Synthetic Studies of Psilocin Analogs Having Either a Formyl Group or Bromine Atom at the 5- or 7-Position

Fumio Yamada, Mayumi Tamura, Atsuko Hasegawa, and Masanori Somei

Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-0934, Japan.
Received August 29, 2001; accepted October 2, 2001

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-benzoxoyindole-3-carbaldehyde (19, 25, 29, 30), 4-benzoxoyindole-3-acetonitriles (20, 31), and 4-benzoxoy-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

Psilocin5—10 (1a, Chart 1) and psilocybin11 (1b) are well known indole alkaloids which cause powerful psychotomimetic effect. 23 With an aim to carry out their structure—activity relationship studies, several efforts have thus far been reported. 3,4 In 1959, Hofmann and co-workers, 5 and in 1985, Repke and co-workers 6 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 7 for 1a in 50% overall yield as shown in Chart 1 in 1998. Since then, two groups have reported another synthetic methods for 1a. 8

Our synthesis of 1a consists of only five steps from indole-3-carbaldehyde (3) through 4-benzoxoyindole-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 (POCl3) 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 improved 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-butoxycarboxyloxy-N,N-dimethyltryptamine (12) in 78 and 66% yields, respectively, by treating with excess di-tert-butylicarbonate ([Boc]₂O) in the presence of 4-(dimethylamino)pyridine (DMAP).

Comparison of 1H-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, 9 and 10 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 Br₂ in AcOH, N-bromosuccinimide (NBS) in CHCl₃, and pyridinium bromide perbromide (Py·HBr·Br₂) in CH₂Cl₂—AcOH 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·Br₂ proceeds in moderate yield in CH₂Cl₂ 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·Br₂ (1.2 mol eq) in CH₂Cl₂—AcOH (10:1, v/v) at room temperature.

Acetylation of the mixture of 13 and 14 with Ac₂O—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

* To whom correspondence should be addressed. e-mail: somei@dbs.p.kanazawa-u.ac.jp

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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-Benzylxoyindole-3-carbaldehydes, 4-Hydroxy-, and 4-Benzylxoyindole-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-benzylxoyindole-3-carbaldehydes, and 4-hydroxy- and 4-benzylxoyindole-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·Br₂ in CHCl₃–Et₂O (1:1, v/v). Regioselective introduction of a bromine atom into the 7-position was observed to give 4-benzyloxy-7-bromomindole-3-carbaldehyde (19) in 62% yield. Under similar reaction conditions, 5 provided a 63% yield of 4-benzyloxy-7-bromomindole-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-bromomindol-3-yl)methylformamide (21), by employing our reaction using NaCN in the presence of NaBH₄ in NH₂CHO–MeOH.

Bromination of 22, prepared by catalytic hydrogenation of 4 over 10% Pd·C in 76% yield, with Py·HBr·Br₂ in CHCl₃–tetrahydrofuran (THF) (1:1, v/v) 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 K₂CO₃ in DMF afforded the same 1-benzyl-4-benzyloxy-7-bromomindole-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)₂O (1 mol eq) in CH₂Cl₂ in the presence of Et₃N 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 the same 1-benzyl-4-benzyloxy-7-bromomindole-3-carbaldehyde (25) in 98 and 93% yields, respectively.

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gave a 93% yield of 23, which was identical with the sample obtained by bromination of 22. Comparison of $^1$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-carboxaldehyde (30) and -acetonitrile (31) from 28. Thus, the compound 28 was converted to 4-benzyloxy-5-bromo-1-tert-butoxycarbonylindole-3-carboxaldehyde (29) in 98% yield by the reaction with benzyl bromide and K$_2$CO$_3$. Subsequent hydrolysis of 29 with NaOH in MeOH afforded 30 in 97% yield. Treatment of 30 with NaCN in the presence of NaBH$_4$ in NH$_2$CHO–MeOH afforded 31 in 97% yield. The compound 32 could also be prepared in an alternative route. Reduction of 20 with LiAlH$_4$ in Et$_2$O afforded 4-benzyloxy-7-bromotryptamine (33) in 86% yield together with a 11% yield of 6.5) Subsequent dimethylation of 33 with containing derivatives, and to find another synthetic approach to 5- (13) and 7-bromopsilocin (14) (Chart 5).

