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Synthesis of *dl*-4-Hydroxycrebanine[1)]

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4-Hydroxycrebanine (**2**), a natural product from *Stephania sasakii* HAYATA, was synthesized *via* 1-(6′-bromo-2′,3′-dimethoxybenzyl)-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**17**), which was obtained by Bobbitt's modification of the Pomeranz–Fritsch cyclization of *N*-[2-(6′-bromo-2′,3′-dimethoxyphenyl)-1-(3,4-methylenedioxy phenyl)ethyl]aminoacetaldehyde diethyl acetal (**12**). Irradiation of the compound (**17**) with the *cis* relationship of C_1-H and C_4-H gave *dl*-4-hydroxycrebanine (**2**) and its isomer (**2a**). The stereostructures of the two isomers were established firmly by direct comparison of the proton nuclear magnetic resonance spectra.

Keywords——*Stephania sasakii* HAYATA; 4-hydroxycrebanine; 4-hydroxyaporphine alkaloid; Pomeranz–Fritsch cyclization; irradiation; absolute configuration

In part XV[2)] of a series of papers, we reported that Bobbitt's modification of the Pomeranz–Fritsch cyclization of *N*-[2-(2′-bromophenyl)-1-(3,4-methylenedioxyphenyl)-ethyl]aminoacetaldehyde diethyl acetal or its *N*-methyl derivatives (**11** or **13**) in concentrated hydrochloric acid afforded the corresponding 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives (**14** or **15**) with the *cis* relationship of C_1-H and C_4-H without formation of the isopavine-type compound (**18**). Irradiation of **15** produced *dl*-steporphine (**1**), which was identified with the natural product from *Stephania sasakii* HAYATA[3)] except for the optical rotation. This synthesis provided a general method for the synthesis of aporphine-type alkaloids having an alcoholic hydroxyl group at the 4-position.[2)]

This paper describes the synthesis of *dl*-4-hydroxycrebanine (**2**)[4)] by a synthetic route similar to that used for **1**,[2)] as shown in Chart 1, and the stereochemical examination of the synthetic product.

One of the starting materials, 6-bromo-2,3-dimethoxyphenylacetic acid (**7**), was obtained in good yield *via* the corresponding benzyl alcohol (**4**), the benzyl chloride (**5**) and the benzyl cyanide derivatives (**6**) from 6-bromo-2,3-dimethoxybenzaldehyde (**3**).[5)] The Friedel–Crafts reaction of 1,3-benzodioxole (**8**)[6)] with the acid chloride derived from **7** at −50 °C in methylene chloride afforded α-(6′-bromo-2′,3′-dimethoxyphenyl)-3,4-methylenedioxyacetophenone (**9**) as colorless needles, mp 116—117 °C, in 60.7% yield. This acetophenone derivative (**9**) was condensed with aminoacetaldehyde diethyl acetal to give the corresponding ketimine derivative (**10**), which, without purification, was reduced with sodium borohydride to afford *N*-[2-(6′-bromo-2′,3′-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-ethyl]aminoacetaldehyde diethyl acetal (**12**) in 90.6% yield based on **9**. Bobbitt's modification[7)] of the Pomeranz–Fritsch cyclization of **12** in concentrated hydrochloric acid afforded a mixture consisting of two diastereomers (**16** and **16a**) in 93.6% total yield. Although the two stereoisomers were not isolated in pure form from the mixture, the *N*-methyl derivatives derived from the above mixture were separated by silica gel column chromatography into two stereoisomers (**17** and **17a**, respectively) in a ratio of *ca.* 4:1; **17**, colorless needles, mp 134—137 °C, and **17a**, colorless amorphous. In the proton nuclear magnetic

