

## Synthetic Studies of Psilocin Analogs Having Either a Formyl Group or Bromine Atom at the 5- or 7-Position<sup>1)</sup>

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**Psilocin analogs having either a formyl group (9–12) or a bromine atom (13–18) at the 5- or 7-position have been prepared for the first time. Syntheses of 5- and 7-bromo derivatives of 4-hydroxy- (23, 24, 28) and 4-benzyloxyindole-3-carbaldehyde (19, 25, 29, 30), 4-benzyloxyindole-3-acetonitriles (20, 31), and 4-benzyloxy-*N,N*-dimethyltryptamine (32, 34, 35) have also been established.**

**Key words** 5-formylpsilocin; 5-bromopsilocin; 4-benzyloxy-5-bromoindole-3-carbaldehyde; 4-benzyloxy-5-bromo-*N,N*-dimethyltryptamine; psilocin

Psilocin<sup>2–6)</sup> (**1a**, Chart 1) and psilocybin<sup>2)</sup> (**1b**) are well known indole alkaloids which cause powerful psychotomimetic effect.<sup>2)</sup> With an aim to carry out their structure–activity relationship studies, several efforts have thus far been reported.<sup>3,4)</sup> In 1959, Hofmann and co-workers,<sup>3)</sup> and in 1985, Repke and co-workers<sup>4)</sup> had undertaken syntheses of psilocin analogs. Their interests were focused mainly on the modification of the side chain at the 3-position of **1a**. As a result, various compounds shown in a general formula **2** were produced. However, to our knowledge, no reports are known about the modification on the benzene part of indole nucleus of **1a**.

With an expectation that suitable lead compounds for psychotic diseases, such as depression, schizophrenia, Alzheimer's disease, and so on, could be discovered among psilocin derivatives and analogs, we have created a simple preparative method<sup>5)</sup> for **1a** in 50% overall yield as shown in Chart 1 in 1998. Since then, two groups have reported another synthetic methods for **1a**.<sup>6)</sup>

Our synthesis of **1a** consists of only five steps from indole-3-carbaldehyde (**3**) through 4-benzyloxyindole-3-carbaldehyde (**4**), -indole-3-acetonitrile (**5**), -tryptamine (**6**), and -*N,N*-dimethyltryptamine (**7**) as useful synthetic intermediates.

In this paper, we wish to report about the success in the preparations of analogs of **1a** as shown in a general formula **8**, and also bromine derivatives of **4**, **5**, and **7**.

**Syntheses of 5- and 7-Formyl-4-hydroxy-*N,N*-dimethyltryptamines from Psilocin** As psilocin analogs and key intermediates for further structural manipulations, we needed 5-formyl- (**9**, 5-formylpsilocin, Chart 2) and 7-formyl-4-hydroxy-*N,N*-dimethyltryptamine (**10**, 7-formylpsilocin). With **1a** in hand, its Vilsmeier reaction with *N,N*-dimethylformamide (DMF) and phosphorus oxychloride (POCl<sub>3</sub>) was carried out to afford **9** as an unstable oil and **10** as stable crystals in varied yields, depending on the reaction conditions. Typical results are summarized in Table 1.

To our surprise, in all cases (entries 1–4), significant amount of unreacted starting material was recovered in spite of employing excess amount of Vilsmeier reagent (5–10 mol eq). For this reason, the yields of **9** and **10** are low within the range of 17–31% and 11–13%, respectively. When the reaction temperature was raised from room temperature to 58 °C (entry 5), the yield of **10** was slightly im-

proved to 26%, while the recovery of **1a** was still observed. Another interesting finding is that the yield of **9** seems to be almost constant irrespective of the examined reaction conditions (entries 2–5).

For the structural confirmations of **9** and **10**, they were converted to 5-formyl- (**11**) and 7-formyl-1-*tert*-butoxycarbonyl-4-*tert*-butoxycarbonyloxy-*N,N*-dimethyltryptamine (**12**) in 78 and 66% yields, respectively, by treating with excess di-*tert*-butyl dicarbonate [(Boc)<sub>2</sub>O] in the presence of 4-(dimethylamino)pyridine (DMAP).

Comparison of <sup>1</sup>H-NMR spectrum of **11** with that of **9** clearly shows that the C-7 proton signal of **11** resonated at lower magnetic field by *ca.* 1.3 ppm than that of **9**. This anisotropy effect, caused by the Boc group introduced into the 1-position, proves that **9** and **11** are 5-formyl compounds. On the other hand, no anisotropic effect on the aromatic protons was observed in the cases of **10** and **12**. Therefore, **10** and **12** are determined to be 7-formyl derivatives. Consequently, we have succeeded in the first syntheses of 5-formyl- (**9**) and 7-formylpsilocins (**10**).

**Syntheses of 5- and 7-Bromo-4-hydroxy-*N,N*-dimethyltryptamines from Psilocin** We next attempted to introduce a bromine atom directly onto the benzene part of **1a** for obtaining 5-bromo- (**13**, 5-bromopsilocin, Chart 3) and 7-bromo-4-hydroxy-*N,N*-dimethyltryptamines (**14**, 7-bromopsilocin). It is interesting to note that bromination of **1a** with such reagents as Br<sub>2</sub> in AcOH, *N*-bromosuccinimide (NBS) in CHCl<sub>3</sub>, and pyridinium bromide perbromide (Py·HBr·Br<sub>2</sub>) in CHCl<sub>3</sub>–Et<sub>2</sub>O,<sup>7)</sup> did not occur. Under forced reaction conditions, only a small amount of brominated compounds were produced. Finally, we have found that bromination with Py·HBr·Br<sub>2</sub> proceeds in moderate yield in CH<sub>2</sub>Cl<sub>2</sub> containing a small amount of AcOH. As a result, an inseparable mixture of unstable **13** and **14** (in a ratio of 1 : 9), quite unstable 5,7-dibromo-4-hydroxytryptamine (**15**), and **1a** were obtained in 44, 16, and 14% yields, respectively, by the reaction of **1a** with Py·HBr·Br<sub>2</sub> (1.2 mol eq) in CH<sub>2</sub>Cl<sub>2</sub>–AcOH (10 : 1, v/v) at room temperature.

Acetylation of the mixture of **13** and **14** with Ac<sub>2</sub>O–pyridine produced readily separable 4-acetoxy-5-bromo-*N,N*-dimethyltryptamine (**16**) and 4-acetoxy-7-bromo-*N,N*-dimethyltryptamine (**17**) as stable compounds, respectively. Acetylation of **15** with the same reagent afforded stable **18**.

Based on these findings, the isolation process of products

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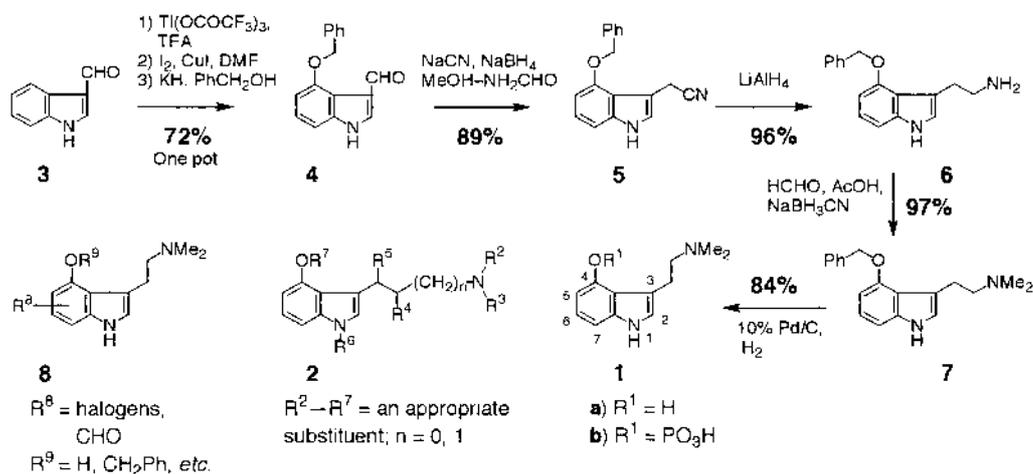


