A novel synthesis of
3,4,5,6-tetrahydro-7-hydroxy-1H-azepino[5,4,3-
cd] indole derivatives from serotonin¹

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A NOVEL SYNTHESIS OF 3,4,5,6-TETRAHYDRO-7-HYDROXY-1*H*-AZEPINO[5,4,3-*cd*]INDOLE DERIVATIVES FROM SEROTONIN¹

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Abstract – Utilizing novel *Nb*-substituted serotonins, 5- and/or 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole derivatives are produced simply by treating serotonins with aldehydes under basic conditions. Synthesis of 2,2a,3,4,5,6-hexahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole-2-one derivatives is also reported.

In our synthetic project for discovering new biologically active compounds, we have thus far succeeded in the creation of efficient synthetic methods^{3a-d} with high originality rate,^{4a,c-e} intellectual property factor,^{4a,b} and application potential factor^{4a,b} culminating in the production of novel leads for an α_2 -blocker,^{3d,5} an inhibitor of platelet aggregation,^{3c,6} an anti-osteoporosis agent,^{3d,7} and potent root growth promotor.^{3a,b,8} These results are based on our hypothesis^{8,9} that any metabolite of tryptophan has each own function *in vivo*, and the combination of each structure is a promising method for designing a new possible drug.⁹

Figure 1

Nb-cyclohexylcarbonyl- (**7d**), and *Nb*-benzoylserotonins (**7e**) in 96, 88, 97, and 90% yields, respectively. Subsequent reduction of **7a** with LiAlH₄ in refluxing THF afforded *Nb*-pentylserotonin (**8a**) in 85% yield. The compounds, **7b**, **7c**, and **7d**, were similarly converted to *Nb*-nonyl- (**8b**), *Nb*-hexadecyl- (**8c**), and *Nb*-cyclohexylmethylserotonins (**8d**) in 81, 89, and 74% yields, respectively. It is interesting to note that the reduction of **7e** under the same reduction conditions produced the desired *Nb*-benzylserotonin (**8e**) in only 47% yield together with 21% yield of unwanted **1b** and 13% yield of the unreacted starting material. Addition of excess amount of LiAlH₄ and longer refluxing time did not improve the yield effectively. As an alternative method, the reductive benzylation utilizing benzaldehyde and sodium cyanoborohydride was employed to **1b**·HCl, but the yield of **8e** was almost the same 56%.

Since various types of *Nb*-substituted serotonins are known as biologically active alkaloids,¹⁷ it would be safe to expect that the compounds, **7** and **8**, have biological activities as well.

II. Synthesis of Novel 5- and 6-Substituted 3,4,5,6-Tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole Derivatives

Employing our basic conditions¹⁵ to the reaction of the above-mentioned *Nb*-substituted serotonins (**8a—e**) with aldehydes, selective preparation of various 5- and 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole derivatives was successfully realized.

Thus, the reaction of **8a** with acetaldehyde in Et₃N-MeOH at room temperature for 2.5 h afforded 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-5-pentyl-1*H*-azepino[5,4,3-*cd*]indole (**10a**) in 90% yield without the formation of the corresponding β-carboline (**9a**). Under similar reaction conditions, **8b**, **8c**, **8d**, and **8e** reacted with acetaldehyde to give **10b**, **10c**, **10d**, and **10e** in 97, 91, 80, and 89% yields, respectively. When decanal was employed instead of acetaldehyde in the reaction of **8a**, **8b**, and **8c**, the corresponding **11a**, **11b**, and **11c** were obtained in 76, 81, and 76% yields, respectively. In all of the above reactions, formation of the corresponding β-carbolines as by-products was not detected at all.

The 5-unsubstituted 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-azepino[5,4,3-*cd*]indole (**12a**) was obtained in 91% yield by the reductive debenzoylation of **10e** with 10% Pd/C at 1 atm hydrogen. The compound (**12a**) would be a useful starting material for the preparations of various 5-substituted derivatives. Treatment of **10e** with Ac₂O and Boc₂O afforded **12b** and **12c** in 95 and 52% yields, respectively.

We next examined whether we can prepare 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles having a bulky substituent at the 5- and 6-positions employing **8a** as a serotonin component. At room temperature the reaction of **8a** with benzaldehyde (**13a**) in Et₃N-MeOH did not take place, but the reflux temperature and longer reaction time (15 h) made it possible to form 3,4,5,6-tetrahydro-7-hydroxy-5-pentyl-6-phenyl-1*H*-azepino[5,4,3-*cd*]indole (**14a**) in 86% yield. Under the same conditions, slow reaction took place upon the reaction of **8a** with more crowded 2-methylpropanal (**13b**). The desired

product, 3,4,5,6-tetrahydro-7-hydroxy-6-isopropyl-5-pentyl-1*H*-azepino[5,4,3-*cd*]indole (**14b**), was obtained in 49% yield in addition to 11% yield of unwanted **10a** and 23% yield of unreacted starting material. In the reaction of **8a** with bulky 2,2-dimethylpropanal (**13c**) at reflux temperature for 15 h, the formation of the desired product (**14c**) was not detected at all, while **10a** and unreacted starting material were obtained in 15 and 66% yields, respectively. The severe steric hindrance between 5 and 6 positions clearly precluded the formation of the seven-membered ring.

The isolation of **10a** in the above two reactions proved the presence of the competing reaction of **8a** with acetaldehyde, formed *in situ* from Et₃N. The mechanism of the formation of acetaldehyde from Et₃N in the reaction system is explained in detail in our previous paper.¹⁵

Scheme 2

III. Synthesis of 2,2a,3,4,5,6-Hexahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole-2-one Derivatives

Treatment of 5-benzyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-azepino[5,4,3-*cd*]indole (**10e**) with bromine in AcOH produced 5-benzyl-2,2a,3,4,5,6-hexahydro-7-hydroxy-6-methyl-1*H*-azepino[5,4,3-*cd*]indole-2-one (**15a**) and its 8-bromo derivative (**16a**) in 16 and 83% yields, respectively (Scheme 3). The formation of 2,2a,3,4,5,6-hexahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole-2-one skeleton can be explained by the initial generation of 2-bromo-3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole, followed by hydrolysis of the labile 2-bromo substituent. Similarly, 5-cyclohexylmethyl derivatives, **15b** and **16e**, were prepared from **10d** in 17 and 52% yields, respectively.

Further treatment of **16a** with diazomethane afforded **16b** in 95% yield. The reactions of **10d** and **16a** with Ac₂O in pyridine gave **17** and **16c** in 86 and 88% yields, respectively, while the reaction of **16a** with

Boc₂O in the presence of DMAP provided **16d** in 46% yield. Similar reactions of **16e** with Ac₂O and Boc₂O afforded the corresponding **16f** and **16g** in 83 and 71% yields, respectively. Since the C—Br bond of these compounds can be manipulated to various functional groups, these compounds would be useful for the preparation of 8-substituted 2,2a,3,4,5,6-hexahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole-2-ones.

