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Synthesis of *dl*-Steporphine. The Alkaloids of *Stephania sasakii* HAYATA. XV

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The synthesis of *dl*-steporphine (**1**), an aporphine-type alkaloid having a hydroxyl group at the 4-position, is described. The acetophenone derivative (**4**), prepared from **2** and **3** by Friedel–Crafts reaction, was condensed with aminoacetaldehyde diethyl acetal to afford the ketimine derivative (**5**). The product (**6**), from the sodium borohydride reduction of **5** or its *N*-methyl derivative (**7**) was subjected to hydrolytic cyclization in concentrated hydrochloric acid to afford stereospecifically 1-(2-bromobenzyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**8**) or its *N*-methyl derivative (**9**), respectively, with a *cis* relationship between C_1–H and C_4–H. The stereospecificity is presumed to be due to intramolecular hydrogen bonding between the alcoholic hydroxyl group and the bromo atom. Irradiation of **9** in dilute hydrochloric acid afforded *dl*-steporphine (**1**). This is the first stereospecific synthesis of 4-hydroxyaporphine-type alkaloids, and the method should be adaptable to the synthesis of other alkaloids of this type.

Keywords——4-hydroxyaporphine; steporphine; *Stephania sasakii* HAYATA; Pomeranz–Fritsch reaction; stereospecific cyclization; intramolecular hydrogen bonding; photosynthesis

The alkaloid steporphine, which was isolated from *Stephania sasakii* HAYATA (Menispermaceae), was assigned the structure (**1**) and was the first reported example of an aporphine-type alkaloid having a hydroxyl group at the 4-position.[2,3] Eight other naturally occurring alkaloids of this type have subsequently been isolated.[3,4] Their structures, configurations at C_1-H and C_4-H, and conformations of the hydroxyl group at C-4 have been determined by analysis of their proton nuclear magnetic resonance spectra (^{1}H-NMR), infrared spectra (IR) and specific rotation or optical rotatory dispersion (ORD) curves,[3,4] and confirmed by X-ray crystallographic analysis of *N*,*O*-diacetyl-4-hydroxynantenine.[5] Until now, this type of alkaloid has only been synthesized *via* 4-hydroxylation with lead tetraacetate[6] or oxyvanadium trifluoride[7] of the corresponding aporphine or 1-(substituted benzyl)-*N*-methyl-1,2,3,4,-tetrahydroisoquinoline.

A major problem encountered in synthesizing 4-hydroxyaporphine is the synthesis of the starting material, 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (BHTIQ). Several reports[8–11] on BHTIQ synthesis have appeared, and acid-catalyzed cyclization of the corresponding aminoacetaldehyde diethyl acetal derivative is commonly used. However, two problems are encountered in this cyclization. First, this type of compound is an intermediate in a direct process leading to the isopavine-type alkaloids (**10**) and complete prevention of the formation of such products is difficult. The other problem is producing the desired stereospecific configuration between C_1-H and C_4-H is this cyclization. The first problem was solved by substituting a nitro group at the 2′-position in the benzyl moiety[10] and masking the basic nitrogen as the urethane derivative,[11] but the second problem could not be solved even after a detailed study by Elliott and co-workers,[11] and other reports[8–10] do not discuss the relevant stereochemistry, although there has been a report of sodium borohydride reduction of the corresponding 4-keto compound giving only the *cis* form. Here we describe the successful stereospecific synthesis of *dl*-1-(2-bromobenzyl)-2-methyl-4-hydroxy-6,7-methyl-

