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New 5-HT_3 (Serotonin-3) Receptor Antagonists. III. An Efficient Synthesis of Carbon 14-Labeled (+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one Hydrochloride (FK 1052)

Masayuki Kato,* Shigetaka Nishino, Kiyotaka Ito, and Hisashi Takasugi

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan.

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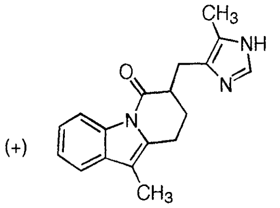
(+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one hydrochloride (FK 1052, 1) is a highly potent 5-HT_3 (serotonin-3) receptor antagonist. For the study of the metabolism and disposition of FK 1052 (1), we synthesized carbon 14-labeled FK 1052 in three steps from 10-demethyl FK 1052 (8). The Mannich reaction and subsequent hydrogenolysis of the dimethylaminomethyl group enabled the efficient introduction of one carbon atom at the 10-position of the pyrido[1,2-*a*]indol-6(7*H*)-one ring. The Mannich reaction of (+)-8,9-dihydro-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (8) with [^{14}C]paraformaldehyde and dimethylamine hydrochloride gave the [^{14}C]-10-dimethylaminomethyl compound (20). Subsequent hydrogenolysis of 20 with palladium on carbon and ammonium formate, followed by recrystallization of the salt with (+)-di-*p*-toluoyl-D-tartaric acid, gave [^{14}C]FK 1052 with a radiochemical purity of 99.4% and an enantiomeric excess of more than 97%.

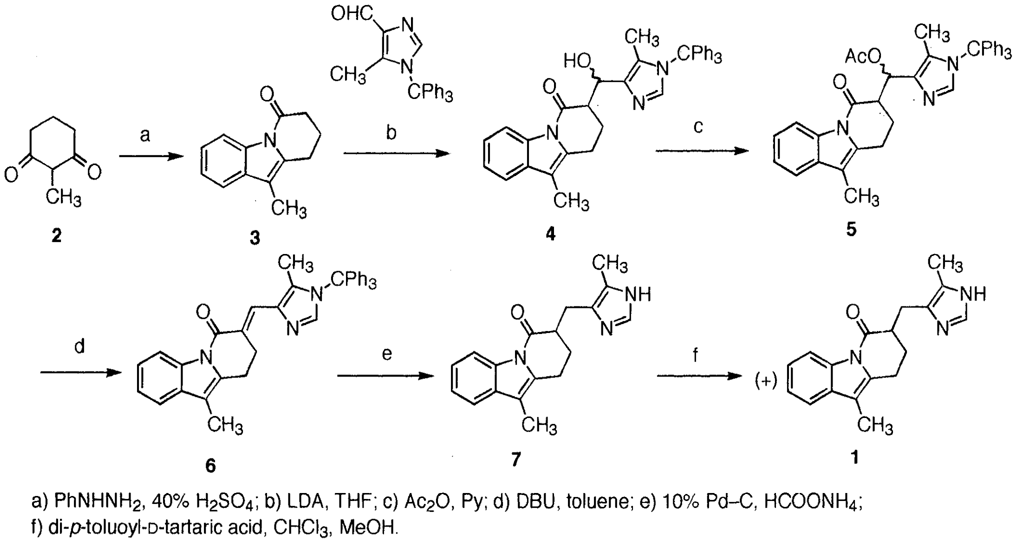
Key words pyrido[1,2-*a*]indol-6(7*H*)-one; ^{14}C-labeled compound; 5-HT_3 receptor antagonist; Mannich reaction