Scheme 3

In conclusion, we established that our reaction of serotoninins with aldehydes under basic conditions is a general and convenient synthetic method for creating novel 7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles. We also succeeded in the synthesis of novel 2,2a,3,4,5,6-hexahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole-2-ones. Biological evaluation of the compounds reported in this paper is now in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with Horiba FT-720 spectrophotometer and ¹H-NMR spectra with JEOL GSX 500 spectrometer with tetramethylsilane as an internal standard. MS were recorded on JEOL JMS-SX 102A spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF₂₄₅ (Type 60) (SiO₂). Column chromatography was performed on silica gel (SiO₂, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

Nb-Pentanoylserotonin (7a) from Serotonin·HCl (1b·HCl) — **General procedure:** a solution of ClCO₂Me (254.0 mg, 2.7 mmol) in anhydrous CHCl₃ (5.0 mL) was added to a solution of pentanoic acid (275.0 mg, 2.7 mmol) and Et₃N (545.1 mg, 5.4 mmol) in anhydrous CHCl₃ (5.0 mL) under ice cooling and the mixture was stirred at rt for 20 min. The resulting mixture was added to a solution of **1b·HCl** (520.3 mg, 2.5 mmol) in anhydrous DMF (5.0 mL) and the mixture was stirred at rt for 30 min. After

addition of H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1, v/v) to give **7a** (583.2 mg, 92%). **7a**: colorless viscous oil. IR (film): 3309, 1628, 1541, 1458, 1188 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.88 (3H, t, *J*=7.4 Hz), 1.30 (2H, sex, *J*=7.4 Hz), 1.52 (2H, quint, *J*=7.4 Hz), 2.12 (2H, t, *J*=7.4 Hz), 2.90 (2H, t, *J*=6.8 Hz), 3.57 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz on addition of D₂O), 5.57 (2H, br s, disappeared on addition of D₂O), 6.80 (1H, dd, *J*=8.5, 2.2 Hz), 6.99 (1H, d, *J*=1.7 Hz, collapsed to s on addition of D₂O), 7.03 (1H, d, *J*=2.2 Hz), 7.22 (1H, d, *J*=8.5 Hz), 7.95 (1H, br s, disappeared on addition of D₂O). HR-MS *m/z*: Calcd for C₁₅H₂₀N₂O₂: 260.1525. Found: 260.1520.

Nb-Nonanoylserotonin (7b) from 1b·HCl — In the general procedure, ClCO₂Me (252.9 mg, 2.7 mmol), anhydrous CHCl₃ (5.0 mL), nonanoic acid (426.1 mg, 2.7 mmol), Et₃N (544.4 mg, 5.4 mmol), anhydrous CHCl₃ (5.0 mL), **1b·HCl** (520.0 mg, 2.5 mmol), and anhydrous DMF (5.0 mL) were used. After column chromatography, **7b** (739.0 mg, 96%) was obtained. **7b**: colorless viscous oil. IR (film): 3307, 2925, 2854, 1628, 1541, 1458 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.87 (3H, t, *J*=7.0 Hz), 1.20–1.30 (10H, m), 1.58 (2H, quint, *J*=7.0 Hz), 2.11 (2H, t, *J*=7.0 Hz), 2.90 (2H, t, *J*=6.8 Hz), 3.58 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz on addition of D₂O), 5.35 (1H, br s, disappeared on addition of D₂O), 5.50 (1H, br t, *J*=6.8 Hz, disappeared on addition of D₂O), 6.80 (1H, dd, *J*=8.5, 2.2 Hz), 6.99 (1H, d, *J*=2.0 Hz, collapsed to s on addition of D₂O), 7.02 (1H, d, *J*=2.2 Hz), 7.22 (1H, d, *J*=8.5 Hz), 7.93 (1H, br s, disappeared on addition of D₂O). HR-MS *m/z*: Calcd for C₁₉H₂₈N₂O₂: 316.2151. Found: 316.2146.

Nb-Hexadecanoylserotonin (7c) from 1b·HCl — In the general procedure, ClCO₂Me (252.5 mg, 2.7 mmol), anhydrous CHCl₃ (5.0 mL), hexadecanoic acid (690.3 mg, 2.7 mmol), Et₃N (544.3 mg, 5.4 mmol), anhydrous CHCl₃ (5.0 mL), **1b·HCl** (520.0 mg, 2.5 mmol), and anhydrous DMF (5.0 mL) were used. After column chromatography, **7c** (887.4 mg, 88%) was obtained. **7c**: mp 121–122 °C (colorless powder, recrystallized from CHCl₃–MeOH). IR (KBr): 3415, 3307, 2918, 2848, 1635, 1541 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.88 (3H, t, *J*=7.0 Hz), 1.21–1.28 (24H, m), 1.57 (2H, quint, *J*=7.0 Hz), 2.11 (2H, t, *J*=7.0 Hz), 2.90 (2H, t, *J*=6.8 Hz), 3.58 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz on addition of D₂O), 4.93 (1H, br s, disappeared on addition of D₂O), 5.51 (1H, br t, *J*=6.8 Hz, disappeared on addition of D₂O), 6.79 (1H, dd, *J*=8.5, 2.2 Hz), 7.01 (1H, d, *J*=2.0 Hz, collapsed to s on addition of D₂O), 7.03 (1H, d, *J*=2.2 Hz), 7.23 (1H, d, *J*=8.5 Hz), 7.89 (1H, br s, disappeared on addition of D₂O). MS *m/z*: 414 (M⁺). *Anal.* C₂₆H₄₂N₂O₂: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.05; H, 10.38; N, 6.72.

Nb-Cyclohexylcarbonylserotonin (7d) from 1b·HCl — In the general procedure, ClCO₂Me (486.9 mg, 5.2 mmol), anhydrous CHCl₃ (10 mL), cyclohexanecarboxylic acid (655.3 mg, 5.2 mmol), Et₃N (1.07 g, 10.3 mmol), anhydrous CHCl₃ (10 mL), **1b·HCl** (995.7 mg, 4.7 mmol), and anhydrous DMF (10 mL) were used. After column chromatography, **7d** (1.30 g, 97%) was obtained. **7d**: colorless foam. IR (KBr):

3317, 2929, 1631, 1531 cm^{-1} . ^1H -NMR (DMSO-d_6) δ : 1.10—1.25 (3H, m), 1.33 (2H, q, $J=10.3$ Hz), 1.60 (1H, br d, $J=10.3$ Hz), 1.65—1.71 (4H, m, $J=9.3$ Hz), 2.07 (1H, tt, $J=11.3, 3.0$ Hz), 2.70 (2H, t, $J=7.4$ Hz), 3.24—3.28 (2H, m, collapsed to t, $J=7.4$ Hz on addition of D_2O), 6.58 (1H, dd, $J=8.8, 2.2$ Hz), 6.82 (1H, d, $J=2.2$ Hz), 6.99 (1H, d, $J=2.0$ Hz), 7.11 (1H, d, $J=8.8$ Hz), 7.69 (1H, br t, $J=5.5$ Hz, disappeared on addition of D_2O), 8.55 (1H, br s, disappeared on addition of D_2O), 10.41 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$: 286.1681. Found: 286.1682.

