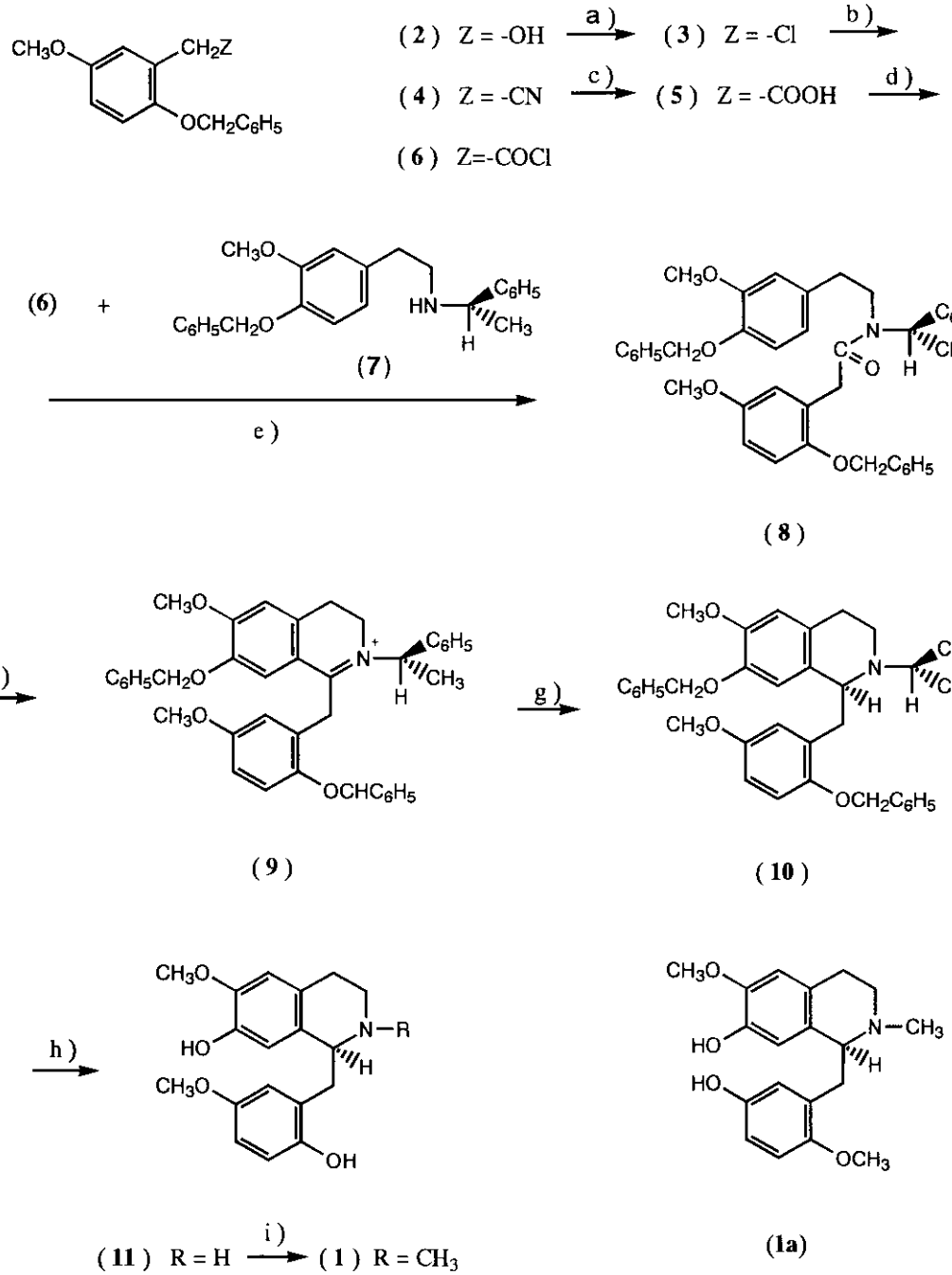
ASYMMETRIC SYNTHESIS OF SO-CALLED "DEHASSILINE" ISOMER, (*S*)-1-(2'-HYDROXY-5'-METHOXYBENZYL)-7-HYDROXY-6-METHOXY-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE

Akiko Watanabe and Jun-ichi Kunitomo*

Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koushien Kyuban-cho, Nishinomiya, 663-8179 Japan

Abstract -- A so-called "dehassiline" isomer, (*S*)-1-(2'-hydroxy-5'-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1) was asymmetrically synthesized *via* the stereoselective reduction with sodium borohydride at -78°C of the corresponding 3,4-dihydroisoquinolinium ion possessing a chiral auxiliary. The spectral data for the synthetic compound (1) differed from those reported for natural dehassiline, the structure of which must be reexamined.