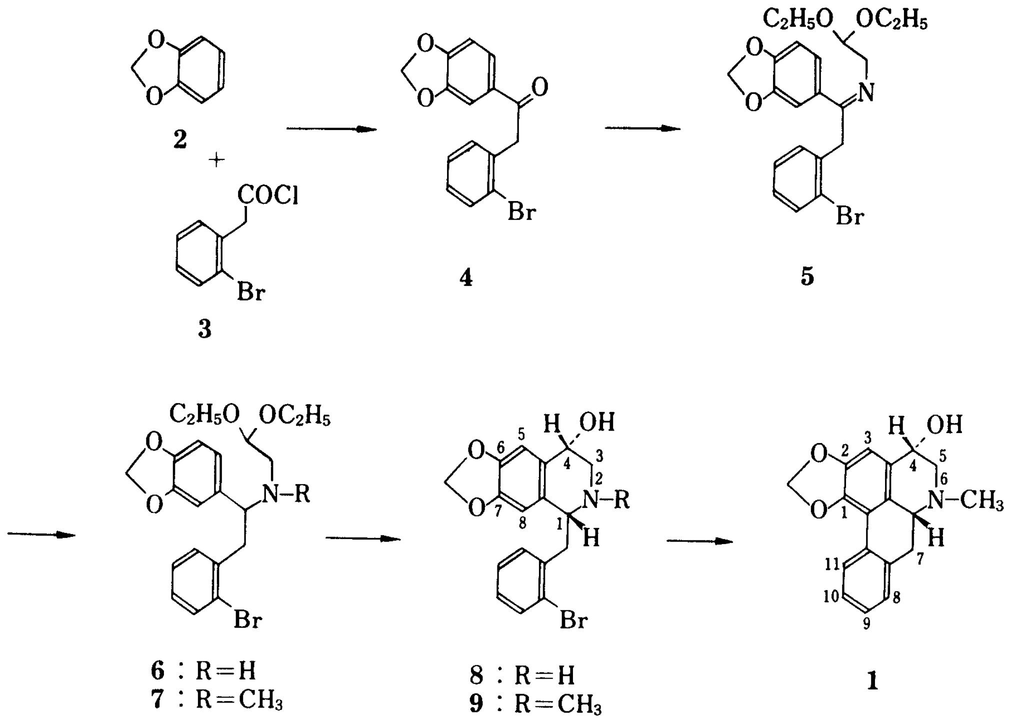

Chart 1

enedioxy-1,2,3,4-tetrahydroisoquinoline (**9**) in high yield for use as a key intermediate in the synthesis of *dl*-steporphine (**1**). This is the first report of the stereospecific synthesis of 4-hydroxyaporphine-type alkaloids.

The synthetic route is shown in Chart 1. The starting material, 2-(*o*-bromophenyl)-3',4'-methylenedioxyacetophenone (**4**), was obtained in 90.2% yield by the carefully controlled Friedel-Crafts acylation[10] of benzodioxole (**2**)[12] with 2-bromophenylacetyl chloride (**3**). This ketone (**4**) was condensed with aminoacetaldehyde diethyl acetal in the presence of titanium tetrachloride[13] to give the corresponding ketimine derivative (**5**), which was reduced with sodium borohydride in the usual manner to afford *N*-[α-(2-bromobenzyl)-3,4-methylenedioxybenzyl]aminoacetaldehyde diethyl acetal (**6**) in a high yield (83.6%) based on the starting material (**4**). Treatment of this compound (**6**) with concentrated hydrochloric acid according to Bobbit's modification of the Pomeranz-Fritsch cyclization[14] afforded 1-(2-bromobenzyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**8**) as colorless needles, mp 137—138°C in 73.2% yield. Similar cyclization of the *N*- methylaminoacetaldehyde diethyl acetal derivative (**7**) which was the reaction product of Eschweiler-Clarke *N*-methylation of compound (**6**), afforded 1-(2-bromobenzyl)-2-methyl-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**9**) as colorless needles, mp 131—132°C, in 68.2% yield. This compound (**9**) was also obtained by *N*-methylation of compound (**8**). The ultraviolet (UV) spectrum, IR, ^{1}H-NMR, mass spectrum (MS) and elemental analyses of these compounds confirmed that their formulae were **8** and **9**. In the ^{1}H-NMR, the signal assignable to the hydrogen geminal to a hydroxyl group at C-4 in compound (**8**) or (**9**) appeared at δ 4.44 or 4.52, respectively, and demonstrated the *cis* relationship between C_1-H and C_4-H (in the case of the *trans* relationship, C_4-H would be at δ 4.7—4.9).[3,4,6,7] The signal of the aromatic proton at C-5 appeared at δ 6.85 or 6.82, respectively, which indicates that the C_4-OH group is pseudoaxial (in the case of the C_4-OH pseudo-equatorial isomer, C_5-H would be above δ 7.1).[11] The stretching band of the alcoholic hydroxy group at 3350—3400 or 3300—3550 cm^{-1} in these IR spectra was considered to be evidence of intramolecular hydrogen bonding (dilution method; 7×10^{-3} M). Accordingly, the alcoholic hydoxyl group was concluded to have pseudoaxial bonding.[3,4] When the mother liquor of the cyclized products was carefully examined, the diastereomer of compound (**8**) or (**9**) and the corresponding isopavine-type alkaloid (**10**) could not be detected.

