 8.09 (1H, br s). ^{13}C NMR (100 MHz) *δ*: 31.0, 50.4, 52.3, 55.5, 57.5, 65.3, 103.5, 110.4, 110.5, 112.6, 114.1, 114.2, 115.4, 117.8, 123.5, 126.7, 127.6, 127.7, 128.0, 128.8, 131.77, 131.81, 132.1, 137.6, 153.9, 155.0, 161.2, 174.8. HRESIMS: *m*/*z* 494.2078 (calcd for $C_{30}H_{28}N_3O_4$: 494.2080).

*4.1.15. 6-[1-Benzyl-5-hydroxy-1H-indol-3-yl]-7-hydroxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid (**21**).* Under Ar, to a solution of **20** (143 mg, 0.29 mmol) in CH_2Cl_2 (1 mL) was added 1 M CH_2Cl_2 solution of BBr_3 (3.00 mL, 3.00 mmol) at room temperature. The reaction mixture was refluxed for 2 h. After cooling at room temperature, ice and 1 N HCl aq were added to the reaction mixture. The water layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography ($CHCl_3$/MeOH=5:1) to give **21** (4.2 mg, 3%) as a yellow amorphous solid. Mp: >300 °C. ^1H NMR (400 MHz, CD_3OD) *δ*: 3.13 (1H, dd, *J*=14.8, 11.2 Hz), 3.69 (1H, d, *J*=14.8 Hz), 4.39 (1H, d, *J*=11.2 Hz), 5.44 (2H, s), 6.80 (1H, dd, *J*=8.8, 2.4 Hz), 6.85 (1H, d, *J*=8.8 Hz), 7.24–7.38 (9H, m), 7.65 (1H, d, *J*=8.8 Hz), 7.99 (1H, s). ^{13}C NMR (100 MHz, CD_3OD) *δ*: 33.4, 50.7, 103.9, 112.5, 112.6, 113.3, 121.2, 126.4, 126.9, 127.1, 127.7, 128.6, 131.3, 131.9, 136.2, 139.7, 154.5, 157.3, 197.0. HRESIMS: *m*/*z* 452.1566 (calcd for $C_{27}H_{22}N_3O_4$: 452.1610).

*4.1.16. [5-Methoxy-1H-indol-3-yl]-[5-methoxy-1H-indol-4-yl]-methanone (**22**).* A suspension of **14** (3.33 g, 5.29 mmol) and powdered KOH (3.08 g, 54.9 mmol) in MeOH (30 mL) and THF (30 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into 10% HCl aq and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (*n*-hexane/AcOEt=1:4 to 0:1) to give **22** (1.46 g, 86%) as a colorless solid. Mp: 228–232 °C. IR (ATR, cm^{-1}): 3738. ^1H NMR (400 MHz, DMSO) *δ*: 3.69 (3H, s), 3.79 (3H, s), 6.06 (1H, ddd, *J*=2.8, 2.0, 0.8 Hz), 6.86 (1H, dd, *J*=8.8, 2.8 Hz), 7.00 (1H, d, *J*=8.8 Hz), 7.29 (1H, t, *J*=2.8 Hz), 7.37 (1H, d, *J*=8.8, 0.4 Hz), 7.41 (1H, d, *J*=2.8 Hz), 7.45 (1H, dd, *J*=8.8, 0.8 Hz), 7.68 (1H, d, *J*=2.0 Hz). ^{13}C NMR (100 MHz, DMSO) *δ*: 55.9, 57.9, 100.4, 103.6, 109.2, 113.1, 113.4, 113.6, 118.0, 122.0, 126.9, 127.3, 127.6, 132.2, 132.3, 136.8, 150.0, 156.1, 190.5. HRESIMS: *m*/*z* 321.1243 (calcd for $C_{19}H_{17}N_2O_3$: 321.1239).