Chart 1

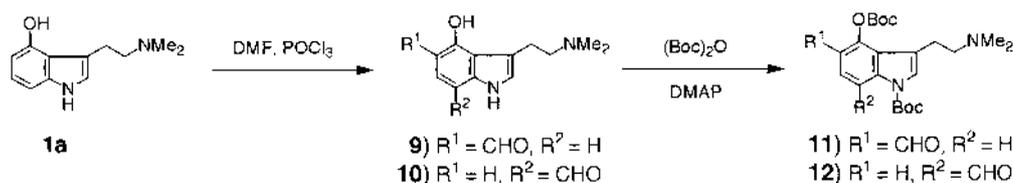


Chart 2

Table 1. Vilsmeier Reaction of Psilocin (**1a**)

Entry	Reaction conditions			Yield (%)		
	POCl <sub>3</sub> (mol eq)	Temp. (°C)	Time (h)	9	10	1a
1	5	r.t.	14	17	11	47
2	5	r.t.	23	29	13	46
3	5	r.t.	72	31	11	30
4	10	r.t.	95	27	12	40
5	5	58	23	28	26	29

was improved as follows. After bromination of **1a**, the reaction mixture was subjected to column chromatography. Readily isolated unstable **15** and the mixture of **13** and **14** were immediately acetylated, separately. Consequently, **16**–**18** were obtained from **1a** in 4, 34, and 14% overall yields, respectively. Alkaline hydrolysis of **16** with LiOH in MeOH provided 5-bromopsilocin (**13**) but the yield was 29% because of its unstable nature. Under the same reaction conditions, hydrolysis of **17** smoothly provided 7-bromopsilocin (**14**) in 82% yield.

**Preparations of Bromine Containing 4-Hydroxy- and 4-Benzyloxyindole-3-carbaldehydes, 4-Hydroxy-, and 4-Benzyloxyindole-3-acetonitriles** Structure–activity relationship study requires a lot of compounds structurally related to the target compound. From this point of view, we next planned to prepare various 4-hydroxy- and 4-benzyloxyindole-3-carbaldehydes, and 4-hydroxy- and 4-benzyloxyindole-3-acetonitriles, having a bromine atom either at 5- or 7-Position (Chart 4).

Making use of synthetic intermediates involved in the pathway to **1a** (Chart 1), we first examined bromination of **4**

with Py·HBr·Br<sub>2</sub> in CHCl<sub>3</sub>–Et<sub>2</sub>O (1 : 1, v/v).<sup>7</sup> Regioselective introduction of a bromine atom into the 7-position was observed to give 4-benzyloxy-7-bromoindole-3-carbaldehyde (**19**) in 62% yield. Under similar reaction conditions, **5** provided a 63% yield of 4-benzyloxy-7-bromoindole-3-acetonitrile (**20**). The compound **20** was alternatively obtained in 74% yield directly from **19** together with a 17% yield of *N*-(4-benzyloxy-7-bromoindol-3-yl)methylformamide (**21**), by employing our reaction<sup>8</sup> using NaCN in the presence of NaBH<sub>4</sub> in NH<sub>2</sub>CHO–MeOH.

Bromination of **22**, prepared by catalytic hydrogenation of **4** over 10% Pd–C in 76% yield, with Py·HBr·Br<sub>2</sub> in CHCl<sub>3</sub>–tetrahydrofuran (THF) (1 : 1, v/v)<sup>9</sup> provided 5-bromo- (**23**) and 7-bromo-4-hydroxyindole-3-carbaldehyde (**24**) in 10 and 84% yields, respectively. Treatments of **19** and **24** with an excess amount of benzyl bromide and K<sub>2</sub>CO<sub>3</sub> in DMF afforded the same 1-benzyl-4-benzyloxy-7-bromoindole-3-carbaldehyde (**25**) in 98 and 93% yields, respectively.

In order to attain regioselective bromination at the 5-position, an attempt was made by putting a sterically bulky group onto the 1-position. The reaction of **22** with (Boc)<sub>2</sub>O (1 mol eq) in CH<sub>2</sub>Cl<sub>2</sub> in the presence of Et<sub>3</sub>N and *N,N*-dimethylaminopyridine (DMAP) gave 1-*tert*-butoxycarbonyl-4-hydroxyindole-3-carbaldehyde (**26**) in 97% yield. The introduction of Boc group into the 1-position instead of the phenolic oxygen is confirmed by the following reactions; 1) treatment of **26** with benzyl bromide and KO-*tert*-Bu in DMF afforded **27** in 63% yield, 2) subsequent hydrolysis of **27** with NaOH in MeOH produced **4** in a quantitative yield.

As the structure of **26** was established, its bromination was examined with Py·HBr·Br<sub>2</sub> in CHCl<sub>3</sub>–THF (1 : 1, v/v). As expected, 5-bromo-1-*tert*-butoxycarbonyl-4-hydroxyindole-3-carbaldehyde (**28**) was produced as a sole product in 85% yield. Removal of Boc group in **28** with NaOH in MeOH

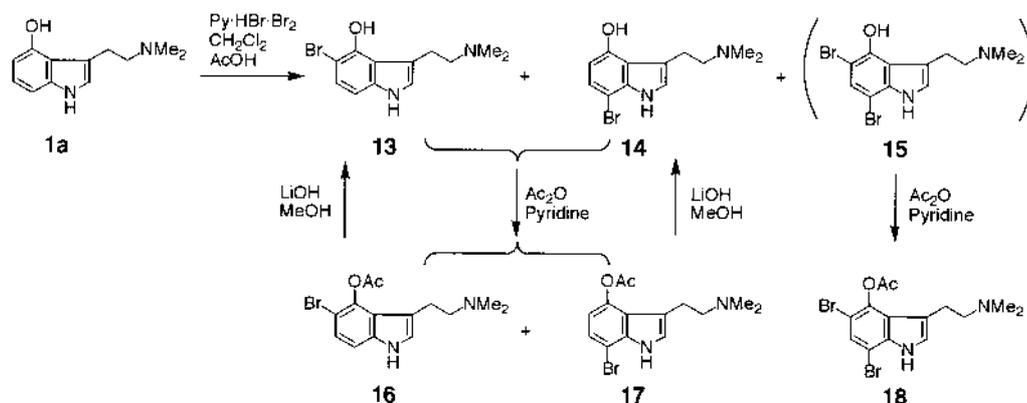


Chart 3

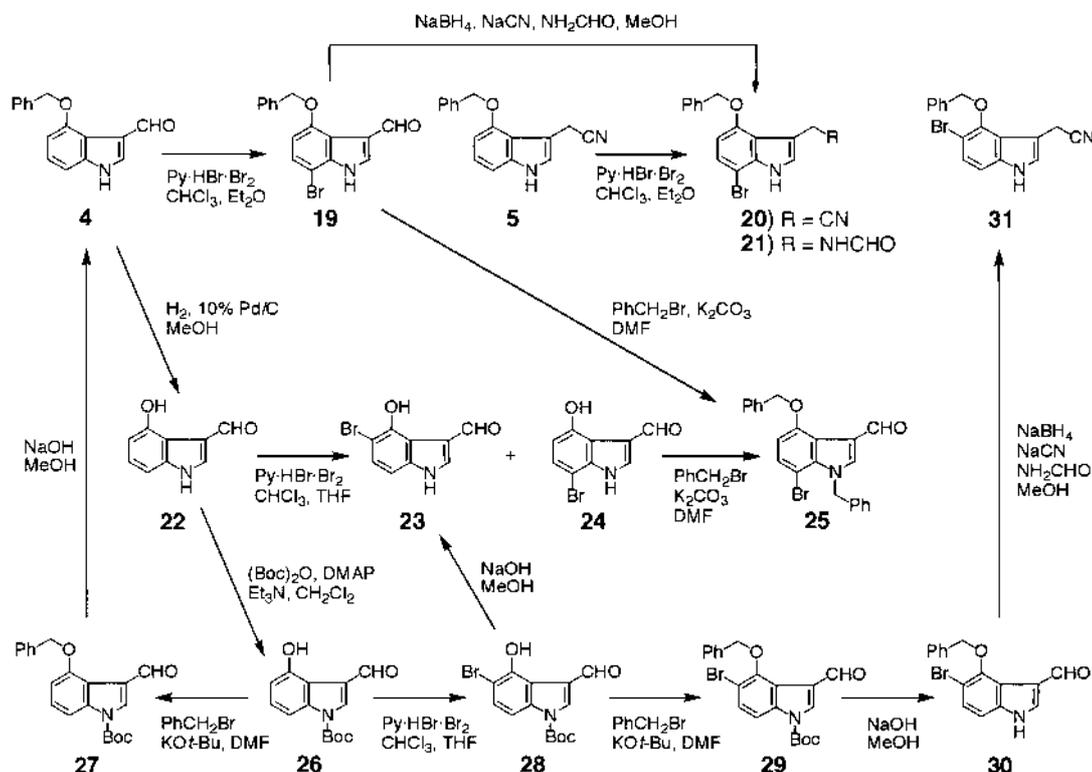


Chart 4

gave a 93% yield of **23**, which was identical with the sample obtained by bromination of **22**. Comparison of  $^1\text{H-NMR}$  spectra of **23** and **28** clearly shows an anisotropy effect of the Boc group on the C-7 proton by about 0.6 ppm, proving that these are 5-brominated compounds.

