ASYMMETRIC SYNTHESIS OF (*R*)-1-(2-METHOXY-3,4-METHYLENEDIOXYBENZYL)-2-METHYL-6,7-METHYLENEDIOXY-1,2,3,4-TETRAHYDROISOQUINOLINE (SO-CALLED "FUMARIZINE")

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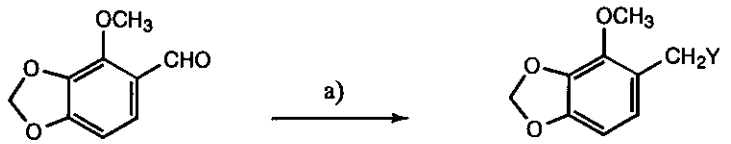
Abstract -- (*R*)-1-(2-Methoxy-3,4-methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (so-called "fumarizine") (1) was synthesized *via* the stereoselective reduction of the corresponding chiral iminium ion (11), which was obtained by the Bischler-Napieralski cyclization of *N*-[(*R*)-1-phenylethyl]-*N*-[2-(3,4-methylenedioxyphenylethyl)]-2-(2-methoxy-3,4-methylenedioxyphenyl)acetamide (10). The synthetic compound (1) was shown to differ from natural fumarizine, the structure of which is not formula (1).

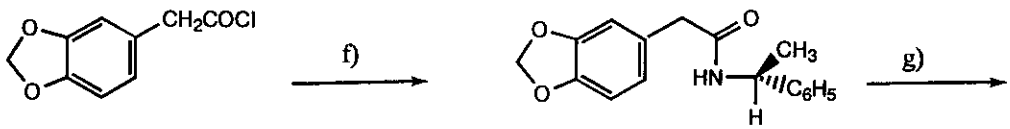
The natural alkaloid fumarizine,[1] which was isolated from *Fumaria indica* L. (Fumaraceae), was assigned the structure, (*R*)-1-(2-methoxy-3,4-methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (1) on the basis of ^{1}H-nmr spectral evidence and salient features of NOE. However, the absolute configuration of the asymmetric carbon atom at C-1 position was ambiguous, because the data of specific rotation or ORD for the alkaloid was not recorded. This paper decribes the synthesis of (*R*)-compound (1) *via* the stereoselective reduction by Polniaszek's method [2,3] as shown in the scheme.

One of the starting materials, 2-methoxy-3,4-methylenedioxyphenylacetic

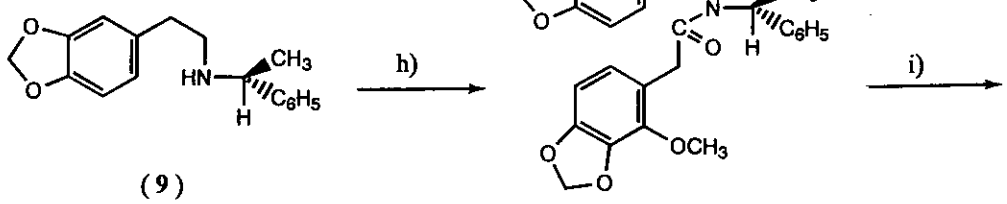


(2)

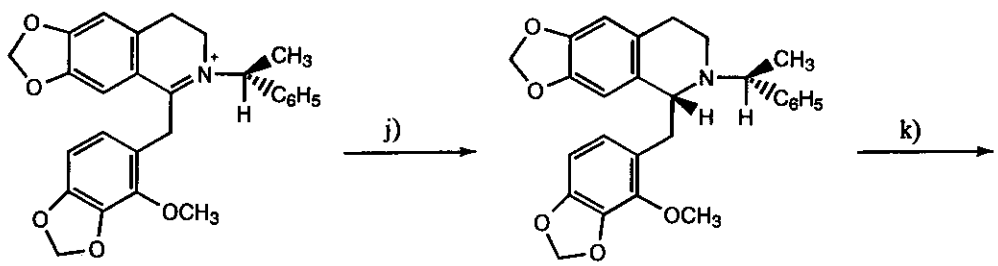
(3) Y = -OH —b)→ (4) Y = -Cl —c)→
(5) Y = -CN —d)→ (6) Y = -COOH —e)→
(7) Y = -COCl



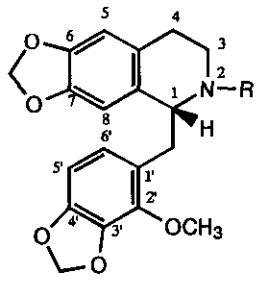
(8)