Nb-Benzoylserotonin (7e) from 1b·HCl — In the general procedure, ClCO_2Me (103.4 mg, 1.1 mmol), anhydrous CHCl_3 (2.0 mL), benzoic acid (127.0 mg, 1.0 mmol), Et_3N (212.5 mg, 2.1 mmol), anhydrous CHCl_3 (2.0 mL), **1b·HCl** (202.7 mg, 1.0 mmol), and anhydrous DMF (2.0 mL) were used. After column chromatography, **7e** (240.5 mg, 90%) was obtained. **7e**: mp 208—209 $^\circ\text{C}$ (colorless prisms, recrystallized from MeOH). IR (KBr): 3425, 1645, 1537, 1377, 1186, 939, 850, 795, 710, 625 cm^{-1} . ^1H -NMR (DMSO-d_6) δ : 2.86 (2H, t, $J=7.6$ Hz), 3.51 (2H, td, $J=7.6, 6.1$ Hz), 6.59 (1H, dd, $J=8.5, 2.2$ Hz), 6.89 (1H, d, $J=2.2$ Hz), 7.06 (1H, d, $J=2.2$ Hz), 7.12 (1H, d, $J=8.5$ Hz), 7.46 (2H, t, $J=7.8$ Hz), 7.52 (1H, tt, $J=7.8, 1.5$ Hz), 7.85 (2H, dd, $J=7.8, 1.5$ Hz), 8.56 (1H, t, $J=6.1$ Hz), 8.57 (1H, s, disappeared on addition of D_2O), 10.46 (1H, br s). MS m/z : 280 (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.73; H, 5.72; N, 9.86.

Nb-Pentylserotonin (8a) from 7a — General Procedure: LiAlH_4 (765.0 mg, 20.1 mmol) was added to a solution of **7a** (522.4 mg, 2.0 mmol) in anhydrous THF (20.0 mL) under ice cooling and the mixture was refluxed for 10 h with stirring. After addition of MeOH and 10% Rochelle salt under ice cooling, the whole was extracted with CHCl_3 . The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH–28% NH_4OH (46:3:0.3, v/v) to give **8a** (417.9 mg, 85%). **8a**: pale yellow viscous oil. IR (film): 2929, 2856, 1468, 1213 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.86 (3H, t, $J=7.0$ Hz), 1.21—1.32 (4H, m), 1.51 (2H, quint, $J=7.0$ Hz), 2.65 (2H, t, $J=7.0$ Hz), 2.92—3.00 (4H, m), 6.78 (1H, dd, $J=8.5, 2.2$ Hz), 6.95 (1H, d, $J=2.2$ Hz), 6.99 (1H, br s), 7.20 (1H, d, $J=8.5$ Hz), 7.97 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$: 246.1732. Found: 246.1737.

Nb-Nonylserotonin (8b) from 7b — In the general procedure, LiAlH_4 (889.8 mg, 18.7 mmol), **7b** (739.0 mg, 2.3 mmol), and anhydrous THF (20.0 mL) were used. After column chromatography, **8b** (572.5 mg, 81%) was obtained. **8b**: yellow viscous oil. IR (film): 2925, 2854, 1468, 1458, 1213 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.87 (3H, t, $J=7.0$ Hz), 1.19—1.29 (12H, m), 1.49 (2H, br quint, $J=7.0$ Hz), 2.65 (2H, t, $J=7.0$ Hz), 2.91—2.99 (4H, m), 6.77 (1H, dd, $J=8.5, 2.2$ Hz), 6.95 (1H, d, $J=2.2$ Hz), 6.99 (1H, br s), 7.20 (1H, d, $J=8.5$ Hz), 7.95 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}$: 302.2358. Found: 302.2359.

Nb-Hexadecylserotonin (8c) from 7c — In the general procedure, LiAlH_4 (741.9 mg, 19.5 mmol), **7c**

(808.0 mg, 2.0 mmol), and anhydrous THF (20.0 mL) were used. After column chromatography, **8c** (696.4 mg, 89%) was obtained. **8c**: pale brown viscous oil. IR (film): 2924, 2852, 1468, 1458, 1215 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, t, $J=6.8$ Hz), 1.20–1.31 (26H, m), 1.49 (2H, br quint, $J=6.8$ Hz), 2.64 (2H, t, $J=6.8$ Hz), 2.91–2.99 (4H, m), 6.77 (1H, dd, $J=8.5, 2.2$ Hz), 6.95 (1H, d, $J=2.2$ Hz), 7.00 (1H, br s), 7.20 (1H, d, $J=8.5$ Hz), 7.94 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{26}\text{H}_{44}\text{N}_2\text{O}$: 400.3453. Found: 400.3460.

Nb-Cyclohexylmethylserotonin (8d) from 7d — In the general procedure, LiAlH_4 (712.5 mg, 15.0 mmol), **7d** (537.1 mg, 1.9 mmol), and anhydrous THF (20.0 mL) were used. After column chromatography, **8d** (376.9 mg, 74%) was obtained. **8d**: yellow foam. IR (KBr): 3292, 2922, 2850, 1456 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.83–0.91 (2H, m), 1.08–1.25 (3H, m), 1.44–1.53 (1H, m), 1.61–1.71 (5H, m), 2.50 (2H, d, $J=6.8$ Hz), 2.90–2.97 (4H, m), 6.76 (1H, dd, $J=8.8, 2.3$ Hz), 6.94 (1H, d, $J=2.3$ Hz), 6.98 (1H, d, $J=2.0$ Hz, collapsed to s on addition of D_2O), 7.19 (1H, d, $J=8.8$ Hz), 7.93 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}$: 272.1889. Found: 272.1885.

Nb-Benzylserotonin (8e) from 7e — In the general procedure, LiAlH_4 (72.5 mg, 1.9 mmol), **7e** (51.8 mg, 0.2 mmol), and anhydrous THF (5.0 mL) were used. After column chromatography, unreacted **7e** (6.5 mg, 13%), **8e** (23.0 mg, 47%), and serotonin (**1b**, 6.9 mg, 21%) were obtained. **8e**: colorless oil. IR (film): 3410, 3286, 1454, 1215, 750 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.90–2.92 (2H, m), 2.95–2.98 (2H, m), 3.60 (2H, br s, disappeared on addition of D_2O), 3.81 (2H, s), 6.75 (1H, dd, $J=8.7, 2.2$ Hz), 6.87 (1H, d, $J=2.2$ Hz), 6.92 (1H, d, $J=1.7$ Hz, collapsed to s on addition of D_2O), 7.16 (1H, d, $J=8.7$ Hz), 7.20–7.29 (5H, m), 7.97 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$: 266.1420. Found: 266.1418.

Nb-Benzylserotonin (8e) from 1b·HCl — A solution of benzaldehyde (504.5 mg, 4.8 mmol) in MeOH (5.0 mL) was added to a solution of **1b·HCl** (336.3 mg, 1.6 mmol) and NaCNBH_3 (95%, 315.0 mg, 4.8 mmol) in MeOH (20.0 mL) and the mixture was stirred at rt for 30 min. After addition of H_2O , the whole was made alkaline (pH=9) with 8% NaOH and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH–28% NH_4OH (46:3:0.3, v/v) to give **8e** (237.5 mg, 56%).

