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A NOVEL PREPARATION OF 3-HYDROXY-3*H*-INDOLE-3-ETHANAMINES AND -3*H*-INDOLE-3-ACETAMIDES HAVING EITHER A 4-MORPHOLINYL OR 1-PYRROLIDINYL GROUP AT THE 2-POSITION[1]

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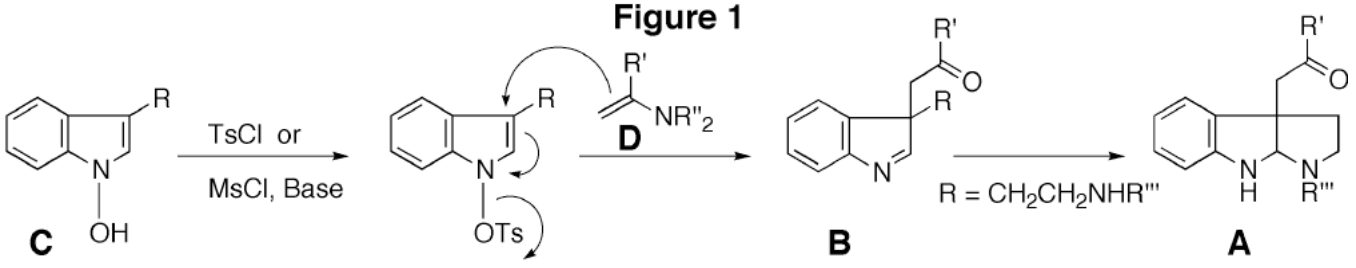
Abstract – A novel synthetic method is discovered for 3-hydroxy-3*H*-indole-3-ethanamines and -3*H*-indole-3-acetamides having either a 4-morpholinyl or 1-pyrrolidinyl group at the 2-position by reacting the corresponding 1-hydroxyindoles with enamines in the presence of tosyl or mesyl chloride. A plausible mechanism is proposed.

In our ongoing project to devise new reactions characteristic to 1-hydroxyindole skeletons,[2] we have thus far studied the reactions of 1-hydroxyindole-3-ethanamine derivatives with either mesyl chloride[3] (MsCl) or tosyl chloride[4] (TsCl) in the absence or presence[5] of nucleophiles. As a result, useful building blocks are now readily available for pyrrolo[2,3-*b*]indoles,[2,3] 4*H*-1,3-dioxolo[4,5-*b*]indoles,[2,4] and core structures of leptosins,[2,5] one family of indole alkaloids.

On the basis of the above data and the literature results,[6] we have designed a novel route to produce type **A** compounds through the intermediates (**B**) as shown in general formulas in Figure 1 by reacting 1-hydroxyindoles (**C**) with tosyl or mesyl chloride in the presence of enamines (**D**).