The 1-benzylisoquinoline alkaloid, dehassiline, which was isolated from the bark of *Dehassia kurzii* (Lauraceae), was assigned the structure, (*S*)-1-(2'-methoxy-5'-hydroxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1a) on the basis of spectral evidence.[1] Previously,[2] we reported the asymmetric synthesis of optically active compound (1a), but ^{1}H-NMR data of this compound (1a) were appreciably different from those of the naturally occurring (+)-dehassiline. Compared with the δ value of the N-methyl (δ 2.43), C-1 proton (δ 3.77) and C-8 aromatic proton (δ 6.43) of synthetic compound (1a), the N-methyl (δ 2.61) of the natural product appeared downfield, with C-1 and C-8 protons at δ 3.42 and δ 6.14, respectively. A downfield chemical shift (δ ca 2.6) of the N-methyl occurs when this type of alkaloid has a hydroxyl group at the C-2 in benzyl moiety.[3,4] Herein, we describe the asymmetric synthesis of (*S*)-(+)-dehassiline isomer, [(*S*)-(+)-1-(2'-hydroxy-5'-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline] (1), by a synthetic route similar to that used for compound (1a) as shown in scheme.[2,5]



a) $SOCl_2$, *N,N*-dimethylaniline/benzene *b)* NaCN/DMSO
c) KOH/diethylene glycol *d)* $SOCl_2$/benzene
e) Na_2CO_3 *f)* $POCl_3$/toluene *g)* $NaBH_4$/MeOH
h) 10% Pd-C/EtOH-HCl *i)* HCHO, $NaBH_4$/MeOH

Table ^{1}H- and ^{13}C-NMR Chemical Shift Assignments of Synthetic Compound (1) and (+)-Dehassiline

	synthetic compound		natural product	
	δ ^{13}C	δ ^{1}H	δ ^{13}C	δ ^{1}H
C-1	65.03	3.84(m)	65.98	3.42(dd, J_1=5.0 Hz, J_2=7.8 Hz)
C-3	46.80	2.82(ddd,J_1=12.8 Hz, J_2=5.3 Hz, J_3=5.3 Hz) 3.38(ddd,J_1=12.4 Hz, J_2=8.6 Hz, J_3=4.7 Hz)	47.34	2.81(dd, J_1=13.4 Hz, J_2=7.0 Hz) 3.14(ddd,J_1=13.4 Hz, J_2=7.8 Hz,J_3=3.5 Hz)
C-4	23.93	2.63(ddd,J_1=16.2 Hz, J_2=5.1 Hz, J_3=5.1 Hz) 2.74(ddd,J_1=17.1 Hz, J_2=8.2 Hz, J_3=4.7 Hz	25.05	2.58(dd, J_1=12.5 Hz, J_2=7.8 Hz) 2.73(dd, J_1=12.5 Hz, J_2=5.0 Hz)
C-5a	127.60		133.04	
C-5	110.41	6.48(s)	121.96	6.67(s)
C-6	152.36[a]		145.52	
C-7	145.45[b]		148.22	
C-8	113.30	6.70(s)	112.61	6.14(s)
C-8a	124.91		124.82	
C-α	40.80	2.98(dd, J_1=15.0 Hz, J_2=2.1 Hz) 3.00(dd, J_1=7.3 Hz, J_2=7.9 Hz)	40.82	2.67(dd, J_1=13.7 Hz, J_2=5.0 Hz) 3.00(dd, J_1=13.7 Hz, J_2=7.8 Hz)
C-1'	126.48		129.48	
C-2'	144.47[a]		145.46	
C-3'	117.84	6.76(d, J=8.6 Hz)	117.68	6.82(d, J=8.1 Hz)
C-4'	113.60	6.63(dd, J_1=8.6 Hz, J_2=3.4 Hz)	115.60	6.52(dd, J_1=8.1 Hz, J_2=2.1 Hz)
C-5'	151.13[b]		147.76	
C-6'	117.03	6.48(d, J=3.4 Hz)	112.81	6.62(d, J=2.1 Hz)
OCH_3	55.86[c]	3.68(s)	54.4	3.81(s)
OCH_3	55.90[d]	3.83(s)	56.3	3.82(s)
NCH_3	42.00	2.57(s)	41.9	2.61(s)

*Assignments of a,b or c,d on ^{13}C-NMR(δ value) may be interchangeable.