3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-5-pentyl-1H-azepino[5,4,3-cd]indole (10a) from 8a — **General Procedure**: a solution of acetaldehyde (15.8 mg, 0.4 mmol) in MeOH (3.0 mL) was added to a solution of **8a** (29.5 mg, 0.1 mmol) in Et_3N (3.0 mL) under ice cooling and the mixture was stirred at rt for 2.5 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH–28% NH_4OH (46:1:0.1, v/v) to give **10a** (29.3 mg, 90%). **10a**: colorless foam. IR (KBr): 3400, 2929, 1581, 1435, 1375 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (3H, t, $J=7.1$ Hz), 1.20–1.35 (4H, m), 1.47 (3H, d, $J=6.8$ Hz), 1.55–1.63 (2H, m), 2.64–2.70 (1H, m),

2.75—2.81 (1H, m), 2.90 (1H, br d, $J=16.1$ Hz), 3.09 (1H, br d, $J=14.5$ Hz), 3.20 (1H, ddd, $J=16.1, 12.9, 4.0$ Hz), 3.58 (1H, br t, $J=14.5$ Hz), 4.33 (1H, br s, disappeared on addition of D₂O), 4.73 (1H, br s), 6.64 (1H, d, $J=8.5$ Hz), 6.94 (1H, s), 7.04 (1H, d, $J=8.5$ Hz), 7.86 (1H, br s, disappeared on addition of D₂O). HR-MS m/z : Calcd for C₁₇H₂₄N₂O: 272.1889. Found: 272.1888.

3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-5-nonyl-1H-azepino[5,4,3-*cd*]indole (10b) from 8b — In the general procedure, acetaldehyde (15.3 mg, 0.4 mmol), MeOH (3.0 mL), **8b** (35.0 mg, 0.1 mmol), and Et₃N (3.0 mL) were used. After column chromatography, **10b** (37.0 mg, 97%) was obtained. **10b**: colorless foam. IR (KBr): 3400, 2927, 2852, 1581, 1435, 1375 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.86 (3H, t, $J=6.8$ Hz), 1.19—1.31 (12H, m), 1.48 (3H, d, $J=6.6$ Hz), 1.53—1.69 (2H, m), 2.63—2.72 (1H, m), 2.75—2.84 (1H, m), 2.91 (1H, br d, $J=18.1$ Hz), 3.09 (1H, br d, $J=13.9$ Hz), 3.21 (1H, ddd, $J=16.1, 13.0, 4.0$ Hz), 3.59 (1H, br t, $J=13.0$ Hz), 4.40 (1H, br s, disappeared on addition of D₂O), 4.72 (1H, br s), 6.65 (1H, d, $J=8.5$ Hz), 6.94 (1H, s), 7.04 (1H, d, $J=8.5$ Hz), 7.86 (1H, br s, disappeared on addition of D₂O). HR-MS m/z : Calcd for C₂₁H₃₂N₂O: 328.2514. Found: 328.2505.

5-Hexadecyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-*cd*]indole (10c) from 8c — In the general procedure, acetaldehyde (15.5 mg, 0.4 mmol), MeOH (3.0 mL), **8c** (47.2 mg, 0.1 mmol), and Et₃N (3.0 mL) were used. After column chromatography, **10c** (45.7 mg, 91%) was obtained. **10c**: colorless solid. IR (KBr): 3400, 2922, 2852, 1579, 1466, 1435, 1378 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (3H, t, $J=6.8$ Hz), 1.20—1.30 (26H, m), 1.47 (3H, d, $J=6.6$ Hz), 1.50—1.61 (2H, m), 2.63—2.69 (1H, m), 2.75—2.81 (1H, m), 2.90 (1H, br d, $J=12.9$ Hz), 3.08 (1H, br d, $J=14.0$ Hz), 3.20 (1H, ddd, $J=15.9, 12.5, 5.3$ Hz), 3.58 (1H, br t, $J=12.5$ Hz), 4.30 (1H, br s, disappeared on addition of D₂O), 4.71 (1H, br q, $J=6.6$ Hz), 6.63 (1H, d, $J=8.5$ Hz), 6.93 (1H, s), 7.04 (1H, d, $J=8.5$ Hz), 7.85 (1H, br s, disappeared on addition of D₂O). HR-MS m/z : Calcd for C₂₈H₄₆N₂O: 426.3610. Found: 426.3613.

5-Cyclohexylmethyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-*cd*]indole (10d) from 8d — In the general procedure, acetaldehyde (14.5 mg, 0.3 mmol), MeOH (2.5 mL), **8d** (30.0 mg, 0.1 mmol), and Et₃N (3.0 mL) were used. After column chromatography, **10d** (26.4 mg, 80%) was obtained. **10d**: yellow foam. IR (KBr): 3402, 2922, 1579, 1435, 1367 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.80—0.89 (2H, m), 1.10—1.28 (3H, m), 1.46 (3H, d, $J=6.7$ Hz), 1.59 (1H, br s), 1.62—1.71 (3H, m), 1.80 (2H, br t, $J=16.8$ Hz), 2.48 (1H, br dd, $J=12.2, 6.7$ Hz), 2.64 (1H, dd, $J=12.2, 6.7$ Hz), 2.87 (1H, d, $J=15.9$ Hz), 3.01 (1H, br d, $J=14.0$ Hz), 3.22 (1H, ddd, $J=16.5, 12.8, 3.7$ Hz), 3.59 (1H, br t, $J=12.8$ Hz), 4.62 (1H, br s), 6.64 (1H, d, $J=8.2$ Hz), 6.92 (1H, s), 7.03 (1H, d, $J=8.2$ Hz), 7.82 (1H, s, disappeared on addition of D₂O). HR-MS m/z : Calcd for C₁₉H₂₆N₂O: 298.2046. Found: 298.2051.

5-Benzyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-*cd*]indole (10e) from 8e — In the general procedure, acetaldehyde (138.6 mg, 3.2 mmol), MeOH (10.0 mL), **8e** (270.6 mg, 1.0 mmol), and Et₃N (10.0 mL) were used. After column chromatography, **10e** (264 mg, 89%) was obtained. **10e**:

colorless foam. IR (KBr): 3400, 1579, 1435, 1371, 1296, 1240 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (3H, t, $J=7.1$ Hz), 2.86 (1H, br dt, $J=16.2, 2.7$ Hz), 3.07 (1H, dq, $J=14.5, 2.3$ Hz), 3.21 (1H, ddd, $J=13.3, 4.8, 1.6$ Hz), 3.63 (1H, td, $J=13.8, 3.2$ Hz), 3.86 (1H, d, $J=13.7$ Hz), 4.00 (1H, d, $J=13.7$ Hz), 4.24 (1H, br s), 4.65 (1H, q, $J=7.1$ Hz), 6.65 (1H, d, $J=8.5$ Hz), 6.94 (1H, s), 7.06 (1H, d, $J=8.5$ Hz), 7.23 (1H, t, $J=7.3$ Hz), 7.30 (2H, t, $J=7.3$ Hz), 7.37 (2H, d, $J=7.3$ Hz), 7.88 (1H, br s). MS m/z : 292 (M^+). HR-MS m/z : Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$: 292.1576. Found: 292.1573.