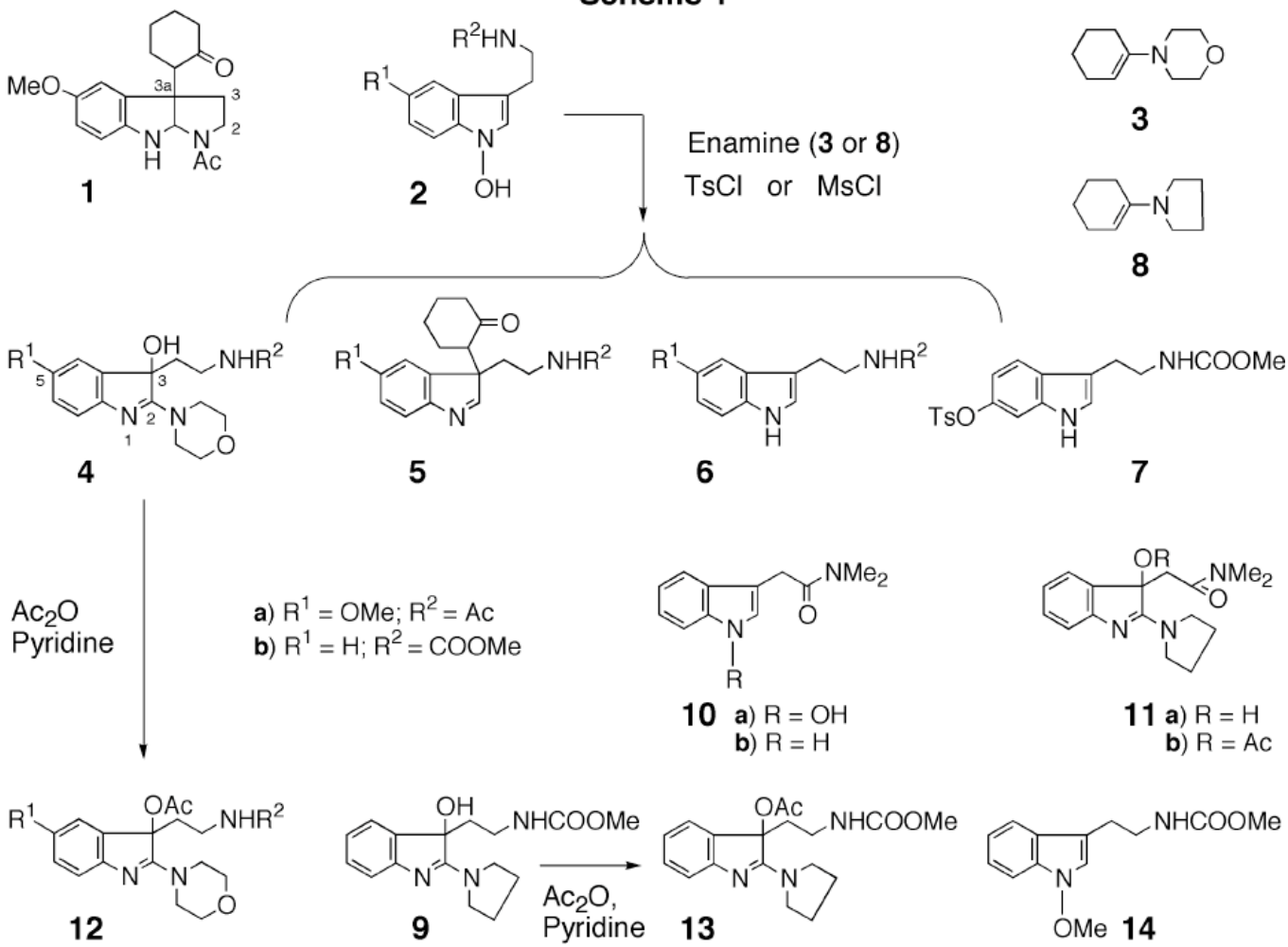
Figure 1



With an expectation to obtain 3a-substituted pyrrolo[2,3-*b*]indole derivative (**1**), TsCl was added to a

mixture of 1-hydroxymelatonin[7] (**2a**), 1-(4-morpholinyl)cyclohexene (**3**), and Et_3N in $CHCl_3$ at room temperature. To our surprise, the major product was a 37% yield of an unusual *N*b-acetyl-3-hydroxy-5-methoxy-2-(4-morpholinyl)-3*H*-indole-3-ethanamine (**4a**). The formation of the expected **1** was not observed at all while its intermediate, 2-[3-(2-acetylaminoethyl)-5-methoxy-3*H*-indol-3-yl]cyclohexanone (**5a**), was isolated in 4% yield together with 8% yield of melatonin (**6a**). In the same reaction, when MsCl was employed instead of TsCl, yields of **4a**, **5a**, and **6a** were 20, 6, and 17%, respectively. The reaction of 1-hydroxy-*N*b-methoxycarbonylindole-3-ethanamine (**2b**) with TsCl in the presence of **3** and Et_3N in $CHCl_3$ provided 3-hydroxy-*N*b-methoxycarbonyl-2-(4-morpholinyl)-3*H*-indole-3-ethanamine (**4b**) and *N*b-methoxycarbonyl-6-tosyloxyindole-3-ethanamine (**7**) in 44 and 11% yields, respectively.

Scheme 1

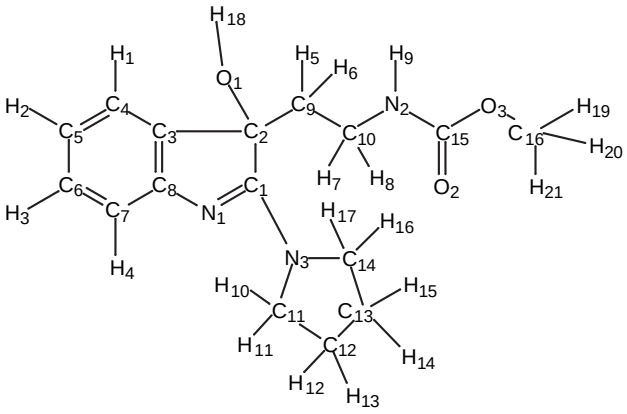


When the enamine component was changed from **3** to 1-(1-pyrrolidinyl)cyclohexene (**8**), **2b** afforded 3-hydroxy-*N*b-methoxycarbonyl-2-(1-pyrrolidinyl)-3*H*-indole-3-ethanamine (**9**) as a sole isolable product in 38% yield by the reaction with TsCl. Similarly, 1-hydroxy-*N*,*N*-dimethylindole-3-acetamide (**10a**) reacted with **8** to provide 3-hydroxy-*N*,*N*-dimethyl-2-(1-pyrrolidinyl)-3*H*-indole-3-acetamide (**11a**) and *N*,*N*-dimethylindole-3-acetamide (**10b**) in 21 and 26% yields, respectively.