Bromination of 7 with Py·HBr·Br$_2$ in CHCl$_3$–Et$_2$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 Br$_2$ in AcOH and NBS in CHCl$_3$ under various reaction conditions in vain. Use of the HBr salt of 7 as a substrate was unsuccessful, either, under the same reaction conditions. Subsequent catalytic hydrogenation of 32 over 10% Pd–C in MeOH completely removed the bromine atom and produced 1a in almost quantitative yield. However, 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 LiAlH$_4$ in Et$_2$O afforded 4-benzyloxy-7-bromotryptamine (33) in 86% yield together with a 11% yield of 6.5)
formaldehyde and NaBH$_4$CN in AcOH$^{10}$ furnished 32 in 91% yield.

On the other hand, treatment of 7 with (Boc)$_2$O in CH$_3$Cl$_2$ in the presence of DMAP afforded 4-benzyloxy-1-tert-butoxycarbonyl-N,N-dimethyltryptamine (36) in 96% yield. Debenzylation 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 Py·HBr·Br$_2$ in CHCl$_3$–Et$_2$O (1:1, v/v) proceeded regioselectively to give 5-bromo-1-tert-butoxycarbonyl-N,N-dimethyl-4-hydroxytryptamine (38) in 87% yield, just as observed in the bromination of 26. Finally, deprotection of the Boc group of 38 with CF$_3$COOH furnished 5-bromopsilocin (13) in 97% yield. Thus, preparation of relatively unstable compounds described in this paper are in progress.

Biological evaluations of new 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 $^1$H-NMR spectra with a JEOL GX5-500 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 silicone gel (SiO$_2$, 100–200 mesh, from Kanto Chemical Co., Inc.). Preparative thin layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF$_254$ (type 60) (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 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 KH and benzylbromide in DMF (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 worked up and purified as described in entry 1. (2.6 mg, 11%), unreacted 1a (2.9 mg, 13%), unreacted 7-Formyl-4-hydroxy-N,N-dimethyltryptamine (9) and 7-Formyl-4-hydroxy-N,N-dimethyltryptamine (10) from Psilocin (1a) Entry 2: Anhydrous DMF (1 ml) was added to an ice-cooled 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 KH and benzylbromide in DMF (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 worked up and purified as described in entry 1. (2.6 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 cm$^{-1}$. $^1$H-NMR (CD$_3$OD) $\delta$: 2.13 (6H, s), 2.82 (2H, t, $J=8.5$ Hz), 6.98 (1H, d, $J=7.5$ Hz), 7.28 (1H, d, $J=8.5$ Hz). High-resolution MS $m/z$: Calcled for C$_9$H$_8$N$_2$O: 232.1212. Found: 232.1213. 10: mp 220.5–222.5°C (colorless prisms, recrystallized from AcOEt-hexane). IR (KBr): 3380, 1634, 1583 cm$^{-1}$. $^1$H-NMR (CD$_3$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 (M$^+$). Anal. Calcld for C$_{10}$H$_9$N$_2$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 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 (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 POCl$_3$ (102.4 mg, 0.67 mmol) and the mixture was stirred for 10 min at room temperature. At 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 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 POCI3 (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, 29%), unreacted 1a (6.2 mg, 29%), and 9 (6.6 mg, 28%) were obtained in the order of elution.

1734, 1690, 1608 cm–1

After evaporation of the solvent under reduced pressure, the residue was chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (4:6:5:0.5, v/v) to give 11 (15.3 mg, 78%).

11: mp 109—111 °C (colorless prisms, recrystallized from hexane). IR (KBr): 1751, 1734, 1690, 1608 cm–1. 1H-NMR (CDCl3): δ: 1.57 (9H, s), 1.68 (9H, s), 2.35 (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+). Anal. Calcd for C14H17BrN2O2: C, 46.7; H, 3.8; N, 8.6. Found: C, 46.3, H, 3.6, N, 8.4.