One of the starting materials, 2-benzyloxy-5-methoxyphenylacetic acid (**5**), mp 111~112°C, was obtained in a good yield *via* the corresponding benzyl chloride (**3**), and the benzyl cyanide (**4**), from the reduction product (**2**) with $NaBH_4$ of 2-benzyloxy-5-methoxybenzaldehyde.[6]

The Schotten-Baumann reaction of the (*S*)-chiral amine (**7**)[2] with the acid chloride (**6**) derived from the carboxylic acid (**5**) afforded the amide (**8**) as a pale yellow oily substance. The Bischler-Napieralski reaction of the amide (**8**) with $POCl_3$ in dry toluene afforded the iminium ion (**9**), which was stereoselectively reduced with sodium borohydride in MeOH at -78°C by Polniaszek's method[5] afforded (*S*)-1-(2'-benzyloxy-5'-methoxybenzyl)-2-[(*S*)-1-phenylethyl]-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline (**10**) as a pale yellow oily substance, $[\alpha]_D$ +64.1° (c = 0.38, $CHCl_3$), in 87.7% total yield from **8**. The optical purity was determined to be 99.0% ee by HPLC with a chiral stationary phase based on a derivatized amylose, CHIRALCEL OD. The deletion of chiral auxiliary and *O*-debenzylation by catalytic hydrogenation of the optical active substituted 1,2,3,4-tetrahydoisoquinoline (**10**) gave (*S*)-1-(2-hydroxy-5-methoxy-benzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**11**) as colorless prisms, mp 191~192°C, $[\alpha]_D$ +58.0° (c = 0.22, $CHCl_3$). Finally, N-methylated of **11** with formaldehyde and $NaBH_4$ produced (*S*)-1-(2'-hydroxy-5'-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline (**1**), $[\alpha]_D$ -41.0° (c = 0.44, $CHCl_3$) as a pale yellow oil showing a single spot on TLC. The specific rotation was levorotatory in different with that of compound (**1a**), $[\alpha]_D$ +63.9° ($CHCl_3$), but ORD of compound (**1**) was found to show a negative Cotton effect, and the configuration of this compound (**1**) was corrected to S-configuration.[3,4]

The ^1H-NMR of synthetic product (**1**) showed that the signal of the N-methyl (δ 2.57) was superimposable on that of the naturally occurring (+)-dehessiline[1] as shown in the table, but not those of at C-1, C-5 protons and C-8 aromatic protons. Thus the structure of this alkaloid must be reexamined.

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were measured on a JEOL FX-200 spectrometer in $CDCl_3$ solution with tetramethylsilane as a standard. UV and IR spectra were taken on a Shimadzu UV-160 and Shimadzu IR-435 spectrophotomer, respectively. MS spectra were obtained by using JEOL JMS DX-303 EIMS spectrometer. Specific rotations were measured on a JASCO DIP-360 polarimeter, ORD and CD were determined using JASCO J-725

spectropolarimeter (ORDM-317 ORD attachment). Column chromatography and preparative TLC were carried out on Wakogel C-200 (100~200 mesh) and with silica gel $60F_{254}$, Merck. Most organic extracts were dried over anhyd. $MgSO_4$.

2-Benzyloxy-5-methoxybenzyl alcohol (2) To a stirred solution of 2-benzyloxy-5-methoxybenzaldehyde[6] (4.84 g, 0.02 mol) in 90% *aq.* MeOH (150 mL) was gradually added $NaBH_4$ (2.27 g, 0.06 mol) at 0~5°C. The mixture was stirred at the same temperature for 2 h, excess of $NaBH_4$ was decomposed with 20% *aq.* AcOH and most of the solvent was removed by evaporation *in vacuo*. The residue was extracted with CH_2CH_2, the CH_2Cl_2 extract was washed with a saturated *aq.* solution of $NaHCO_3$ and water. The solvent was removed by evaporation. The residue recrystallized from ether-petroleum ether mixture gave colorless needles (2), mp 48~49° (4.30 g, 88.1%). UV λ_{max}^{EtOH} nm(log ε): 203(4.57), 228 (3.39), 290(3.55); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600(OH); ^{1}H-NMR δ: 3.77(3H, s, OCH_3), 4.70(2H, s, CH_2OH), 5.07(2H, s, CH_2Ph), 6.74~6.91(3H, m, arom.H×3), 7.30~ 7.43(5H, m, arom.H×5); EIMS (70 eV) $^m/_z$ (rel. intensity): 244(M^+, 9.5), 152(7.1), 136(100), 125(27.7), 91(89.4); Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75: H, 6.60. Found: C, 73.55; H, 6.69.