Treatments of **4a**, **4b**, **9**, and **11a** with acetic anhydride and pyridine at room temperature afforded **12a**, **12b**, **13**, and **11b** in 78, 72, 67, and 59% yields, respectively, proving the presence of a hydroxy group in these molecules. Although the structures were deduced as they are depicted in Scheme 1 based on these chemical behaviors and spectroscopic data, we needed further confirmation. Luckily, compound (**9**) became suitable prisms for X-Ray single crystallographic analysis. The results shown in Figure 2-**b** clearly demonstrated the presence of a covalent bond connecting the *N*-1 (N_3 in Figure 2-**a**) of pyrrolidine to the *C*-2 (C_1 in Figure 2-**a**) of the indole molecule. Positional parameters are shown in Table 1.

Figure 2

a) Numbering of Atoms of **9**



b) ORTEP Drawing of **9** (R = 0.036)

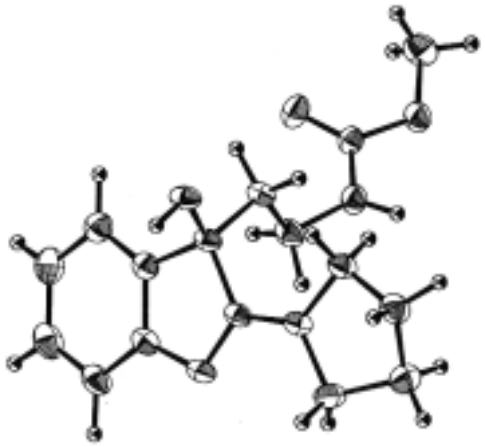


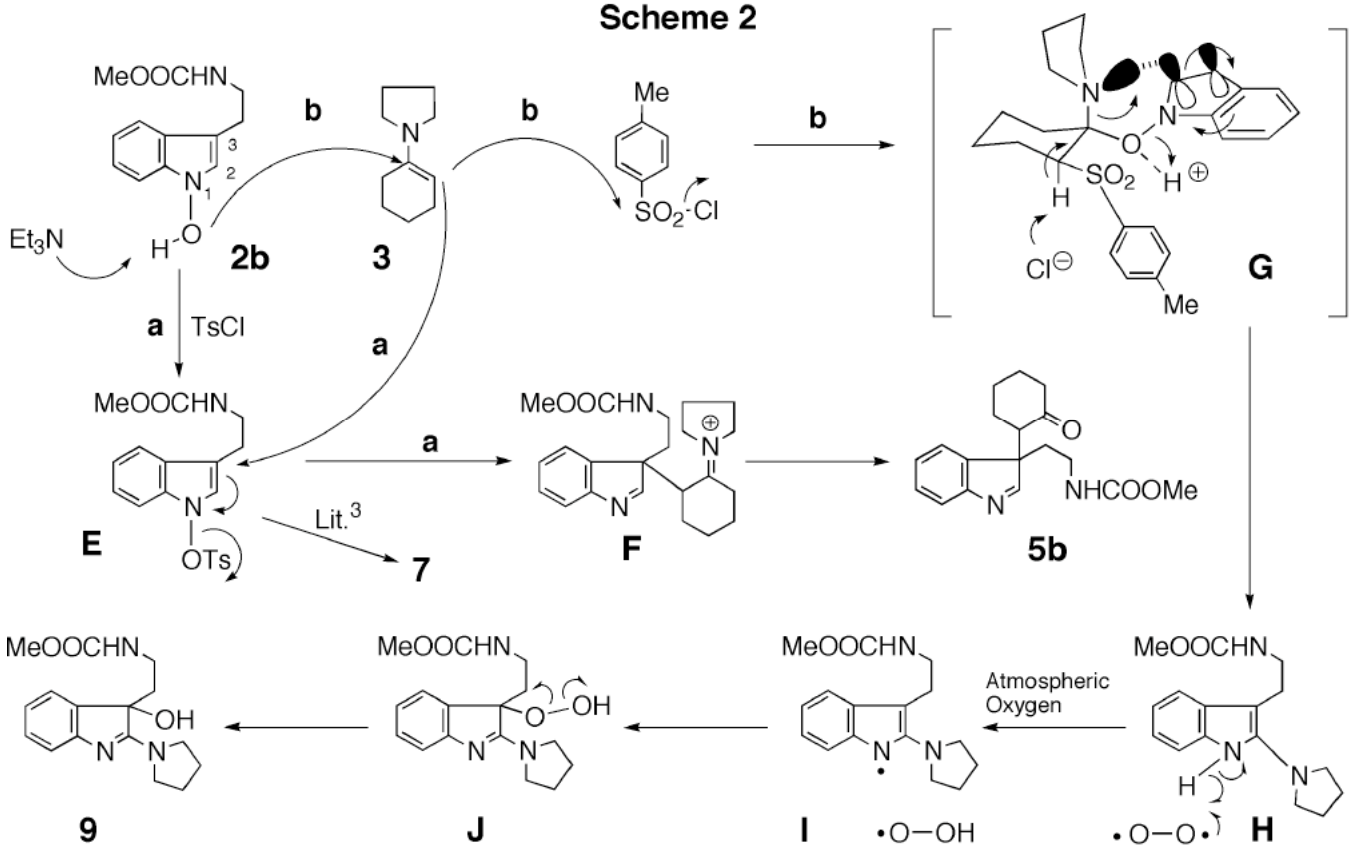
Table 1. Positional Parameters and *B* (eq) for **9**