*4.1.17. [5-Methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-[5-methoxy-1-1H-indol-4-yl]-methanone (**23**).* Under Ar, to a solution of **22** (2.70 g, 8.43 mmol) and NEt_3 (7.00 mL, 50.2 mmol) in CH_2Cl_2 (40 mL) was added TsCl (4.00 g, 21.0 mmol) and the mixture was stirred at room temperature for 7 h. The reaction mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=1:1) to give **23** as a colorless amorphous solid (3.40 g, 85%). Mp: 106–109 °C. IR (ATR, cm^{-1}): 3334, 1631. ^1H NMR (400 MHz) *δ*: 2.37 (3H, s), 3.79 (3H, s), 3.88 (3H, s), 6.37 (1H, ddd, *J*=3.2, 2.0, 0.8 Hz), 7.00 (1H, dd, *J*=8.8, 2.8 Hz), 7.01 (1H, d, *J*=8.8 Hz), 7.22 (1H, d, *J*=2.8 Hz), 7.25 (2H, d, *J*=8.6 Hz), 7.49 (1H, dd, *J*=8.8, 0.8 Hz), 7.73 (2H, d, *J*=8.6 Hz), 7.83 (1H, d, *J*=8.8 Hz), 7.84 (1H, s), 7.96 (1H, d, *J*=2.8 Hz), 8.30 (1H, br s). ^{13}C NMR (100 MHz) *δ*: 21.6, 55.7, 57.5, 101.8, 104.6, 109.1, 113.6, 114.0, 115.4, 120.2, 122.1, 126.4, 127.1, 127.4, 129.1, 129.5, 130.0, 131.7, 134.6, 135.9, 145.6, 151.4, 157.6, 191.1. HRESIMS: *m*/*z* 497.1159 (calcd for $C_{26}H_{22}N_2NaO_5S$: 497.1157).

*4.1.18. 2-Acetylamino-3-{4-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indole-3-carbonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**24**).* Under Ar, to a mixture of **23** (405 mg, 0.85 mmol) in AcOH (4 mL) and Ac_2O (0.24 mL, 2.54 mmol) was added L-serine (144 mg, 1.37 mmol) and the solution was stirred for 3 h at 80 °C. After cooling to room temperature, the reaction mixture was diluted with Et_2O and adjusted with 30% NaOH aq to pH 10. The partitioned water layer was ice-cooled and then, the organic layer was diluted with additional Et_2O and extracted with 10% NaOH aq. The combined water layer was acidified (pH 3) with 10% HCl aq and the water layer was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography ($CHCl_3$/MeOH=10:1) to give **24** (348 mg, 68%) as a brownish powder. Mp: 149–151 °C. IR (ATR, cm^{-1}): 3254, 1716, 1619. ^1H NMR (400 MHz, CD_3OD) *δ*: 1.81 (3H, s), 2.35 (3H, s), 2.65 (1H, dd, *J*=14.8, 10.0 Hz), 2.95 (1H, dd, *J*=14.8, 4.8 Hz), 3.74 (3H, s), 3.83 (3H, s), 4.36 (1H, dd, *J*=10.0, 4.8 Hz), 6.99 (1H, dd, *J*=8.8, 2.5 Hz), 7.08 (1H, d, *J*=8.8 Hz), 7.16 (1H, br s), 7.31 (2H, d, *J*=8.2 Hz), 7.52 (1H, d, *J*=8.8 Hz), 7.77 (2H, d, *J*=8.2 Hz), 7.79 (1H, s), 7.83 (1H, d, *J*=8.8 Hz), 10.6 (0.6H, br s). ^{13}C NMR (100 MHz, CD_3OD) *δ*: 20.1, 20.8, 28.0, 53.1, 54.6, 56.6, 104.3, 107.9, 109.3, 113.3, 113.8, 114.7, 119.8, 123.0, 124.4, 126.1, 126.9, 128.5, 129.7, 129.9, 133.0, 134.2, 136.2, 146.1, 150.4, 157.8, 171.5, 173.7, 193.8. HRESIMS: *m*/*z* 604.1761 (calcd for $C_{31}H_{30}N_8O_6S$: 604.1754).

