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

<table>
<thead>
<tr>
<th>著者</th>
<th>岩田 孝治, 寺内 佐知子, 宮島 花子, 石倉 実男, 今井 俊ノリ</th>
</tr>
</thead>
<tbody>
<tr>
<td>書籍名</td>
<td>Heterocycles</td>
</tr>
<tr>
<td>号数</td>
<td>83</td>
</tr>
<tr>
<td>巻数</td>
<td>11</td>
</tr>
<tr>
<td>ページ範囲</td>
<td>2547-2562</td>
</tr>
<tr>
<td>発行年月日</td>
<td>2011-10-31</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2297/29567">http://hdl.handle.net/2297/29567</a></td>
</tr>
</tbody>
</table>

doi: 10.3987/COM-11-12345
A NOVEL SYNTHESIS OF 3,4,5,6-TETRAHYDRO-7-HYDROXY-1H-azerpine[5,4,3-cd]indole derivatives from serotonin

Koji Yamada, a Sakiko Teranishi, b Ayako Miyashita, b Minoru Ishikura, a and Masanori Somei a,b,c

 a Faculty of Pharmaceutical Sciences, Health Science University of Hokkaido, Ishikari-Tobetsu, Hokkaido, 061-0293, Japan
 b Faculty of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan
e-mail address: somei.home@topaz.plala.or.jp

Abstract – Utilizing novel Nb-substituted serotonins, 5- and/or 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1H-azerpine[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-1H-azerpine[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 a,b,c,d with high originality rate, e intellectual property factor, e,f and application potential factor a,b,c,d,e,f culminating in the production of novel leads for an α5-blocker, f,g an inhibitor of platelet aggregation, f,g,h an anti-osteoporosis agent, f,g,h,i and potent root growth promotor. f,g,h,i These results are based on our hypothesis f,g,h,i 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. g,h,i

**Figure 1**
Tryptamine\(^{10}\) (1a), serotonin\(^{11}\) (1b), aurantioclavine\(^{12}\) (2a), and clavicipitic acid\(^{12}\) (2b) are well known natural products metabolized from tryptophan (Figure 1). Tryptamine (1a) is a minor amine in our body and its function has not been established yet.\(^{10}\) We created Nb-acyltryptamines (1c) and found them having potent activity as an \(\alpha_2\)-blocker.\(^{3c,4,5}\) Recently, we have also disclosed that 1c is an inhibitor for osteoblast differentiation\(^{13}\) and apoptosis,\(^{14}\) and even a stimulator of mineralization in osteoblasts.\(^ {14}\) Serotonin (1b) is an important chemical transmitter in the central nervous system.\(^{11}\) Aurantioclavine (2a), and clavicipitic acid (2b) are members of ergot alkaloid.\(^{12}\)

According to our hypothesis,\(^{8,9}\) when we unite the skeleton of 1b with that of 1c, 2a, and 2b, we get novel chimera compounds such as Nb-substituted serotonin derivatives (3) and 3,4,5,6-tetrahydro-7-hydroxy-1H-azepino[5,4,3-cd]indole derivatives (4). In addition, we can expect that compounds 1c would be metabolized in our body to the corresponding 5-hydroxy compounds (3). The multimodal bioactivity of 1c might be originated from the function of 3 themselves. Therefore, we could expect 3 and 4 to become useful candidates for new biologically active substances.

**Scheme 1**

On the other hand, in our preliminary study\(^ {15}\) aiming at the synthesis of both compounds, 3 and 4, we reported an interesting finding that under basic conditions the reaction of 1b with acetaldehyde and benzaldehyde generated 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1H-azepino[5,4,3-cd]indoles (5), despite under acidic conditions the well known Pictet-Spengler\(^ {16}\) reaction took place resulting in the formation of 1-substituted 6-hydroxy-\(\beta\)-carbolines (6, Scheme 1).

With an attempt to enlarge the scope of our above findings and to find new biologically active compounds, we now wish to describe the preparation of novel Nb-substituted serotonins (3) and 5- and/or 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1H-azepino[5,4,3-cd]indole derivatives (4).