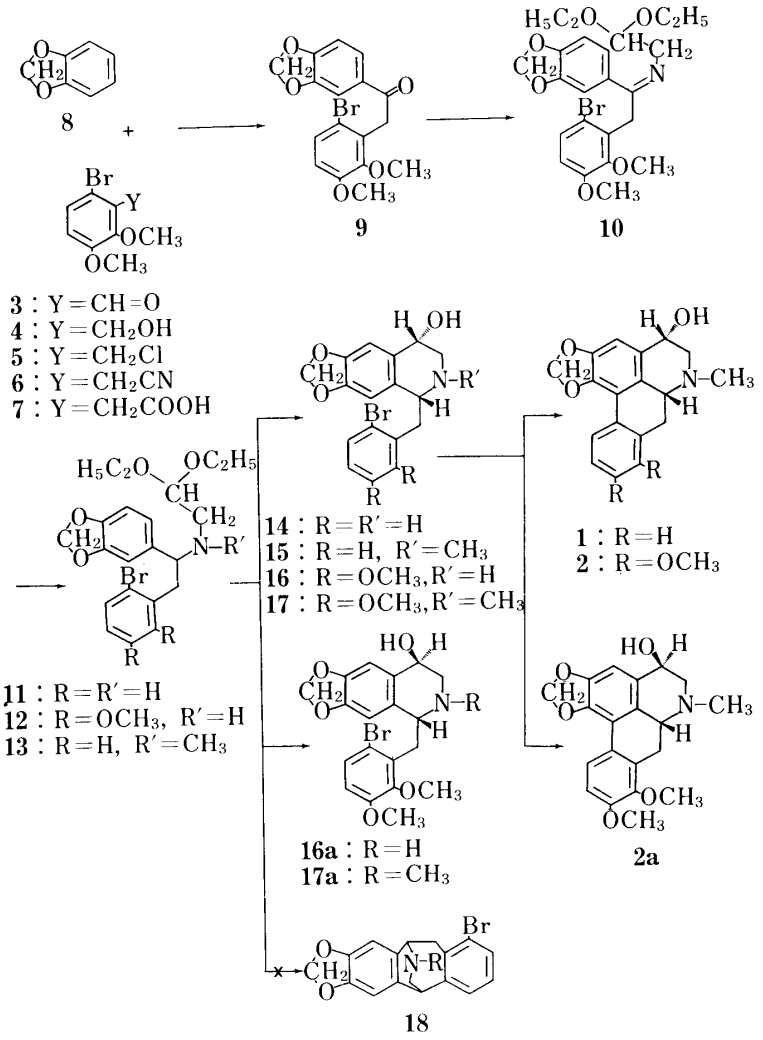

Chart 1

resonance (^{1}H-NMR) spectra, the signal of C_4-H geminal to an alcoholic hydroxyl group of **17a** appeared at δ 4.66 as a double doublet somewhat downfield compared with that of **17**, which appeared at δ 4.49 as a triplet. These finding were well explained by assuming that the C_4-H bonding of **17** is quasi-equatorial and that of **17a** is quasi-axial.

Irradiation of **17** in methanol and dilute hydrochloric acid afforded two diastereoisomers of 4-hydroxyaporphine (**2** and **2a**) in *ca.* 2 : 1 ratio, and these were separated by column chromatography. The *cis* and *trans* relationships of C_4-H and C_{6a}-H in these two diastereoisomers (**2** and **2a**, respectively) were deduced from the ^{1}H-NMR spectra examination. Compound **2** was identified with natural 4-hydroxycrebanine (**2**), except for the optical rotation, based on direct comparison of their spectra [ultraviolet spectra (UV), infrared spectra (IR), mass spectra (MS), ^{1}H-NMR] and thin-layer chromatograms (TLC). In the ^{1}H-NMR spectrum of **2a**, colorless needles, mp 195—196 °C, the signal due to C_4-H appeared at δ 4.95 as a double doublet somewhat downfield compared with that of **2** (δ 4.46), and the signal due to the aromatic proton at the C-3 position appeared downfield at δ 7.00 compared with that of **2** (δ 6.79). These ^{1}H-NMR spectral observations suggested that C_4-H and C_3-H of **2a** are situated in close proximity to the lone pair electrons on the nitrogen atom and the hydroxyl group, respectively. Therefore, the C_4-H bonding should be quasi-axial and the hydroxyl bonding should be quasi-equatorial in compound **2a**.