atom	*x*	*y*	*z*	*B*(eq)	atom	*x*	*y*	*z*	*B*(eq)
O (1)	0.7438 (1)	0.02140 (6)	0.8470 (1)	3.42 (5)	H (1)	0.859 (2)	0.146 (1)	0.642 (2)	4.62 (1)
O (2)	0.5400 (1)	0.30087 (6)	0.7840 (1)	4.23 (6)	H (2)	1.097 (2)	0.202 (1)	0.598 (2)	5.34 (1)
O (3)	0.3918 (1)	0.32534 (6)	0.9616 (1)	4.03 (5)	H (3)	1.296 (3)	0.195 (1)	0.766 (2)	5.85 (2)
N (1)	1.0247 (1)	0.08711 (7)	1.0900 (1)	3.19 (6)	H (4)	1.289 (2)	0.146 (1)	1.000 (2)	4.21 (1)
N (2)	0.5903 (2)	0.25496 (8)	1.0102 (2)	3.71 (6)	H (5)	0.633 (2)	0.147 (1)	0.806 (2)	3.57 (1)
N (3)	0.8052 (1)	0.04772 (7)	1.1791 (1)	3.31 (6)	H (6)	0.590 (2)	0.1200 (9)	0.950 (2)	3.065 (9)
C (1)	0.8791 (2)	0.07150 (8)	1.0708 (2)	2.90 (6)	H (7)	0.776 (2)	0.237 (1)	0.917 (2)	4.49 (1)
C (2)	0.8020 (2)	0.08534 (8)	0.9157 (2)	2.95 (6)	H (8)	0.782 (2)	0.202 (1)	1.073 (2)	4.42 (1)
C (3)	0.9374 (2)	0.11702 (8)	0.8492 (2)	3.19 (6)	H (9)	0.553 (2)	0.248 (1)	1.096 (2)	4.67 (1)
C (4)	0.9471 (2)	0.1475 (1)	0.7146 (2)	3.89 (8)	H (10)	0.939 (2)	0.086 (1)	1.349 (2)	5.06 (1)
C (5)	1.0842 (2)	0.1779 (1)	0.6861 (2)	4.66 (9)	H (11)	0.946 (2)	−0.000 (1)	1.342 (2)	4.67 (1)
C (6)	1.2078 (2)	0.1762 (1)	0.7905 (2)	4.7 (1)	H (12)	0.695 (3)	0.085 (1)	1.435 (2)	6.06 (2)
C (7)	1.1974 (2)	0.1468 (1)	0.9263 (2)	4.08 (8)	H (13)	0.783 (2)	0.012 (1)	1.511 (2)	4.71 (1)
C (8)	1.0599 (2)	0.11724 (8)	0.9553 (2)	3.26 (7)	H (14)	0.531 (3)	−0.008 (1)	1.349 (2)	4.94 (1)
C (9)	0.6712 (2)	0.13944 (9)	0.9094 (2)	3.16 (7)	H (15)	0.662 (3)	−0.059 (1)	1.321 (2)	6.86 (2)
C (10)	0.7184 (2)	0.2112 (1)	0.9795 (2)	3.76 (7)	H (16)	0.578 (2)	0.064 (1)	1.157 (2)	4.41 (1)
C (11)	0.8795 (2)	0.0438 (1)	1.3295 (2)	4.07 (8)	H (17)	0.625 (2)	−0.010 (1)	1.097 (2)	4.13 (1)
C (12)	0.7475 (2)	0.0348 (1)	1.4190 (2)	4.42 (8)	H (18)	0.818 (3)	−0.012 (1)	0.856 (2)	5.11 (2)
C (13)	0.6342 (2)	−0.0080 (1)	1.3209 (2)	4.40 (9)	H (19)	0.340 (3)	0.396 (1)	0.808 (2)	6.42 (2)
C (14)	0.6449 (2)	0.0239 (1)	1.1724 (2)	3.75 (8)	H (20)	0.221 (3)	0.391 (1)	0.913 (2)	6.93 (2)
C (15)	0.5102 (2)	0.29353 (8)	0.9084 (2)	3.05 (6)	H (21)	0.254 (3)	0.333 (1)	0.783 (3)	6.79 (2)
C (16)	0.2910 (3)	0.3644 (1)	0.8580 (3)	4.9 (1)					