2-Benzyloxy-5-methoxybenzyl chloride (3) The anhydrous benzene (24 mL) solution of thionyl chloride (12 mL, 0.16 mol) was added dropwise to the mixture of benzyl alcohol (2) (13.25 g, 0.054 mol) and *N,N*-dimethylaniline (14.03 mL, 0.11 mol) in anhydrous benzene (70 mL) with stirring at 0~5°C. The reaction mixture was continuously stirred at 100°C for 2 h, then washed with 10% *aq.* HCl and water. The benzene layer was dried over anhyd. $CaCl_2$ and treated in the usual manner to give the residue, whose column chromatography on silica gel with hexane gave a pale yellow oil (3) (14.64 g, guant.). UV λ_{max}^{EtOH} nm(log ε): 205(4.57), 230(sh, 3.97); ^{1}H-NMR δ: 3.78(3H, s, OCH_3), 4.67(2H, s, CH_2Cl), 5.09(2H, s, OCH_2Ph), 6.77~6.97(3H, m, arom.H×3), 7.28~7.48(5H, m, arom. H×5); EIMS (70 eV) $^m/_z$ (rel. intensity): 264(5.3), 262(M^+, 15.3), 227(M^+-Cl, 6.9), 173(3.1), 171(8.8), 136(62.9), 91(100).

2-Benzyloxy-5-methoxyphenylacetonitrile (4) To a suspension of sodium cyanide (5.78 g, 0.12 mol) in dimethyl sulfoxide (DMSO, 58 mL) was added dropwise the benzyl chloride (3) (15.48 g, 0.059 mol) in DMSO (50 mL) at rt with stirring. After further stirring at 40~50°C for 1 h, the resultant reaction mixture was poured into ice water (500 mL), and the precipitate was collected by filtration. The precipitate was recrystallized from dil. EtOH

to afford the phenylacetonitrile (4), colorless prism, mp 55~56°C (12.92 g, 86.6%). UV λ_{max}^{EtOH} nm(log ε): 203(4.52), 228(4.09); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250(C≡N); ^{1}H-NMR δ: 3.70(2H, s, CH_2CN), 3.78(3H, s, OCH_3), 5.06(2H, s, OCH_2Ph), 6.77~6.97(3H, m, arom.H×3), 7.33~7.44(5H, m, arom.H×5); EIMS (70 eV) $^m/_z$ (rel. intensity): 253(M^+, 63.6), 162(10.3), 91(100); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.63; H, 6.05; N, 5.53.

2-Benzyloxy-5-methoxyphenylacetic acid (5) A mixture of the phenylacetonitrile (4) (12.92 g, 0.051 mol), 25% ethanolic KOH solution (177 mL) and diethylene glycol (50 mL) was refluxed until the evolution of ammonia ceased (20 h). Then the reaction mixture was acidified with 10% *aq.* HCl to yield a solid. The solid collected by filtration was recrystallized from benzene-petroleum ether to afford colorless needles (5), mp 111~112°C (10.78 g, 77.6%). UV λ_{max}^{EtOH} nm(log ε): 203(4.49), 230(sh, 3.91); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710(C=O); ^{1}H-NMR δ: 3.68(2H, s, $C\underline{H}_2COOH$), 3.76(3H, s, OCH_3), 5.02(2H, s, $OC\underline{H}_2Ph$), 6.73~6.88(3H, m, arom.H×3), 7.25~7.40(5H, m, arom.H×5); EIMS (70 eV) $^m/_z$ (rel. intensity): 272(M^+, 46.8), 181(M^+-$C_6H_5CH_2$, 12.5), 164(30.9), 137(25.4), 91(100); Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.62; H, 5.93.