The present synthesis led to a pair of diastereomers (**2** and **2a**), the stereostructures of

which were established firmly by direct comparison of their ^{1}H-NMR spectra. The absolute configurations of two asymmetric centers of 4-hydroxycrebanine (**2**; **4**: *S* and **6a**: *R*) from the natural source had been established by stereochemical examination of the stereoselective hydroxylation product of (*R*)-crebanine[7] with vanadium oxytrifluoride,[4] and the present results strongly support the configurational assignment.

Experimental

All melting points were determined on a Yanagimoto microscopic hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. MS were determined using a Hitachi RMU-6 spectrometer with a heated direct inlet. For column and preparative TL chromatographies, Silica gel 60 (70—230 mesh), and Silica gel GF_{254}, Merck, were used, respectively. All organic extracts were dried over $MgSO_4$.

6-Bromo-2,3-dimethoxybenzyl Alcohol (4)——A solution of 6-bromo-2,3-dimethoxybenzaldehyde (**3**)[5] (2.45 g) in anhyd. tetrahydrofuran (8.0 ml) was gradually added dropwise to a suspension of $NaBH_4$ (0.79 g) in anhyd. tetrahydrofuran (10.5 ml) with stirring at room temperature for 1 h. After further stirring of the mixture with heating for 1 h, the excess $NaBH_4$ was destroyed with 20% AcOH and the solvent was evaporated off *in vacuo*. The residue was extracted several times with Et_2O, then the ethereal extract was washed with 5% aqueous $NaHCO_3$ and water, dried and evaporated, leaving a crystalline solid which was recrystallized from petroleum ether to give colorless needles, mp 74—75 °C. Yield 2.07 g (83.8%). UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 230 (sh, 3.91), 288 (3.30). IR $\nu_{max}^{CHCl_3}$: 3600 cm^{-1} (OH). ^{1}H-NMR δ: 2.33 (1H, t, J=6.8 Hz, OH, signal disappeared upon addition of deuterium oxide), 3.85, 3.90 (3H×2, each s, $OCH_3\times2$), 4.83 (2H, d, J=6.8 Hz, CH_2), 6.78 (1H, d, J=8.9 Hz, C_4-H), 7.26 (1H, d, J=8.9 Hz, C_5-H). MS *m/z* (%): 248 (97.2), 246 (M^+, base peak), 233 (248−CH_3, 25.7), 231 (M^+-CH_3, 28.0). *Anal.* Calcd for $C_9H_{11}BrO_3$ (M_r, 247.09): C, 43.74; H, 4.49. Found: C, 43.53; H, 4.54.

6-Bromo-2,3-dimethoxybenzyl Chloride (5)——A solution of thionyl chloride (5.4 ml) and anhyd. benzene was gradually added dropwise to a solution of benzyl alcohol (**4**) (10.65 g) and *N*,*N*-dimethylaniline (5.5 ml) in anhyd. benzene (56 ml) at room temperature for 1 h. After further stirring at 100 °C for 30 min, the mixture was washed with 10% HCl, then dried and evaporated, giving a pale yellow product, which was recrystallized from petroleum ether to give colorless needles, mp 68—69 °C. Yield 10.74 g (94.1%). UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 239 (sh, 3.84), 294 (3.33). ^{1}H-NMR δ: 3.85, 3.95 (3H×2, each s, $OCH_3\times2$), 4.82 (2H, s, CH_2), 6.79 (1H, d, J=9.0 Hz, C_4-H), 7.31 (1H, d, J=9.0 Hz, C_5-H). MS *m/z* (%): 268 (25.9), 266 (base peak), 264 (M^+, 77.7), 231 (268 or 266−Cl, 31.1), 216 (231−CH_3, 46.2). *Anal.* Calcd for $C_9H_{10}BrClO_2$ (M_r, 265.54): C, 40.71; H, 3.79. Found: C, 40.89; H, 3.81.