5-Hydroxytryptamine (5-HT) is a neurotransmitter involved in a variety of pharmacological effects and its receptors are classified into several subtypes.[1] Recently, the 5-HT_3 receptor subtype has attracted much attention because of the effectiveness of 5-HT_3 receptor antagonists in the treatment of chemotherapy-induced emesis.[2] In addition, the 5-HT_3 receptor was found in the peripheral and central nervous systems.[3] Antagonism of the 5-HT_3 receptor is expected to be useful for the treatment of psychosis, anxiety, migraine, schizophrenia, and irritable bowel syndrome.[4] During the course of our investigations of 5-HT_3 receptor antagonists, we identified (+)-8,9-dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one hydrochloride (FK 1052, **1**) as the potent 5-HT_3 receptor antagonist.[5] FK 1052 (**1**) is currently undergoing clinical trials for the treatment of gastrointestinal disorders. For the study of the metabolism and disposition of FK 1052, we needed to develop an efficient route for the preparation of a carbon 14-labeled FK 1052. In this paper, we report a new method for introducing a methyl group at the 10-position of the pyrido[1,2-*a*]indol-6(7*H*)-one ring and an efficient synthesis of ^{14}C-labeled FK 1052 by applying this procedure.



FK 1052 (**1**)

Chart 1



a) $PhNHNH_2$, 40% H_2SO_4; b) LDA, THF; c) Ac_2O, Py; d) DBU, toluene; e) 10% Pd–C, $HCOONH_4$; f) di-*p*-toluoyl-D-tartaric acid, $CHCl_3$, MeOH.

Chart 2

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* To whom correspondence should be addressed.

Chemistry

Route Selection The 10-methyl group of FK 1052 (**1**) was considered to be an appropriate substituent for introducing a ^{14}C-atom into the pyrido[1,2-*a*]indole ring moiety. The original route for the synthesis of FK 1052 was not suitable for the synthesis of ^{14}C-labeled FK 1052 because it was long and involved optical resolution in the final step (Chart 2). It is preferable to introduce the [^{14}C]methyl group at a late stage of the synthesis. Thus, we investigated a more efficient route that can introduce a [^{14}C]methyl group into the already resolved pyrido[1,2-*a*]indol-6(7*H*)-one derivative in the final step.

10-Demethyl FK 1052 (**8**) would be a suitable precursor for ^{14}C-labeled **1**, if we could introduce one carbon at the 10-position of **8** (Chart 3). The Mannich reaction was the method of choice for introducing a ^{14}C atom at the 10-position of **8**, because the Mannich reaction of indole derivatives exclusively affords products having the aminomethyl side chain at the 3-position.[6] Furthermore, ^{14}C-labeled paraformaldehyde, the starting material, is commercially available in high specific activity.

Chemistry The optically active **8** was prepared according to the route shown in Chart 4. The key intermediate, 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**13**) has been reported in the literature,[7] but full details were not given. We prepared **13** by a modification of the literature procedure. The imide **10** prepared from *o*-toluidine and glutaric anhydride was brominated by heating at 85 °C with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide, affording the monobromo compound **11** in 84% yield. Compound **11** was converted to the phosphonium salt **12** by treatment with triphenylphosphine in chloroform (93% yield). Intramolecular Wittig reaction of **12** was accomplished by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide (DMF) to give **13** in 51% yield. Treatment of **13** with lithium diisopropylamide (LDA), followed by reaction with 5-methyl-1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde, gave the alcohol (**14**) (79% yield) as a diastereomeric mixture. Acetylation of **14** with acetic anhydride and pyridine gave the acetate (**15**) (82% yield), which was converted to the olefin (**16**) by reaction with DBU (94% yield). The triphenylmethyl group of **16** was removed by treatment with aqueous acetic acid to give compound **17** in 96% yield. Hydrogenation of **17** with palladium on carbon (Pd–C) and ammonium formate in a mixture of tetrahydrofuran and ethanol at 60 °C gave the racemic compound **18** in 77% yield. The (+)-enantiomer **8** was prepared by fractional recrystallization of the diastereomeric salts of **18** and (+)-di-*p*-toluoyl-D-tartaric acid.