3,4,5,6-Tetrahydro-7-hydroxy-6-nonyl-5-pentyl-1H-azepino[5,4,3-*cd*]indole (11a) from 8a — **General Procedure:** A solution of decanal (57.1 mg, 0.4 mmol) in MeOH (3.0 mL) was added to a solution of **8a** (30.0 mg, 0.1 mmol) in Et_3N (3.0 mL) under ice cooling, and the mixture was stirred at rt for 3.5 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH–28% NH_4OH (46:1:0.1, v/v) to give **11a** (35.7 mg, 76%). **11a**: colorless viscous oil. IR (film): 3408, 2925, 2854, 1579, 1466, 1437, 1375, 1369 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (3H, t, $J=7.1$ Hz), 0.87 (3H, t, $J=7.1$ Hz), 1.21–1.35 (18H, m), 1.39–1.60 (2H, m), 1.63–1.70 (1H, m), 1.78–1.86 (1H, m), 2.58–2.64 (1H, m), 2.80 (1H, ddd, $J=12.7, 8.3, 5.6$ Hz), 2.86 (1H, br d, $J=16.1$ Hz), 3.10 (1H, br d, $J=16.1$ Hz), 3.24 (1H, ddd, $J=16.1, 12.7, 4.3$ Hz), 3.49 (1H, br t, $J=12.7$ Hz), 4.48 (2H, br s), 6.64 (1H, d, $J=8.3$ Hz), 6.91 (1H, s), 7.01 (1H, d, $J=8.3$ Hz), 7.84 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{25}\text{H}_{40}\text{N}_2\text{O}$: 384.3140. Found: 384.3130.

3,4,5,6-Tetrahydro-7-hydroxy-5,6-dinonyl-1H-azepino[5,4,3-*cd*]indole (11b) from 8b — In the general procedure, decanal (57.7 mg, 0.4 mmol), MeOH (3.0 mL), **8b** (37.2 mg, 0.1 mmol), and Et_3N (3.0 mL) were used. After column chromatography, **11b** (43.8 mg, 81%) was obtained. **11b**: colorless viscous oil. IR (film): 3402, 2924, 2852, 1577, 1466, 1435, 1369 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (3H, t, $J=7.1$ Hz), 0.87 (3H, t, $J=7.1$ Hz), 1.21–1.34 (26H, m), 1.40–1.60 (2H, m), 1.63–1.70 (1H, m), 1.77–1.85 (1H, m), 2.58–2.64 (1H, m), 2.80 (1H, ddd, $J=12.5, 8.1, 6.1$ Hz), 2.86 (1H, br d, $J=15.9$ Hz), 3.10 (1H, br d, $J=15.9$ Hz), 3.24 (1H, ddd, $J=15.9, 12.5, 3.7$ Hz), 3.48 (1H, br t, $J=12.5$ Hz), 4.28 (1H, br s, disappeared on addition of D_2O), 4.47 (1H, br dd, $J=10.0, 4.5$ Hz), 6.64 (1H, d, $J=8.3$ Hz), 6.91 (1H, br s), 7.02 (1H, d, $J=8.3$ Hz), 7.83 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}$: 440.3766. Found: 440.3761.

5-Hexadecyl-3,4,5,6-tetrahydro-7-hydroxy-6-nonyl-1H-azepino[5,4,3-*cd*]indole (11c) from 8c — In the general procedure, decanal (56.7 mg, 0.4 mmol), MeOH (3.0 mL), **8c** (48.5 mg, 0.1 mmol), and Et_3N (3.0 mL) were used. After column chromatography, **11c** (49.9 mg, 76%) was obtained. **11c**: colorless viscous oil. IR (film): 3402, 2924, 2852, 1577, 1466, 1435, 1369 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (3H, t, $J=6.8$ Hz), 0.88 (3H, t, $J=6.8$ Hz), 1.23–1.33 (40H, m), 1.49–1.57 (2H, m), 1.63–1.69 (1H, m), 1.76–1.84 (1H, m), 2.57–2.62 (1H, m), 2.77–2.87 (2H, m), 3.09 (1H, br d, $J=14.5$ Hz), 3.24 (1H, ddd, $J=14.5, 12.5, 4.3$ Hz), 3.48 (1H, ddd, $J=14.5, 10.5, 3.3$ Hz), 4.23 (1H, br s, disappeared on addition of

D₂O), 4.46 (1H, dd, $J=10.5, 4.4$ Hz), 6.64 (1H, d, $J=8.3$ Hz), 6.91 (1H, s), 7.02 (1H, d, $J=8.3$ Hz), 7.82 (1H, br s, disappeared on addition of D₂O). HR-MS m/z : Calcd for C₃₆H₆₂N₂O: 538.4862. Found: 538.4876.

3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-*cd*]indole (12a) from 10e — A suspension of **10e** (25.2 mg, 0.01 mmol) and 10% Pd/C (5.4 mg) in MeOH (3.0 mL) was stirred at rt for 3 h under hydrogen atmosphere. The resulting mixture was filtered and the filtrate was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% NH₄OH (46:10:1, v/v) to give **12a** (15.8 mg, 91%). **12a**: pale brown oil. IR (film): 3399, 3299, 1579, 1417, 794 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.49 (3H, d, $J=6.8$ Hz), 2.93–3.01 (1H, m), 3.10–3.15 (2H, m), 3.35–3.41 (1H, m), 4.91 (1H, q, $J=6.8$ Hz), 6.63 (1H, d, $J=8.6$ Hz), 6.95 (1H, s), 7.03 (1H, d, $J=8.6$ Hz). HR-MS m/z : Calcd for C₁₂H₁₄N₂O: 202.1107. Found: 202.1110.

7-Acetoxy-5-acetyl-3,4,5,6-tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (12b) from 12a — Acetic anhydride (1 mL) was added to a solution of **12a** (46.7 mg, 0.2 mmol) in pyridine (2.0 mL) at rt and the mixture was stirred at rt for 2 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (98:2, v/v) to give **12b** (63.1 mg, 95%). **12b**: pale brown foam. IR (KBr): 1755, 1628, 1616, 1425 cm⁻¹. ¹H-NMR (CDCl₃, rotamer ratio, 5:2. On heating, **12b** decomposed) δ : 1.42 (6/7H, d, $J=7.3$ Hz), 1.55 (15/7H, d, $J=7.3$ Hz), 2.14 (15/7H, s), 2.22 (6/7H, s), 2.37 (6/7H, s), 2.39 (15/7H, s), 2.98 (5/7H, dt, $J=15.9, 2.4$ Hz), 3.09–3.17 (4/7H, m), 3.34 (5/7H, m), 3.45 (5/7H, td, $J=13.3, 2.6$ Hz), 3.82–3.93 (4/7H, m), 4.43 (5/7H, dt, $J=13.3, 3.4$ Hz), 5.43 (5/7H, q, $J=7.3$ Hz), 6.58 (2/7H, q, $J=7.3$ Hz), 6.83 (5/7H, d, $J=8.5$ Hz), 6.87 (2/7H, d, $J=8.5$ Hz), 7.00 (2/7H, br s), 7.01 (5/7H, br s), 7.17 (2/7H, d, $J=8.5$ Hz), 7.23 (5/7H, d, $J=8.5$ Hz), 8.20 (2/7H, br s, disappeared on addition of D₂O), 8.23 (5/7H, br s, disappeared on addition of D₂O). MS m/z : 286 (M⁺). HR-MS m/z : Calcd for C₁₆H₁₈N₂O₃: 286.1318. Found: 286.1313.