Thus, the cyclization of compounds (**6**) and (**7**) proceeded stereospecifically and this synthetic method overcame the above-described two problems in the synthesis of 4-hydroxybenzyl-1,2,3,4-tetrahydroisoquinoline derivatives (BHTIQ). The success of stereospecific cyclization can probably be explained as the following reason. The mechanism of this cyclization, as described by Elliott and co-workers,[11] is shown in Chart 2. With electrophilic substitution at the aromatic ring of the aldehyde (B) produced *via* the double-charge ion (A), intramolecular hydrogen bonding probably occurs between the bromo atom and the hydroxyl group, and stabilizes the compound.[15] In the Dreiding model based on a *cis* relationship between C_1-H and C_4-H and pseudo-axial orientation of C_4-OH, the distance between Br···H(O) is found to be sufficiently close for this intramolecular hydrogen bonding to occur. The N···H(O) intramolecular hydrogen bonding does not occur here because the basicity of the nitrogen is lost due to the presence of the concentrated hydrochloric acid. The reason for complete prevention of the cyclization to the corresponding isopavine-type alkaloid (**10**) from the BHTIQ derivatives [(**8**) or (**9**)] is probably the absence of an electron-donating group in the benzyl moiety at the C-1 position.[16]

The configurations at C_1-H and C_4-H of compound (**9**) are the same as those of the natural product, steporphine (**1**), and compound (**9**) thus represents a key intermediate for further cyclization to the desired compound.

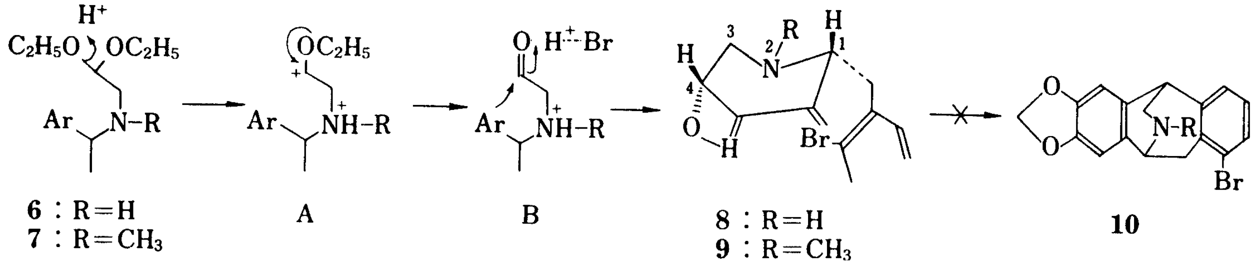

Chart 2

Irradiation of compound (**9**) in dilute hydrochloric acid and methanol as described for the photosynthesis of 7-hydroxyaporphine[17] produced *dl*-steporphine (**1**) as colorless needles, mp 172—173°C, in 17.0% yield. Its identity was confirmed by direct comparison of the spectra (UV, IR, ^{1}H-NMR and MS) and thin-layer chromatographic (TLC) behavior with those of the natural product.

This synthetic method should be adaptable to the syntheses of 4-hydroxyaporphine-type alkaloids with a *cis* relationship between C_4-H and C_{6a}-H.

Experimental

All mp were determined with a Yanagimoto microscopic hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian A-60 or JNM-FX 200 spectrometer in $CDCl_3$ with Me_4Si as an internal standard. MS were recorded on a Hitachi RMU-6 spectrometer with a heated direct inlet system at 70 eV.

2-(*o*-Bromophenyl)-3′,4′-methylenedioxyacetophenone (4)——A solution of 1,3-benzodioxole (**2**) (14.9 g, 0.122 mol) in CH_2Cl_2 (50 ml) was added dropwise over a period of 2 h, with stirring, to a solution of 2-bromophenylacetyl chloride (**3**) [formed from 2-bromophenylacetic acid (33.07 g, 0.154 mol) and thionyl chloride (80 ml) in the usual way] in CH_2Cl_2 (200 ml) containing anhyd. aluminium chloride (23.90 g) at −40° to −50°C. The excess reagent was decomposed with 10% NaOH aqueous solution. The organic solvent layer was concentrated and the residue was extracted five times with Et_2O. The Et_2O layer was washed with water, dried over $MgSO_4$, and concentrated to give a brown solid, which was recrystallized from hexane–Et_2O mixture to afford the acetophenone derivative (**4**) (35.12 g, yield 90.2%) as colorless needles, mp 90—91°C. UV λ_{max}^{EtOH} nm (log ε): 229 (4.34), 276 (3.87), 312 (3.94). IR ν_{max}^{KBr} cm^{-1}: 1685 (C=O). ^1H-NMR δ: 4.37 (2H, s, CH_2), 6.03 (2H, s, OCH_2O), 6.87 (1H, d, J=8.5 Hz, Ar–H), 7.23 (1H, s, Ar–H), 7.26 (1H, s, Ar–H), 7.68 (1H, dd, J=2.5, 8.5 Hz, Ar–H), 7.05—7.70 (3H, m, Ar–H×3). MS m/z (%): 320 (isotope peak, 16.6), 318 (M^+, 17.1), 239 (M^+-Br, 23.9), 149 ($M^+-CH_2C_6H_4Br$, 100), 121 (149−CO, 34.3). *Anal.* Calcd for $C_{15}H_{13}BrO_3$ (m. w., 319.15): C, 56.47; H, 3.48. Found: C, 56.43; H, 3.46.