**I. Synthesis of Novel Nb-Substituted Serotonins**

To meet our end, we needed various Nb-substituted serotonin derivatives. They are obtained by acylation of serotonin, followed by reduction of the resultant Nb-acylated serotonin derivatives (Scheme 2). Thus, serotonin hydrochloride (1b-HCl) was reacted with pentanoic acid by mixed anhydride method using methyl chloroformate in DMF–CHCl\(_3\) in the presence of Et\(_3\)N at room temperature to give Nb-pentanoylserotonin (7a) in 92% yield. Similar reactions of 1b-HCl with nonanoic acid, hexadecanoic acid, cyclohexanecarboxylic acid, and benzoic acid afforded Nb-nonanoyl- (7b), Nb-hexadecanoyl- (7c),
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-cyclohexymethylserotonins (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 benzylaion 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 serotoninins 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-1H-azepino[5,4,3-
cd]indole Derivatives  
Employing our basic conditions¹⁵ to the reaction of the above-mentioned Nb-substituted serotoninins 
(8a—e) with aldehydes, selective preparation of various 5- and 6-substituted 3,4,5,6-tetrahydro-7-
hydroxy-1H-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-1H-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-1H-azepino[5,4,3-cd]indole (12a) was 
obtained in 91% yield by the reductive debenzylation 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-1H-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-1H-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-1H-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](image)

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

Treatment of 5-benzyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-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-1H-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-1H-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-1H-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-1H-azepino[5,4,3-cd]indole-2-ones.

**Scheme 3**

In conclusion, we established that our reaction of serotonins with aldehydes under basic conditions is a general and convenient synthetic method for creating novel 7-hydroxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indoles. We also succeeded in the synthesis of novel 2,2a,3,4,5,6-hexahydro-7-hydroxy-1H-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.

**N⁶-Pentanoylserotonin (7a) from Serotonin-HCl (1b-HCl) — General procedure:** a solution of CICO₂Me (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 H$_2$O, the whole was extracted with CHCl$_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na$_2$SO$_4$, and 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 7a (583.2 mg, 92%). 7a: colorless viscous oil. IR (film): 3309, 1628, 1541, 1458, 1188 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 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 D$_2$O), 5.57 (2H, br s, disappeared on addition of D$_2$O), 6.80 (1H, dd, $J$=8.5, 2.2 Hz), 6.99 (1H, d, $J$=1.7 Hz, collapsed to s on addition of D$_2$O), 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 D$_2$O). HR-MS m/z: Calcd for C$_{15}$H$_{20}$N$_2$O$_2$: 260.1525. Found: 260.1520.

**Nb-Nonanoylserotonin (7b) from 1b-HCl** — In the general procedure, CICO$_2$Me (252.9 mg, 2.7 mmol), anhydrous CHCl$_3$ (5.0 mL), nonanoic acid (426.1 mg, 2.7 mmol), Et$_3$N (544.4 mg, 5.4 mmol), anhydrous CHCl$_3$ (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$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 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 D$_2$O), 5.35 (1H, br s, disappeared on addition of D$_2$O), 5.50 (1H, br t, $J$=6.8 Hz, disappeared on addition of D$_2$O), 6.80 (1H, dd, $J$=8.5, 2.2 Hz), 6.99 (1H, d, $J$=2.0 Hz, collapsed to s on addition of D$_2$O), 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 D$_2$O). HR-MS m/z: Calcd for C$_{19}$H$_{28}$N$_2$O$_2$: 316.2151. Found: 316.2146.

**Nb-Hexadecanoylserotonin (7c) from 1b-HCl** — In the general procedure, CICO$_2$Me (252.5 mg, 2.7 mmol), anhydrous CHCl$_3$ (5.0 mL), hexadecanoic acid (690.3 mg, 2.7 mmol), Et$_3$N (544.3 mg, 5.4 mmol), anhydrous CHCl$_3$ (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 CHCl$_3$–MeOH). IR (KBr): 3415, 3307, 2918, 2848, 1635, 1541 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) $\delta$: 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 D$_2$O), 4.93 (1H, br s, disappeared on addition of D$_2$O), 5.51 (1H, br t, $J$=6.8 Hz, disappeared on addition of D$_2$O), 6.79 (1H, dd, $J$=8.5, 2.2 Hz), 7.01 (1H, d, $J$=2.0 Hz, collapsed to s on addition of D$_2$O), 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 D$_2$O). MS m/z: 414 (M$^+$$\cdot$). Anal. C$_{26}$H$_{42}$N$_2$O$_2$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.05; H, 10.38; N, 6.72.

