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

HETEROCYCLES, Vol. , No. , , pp. -,
Received, , Accepted, , Published online, (Please do not delete.)

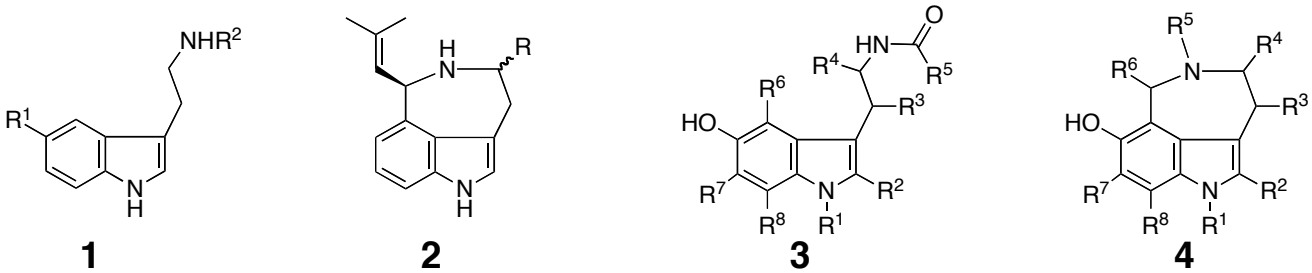
# A NOVEL SYNTHESIS OF 3,4,5,6-TETRAHYDRO-7-HYDROXY-1*H*-AZEPINO[5,4,3-*cd*]INDOLE DERIVATIVES FROM SEROTONIN[1]

**Koji Yamada,[a] Sakiko Teranishi,[b] Ayako Miyashita,[b] Minoru Ishikura,[a] and Masanori Somei*[b,2]**

[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 *N*b-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 $\alpha_2$-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]




**1** **2** **3** **4**

**a**) $R^1 = R^2 = H$
**b**) $R^1 = OH$, $R^2 = H$
**c**) $R^1 = H$, $R^2$ = acyl

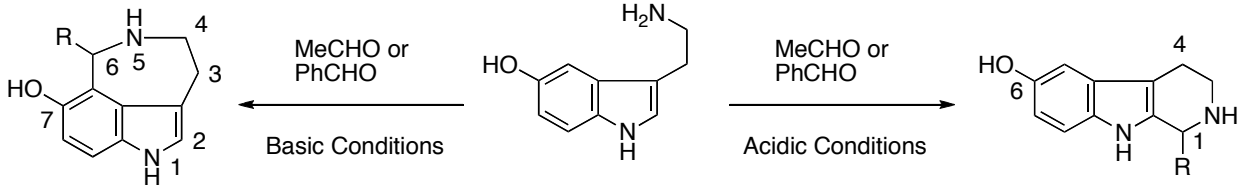
**a**) R = H; **b**) R = $CO_2H$

$R^1$—$R^8$ = an appropriate substituent

**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 *N*b-acyltryptamines (**1c**) and found them having potent activity as an $\alpha_2$-blocker.[3c,d,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 *N*b-substituted serotonin derivatives (**3**) and 3,4,5,6-tetrahydro-7-hydroxy-1*H*-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.




**5** R = Me or Ph — **1b** — **6** R = Me or Ph

**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-1*H*-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-β-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 *N*b-substituted serotonins (**3**) and 5- and/or 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole derivatives (**4**).

**I. Synthesis of Novel *N*b-Substituted Serotonins**

To meet our end, we needed various *N*b-substituted serotonin derivatives. They are obtained by acylation of serotonin, followed by reduction of the resultant *N*b-acylated serotonins (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 $Et_3N$ at room temperature to give *N*b-pentanoylserotonin (**7a**) in 92% yield. Similar reactions of **1b**·HCl with nonanoic acid, hexadecanoic acid, cyclohexanecarboxylic acid, and benzoic acid afforded *N*b-nonanoyl- (**7b**), *N*b-hexadecanoyl- (**7c**),

*N*b-cyclohexylcarbonyl- (**7d**), and *N*b-benzoylserotonins (**7e**) in 96, 88, 97, and 90% yields, respectively. Subsequent reduction of **7a** with $LiAlH_4$ in refluxing THF afforded *N*b-pentylserotonin (**8a**) in 85% yield. The compounds, **7b**, **7c**, and **7d**, were similarly converted to *N*b-nonyl- (**8b**), *N*b-hexadecyl- (**8c**), and *N*b-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 *N*b-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 $LiAlH_4$ 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 *N*b-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 conditions[15] to the reaction of the above-mentioned *N*b-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.