N-[α-(2-Bromobenzyl)-3,4-methylenedioxybenzyl]aminoacetaldehyde Diethyl Acetal (6)——A solution of titanium tetrachloride (5.4 g) in dry benzene (50 ml) was slowly added over a period of 1 h to a stirred solution of the acetophenone derivative (**4**) (15.17 g, 4.75×10^{-2} mol) and aminoacetaldehyde diethyl acetal (50 g) in dry benzene (70 ml) at 0—5°C under an argon atmosphere. Stirring was continued for 30 min at the same temperature and then for 3 d at room temperature. The reaction mixture was poured into ice water, then made basic with concentrated NH_4OH aqueous solution, and extracted with Et_2O. The Et_2O layer was washed with water and dried over $MgSO_4$. Removal of the solvent left a brownish oily ketimine (**5**), which gave essentially a single spot on TLC. Compound (**5**) was used without purification in the following reaction.

$NaBH_4$ (30 g) was gradually added to a solution of **5** in MeOH (80 ml) with stirring at 0°C. After further stirring for 3 h at room temperature, the mixture was acidified with 10% AcOH, MeOH was evaporated off *in vacuo*, and the residue was made basic with concentrated NH_4OH aqueous solution then extracted with CH_2Cl_2. The extract was treated in the usual manner to afford a brownish oily substance, which was purified by silica gel column chromatography. The fraction eluted with 50% hexane–CH_2Cl_2 gave the N-substituted aminoacetaldehyde diethyl acetal (**6**) as a colorless oil [17.34 g, 83.6% yield based on compound (**4**)], which showed a single spot on TLC. UV λ_{max}^{EtOH} nm (log ε): 242 (sh, 3.02), 290 (2.91). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH). ^1H-NMR δ: 1.10 (6H, t, J=8.0 Hz, $CH_3\times2$), 1.70 (1H, broad, NH), 2.52 (2H, d, J=6.0 Hz, $-\underline{CH_2}NH$), 2.97 (2H, d, J=7.0 Hz, o-$BrC_6H_4CH_2$), 3.22—3.74 (4H, m, $O\underline{CH_2}CH_3\times2$), 3.91 (1H, t, J=7.0 Hz, $C\underline{H}NH$), 4.50 (1H, t, J=6.0 Hz, $(C_2H_5O)_2C\underline{H}$), 5.90 (2H, s, OCH_2O), 6.70—7.60 (7H, m, Ar–H×7). MS m/z (%): 392 (2.6), 390 ($M^+-OC_2H_5$, 2.7), 346 (3.6), 344 ($M^+-OC_2H_5\times2-H$, 3.9), 305 (18.9), 303 ($M^+-(C_2H_5O)_2CHCH_2NH$, 18.9), 266 ($M^+-CH_2C_6H_4Br$, 100), 220 ($266-OC_2H_5$, 16.4), 219 (220−H, 87.7).

