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Registry No. **1a**, 4744-72-3; **6** (R = Me), 21769-95-9; **6** (R = Et), 126664-29-7; **6** (R = Pr), 126664-30-0; **6** (R = Bu), 126664-31-1; **6** (R = CH_2Cl), 126664-32-2; **6** (R = Ph), 126664-33-3; **7** (R = Me), 6495-44-9; **7** (R = Et), 126664-34-4; **7** (R = Pr), 126664-35-5; **7** (R = Bu), 126693-72-9; **7** (R = CH_2Cl), 126664-36-6; **7** (R = Ph), 126664-37-7; acetic anhydride, 108-24-7; propanoic anhydride, 123-62-6; butanoic anhydride, 106-31-0; pentanoic anhydride, 2082-59-9; chloroacetic anhydride, 541-88-8; benzoic anhydride, 93-97-0.

Supplementary Material Available: Tables of atomic fractions coordinates, anisotropic thermal parameters, bond distances, and bond angles for **6** and **7** (12 pages); listings of observed and calculated structure factors for **6** and **7** (27 pages). Ordering information is given on any current masthead page.

Practical Synthesis of 5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol (Cotarnine)

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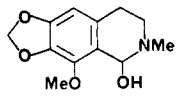
5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol (cotarnine, **1**), an oxidative degradation product of (3*S*)-6,7-dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (noscapine), has efficiently been synthesized from 2-methoxy-3,4-(methylenedioxy)benzaldehyde (**7**) in 66% overall yield. [*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]-*N*-methylamino]acetaldehyde dimethyl acetal, obtained by reductive amination of **7** with aminoacetaldehyde dimethyl acetal followed by *N*-methylation, was cyclized in acid to 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (**12**). The major byproduct of the cyclization was C-8 methoxy derivative of **12**, and the amount of this byproduct was decreased by removal of MeOH formed in the reaction mixture. Acetylation of the hydroxyl group in **12** and hydrogenolysis gave 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (hydrocotarnine), which was oxidized with I_2 followed by basification to afford **1**.

5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo-[4,5-*g*]isoquinolin-5-ol (cotarnine, **1**) has been obtained for



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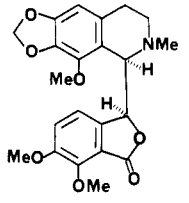
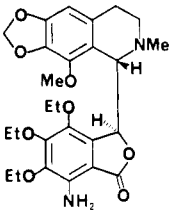
the first time by the oxidative degradation of (3*S*)-6,7-dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (noscapine, **2**),[1] which is an isoquinoline alkaloid isolated from



2

opium. Compound **1** shows hemostatic activity and is the key component in the preparation of (3*RS*)-7-amino-4,5,6-triethoxy-3-[(5*RS*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (tritoqualine, **3**). This is clinically used as an antiallergic drug[2,3]



3

and has recently been shown to have a preventive effect on liver injury in rats induced by treatment with CCl_4 and other biological activities.[4] Clinical consumption of **2** as an antitussive causes a short supply of **2**, and the preparation of **1** from other starting materials is thus desired.

Since Salway's first total synthesis of **1** from amide **4a**,[5] several related syntheses[6-8] have been reported using the Bischler–Napieralski reaction[9] of **4b** and **4c** to construct 3,4-dihydroisoquinolines (Scheme I). In these methods the cyclization reactions can proceed in two directions. For

(1) (a) Wöhler, F. *Liebigs Ann. Chem.* **1844**, *50*, 1. (b) Tanaka, Y.; Midzuno, T.; Okami, T. *Yakugaku Zasshi* **1930**, *50*, 559.

(2) Hahn, F.; Teschendorf, H. J.; Kretzschmar, R.; Gossow, U.; Glanzmann, Ch.; Filipowski, P.; Somorjai, K. *Arzneim.-Forsch.* **1970**, *20*, 1490.

(3) Fr. Patent, 1 295 309, 1962 (to Lab. de Resherches Biol. Laborec); *Chem. Abstr.* **1962**, *57*, 16576.

(4) (a) Umezu, K.; Yuasa, S.; Sudoh, A. *Oyo Yakuri*, **1985**, *29*, 381. (b) Umezu, K.; Yuasa, S.; Sudoh, A. *Nippon Yakurigaku Zasshi*, **1985**, *85*, 185. (c) Yuasa, S.; Sudoh, A.; Toshida, K.; Takechi, M.; Umezu, K. *Ibid.* **1985**, *85*, 249.