Further structural confirmations were obtained in the process of preparing 4-benzyloxy-5-bromoindole-3-carbaldehyde (**30**) and -acetonitrile (**31**) from **28**. Thus, the compound **28** was converted to 4-benzyloxy-5-bromo-1-*tert*-butoxycarbonylindole-3-carbaldehyde (**29**) in 98% yield by the reaction with benzyl bromide and  $\text{K}_2\text{CO}_3$ . Subsequent hydrolysis of **29** with  $\text{NaOH}$  in  $\text{MeOH}$  afforded **30** in 97% yield. Treatment of **30** with  $\text{NaCN}$  in the presence of  $\text{NaBH}_4$  in  $\text{NH}_2\text{CHO-MeOH}$ <sup>8</sup> afforded **31** in 97% yield.

**Bromine Containing Derivatives of 7 and Another Synthetic Approach to 5- and 7-Bromopsilocin** With the compound **7** in hand, we next tried to produce its bromine

containing derivatives, and to find another synthetic approach to 5- (**13**) and 7-bromopsilocin (**14**) (Chart 5).

Bromination of **7** with  $\text{Py} \cdot \text{HBr} \cdot \text{Br}_2$  in  $\text{CHCl}_3\text{-Et}_2\text{O}$  (1 : 1, v/v) provided 4-benzyloxy-7-bromo-*N,N*-dimethyltryptamine (**32**) in 31% yield. Attempts to improve the yield were made by employing  $\text{Br}_2$  in  $\text{AcOH}$  and  $\text{NBS}$  in  $\text{CHCl}_3$  under various reaction conditions *in vain*. Use of the  $\text{HBr}$  salt of **7** as a substrate was unsuccessful, either, under the same reaction conditions. Subsequent catalytic hydrogenation of **32** over 10%  $\text{Pd-C}$  in  $\text{MeOH}$  completely removed the bromine atom and produced **1a** in almost quantitative yield. However,  $\text{BBr}_3$  was found to be the reagent of choice for debenzylation. As a result, 7-bromopsilocin (**14**) was obtained in 41% yield.

The compound **32** could also be prepared in an alternative route. Reduction of **20** with  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$  afforded 4-benzyloxy-7-bromotryptamine (**33**) in 86% yield together with a 11% yield of **6**.<sup>5</sup> Subsequent dimethylation of **33** with

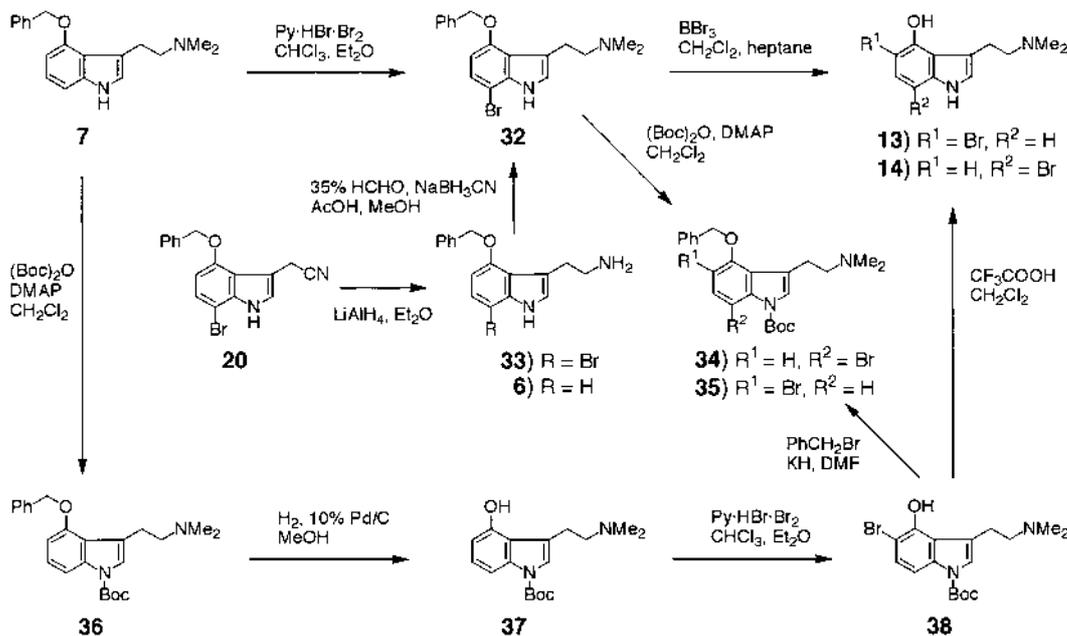


Chart 5

formaldehyde and  $\text{NaBH}_3\text{CN}$  in  $\text{AcOH}$ <sup>10</sup> furnished **32** in 91% yield.

On the other hand, treatment of **7** with  $(\text{Boc})_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of DMAP afforded 4-benzyloxy-1-*tert*-butoxycarbonyl-*N,N*-dimethyltryptamine (**36**) in 96% yield. Debzylation of **36** by the catalytic hydrogenation over 10% Pd-C in MeOH produced 1-*tert*-butoxycarbonyl-*N,N*-dimethyl-4-hydroxytryptamine (**37**) in 93% yield. Bromination of **37** with  $\text{Py}\cdot\text{HBr}\cdot\text{Br}_2$  in  $\text{CHCl}_3\text{-Et}_2\text{O}$  (1 : 1, v/v) proceeded regioselectively to give 5-bromo-1-*tert*-butoxycarbonyl-4-hydroxy-*N,N*-dimethyltryptamine (**38**) in 87% yield, just as observed in the bromination of **26**. Finally, deprotection of the Boc group of **38** with  $\text{CF}_3\text{COOH}$  furnished 5-bromopsilocin (**13**) in 97% yield. Thus, preparation of relatively unstable **13** by this route is far better than the direct bromination of **1a** as described above.

Both *N*- and *O*-protected bromopsilocin would be a good synthetic intermediate for future use. So, we prepared 4-benzyloxy-7-bromo-1-*tert*-butoxycarbonyl-*N,N*-dimethyltryptamine (**34**) in 83% yield by treating **32** with  $(\text{Boc})_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of DMAP. The other isomer, 4-benzyloxy-5-bromo-1-*tert*-butoxycarbonyl-*N,N*-dimethyltryptamine (**35**) was obtained in 43% yield by benzylation of **38** using KH and benzylbromide in DMF.

In conclusion, we have succeeded for the first time in developing synthetic methods for psilocin analogs having either a formyl group (**9**–**12**) or bromine atom (**13**–**18**) at the 5- or 7-position. Preparations of 5- and 7-bromo derivatives of 4-hydroxy- (**23**, **24**, **28**) and 4-benzyloxyindole-3-carbaldehydes (**19**, **25**, **29**, **30**), 4-benzyloxyindole-3-acetonitriles (**20**, **31**), and 4-benzyloxy-*N,N*-dimethyltryptamines (**32**, **34**, **35**) have also been established. These compounds would be suitable for further manipulations. Biological evaluations of new compounds described in this paper are in progress.

#### Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu

IR-420 or Horiba FT-720 spectrophotometer, and <sup>1</sup>H-NMR spectra with a JEOL GSX-500 spectrometer, with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A or JEOL JMS-GCmate spectrometer. Column chromatography was performed on silica gel ( $\text{SiO}_2$ , 100–200 mesh, from Kanto Chemical Co., Inc.). Preparative thin layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF<sub>254</sub> (type 60) ( $\text{SiO}_2$ ).