***N*-[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-benzyloxy-5-methoxyphenyl]acetamide (8)** An anhydrous ether solution (30 ml) of 5-benzyloxy-2-methoxyphenylacetyl chloride (6), prepared from the carboxylic acid (5) (2.18 g, 8.0 mmol) and excess $SOCl_2$ by the usual way, was added dropwise to a mixure of an ether (100 mL) solution of the amine (7)[2] (3.00 g, 8.3 mmol) and 5% *aq.* Na_2CO_3 (100 mL, 46.7 mmol) solution with stirring at 0~5°C. After further stirring for 2 h at the same temperature, the organic layer was separated, and the layer was washed successively with 5% *aq.* HCl solution and water, and drid. Removal of the solvent by evaporation left a residue, which was chromatographed with hexane-CH_2Cl_2 [3:2 ($^v/_v$)] to give the amide (8) (4.81 g, 94.2%) as a pale yellow oily substance showing a single spot on TLC. $[\alpha]_D$ -49.4° (c = 0.29, $CHCl_3$); UV λ_{max}^{EtOH} nm(log ε): 203(4.81), 230(sh, 4.18); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660(C=O); ^{1}H-NMR δ: 1.36(3H, d, J = 6.8 Hz, CH_3), 2.01~2.76, 3.12~3.25(2H×2, m, CH_2×2), 3.78, 3.80(3H×2, s, OCH_3×2), 3.88 (2H, s, CH_2) 4.98(2H, d, J = 3.2 Hz, $OC\underline{H}_2Ph$), 5.07(2H, s, $OC\underline{H}_2Ph$), 5.22 (1H, q, J = 6.84, CH), 6.25~7.11(6H, m, arom.H×6), 7.22~7.43(5H×3, m, arom.H×15); EIMS (70 eV) $^m/_z$ (rel. intensity): 615(M^+, 18.7), 525(8.5), 375(41.2), 284(15.2), 268(21.2), 240(49.1), 164(32.3), 134(28.2), 105 (71.1), 91(100).

(*S*)-1-(2'-Benzyloxy-5'-methoxybenzyl)-*N*-[(*S*)-phenylethyl]-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (10) A mixture of the amide (**8**) (4.80 g, 7.8 mmol) and $POCl_3$ (20.00 mL, 0.22 mmol) in dry toluene (50.0 mL) was refluxed for 3.5 h. Evaporation of excess reagent and solvent left a residue, which was thoroughly washed with petroleum ether. The residue (iminium ion, **9**) was used for the following reaction without purification. To a stirred solution of the above iminium ion (**9**) in MeOH (250 mL), $NaBH_4$ (5.9 g, 0.16 mol) was added in portions at -78°C. After the reaction mixture was stirred at the same temperature for 2 h, excess $NaBH_4$ was decomposed by addition of 10% *aq.* AcOH and most of the solvent was evaporated *in vacuo*. The residual was made alkaline with 10% *aq.* NH_4OH solution, and extracted repeatedly with CH_2Cl_2. Usual work-up of the CH_2Cl_2 layer gave an oily residue, whose column chromatography on silica gel with hexane-CH_2Cl_2 [9:1 ($^v/_v$)] gave a pale yellow oil (**10**), (4.88 g, *guant. from* **8**) showing a single spot on TLC. $[\alpha]_D$ +64.1° (c= 0.38, $CHCl_3$); 99.0% ee[CHIRALCEL OD column (4.6 × 250 mm) (Daicel Chemical Industries, Ltd., Tokyo, JAPAN), mobile phase: hexane-2-propanol [9:1 ($^v/_v$)] including 0.1% diethylamine, flow rate: 0.5 mL/min, detection: 254 nm]; UV λ_{max}^{EtOH} nm(log ε); 203(4.81), 230(sh, 4.10); ^{1}H-NMR δ: 1.25(3H, d, J = 6.4 Hz, CH_3), 2.41~3.31(2H×3, *m*, CH_2×2), 3.77, 3.82(3H×2, s, OCH_3×2), 3.84(1H, br, C-1), 4.24(1H, br, CH), 4.46(2H, S, $OC\underline{H}_2Ph$), 4.72(2H, d, J = 11.0 Hz), 6.56~6.90(5H, m, arom.H×5), 7.08~7.48(5H×3, m, arom.H×15); EIMS (70 eV) $^m/_z$ (rel. intensity); 599(M^+, 0.1), 372(100), 268(27.6), 177 (12.0), 148(5.4), 105(24.2), 91(18.5).