(5) Salway, A. H. *J. Chem. Soc.* **1910**, *97*, 1208.

(6) Decker, H.; Becker, P. *Liebigs Ann. Chem.* **1912**, *395*, 328.

(7) Kindler, K.; Peschke, W. *Arch. Pharm. (Weinheim, Ger.)* **1932**, *270*, 353.

(8) Dallacker, F.; Bernabei, D.; Katzke, R.; Benders, P.-H. *Chem. Ber.* **1971**, *104*, 2526.

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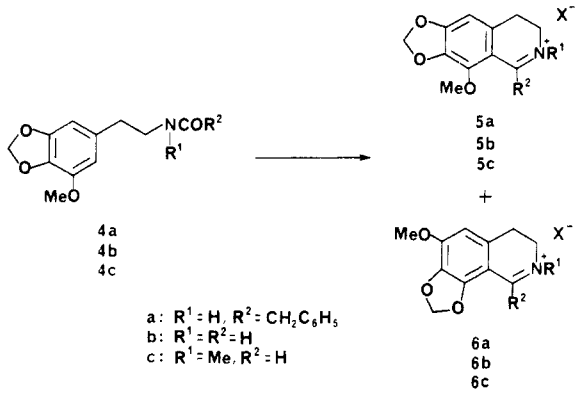
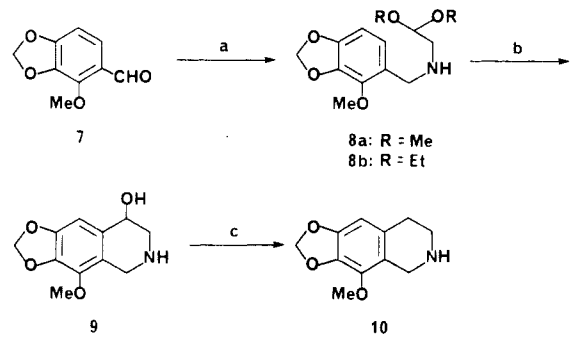
0022-3263/90/1955-3767$02.50/0

Scheme I



Scheme II[a]



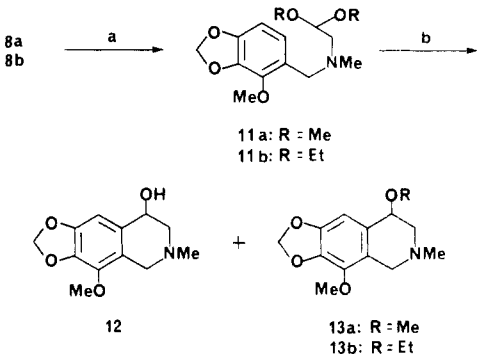
[a] (a) 7 → 8a, $H_2NCH_2CH(OMe)_2$, H_2, Pd-C, MeOH; 7 → 8b, $H_2NCH_2CH(OEt)_2$, H_2, Pd-C, EtOH; (b) 6 N HCl; (c) H_2, Pd-C.

example, in the cyclization of **4a**,[5] **5a** was formed along with the undesirable isomer **6a**, and the separation of their hydrochlorides (X = Cl) by fractional crystallization was troublesome. Although in the cyclization of **4b**[6] or **4c**[7,8] the amount of isomer **6b** or **6c** has not been reported, we found that 6–11% was formed under the reported reaction conditions;[10] neither isomer could be easily removed from the desired **5b** or **5c** by recrystallization.[11] Furthermore, the preparation of amides **4a**, **4b**, and **4c** requires many steps. These disadvantages in the synthesis of **1** prompted us to investigate a new method of synthesizing this compound. Here, we report a new practical synthesis of **1** starting from 2-methoxy-3,4-(methylenedioxy)benzaldehyde (**7**),[12] using the Bobbitt modification[13] of the Pomeranz–Fritsch isoquinoline synthesis as the key step.[14]

Results and Discussion

The first approach is depicted in Scheme II. Hydrogenation of a mixture of aldehyde **7**[12] and aminoacetaldehyde dimethyl acetal in MeOH over Pd on carbon gave acetal **8a** in 98% yield. This was dissolved in 6 N HCl (7.5 mL/mmol **8a**) and allowed to stand at room temperature for 4 days according to Bobbitt's procedure.[13] Recrystallization from EtOH gave **9** in the low yield of 33% due to the difficulty of purification. Alternatively, without isolation, **9** was hydrogenolyzed over Pd on carbon to afford **10** in 55% yield. Conversion of **10** to **1** has successively been achieved via **5b**.[15] Because the yield of **10** was relatively low and hydrogenolysis required a large amount of catalyst and long reduction time, these methods are unsuitable for a practical synthesis. The reaction of acetal **11a** was then examined (Scheme III) to reduce these disadvantages.