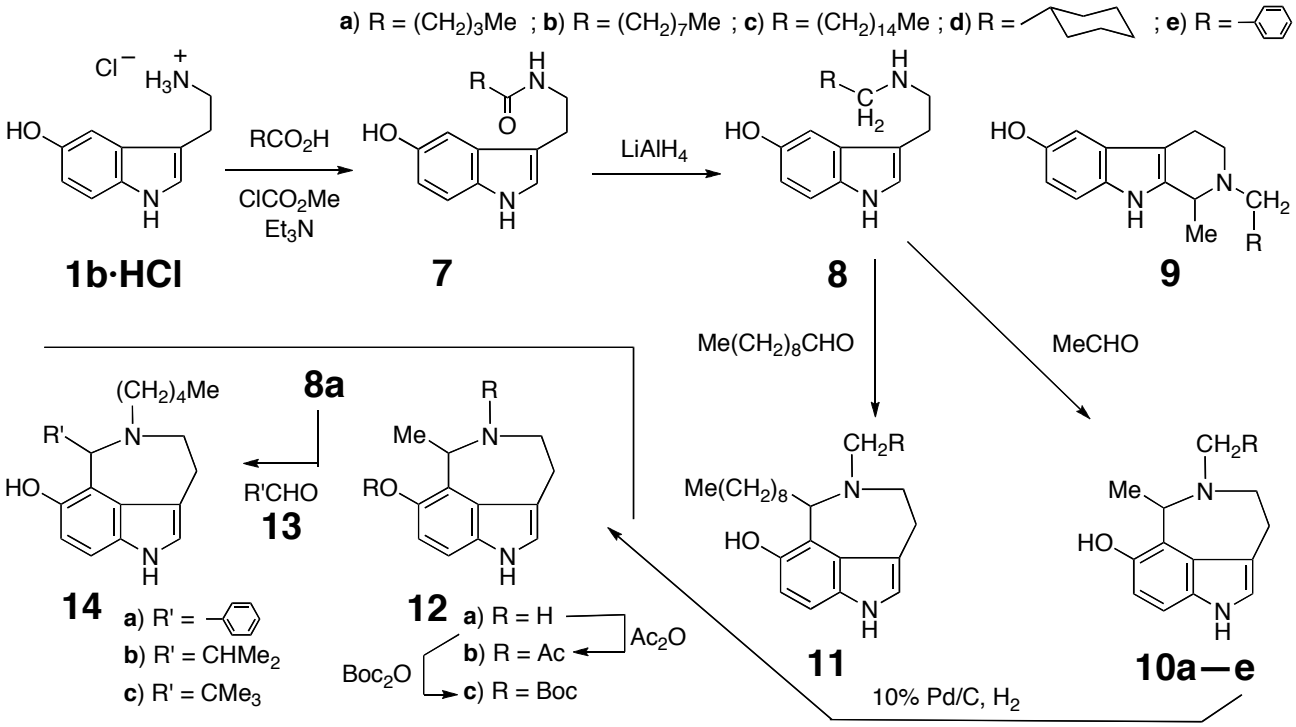
Thus, the reaction of **8a** with acetaldehyde in $Et_3N$-MeOH at room temperature for 2.5 h afforded 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-5-pentyl-1*H*-azepino[5,4,3-*cd*]indole (**10a**) in 90% yield without the formation of the corresponding β-carboline (**9a**). Under similar reaction conditions, **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 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 $Ac_2O$ and $Boc_2O$ 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 $Et_3N$-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 $Et_3N$. The mechanism of the formation of acetaldehyde from $Et_3N$ in the reaction system is explained in detail in our previous paper.[15]