(*S*)-1-(2'-Hydroxy-5'-methoxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (11) A mixture of **10** (1.67 g, 2.80 mmol) and 10% Pd-C (*ca.* 0.2 g) in EtOH (*ca.* 120 mL) containing conc.HCl (12 mL) was shaken at rt under a hydrogen atmosphere (2.60 $^{kg}/_{cm^2}$) for 41 h using a medium-pressure catalytic hydrogenator. The catalyst was removed by filtration and most EtOH was removed by evaporation *in vacuo*. The residual solution was made alkaline with 10% *aq.* NH_4OH solution and extracted with CH_2Cl_2. After usual work-up the extract yielded a residue, which was recrystallized from $CHCl_3$ to afford colorless prism (**11**), mp 191~192°C (0.77 g, 87.7%). $[\alpha]_D$ +58.0° (c = 0.22, $CHCl_3$); ORD (c = 1.0×10^{-4}, EtOH) [M] (nm): -5769° (307) (trough), +9167° (290) (peak); CD (c = 1.0×10^{-4}, EtOH) [θ] (nm):-4573° (300), +4923° (282) ;UV λ_{max}^{EtOH} nm(log ε): 204(4.80), 227(sh, 4.21), 292(3.98); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520(OH); ^{1}H-NMR δ: 2.72~3.39(2H×3, m,

CH_2×3), 3.73, 3.85(3H×2, s, OCH_3×2), 4.36(1H, d, J = 7.81 Hz, C-1), 6.52(1H, s, C-5), 6.60(1H, d, J = 3.2 Hz, C-6'), 6.66(1H, dd, J_1 = 8.7 H_z, J_2 = 3.1 Hz, C-4'), 6.74(1H, s, C-8), 6.85(1H, d, J = 8,5 Hz, C-3'); EIMS (70 eV) $^m/_z$ (rel. intensity): 315(M^+, 8.2), 178(100), 163(18.2), 149(7.5); Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.36; H, 6.81; N, 4.55.

(*S*)-1-(2'-Hydroxy-5'-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1) Tetrahydroisoquinoline derivative (11) (0.63 g, 2 mmol) was dissolved in MeOH (60 mL), and a solution of 35% HCHO (6.00 mL, 70 mmol) was added. To the methanolic solution, 0.95 g (25 mmol) of $NaBH_4$ was added. After the reaction mixture was stirred 1 h at rt, the excess reagent was decomposed by addition of 10% *aq.* AcOH solution, and most of the solvent was removed by evaporation *in vacuo.* The residue was then made alkaline with 10% *aq.* NH_4OH solution, extracted repeatedly with CH_2Cl_2. Usual work-up of the CH_2Cl_2 layer gave an oily residue, whose column chromatography on silica gel with hexane-CH_2Cl_2 [3:2 ($^v/_v$)] gave a pale yellow oil (1), showing a single spot on TLC (0.58 g, 88.15%). The ^{1}H-NMR and ^{13}C-NMR data of 1 are shown in the Table. $[\alpha]_D$ -40.9°(c = 0.44, $CHCl_3$); ORD (c = 1.0×10^{-4}, EtOH) [M] (nm):-5769° (307) (trough), +9167° (290) (peak); CD (c = 1.0×10^{-4}, EtOH) [θ] (nm): -9538° (297), +7692° (281); UV λ_{max}^{EtOH} nm(log ε): 203(4.77), 228(sh. 4.14), 292(3.90) $\lambda_{max}^{EtOH\cdot KOH}$ nm(log ε): 214(4.54), 302(3.98); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520(OH); EIMS (70eV) $^m/_z$ (rel. intensity): 329(M^+, 6.6), 192(100), 177(22.1), 149(5.2), 148(5.6).

ACKNOWLEDGMENT

We are grateful to the staff of the instrumental analysis center of our university for MS, ^{1}H- and ^{13}C-NMR spectral measurements.

REFERENCES

1. Atta-ur-Rhaman, A.Pervin, and M.A.Rhaman, *Fitoterapia,* 1991, **62**, 261 (*Chem. Abstr.*, 1992, **117**, 86634).
2. K.Takaba, J.Haginaka, J.Kunitomo, and T.Shingu, *Heterocycles*, 1997, **45**, 1111.
3. J.Kunitomo, K.Morimoto, K.Yamamoto, Y.Yoshikawa, K.Azuma, and K.Fujitani, *Chem. Pharm. Bull.*, 1971, **19**, 2197.
4. M.Tomita, H.Fujitani, S-T. Lu, and S.M. Kupchan, *Chem. Pharm. Bull.*, 1967, **15**, 959.
5. R.P.Polniaszek, *J. Chem. Educ.*, 1989, **66**, 970.
6. Th. Kappe and Th. Witoszynskyj, *Arch. Pharm.*, 1975, **308**, 339.

Received, 12th March, 1998