A plausible mechanism for the formations of **4**, **5**, and **7** is shown in Scheme 2 using **2b** as a

representative. Following the route **a**, tosylation of **2b** and subsequent nucleophilic attack on the resultant tosylate (**E**) at the 3-position by the enamine (**3**) can afford **5b** through **F** after work-up, and this is an expected reaction pathway. On the other hand, following the route **b**, tosylation[8] of the enamine (**3**) would occur simultaneously with the attack by the 1-hydroxy oxygen of **2b** to generate the intermediate (**G**), in which nitrogen lone pair orbital of pyrrolidine can interact with the π-orbital (2,3-bond) of indole. Subsequent acid catalyzed O—N bond cleavage results in the formation of **H** following the electron movement as shown by the curved arrows. Highly electron rich compound (**H**) would be oxidized to the final product (**9**) through intermediates (**I**) and (**J**) under atmospheric oxygen.

Scheme 2



The above mechanism necessitates 1-hydroxyindole structures as an essential component. In order to determine this point, a 1-methoxy compound was employed in the above reaction. Thus the reaction of *N*b-methoxycarbonyl-1-methoxyindole-3-ethanamine (**14**) with **8** by the action of TsCl in $CHCl_3$ afforded a total recovery of **14** in accord with the above mechanism.

In summary, we have discovered a novel synthetic method for 3-hydroxy-3*H*-indole-3-ethanamines and 3-hydroxy-3*H*-indole-3-acetamides carrying either a 4-morpholinyl or 1-pyrrolidinyl group at the 2-position by reacting the corresponding 1-hydroxyindoles with enamines in the presence of tosyl or mesyl chloride. Studies are in progress to establish scope and limitations of this new type of reaction characteristic to 1-hydroxyindole skeletons.

EXPERIMENTAL

IR spectra were determined with a Shimadzu IR-420 or HORIBA FT-720 spectrophotometer and ^{1}H-NMR spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

***N*b-Acetyl-3-hydroxy-5-methoxy-2-(4-morpholinyl)-3*H*-indole-3-ethanamine (4a), 2-[3-(2-Acetyl-aminoethyl)-5-methoxy-3*H*-indol-3-yl]cyclohexanone (5a), and Melatonin (6a) from 1-Hydroxy-melatonin (2a) : TsCl method** — TsCl (102.3 mg, 0.51 mmol) was added to a solution of **2a** (102.4 mg, 0.41 mmol) in anhydrous $CHCl_3$ (5.0 mL) and Et_3N (0.5 mL, 3.56 mmol) and 1-(4-morpholinyl)-cyclohexene (207.3 mg, 1.24 mmol) at 0°C and the mixture was stirred at 0°C for 1 h. After addition of H_2O under ice cooling, 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 an oil, which was column-chromatographed repeatedly on SiO_2 sequentially with $CHCl_3$ and AcOEt to give **4a** (50.3 mg, 37%), **6a** (7.3 mg, 8%) and **5a** (5.4 mg, 4%) in the order of elution. **4a**: colorless oil. IR (film): 3284, 1652, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.78 (3H, s), 2.13—2.23 (2H, m), 2.86—2.93 (1H, m), 3.10—3.17 (1H, m), 3.68—3.78 (8H, m), 3.73 (3H, s), 5.49 (1H, br t, *J*=5.5 Hz, disappeared on addition of D_2O), 6.71—6.74 (2H, m), 6.93—6.96 (1H, m). HRMS *m/z*: Calcd for $C_{17}H_{23}N_3O_4$: 333.1688. Found: 333.1682. **5a**: mp 193—194°C (colorless needles recrystallized from AcOEt–MeOH). IR (KBr): 3299, 1708, 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.76—1.86 (1H, m), 1.89—1.99 (1H, m), 1.93 (3H, s), 2.11—2.18 (1H, m), 2.19—2.27 (2H, m), 2.44—2.49 (1H, m), 2.50—2.58 (1H, m), 2.61—2.67 (1H, m), 2.88—3.00 (2H, m), 3.49—3.56 (1H, m), 3.60—3.68 (1H, m), 3.85 (3H, s), 4.92 (1H, dd, *J*=13.0, 5.7 Hz), 5.57 (1H, br s, disappeared on addition of D_2O), 6.85 (1H, dd, *J*=8.6, 2.4 Hz), 6.94 (1H, s), 7.02 (1H, d, *J*=2.4 Hz), 7.03 (1H, d, *J*=8.6 Hz). MS *m/z*: 328 (M^+). *Anal.* Calcd for $C_{19}H_{24}N_2O_3 \cdot 1/2H_2O$: C, 67.65; H, 7.42; N, 8.31. Found: C, 67.86; H, 7.27; N, 8.38.