We turned our attention to the Mannich reaction of the pyrido[1,2-*a*]indol-6(7*H*)-one ring (Chart 5). Reaction of **13** with 50% dimethylamine solution and 35% formalin in acetic acid at 55 °C gave the desired dimethylaminomethyl compound **19** in 67% yield. Hydrogenolysis of **19** with Pd–C and ammonium formate in refluxing ethanol gave **3** (62% yield). The same method was applied to the racemic compound **18** (Chart 6). Treatment of **18** with 50% dimethylamine solution and 35% formalin in acetic acid gave the dimethylaminomethyl compound **21** in 47% yield. Use of paraformaldehyde instead of formalin

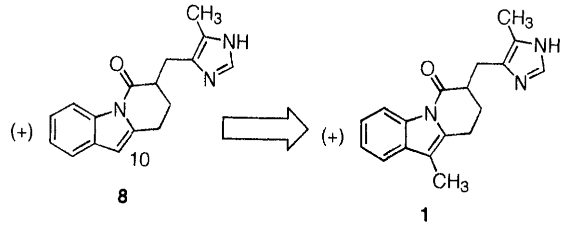
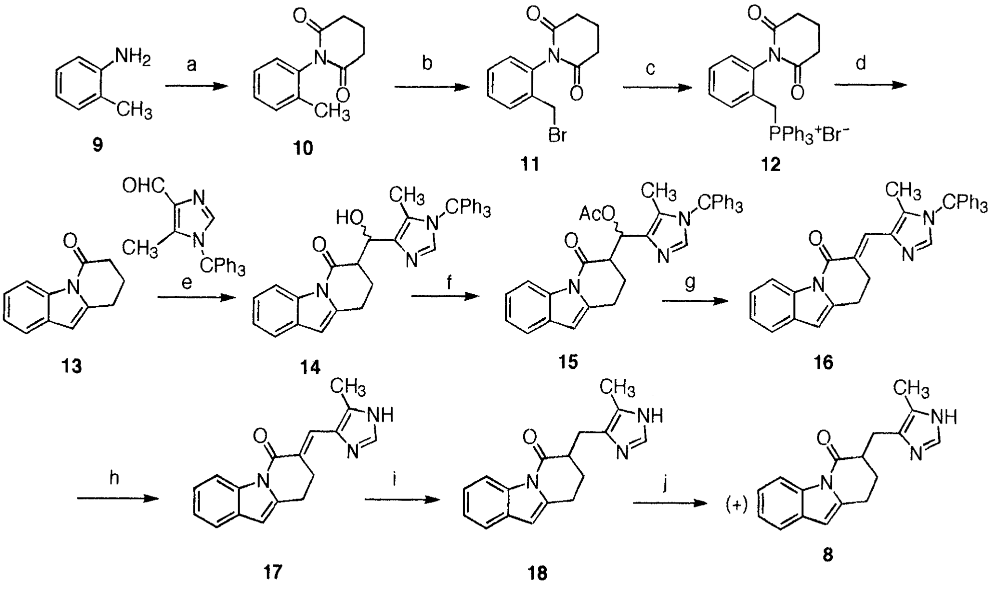


Chart 3



a) glutaric anhydride; b) NBS, $(PhCOO)_2$, CCl_4; c) PPh_3, $CHCl_3$; d) DBU, DMF; e) LDA, THF; f) Ac_2O, Py; g) DBU, toluene; h) AcOH, H_2O; i) 10% Pd–C, $HCOONH_4$, THF, H_2O; j) di-*p*-toluoyl-D-tartaric acid, MeOH, $CHCl_3$.

Chart 4

improved the yield to 52% (method A). Use of dimethylamine hydrochloride as the amine component further improved the yield to 72% (method B). In the reaction of **18**, the bis(dimethylaminomethyl) compound **22**, in which another dimethylaminomethyl group was introduced at the 2-position of the imidazole ring, was isolated as a minor product. Hydrogenolysis of **21** by Pd–C and ammonium formate gave **7** in 60% yield. The enantiomer **8** was similarly converted to compound **1** *via* **20**. However, partial racemization of **1** was observed during the reaction sequence, lowering the optical purity of compound **1** formed. Crude **1** was purified by fractional recrystallization of the diastereomeric salts with (+)-di-*p*-toluoyl-D-tartaric acid. Optically active **1** was obtained after liberation of the free base and conversion to the hydrochloride salt. The compound was identical chromatographically and spectroscopically with the product prepared *via* the route in Chart 2. We applied this procedure to the synthesis of ^{14}C-labeled **1**. The Mannich reaction of **8** with [^{14}C]paraformaldehyde (12.0 mCi/mmol) proceeded as expected to afford ^{14}C-labeled **20**, which was converted to optically active [^{14}C]FK 1052 (**1**) with a radiochemical purity of more than 99.4% and an enantiomeric excess of more than 97% ee. The specific activity was 12.0 mCi/mmol. The overall yield of ^{14}C-labeled **1** from [^{14}C]paraformaldehyde was 18% in three steps.