Scheme III[a]



[a] (a) **8a** → **11a**, CH_2O_{aq}, H_2, Pd-C, MeOH; **8b** → **11b**, CH_2O_{aq}, H_2, Pd-C, EtOH; (b) 6 N HCl or 6 N H_2SO_4.

Table I. Effects of Reaction Condition on the Cyclization of 11a[a]

entry	acid (mL/mmol **11a**)	temp (°C)	time (h)	product (HPLC, %) **12**	**13a**
1	6 N HCl (7.5)	25	24	89	7.6
2	6 N HCl (2.0)	25	24	68	14[b]
3	6 N HCl (2.0)	25	75	79	20
4	6 N H_2SO_4 (7.5)	25	24	8.9	0[b,c]
5	6 N H_2SO_4 (2.0)	60	1.5	46	4.8[b,c]
6	6 N H_2SO_4 (2.0)	60	6	85	13
7	6 N H_2SO_4 (1.33)	60	6	82	16
8	12 N H_2SO_4 (1.0) MeOH (1:1 vol)	60	6	5.9	21[b,c]
9	6 N methanolic H_2SO_4 (2.0)	60	6	0	0[c]
10	6 N H_2SO_4 (2.0)	60	6	94	1.4[d]

[a] The reaction was carried out using 3 mmol of **11a**. [b] The reaction intermediate (t_R = 13.2 min) remained. [c] The starting material **11a** remained. [d] N_2 was bubbled into the solution during the reaction with the addition of H_2O to keep the reaction volume constant.

Acetal **11a** was easily prepared by the reductive N-methylation of **8a** with formaldehyde over Pd on carbon in MeOH in 99% yield. The cyclization of **11a** in 6 N HCl (7.5 mL/mmol **11a**) for 24 h at room temperature gave 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (**12**) in 75% yield after recrystallization from EtOH. 5,6,7,8-Tetrahydro-4,8-dimethoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (**13a**) was isolated from the mother liquor as a byproduct by column chromatography on silica gel. In the reaction of diethyl acetal **11b**, **12** was isolated in 78% yield and 5,6,7,8-tetrahydro-8-ethoxy-4-methoxy-6-methyl-1,3-dioxolo-[4,5-*g*]isoquinoline (**13b**) was formed as a byproduct. Although Bobbitt et al.[13a] obtained the dimer or trimer of isoquinoline in the prolonged reaction of [*N*-(3-hydroxy-4-

(10) Umezawa, B.; Morita, Y.; Shirasaka, T. Jpn. Kokai Tokkyo Koho JP 62 223184, 1987; *Chem. Abstr.* **1988**, *108*, 167452.
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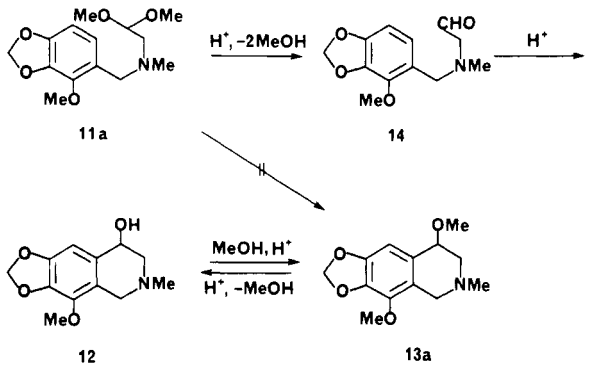
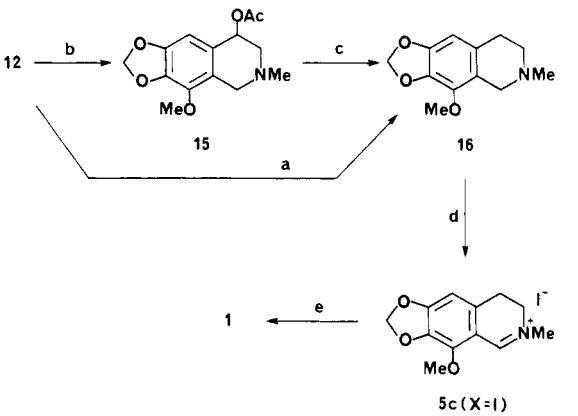
(12) Brownell, W. B.; Weston, A. W. *J. Am. Chem. Soc.* **1951**, *73*, 4971.
(13) (a) Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L.; Ebermann, R. *J. Org. Chem.* **1965**, *30*, 2247. (b) Bobbit, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *Ibid.* **1967**, *32*, 2225. (c) Bobbitt, J. M.; Sih, J. C. *Ibid.* **1968**, *33*, 856. (d) Bobbitt, J. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Ed.; Academic Press: New York, 1973; Vol. 15, p 99.
(14) (a) Morita, Y.; Imaki, N.; Takayanagi, H.; Shirasaka, T. Jpn. Kokai Tokkyo Koho JP 62 48678, 1987. (b) Morita, Y.; Imaki, N.; Takayanagi, H.; Shirasaka, T. Jpn. Kokai Tokkyo Koho JP 62 56492, 1987. (c) Morita, Y.; Imaki, N.; Takuma, Y.; Shirasaka, T.; Shimpuku, T. Jpn. Kokai Tokkyo Koho JP 62 61968, 1987. (d) Morita, Y.; Imaki, N.; Shirasaka, T.; Shimpuku, T. Jpn. Kokai Tokkyo Koho JP 62 61982, 1987.
(15) Morita, Y.; Imaki, N.; Shirasaka, T. Jpn. Kokai Tokkyo Koho, JP 62 84088, 1987; *Chem. Abstr.* **1987**, *107*, 198725.