6-Bromo-2,3-dimethoxybenzyl Cyanide (6)——A solution of the benzyl chloride (**5**) (4.0 g) and dimethylsulfoxide (DMSO, 12 ml) was added dropwise to a suspension of sodium cyanide (2.0 g) and DMSO (8 ml) over 1 h. After further stirring at 40—50 °C for 1 h, the mixture was poured into ice water and the precipitate was removed by filtration. The mother liquor was extracted several times with Et_2O, and the ethereal layer was treated by the usual method to yield a residue. The precipitate and the residue were recrystallized from dil EtOH to afford colorless needles, mp 70 °C. Yield 7.30 g (91.8%). UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 233 (4.02), 288 (3.39). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 cm^{-1} (CN). ^{1}H-NMR δ: 3.90, 3.99 (3H×2, each s, $OCH_3\times2$), 6.83 (1H, d, J=10.0 Hz, C_4-H), 7.33 (1H, d, J=10.0 Hz, C_5-H). MS *m/z* (%): 257 (95.8), 255 (M^+, base peak), 242 (33.3), 240 (M^+-CH_3, 33.5), 215 (16.7), 214 (240−CN, 12.5), 213 (20.8). *Anal.* Calcd for $C_{10}H_{10}BrNO_2$ (M_r, 256.10): C, 46.89; H, 3.94; N, 5.47. Found: C, 46.74; H, 3.94; N, 5.37.

6-Bromo-2,3-dimethoxyphenylacetic Acid (7)——A solution of benzyl cyanide (**6**, 5.12 g) in 40% KOH (50 ml) and diethylene glycol (40 ml) was refluxed for 8 h until the evolution of ammonia gas ceased. After the reaction, the solution was poured into water and washed with Et_2O once. The aqueous solution was acidified with 10% HCl aqueous and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried. Removal of the solvent gave a residue which recrystallized from petroleum ether and benzene mixture to give colorless needles, mp 136 °C. Yield 3.51 g (63.8%). UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 225 (3.97), 285 (3.08). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—3500 (OH), 1710 (C=O). ^{1}H-NMR δ: 3.85, 3.90 (3H×2, each s, $OCH_3\times2$), 6.78 (1H, d, J=9.0 Hz, C_4-H), 7.30 (1H, d, J=9.0 Hz, C_5-H). MS *m/z* (%): 276 (86.3), 274 (M^+, 87.5), 230 (M^+-CO_2, 9.9), 215 (230−CH_3, 37.5), 195 (M^+−Br, base peak). *Anal.* Calcd for $C_{10}H_{11}BrO_4$ (M_r, 275.10): C, 43.66; H, 4.03. Found: C, 43.53; H, 4.01.

α-(6′-Bromo-2′,3′-dimethoxyphenyl)-3,4-methylenedioxyacetophenone (9)——A CH_2Cl_2 (15 ml) solution of 6-bromo-2,3-dimethoxyphenylacetyl chloride, which was prepared from **7** (2.75 g) with excess thionyl chloride (6.5 ml) by the usual method, was added dropwise to a CH_2Cl_2 solution of 1,3-benzodioxole (**8**)[6] (1.22 g) and stannic chloride (3.37 g) at −50±10 °C for 1 h with stirring. Stirring was continued for 2 h at the same temperature. The mixture was poured into 6 N HCl, stirred overnight and extracted several times with CH_2Cl_2. The CH_2Cl_2 layer was treated in the usual way. The residue was taken up in CH_2Cl_2 and chromatographed on silica gel. Elution with CH_2Cl_2–benzene (1 : 5) gave the acetophenone (**9**), which was recrystallized from MeOH, giving colorless needles, mp 116—117 °C. Yield 2.30 g (60.7%). UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 229 (4.41), 276 (3.88), 310 (3.86). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 cm^{-1} (C=O). ^{1}H-