In conclusion, we have developed a new procedure for introducing a methyl group at the 10-position of the pyrido[1,2-*a*]indol-6(7*H*)-one ring with the Mannich reaction, followed by hydrogenolysis of the dimethylaminomethyl group. ^{14}C-Labeled FK 1052 (**1**) was efficiently prepared by this procedure in three steps from the 10-demethyl compound (**8**).

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on Varian EM-390 (90 MHz) and Bruker AC-200p (200 MHz) spectrometers with tetramethylsilane as an internal standard. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. Mass spectra were obtained with a JEOL JMS D-300 mass spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck, No. 7734). Optical purity of compounds **1** and **8** was determined by HPLC using a 4 × 100 mm Chiral-AGP (Chromtech) column with CH_3CN–0.02 M phosphate buffer (pH 5.0) as the mobile phase.

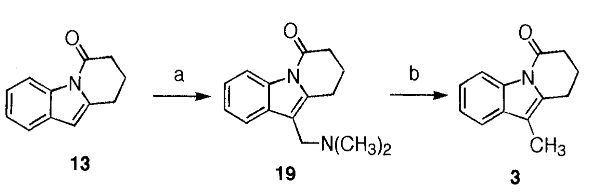
1-(2-Methylphenyl)-2,6-piperidinedione (**10**) was prepared in a similar manner to that described in the literature for 1-phenyl-2,6-piperidinedione.[8]

1-[2-(Bromomethyl)phenyl]-2,6-piperidinedione (11) A solution of **10** (34.3 g, 0.183 mol), NBS (35.9 g, 0.202 mol), and benzoyl peroxide (4.4 g, 18.3 mmol) in CCl_4 (900 ml) was heated at 85 °C for 1.5 h. After cooling, the mixture was diluted with aqueous $NaHCO_3$. The precipitate formed was collected by filtration, washed with CCl_4 and H_2O, and dried to give **11** (39.1 g, 76%), mp 124—130 °C. The filtrate was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The oil obtained was crystallized from EtOAc to give another crop of **11** (4.2 g, 8%). IR (Nujol): 1730, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m), 2.76 (4H, m), 4.43 (2H, s), 7.12 (1H, m), 7.37—7.58 (3H, m). *Anal.* Calcd for $C_{12}H_{12}BrNO_2 \cdot 0.25CCl_4$: C, 45.89; H, 3.77; N, 4.37. Found: C, 45.98; H, 3.44; N, 4.43. MS *m/z*: 281, 283 (M$^+$).

[2-(2,6-Dioxopiperidin-1-yl)phenylmethyl]triphenylphosphonium Bromide (12) A solution of **11** (61.6 g, 0.218 mol) and Ph_3P (63.0 g, 0.24 mol) in $CHCl_3$ (1.2 l) was refluxed for 48 h. The mixture was evaporated to 700 ml under atmospheric pressure and diluted with ether (800 ml). The precipitate formed was collected, washed with ether, and dried to give **12** (110.4 g, 93%), mp 220—230 °C. IR (Nujol): 1720, 1680, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.94—2.04 (2H, m), 2.34—2.74 (4H, m), 4.83 (2H, d, J=15 Hz), 7.00—7.95 (19H, m).