*4.1.19. 2-Acetylamino-3-{4-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indole-3-carbonyl]-5-methoxy-1H-indol-3-yl}-propionic acid methyl ester (**25a**).* Under Ar, to a suspension of **24** (407 mg, 0.67 mmol) and K_2CO_3 (192 mg, 1.39 mmol) in DMF (4 mL) was added methyl iodide (0.06 mL, 0.96 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=1:3 to 0:1) to give **25a** as a yellow powder (338 mg, 81%). Mp: 127–129 °C. IR (ATR, cm^{-1}): 3258, 1737, 1636. ^1H NMR (400 MHz) *δ*: 1.85 (3H, s), 2.37 (3H, s), 2.65 (1H, dd, *J*=15.2, 10.4 Hz), 2.92 (1H, dd, *J*=15.2, 4.0 Hz), 3.50 (3H, s), 3.75 (3H, s), 3.90 (3H, s), 4.60 (1H, ddd, *J*=10.4, 8.0, 4.0 Hz), 6.99 (1H, d, *J*=8.8 Hz), 7.00 (1H, dd, *J*=9.2, 2.4 Hz), 7.08 (1H, d, *J*=2.4 Hz), 7.25 (2H, d, *J*=8.4 Hz), 7.45 (1H, d, *J*=8.8 Hz), 7.73 (2H, d, *J*=8.4 Hz), 7.77 (1H, s), 7.81 (1H, d, *J*=9.2 Hz), 7.90 (1H, br s). ^{13}C NMR (100 MHz) *δ*: 21.6, 22.9, 27.5, 52.0, 54.4, 55.8, 57.4, 104.7, 108.5, 110.2, 113.4, 114.0, 115.5, 119.9, 123.0, 125.2, 125.7, 127.1, 128.5, 129.6, 130.1, 132.2, 134.4, 136.2, 145.8, 150.6, 157.8, 170.5, 172.3, 194.0. HRESIMS: *m*/*z* 640.1681 (calcd for $C_{32}H_{31}N_3NaO_8S$: 640.1730).

*4.1.20. 2-Acetylamino-3-{4-[5-methoxy-1-(toluene-4-sulfonyl)-1H-indole-3-carbonyl]-5-methoxy-1H-indol-3-yl}-propionic acid ethyl ester (**25b**).* Under Ar, to a suspension of **24** (1.60 g, 2.65 mmol) and K_2CO_3 (731 mg, 5.29 mmol) in DMF (20 mL) was added ethyl iodide (0.37 mL, 4.63 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 10% HCl aq and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The

residue was purified by SiO_2-column chromatography (*n*-hexane/AcOEt=1:3 to 0:1) to give **25b** as a yellow powder (1.37 g, 82%). Mp: 109–110 °C. IR (ATR, cm^{-1}): 3313, 1734, 1644. ^1H NMR (400 MHz) δ: 0.99 (3H, t, *J*=7.6 Hz), 1.85 (3H, s), 2.35 (3H, s), 2.65 (1H, dd, *J*=15.0, 10.4 Hz), 2.93 (1H, dd, *J*=15.2, 4.3 Hz), 3.73 (3H, s), 3.87 (3H, s), 3.97 (2H, ddq, *J*=7.6, 7.6, 3.6 Hz), 4.58 (1H, ddd, *J*=10.4, 7.6, 4.3 Hz), 6.95 (1H, d, *J*=8.8 Hz), 7.00 (1H, dd, *J*=8.8, 2.4 Hz), 7.04 (1H, d, *J*=2.4 Hz), 7.09 (1H, br s), 7.24 (2H, d, *J*=8.4 Hz), 7.42 (1H, d, *J*=8.8 Hz), 7.73 (2H, d, *J*=8.4 Hz), 7.79 (1H, s), 7.81 (1H, d, *J*=8.8 Hz), 7.91 (1H, br s), 9.22 (1H, br d, *J*=3.6 Hz). ^{13}C NMR (100 MHz) δ: 13.9, 21.6, 22.9, 27.6, 54.6, 55.7, 57.4, 61.1, 104.7, 108.3, 109.6, 113.6, 114.0, 115.4, 119.7, 123.1, 125.1, 126.1, 127.1, 128.6, 129.7, 130.1, 132.3, 134.4, 136.3, 145.9, 150.5, 157.8, 170.8, 172.0, 194.2. HRESIMS: *m*/*z* 670.1627 (calcd for $C_{33}H_{33}KN_3O_8S$: 670.1625).