Scheme IV



Scheme V[a]



[a] (a) H_2, Pd–C, 6 N HCl; (b) AcCl, CH_2Cl_2; (c) H_2, Pd–C, EtOH; (d) I_2, KOAc, EtOH; (e) NaOH, H_2O.

methoxybenzyl)amino]acetaldehyde diethyl acetal, similar byproducts were not detected in 24-h reaction of **11a** or **11b**. The various reaction conditions using acetal **11a** were examined, and the results are shown in Table I.

A decrease in the amount of 6 N HCl or replacement by 6 N H_2SO_4 retarded the reaction. The amount of byproduct **13a** increased as the amount of acid was decreased. Addition of MeOH to the reaction mixture retarded the reaction and increased the amount of byproduct **13a**, and the reaction did not take place in 6 N methanolic H_2SO_4. In addition, bubbling of N_2 into the solution during the reaction decreased the amount of **13a** and increased the yield of **12**. From these results, the cyclization reaction path of acetal **11a** would be presumed as shown in Scheme IV.

Acetal **11a** is first hydrolyzed into aldehyde **14**,[13b] which is then cyclized with acid catalyst to give the product **12**. The presence of intermediate **14** was confirmed by ^1H NMR measurement in the reaction mixture prepared by the short treatment of **11a** with acid. The ^1H NMR spectrum in $CDCl_3$ showed a triplet peak at δ 9.65, indicating the presence of aldehyde. HPLC analysis also showed a new peak (t_R = 13.2 min) that would correspond to aldehyde **14**. Although **14** was too unstable to be isolated in pure form, the reduction with $NaBH_4$ of the briefly reacted mixture gave the fully characterized compound 2-[*N*-[2-methoxy-3,4-(methylenedioxy)benzyl]-*N*-methylamino]ethanol. Vinot[16] reported that 4-alkoxy-1,2,3,4-tetrahydroisoquinolines were directly formed from acetals with BF_3 catalyst under anhydrous conditions. Under aqueous condition, however, **13a** or **13b** would be derived from **12** with MeOH or EtOH that is produced by hydrolysis of acetal **11a** or **11b**. In fact, the reaction of **12** with MeOH in 6 N H_2SO_4 at 60 °C gave **13a**. Therefore, it was expected that removal of MeOH from the reaction mixture would suppress the formation of **13a**. This was certainly proved to occur by bubbling N_2 in the reaction mixture. As mentioned earlier, reduction of acid solution volume caused an increase in the amount of **13a**. Even in such a case, **12** would be prepared in high yield provided MeOH were removed from the mixture. Thus, reaction of **11a** in 6 N H_2SO_4 (1.33 mL/mmol **11a**) at 60 °C for 6 h with removal of MeOH under vacuum distillation afforded **12** in 98% analytical yield, and pure **12** was isolated in 87% yield after recrystallization from EtOH.