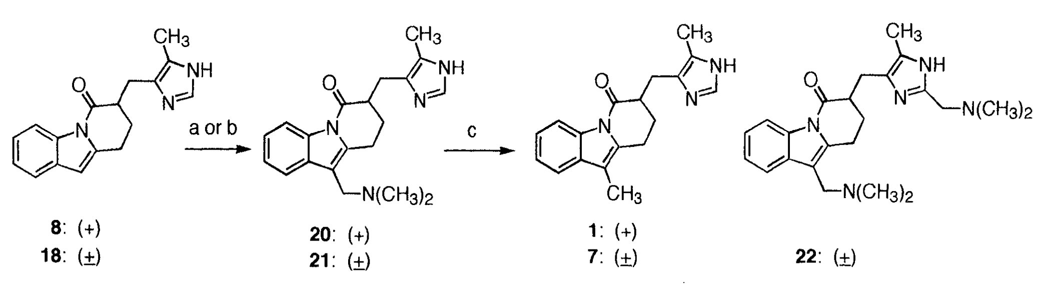
8,9-Dihydropyrido[1,2-*a*]indol-6(7*H*)-one (13) A solution of **12** (2.77 g, 5 mmol) and DBU (2.28 g, 15 mmol) in DMF (20 ml) was heated at 110 °C under nitrogen for 2 h. After cooling, the solution was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O, 2 N HCl, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (CH_2Cl_2) to give **13** (470 mg, 51%), mp 75—77 °C (MeOH) (lit.[7] mp 79—81 °C). IR (Nujol): 1685, 1595 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 2.08 (2H, m), 2.78 (2H, t, J=6 Hz), 2.97 (2H, t, J=6 Hz), 6.32 (1H, s), 7.25 (2H, m), 7.45 (1H, m), 8.44 (1H, m). MS *m/z*: 185 (M$^+$). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.45; H, 6.07; N, 7.47.

8,9-Dihydro-7-[(hydroxy)[5-Methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (14) A solution of **13** (1.22 g, 6.6 mmol) in tetrahydrofuran (THF) (12 ml) was added to a stirred solution of LDA (7.2 mmol; prepared from 866 mg of diisopropylamine and 4.5 ml of 1.60 M *n*-BuLi in hexane) in THF (10 ml) at −70 °C under nitrogen over 15 min. The mixture was stirred at −70 °C for 30 min, and a solution of 5-methyl-1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde[9] (2.55 g, 7.2 mmol) in THF (25 ml) was added over 10 min. After 2 h at −70 °C and 1 h at room temperature, the mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (0.5% MeOH–CH_2Cl_2) to give **14** (2.8 g, 79%) as an amorphous powder. Crystallization from EtOAc–hexane gave an analytical sample, mp 193—198 °C. IR (Nujol): 1700, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (3H, s), 2.00—2.25 (2H, m), 2.80—3.40 (3H, m), 5.10—5.40 (2H, m), 6.40 (1H, s), 7.00—7.40 (19H, m), 8.30—8.50 (1H, m). MS *m/z*: 537 (M$^+$). *Anal.* Calcd for $C_{36}H_{31}N_3O_2$:



a) HCHO, $HN(CH_3)_2$, AcOH, H_2O; b) 10% Pd–C, $HCOONH_4$, EtOH.

Chart 5



a) $(HCHO)_n$, 50% aq. $HN(CH_3)_2$, AcOH (Method A); b) $(HCHO)_n$, $HN(CH_3)_2 \cdot HCl$, AcOH (Method B); c) 10% Pd–C, $HCOONH_4$, THF, EtOH, H_2O.

Chart 6

C, 80.42; H, 5.81; N, 7.82. Found: C, 80.60; H, 6.05; N, 7.77.

7-[(Acetoxy)[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (15) A solution of **14** (1.34 g, 2.5 mmol) and acetic anhydride (1.26 g) in pyridine (20 ml) was stirred at 60 °C for 2 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (0.5% MeOH–CH_2Cl_2) to give **15** (1.18 g, 82%) as an amorphous powder. Crystallization from EtOAc–hexane gave an analytical sample, mp 200—205 °C. IR (film): 1720, 1690, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.44 and 1.47 (3H, each s), 1.94 and 2.05 (3H, each s), 2.00—2.30 (2H, m), 2.80—3.40 (3H, m), 6.27—6.45 (2H, m), 6.98—7.53 (19H, m), 8.27 (1H, m). *Anal.* Calcd for $C_{38}H_{33}N_3O_3\cdot 0.2H_2O$: C, 78.25; H, 5.77; N, 7.20. Found: C, 78.20; H, 5.85; N, 7.11.