5-tert-Butoxycarbonyl-7-tert-butoxycarbonyloxy-3,4,5,6-tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (12c) from 12a — A solution of di-*tert*-butyl dicarbonate (45.6 mg, 0.2 mmol) in anhydrous CHCl₃ (2.0 mL) was added to a solution of **12a** (13.3 mg, 0.07 mmol), DMAP (16.5 mg, 0.1 mmol) in anhydrous CHCl₃ (1.0 mL) at rt and the mixture was stirred at rt for 1 h. After addition of H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (98:2, v/v) to give **12c** (13.7 mg, 52%). **12c**: colorless viscous oil. IR (film): 3386, 2979, 1757, 1691, 1668 cm⁻¹. ¹H-NMR (CDCl₃, rotamer ratio, 1:1. On heating, **12c** decomposed) δ : 1.40 (9/2H, s), 1.45 (3/2H, d, $J=7.1$ Hz), 1.47 (9/2H, s), 1.49 (3/2H, d, $J=7.1$ Hz), 1.56 (9/2H, s), 1.59 (9/2H, s), 2.97 (1H, dd, $J=14.3, 12.3$ Hz), 3.18 (1/2H, t, $J=14.3$ Hz), 3.29 (1/2H, t, $J=14.3$ Hz), 3.50 (1H, m), 3.97 (1/2H, d, $J=14.3$ Hz), 4.12 (1/2H, d, $J=14.3$ Hz), 5.91 (1/2H, q, $J=7.1$ Hz), 6.19 (1/2H, q, $J=7.1$ Hz),

6.89—6.93 (1H, m), 6.97 (1H, br s), 7.13—7.18 (1H, m), 8.08—8.13 (1H, m, disappeared on addition of D₂O). HR-MS *m/z*: Calcd for C₂₂H₃₀N₂O₅: 402.2155. Found: 402.2152.

3,4,5,6-Tetrahydro-7-hydroxy-5-pentyl-6-phenyl-1*H*-azepino[5,4,3-*cd*]indole (14a) from 8a — A solution of benzaldehyde (**13a**, 39.4 mg, 0.4 mmol) in MeOH (3.0 mL) was added to a solution of **8a** (30.0 mg, 0.1 mmol) in Et₃N (3.0 mL) under ice cooling, and the mixture was refluxed for 15 h with stirring. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% NH₄OH (46:1:0.1, v/v) to give **14a** (35.8 mg, 86%). **14a**: mp 166—168 °C (colorless powder, recrystallized from CHCl₃–hexane). IR (KBr): 3448, 3273, 2952, 2931, 1583, 1491, 1435, 1378 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.91 (3H, t, *J*=7.1 Hz), 1.32—1.42 (4H, m), 1.65 (2H, quint, *J*=7.1 Hz), 2.78—2.86 (3H, m), 2.94 (1H, dt, *J*=12.5, 7.1 Hz), 3.13 (1H, td, *J*=14.4, 2.9 Hz), 3.21—3.28 (1H, m), 3.98 (1H, br s, disappeared on addition of D₂O), 5.72 (1H, s), 6.71 (1H, d, *J*=8.5 Hz), 6.96 (1H, s), 7.14 (2H, d, *J*=7.6 Hz), 7.15 (1H, d, *J*=8.5 Hz), 7.19 (1H, t, *J*=7.6 Hz), 7.24 (2H, t, *J*=7.6 Hz), 7.91 (1H, br s, disappeared on addition of D₂O). MS *m/z*: 334 (M⁺). *Anal.* Calcd for C₂₂H₂₆N₂O: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.98; H, 7.91; N, 8.38.

3,4,5,6-Tetrahydro-7-hydroxy-6-isopropyl-5-pentyl-1*H*-azepino[5,4,3-*cd*]indole (14b) from 8a — A solution of 2-methylpropanal (**13b**, 27.2 mg, 0.4 mmol) in MeOH (3.0 mL) was added to a solution of **8a** (30.0 mg, 0.1 mmol) in Et₃N (3.0 mL) under ice cooling, and the mixture was refluxed for 15 h with stirring. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% NH₄OH (46:1:0.1, 46:3:0.3, v/v) to give **14b** (18.5 mg, 49%), **10a** (3.6 mg, 11%), and unreacted **8a** (4.6 mg, 23%) in the order of elution. **14b**: colorless viscous oil. IR (film): 3410, 2956, 2929, 2870, 1577, 1466, 1435, 1363 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.79 (3H, d, *J*=6.6 Hz), 0.87 (3H, t, *J*=6.9 Hz), 1.15 (3H, d, *J*=6.6 Hz), 1.23—1.34 (4H, m), 1.46—1.58 (2H, m), 2.04—2.11 (1H, m), 2.56 (1H, dq, *J*=6.4, 6.2 Hz), 2.65 (1H, dq, *J*=6.4, 6.2 Hz), 2.94 (1H, dt, *J*=15.5, 4.2 Hz), 3.01 (1H, dt, *J*=14.2, 4.6 Hz), 3.08 (1H, ddd, *J*=17.3, 10.3, 3.7 Hz), 3.51 (1H, ddd, *J*=17.3, 10.3, 3.7 Hz), 4.07 (1H, d, *J*=9.5 Hz), 4.20 (1H, br s, disappeared on addition of D₂O), 6.64 (1H, d, *J*=8.5 Hz), 6.89 (1H, br s), 7.03 (1H, d, *J*=8.5 Hz), 7.77 (1H, br s, disappeared on addition of D₂O). HR-MS *m/z*: Calcd for C₁₉H₂₈N₂O: 300.2202. Found: 300.2203.

5-Benzyl-8-bromo- (16a) and 5-Benzyl-2,2a,3,4,5,6-hexahydro-7-hydroxy-6-methyl-1*H*-azepino-[5,4,3-*cd*]indol-2-one (15a) from 10e — A solution (1.5 mL, 0.6 mmol) of Br₂ in AcOH [prepared with Br₂ (287.9 mg, 1.8 mmol) and NaOAc (24.5 mg, 0.3 mmol) in AcOH (5.0 mL)] was added to a solution of **10e** (54.1 mg, 0.2 mmol) in AcOH (5.0 mL), and the mixture was stirred at rt for 2 h. After addition of 10% Na₂S₂O₃ (ca. 0.5 mL), the whole was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (97:3, 95:5, v/v) to give **16a** (59.3 mg, 83%) and **15a** (9.2 mg, 16%) in the order of elution. **16a**: mp 100—105 °C (colorless fine needles,

recrystallized from CHCl_3 –hexane). IR (KBr): 1705, 1620, 1599, 1450, 1313 cm^{-1} . ^1H -NMR (pyridine- d_5) δ : 1.60 (3H, d, $J=7.1$ Hz), 1.99–2.12 (2H, m), 3.13 (1H, dt, $J=14.6$, 2.4 Hz), 3.59 (1H, br t, $J=12.8$ Hz), 3.78 (2H, s), 3.91 (1H, dd, $J=12.8$, 4.3 Hz), 5.12 (1H, q, $J=7.1$ Hz), 7.24 (1H, s), 7.24 (1H, t, $J=7.3$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.45 (2H, d, $J=7.3$ Hz), 11.61 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_2$: 388.0610, 386.0630. Found: 388.0598, 386.0625. *Anal.* Calcd for $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_2$: C, 58.93; H, 4.95; N, 7.23. Found: C, 58.68; H, 4.97; N, 7.30. **15a**: colorless solid. IR (KBr): 3201, 1699, 1618, 1469 cm^{-1} . ^1H -NMR (pyridine- d_5 , 60 °C) δ : 1.64 (3H, d, $J=7.3$ Hz), 2.00–2.16 (2H, m), 3.18 (1H, br d, $J=14.6$ Hz), 3.63 (1H, br t, $J=14.0$ Hz), 3.82 (1H, d, $J=14.0$ Hz), 3.87 (1H, d, $J=14.0$ Hz), 3.90 (1H, dd, $J=12.8$, 4.3 Hz), 5.09 (1H, q, $J=7.3$ Hz), 6.76 (1H, d, $J=8.1$ Hz), 6.97 (1H, d, $J=8.1$ Hz), 7.21 (1H, t, $J=7.3$ Hz), 7.29 (2H, t, $J=7.3$ Hz), 7.48 (2H, d, $J=7.3$ Hz), 10.88 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$: 308.1525. Found: 308.1506.