NMR δ: 3.76, 3.86 (3H × 2, each s, OCH_3 × 2), 4.47 (2H, s, CH_2), 6.06 (2H, s, OCH_2O), 6.78 (1H, d, J=9.0 Hz, $C_{4'}$-H), 6.90 (1H, d, J=8.0 Hz, C_5-H), 7.31 (1H, d, J=9.0 Hz, $C_{5'}$-H), 7.55 (1H, d, J=2.0 Hz, C_2-H), 7.73 (1H, dd, J=2.0 Hz, 8.0 Hz, C_6-H). MS *m/z* (%): 380 (4.0), 378 (M^+, 4.0), 299 ($M^+ - Br$, 45.5), 149 ($M^+ - C_6H_2Br(OCH_3)_2CH_2$, base peak). *Anal.* Calcd for $C_{17}H_{15}BrO_5$ (M_r, 379.21): C, 53.84; H, 3.99. Found: C, 53.57; H, 3.89.

***N*-[2-(6′-Bromo-2′,3′-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethyl]aminoacetaldehyde Diethyl Acetal (12)**——A solution of titanium tetrachloride (1.4 g) in dry benzene (40 ml) was added dropwise to a solution of the acetophenone derivative (**9**) (4.56 g) and aminoacetaldehyde diethyl acetal (12.3 g) in dry benzene (120 ml) with stirring at 0—5 °C for 1 h under a stream of argon gas. The mixture was stirred at the same temperature for 30 min, then refluxed for 40 h on a Dean Strak apparatus, poured into water, made alkaline with concentrated NH_4OH aqueous solution and extracted several times with Et_2O. The extract was washed with water, dried and evaporated, leaving the ketimine derivative (**10**) as a pale brown oily substance which gave nearly a single spot on TLC. This compound (**10**) was used for the following reaction without purification.

$NaBH_4$ (7.76 g) was added to a solution of **10** in MeOH (100 ml), and the mixture were stirred at room temperature for 3 h. Next, 10% AcOH was added to the reaction mixture, the excess reagent was decomposed and MeOH was removed by evaporation *in vacuo*. The residual solution was made alkaline with concentrated NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed, dried and concentrated. The residue was recrystallized from petroleum ether–ether, affording colorless plates, mp 85—86 °C. Yield 5.41 g (90.6% from **9**). UV λ_{max}^{EtOH} nm (log ε): 235 (sh, 4.19), 290 (3.89). ^{1}H-NMR δ: 1.11 (3H × 2, each t, J=7.0 Hz, CH_3 × 2), 1.62 (1H, s, NH), 2.44 (1H, dd, J=6.0, 12.0 Hz, $NHCH_2$), 2.55 (1H, dd, J=5.5, 12.0 Hz, $NHCH_2$), 2.96 (1H, dd, J=5.0, 13.0 Hz, $ArCH_2$), 3.11 (1H, dd, J=8.0, 13.0 Hz, $ArCH_2$), 3.24—3.71 (4H, m, OCH_2CH_3 × 2), 3.76 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.90—3.97 (1H, m, CHNH), 4.48 (1H, t, J=5.5 Hz, $(C_2H_5O)_2CH$), 5.93 (2H, s, OCH_2O), 6.66—7.26 (5H, m, Ar-H × 5). MS *m/z* (%): 497 (0.5), 496 (M^+, 0.1), 365 ($497-(C_2H_5O)_2CHCH_2NH$, 2.3), 363 ($M^+ - (C_2H_5O)_2CHCH_2NH$, 8.9), 266 ($M^+ - CH_2C_6H_2Br(OCH_3)_2$, 98.6), 220 ($266-OC_2H_5$, base peak), 174 (19.8), 149 (10.4), 135 (15.8), 103 (19.6). *Anal.* Calcd for $C_{22}H_{30}BrNO_6$ (M_r, 496.39): C, 55.65; H, 6.09; N, 2.82. Found: C, 55.69; H, 6.30; N, 2.77.

1-(6′-Bromo-2′,3′-dimethoxybenzyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (16 and 16a)——The *N*-substituted aminoacetaldehyde diethyl acetal (**12**) (0.49 g) with 6 N HCl (12.0 ml) was stirred at room temperature for 3 d. The reaction mixture was made alkaline with concentrated NH_4OH and extracted several times with Et_2O. The Et_2O layer was washed with water, dried and concentrated. The residue (0.39 g, 93.6%) was confirmed to be a mixture of diastereomers, **16** and **16a**, but could not be separated by column chromatography.