MsCl method — In the same procedure as described in the above TsCl method, MsCl (78.2 mg, 0.68 mmol) instead of TsCl, **2a** (130.3 mg, 0.53 mmol) in anhydrous $CHCl_3$ (5.0 mL), Et_3N (0.5 mL, 3.56 mmol), and 1-(4-morpholinyl)cyclohexene (878.1 mg, 5.25 mmol) were used. After the same work-up and column-chromatography, **4a** (34.4 mg, 20%), **6a** (20.6 mg, 17%) and **5a** (10.4 mg, 6%) were obtained in the order of elution.

3-Hydroxy-*N*b-methoxycarbonyl-2-(4-morpholinyl)-3*H*-indole-3-ethanamine (4b) and *N*b-Methoxycarbonyl-6-tosyloxyindole-3-ethanamine (7) from 1-Hydroxy-*N*b-methoxycarbonylindole-3-ethanamine (2b) — In the same procedure and work-up as described in the above TsCl method, TsCl (54.5 mg, 0.29 mmol, **2b** (51.5 mg, 0.22 mmol) in $CHCl_3$ (2.0 mL), Et_3N (0.25 mL) and 1-(4-

morpholinyl)cyclohexene (110.4 mg, 0.66 mmol) in $CHCl_3$ (0.5 mL) were used. After column-chromatography with $CHCl_3$–MeOH (99:1, v/v) followed by $CHCl_3$–MeOH (97:3, v/v) afforded **7** (9.6 mg, 11%) and **4b** (30.6 mg, 44%) in the order of elution. **4b**: colorless oil. IR (film): 3338, 1701, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.18—2.29 (2H, m), 2.89—2.99 (2H, m), 3.63 (3H, s), 3.71—3.82 (8H, m), 4.78 (1H, br s), 6.92 (1H, dt, *J*=0.8, 7.5 Hz), 7.04 (1H, br d, *J*=7.5 Hz), 7.15 (1H, dd, *J*=7.5, 0.8 Hz), 7.22 (1H, dt, *J*=0.8, 7.5 Hz). HRMS (FAB$^+$) *m/z*: Calcd for $C_{16}H_{22}N_3O_4$ (MH^+): 320.1611. Found: 320.1613. **7**: pale yellow oil. IR (film): 3410, 3319, 1701, 1529, 1458, 1367 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.44 (3H, s), 2.92 (2H, t, *J*=6.6 Hz), 3.46 (2H, q, *J*=6.6 Hz, collapsed to t on addition of D_2O), 3.65 (3H, s), 4.75 (1H, br s, disappeared on addition of D_2O), 6.61 (1H, br d, *J*=8.6 Hz), 7.04 (1H, d, *J*=2.0 Hz, collapsed to s on addition of D_2O), 7.13 (1H, br s), 7.29 (2H, d, *J*=8.2 Hz), 7.41 (1H, d, *J*=8.6 Hz), 7.71 (2H, d, *J*=8.2 Hz), 8.20 (1H, br s, disappeared on addition of D_2O). HRMS *m/z*: Calcd for $C_{19}H_{20}N_2O_5S$: 388.1092. Found: 388.1100. The NMR spectrum of **7** is superimposable on that of authentic *N*b-acetyl-6-tosyloxyindole-3-ethanamine.[4] This fact proves that **7** has a 6-tosyloxyindole structure.