**Nb-Cyclohexylcarboxylyserotonin (7d) from 1b-HCl** — In the general procedure, CICO$_2$Me (486.9 mg, 5.2 mmol), anhydrous CHCl$_3$ (10 mL), cyclohexanecarboxylic acid (655.3 mg, 5.2 mmol), Et$_3$N (1.07 g, 10.3 mmol), anhydrous CHCl$_3$ (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-d₆) 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 D₂O), 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=5.5Hz, disappeared on addition of D₂O), 8.55 (1H, br s, disappeared on addition of D₂O), 10.41 (1H, br s, disappeared on addition of D₂O). HR-MS m/z: Calcld for C₁₈H₂₂N₂O₂: 286.1681. Found: 286.1682.

**Nb-Benzoylserotonin (7e) from 1b-HCl** — In the general procedure, ClCO₂Me (103.4 mg, 1.1 mmol), anhydrous CHCl₃ (2.0 mL), benzoic acid (127.0 mg, 1.0 mmol), Et₃N (212.5 mg, 2.1 mmol), anhydrous CHCl₃ (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 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3425, 1645, 1537, 1377, 1186, 939, 850, 795, 710, 625 cm⁻¹. ¹H-NMR (DMSO-d₆) 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 D₂O), 10.46 (1H, br s). MS m/z: 280 (M⁺). Anal. Calcld for C₁₉H₁₆N₂O₂: 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: LiAlH₄ (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 CHCl₃. 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–28% NH₄OH (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 (CDCl₃) 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 D₂O). HR-MS m/z: Calcld for C₁₅H₁₆N₂O₂: 246.1732. Found: 246.1737.

**Nb-Nonylserotonin (8b) from 7b** — In the general procedure, LiAlH₄ (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 (CDCl₃) 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 D₂O). HR-MS m/z: Calcld for C₁₉H₁₈N₂O₂: 302.2358. Found: 302.2359.

**Nb-Hexadecylserotonin (8c) from 7c** — In the general procedure, LiAlH₄ (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. 
¹H-NMR (CDCl₃) 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 D₂O). HR-MS m/z: Calcd for C₉₂H₄₅N₂O: 400.3453. Found: 400.3460.

Nb-Cyclohexylnethylserotonin (8d) from 7d — In the general procedure, LiAlH₄ (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. ¹H-NMR (CDCl₃) 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 D₂O), 7.19 (1H, d, J=8.8 Hz), 7.93 (1H, br s, disappeared on addition of D₂O). HR-MS m/z: Calcd for C₁₇H₂₄N₂O: 272.1889. Found: 272.1885.

Nb-Benzylserotonin (8e) from 7e — In the general procedure, LiAlH₄ (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. ¹H-NMR (CDCl₃) δ: 2.90–2.92 (2H, m), 2.95–2.98 (2H, m), 3.60 (2H, br s, disappeared on addition of D₂O), 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 D₂O), 7.16 (1H, d, J=8.7 Hz), 7.20–7.29 (5H, m), 7.97 (1H, br s, disappeared on addition of D₂O). HR-MS m/z: Calcd for C₁₇H₁₉₂N₂O: 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 NaCNBH₃ (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 H₂O, the whole was made alkaline (pH=9) with 8% NaOH and extracted with AcOEt. 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–28% NH₄OH (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 Et₃N (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 SiO₂ with CHCl₃–MeOH–28% NH₄OH (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. ¹H-NMR (CDCl₃) 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 C₁₇H₁₅N₂O: 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 C₂₁H₂₅N₂O: 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 C₂₃H₄₆N₂O: 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. ¹H-NMR (CDCl₃) 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 C₁₉H₂₀N₂O: 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 Et₃N (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 SiO₂ with CHCl₃-MeOH–28% NH₄OH (46:1:0.1, v/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. ¹H-NMR (CDCl₃) 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 D₂O). HR-MS m/z: Calcd for C₂₂H₂₄N₂O: 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 Et₃N (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. ¹H-NMR (CDCl₃) 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 D₂O), 4.47 (1H, br dd, J=10.0, 4.5 Hz), 6.64 (1H, d, J=8.3 Hz), 6.91 (1H, brs), 7.02 (1H, d, J=8.3 Hz), 7.83 (1H, br s, disappeared on addition of D₂O). HR-MS m/z: Calcd for C₂₅H₂₆N₂O: 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 Et₃N (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. ¹H-NMR (CDCl₃) 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 C₃₆H₆₂N₂O₅: 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 (CD₂OD) 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 C₁₉H₁₄N₂O: 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 C₁₉H₁₈N₂O₅: 286.1318. Found: 286.1313.