17-Bromo-4-hydroxy-7-indole-3-acetonitrile (20) from 4-Benzoyloxyindole-3-acetonitrile (21)

17-Bromo-4-hydroxy-7-indole-3-acetonitrile (20) from 4-Benzoyloxyindole-3-acetonitrile (21) was synthesized by the procedure described in entry 5, 1BBr (21.6 mg, 34% from 12) was added to a solution of 12 (14.8 mg, 0.06 mmol) in anhydrous DMF (2 ml), and the mixture was stirred at room temperature for 5 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (4:6:5:0.5, v/v) to give 20 (7.4 mg, 66%).


4-Benzoyloxy-7-bromoiindole-3-carboxaldehyde (19) from 4-Benzoyloxyindole-3-carboxaldehyde (4)

4-Benzoyloxy-7-bromoiindole-3-carboxaldehyde (19) from 4-Benzoyloxyindole-3-carboxaldehyde (4) was synthesized by the procedure described in entry 5, 1BBr (57.4 mg, 0.18 mmol) was added to a solution of 4 (38.8 mg, 0.16 mmol) in CHCl3-EtOH (1:1, v/v), and the mixture was stirred at room temperature for 5 h. The reaction mixture was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (4:6:5:0.5, v/v) to give 19 (16.8 mg, 20%).


4-Benzoyloxy-7-nitroindole-3-carboxaldehyde (23) from 4-Benzoyloxyindole-3-carboxaldehyde (4)

4-Benzoyloxy-7-nitroindole-3-carboxaldehyde (23) from 4-Benzoyloxyindole-3-carboxaldehyde (4) was synthesized by the procedure described in entry 5, 1BBr (35.8 mg, 0.17 mmol) was added to a solution of 5 (41.4 mg, 0.16 mmol) in CHCl3-EtOH (1:1, v/v), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (4:6:5:0.5, v/v) to give 23 (7.3 mg, 63%) and unreacted 5 (6.4 mg, 15%).


4-Benzoyloxy-7-nitroindole-3-carboxaldehyde (23) from 4-Benzoyloxyindole-3-carboxaldehyde (4)

4-Benzoyloxy-7-nitroindole-3-carboxaldehyde (23) from 4-Benzoyloxyindole-3-carboxaldehyde (4) was synthesized by the procedure described in entry 5, 1BBr (35.8 mg, 0.17 mmol) was added to a solution of 5 (41.4 mg, 0.16 mmol) in CHCl3-EtOH (1:1, v/v), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (4:6:5:0.5, v/v) to give 23 (7.3 mg, 63%) and unreacted 5 (6.4 mg, 15%).

Compound 25 from 24 A solution of benzyl bromide (28.3 mg, 0.17 mmol) in CHCl3–MeOH (15 ml) was added to a suspension of 19 (20.0 mg, 0.061 mmol) and K2CO3 (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 Na2SO4, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO2 with AcOEt–hexane (1:1, v/v) to give 26 (25.0 mg, 98%).

1-Benzyl-4-benzyloxy-7-bromomido-3-carboxaldehyde (25) from 19 A solution of benzyl bromide (28.3 mg, 0.17 mmol) in CHCl3–MeOH (15 ml) was added to a suspension of 19 (20.0 mg, 0.061 mmol) and K2CO3 (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 Na2SO4, and evaporated under reduced pressure to leave a crystalline solid, which was column-chromatographed on SiO2 with AcOEt–hexane (1:1, v/v) to give 26 (25.0 mg, 98%).
4-Benzylx-5-bromomido-3-acetoin (31) from NaHBN (5.7 mg, 0.15 mmol) was added to a solution of 30 (32.2 mg, 0.098 mmol) in NH4O-CH2-OH (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 (5.28 mg, 0.18 mmol) and the whole was refluxed on oil bath at 100 °C for 2 h with stirring. After cooling to room temperature, 6.71 (1H, d, J = 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.24 (1H, br, s) was added and the mixture was extracted with CHCL3. The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCL3-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$^{-1}$. H-NMR (CDCl3) δ: 3.78 (2H, d, J = 1.12 Hz), 5.18 (2H, s), 7.07 (1H, d, J = 8.5 Hz), 7.19 (1H, d, J = 2.7, 1.2 Hz, collapsed to s on addition of D2O), 7.38 (1H, d, J = 8.5 Hz), 7.53 (1H, d, J = 7.5 Hz), 7.57 (1H, d, J = 1.8 Hz, brs, disappeared on addition of D2O). MS m/z: 340 and 342 (M$^+$ Br$^+$, 8%). Anal. Caled for C$_{19}$H$_{21}$BrN$_2$O: C, 61.13; H, 5.67; N, 7.50. Found: C, 61.16; H, 5.57; N, 7.39.