N-[α-(2-Bromobenzyl)-3,4-methylenedioxybenzyl]-N-methylaminoacetaldehyde Diethyl Acetal (7)——A 10% HCHO-MeOH solution (12.5 ml) was added dropwise to a solution of compound (**6**) (2.58 g) in MeOH (42 ml) with stirring at room temperature. The mixture was stirred continuously for 1 h at the same temperature, then $NaBH_4$ (2.5 g) was gradually added at 0—5°C. The mixture was continuously stirred for 1 h at room temperature, then the excess reagent was decomposed by adding 10% AcOH solution. The solution was made basic with concentrated NH_4OH aqueous solution and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and concentrated to afford the N-methyl derivative (**7**) as a colorless oily compound (2.16 g, 85.2%), which showed a single spot on TLC. UV λ_{max}^{EtOH} nm (log ε): 239 (sh, 3.85), 289 (3.72). ^1H-NMR δ: 1.16, 1.17 (3H×2, t, $OCH_2C\underline{H_3}\times2$), 2.35 (3H, s, NCH_3), 2.52, 2.62 (1H×2, dd, J=5.0, 14.0 Hz, $-NHC\underline{H_2}CH-$), 2.96 (1H, dd, J=8.5, 13.5 Hz, o-$BrC_6H_4C\underline{H_2}$), 3.88 (1H, dd, J=6.5, 8.5 Hz, $-C\underline{H}NCH_3$), 4.49 (1H, t, J=5.0 Hz, $(C_2H_5O)_2C\underline{H}-$), 5.91, 5.92 (1H×2, d×2, J=1.5 Hz, OCH_2O), 6.54—7.50 (7H, m, Ar–H×7). MS m/z (%): 305 (isotope peak, 34.1), 303 ($M^+-(C_2H_5O)_2CHCH_2NHCH_3$, 35.1), 280 ($M^+-BrC_6H_4CH_2$, 100).

1-(2-Bromobenzyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (8)——A mixture of the aminoacetaldehyde diethyl acetal derivative (**6**) (6.3 g) and 6 N HCl (150 ml) was stirred for 8 d at room temperature. The mixture was made basic with concentrated NH_4OH aqueous solution and extracted with CH_2Cl_2. The organic layer was treated in the usual manner to afford a pale brownish solid, which was recrystallized from Me_2CO to give the corresponding 1,2,3,4-tetrahydro-4-isoquinolinol (**8**) (4.28 g, 73.2% yield) as colorless needles, mp 137—138°C. UV λ_{max}^{EtOH} nm (log ε): 241 (sh, 3.80), 294 (3.65). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350—3400 (NH, OH). ^1H-NMR δ: 2.79 (1H, dd, J=10.5, 13.5 Hz, o-$BrC_6H_4CH_2$), 2.93, 3.15 (2H, dd, ×2, J=2.5, 12.0 Hz, C_3-H×2), 3.57 (1H, dd, J=3.0, 13.5 Hz, o-$BrC_6H_4CH_2$), 4.21 (1H, dd, J=3.0, 10.5 Hz, C_1-H), 4.44 (1H, t, J=2.5 Hz, C_4-H), 5.95 (2H, s, OCH_2O), 6.85 (1H, s, C_5-H), 6.93 (1H, s, C_8-H), 7.10—7.63 (4H, m, Ar–H×4). MS m/z (%): 364 (isotope peak, 0.4), 362 (M^+, 1.2), 280 ($M^+-Br-2H$, 2.0), 262 ($280-H_2O$, 44.5), 193 ($M^+-CH_2C_6H_4Br$, 64.8), 192 (193−H, 100), 174 ($192-H_2O$, 54.2). *Anal.* Calcd for $C_{17}H_{16}BrNO_3$ (m. w., 362.22): C, 56.36; H, 4.45; N, 3.87. Found: C, 56.24; H, 4.40; N, 3.63.

1-(2-Bromobenzyl)-2-methyl-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (9)——(a) From Compound (**8**): Treatment of compound (**8**) (3.0 g) in MeOH (50 ml) with 10% HCHO–MeOH solution (15 ml) and $NaBH_4$ (3.0 g) as described above for the N-methylation of compound (**6**) afforded the N-methyl derivative (**9**), which was recrystallized from Me_2CO to give colorless needles, mp 131—132°C (2.6 g, 83.3% yield). UV λ_{max}^{EtOH} nm (log ε): 240 (sh, 3.80), 294 (3.59). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—3550 (OH). ^1H-NMR δ: 2.52 (3H, s, NCH_3), 2.83 (1H, dd, J=3.5, 12.0 Hz, C_3-H), 3.01 (1H, dd, J=5.5, 12.0 Hz, C_3-H), 3.19, 3.28 (1H×2, dd, ×2, J=5.5, 13.5 Hz, o-$BrC_6H_4C\underline{H_2}$), 3.85 (1H, t, J=5.5 Hz, C_1-H), 4.52 (1H, t, J=5.5 Hz, C_4-H), 5.91 (2H, dd, J=1.5, 10.5 Hz, OCH_2O), 6.37 (1H, s, C_8-H), 6.82 (1H, s, C_5-H), 6.97—7.56 (4H, m, Ar–H×4). MS m/z (%): 377, 375 (M^+, 2.1, 1.6), 359, 357 (M^+-H_2O, 3.4, 4.5), 206 ($M^+-CH_2C_6H_4Br$, 100), 188 ($206-H_2O$, 66.3), 171, 169 ($CH_2C_6H_4Br$, 19.9, 21.1). *Anal.* Calcd for $C_{18}H_{18}BrNO_3$ (m. w., 376.25): C, 57.46; H, 4.82; N, 3.72. Found: C, 57.49; H, 4.83; N, 3.73.