5-tert-Butoxycarbonyl-7-tert-butoxy carbonyloxy-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 C₂₂H₂₀N₂O₅: 402.2155. Found: 402.2152.

3,4,5,6-Tetrahydro-7-hydroxy-5-pentyl-6-phenyl-1H-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 C₂₂H₁₉N₅O: 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-1H-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 C₁₉H₂₂N₂O: 300.2202. Found: 300.2203.

5-Benzyl-8-bromo- (16a) and 5-Benzyl-2,2a,3,4,5,6-hexahydro-7-hydroxy-6-methyl-1H-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 CHCl₃–hexane). IR (KBr): 1705, 1620, 1599, 1450, 1313 cm⁻¹. ¹H-NMR (pyridine-d₅) 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 D₂O). HR-MS m/z: Calcd for C₁₉H₁₉BrN₂O₃: 388.0610, 386.0630. Found: 388.0598, 386.0625. Anal. Calcd for C₁₉H₁₉BrN₂O₃: 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-d₅, 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 D₂O). HR-MS m/z: Calcd for C₁₉H₁₉BrN₂O₃: 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 CH₂N₂ in Et₂O 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 SiO₂ with CHCl₃–MeOH (99:1, v/v) to give 16b (40.3 mg, 95%). 16b: mp 168—169 °C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 1701, 1604, 1452 cm⁻¹. ¹H-NMR (pyridine-d₅) 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 D₂O). MS m/z: 402 (M⁺), 400 (M⁺). Anal. Calcd for C₂₀H₂₁BrN₂O₂·1/2H₂O: 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 SiO₂ with CHCl₃–MeOH (98:2, v/v) to give 16c (33.0 mg, 88%). 16c: mp 242—244 °C (decomp., colorless powder, recrystallized from CHCl₃–hexane). IR (KBr): 1772, 1722, 1614 cm⁻¹. ¹H-NMR (pyridine-d₅, 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 D₂O). HR-MS m/z: Calcd for C₂₁H₂₃BrN₂O₃: 430.0715, 428.0736. Found: 430.0736, 428.0748. Anal. Calcd for C₂₁H₂₃BrN₂O₃·1/2H₂O: 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 CHCl₃ (1.0 mL) was added to a solution of 16a (22.6 mg, 0.06 mmol), DMAP (4.0 mg, 0.03 mmol), and Et₃N (29.2 mg, 0.3 mmol) in anhydrous CHCl₃ (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 SiO₂ developed with CHCl₃. Extraction of the band having an Rf value of 0.23—0.13 with CHCl₃–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-d₅) 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 C₃₀H₂₉BrN₂O₅: 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 Br₂ in AcOH [prepared with Br₂ (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% Na₂S₂O₃ (0.2 mL), the whole 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 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-d₅) 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 q, 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 D₂O), 11.58 (1H, s, disappeared on addition of D₂O). HR-MS m/z: Calcd for C₁₀H₂₉BrN₂O₅: 394.1079, 392.1099. Found: 394.1080, 392.1093. 15b: yellow oil. IR (film): 3255, 2924, 1689, 1467 cm⁻¹. ¹H-NMR (pyridine-d₅) 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 q, 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 D₂O), 11.31 (1H, s, disappeared on addition of D₂O). HR-MS m/z: Calcd for C₁₀H₁₉N₂O₅: 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 C₂₁H₂₁BrN₂O₂: 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-1H-azepino[5,4,3-cd]indol-2-one (16g) from 16e — A solution of di-tert-butyldicarbonate (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 Rf 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-1H-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

REFERENCES AND NOTES

2. Professor Emeritus of Kanazawa University. Present address: Matshidai 56-7, Matsudo, Chiba 270-
2214, Japan.