8,9-Dihydro-6-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methylene]pyrido[1,2-*a*]indol-6(7*H*)-one (16) A solution of **15** (1.54 g, 2.7 mmol) and DBU (762 mg, 5.0 mmol) in toluene (30 ml) was stirred at 60 °C for 2 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue on silica gel ($CHCl_3$) afforded **16** (1.3 g, 94%). Recrystallization from CH_2Cl_2–MeOH gave an analytical sample, mp 165—170 °C. IR (Nujol): 1680, 1665, 1615, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.61 (3H, s), 3.02 (2H, t, J=7 Hz), 3.60 (2H, t, J=7 Hz), 6.47 (1H, s), 7.10—7.60 (19H, m), 7.61 (1H, s), 8.37 (1H, m). *Anal.* Calcd for $C_{36}H_{29}N_3O\cdot 0.25H_2O$: C, 82.49; H, 5.67; N, 8.02. Found: C, 82.68; H, 5.71; N, 8.07.

8,9-Dihydro-7-[(5-methyl-1*H*-imidazol-4-yl)methylene]pyrido[1,2-*a*]indol-6(7*H*)-one (17) A solution of **16** (21.3 g, 0.041 mol) in AcOH–H_2O (6 : 1, 560 ml) was heated at 80 °C for 70 min. After evaporation of the solvent, the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The precipitate formed was collected to give **17** (5.8 g, 51%). The organic layer of the filtrate was separated, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Crystallization of the residue from $CHCl_3$–toluene gave another crop of **17** (5.1 g, 45%), mp 214—215 °C. IR (Nujol): 1680, 1620, 1585 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s), 3.01 (2H, t, J=7 Hz), 3.56 (2H, t, J=7 Hz), 6.46 (1H, s), 7.25 (2H, m), 7.52 (1H, m), 7.66 (1H, s), 7.74 (1H, s), 8.40 (1H, m). *Anal.* Calcd for $C_{17}H_{15}N_3O\cdot 0.1H_2O$: C, 73.15; H, 5.49; N, 15.05. Found: C, 73.29; H, 5.40; N, 14.83.

8,9-Dihydro-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (18) A mixture of **17** (10.9 g, 0.040 mol), 10% Pd–C (3.3 g), and ammonium formate (17.2 g, 0.273 mol) in EtOH–THF–H_2O (13 : 11 : 3, 270 ml) was heated at 60 °C for 2 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in 10% MeOH–$CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH–hexane gave **18** (8.5 g, 77%), mp 195—197 °C. IR (Nujol): 1690, 1585, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.75—2.02 (2H, m), 2.11 (3H, s), 2.65—3.20 (5H, m), 6.41 (1H, s), 7.24 (2H, m), 7.41 (1H, s), 7.51 (1H, m), 8.35 (1H, m). *Anal.* Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.00; H, 6.18; N, 15.01.

(+)-8,9-Dihydro-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (8) Compound **18** (2.79 g, 10 mmol) and (+)-di-*p*-toluoyl-D-tartaric acid (3.86 g, 10 mmol) were dissolved in a mixture of MeOH–$CHCl_3$ (8 : 2, 84 ml). The solution was allowed to stand at 0 °C for 24 h to give crystals (2.17 g). Two further recrystallizations of this product from MeOH–$CHCl_3$ (8 : 2) gave 0.98 g of crystals. A part of the crystals (124 mg) was neutralized with aqueous $NaHCO_3$ and extracted with 10% MeOH–$CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% MeOH–$CHCl_3$) to give **8** (51 mg). Yield 14%. $[\alpha]_D^{25}$ +57.9° (c=1.02, 10% MeOH–$CHCl_3$). Optical purity determined by chiral HPLC was 88.0% ee. Spectral data are the same as those of **18**. A small amount of **8** was recrystallized from $CHCl_3$–hexane for elemental analysis. mp 198—202 °C. *Anal.* Calcd for $C_{17}H_{17}N_3O\cdot 0.2H_2O$: C, 72.16; H, 6.11; N, 14.85. Found: C, 72.36; H, 6.11; N, 14.79.