**5-Formyl-4-hydroxy-*N,N*-dimethyltryptamine (9) and 7-Formyl-4-hydroxy-*N,N*-dimethyltryptamine (10) from Psilocin (1a)** Entry 1: Anhydrous DMF (1 ml) was added to an ice-cooled  $\text{POCl}_3$  (91.0 mg, 0.59 mmol) and the mixture was stirred for 10 min at room temperature. To the resulting viscous solution was added a solution of **1a** (22.4 mg, 0.11 mmol) in anhydrous DMF (2 ml) and stirring was continued for 14 h at room temperature. The reaction mixture was made basic by adding 2N NaOH at 0°C and the whole was stirred at room temperature for 1 h. After adjusting pH to 7–8 with 1N HCl, the whole was extracted with  $\text{CHCl}_3\text{-MeOH}$  (95 : 5, v/v). The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3\text{-MeOH}$ –28% aq.  $\text{NH}_3$  (46 : 5 : 0.5, v/v) to give **10** (2.8 mg, 11%), unreacted **1a** (10.6 mg, 47%), and **9** (4.2 mg, 17%) in the order of elution. **9**: Unstable yellow oil. IR (film): 3200, 1628  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 2.43 (6H, s), 2.82 (2H, t,  $J=7.5$  Hz), 3.10 (2H, t,  $J=7.5$  Hz), 6.89 (1H, d,  $J=8.5$  Hz), 6.99 (1H, s), 7.28 (1H, d,  $J=8.5$  Hz), 9.88 (1H, s). High-resolution MS  $m/z$ : Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$ : 232.1212. Found: 232.1213. **10**: mp 220.5–222.5°C (colorless prisms, recrystallized from  $\text{AcOEt}$ -hexane). IR (KBr): 3380, 1634, 1583  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 2.62 (6H, s), 3.04–3.09 (2H, m), 3.10–3.15 (2H, m), 6.38 (1H, d,  $J=8.3$  Hz), 6.98 (1H, s), 7.43 (1H, d,  $J=8.3$  Hz), 9.59 (1H, s). MS  $m/z$ : 232 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$ : C, 67.22; H, 6.94; N, 12.06. Found: C, 67.30; H, 6.96; N, 12.03.

Entry 2: Anhydrous DMF (1 ml) was added to an ice-cooled  $\text{POCl}_3$  (95.6 mg, 0.62 mmol) and the mixture was stirred for 10 min at room temperature. To the resulting viscous solution was added a solution of **1a** (19.0 mg, 0.093 mmol) in anhydrous DMF (2 ml) and stirring was continued for 23 h at room temperature. After work-up and purification as described in entry 1, **10** (2.9 mg, 13%), unreacted **1a** (8.8 mg, 46%), and **9** (6.2 mg, 29%) were obtained in the order of elution.

Entry 3: Anhydrous DMF (1 ml) was added to an ice-cooled  $\text{POCl}_3$  (102.4 mg, 0.67 mmol) and the mixture was stirred for 10 min at room temperature. To the resulting viscous solution was added a solution of **1a** (21.4 mg, 0.11 mmol) in anhydrous DMF (2 ml) and stirring was continued for 72 h at room temperature. After work-up and purification as described in entry 1, **10** (2.6 mg, 11%), unreacted **1a** (6.4 mg, 30%), and **9** (7.5 mg, 31%) were obtained in the order of elution.

Entry 4: Anhydrous DMF (1 ml) was added to an ice-cooled  $\text{POCl}_3$

(170.8 mg, 1.11 mmol) and the mixture was stirred for 10 min at room temperature. To the resulting viscous solution was added a solution of **1a** (21.2 mg, 0.10 mmol) in anhydrous DMF (2 ml) and stirring was continued for 95 h at room temperature. After work-up and purification as described in entry 1, **10** (3.0 mg, 12%), unreacted **1a** (8.5 mg, 40%), and **9** (6.4 mg, 27%) were obtained in the order of elution.

Entry 5: Anhydrous DMF (1 ml) was added to an ice-cooled POCl<sub>3</sub> (96.4 mg, 0.62 mmol) and the mixture was stirred for 10 min at room temperature. To the resulting viscous solution was added a solution of **1a** (21.6 mg, 0.11 mmol) in anhydrous DMF (2 ml) and stirring was continued for 23 h at 58 °C. After work-up and purification as described in entry 1, **10** (6.4 mg, 26%), unreacted **1a** (6.2 mg, 29%), and **9** (6.8 mg, 28%) were obtained in the order of elution.

**1-tert-Butoxycarbonyl-4-tert-butoxycarbonyloxy-5-formyl-N,N-dimethyltryptamine (11) from 9** A solution of **9** (10.4 mg, 0.045 mmol), DMAP (5.6 mg, 0.046 mmol), and Boc<sub>2</sub>O (0.04 ml, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was stirred for 18 h at room temperature. The mixture was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH (95 : 5, v/v) to give **11** (15.1 mg, 78%). **11**: mp 109–111 °C (colorless prisms, recrystallized from hexane). IR (KBr): 1751, 1734, 1690, 1608 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.57 (9H, s), 1.68 (9H, s), 2.38 (6H, s), 2.72 (2H, t, *J* = 7.9 Hz), 2.94 (2H, t, *J* = 7.9 Hz), 7.56 (1H, s), 7.81 (1H, d, *J* = 8.7 Hz), 8.21 (1H, d, *J* = 8.7 Hz), 10.05 (1H, s). MS *m/z*: 432 (M<sup>+</sup>). Anal. Calcd for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: C, 63.87; H, 7.46; N, 6.48. Found: C, 63.79; H, 7.58; N, 6.42.

**1-tert-Butoxycarbonyl-4-tert-butoxycarbonyloxy-7-formyl-N,N-dimethyltryptamine (12) from 10** A solution of **10** (6.0 mg, 0.026 mmol), DMAP (3.0 mg, 0.025 mmol), and Boc<sub>2</sub>O (0.05 ml, 0.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was stirred for 18 h at room temperature. The mixture was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH (95 : 5, v/v) to give **12** (7.4 mg, 66%). **12**: Colorless oil. IR (film): 1758, 1735, 1689 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.57 (9H, s), 1.62 (9H, s), 2.36 (6H, s), 2.66 (2H, t, *J* = 7.8 Hz), 2.93 (2H, t, *J* = 7.8 Hz), 7.19 (1H, d, *J* = 8.3 Hz), 7.39 (1H, s), 7.75 (1H, d, *J* = 8.3 Hz), 10.44 (1H, s). High-resolution MS *m/z*: Calcd for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: 432.2260. Found: 432.2261.

**4-Acetoxy-5-bromo-N,N-dimethyltryptamine (16), 4-Acetoxy-7-bromo-N,N-dimethyltryptamine (17), and 4-Acetoxy-5,7-dibromo-N,N-dimethyltryptamine (18) from 1a** Py·HBr·Br<sub>2</sub> (42.2 mg, 0.13 mmol) was added to a solution of **1a** (22.4 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) and AcOH (0.3 ml), and the mixture was stirred at room temperature for 5 h. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed repeatedly on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46 : 5 : 0.5, v/v) to give quite unstable **15** (6.3 mg, 16%), a mixture (13.8 mg, 44%) of unstable **13** and **14** (in a ratio of 1 : 9, calculated by <sup>1</sup>H-NMR) and unreacted **1a** (3.1 mg, 14%) in the order of elution. Compound **15** was so unstable that spectral data of pure sample were not obtained. Ac<sub>2</sub>O (1 ml) was added to a solution of the mixture of **13** and **14** (13.8 mg) in pyridine (2 ml), and the mixture was stirred at room temperature for 23 h. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed repeatedly on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46 : 5 : 0.5, v/v) to give **17** (12.0 mg, 34% from **1a**) and **16** (1.3 mg, 4% from **1a**) in the order of elution. **16**: Colorless oil. IR (film): 3390, 1763 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.31 (6H, s), 2.45 (3H, s), 2.59 (2H, t, *J* = 7.7 Hz), 2.85 (2H, t, *J* = 7.7 Hz), 6.93 (1H, dt, *J* = 2.2, 1.1 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.04 (1H, d, *J* = 8.5 Hz), 7.28 (1H, d, *J* = 8.5 Hz), 8.30 (1H, br s, disappeared on addition of D<sub>2</sub>O). High-resolution MS *m/z*: Calcd for C<sub>14</sub>H<sub>17</sub><sup>79</sup>BrN<sub>2</sub>O<sub>2</sub>: 324.0473. Found: 324.0463. Calcd for C<sub>14</sub>H<sub>17</sub><sup>81</sup>BrN<sub>2</sub>O<sub>2</sub>: 326.0453. Found: 326.0458. **17**: Colorless oil. IR (film): 3367, 1763 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.31 (6H, s), 2.40 (3H, s), 2.59 (2H, t, *J* = 7.9 Hz), 2.90 (2H, t, *J* = 7.9 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 7.04 (1H, dt, *J* = 2.2, 1.1 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.28 (1H, d, *J* = 8.3 Hz), 8.26 (1H, br s, disappeared on addition of D<sub>2</sub>O). High-resolution MS *m/z*: Calcd for C<sub>14</sub>H<sub>17</sub><sup>79</sup>BrN<sub>2</sub>O<sub>2</sub>: 324.0473. Found: 324.0470. Calcd for C<sub>14</sub>H<sub>17</sub><sup>81</sup>BrN<sub>2</sub>O<sub>2</sub>: 326.0453. Found: 326.0444. Ac<sub>2</sub>O (0.5 ml) was added to a solution of **15** (6.3 mg, 0.017 mmol) in pyridine (1 ml), and the mixture was stirred at room temperature for 20 h. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed repeatedly on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46 : 5 : 0.5, v/v) to give **18** (6.1 mg, 14% from **1a**). **18**: Colorless oil. IR (film): 3359, 1759 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.30 (6H, s), 2.45 (3H, s), 2.57 (2H, t, *J* = 7.8 Hz), 2.84 (2H, t, *J* = 7.8 Hz), 7.05 (1H, br d, *J* = 2.2 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.50 (1H, s), 8.34 (1H, br s, disappeared on addition of D<sub>2</sub>O). High-resolution MS *m/z*: Calcd for C<sub>14</sub>H<sub>16</sub><sup>79</sup>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 401.9579. Found: 401.9566. Calcd