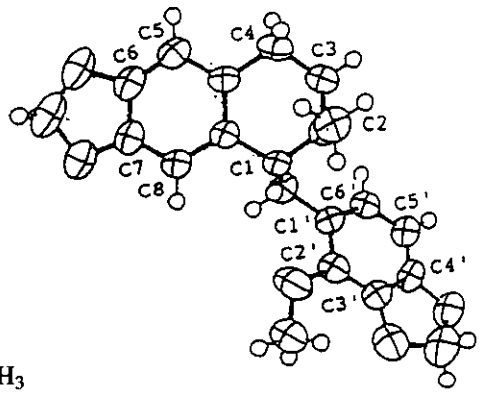


(9) (10)



(11) (12)





(13) R = -H $\xrightarrow{l)}$ (1) R = -CH_3

a) $NaBH_4$/MeOH *b)* $SOCl_2$/benzene *c)* NaCN/DMSO *d)* KOH
e) $SOCl_2$/benzene *f)* (*R*)-1-phenylethylamine/Na_2CO_3
g) BF_3-Et_2O,BH_3-THF *h)* (7)/Na_2CO_3 *i)* $POCl_3$/toluene
j) $NaBH_4$/MeOH *k)* H_2,5% Pd-C/EtOH *l)* HCHO,$NaBH_4$/MeOH

acid (6), mp 119-121°C, was obtained in good yield *via* the corresponding benzyl alcohol (3), the benzyl chloride (4), and the benzyl cyanide derivative (5), from 2-methoxy-3,4-methylenedioxybenzaldehyde (2).[4] *N*-[(*R*)-1-Phenylethyl]-2-(3,4-methylenedioxyphenyl)ethylamine (9), was obtained by reduction by BH_3-THF of the amide (8), which was prepared by condensation with acid chloride derived from 3,4-methylenedioxyphenylacetic acid [5] and (*R*)-1-phenylethylamine.

The Schotten-Baumann reaction of the chiral amine (9) with the acid chloride (7) derived from 2-methoxy-3,4-methylenedioxyphenylacetic acid (6) afforded the amide (10) as a colorless oily substance showing a single spot on tlc. The Bischler-Napieralski reaction of the amide (10) with $POCl_3$ in dry toluene afforded the imine ion (11), which, without purification, was stereoselectively reduced with sodium borohydride in MeOH at -78°C by Polniaszek's method [2,3] affording (*R*)-1-(2-methoxy-3,4-methylenedioxybenzyl)-2-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (12) as a pale yellow oily substance showing a single spot on tlc. Catalytic hydrogenation of the *N*-substituted tetrahydroisoquinoline (12) over palladium charcoal in ethanol containing concentrated hydrochloric acid gave an *N*-unsubstituted tetrahydroisoquinoline derivative (13) as colorless needles, mp 102-104°C, $[\alpha]_D$ +3.7° (in $CHCl_3$), 30.0% total yield from 9. Treatment of 13 with

formaldehyde and $NaBH_4$ afforded the *N*-methyl derivative, (*R*)-1-(2-methoxy-3,4-methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**1**) as colorless needles, mp 135-136°C, $[\alpha]_D$ -63.2° (in $CHCl_3$). An alkaloid having this formula has been isolated from *Fumaria indica* L. (Fumaraceae) and named "fumarizine".[1] The physical constants and spectral data of synthetic alkaloid (**1**) were, however, different from those reported for the natural fumarizine as shown in the Table.

To confirm our findings, we determined the crystal structure of synthetic alkaloid (**1**) by the X-Ray diffraction method and determined its structure as formula (**1**). The position of the methylenedioxy group in the benzene rings and absolute configuration of the asymmetric carbon atom at the C-1 position in natural fumarizine must be re-examined.