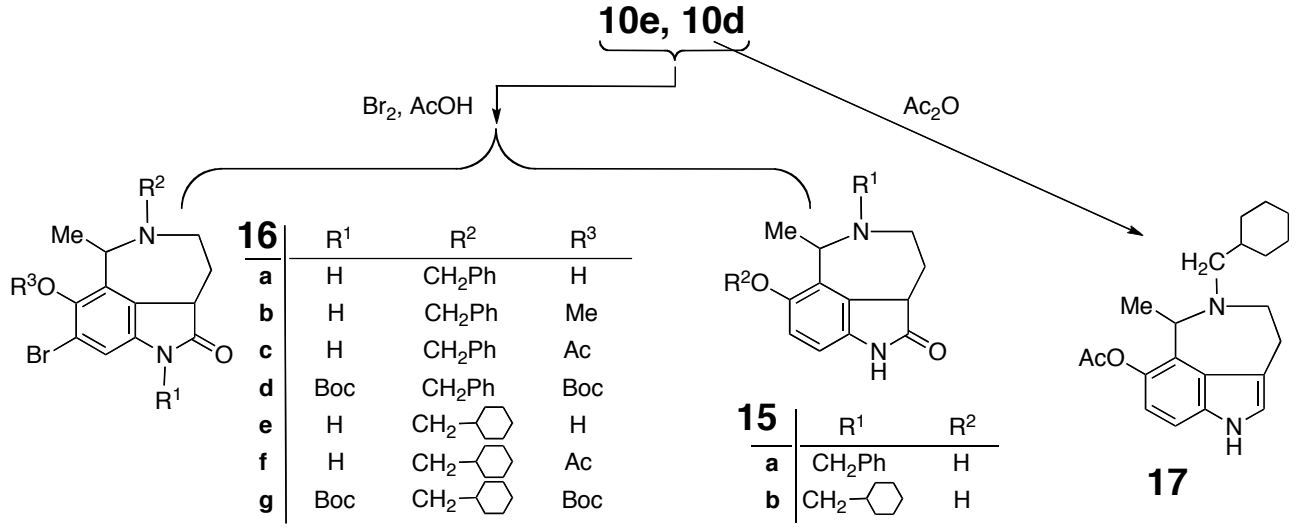

**Scheme 2**

**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 $Ac_2O$ in pyridine gave **17** and **16c** in 86 and 88% yields, respectively, while the reaction of **16a** with

$Boc_2O$ in the presence of DMAP provided **16d** in 46% yield. Similar reactions of **16e** with $Ac_2O$ and $Boc_2O$ 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 serotonins 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 $^1$H-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 $GF_{245}$ (Type 60) ($SiO_2$). Column chromatography was performed on silica gel ($SiO_2$, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

***N*b-Pentanoylserotonin (7a) from Serotonin·HCl (1b·HCl)** — **General procedure**: a solution of $ClCO_2Me$ (254.0 mg, 2.7 mmol) in anhydrous $CHCl_3$ (5.0 mL) was added to a solution of pentanoic acid (275.0 mg, 2.7 mmol) and $Et_3N$ (545.1 mg, 5.4 mmol) in anhydrous $CHCl_3$ (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 $H_2O$, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). 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 (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 ($CDCl_3$) 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 $D_2O$), 5.57 (2H, br s, disappeared on addition of $D_2O$), 6.80 (1H, dd, *J*=8.5, 2.2 Hz), 6.99 (1H, d, *J*=1.7 Hz, collapsed to s on addition of $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1520.

***N*b-Nonanoylserotonin (7b) from 1b·HCl** — In the general procedure, $ClCO_2Me$ (252.9 mg, 2.7 mmol), anhydrous $CHCl_3$ (5.0 mL), nonanoic acid (426.1 mg, 2.7 mmol), $Et_3N$ (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 ($CDCl_3$) 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 $D_2O$), 5.35 (1H, br s, disappeared on addition of $D_2O$), 5.50 (1H, br t, *J*=6.8 Hz, disappeared on addition of $D_2O$), 6.80 (1H, dd, *J*=8.5, 2.2 Hz), 6.99 (1H, d, *J*=2.0 Hz, collapsed to s on addition of $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{19}H_{28}N_2O_2$: 316.2151. Found: 316.2146.

***N*b-Hexadecanoylserotonin (7c) from 1b·HCl** — In the general procedure, $ClCO_2Me$ (252.5 mg, 2.7 mmol), anhydrous $CHCl_3$ (5.0 mL), hexadecanoic acid (690.3 mg, 2.7 mmol), $Et_3N$ (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 ($CDCl_3$) 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 $D_2O$), 4.93 (1H, br s, disappeared on addition of $D_2O$), 5.51 (1H, br t, *J*=6.8 Hz, disappeared on addition of $D_2O$), 6.79 (1H, dd, *J*=8.5, 2.2 Hz), 7.01 (1H, d, *J*=2.0 Hz, collapsed to s on addition of $D_2O$), 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 $D_2O$). MS *m/z*: 414 ($M^+$). *Anal.* $C_{26}H_{42}N_2O_2$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.05; H, 10.38; N, 6.72.