8,9-Dihydro-10-(dimethylaminomethyl)pyrido[1,2-*a*]indol-6(7*H*)-one (19) A solution of **13** (500 mg, 2.7 mmol), 50% aqueous dimethylamine (0.32 ml, 3.5 mmol) and 35% formalin (0.32 ml, 3.8 mmol) in AcOH (2.5 ml) was stirred at 50 °C for 24 h. After evaporation of the solvent, the residue was diluted with H_2O, made basic with 2 N NaOH, and extracted with $CHCl_3$. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$–hexane recovered the starting material **13** (80 mg, 16%). Further elution with 10% MeOH–$CHCl_3$ gave **19** (436 mg, 67%) as an oil. IR (film): 1705, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (2H, m), 2.27 (6H, s), 2.79 (2H, t, J=6 Hz), 2.99 (2H, t, J=6 Hz), 3.49 (2H, s), 7.28 (2H, m), 7.61 (1H, m), 8.46 (1H, m). MS m/z: 242 (M$^+$).

8,9-Dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (3) A mixture of **19** (42 mg, 0.17 mmol), 10% Pd–C (24 mg), and ammonium formate (88 mg, 1.4 mmol) in EtOH (1.3 ml) was stirred at 75 °C. After 1.5 h, ammonium formate (95 mg, 1.5 mmol), 10% Pd–C (30 mg), and EtOH (0.5 ml) were added and the mixture was heated at 75 °C for a further 1.5 h. After evaporation of the solvent, the residue was neutralized with 3 N NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give **3** (21 mg, 62%), mp 76—78 °C (lit.[10] mp 81 °C). Compound **3** obtained was identical chromatographically and spectroscopically with the product prepared *via* the literature procedure.[11] IR (Nujol): 1675, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.20 (2H, m), 2.10 (3H, s), 2.60—2.90 (4H, m), 7.20 (2H, m), 7.40 (1H, m), 8.30 (1H, m).

8,9-Dihydro-10-(dimethylaminomethyl)-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (21) Method A: A mixture of **18** (279 mg, 1 mmol), 50% aqueous dimethylamine (0.14 ml, 1.5 mmol), and paraformaldehyde (42 mg, 1.4 mmol) in AcOH (2 ml) was stirred at 70 °C for 48 h. After evaporation of the solvent, the residue was neutralized with 3 N NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel (10% MeOH–$CHCl_3$) gave **21** (176 mg, 52%) as an oil, which was crystallized from MeOH–H_2O, mp 202—203 °C. IR (Nujol): 1690, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77—2.10 (2H, m), 2.11 (3H, s), 2.15 (6H, s), 2.65—2.83 (2H, m), 3.04—3.20 (3H, m), 3.43 (2H, s), 7.25 (2H, m), 7.41 (1H, s), 7.61 (1H, m), 8.35 (1H, m). *Anal.* Calcd for $C_{20}H_{24}N_4O\cdot 0.2H_2O$: C, 70.64; H, 7.23; N, 16.47. Found: C, 70.74; H, 7.12; N, 16.37. Further elution with 20% MeOH–$CHCl_3$ gave the bis(dimethylaminomethyl) compound **22** (41 mg, 10%) as an oil. IR (film): 1690, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76—2.05 (2H, m), 2.07 (3H, s), 2.13 (6H, s), 2.17 (6H, s), 2.60—2.83 (2H, m), 2.99—3.17 (3H, m), 3.33 (2H, s), 3.46 (2H, s), 7.23 (2H, m), 7.62 (1H, m), 8.35 (1H, m). MS m/z: 393 (M$^+$). Use of 35% formalin instead of paraformaldehyde slightly decreased the yield (47%).