*4.1.21. 6-[5-Methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-7-methoxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid methyl ester (**26a**).* A suspension of **25a** (148 mg, 0.24 mmol) in MeOH (2 mL) and 3 N HCl aq (2 mL) was refluxed for 20 h. After cooling to room temperature, the reaction mixture was poured into satd $NaHCO_3$ aq. The water layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (AcOEt only) to give **26a** (31.1 mg, 23%) as a yellow powder. Mp: 128–130 °C. IR (ATR, cm^{-1}): 3419, 1732, 1592. ^1H NMR (400 MHz) δ: 2.32 (3H, s), 3.17 (3H, s), 3.17 (1H, ddd, *J*=15.2, 10.0, 1.2 Hz), 3.44 (3H, s), 3.49 (1H, d, *J*=15.2 Hz), 3.81 (3H, s), 3.87 (3H, s), 4.68 (1H, d, *J*=10.0 Hz), 6.93 (1H, dd, *J*=9.0, 2.5 Hz), 6.93 (1H, d, *J*=8.8 Hz), 7.05 (1H, s), 7.17 (2H, d, *J*=8.2 Hz), 7.43 (1H, s), 7.44 (1H, d, *J*=8.8 Hz), 7.65 (1H, d, *J*=2.8 Hz), 7.72 (2H, d, *J*=8.2 Hz), 7.87 (1H, d, *J*=8.8 Hz), 8.24 (1H, br s). ^{13}C NMR (100 MHz) δ: 21.5, 30.5, 52.3, 55.3, 56.8, 65.5, 104.1, 109.9, 113.1, 114.0, 114.4, 114.77, 114.83, 123.7, 124.4, 126.9, 127.1, 128.0, 129.7, 129.8, 130.7, 131.5, 135.1, 144.9, 153.8, 156.8, 160.3, 174.1. HRESIMS: *m*/*z* 558.1741 (calcd for $C_{30}H_{28}N_3O_6S$: 558.1699).

*4.1.22. 6-[5-Methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-7-methoxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid ethyl ester (**26b**).* A suspension of **25b** (1.37 g, 2.17 mmol) in EtOH (15 mL) and 3 N HCl aq (10 mL) was refluxed for 20 h. After cooling to room temperature, the reaction mixture was poured into satd $NaHCO_3$ aq. The water layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by NH-column chromatography (AcOEt only) to give **26b** (865 mg, 70%) as a yellow powder. Mp: 124–126 °C. IR (ATR, cm^{-1}): 3419, 1732, 1592. ^1H NMR (400 MHz) δ: 0.99 (3H, t, *J*=7.2 Hz), 2.33 (3H, s), 3.17 (1H, ddd, *J*=15.6, 10.0, 1.6 Hz), 3.45 (3H, s), 3.49 (1H, d, *J*=15.6 Hz), 4.27–4.40 (2H, m), 4.66 (1H, d, *J*=10.0 Hz), 6.93 (1H, dd, *J*=9.0, 2.5 Hz), 6.94 (1H, d, *J*=8.8 Hz), 7.07 (1H, s), 7.18 (2H, d, *J*=8.2 Hz), 7.42 (1H, s), 7.45 (1H, d, *J*=8.8 Hz), 7.67 (1H, d, *J*=2.5 Hz), 7.72 (2H, d, *J*=8.2 Hz), 7.87 (1H, d, *J*=9.0 Hz), 8.14 (1H, br s). ^{13}C NMR (100 MHz) δ: 14.4, 21.5, 30.4, 55.5, 56.8, 61.1, 65.6, 104.8, 109.9, 113.2, 113.9, 114.0, 114.7, 115.0, 123.6, 124.4, 126.9, 127.2, 128.1, 129.7, 129.9, 130.7, 131.5, 135.2, 144.8, 153.8, 156.8, 160.1, 173.5. HRESIMS: *m*/*z* 572.1850 (calcd for $C_{31}H_{30}N_3O_6S$: 572.1855).