***N*b-Cyclohexylcarbonylserotonin (7d) from 1b·HCl** — In the general procedure, $ClCO_2Me$ (486.9 mg, 5.2 mmol), anhydrous $CHCl_3$ (10 mL), cyclohexanecarboxylic acid (655.3 mg, 5.2 mmol), $Et_3N$ (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 $cm^{-1}$. $^1$H-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*=5.5Hz, 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 $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1682.

***N*b-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 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3425, 1645, 1537, 1377, 1186, 939, 850, 795, 710, 625 $cm^{-1}$. $^1$H-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 $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.73; H, 5.72; N, 9.86.

***N*b-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 $cm^{-1}$. $^1$H-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 $C_{15}H_{22}N_2O$: 246.1732. Found: 246.1737.

***N*b-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 $cm^{-1}$. $^1$H-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 $C_{19}H_{30}N_2O$: 302.2358. Found: 302.2359.

***N*b-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 $cm^{-1}$. $^1$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 $C_{26}H_{44}N_2O$: 400.3453. Found: 400.3460.

***N*b-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 $cm^{-1}$. $^1$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 $C_{17}H_{24}N_2O$: 272.1889. Found: 272.1885.

***N*b-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 $cm^{-1}$. $^1$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 $C_{17}H_{18}N_2O$: 266.1420. Found: 266.1418.

***N*b-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-1*H*-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 $cm^{-1}$. $^1$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 $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{17}H_{24}N_2O$: 272.1889. Found: 272.1888.

**3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-5-nonyl-1*H*-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 $Et_3N$ (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 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) 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 $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{21}H_{32}N_2O$: 328.2514. Found: 328.2505.

**5-Hexadecyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-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 $Et_3N$ (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 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) 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 $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{28}H_{46}N_2O$: 426.3610. Found: 426.3613.

**5-Cyclohexylmethyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-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 $Et_3N$ (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 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{19}H_{26}N_2O$: 298.2046. Found: 298.2051.

**5-Benzyl-3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-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 $Et_3N$ (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 $cm^{-1}$. $^1$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 $C_{19}H_{20}N_2O$: 292.1576. Found: 292.1573.

**3,4,5,6-Tetrahydro-7-hydroxy-6-nonyl-5-pentyl-1*H*-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 $cm^{-1}$. $^1$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 $C_{25}H_{40}N_2O$: 384.3140. Found: 384.3130.

**3,4,5,6-Tetrahydro-7-hydroxy-5,6-dinonyl-1*H*-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 $cm^{-1}$. $^1$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*=15.9Hz), 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, brs), 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 $C_{29}H_{48}N_2O$: 440.3766. Found: 440.3761.

**5-Hexadecyl-3,4,5,6-tetrahydro-7-hydroxy-6-nonyl-1*H*-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 $cm^{-1}$. $^1$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

$D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{36}H_{62}N_2O$: 538.4862. Found: 538.4876.

**3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-1*H*-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 $SiO_2$ with $CHCl_3$–MeOH–28% $NH_4OH$ (46:10:1, v/v) to give **12a** (15.8 mg, 91%). **12a**: pale brown oil. IR (film): 3399, 3299, 1579, 1417, 794 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) 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 $C_{12}H_{14}N_2O$: 202.1107. Found: 202.1110.

**7-Acetoxy-5-acetyl-3,4,5,6-tetrahydro-6-methyl-1*H*-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 $SiO_2$ with $CHCl_3$–MeOH (98:2, v/v) to give **12b** (63.1 mg, 95%). **12b**: pale brown foam. IR (KBr): 1755, 1628, 1616, 1425 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 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 $D_2O$), 8.23 (5/7H, br s, disappeared on addition of $D_2O$). MS *m/z*: 286 ($M^+$). HR-MS *m/z*: Calcd for $C_{16}H_{18}N_2O_3$: 286.1318. Found: 286.1313.