1-(6′-Bromo-2′,3′-dimethoxybenzyl)-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (17 and 17a)——A 10% formaldehyde methanol solution (1.76 ml) was added slowly to a suspension of a stereoisomer mixture of **16** and **16a** (0.39 g) in MeOH (3.0 ml) with stirring at room temperature. After 1 h, the reaction solution was cooled in an ice bath and excess $NaBH_4$ (0.36 g) was added. One hour later, the excess $NaBH_4$ was decomposed with 10% AcOH and extracted with CH_2Cl_2 after the mixture had been made alkaline with concentrated NH_4OH aqueous solution. The CH_2Cl_2 layer was treated by the usual method and the residue was subjected to silica gel column chromatography. Stereoisomers **17** and **17a** were separated by column chromatography with acetone–CH_2Cl_2 (1:9). Compound **17** was recrystallized from MeOH, affording colorless needles, mp 134—137 °C. Yield 238 mg (64.0%). UV λ_{max}^{EtOH} nm (log ε): 240 (sh, 4.05), 289 (3.75). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 cm^{-1} (OH). ^{1}H-NMR δ: 2.62 (3H, s, NCH_3), 2.88 (1H, dd, J=2.0, 13.0 Hz, C_3-H), 2.94 (1H, dd, J=9.0, 12.5 Hz, $ArCH_2$), 3.23 (1H, dd, J=5.5, 12.5 Hz, $ArCH_2$), 3.45 (1H, dd, J=3.0, 13.0 Hz, C_3-H), 3.64, 3.84 (3H × 2, each s, OCH_3 × 2), 4.22 (1H, dd, J=5.5, 8.5 Hz, C_1-H), 4.49 (1H, t, J=2.0 Hz, C_4-H), 5.79 (1H, s, C_8-H), 5.84 (2H, dd, J=1.5, 5.5 Hz, OCH_2O), 6.71 (1H, d, J=9.0 Hz, $C_{4'}$-H), 6.85 (1H, s, C_5-H), 7.21 (1H, d, J=9.0 Hz, $C_{5'}$-H). MS *m/z* (%): 207 (15.4), 206 ($M^+ - CH_2C_6H_2Br(OCH_3)_2$, base peak), 188 (17.5). *Anal.* Calcd for $C_{20}H_{22}BrNO_5$ (M_r, 436.30): C, 55.05; H, 5.08; N, 3.21. Found: C, 55.16; H, 4.98; N, 3.11. Compound **17a** was a colorless amorphous powder showing a single spot on TLC. Yield 60 mg (16.1%). UV λ_{max}^{EtOH} nm (log ε): 240 (sh, 4.07), 290 (3.79). IR $\nu_{max}^{CHCl_3}$: 3400 cm^{-1} (OH). ^{1}H-NMR δ: 2.36 (3H, s, NCH_3), 2.89 (1H, dd, J=4.0, 12.0 Hz, C_3-H), 3.00 (1H, dd, J=6.5, 13.0 Hz, $ArCH_2$), 3.10 (1H, dd, J=6.5, 12.0 Hz, C_3-H), 3.29 (1H, dd, J=8.0, 13.0 Hz, $ArCH_2$), 3.74, 3.85 (3H × 2, each s, OCH_3 × 2), 4.00 (1H, t, J=6.5 Hz, C_1-H), 4.66 (1H, dd, J=1.5, 6.5 Hz, C_4-H), 5.88 (2H, dd, J=1.5, 2.5 Hz, OCH_2O), 6.30 (1H, s, C_8-H), 6.72 (1H, d, J=9.0 Hz, $C_{4'}$-H), 6.90 (1H, s, C_5-H), 7.25 (1H, dd, J=9.0 Hz, $C_{5'}$-H). MS *m/z* (%): 207 (14.0), 206 ($M^+ - CH_2C_6H_2Br(OCH_3)_2$, base peak), 178 (61.1).