(b) From Compound (**7**): A mixture of compound (**7**) (820 mg) and 6 N HCl (20 ml) was stirred for 8 d at room temperature as described above for the cyclization of compound (**6**). The reaction product was treated in the usual manner to afford a pale yellowish oily substance, which was recrystallized from Me_2CO to give colorless needles, mp 137—138°C (467.5 mg, 68.2% yield). This product was identified as compound (**9**) by direct comparison (mixed mp, ^{1}H-NMR, IR and TLC).

Acetate of Compound (**9**)——A mixture of compound (**8**) (0.25g), acetic anhydride (2 ml) and pyridine (0.5 ml) was kept at room temperature. After 1 d, the mixture was poured into ice water, made alkaline with aqueous 10% NH_4OH aqueous solution and extracted with Et_2O. The Et_2O layer was washed, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave a colorless oily substance showing a single spot on TLC. The yield was quantitative. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 ($OCOCH_3$). ^{1}H-NMR δ: 2.16 (3H, s, $COCH_3$), 2.49 (3H, s, NCH_3), 3.02 (1H, dd, $J=6.0$, 13.0 Hz, o-BrC_6H_4-$C\underline{H}_2$), 3.15 (2H, d, $J=7.0$ Hz, C_4–H), 3.27 (1H, dd, $J=6.5$, 13.0 Hz, o-$BrC_6H_4C\underline{H}_2$), 3.86 (1H, t, $J=6.8$ Hz, C_1–H), 5.88, 5.91 (2H, dd, $J=1.5$, 3.5 Hz, OCH_2O), 5.98 (1H, t, $J=7.0$ Hz, C_4–H), 6.23 (1H, s, C_8–H), 6.74 (1H, s, C_5–H), 7.04—7.24 (3H, m, Ar–H × 3), 7.53—7.58 (1H, m, Ar–H).

***dl*-Steporphine** (**1**)——A mixture of compound (**9**) (376.2 mg), 6 N HCl (20 ml), MeOH (120 ml) and water (140 ml) was irradiated with a 100 W high-pressure mercury lamp for 6 h. The MeOH was evaporated off *in vacuo*, and the aqueous solution was washed with Et_2O, made basic with 10% NaOH aqueous solution and extracted with Et_2O. The extract was washed with water, dried over $MgSO_4$ and concentrated to give a brownish oily substance. This residue was subjected to silica gel column chromatography, and the fraction eluted with CH_2Cl_2 was recrystallized from Me_2CO–Et_2O to give *dl*-steporphine (**1**) as colorless needles, mp 172—173°C (50.2 mg, 17.0% yield). UV λ_{max}^{EtOH} nm (log ε): 239 (4.14), 273 (4.14), 293 (sh, 3.78), 312 (3.47). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—3550 (OH). ^{1}H-NMR δ: 2.57 (3H, s, NCH_3), 2.65, 3.11 (1H × 2, dd × 2, $J=2.5$, 12.0 Hz, C_5–H × 2), 2.67 (1H, t, $J=15.5$ Hz, C_7–H), 3.15 (1H, m, C_{6a}–H), 3.18 (1H, dd, $J=13.0$, 15.5 Hz, C_7–H), 4.46 (1H, t, $J=2.5$ Hz, $C\underline{H}(OH)$), 5.92, 6.12 (1H, d × 2, $J=2.0$ Hz, OCH_2O), 6.82 (1H, s, C_3–H), 7.23—7.35 (3H, m, Ar–H × 3), 8.06 (1H, d, $J=7.5$ Hz, C_{11}–H). MS m/z (%): 295 (M^+, 27.9), 294 (M^+-H, 20.9), 276 ($294-H_2O$, 20.0), 275 (56.5), 252 ($M^+-CH_3N{=}CH_2$, 100). *Anal.* Calcd for $C_{18}H_{17}NO_3$ (m. w., 295.32): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.42; H, 5.80; N, 4.81.

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