3-Hydroxy-*N*b-methoxycarbonyl-2-(1-pyrrolidinyl)-3*H*-indole-3-ethanamine (9) from 2b — In the same procedure and work-up as described in the above TsCl method, TsCl (54.1 mg, 0.28 mmol), **2b** (51.1 mg, 0.22 mmol) in $CHCl_3$ (2.0 mL) and Et_3N (0.25 mL), and 1-(1-pyrrolidinyl)cyclohexene (98.9 mg, 0.65 mmol) in $CHCl_3$ (0.5 mL) were used. After column-chromatography on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:5:0.5, v/v) afforded **9** (24.8 mg, 38%). **9**: mp 220.0—221.0°C (colorless prisms, recrystallized from $CHCl_3$-hexane). IR (KBr): 3325, 1693, 1595, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) □: 1.77—1.86 (2H, m), 1.87—1.99 (2H, m), 2.09 (1H, dt, *J*=5.3, 12.1 Hz), 2.16 (1H, dt, *J*=5.3, 12.1 Hz), 2.43—2.55 (1H, m), 2.73 (1H, sep, *J*=5.3 Hz), 3.45—3.49 (2H, m), 3.46 (3H, s), 3.55—3.68 (1H, m), 4.13—4.23 (1H, m), 6.01 (1H, s, disappeared on addition of D_2O), 6.78 (1H, t, *J*=7.4 Hz), 6.85 (1H, d, *J*=7.4 Hz), 6.93 (1H, br t, *J*=5.0 Hz, disappeared on addition of D_2O), 7.08 (1H, t, *J*=7.4 Hz), 7.09 (1H, d, *J*=7.4 Hz). MS *m/z*: 303 (M^+). *Anal.* Calcd for $C_{16}H_{21}N_3O_3 \cdot 1/4H_2O$: C, 62.42; H, 7.04; N, 13.65. Found: C, 62.66; H, 6.95; N, 13.54.

3-Hydroxy-*N*,*N*-dimethyl-2-(1-pyrrolidinyl)-3*H*-indole-3-acetamide (11a) and *N*,*N*-Dimethyl-indole-3-acetamide (10b) from 1-Hydroxy-*N*,*N*-dimethylindole-3-acetamide (10a) — In the same procedure and work-up as described in the above TsCl method, TsCl (59.5 mg, 0.31 mmol), **10a** (52.3 mg, 0.20 mmol) in $CHCl_3$ (2.0 mL) and Et_3N (0.25 mL), and 1-(1-pyrrolidinyl)cyclohexene (112.2 mg, 0.72 mmol) in $CHCl_3$ (0.5 mL) were used. After column-chromatography on SiO_2 with $CHCl_3$–MeOH (97:3, v/v), followed by $CHCl_3$–MeOH–28% NH_3 (46:2:0.2, v/v) afforded **10b** (12.8 mg, 26%) and **11a** (14.7 mg, 21%) in the order of elution. **11a**: colorless oil. IR (film): 3261, 1622, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.85—2.03 (4H, m), 2.68 (1H, d, *J*=15.4 Hz), 2.77 (3H, s), 3.01 (3H, s), 3.01 (1H, d, *J*=15.4

Hz), 3.64 (3H, br s), 4.48 (1H, br s), 6.80 (1H, t, *J*=7.4 Hz), 7.07 (1H, d, *J*=7.4 Hz), 7.15 (1H, t, *J*=7.4 Hz), 7.17 (1H, br d, *J*=7.4 Hz). HRMS *m/z*: Calcd for $C_{16}H_{21}N_3O_2$: 287.1634. Found: 287.1628.

3-Acetoxy-*N*b-acetyl-2-(4-morpholinyl)-3*H*-indole-3-ethanamine (12a) from 4a — A solution of **4a** (18.9 mg, 0.057 mmol) in Ac_2O (2.0 mL, 21.2 mmol) was stirred at 70°C for 2 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:3:0.3, v/v) to give **12a** (16.2 mg, 78%). **12a**: colorless viscous oil. IR (film): 3288, 1751, 1654, 1567 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.81 (3H, s), 2.05 (3H, s), 2.26—2.36 (2H, m), 2.93—3.00 (1H, m), 3.04—3.11 (1H, m), 3.60—3.82 (8H, m), 3.77 (3H, s), 5.28 (1H, br t, *J*=6.4 Hz, disappeared on addition of D_2O), 6.67 (1H, d, *J*=2.6 Hz), 6.77 (1H, dd, *J*=8.5, 2.6 Hz), 7.05 (1H, d, *J*=8.5 Hz). HRMS *m/z*: Calcd for $C_{19}H_{25}N_3O_5$: 375.1794. Found: 375.1791.