for C<sub>14</sub>H<sub>16</sub><sup>79</sup>Br<sup>81</sup>BrN<sub>2</sub>O<sub>2</sub>: 403.9558. Found: 403.9559. C<sub>14</sub>H<sub>16</sub><sup>81</sup>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 405.9537. Found: 405.9543.

**5-Bromo-4-hydroxy-N,N-dimethyltryptamine (13) from 16** LiOH (11.5 mg, 0.48 mmol) was added to a solution of **16** (12.8 mg, 0.039 mmol) in MeOH (2 ml), and the mixture was stirred at room temperature for 2 h. After addition of AcOH (0.1 ml) to the reaction mixture, the solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46 : 5 : 0.5, v/v) to give unstable **13** (3.7 mg, 29%) and unreacted **16** (3.3 mg, 22%) in the order of elution. **13**·1/2AcOEt: mp 139–141 °C (dec., colorless prisms, recrystallized from AcOEt). IR (KBr): 3230, 1726, 1471, 1439 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.26 (3/2H, t, *J* = 7.1 Hz), 1.60 (1H, br s, disappeared on addition of D<sub>2</sub>O), 2.04 (3/2H, s), 2.41 (6H, s), 2.70–2.73 (2H, m), 2.92–2.95 (2H, m), 4.12 (1H, q, *J* = 7.1 Hz), 6.73 (1H, d, *J* = 8.6 Hz), 6.83 (1H, br d, *J* = 2.2 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.26 (1H, d, *J* = 8.6 Hz), 7.90 (1H, br s, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 282 and 284 (M<sup>+</sup> <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>12</sub>H<sub>15</sub>BrN<sub>2</sub>O·1/2C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>: C, 51.39; H, 5.85; N, 8.56. Found: C, 51.17; H, 5.79; N, 8.40.

**7-Bromo-4-hydroxy-N,N-dimethyltryptamine (14) from 17** LiOH (10.8 mg, 0.45 mmol) was added to a solution of **17** (12.8 mg, 0.039 mmol) in MeOH (2 ml), and the mixture was stirred at room temperature for 10 min. After addition of AcOH (0.1 ml) to the reaction mixture, the solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46 : 5 : 0.5, v/v) to give **14** (9.2 mg, 82%). **14**: mp 148–150 °C (dec., colorless prisms, recrystallized from AcOEt). IR (KBr): 3246, 1498, 1342, 833 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 2.36 (6H, s), 2.74 (2H, t, *J* = 6.7 Hz), 3.00 (2H, t, *J* = 6.7 Hz), 6.28 (1H, d, *J* = 8.1 Hz), 6.95 (1H, s), 7.00 (1H, d, *J* = 8.1 Hz). MS *m/z*: 282 and 284 (M<sup>+</sup> <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>12</sub>H<sub>15</sub>BrN<sub>2</sub>O: C, 50.90; H, 5.34; N, 9.89. Found: C, 51.00; H, 5.34; N, 9.62.

**4-Benzyloxy-7-bromoindole-3-carbaldehyde (19) from 4-Benzyloxyindole-3-carbaldehyde (4)** Py·HBr·Br<sub>2</sub> (57.4 mg, 0.18 mmol) was added to a solution of **4** (38.8 mg, 0.16 mmol) in CHCl<sub>3</sub>-Et<sub>2</sub>O (1 : 1, v/v, 16 ml), and the mixture was stirred at room temperature for 5 h. The reaction mixture was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> to give **19** (31.4 mg, 62%) from AcOEt-hexane (1 : 3, v/v) eluent and unreacted **4** (7.8 mg, 20%) from AcOEt-hexane (1 : 1, v/v) eluent. **19**: mp 186–188 °C (colorless needles, recrystallized from MeOH). IR (KBr): 3300, 1635 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.25 (2H, s), 6.70 (1H, d, *J* = 8.3 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 7.33–7.43 (3H, m), 7.45–7.49 (2H, m), 7.97 (1H, d, *J* = 2.9 Hz, collapsed to s on addition of D<sub>2</sub>O), 8.93 (1H, br s, disappeared on addition of D<sub>2</sub>O), 10.48 (1H, s). MS *m/z*: 329 and 331 (M<sup>+</sup> <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>BrNO<sub>2</sub>: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.19; H, 3.63; N, 4.15.

**4-Benzyloxy-7-bromoindole-3-acetonitrile (20) from 4-Benzyloxyindole-3-acetonitrile (5)** Py·HBr·Br<sub>2</sub> (53.8 mg, 0.17 mmol) was added to a solution of **5** (41.4 mg, 0.16 mmol) in CHCl<sub>3</sub>-Et<sub>2</sub>O (1 : 1, v/v, 8 ml), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1 : 4, v/v) to give **20** (33.7 mg, 63%) and unreacted **5** (6.4 mg, 15%). **20**: mp 150–151 °C (colorless leaves, recrystallized from Et<sub>2</sub>O-hexane). IR (KBr): 3350, 2260, 1616 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.99 (2H, d, *J* = 1.0 Hz), 5.16 (2H, s), 6.49 (1H, d, *J* = 8.3 Hz), 7.19 (1H, dt, *J* = 2.2, 1.0 Hz, collapsed to br s on addition of D<sub>2</sub>O), 7.23 (1H, d, *J* = 8.3 Hz), 7.33–7.44 (3H, m), 7.45–7.49 (2H, m), 8.27 (1H, br s, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 340 and 342 (M<sup>+</sup> <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>BrN<sub>2</sub>O: C, 59.84; H, 3.84; N, 8.21. Found: C, 60.12; H, 3.79; N, 8.10.