**5-*tert*-Butoxycarbonyl-7-*tert*-butoxycarbonyloxy-3,4,5,6-tetrahydro-6-methyl-1*H*-azepino[5,4,3-*cd*]-indole (12c) from 12a** — A solution of di-*tert*-butyl dicarbonate (45.6 mg, 0.2 mmol) in anhydrous $CHCl_3$ (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 $CHCl_3$ (1.0 mL) at rt and the mixture was stirred at rt for 1 h. After addition of $H_2O$, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). 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 (98:2, v/v) to give **12c** (13.7 mg, 52%). **12c**: colorless viscous oil. IR (film): 3386, 2979, 1757, 1691, 1668 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{22}H_{30}N_2O_5$: 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 $Et_3N$ (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 $SiO_2$ with $CHCl_3$–MeOH–28% $NH_4OH$ (46:1:0.1, v/v) to give **14a** (35.8 mg, 86%). **14a**: mp 166—168 °C (colorless powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3448, 3273, 2952, 2931, 1583, 1491, 1435, 1378 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) 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 $D_2O$), 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 $D_2O$). MS *m/z*: 334 ($M^+$). *Anal*. Calcd for $C_{22}H_{26}N_2O$: 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 $Et_3N$ (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 $SiO_2$ with $CHCl_3$–MeOH–28% $NH_4OH$ (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 ($CDCl_3$) 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 $D_2O$), 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{19}H_{28}N_2O$: 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 $Br_2$ in AcOH [prepared with $Br_2$ (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% $Na_2S_2O_3$ (ca. 0.5 mL), the whole was evaporated under reduced pressure to leave a residue, which was column-chromatographed on $SiO_2$ with $CHCl_3$–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 $cm^{-1}$. $^1$H-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 $C_{19}H_{19}BrN_2O_2$: 388.0610, 386.0630. Found: 388.0598, 386.0625. *Anal.* Calcd for $C_{19}H_{19}BrN_2O_2$: 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 $cm^{-1}$. $^1$H-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 $C_{19}H_{20}N_2O_2$: 308.1525. Found: 308.1506.

**5-Benzyl-8-bromo-2,2a,3,4,5,6-hexahydro-7-methoxy-6-methyl-1*H*-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 $cm^{-1}$. $^1$H-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 $C_{20}H_{21}BrN_2O_2 \cdot 1/2H_2O$: 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-1*H*-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 $cm^{-1}$. $^1$H-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 $C_{21}H_{21}BrN_2O_3$: 430.0715, 428.0736. Found: 430.0736, 428.0748. *Anal.* Calcd for $C_{21}H_{21}BrN_2O_3 \cdot 1/2H_2O$: 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-1*H*-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 *Rf* 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 $cm^{-1}$. $^1$H-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 $C_{29}H_{35}BrN_2O_6$: 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-1*H*-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% $Na_2S_2O_3$ (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 $cm^{-1}$. $^1$H-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 $C_{19}H_{25}BrN_2O_2$: 394.1079, 392.1099. Found: 394.1080, 392.1093. **15b**: yellow oil. IR (film): 3255, 2924, 1689, 1467 $cm^{-1}$. $^1$H-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 $C_{19}H_{26}N_2O_2$: 314.1994. Found: 314.1989.

**7-Acetoxy-8-bromo-5-cyclohexylmethyl-2,2a,3,4,5,6-hexahydro-6-methyl-1*H*-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 $SiO_2$ with $CHCl_3$–MeOH–28% $NH_4OH$ (46:2:0.2, v/v) to give **16f** (20.8 mg, 83%). **16f**: colorless solid. IR (KBr): 2924, 1768, 1716, 1612 $cm^{-1}$. $^1$H-NMR (pyridine-$d_5$) 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 $D_2O$). HR-MS *m/z*: Calcd for $C_{21}H_{27}BrN_2O_3$: 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 $CHCl_3$ (3.0 mL) was added to a solution of **16e** (13.9 mg, 0.04 mmol), DMAP (9.5 mg, 0.08 mmol), and $Et_3N$ (22.3 mg, 0.2 mmol) in anhydrous $CHCl_3$ (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 $SiO_2$ developed with $CHCl_3$–MeOH (99:1, v/v). Extraction of the band having an *Rf* value of 0.40—0.30 with $CHCl_3$–MeOH (95:5, v/v) gave **16g** (15.0 mg, 71%). **16g**: colorless solid. IR (KBr): 2927, 1797, 1765, 1732, 1456, 1273, 1252, 1149 $cm^{-1}$. $^1$H-NMR (pyridine-$d_5$) 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 $C_{29}H_{41}BrN_2O_6$: 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 $SiO_2$ with $CHCl_3$–MeOH–28% $NH_4OH$ (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 $cm^{-1}$. $^1$H-NMR (pyridine-$d_5$) 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 $C_{21}H_{28}N_2O_2$: 340.2151. Found: 340.2145