Table

	synthetic (1)	natural product
mp	135-136°	amorphous
$[\alpha]_D$ ($CHCl_3$)	-63.2° (c=0.44)	no data
Uv λ_{max}^{EtOH} nm(log ε):	205(4.69),238(sh)(3.98) 287(3.71)	240,245,285
Ir $\nu_{max}^{CHCl_3}$ cm^{-1}	2870,935	1580,1485,1150,1050
^{1}H-Nmr($CDCl_3$) δ:		
NCH_3	2.45(s)	2.67(s)
OCH_3	3.95(s)	3.84(s)
OCH_2O	5.85(dd,J=1.5,J=2.9 Hz)	5.88, 5.90(d)
	5.92(s)	5.92, 5.93(s)
CH_2	2.51~3.27(6H,m)	3.00(m,benzyl), 3.30(m,C-4), 3.76(m,C-3)
CH	3.69(1H,t,C_1-H)	
Arom.-H	6.22(s,C-8)	6.45(s, C-5)
	6.43(d,J=7.8 Hz, C-6')	6.62(s, C-8)
	6.49(d,J=8.1 Hz, C-5')	6.68(d, J=8.1 Hz, C-6')
	6.54(s,C-5)	6.75(d, J=8.1 Hz, C-5')
Ms(m/z)	355(M^+,0.31%),190(100%) 149(0.05%)	355(M^+,17%),340(23%) 190(82%),148(100%)

EXPERIMENTAL

All melting points were determined on a Yanagimoto microscopic hot-stage apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a JEOL FX-200 spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Ir and uv spectra were recorded on a Shimadzu IR-435 and Shimadzu UV-160 spectrophotometer, respectively. Ms were obtained using a JEOL JMS DX-303 ei mass spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography and preparative thin layer chromatography (tlc) were carried out on Wakogel C-200 (100~200 mesh) and with silica gel $60F_{254}$ (Merck).

2-Methoxy-3,4-methylenedioxybenzyl alcohol (3) To a stirred solution of 2-methoxy-3,4-methylenedioxybenzaldehyde (2) (18.0 g, 0.10 mol) in 90% aq. MeOH (50 ml) was added gradually $NaBH_4$ (11.3 g, 0.30 mol) at 0~5°C. After 2 h, the excess of $NaBH_4$ was destroyed with 20% aq. AcOH, and most of MeOH evaporated to dryness *in vacuo*. The residue was extracted with CH_2Cl_2, the CH_2Cl_2 extract was washed with a saturated aq. solution of $NaHCO_3$ and water, and evaporated leaving the corresponding benzyl alcohol (3) as a pale yellow oily substance which appeared as a single spot on tlc. yield 18.0 g (98.9 %), uv λ_{max}^{EtOH} nm(log ε): 208(4.51); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590(OH); ^{1}H-nmr δ: 2.14(1H, t, OH), 4.06(3H, s, OCH_3), 4.58(2H, d, J = 6.3 Hz, CH_2), 5.93(2H, s, OCH_2O), 6.48(1H, d, J = 8.0 Hz, C_6-H), 6.75(1H, d, J = 8.0 Hz, C_5-H); EIms(70 eV) m/z (rel. intensity): 182(M^+, 100), 165(M^+-OH, 83).

2-Methoxy-3,4-methylenedioxybenzyl chloride (4) The anhydrous benzene (15.0 ml) solution of thionyl chloride (22.0 ml, 0.303 mol) was added to the benzyl alcohol (3) (5.46 g, 0.03 mol) and *N,N*-dimethylaniline (7.0 ml, 0.055 mol) in anhydrous benzene (80 ml) with stirring at 0~5°C. The reaction mixture was heated at 100°c for 4 h, then washed with 10% aq. HCl, and evaporated, giving a pale yellow oily product (4). This compound was used for subsequence reaction without purification.

2-Methoxy-3,4-methylenedioxyphenylacetonitrile (5) To a suspension of sodium cyanide (8.70 g, 0.178 mol) in dimethyl sulfoxide (DMSO, 200 ml) was added dropwise the benzyl chloride (4) (7.11 g, 0.035 mol) in DMSO (50.0 ml) at room temperature with stirring. After further stirring at 40~50°C for 2 h, the resultant reaction mixture was poured into ice water (500 ml), and the precipitate was removed by filtration. The precipitate was

recrystallized from dil. EtOH to afford colorless needles (5), mp 98~99°C. yield, 6.32 g (96.5 % from 3). uv λ_{max}^{EtOH} nm(log ε): 209(4.60); ir $\nu_{max}^{CHCl_3}$ cm^1: 2250(CN); ^{1}H-nmr δ: 3.59(2H, s, CH_2CN), 4.07(3H, s, OCH_3), 5.95(2H, s, OCH_2O), 6.51(1H, d, J = 8.0 Hz, C_6-H), 6.79(1H, d, J = 7.8 Hz, C_5-H); EIms (70 eV) $^m/_z$ (rel. intensity): 191(M^+, 100), 176(M^+-CH_3, 39); Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.83; H, 4.73; N, 7.30.