Conversion of **12** to **1** is depicted in Scheme V. Alcohol **12** in HCl was reduced to 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (hydrocotarnine, **16**) according to Bobbitt's procedure. (See Experimental Section.) This reduction, however, requires a long time and a large amount of Pd on carbon as in the reduction of **9**. Hydrogenolysis at high temperature and high pressure gave unsatisfactory results because **12** was unstable in the hot acidic solution over a long period. Hydrogenolysis of **12** under a neutral condition, such as in EtOH, was unsuccessful. On the other hand, C-8 acetoxy derivative **15** was expected to be hydrogenolyzed in EtOH.[17] Acetylation of **12** with acetyl chloride in CH_2Cl_2 gave **15** in 99% yield, which was smoothly hydrogenolyzed in EtOH over Pd on carbon to afford **16** in 95% yield. Then, **16** was oxidized to 7,8-dihydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolinium iodide (cotarnine iodide, **5c**, X = I) with 1.05 equiv of I_2 in the presence of potassium acetate in refluxing EtOH. Isoquinolinium iodide **5c** (X = I) was collected by filtration after being cooled as a yellow solid containing 27% potassium iodide. The oxidation at room temperature stopped at ca. 80% conversion, because the remaining I_2 would form triiodide of **1**.[18] Refluxing the reaction mixture completed the oxidation. This oxidation step was also carried out without isolation of **16** after hydrogenolysis of **15** in EtOH. Basification of **5c** (X = I) with NaOH in H_2O in the presence of a small amount of sodium sulfite gave **1** in 83% yield based on **16** as a off-white crystal, which was as pure as that obtained by oxidation of **2**[1b] by HPLC analysis. Sodium sulfite was necessary to destroy a small amont of triiodide contaminating **5c** (X = I). Recrystallization of **1** from benzene[5,7,8] caused some decomposition and was unable to improve the purity. Dissolving **1** in dilute HCl followed by basification with NaOH gave the pure sample.

In these procedures, **1** was prepared from aldehyde **7** with an overall yield of ca. 66% and is useful for syntheses for other isoquinoline alkaloids. The efficient preparation of aldehyde **7** will be reported elsewhere.

Experimental Section

General Method. Melting points were determined with a Mettler FP-61 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer, using tetramethylsilane as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a JASCO A-102 spectrometer. The microanalyses were performed at the Analysis Laboratory in the Research Center of Mitsubishi Kasei Corporation. HPLC was carried out on a Shimadzu LC-6A liquid

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chromatograph equipped with a Nucleosil ODS column (4.6 mm × 25 cm) and a UV detector and operated at a flow rate of 1 mL/min with a solvent composed of MeCN–H_2O–0.1 N octanesulfonic acid aqueous solution (25:65:10).

[*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]amino]acetaldehyde Dimethyl Acetal (8a). A mixture of 2-methoxy-3,4-(methylenedioxy)benzaldehyde (**7**)[12] (21.62 g, 0.12 mol) and aminoacetaldehyde dimethyl acetal (12.62 g, 0.12 mol) in MeOH (80 mL) was hydrogenated over 5% Pd on carbon (2.0 g) at room temperature for 2 h. The catalyst was removed by filtration, and the solvent was evaporated in vacuo to give **8a** as a clear oil (31.69 g, 98% yield), which was used in the next step without further purification. Distillation under reduced pressure gave an analytical sample: bp 148–150 °C/2 mmHg; IR (neat) 1470, 1260, 1220, 1130, 1070, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (br s, 1 H), 2.69 (d, 2 H, J = 5.6 Hz), 3.35 (s, 6 H), 3.71 (s, 2 H), 4.01 (s, 3 H), 4.47 (t, 1 H, J = 5.6 Hz), 5.91 (s, 2 H), 6.46 (d, 1 H, J = 8.0 Hz), 6.69 (d, 1 H, J = 8.0 Hz). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.64; H, 7.24; N, 4.98.

5,6,7,8-Tetrahydro-4-methoxy-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (9). A solution of **8a** (5.39 g, 20 mmol) in 6 N HCl (150 mL) was allowed to stand at room temperature for 4 days. (The reaction was followed by HPLC analysis.) The reaction mixture containing yellow crystals was made basic with 25% NaOH and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residual solid was recrystallized from EtOH to afford **9** (1.47 g, 33% yield). This was again recrystallized from EtOH to afford an analytical sample, mp 124–125 °C: IR (KBr) 2905, 1620, 1465, 1250, 1055, 1030, and 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (br s, 2 H), 2.92 (dd, 1 H, J = 12.8, 2.8 Hz), 3.14 (dd, 1 H, J = 12.8, 2.8 Hz), 3.65 (d, 1 H, J = 16.6 Hz), 3.93 (d, 1 H, J = 16.6 Hz), 3.98 (s, 3 H), 4.40 (t, 1 H, J = 2.8 Hz), 5.88 (s, 2 H), 6.56 (s, 1 H). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.50; H, 5.92; N, 6.23.