**Compound 20 and N-(4-Benzyloxy-7-bromoindol-3-yl)methylformamide (21) from 19** NaBH<sub>4</sub> (3.5 mg, 0.092 mmol) was added to a solution of **19** (18.6 mg, 0.056 mmol) in NH<sub>2</sub>CHO-MeOH (1 : 1, v/v, 4 ml), and the mixture was stirred for 0.5 h. To the reaction mixture was added NaCN (30.2 mg, 0.62 mmol) and the whole was refluxed on oil bath at 100 °C for 3 h with stirring. After cooling to room temperature, brine was added and the whole was extracted with CHCl<sub>3</sub>. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> to give **20** (14.2 mg, 74%) from CHCl<sub>3</sub> eluent and **21** (3.4 mg, 17%) from CHCl<sub>3</sub>-MeOH (95 : 5, v/v) eluent. **21**: mp 182–183 °C (colorless needles, recrystallized from AcOEt). IR (KBr): 3290, 3230, 1639 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, rotational isomers existed) δ: 4.53 (2/7H, d, *J* = 6.4 Hz), 4.58 (12/7H, d, *J* = 6.1 Hz), 5.17 (2/7H, s), 5.20 (12/7H, s), 5.99 (1/7H, br s, disappeared on addition of D<sub>2</sub>O), 6.22 (6/7H, br s, disappeared on addition of D<sub>2</sub>O), 6.52 (1/7H, d, *J* = 8.3 Hz), 6.56

(6/7H, d,  $J=8.3$  Hz), 7.05 (1/7H, d,  $J=2.1$  Hz), 7.14 (6/7H, d,  $J=2.4$  Hz), 7.24 (1/7H, d,  $J=8.3$  Hz), 7.25 (6/7H, d,  $J=8.3$  Hz), 7.34—7.49 (5H, m), 7.92 (6/7H, d,  $J=1.7$  Hz, collapsed to s on addition of D<sub>2</sub>O), 8.02 (1/7H, d,  $J=12.0$  Hz, collapsed to s on addition of D<sub>2</sub>O), 8.24 (1H, brs, disappeared on addition of D<sub>2</sub>O). MS  $m/z$ : 358 and 360 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>17</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 56.84; H, 4.21; N, 7.80. Found: C, 56.99; H, 4.18; N, 7.58.

**4-Hydroxyindole-3-carbaldehyde (22) from 4** A suspension of **4** (187.1 mg, 0.75 mmol) and 10% Pd-C (82.0 mg) in MeOH (15 ml) was stirred at room temperature for 1 h under H<sub>2</sub> atmosphere. The reaction mixture was filtered through SiO<sub>2</sub> to remove Pd-C and the filtrate was evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from CHCl<sub>3</sub>-MeOH to give **22** (70.6 mg). The mother liquor was purified by p-TLC on SiO<sub>2</sub> with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (97:3, v/v) as a developing solvent. Extraction of the band having an  $R_f$  value of 0.42—0.31 with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (95:5, v/v) gave **22** (20.4 mg). The total yield of **22** was 91.0 mg (76%). mp, <sup>1</sup>H-NMR, and IR spectra of **22** were identical with those of the authentic sample **22** reported by us.<sup>12)</sup>

**5-Bromo-4-hydroxyindole-3-carbaldehyde (23) and 7-Bromo-4-hydroxyindole-3-carbaldehyde (24) from 22** Py·HBr·Br<sub>2</sub> (172.4 mg, 0.54 mmol) was added to a solution of **22** (77.6 mg, 0.48 mmol) in CHCl<sub>3</sub>-THF (1:1, v/v, 40 ml), and the mixture was stirred for 1 h at room temperature. The reaction mixture was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1:1, v/v) to give **24** (96.7 mg, 84%), unreacted **22** (6.8 mg, 6%), and **23** (11.5 mg, 10%) in the order of elution. **23**: mp 224—226 °C (dec., pale yellow needles, recrystallized from MeOH). IR (KBr): 3300, 1600 cm<sup>-1</sup>. <sup>1</sup>H-NMR (Dimethylsulfoxide (DMSO-*d*<sub>6</sub>))  $\delta$ : 6.94 (1H, d,  $J=8.5$  Hz), 7.36 (1H, d,  $J=8.5$  Hz), 8.43 (1H, s), 9.65 (1H, s), 11.40 (1H, s, disappeared on addition of D<sub>2</sub>O), 12.54 (1H, brs, disappeared on addition of D<sub>2</sub>O). MS  $m/z$ : 239 and 241 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>9</sub>H<sub>6</sub>BrNO<sub>2</sub>: C, 45.03; H, 2.52; N, 5.83. Found: C, 45.11; H, 2.52; N, 5.63. **24**: mp 212—214 °C (dec., pale yellow needles, recrystallized from MeOH). IR (KBr): 3220, 1618 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 6.53 (1H, d,  $J=8.4$  Hz), 7.32 (1H, d,  $J=8.4$  Hz), 8.43 (1H, s), 9.70 (1H, s), 10.64 (1H, s, disappeared on addition of D<sub>2</sub>O), 12.57 (1H, brs, disappeared on addition of D<sub>2</sub>O). MS  $m/z$ : 239 and 241 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>9</sub>H<sub>6</sub>BrNO<sub>2</sub>: C, 45.03; H, 2.52; N, 5.83. Found: C, 45.13; H, 2.50; N, 5.55.

**1-Benzyl-4-benzyloxy-7-bromoindole-3-carbaldehyde (25) from 19** A solution of benzyl bromide (28.3 mg, 0.17 mmol) in DMF (1 ml) was added to a suspension of **19** (20.0 mg, 0.061 mmol) and K<sub>2</sub>CO<sub>3</sub> (27.2 mg, 0.20 mmol) in DMF (1 ml), and the mixture was stirred at room temperature for 24 h. After addition of brine, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-hexane (7:3, v/v) to give **25** (25.0 mg, 98%). **25**: mp 171—172 °C (colorless needles, recrystallized from AcOEt). IR (KBr): 1662 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 5.24 (2H, s), 5.84 (2H, s), 6.67 (1H, d,  $J=8.5$  Hz), 7.04—7.08 (2H, m), 7.26—7.43 (7H, m), 7.44—7.48 (2H, m), 7.80 (1H, s), 10.47 (1H, s). MS  $m/z$ : 419 and 421 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>23</sub>H<sub>18</sub>BrNO<sub>2</sub>: C, 65.73; H, 4.32; N, 3.33. Found: C, 65.72; H, 4.26; N, 3.19.

**Compound 25 from 24** A solution of benzyl bromide (64.1 mg, 0.38 mmol) in DMF (1 ml) was added to a suspension of **24** (16.0 mg, 0.067 mmol) and K<sub>2</sub>CO<sub>3</sub> (29.8 mg, 0.22 mmol) in DMF (1 ml), and the mixture was stirred at room temperature for 24 h. After addition of brine, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-hexane (1:1, v/v) to give **25** (26.1 mg, 93%).

**1-tert-Butoxycarbonyl-4-hydroxyindole-3-carbaldehyde (26) from 22** DMAP (14.3 mg, 0.12 mmol) and a solution of Boc<sub>2</sub>O (134.8 mg, 0.62 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) were successively added to a solution of **22** (98.0 mg, 0.61 mmol) in CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>N (9:1, v/v, 10 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-hexane (1:1, v/v) to give **26** (153.3 mg, 97%). **26**: mp 169—171 °C (pale yellow needles, recrystallized from AcOEt). IR (KBr): 1756, 1637 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.71 (9H, s), 6.84 (1H, dd,  $J=8.1$ , 0.7 Hz), 7.31 (1H, dd,  $J=8.3$ , 8.1 Hz), 7.61 (1H, d,  $J=8.3$  Hz), 8.25 (1H, s), 9.76 (1H, s), 10.13 (1H, s, disappeared on addition of D<sub>2</sub>O). MS  $m/z$ : 261 ( $M^+$ ). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>4</sub>: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.20; H, 5.80; N, 5.19.

**4-Benzoyloxy-1-tert-butoxycarbonylindole-3-carbaldehyde (27) from 26**

KO-*tert*-Bu (17.3 mg, 0.15 mmol) was added to a solution of **26** (29.1 mg, 0.11 mmol) in anhydrous DMF (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 10 min. To this orange solution was added a solution of benzyl bromide (18.8 mg, 0.11 mmol) in anhydrous DMF (1 ml) and stirring was continued at room temperature for 1 h. Saturated NH<sub>4</sub>Cl solution was added at 0 °C and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub> to give **27** (24.7 mg, 63%). **27**: mp 171—173 °C (colorless prisms, recrystallized from AcOEt). IR (KBr): 1730, 1665 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.67 (9H, s), 5.26 (2H, s), 6.89 (1H, d,  $J=8.3$  Hz), 7.30 (1H, t,  $J=8.3$  Hz), 7.32—7.42 (3H, m), 7.44—7.48 (2H, m), 7.87 (1H, d,  $J=8.3$  Hz), 8.24 (1H, s), 10.54 (1H, s). MS  $m/z$ : 351 ( $M^+$ ). Anal. Calcd for C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.70; H, 6.08; N, 3.89.