(51.5 mg, 0.18 mmol) in CHCl3–Et2O (1 : 1, v/v, 10 ml), and the mixture was stirred at room temperature for 25 h. The reaction mixture was column-chromatographed on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:6:5:0.5, v/v) to give Compound 13 from 32 (36.8 mg, 92%). Compound 14 from 32 BBr$_3$ in heptane (1 M, 0.23 ml, 0.23 mmol) was added to a solution of Boc$_2$O (0.05 ml, 0.22 mmol) was added to a solution of 7 (20.0 mg, 31%).

A solution of NaBH$_3$CN (71.4 mg, 1.14 mmol) was added to a solution of 6 (30.0 mg, 0.028 mmol) in CH$_2$Cl$_2$ (1 ml) at 0 °C and the mixture was stirred for 4 h at room temperature. The reaction mixture was column-chromatographed on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give 32 (18.1 mg, 41%).

A solution of NaBH$_3$CN (71.4 mg, 1.14 mmol) was added to a solution of 6 (30.0 mg, 0.028 mmol) in CH$_2$Cl$_2$ (1 ml) at 0 °C and the mixture was stirred for 4 h at room temperature. The reaction mixture was column-chromatographed on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give 32 (18.1 mg, 41%).

The mixture was washed with brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3-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$^{-1}$. H-NMR (CDCl3) δ: 3.78 (2H, d, J = 1.12 Hz), 5.18 (2H, s), 7.07 (1H, d, J = 8.5 Hz), 7.19 (1H, d, J = 2.7, 1.2 Hz, collapsed to s on addition of D2O), 7.38 (1H, d, J = 8.5 Hz), 7.53 (1H, d, J = 7.5 Hz), 7.57 (1H, d, J = 1.8 Hz, brs, disappeared on addition of D2O). MS m/z: 340 and 342 (M$^+$ Br$^+$, 8%). Anal. Caled for C$_{19}$H$_{21}$BrN$_2$O: C, 61.13; H, 5.67; N, 7.50. Found: C, 61.16; H, 5.57; N, 7.39.

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$_2$SO$_4$, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give 14 (6.4 mg, 41%).

4-Benzylx-7-bromo-1-N,N-dimethyltryptamine (33) and 4-Benzylx-7-bromo-1-N,N-dimethyltryptamine (34) from 32 (Boc$_2$O) (0.03 ml, 0.13 mmol) was added to a solution of (20.0 mg, 0.054 mmol) in MeOH (95 : 5, v/v). The mixture was stirred at room temperature for 1 h. After addition of MeOH (2 ml), the mixture was stirred for an additional 1 h. The whole was column-chromatographed repeatedly on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give Compound 13 from 32 (20.0 mg, 31%).

This compound was added to a solution of benzyl bromide (15.4 mg, 0.09 mmol) in anhydrous DMF (1 ml), and stirring was continued at room temperature for 10 min. To the resulting suspension was added a solution of 38 (98.0 mg, 87%). Compound 14 from 32 (20.0 mg, 31%).

The mixture was stirred at room temperature for 10 min. To the resulting suspension was added a solution of 38 (98.0 mg, 87%). Compound 14 from 32 (20.0 mg, 31%).

The mixture was stirred for 4 h at room temperature. The reaction mixture was column-chromatographed on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give 13 (7.3 mg, 97%).

4-Benzylx-7-bromo-1-N,N-dimethyltryptamine (34) from 32 (Boc$_2$O) (0.03 ml, 0.13 mmol) was added to a solution of (20.0 mg, 0.054 mmol) in MeOH (95 : 5, v/v). The mixture was stirred at room temperature for 1 h. After addition of MeOH (2 ml), the mixture was stirred for an additional 1 h. The whole was column-chromatographed repeatedly on SiO2 with CHCl3–MeOH–28%aq.NH$_3$ (4:5:0.5, v/v) to give 13 (7.3 mg, 97%).