2-Methoxy-3,4-methylenedioxyphenylacetic acid (6) The above benzyl cyanide (5) (1.91 g, 0.01 mol) was refluxed for 21 h with 25 % ethanolic KOH solution (25.0 ml) and diethylene glycol (10.0 ml) until the evolution of ammonia ceased. The reaction mixture was made acidified with 10 % aq. HCl and extracted into CH_2Cl_2. The CH_2Cl_2 extract was washed with water and evaporated to afford crystalline solid. Recrystallization from dil. EtOH gave colorless needles (6), mp 119~121°C. yield 1.80 g (85.7 %). uv λ_{max}^{EtOH} nm(log ε): 208(4.53); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500(OH), 1710(C=O); ^{1}H-nmr δ: 3.59(2H, s, CH_2COOH), 3.99(3H, s, OCH_3), 5.93(2H, s, OCH_2O), 6.49(1H, d, J = 8.1 Hz, C_6-H), 6.65(1H, d, J = 7.8 Hz, C_5-H); EIms (70 eV) $^m/_z$ (rel. intensity): 210(M^+, 60), 165(M^+-COOH); Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.02; H, 4.81.

***N*-[(*R*)-1-Phenylethyl]-2-(3,4-methylenedioxyphenyl)acetamide (8)** To an ether solution of (*R*)-1-phenylethylamine (4.34 ml, 0.034 mol) and 90 ml of 5% aq. Na_2CO_3 solution (4.5 g, 0.042 mol) was slowly added dropwise an anhyd. ether solution of 3,4-methylenedioxyphenylacetyl chloride prepared from 3,4-methylenedioxyphenylacetic acid [5] (5.0 g, 0.028 mol) and excess thionyl chloride (10 ml, 0.138 mol) by the usual method, with stirring at 0~5°C for 1 h. Stirring was continued for 1 h at the same temperature, and the precipitates were filtrated off and dissolved in CH_2Cl_2. The CH_2Cl_2 solution and the ether layer of the filtrate were washed successively with 10 % aq. HCl solution, 5 % aq. NaOH solution and water, respectively. The organic solution was dried, and removal of the solvent by evaporation left the residue, which was recrystallized from ethanol-hexane to furnish the correspondig optically active acetamide (8), colorless needles, mp 97~100°C (7.55 g, 98.2 %). $[\alpha]_D^{26}$ -15.2° (*c* = 0.20,$CHCl_3$); uv λ_{max}^{EtOH} nm (log ε): 203(4.62), 258(2.79), 287(3.60); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410(NH), 1660(C=O); ^{1}H-nmr δ: 1.41(3H, d, J = 6.8 Hz, CH_3), 3.48(2H, s, CH_2), 5.12(1H, m, CH), 5.62(1H, br., NH), 5.97(2H, d, J = 0.5 Hz, OCH_2O), 6.67~6.80(3H, m, arom.H×3), 7.19~7.36(5H, m,arom.H×5); EIms (70 eV) $^m/_z$

(rel. intensity): 283(M^+, 82.0), 135(100), 105(57.0); Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.89; H, 6.07; N, 4.92.

***N*-[(*R*)-1-Phenylethyl]-2-(3,4-methylenedioxyphenyl)ethylamine (9)** To the above amide (*8*) (*3.60 g, 0.013 mol*) *in anhyd. THF (60 ml) were carefully* added dropwise BF_3 ether complex (abt. 47 %, 1.5 ml, 5 mmol) and 1.0 M BH_3 THF complex (30.0 ml, 0.03 mol) at room temperature. The solution was further heated for 2.5 h at 70~80°C under argon. After reaction, the excess reagent was destroyed with 5N aq. HCl solution (90 ml) and the solvent was evaporated off *in vacuo*. The aqueous solution was made alkaline with 10 % aq. NaOH solution and extracted with CH_2Cl_2. The extract was washed with water, dried and the solvent was evaporated off to give a pale yellow oil (**9**) (2.81 g, 82.2 %) showing a single spot on tlc. $[\alpha]_D^{24}$ +47.8° (c = 0.21,$CHCl_3$); uv λ_{max}^{EtOH} nm(log ε): 203(4.70), 287(3.75); ^{1}H-nmr δ: 1.32(3H, d, J = 6.6 Hz, CH_3), 1.39(1H, broad, NH), 2.68(4H, m, CH_2×2), 3.75(1H, q, J = 6.6 Hz, CH), 5.91(2H, d, J = 0.5 Hz, OCH_2O), 6.58~6.74(3H, m, arom.H×3), 7.18~7.35(5H, m, arom.H×5); eims (70 eV) $^m/_z$ (rel. intensity); 269(M^+, 8.0), 134(57.0), 105(100). The hydrochloride was obtained as colorless needles, mp 213~215°C, from MeOH-Me_2CO. Anal. Calcd for $C_{17}H_{19}NO_2 \cdot HCl$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.59; H, 6.71; N, 4.58.