5-Benzyl-8-bromo-2,2a,3,4,5,6-hexahydro-7-methoxy-6-methyl-1H-azepino[5,4,3-*cd*]indol-2-one (16b) from 16a — Excess amount of CH_2N_2 in Et_2O was added to a solution of **16a** (40.9 mg, 0.1 mmol) in MeOH (5.0 mL) at rt and the mixture was refluxed for 15 min with stirring. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH (99:1, v/v) to give **16b** (40.3 mg, 95%). **16b**: mp 168–169 °C (colorless prisms, recrystallized from CHCl_3 –hexane). IR (KBr): 1701, 1604, 1452 cm^{-1} . ^1H -NMR (pyridine- d_5) δ : 1.57 (3H, d, $J=7.3$ Hz), 1.94 (1H, dq, $J=2.0$, 12.5 Hz), 2.01–2.06 (1H, m), 3.04 (1H, dt, $J=15.1$, 2.9 Hz), 3.52 (1H, br ddd, $J=14.4$, 12.2, 2.0 Hz), 3.63 (3H, s), 3.68–3.74 (2H, m), 3.87 (1H, dd, $J=12.7$, 3.9 Hz), 4.64 (1H, q, $J=7.3$ Hz), 7.17 (1H, s), 7.27 (1H, t, $J=7.3$ Hz), 7.36 (2H, t, $J=7.3$ Hz), 7.43 (2H, d, $J=7.3$ Hz), 11.77 (1H, s, disappeared on addition of D_2O). MS m/z : 402 (M^+), 400 (M^+). *Anal.* Calcd for $\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{O}_2 \cdot 1/2\text{H}_2\text{O}$: C, 58.55; H, 5.40; N, 6.83. Found: C, 58.75; H, 5.29; N, 6.83.

7-Acetoxy-5-benzyl-8-bromo-2,2a,3,4,5,6-hexahydro-6-methyl-1H-azepino[5,4,3-*cd*]indol-2-one (16c) from 16a — Acetic anhydride (1.0 mL) was added to a solution of **16a** (34.0 mg, 0.09 mmol) in pyridine (2.0 mL) and the mixture was stirred at rt for 1 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH (98:2, v/v) to give **16c** (33.0 mg, 88%). **16c**: mp 242–244 °C (decomp., colorless powder, recrystallized from CHCl_3 –hexane). IR (KBr): 1772, 1722, 1614 cm^{-1} . ^1H -NMR (pyridine- d_5 , 60 °C) δ : 1.55 (3H, t, $J=7.3$ Hz), 1.94 (1H, qd, $J=12.2$, 2.4 Hz), 2.02–2.07 (1H, m), 2.13 (3H, s), 3.09 (1H, dt, $J=15.1$, 3.2 Hz), 3.57 (1H, br t, $J=12.5$ Hz), 3.67–3.75 (2H, m), 3.87 (1H, dd, $J=12.5$, 4.0 Hz), 4.33 (1H, q, $J=7.3$ Hz), 7.13 (1H, s), 7.26 (1H, t, $J=7.4$ Hz), 7.34 (2H, t, $J=7.4$ Hz), 7.38 (2H, d, $J=7.4$ Hz), 11.54 (1H, br s, disappeared on addition of D_2O). HR-MS m/z : Calcd for $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{O}_3$: 430.0715, 428.0736. Found: 430.0736, 428.0748. *Anal.* Calcd for $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{O}_3 \cdot 1/2\text{H}_2\text{O}$: C, 57.54; H, 5.06; N, 6.39. Found: C, 57.73; H, 4.88; N, 6.35.

5-Benzyl-8-bromo-1-tert-butoxycarbonyl-7-tert-butoxycarbonyloxy-2,2a,3,4,5,6-hexahydro-6-methyl-1H-azepino[5,4,3-cd]indol-2-one (16d) from 16a — A solution of di-*tert*-butyl dicarbonate (63.2 mg, 0.3 mmol) in anhydrous CHCl_3 (1.0 mL) was added to a solution of **16a** (22.6 mg, 0.06 mmol), DMAP (4.0 mg, 0.03 mmol), and Et_3N (29.2 mg, 0.3 mmol) in anhydrous CHCl_3 (3.0 mL) at rt, and the mixture was stirred at rt for 30 min. The resulting mixture was evaporated under reduced pressure to leave a residue, which was purified by p-TLC on SiO_2 developed with CHCl_3 . Extraction of the band having an *R_f* value of 0.23–0.13 with CHCl_3 –MeOH (95:5, v/v) gave **16d** (15.7 mg, 46%). **16d**: colorless viscous oil. IR (film): 2981, 1799, 1766, 1732, 1593, 1456 cm^{-1} . ^1H -NMR (pyridine- d_5) δ : 1.49 (9H, s), 1.63 (3H, d, $J=7.1$ Hz), 1.64 (9H, s), 1.90–2.02 (2H, m), 2.98 (1H, d, $J=9.3$ Hz), 3.46 (1H, t, $J=13.2$ Hz), 3.75 (2H, s), 4.06 (1H, dd, $J=12.3, 4.0$ Hz), 4.65 (1H, q, $J=7.1$ Hz), 7.29 (1H, t, $J=7.4$ Hz), 7.37 (2H, t, $J=7.4$ Hz), 7.43 (2H, d, $J=7.4$ Hz), 8.22 (1H, s). HR-MS *m/z*: Calcd for $\text{C}_{29}\text{H}_{35}\text{BrN}_2\text{O}_6$: 588.1658, 586.1678. Found: 588.1628, 586.1696.