*4.1.23. 6-[5-Hydroxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-7-hydroxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid (**27**).* Under Ar, to a solution of **26b** (112 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added 1 M CH_2Cl_2 solution of BBr_3 (1.00 mL, 1.00 mmol) at room temperature. The reaction mixture was refluxed for 2 h. After cooling at room temperature, ice and 1 N HCl aq were added to the reaction mixture. The water layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2-column chromatography ($CHCl_3$/MeOH=5:1) to give **27** (81.0 mg, 80%) as a red amorphous solid. Mp: >300 °C. IR (ATR, cm^{-1}): 3124, 1732, 1585. ^1H NMR (400 MHz, CD_3OD) δ: 2.40 (3H, s), 6.56 (1H, s), 6.73 (1H, d, *J*=8.8 Hz), 6.86 (1H, dd, *J*=8.8, 2.4 Hz), 7.40 (2H, d, *J*=8.0 Hz), 7.46 (1H, s), 7.77 (1H, d, *J*=8.8 Hz), 7.80 (1H, d, *J*=8.8 Hz), 7.92 (2H, d, *J*=8.0 Hz), 8.27 (1H, s). ^{13}C NMR (100 MHz, CD_3OD) δ: 20.4, 31.7, 60.8, 104.0, 111.8, 113.0, 114.5, 114.9, 124.5, 127.3, 127.7, 129.0, 129.6, 130.1, 130.9, 134.7, 146.3, 155.1, 160.8. HRESIMS: *m*/*z* 516.1208 (calcd for $C_{27}H_{22}N_3O_6S$: 516.1229).

*4.1.24. (±)-7-Hydroxy-6-(5-hydroxy-1H-indol-3-yl)-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylic acid (hyrtiazepine) (**1**).* Under Ar, to a solution of **26b** (342 mg, 0.60 mmol) in CH_2Cl_2 (1 mL) was added 1 M CH_2Cl_2 solution of BBr_3 (3.00 mL, 3.00 mmol) at room temperature. The reaction mixture was refluxed for 3 h. After cooling at room temperature, ice and 1 N HCl aq were added to the reaction mixture. The water layer was extracted with a mixed solvent (AcOEt/MeOH=10:1). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Under Ar, the suspension of crude **27** and K_2CO_3 (713 mg, 5.16 mmol) in degassed dry MeOH (5 mL) was refluxed for 3 h. After the reaction mixture was cooled at room temperature, it was acidified with NH_4Cl and filtered through a Celite pad. After removal of the solvent, the residue was purified by SiO_2-column chromatography ($CHCl_3$/MeOH=5:1) to give **1** (113 mg, 52% from **26b**) as a yellow amorphous solid. Mp: 242–256 °C (lit.,[4] no data). IR (ATR, cm^{-1}): 3166, 1726, 1617, 1580. ^1H NMR (400 MHz, CD_3OD) δ: 3.13 (1H, br dd, *J*=15.0, 10.0 Hz), 3.66 (1H, br d, *J*=15.0 Hz), 4.51 (1H, br d, *J*=10.0 Hz), 6.83 (1H, dd, *J*=8.8, 1.8 Hz), 6.84 (1H, d, *J*=8.8 Hz), 7.28 (1H, br s), 7.32 (1H, s), 7.36 (1H, d, *J*=8.8 Hz), 7.66 (1H, d, *J*=8.8 Hz), 7.8 (1H, s). ^{13}C NMR (100 MHz, CD_3OD) δ: 32.8, 60.1, 103.9, 104.8, 110.6, 112.3, 112.6, 113.5, 122.1, 126.0, 126.2, 126.8, 131.2, 132.3, 137.0, 154.0, 158.2, 167.4, 171.2. HRESIMS: *m*/*z* 362.1140 (calcd for $C_{20}H_{16}N_3O_4$: 362.1141).

Supplementary data

Copies of ^1H and ^{13}C NMR spectra are provided. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.029.

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