**Compound 4 from 27** A solution of NaOH (17.9 mg, 0.45 mmol) in MeOH (0.6 ml) was added to a solution of **27** (26.4 mg, 0.075 mmol) in MeOH (2 ml), and the mixture was stirred for 2 h at room temperature. Saturated NH<sub>4</sub>Cl solution was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH (99:1, v/v) to give **4**<sup>5)</sup> (18.8 mg, 100%).

**5-Bromo-1-tert-butoxycarbonyl-4-hydroxyindole-3-carbaldehyde (28) from 26** Py·HBr·Br<sub>2</sub> (119.6 mg, 0.37 mmol) was added to a solution of **26** (84.7 mg, 0.32 mmol) in CHCl<sub>3</sub>-THF (1:1, v/v, 8 ml), and the mixture was stirred at room temperature for 22 h. The reaction mixture was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from AcOEt to give **28** (70.0 mg) as pale yellow needles. The mother liquor was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1:4, v/v) to give **28** (23.3 mg). The total yield of **28** was 93.3 mg (85%). **28**: mp 236—238 °C (dec.). IR (KBr): 1764, 1640 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.66 (9H, s), 7.52 (1H, d,  $J=8.8$  Hz), 7.56 (1H, d,  $J=8.8$  Hz), 8.80 (1H, s), 9.88 (1H, s), 11.08 (1H, brs, disappeared on addition of D<sub>2</sub>O). MS  $m/z$ : 339 and 341 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>14</sub>H<sub>14</sub>BrNO<sub>4</sub>: C, 49.43; H, 4.15; N, 4.12. Found: C, 49.47; H, 4.08; N, 3.92.

**Compound 23 from 28** A solution of NaOH (10.2 mg, 0.23 mmol) in MeOH (0.5 ml) was added to a solution of **28** (10.7 mg, 0.031 mmol) in MeOH (2 ml), and the mixture was stirred for 2.5 h at room temperature. Saturated NH<sub>4</sub>Cl solution was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1:1, v/v) to give **23** (7.1 mg, 93%).

**4-Benzoyloxy-5-bromo-1-tert-butoxycarbonylindole-3-carbaldehyde (29) from 28** KO-*tert*-Bu (24.5 mg, 0.22 mmol) was added to a solution of **28** (36.2 mg, 0.11 mmol) in anhydrous DMF (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 10 min. To this orange solution was added a solution of benzyl bromide (36.3 mg, 0.21 mmol) in anhydrous DMF (1 ml) and stirring was continued at room temperature for 1 h. Saturated NH<sub>4</sub>Cl solution was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1:4, v/v) to give **29** (44.9 mg, 98%). **29**: mp 154—156 °C (colorless needles, recrystallized from MeOH). IR (KBr): 1743, 1678 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.68 (9H, s), 5.15 (2H, s), 7.34—7.42 (3H, m), 7.49—7.54 (2H, m), 7.59 (1H, d,  $J=8.8$  Hz), 7.95 (1H, d,  $J=8.8$  Hz), 8.23 (1H, s), 10.31 (1H, s). MS  $m/z$ : 429 and 431 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for C<sub>21</sub>H<sub>20</sub>BrNO<sub>4</sub>: C, 58.62; H, 4.69; N, 3.26. Found: C, 58.52; H, 4.69; N, 3.06.

**4-Benzoyloxy-5-bromoindole-3-carbaldehyde (30) from 29** A solution of NaOH (161.8 mg, 4.05 mmol) in MeOH (10 ml) was added to a solution of **29** (288.8 mg, 0.67 mmol) in MeOH (20 ml), and the mixture was stirred at room temperature for 2 h. Saturated NH<sub>4</sub>Cl solution was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a crystalline solid, which was recrystallized from MeOH to give **30** (141.2 mg) as colorless needles. The mother liquor was column-chromatographed on SiO<sub>2</sub> with AcOEt-hexane (1:1, v/v) to give **30** (72.7 mg). Total yield of **30** was 213.9 mg (97%). **30**: mp 167—170 °C. IR (KBr): 3153, 1651, 1630 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 5.15 (2H, s), 7.14 (1H, d,  $J=8.6$  Hz), 7.33—7.42 (3H, m), 7.47 (1H, d,  $J=8.6$  Hz), 7.56—7.60 (2H, m), 7.91 (1H, d,  $J=2.9$  Hz, collapsed to s on addition of D<sub>2</sub>O), 9.15 (1H, brs, disappeared on addition of D<sub>2</sub>O), 10.29 (1H, s). MS  $m/z$ : 329 and 331 ( $M^+$  <sup>79</sup>Br, <sup>81</sup>Br). Anal. Calcd for

$C_{16}H_{12}BrNO_2$ : C, 58.20; H, 3.66; N, 4.24. Found: C, 58.21; H, 3.61; N, 4.05.

**4-Benzoyloxy-5-bromoindole-3-acetonitrile (31) from 30**  $NaBH_4$  (5.7 mg, 0.15 mmol) was added to a solution of **30** (32.2 mg, 0.098 mmol) in  $NH_2CHO$ -MeOH (1 : 1, v/v, 4 ml), and the mixture was stirred at room temperature for 0.5 h. To the reaction mixture was added NaCN (52.8 mg, 1.08 mmol) and the whole was refluxed on oil bath at 100 °C for 2 h with stirring. After cooling to room temperature, brine was added and 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 an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH (99 : 1, v/v) to give **31** (32.2 mg, 97%). **31**: mp 134–136 °C (colorless needles, recrystallized from AcOEt-hexane). IR (KBr): 3435, 2247  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 3.78 (2H, d,  $J=1.2$  Hz), 5.18 (2H, s), 7.07 (1H, d,  $J=8.5$  Hz), 7.19 (1H, dt,  $J=2.7, 1.2$  Hz, collapsed to br s on addition of  $D_2O$ ), 7.38 (1H, d,  $J=8.5$  Hz), 7.38–7.45 (3H, m), 7.54–7.57 (2H, m), 8.23 (1H, br s, disappeared on addition of  $D_2O$ ). MS  $m/z$ : 340 and 342 ( $M^+$   $^{79}Br$ ,  $^{81}Br$ ). Anal. Calcd for  $C_{17}H_{13}BrN_2O$ : C, 59.84; H, 3.84; N, 8.21. Found: C, 59.84; H, 3.81; N, 8.07.

**4-Benzoyloxy-7-bromo-N,N-dimethyltryptamine (32) from 4-Benzoyloxy-N,N-dimethyltryptamine (7)**  $Py \cdot HBr \cdot Br_2$  (112.8 mg, 0.35 mmol) was added to a solution of **7** (51.5 mg, 0.18 mmol) in  $CHCl_3$ - $Et_2O$  (1 : 1, v/v, 10 ml), and the mixture was stirred at room temperature for 25 h. The reaction mixture was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **32** (20.0 mg, 31%). **32**: mp 163–164 °C (colorless prisms, recrystallized from AcOEt). IR (KBr): 2780 (br), 1614, 1511  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.14 (6H, s), 2.58 (2H, t,  $J=7.9$  Hz), 3.02 (2H, t,  $J=7.9$  Hz), 5.17 (2H, s), 6.45 (1H, d,  $J=8.3$  Hz), 6.96 (1H, br d,  $J=2.2$  Hz, collapsed to s on addition of  $D_2O$ ), 7.17 (1H, d,  $J=8.3$  Hz), 7.30–7.41 (3H, m), 7.46–7.50 (2H, m), 8.15 (1H, br s, disappeared on addition of  $D_2O$ ). MS  $m/z$ : 372 and 374 ( $M^+$   $^{79}Br$ ,  $^{81}Br$ ). Anal. Calcd for  $C_{19}H_{21}BrN_2O$ : C, 61.13; H, 5.67; N, 7.50. Found: C, 61.16; H, 5.57; N, 7.39.

**Compound 14 from 32**  $BBr_3$  in heptane (1 ml, 0.23 ml, 0.23 mmol) was added to a solution of **32** (20.7 mg, 0.056 mmol) in  $CH_2Cl_2$  (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 1 h under Ar atmosphere. After addition of MeOH (2 ml), the mixture was stirred for an additional 1 h. The whole was column-chromatographed repeatedly on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **14** (6.4 mg, 41%).