8-Bromo- (16e) and 5-Cyclohexylmethyl-2,2a,3,4,5,6-hexahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-cd]indol-2-one (15b) from 10d — A solution (1.0 mL, 0.3 mmol) of Br_2 in AcOH [prepared with Br_2 (252.2 mg, 1.6 mmol) and NaOAc (25.1 mg, 0.3 mmol) in AcOH (5.0 mL)] was added to a solution of **10d** (31.0 mg, 0.1 mmol) in AcOH (3.0 mL), and the mixture was stirred at rt for 2 h. After addition of 10% $\text{Na}_2\text{S}_2\text{O}_3$ (0.2 mL), the whole was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with CHCl_3 –MeOH–28% NH_4OH (46:2:0.2, v/v) to give **16e** (21.4 mg, 52%) and **15b** (5.6 mg, 17%) in the order of elution. **16e**: yellow oil. IR (film): 3236, 2924, 1701, 1618, 1448, 1315 cm^{-1} . ^1H -NMR (pyridine- d_5) δ : 0.72–0.84 (2H, m), 1.04–1.22 (3H, m), 1.51–1.65 (4H, m), 1.60 (3H, d, $J=7.2$ Hz), 1.69 (1H, br d, $J=12.7$ Hz), 1.80 (1H, br d, $J=12.7$ Hz), 1.96 (1H, br qd, $J=13.9, 2.4$ Hz), 2.12 (1H, br d, $J=13.9$ Hz), 2.33–2.41 (2H, m), 3.07 (1H, br dt, $J=15.1, 2.9$ Hz), 3.60 (1H, br t, $J=13.4$ Hz), 3.89 (1H, dd, $J=12.8, 3.8$ Hz), 5.05 (1H, q, $J=7.2$ Hz), 7.18 (1H, s), 10.77 (1H, br s disappeared on addition of D_2O), 11.58 (1H, s, disappeared on addition of D_2O). HR-MS *m/z*: Calcd for $\text{C}_{19}\text{H}_{25}\text{BrN}_2\text{O}_2$: 394.1079, 392.1099. Found: 394.1080, 392.1093. **15b**: yellow oil. IR (film): 3255, 2924, 1689, 1467 cm^{-1} . ^1H -NMR (pyridine- d_5) δ : 0.77–0.89 (2H, m), 1.06–1.24 (3H, m), 1.55–1.70 (4H, m), 1.66 (3H, d, $J=7.3$ Hz), 1.78 (1H, br d, $J=12.5$ Hz), 1.84 (1H, br d, $J=12.5$ Hz), 2.02 (1H, br qd, $J=12.7, 2.1$ Hz), 2.18 (1H, br d, $J=12.7$ Hz), 2.39–2.52 (2H, m), 3.12 (1H, br dt, $J=14.6, 3.0$ Hz), 3.64 (1H, br t, $J=13.1$ Hz), 3.96 (1H, dd, $J=12.7, 3.7$ Hz), 5.05 (1H, q, $J=7.3$ Hz), 6.78 (1H, d, $J=8.1$ Hz), 7.01 (1H, d, $J=8.1$ Hz), 10.92 (1H, br s, disappeared on addition of D_2O), 11.31 (1H, s, disappeared on addition of D_2O). HR-MS *m/z*: Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$: 314.1994. Found: 314.1989.

7-Acetoxy-8-bromo-5-cyclohexylmethyl-2,2a,3,4,5,6-hexahydro-6-methyl-1H-azepino[5,4,3-cd]indol-2-one (16f) from 16e — Acetic anhydride (1.0 mL) was added to a solution of **16e** (22.5 mg, 0.06 mmol) in pyridine (2.0 mL) at rt, and the mixture was stirred at rt for 1.5 h. The resulting mixture was

evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% NH₄OH (46:2:0.2, v/v) to give **16f** (20.8 mg, 83%). **16f**: colorless solid. IR (KBr): 2924, 1768, 1716, 1612 cm⁻¹. ¹H-NMR (pyridine-d₅) δ: 0.77–0.89 (2H, m), 1.11–1.29 (3H, m), 1.43–1.68 (7H, m), 1.75–1.83 (2H, m), 1.91 (1H, br q, *J*=12.2 Hz), 2.07 (1H, br d, *J*=14.0 Hz), 2.34 (2H, br s), 2.43 (3H, s), 3.03 (1H, br dt, *J*=15.0, 2.9 Hz), 3.57 (1H, t, *J*=13.4 Hz), 3.90 (1H, dd, *J*=12.8, 3.7 Hz), 4.33 (1H, br s), 7.15 (1H, s), 11.88 (1H, s, disappeared on addition of D₂O). HR-MS *m/z*: Calcd for C₂₁H₂₇BrN₂O₃: 436.1185, 434.1205. Found: 436.1186, 434.1197.

8-Bromo-1-*tert*-butoxycarbonyl-7-*tert*-butoxycarbonyloxy-5-cyclohexylmethyl-2,2a,3,4,5,6-hexahydro-6-methyl-1*H*-azepino[5,4,3-*cd*]indol-2-one (16g) from 16e — A solution of di-*tert*-butyl dicarbonate (41.8 mg, 0.2 mmol) in anhydrous CHCl₃ (3.0 mL) was added to a solution of **16e** (13.9 mg, 0.04 mmol), DMAP (9.5 mg, 0.08 mmol), and Et₃N (22.3 mg, 0.2 mmol) in anhydrous CHCl₃ (2.0 mL) at rt, and the mixture was stirred at rt for 1.5 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was purified by p-TLC on SiO₂ developed with CHCl₃–MeOH (99:1, v/v). Extraction of the band having an *R_f* value of 0.40–0.30 with CHCl₃–MeOH (95:5, v/v) gave **16g** (15.0 mg, 71%). **16g**: colorless solid. IR (KBr): 2927, 1797, 1765, 1732, 1456, 1273, 1252, 1149 cm⁻¹. ¹H-NMR (pyridine-d₅) δ: 0.77–0.87 (2H, m), 1.09–1.26 (3H, m), 1.46–1.69 (7H, m), 1.57 (9H, s), 1.64 (9H, s), 1.72–1.91 (3H, m), 1.99 (1H, br d, *J*=13.2 Hz), 2.33 (2H, d, *J*=6.6 Hz), 2.98 (1H, dt, *J*=15.1, 2.8 Hz), 3.51 (1H, t, *J*=13.3 Hz), 4.01 (1H, dd, *J*=12.6, 3.8 Hz), 4.48 (1H, br d, *J*=7.0 Hz), 8.18 (1H, s). HR-MS *m/z*: Calcd for C₂₉H₄₁BrN₂O₆: 594.2128, 592.2148. Found: 594.2127, 592.2136.

7-Acetoxy-5-cyclohexylmethyl-2,2a,3,4,5,6-hexahydro-6-methyl-1*H*-azepino[5,4,3-*cd*]indole (17) from 10d — Acetic anhydride (1.0 mL) was added to a solution of **10d** (19.3 mg, 0.07 mmol) in pyridine (2.0 mL) at rt, and the mixture was stirred at rt for 3 h. The resulting mixture was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% NH₄OH (46:1:0.1, v/v) to give **17** (19.0 mg, 86%). **17**: yellow oil. IR (film): 3400, 3246, 2924, 2850, 1751, 1435, 1369 cm⁻¹. ¹H-NMR (pyridine-d₅) δ: 0.79–0.89 (2H, m), 1.10 (1H, tt, *J*=12.5, 3.2 Hz), 1.18–1.27 (3H, m), 1.56–1.72 (6H, m), 1.85 (2H, br t, *J*=12.9 Hz), 2.32 (3H, s), 2.61–2.65 (1H, m), 2.81 (1H, dd, *J*=12.8, 6.7 Hz), 3.00 (1H, br d, *J*=16.4 Hz), 3.15–3.22 (1H, m), 3.37 (1H, ddd, *J*=16.4, 12.5, 4.3 Hz), 3.74 (1H, br t, *J*=13.4 Hz), 4.82 (1H, br s), 7.07 (1H, d, *J*=8.5 Hz), 7.30 (1H, s), 7.38 (1H, d, *J*=8.5 Hz). HR-MS *m/z*: Calcd for C₂₁H₂₈N₂O₂: 340.2151. Found: 340.2145

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