## REFERENCES AND NOTES


1. a) This report is Part 138 of a series entitled "The Chemistry of Indoles"; b) Part 137: K. Yamada and M. Somei, *Heterocycles*, 2011, **84**, COM-11-S(P)56MS, in press.
2. Professor Emeritus of Kanazawa University. Present address: Matsuhidai 56-7, Matsudo, Chiba 270-

2214, Japan.

3. a) M. Somei, *Heterocycles*, 2011, **82**, 1007; b) M. Somei, S. Sayama, K. Naka, K. Shinmoto, and F. Yamada, *Heterocycles*, 2007, **73**, 537; c) M. Somei, *Chemistry*, 2007, **62**, 116; d) M. Somei, T. Iwaki, F. Yamada, Y. Tanaka, K. Shigenobu, K. Koike, N. Suzuki, and A. Hattori, *Heterocycles*, 2006, **68**, 1565.
4. a) Synthetic philosophy: M. Somei, *Heterocycles*, 2008, **75**, 1021; b) Definitions of intellectual property and application potential factors: M. Somei, F. Yamada, Y. Suzuki, S. Ohmoto, and H. Hayashi, *Heterocycles*, 2004, **64**, 483; c) Definition of originality rate: M. Somei, Y. Fukui, M. Hasegawa, N. Oshikiri, and T. Hayashi, *Heterocycles*, 2000, **53**, 1725; d) M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361; e) M. Somei, *J. Synth. Org. Chem. Jpn.*, 1982, **40**, 387.
5. K. Yamada, Y. Tanaka, and M. Somei, *Heterocycles*, 2009, **79**, 635 and references cited therein.
6. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, *Heterocycles*, 1996, **43**, 1855.
7. N. Suzuki, M. Somei, A. Seki, R. J. Reiter, and A. Hattori, *J. Pineal Res.*, 2008, **45**, 229; N. Suzuki, M. Somei, K. Kitamura, R. J. Reiter, and A. Hattori, *J. Pineal Res.*, 2008, **44**, 326.
8. M. Somei, *Yakugaku Zasshi*, 2008, **128**, 527.
9. M. Somei, Topics in Heterocyclic Chemistry, Vol. **6**, ed. by S. Eguchi, Springer-Verlag, Berlin, 2006, p. 77; M. Somei, Advances in Heterocyclic Chemistry, Vol. **82**, ed. by A. R. Katritzky, Elsevier Science, USA, 2002, p. 101; M. Somei, *Heterocycles*, 1999, **50**, 1157; M. Somei, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 205; M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251.
10. R. S. Jones, *Progress in Neurobiology*, 1982, **19**, 117.
11. A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta*, 1955, **38**, 1452 and references cited therein; M. M. Rapport, *J. Biol. Chem.*, 1949, **180**, 961; M. M. Rapport, A. A. Green, and I. H. Page, *Science*, 1948, **108**, 329; M. M. Rapport, A. A. Green, and I. H. Page, *J. Biol. Chem.*, 1948, **176**, 1237.
12. M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi, and T. Naito, "The Alkaloids," Vol. 54, ed. by G. A. Cordell, Academic Press, 2000, p. 191 and references cited therein.
13. Y. Mikami, M. Somei, and M. Takagi, *J. Biochem.,* 2009, **145**, 239.
14. Y. Mikami, M. Somei, and M. Takagi, *Endocrine Journal*, 2009, **56**, 665.
15. M. Somei, S. Teranishi, K. Yamada, and F. Yamada, *Chem. Pharm. Bull.*, 2001, 49, 1159.
16. E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, 95, 1157 and references cited therein.
17. M. Somei, F. Yamada, T. Kurauchi, Y. Nagahama, M. Hasegawa, K. Yamada, S. Teranishi, H. Sato, and C. Kaneko, *Chem. Pharm. Bull.*, 2001, 49, 87; M. Somei, H. Morikawa, K. Yamada, and F. Yamada, *Heterocycles*, 1998, 48, 1117 and references cited therein.