**4-Benzoyloxy-7-bromotryptamine (33) and 4-Benzoyloxytryptamine (6) from 20**  $LiAlH_4$  (111.4 mg, 2.94 mmol) was added to a solution of **20** (209.9 mg, 0.62 mmol) in  $Et_2O$  (15 ml) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. After addition of MeOH and saturated Rochelle salt under ice cooling, the whole was extracted with AcOEt. The extract was washed with brine, dried over  $Na_2SO_4$ , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **33** (181.7 mg, 86%) and **6**<sup>3</sup> (18.4 mg, 11%) in the order of elution. **33**: mp 145–146 °C (colorless needles, recrystallized from AcOEt). IR (KBr): 3350, 3292, 1614, 1508  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.85 (2H, t,  $J=6.8$  Hz), 2.94 (2H, t,  $J=6.8$  Hz), 5.15 (2H, s), 6.50 (1H, d,  $J=8.3$  Hz), 6.99 (1H, s), 7.12 (1H, d,  $J=8.3$  Hz), 7.30–7.35 (1H, m), 7.37–7.42 (2H, m), 7.47–7.52 (2H, m). MS  $m/z$ : 344 and 346 ( $M^+$   $^{79}Br$ ,  $^{81}Br$ ). Anal. Calcd for  $C_{17}H_{17}BrN_2O$ : C, 59.14; H, 4.96; N, 8.11. Found: C, 59.19; H, 5.01; N, 8.08.

**Compound 32 from 33** A solution of  $NaBH_3CN$  (71.4 mg, 1.14 mmol) in MeOH (2 ml) and a solution of 35% HCHO (153.8 mg, 1.79 mmol) in MeOH (2 ml) were successively added to a solution of **33** (144.1 mg, 0.42 mmol) in AcOH (0.6 ml), and the mixture was stirred at room temperature for 4 h. After evaporation of the solvent under reduced pressure, 2 N NaOH was added and 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 solid, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **32** (141.8 mg, 91%).

**4-Benzoyloxy-1-tert-butoxycarbonyl-N,N-dimethyltryptamine (36) from 7**  $(Boc)_2O$  (0.05 ml, 0.22 mmol) was added to a solution of **7** (30.0 mg, 0.10 mmol) and DMAP (3.2 mg, 0.026 mmol) in  $CH_2Cl_2$  (1 ml), and the mixture was stirred at room temperature for 3 h. The reaction mixture was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH (95 : 5, v/v) to give **36** (38.7 mg, 96%). **36**: mp 76–78 °C (colorless needles, recrystallized from MeOH- $H_2O$ ). IR (KBr): 1735  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 1.65 (9H, s), 2.09 (6H, s), 2.58 (2H, t,  $J=8.1$  Hz), 2.94 (2H, t,  $J=8.1$  Hz), 5.17 (2H, s), 6.81 (1H, d,  $J=8.1$  Hz), 7.18 (1H, dd,  $J=8.3, 8.1$  Hz), 7.28 (1H, s), 7.31–7.36 (1H, m), 7.37–7.42 (2H, m), 7.48–7.52 (2H, m), 7.73 (1H, d,  $J=8.3$  Hz). MS  $m/z$ : 394 ( $M^+$ ). Anal. Calcd for  $C_{24}H_{30}N_2O_3$ : C, 73.06; H, 7.67; N, 7.10. Found: C, 73.13; H, 7.74; N, 6.98.

**1-tert-Butoxycarbonyl-4-hydroxy-N,N-dimethyltryptamine (37) from 36** A suspension of **36** (125.1 mg, 0.28 mmol) and 10% Pd-C (39.7 mg) in

MeOH (10 ml) was stirred at room temperature for 2 h under  $H_2$  atmosphere. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 2 : 0.2, v/v) to give **37** (89.7 mg, 93%). **37**: mp 142–144 °C (colorless prisms, recrystallized from MeOH- $H_2O$ ). IR (KBr): 2950, 1726  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.65 (9H, s), 2.37 (6H, s), 2.70–2.75 (2H, m), 2.88–2.93 (2H, m), 6.71 (1H, dd,  $J=8.1, 1.0$  Hz), 7.17 (1H, t,  $J=8.1$  Hz), 7.24 (1H, br s), 7.65 (1H, br d,  $J=8.1$  Hz), 13.45 (1H, br s, disappeared on addition of  $D_2O$ ). MS  $m/z$ : 304 ( $M^+$ ). Anal. Calcd for  $C_{17}H_{24}N_2O_3$ : C, 67.08; H, 7.95; N, 9.20. Found: C, 67.04; H, 8.03; N, 9.08.

**5-Bromo-1-tert-butoxycarbonyl-4-hydroxy-N,N-dimethyltryptamine (38) from 37**  $Py \cdot HBr \cdot Br_2$  (123.5 mg, 0.39 mmol) was added to a solution of **37** (89.4 mg, 0.29 mmol) in  $CHCl_3$ - $Et_2O$  (20 ml, 1 : 1, v/v), and the mixture was stirred for 4 h at room temperature. The reaction mixture was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **38** (98.0 mg, 87%). **38**: mp 160–161 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1723  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 1.64 (9H, s), 2.52 (6H, s), 2.92–2.97 (2H, m), 2.99–3.04 (2H, m), 7.27 (1H, s), 7.30 (1H, d,  $J=8.8$  Hz), 7.41 (1H, d,  $J=8.8$  Hz). MS  $m/z$ : 382 and 384 ( $M^+$   $^{79}Br$ ,  $^{81}Br$ ). Anal. Calcd for  $C_{17}H_{23}BrN_2O_3$ : C, 53.27; H, 6.05; N, 7.31. Found: C, 53.22; H, 6.13; N, 7.19.

**Compound 13 from 38**  $CF_3COOH$  (0.1 ml) was added to a solution of **38** (10.0 mg, 0.028 mmol) in  $CH_2Cl_2$  (1 ml) at 0 °C and the mixture was stirred at room temperature for 24 h. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed repeatedly on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46 : 5 : 0.5, v/v) to give **13** (7.3 mg, 97%).

**4-Benzoyloxy-7-bromo-1-tert-butoxycarbonyl-N,N-dimethyltryptamine (34) from 32**  $(Boc)_2O$  (0.03 ml, 0.13 mmol) was added to a solution of **32** (20.0 mg, 0.054 mmol) and DMAP (4.3 mg, 0.035 mmol) in  $CH_2Cl_2$  (2 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH (95 : 5, v/v) to give **34** (21.8 mg, 83%). **34**: mp 80–82 °C (colorless prisms, recrystallized from petroleum ether). IR (KBr): 1748  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.64 (9H, s), 2.17 (6H, s), 2.65 (2H, t,  $J=8.1$  Hz), 2.99 (2H, t,  $J=8.1$  Hz), 5.14 (2H, s), 6.62 (1H, d,  $J=8.5$  Hz), 7.20 (1H, s), 7.32–7.42 (3H, m), 7.38 (1H, d,  $J=8.5$  Hz), 7.44–7.48 (2H, m). MS  $m/z$ : 472 and 474 ( $M^+$   $^{79}Br$ ,  $^{81}Br$ ). Anal. Calcd for  $C_{24}H_{29}BrN_2O_3 \cdot 1/4H_2O$ : C, 60.32; H, 6.22; N, 5.86. Found: C, 60.33; H, 6.14; N, 5.77.

**4-Benzoyloxy-5-bromo-1-tert-butoxycarbonyl-N,N-dimethyltryptamine (35) from 38** A solution of **38** (31.7 mg, 0.083 mmol) in anhydrous DMF (1 ml) was added to 35% KH (13.7 mg, 0.12 mmol) at 0 °C with stirring, and the mixture was stirred at room temperature for 10 min. To the resulting suspension was added a solution of benzyl bromide (15.4 mg, 0.09 mmol) in anhydrous DMF (1 ml), and stirring was continued at room temperature for 2 h. Water was added at 0 °C and 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 yellow oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH (95 : 5, v/v) to give **35** (16.9 mg, 43%). **35**: Colorless oil. IR (film): 1730  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.66 (9H, s), 2.22 (6H, s), 2.76 (2H, t,  $J=7.9$  Hz), 3.00 (2H, t,  $J=7.9$  Hz), 5.09 (2H, s), 7.34–7.44 (3H, m), 7.38 (1H, s), 7.48 (1H, d,  $J=8.5$  Hz), 7.56–7.61 (2H, m), 7.88 (1H, br d,  $J=8.5$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{24}H_{29}^{79}BrN_2O_3$ : 472.1362. Found: 472.1344. Calcd for  $C_{24}H_{29}^{81}BrN_2O_3$ : 474.1341. Found: 474.1363.

## References and Notes

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