Method B: A mixture of **18** (279 mg, 1.0 mmol), dimethylamine hydrochloride (122 mg, 1.5 mmol), and paraformaldehyde (42 mg, 1.4 mmol) in AcOH (2 ml) was stirred at 55 °C for 25 h. The reaction mixture was worked up in a similar manner to that of Method A to give compound **21** (241 mg, 72%).

8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido-[1,2-*a*]indol-6(7*H*)-one (7) A mixture of **21** (224 mg, 0.67 mmol), 10% Pd–C (210 mg), ammonium formate (500 mg, 7.9 mmol), THF (1 ml), EtOH (2 ml), and H_2O (1 ml) was stirred at 80 °C. After 80 min, 10% Pd–C (100 mg), ammonium formate (300 mg), and H_2O (1 ml) were added. The mixture was stirred at 80 °C for a further 1 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was neutralized with 2 N NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% MeOH–$CHCl_3$) to give **7** (118 mg, 60%), mp 225—229 °C. IR (Nujol): 1700, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.72—2.06 (2H, m), 2.11 (3H, s), 2.14 (3H, s), 2.63—2.80 (2H, m), 2.96—3.21 (3H, m), 7.26 (2H, m), 7.41 (1H, s), 7.48 (1H, m), 8.33 (1H, m). MS m/z: 293 (M$^+$). Compound **7** prepared by this route was identical with **7** from the original route in Chart 2.

(+)-8,9-Dihydro-10-(dimethylaminomethyl)-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (**20**) was prepared from **8** (90.5% ee) by Method B as described for **21**. Yield 66%. The spectral data of **20** were the same as those of **21**.

(+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]-pyrido[1,2-*a*]indol-6(7*H*)-one (**1**) was prepared from **20** by the same procedure as described for **7**. Yield 84%. $[\alpha]_D^{25}$ +41.5° (c=1.06, 10% MeOH–$CHCl_3$). [lit.[5] $[\alpha]_D^{25}$ +63° (c=1.0, 10% MeOH–$CHCl_3$)]. Optical purity determined by chiral HPLC was 59.8% ee. Crystallization of the salt of crude **1** and (+)-di-*p*-toluoyl-D-tartaric acid from

MeOH–$CHCl_3$ (7 : 3) gave pure **1** after neutralization of the salt. Yield based on **20** 58%. $[\alpha]_D^{25}$ +62° ($c=1.0$, 10% MeOH–$CHCl_3$). The spectral data were identical with those of compound **1** obtained *via* the original route in Chart 2.

[^{14}C](+)-8,9-Dihydro-10-(dimethylaminomethyl)-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one ([^{14}C]-20) Compound [^{14}C]-**20** was prepared from **8** (1.82 g, 6.5 mmol), [^{14}C]paraformaldehyde (100 mg, 60 mCi, 600 μCi/mg) and paraformaldehyde (50 mg) by method B as described for **21**. 1.01 g. Yield based on paraformaldehyde, 60%.

[^{14}C](+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)-methyl]pyrido[1,2-*a*]indol-6(7*H*)-one Hydrochloride ([^{14}C]-1 Hydrochloride) Hydrogenolysis of [^{14}C]-**20** (1.01 g, 3.0 mmol) was conducted by the same method as in the case of **21**. The free base of [^{14}C]-**1**: 747 mg. Yield 85%. Two crystallizations of the salt formed from the crude product and (+)-di-*p*-toluoyl-D-tartaric acid from MeOH–$CHCl_3$ (3 : 1) gave pure [^{14}C]-**1** hydrochloride (295 mg, 30%) after neutralization of the salt and conversion to the hydrochloride salt. Total activity: 10.9 mCi. Specific activity: 12.0 mCi/mmol. The enantiomeric excess was more than 97% as determined by reversed-phase HPLC. Analysis by silica gel TLC in AcOEt–acetone–H_2O–HCOOH (10 : 3 : 1 : 1) indicated 99.4% radiochemical purity.

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