5,6,7,8-Tetrahydro-4-methoxy-1,3-dioxolo[4,5-*g*]isoquinoline (10). A solution of **8a** (1.62 g, 6 mmol) in 6 N HCl (45 mL) was allowed to stand at room temperature for 4 days. Five percent Pd on carbon (1.0 g) was added, and the mixture was hydrogenolyzed for 10 h at room temperature. More Pd on carbon (0.5 g) was added, and the mixture was further hydrogenolyzed for 9 h. After removal of catalyst by filtration, the filtrate was concentrated in vacuo. The residue was dissolved in H_2O, and the solution was made basic and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated, and the residual oil was purified by column chromatography on silica gel (5% MeOH–$CHCl_3$ as eluant) to give **10** (0.68 g, 55% yield) as a white solid, which was converted to its hydrobromide, mp 242–243 °C (lit.[19] mp 240 °C).

[*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]-*N*-methylamino]acetaldehyde Dimethyl Acetal (11a). To a solution of **8a** (14.36 g, 53.3 mmol) in MeOH (36 mL) were added 37% formaldehyde (4.76 g, 58.6 mmol) and 5% Pd on carbon (1.0 g), and the mixture was hydrogenated at room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give **11a** as a clear oil (14.93 g, 99% yield), which was pure enough to be used in the next step. Distillation under reduced pressure gave an analytical sample, bp 140–142 °C/2 mmHg: IR (neat) 1475, 1265, 1070, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3 H), 2.56 (d, 2 H, J = 5.3 Hz), 3.33 (s, 6 H), 3.52 (s, 2 H), 3.98 (s, 3 H), 4.54 (t, 1 H, J = 5.3 Hz), 5.92 (s, 2 H), 6.50 (d, 1 H, J = 8.0 Hz), 6.78 (d, 1 H, J = 8.0 Hz). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.02; H, 7.68; N, 4.65.

[*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]amino]acetaldehyde Diethyl Acetal (8b). This compound was prepared in 98% yield following the preparation procedure of **8a** using **7** and aminoacetaldehyde diethyl acetal in EtOH, bp 147–150 °C/0.3 mmHg: IR (neat) 1630, 1495, 1465, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 6 H, J = 6.9 Hz), 1.78 (br s, 1 H), 2.69 (d, 2 H, J = 5.7 Hz), 3.46–3.74 (m, 4 H), 3.71 (s, 2 H), 4.01 (s, 3 H), 4.61 (t, 1 H, J = 5.7 Hz), 5.91 (s, 2 H), 6.46 (d, 1 H, J = 7.8 Hz), 6.69 (d, 1 H, J = 7.8 Hz). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.31; H, 8.09; N, 4.44.

[*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]-*N*-methylamino]acetaldehyde Diethyl Acetal (11b). This compound was prepared in 99% yield following the preparation procedure of **11a** using **8b** and formaldehyde in EtOH, bp 139–142 °C/0.2 mmHg: IR (neat) 1470, 1260, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 6 H, J = 6.9 Hz), 2.28 (s, 3 H), 2.59 (d, 2 H, J = 5.2 Hz), 3.46–3.71 (m, 4 H), 3.52 (s, 2 H), 3.97 (s, 3 H), 4.65 (t, 1 H, J = 5.2 Hz), 5.91 (s, 2 H), 6.50 (d, 1 H, J = 8.1 Hz), 6.80 (d, 1 H, J = 8.1 Hz). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.46; H, 8.39; N, 4.27.