***N*-[(*R*)-1-Phenylethyl]-*N*-[2-(3,4-methylenedioxyphenylethyl)]-2-(2-methoxy-3,4-methylenedioxyphenyl)acetamide (10)** An anhydrous ether solution of 2-methoxy-3,4-methylenedioxyphenylacetyl chloride (**7**), which formed from the corresponding carboxylic acid (**6**) (17.4 g, 0.083 mol) and excess $SOCl_2$ in the usual way, was added dropwise to an ether *solution (300* ml) of the amine (**9**) (22.4 g, 0.083 mol) and 5% aq. Na_2CO_3 solution (300 ml, 0.14 mol) with stirring at 0~5°C. Stirring was continued for 2 h at the same temperature. After reaction, the ether layer was washed successively with 5% aq. Na_2CO_3 solution, 10% aq. HCl solution and water, and dried. Removal of the solvent by evaporation left the residue, which was chromatographed with hexane/CH_2Cl_2 (3:2) to give the amide (**10**) (23.4 g, 61.3 %) as a colorless oily substance. $[\alpha]_D^{22}$ +46.1° (c = 0.28, $CHCl_3$); uv λ_{max}^{EtOH} nm (log ε); 203(4.93); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630(C=O); ^{1}H-nmr δ: 1.54(3H, d, J = 7.1 Hz, CH_3), 2.10~2.76(2H, m, CH_2), 3.05~3.33(2H, m, CH_2), 3.71(2H, s, CH_2), 3.98(3H, s, OCH_3), 5.24(1H, q, J = 6.8 Hz, CH), 5.88(2H, d, J = 5.9 Hz, OCH_2O), 5.92(2H, d, J = 2.2 Hz, OCH_2O), 6.37~6.79(5H, m, arom.H×5), 7.22~7.41(4H, m, arom.H×4); EIms (70 eV) $^m/_z$ (rel. intensity): 461(M^+,

57.8), 314(100), 165(95.3), 148(57.2), 134(89.6), 105(79.7).

1-(2-Methoxy-3,4-methylenedioxybenzyl)-2-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-3,4-dihydroisoquinoline (11) A mixture of the acetamide (**10**) (2.2 g, 4.77 mmol) and $POCl_3$ (12.0 g, 0.078 mol) in dry toluene (25 ml) was heated for 3.5 h at 120~140°C. After reaction, evaporation of excess reagent and the solvent left the residue (**11**), which was washed with petroleum ether, and was used for subsequent reaction without purification.

(*R*)-1-(2-Methoxy-3,4-methylenedioxybenzyl)-2-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (12) To a stirred solution of the iminium ion (**11**) in MeOH (75 ml) was gradually added $NaBH_4$ (2.0 g, 0.053 mol) at -78°C. After stirring for 2 h at the same temperature, excess $NaBH_4$ was decomposed with 20 % aq. AcOH solution and solvent was evaporated *in vacuo*. The residue was diluted with H_2O, made alkaline with 10 % aq. NH_4OH solution and extracted with CH_2Cl_2. The Ch_2Cl_2 layer was washed with water, dried, and the solvent was evaporated off. The residue was purified by column chromatography. Elution with hexane/CH_2Cl_2 (9:1) gave a colorless oil (**12**) (1.8 g, 84.9 % from **10**) showing a single spot on tlc. $[\alpha]_D^{23}$ -31.0° (c = 0.47, $CHCl_3$); uv λ_{max}^{EtOH} nm(log ε): 204(4.70), 290(3.68); ^{1}H-nmr δ: 1.28(3H, d, J = 6.3 Hz, CH_3), 2.34~2.44(1H, m, CH), 2.65~2.99(3H, m, CH×3), 3.22~3.48(2H, m, CH×2), 3.55(3H, s, OCH_3), 3.57~3.68(2H, m, CH×2), 5.86(2H, s, OCH_2O), 5.92(2H, dd, J = 1.5, 7.0 Hz, OCH_2O), 6.32(1H, s, arom.H×1), 6.45(2H, s, arom.H×2), 6.57(1H, s, arom.H×1), 6.82~7.15(5H, m, arom.H×5); EIms (20 eV) $^m/_z$ (rel. intensity): 446(M^++1, 0.69), 358(22.9), 324(7.3), 280(100), 176(77.2), 105(66.7).