3-(2-Acetylaminoethyl)-3-acetoxy-2-(4-morpholinyl)-3*H*-indole (12b) from 4b — Ac_2O (0.5 mL, 5.30 mmol) was added to a solution of **4b** (10.5 mg, 0.03 mmol) in pyridine (1.0 mL) and the mixture was stirred at rt for 4 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **12b** (8.6 mg, 72%). **12b**: colorless oil. IR (film): 3338, 1747, 1716, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.05 (3H, s), 2.27—2.38 (2H, m), 2.82—2.89 (1H, m), 2.98—3.05 (1H, m), 3.64 (3H, s), 3.69—3.81 (8H, m), 4.66 (1H, br s), 6.92 (1H, dt, *J*=1.0, 7.5 Hz), 7.05 (1H, dd, *J*=7.5, 1.0 Hz), 7.12 (1H, br d, *J*=7.5 Hz), 7.24 (1H, dt, *J*=1.0, 7.5 Hz). HRMS *m/z*: Calcd for $C_{18}H_{23}N_3O_5$: 361.1637. Found: 361.1638.

3-Acetoxy-*N*b-methoxycarbonyl-2-(1-pyrrolidinyl)-3*H*-indole-3-ethanamine (13) from 9 — Ac_2O (0.5 mL, 5.30 mmol) was added to a solution of **9** (8.6 mg, 0.0284 mmol) in pyridine (1.0 mL) and the mixture was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:2:0.2, v/v) to give **13** (6.6 mg, 67%). **13**: pale yellow oil. IR (film): 3332, 1749, 1718, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.90—1.99 (4H, m), 2.06 (3H, s), 2.28 (1H, dt, *J*=13.5, 5.9 Hz), 2.53 (1H, quin, *J*=6.9 Hz), 2.80 (1H, sex, *J*=6.9 Hz), 3.06 (1H, sex, *J*=6.9 Hz), 3.44—3.47 (1H, m), 3.55—3.65 (1H, m), 3.61 (3H, s), 3.70—3.79 (2H, m), 4.72 (1H, br s), 6.87 (1H, dt, *J*=1.0, 7.5 Hz), 7.04 (1H, dd, *J*=7.5, 1.0 Hz), 7.13 (1H, br d, *J*=7.5 Hz), 7.21 (1H, dt, *J*=1.0, 7.5 Hz). HRMS *m/z*: Calcd for $C_{18}H_{23}N_3O_4$: 345.1688. Found: 345.1692.

2-[3-Acetoxy-2-(1-pyrrolidinyl)-3*H*-indol-3-yl]-*N*,*N*-dimethylacetamide (11b) from 11a — Ac_2O (0.5 mL, 5.30 mmol) was added to a solution of **11a** (10.1 mg, 0.035 mmol) in pyridine (1.0 mL) and the mixture was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:2:0.2, v/v) to give **11b** (6.8 mg, 59%). **11b**: colorless oil. IR (film): 1749, 1637, 1566 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.90—2.00 (4H, m), 2.11 (3H, s), 2.47 (3H, s), 2.83 (3H, s), 2.93 (1H, d, *J*=14.0 Hz), 3.30 (1H, d, *J*=14.0

Hz), 3.61—3.66 (2H, m), 3.74—3.79 (2H, m), 6.81 (1H, dt, *J*=1.0, 7.4 Hz), 7.10 (1H, dd, *J*=7.4, 1.0 Hz), 7.11 (1H, br d, *J*=7.4 Hz), 7.19 (1H, dt, *J*=1.0, 7.4 Hz). HRMS *m/z*: Calcd for $C_{18}H_{23}N_3O_3$: 329.1740. Found: 329.1737.

X-Ray Crystallographic Analysis of 9 — A single crystal (0.30x0.30x0.50 mm) of **9** was obtained by recrystallization from MeOH. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-*K*α radiation (λ=1.54178 Å). Crystal data: $C_{16}H_{21}N_3O_3$, *M*=303.36, monoclinic, space group $P2_1/c$ (#14), *a*=8.8343 (6) Å, *b*=18.634 (2) Å, *c*=9.235 (1) Å, β=95.964 (7)°, *V*=1512.0 (2) Å^3, *Z*=4, D_{calc}=1.332 g/cm^3, *F*(000)=648, and μ(Cu*K*α)=7.24 cm^{-1}. The structure was solved by direct methods using MITHRIL.[9] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 2086 observed reflections ($I>3.00\sigma(I)$, $2\theta<120.1°$) and 283 variable parameters. The final refinement converged with *R*=0.036 and R_w=0.054.

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