5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (12) and 5,6,7,8-Tetrahydro-4,8-dimethoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (13a). A solution of **11a** (5.67 g, 20 mmol) in 6 N HCl (150 mL) was allowed to stand at room temperature (ca. 25 °C) for 24 h. The solution was made basic with 25% NaOH and extracted with CH_2Cl_2 (80 and 40 mL). The combined extracts were washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residual solid was recrystallized from EtOH to afford pure **12** (3.56 g, 75% yield) as white crystals: mp 153–154 °C; IR (KBr) 1480, 1460, 1265, 1095, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 2.46 (dd, 1 H, J = 11.7, 2.7 Hz), 2.89 (dd, 1 H, J = 11.7, 3.0 Hz), 2.98 (d, 1 H, J = 15.6 Hz), 3.69 (d, 1 H, J = 15.6 Hz), 3.99 (s, 3 H), 4.45 (br s, 1 H), 5.89, (s, 2 H), 6.59 (s, 1 H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.68; H, 6.35; N, 5.89. Column chromatography of the mother liquor on silica gel (3% MeOH–$CHCl_3$ as eluant) gave **13a** (0.35 g, 7.0% yield) as an oil: IR (neat) 1480, 1270, 1085, 1050, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3 H), 2.61–2.83 (m, 2 H), 3.25 (d, 1 H, J = 15.6 Hz), 3.46 (s, 3 H), 3.62 (d, 1 H, J = 15.6 Hz), 3.98 (s, 3 H), 4.25 (t, 1 H, J = 4.4 Hz), 5.88–5.89 (m, 2 H), 6.61 (s, 1 H). Oxalate of **13a** was recrystallized from MeOH to give white crystals, mp 180–181 °C: IR (KBr) 1625, 1480, 1405, 1230, 1085, and 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.75 (s, 3 H), 3.15–3.33 (m, 2 H), 3.38 (s, 3 H), 3.77 (d, 1 H, J = 15.7 Hz), 3.94 (s, 3 H), 3.94 (d, 1 H, J = 15.7 Hz), 4.38 (t, 1 H, J = 3.6 Hz), 6.01 (s, 2 H), 6.70 (s, 1 H). Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.88; H, 5.61; N, 4.09.

5,6,7,8-Tetrahydro-8-ethoxy-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (13b). Cyclization of diethyl acetal **11b** (6.23 g, 20 mmol) in 6 N HCl (150 mL) gave **12** (3.69 g, 78% yield) after recrystallization from EtOH. Column chromatography of the mother liquor on silica gel (3% MeOH–$CHCl_3$ as eluant) gave **13b** (0.33 g, 6.2% yield) as a white solid. Recrystallization from hexane gave an analytical sample, mp 52–53 °C: IR (KBr) 1480, 1460, 1320, 1265, 1090, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 6.9 Hz), 2.46 (s, 3 H), 2.64 (dd, 1 H, J = 11.5, 5.7 Hz), 2.76 (dd, 1 H, J = 11.5, 4.5 Hz), 3.35 (d, 1 H, J = 15.5 Hz), 3.50 (d, 1 H, J = 15.5 Hz), 3.56–3.77 (m, 2 H), 3.97 (s, 3 H), 4.39 (t, 1 H, J = 5.1 Hz), 5.87–5.89 (m, 2 H), 6.64 (s, 1 H). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.47; H, 7.30; N, 5.28.

2-[*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]-*N*-methyl]ethanol from Reaction Mixture of 11a. A solution of **11a** (0.291 g, 1.03 mmol) in 6 N HCl (7.7 mL) was allowed to stand at room temperature for 2 h. To the solution were added 2 N NaOH (23 mL), EtOH (50 mL), and $NaBH_4$ (0.1 g), and then the mixture was stirred for 1 h, concentrated, and extracted with CH_2Cl_2. The extract was concentrated, and the residual oil was purified by column chromatography on silica gel (10% MeOH–$CHCl_3$ as eluant) to afford the title compound (0.051 g, 21% yield) as an oil. This was characterized as its hydrochloride, mp 112–113 °C (recrystallized from acetone): IR (KBr) 3300, 1630, 1495, 1470, 1265, 1235, 1075, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.82 (s, 3 H), 3.01 (br s, 1 H), 3.36 (br s, 1 H), 3.93–4.08 (m, 2 H), 4.10 (s, 3 H), 4.24 (br s, 2 H), 5.99 (s, 2 H), 6.58 (d, 1 H, J = 8.0 Hz), 7.07 (d, 1 H, J = 8.0 Hz). Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.27; H, 6.58; Cl, 12.86; N, 5.08. Found: C, 52.46; H, 6.65; Cl, 12.71; N, 5.07.

8-Methoxy Compound 13a from 12. A solution of **12** (0.712 g, 3 mmol) in 6 N H_2SO_4 (6 mL) and MeOH (6 mL) was stirred at 60 °C for 4 h and cooled. The solution was made basic and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated. Column chromatography of the residue on silica gel (2% MeOH–$CHCl_3$ as eluant)

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gave **13a** (0.39 g, 52% yield) and recovered **12** (0.34 g).