***dl*-4-Hydroxycrebanine (2) and Its Diastereomer (2a)**——A solution of **17** (465 mg) in 6 N HCl (20 ml), MeOH (120 ml) and water (140 ml) was irradiated with a 100-W high-pressure mercury lamp at room temperature for 6 h. Then, the MeOH was removed by evaporation *in vacuo*, and the residual solution was washed once with Et_2O, made alkaline with 10% aqueous NaOH solution and extracted five times with Et_2O. The extract was washed with water, dried and evaporated. The residue was taken up in Et_2O and chromatographed on silica gel using acetone–CH_2Cl_2 (1:49), to provide two diastereomers, *dl*-4-hydroxycrebanine (**2**) and its epimer (**2a**), yield 73.0 mg (19.3%) and 16.0 mg (4.2%), respectively. Compound **2**, pale brownish-yellow amorphous, showing a single spot on TLC, was identified by direct comparison [UV(EtOH), IR ($CHCl_3$), ^{1}H-NMR, MS and TLC] with natural 4-hydroxycrebanine.[4] UV λ_{max}^{EtOH} nm (log ε): 245 (sh, 3.98), 283 (4.05), 320 (sh, 3.31). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 cm^{-1} (OH). ^{1}H-NMR δ:

2.33 (1H, dd, J=1.5, 13.0 Hz, C_7-H), 2.61 (3H, s, NCH_3), 2.67 (1H, dd, J=2.0, 12.0 Hz, C_5-H), 3.04 (1H, dd, J=5.0, 13.0 Hz, C_7-H), 3.12 (1H, dd, J=2.0, 12.0 Hz, C_5-H), 3.82, 3.91 (3H×2, each s, OCH_3×2), 3.86 (1H, dd, J=1.5, 5.0 Hz, C_{6a}-H), 4.46 (1H, t, J=2.0 Hz, -CH(OH)), 5.94, 6.14 (1H×2, each d, J=1.5 Hz, OCH_2O), 6.79 (1H, s, C_3-H), 6.88 (1H, d, J=9.0 Hz, C_{10}-H), 7.81 (1H, d, J=9.0 Hz, C_{11}-H). MS m/z (%): 355 (M^+, 30.0), 354 (22.7), 336 (354−H_2O, 6.8), 335 (18.3), 321 (336−CH_3, 12.7), 320 (13.1), 312 ($M^+-CH_2=NCH_3$, base peak). Compound **2a** was recrystallized from benzene, affording colorless columnar crystals, mp 195—196 °C. UV λ_{max}^{EtOH} nm (log ε): 248 (sh, 4.19), 278 (4.21), 323 (sh, 3.75). IR ν_{max}^{KBr}: 3260 cm^{-1} (OH). ^{1}H-NMR δ: 2.25 (1H, t, J=14.5 Hz, C_7-H), 2.36 (1H, dd, J=9.5, 10.5 Hz, C_5-H), 2.61 (3H, s, NCH_3), 3.12 (1H, dd, J=4.5, 14.5 Hz, C_7-H), 3.30 (1H, dd, J=6.0, 10.5 Hz, C_5-H), 3.65 (1H, dd, J=4.5, 14.5 Hz, C_{6a}-H), 4.95 (1H, dd, J=6.0, 9.5 Hz, -CH(OH)), 5.95, 6.10 (1H×2, each d, J=1.5 Hz, OCH_2O), 7.00 (1H, s, C_3-H), 7.81 (1H, d, J=8.5 Hz, C_{11}-H). MS m/z (%): 355 (M^+, 30.2), 354 (M^+-1, 26.5), 336 (354−H_2O, 10.5), 335 (17.3), 321 (336−CH_3, 13.5), 320 (14.4.), 313 (21.3), 312 ($M^+-CH_2=NCH_3$, base peak). *Anal.* Calcd for $C_{20}H_{21}NO_5$ (M_r, 355,38): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.40; H, 5.83; N, 3.89.

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