(*R*)-1-(2-Methoxy-3,4-methylenedioxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (13) A mixture of (**12**) (1.45 g, 3.26 mmol) and 5% Pd-C (750 mg) in EtOH (*ca.* 60 ml) containing concentrated hydrochloric acid (4 ml) was shaken at room temperature under a hydrogen atmosphere (1.76 $^{kg}/_{cm^2}$) for 32 h using a medium-pressure catalytic hydrogenator. The catalyst was removed by filtration. The filtrate was washed with ether, made alkaline with 10 % aq. NH_4OH solution, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried, and evaporated to dryness leaving a residue. The residue was purified by chromatography, and the fraction eluted with hexane/CH_2Cl_2 (1:1) was recrystallized from ether to give (**13**) as colorless needles, mp. 102~104°C (0.64 g, 57.6 %).

$[\alpha]_D^{25}$ +3.7° (c = 0.27, $CHCl_3$); uv λ_{max}^{EtOH} nm(log ε): 208(4.72), 289(3.75); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300(NH); ^{1}H-nmr δ: 2.13(1H, br, NH), 2.69~2.77(2H, m, CH_2), 2.81~2.98(2H, m, CH_2), 3.11~3.28(2H, m, CH_2), 4.03(3H, s, OCH_3), 4.05~4.07(1H, m, C_1-H), 5.90(2H, s, OCH_2O), 5.93(2H, s, OCH_2O), 6.49(1H, d, J = 7.8 Hz, $C_{6'}$-H), 6.56(1H, s, C_8-H), 6.64(2H, d, J = 7.8 Hz, $C_{5'}$-H), 6.72(1H, s, C_5-H); EIms (20 eV) m/z (rel. intensity); 341(M^+, 0.18), 308(3.44), 280(2.13), 246(3.93), 205(2.24), 204(11.26), 176(100), 149(5.18); Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.83; H, 5.61; N, 4.11.

(*R*)-1-(2-Methoxy-3,4-methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (so-called "fumarizine") (1) Tetrahydroisoquinoline derivates (13) (1.02 g, 3 mmol) was dissolved in MeOH (25.0 ml), and a solution of HCHO (2.5 ml, 0.03 mol of 35 % formalin in 20 ml of MeOH) was added. To the methanolic solution, 0.75 g (0.02 mol) of $NaBH_4$ was added. After the reaction mixture was stirred 1 h at room temperature, the excess reagent was decomposed by adding 10 % aq. AcOH solution, and solvent was removed by evaporation. The residue was then made alkaline with 10 % aq. NH_4OH solution and extracted repeatedly with CH_2Cl_2. The CH_2Cl_2 extract was washed, dried and evaporated. The residue was recrystallized from MeOH and afforded colorless needles (1) (0.86 g, 81.1 %). The physical constants and spectral data of 1 are shown in the Table.

Crystal structure analysis of (1) Crystal data: $C_{20}H_{21}N_1O_5$, Mr = 355.39, monoclinic, space group $P2_1$, a = 8.017(1) Å, b = 10.104(1) Å, c = 10.735(1) Å, β = 93.13(1)°, V = 868.2(2) $Å^3$, Z = 2, D_c = 1.359 $g.cm^{-3}$, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 7.67 cm^{-1}, F(000) = 760. A crystal of dimensions 0.4 × 0.2 × 0.8 mm^3 was used. 1456 independent reflections of 2° < 2θ < 130° were collected using the ω-2θ scanning mode on a Rigaku AFC-5R diffractometer using graphite-monochromated Cu Kα radiation. Intensities were corrected for Lorentz and polarization factors and for absorption effect.
The structure was solved by the direct method. Refinement with anisotropic thermal parameters for non-H atoms and isotropic one for H atoms converged to R = 0.046 and Rw = 0.061 for 1381 observed reflections (Fo>3σ(Fo)).

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