Cyclization of 11a with Removal of MeOH. A solution of **11a** (14.17 g, 50 mmol) in 6 N H_2SO_4 (66.7 mL) was stirred at 60 °C. During the reaction, ca. 60 mL of H_2O was distilled off with MeOH formed under reduced pressure (ca. 150 mmHg) with slow addition of an equal amount of H_2O. After 6 h the reaction mixture was cooled (HPLC analysis showed that the yield of **12** was 98%), made basic with 25% NaOH, and extracted with CH_2Cl_2 (200 and 100 mL). The combined extracts were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo to dryness. Recrystallization of the residual solid from EtOH gave pure **12** (10.37 g, 87% yield).

5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (Hydrocotarnine, 16) Hydrochloride. A solution of **11b** (1.42 g, 5 mmol) in 6 N HCl (37.5 mL) was allowed to stand at 25 °C for 24 h. Five percent Pd on carbon (0.5 g) was added, and the mixture was hydrogenolyzed at room temperature and atmospheric pressure for 10 h, more 5% Pd on carbon (0.5 g) was added, and the mixture was further reduced for 8 h. Catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residual solid was recrystallized from EtOH to afford **16**·HCl (0.82 g, 64% yield), mp 219–221 °C (lit.[20] mp 218 °C).

5,6,7,8-Tetrahydro-8-acetoxy-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (15). To a solution of **12** (4.74 g, 20 mmol) in CH_2Cl_2 (70 mL) was added dropwise acetyl chloride (1.71 mL, 24 mmol) at room temperature, and the mixture was stirred for 1 h. H_2O (30 mL) was added, and the aqueous phase was adjusted to pH 10 with 25% NaOH. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic solutions were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **15** as a white solid (5.55 g, 99% yield). This product was pure enough (HPLC analysis) to be used in the next step. Recrystallization from ethyl acetate–hexane gave an analytical sample, mp 109–110 °C: IR (KBr) 1730, 1480, 1230, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 2.47 (s, 3 H), 2.60 (dd, 1 H, J = 12.5, 3.4 Hz), 2.90 (dd, 1 H, J = 12.5, 3.0 Hz), 3.06 (d, 1 H, J = 15.6 Hz), 3.86 (d, 1 H, J = 15.6 Hz), 3.99 (s, 3 H), 5.87 (t, 1 H, J = 3.2 Hz), 5.90 (s, 2 H), 6.54 (s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02. Found: C, 60.30; H, 6.24; N, 4.99.

16 from 15. A solution of **15** (11.17 g, 40 mmol) in EtOH (60 mL) was hydrogenolyzed over 5% Pd on carbon (2.0 g) at 50 °C for 7 h. Catalyst was removed by filtration, and the filtrate was concentrated in vacuo. To the residue were added H_2O (40 mL) and CH_2Cl_2 (70 mL), and the mixture was made basic with 25% NaOH. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic solutions were washed with H_2O (30 mL), dried over anhydrous $MgSO_4$, and concentrated to afford **16** (8.43 g, 95% yield) as a white solid, which was used in the next step without further purification. Recrystallization from a small amount of hexane afforded a pure sample, mp 40 °C (lit.[1b] mp 54–55 °C). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.88; N, 6.31. The hydrochloride of this compound recrystallized from EtOH gave a sample of mp 222–223 °C.

5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol (Cotarnine, 1). To a solution of **16** (20.59 g, 93.1 mmol) in EtOH (186 mL) were added potassium acetate (10.04 g, 102.3 mmol) and I_2 (24.8 g, 97.7 mmol), and the mixture was refluxed for 3 h and then cooled to 20 °C. The deposited solid was collected by filtration, washed with EtOH (37 mL), and dried to give **5c** (X = I, 40.93 g), which was shown to be 73% pure by HPLC analysis. Recrystallizations from H_2O containing a small amount of sodium sulfite and then from EtOH gave pure **5c** (X = I), mp 183–184 °C (lit.[6] mp 184–186 °C). To a warm solution (40 °C) of crude **5c** (X = I, 14.30 g) and sodium sulfite (0.54 g) in H_2O (140 mL) was added 25% NaOH (20 g) dropwise, and the mixture was stirred for 1 h at 40 °C and then 1 h at 20 °C. The precipitated crystal was collected by filtration, washed with H_2O (2 × 21 mL), and dried to give **1** (6.38 g, 83% yield from 16) as off-white crystals, mp 127–128 °C. HPLC analysis showed that the obtained **1** was as pure as that prepared from **2**.[1b] If necessary, further purification was made by dissolving **1** in 3 N HCl followed by basification with NaOH, mp 127–128 °C (lit. mp 130 °C,[6] 133 °C,[1b] 131–132 °C,[7] 126 °C[8]).

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