Synthesis of C-Nor Emetine Pyman

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The four stereoisomers of C-nor emetine Pyman (2) were synthesized and isolated as their hydrobromides (2a—d·2HBr). Reduction of 3,11b-*trans* dehydro C-nor emetine Pyman (13a) gave an inseparable mixture of 2a and 2b. They were converted into the corresponding 2-phenoxybenzoyl amides (14a, b), and the 3,11b-*trans* $C_{1'}$-epimers, 14a and 14b, were chromatographically separated. Similarly, the 3,11b-*cis* $C_{1'}$-epimers, 14c and 14d, were obtained from *cis* dehydro C-nor emetine Pyman (13b). The configurations of 14a and 14d were determined by X-ray crystallographic analysis. Reduction of 14a—d with $BH_3 \cdot SMe_2$ complex and hydrogenolysis over Pd-catalyst followed by treatment with HBr–AcOH gave 2a—d·2HBr in good yields.

Keywords *trans*-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine 3-substituted; *cis*-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizine 3-substituted; emetine Pyman; synthesis; 3,4-dimethoxytetrahydroisoquinoline; 2-phenoxybenzoyl amide; epimer separation; Bischler–Napieralski reaction

Emetine Pyman, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolonyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1-methyl-2*H*-benzo[*a*]quinolizine (**1**) is the structure proposed for emetine by Brindly and Pyman[1] in 1927. Before Robinson[2] deduced the real structure of emetine in 1948, Sugasawa and his co-workers had made extensive efforts to synthesize **1** and its congener (**2**)[3] from the viewpoints of both pharmacological interest and structural elucidation of emetine. The synthesis of C-nor emetine Pyman (**2**), however, has been accomplished only as a mixture of stereoisomers due to the presence of the three tertiary carbons at C_3, C_{11b}, and $C_{1'}$.[4] In this paper, we will describe the synthesis of the four possible stereoisomers (**2a—d**) of C-nor emetine Pyman (**2**) starting from ethyl 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo-[*a*]quinolizine-3-carboxylate (**3a**).[5]

Methyl *trans*-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-3-propanoate (**8a**), a key intermediate for **2a** and **2b**, was prepared from **3a** by a five-step reaction sequence as illustrated in Chart 2.

The Michael reaction of **3a** with ethyl acrylate in the presence of a catalytic amount of potassium hydroxide (KOH) and alkaline hydrolysis of the adduct (**4**) at 60 °C gave the diacid (**5**) in 89% yield from **3a**. Heating of **5** in dimethylformamide (DMF) followed by esterification of the mono-acid (**6**) with methyl iodide and diisopropylethylamine gave a mixture of *trans* and *cis* lactam ester (**7a** and **7b**) which was separated into the two isomers in 42% and 38% yields, respectively, by column chromatography.

The configurations of **7a** and **7b** were determined to be 3,11b-*trans* and 3,11b-*cis*, respectively, by nuclear Overhauser effect (NOE) experiments. Irradiation of the signal of H_{11b} (δ 4.95) in **7a** led to the enhancement of the H_{6ax} (δ 2.77, 7.0%) and H_{2ax} (δ 1.63, 2.4%) signals, while no NOE was observed between H_{11b} and H_3. On the other hand, irradiation of the signal of H_{11b} (δ 4.58) in **7b** brought about the enhancement (2.8%) of the signal of H_{3ax} (δ 2.49), along with the enhancement of the H_{6ax} (δ 2.58, 9.2%) signal. No NOE was observed between H_{11b} and H_2. The above results indicated that the lactam moiety in **7b** exists in the boat conformation.

Chemoselective reduction of the lactam carbonyl of **7a** using boran–dimethyl sulfide ($BH_3 \cdot SMe_2$) complex under strictly controlled conditions afforded the desired 3,11b-*trans* ester (**8a**) in 87% yield, together with a small amount of the *trans* alcohol (**9a**).

Methyl *cis*-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-3-propanoate (**8b**), which served as the precursor of **2c** and **2d**, was obtained in 90% yield by reduction of **7b** with $BH_3 \cdot SMe_2$ complex under similar conditions.

For the synthesis of **2a** and **2b**, we initially investigated the route **7a**→**10a**→**11a** (Chart 3).

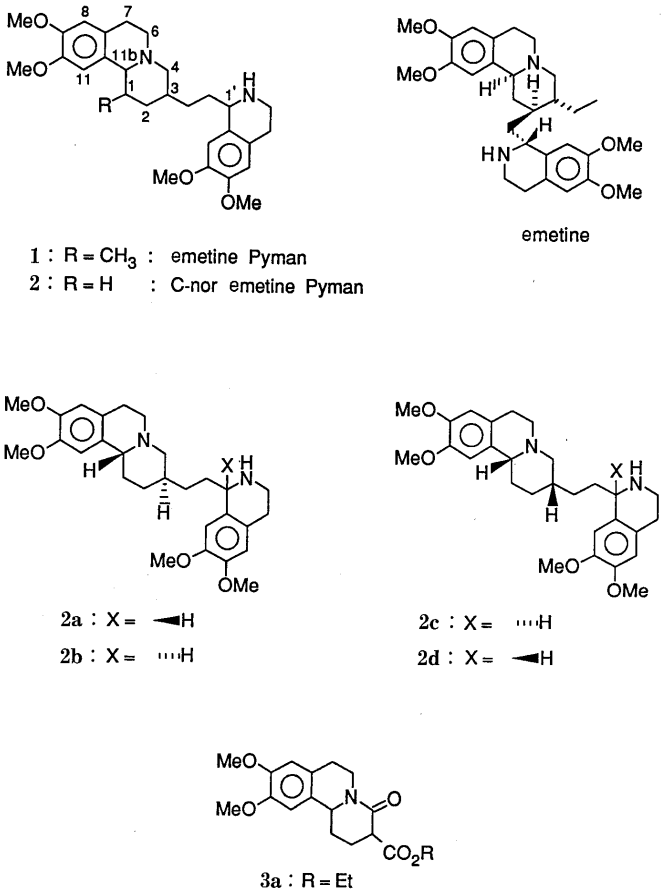


Chart 1

Dedicated to the memory of Professor Shigehiko Sugasawa.

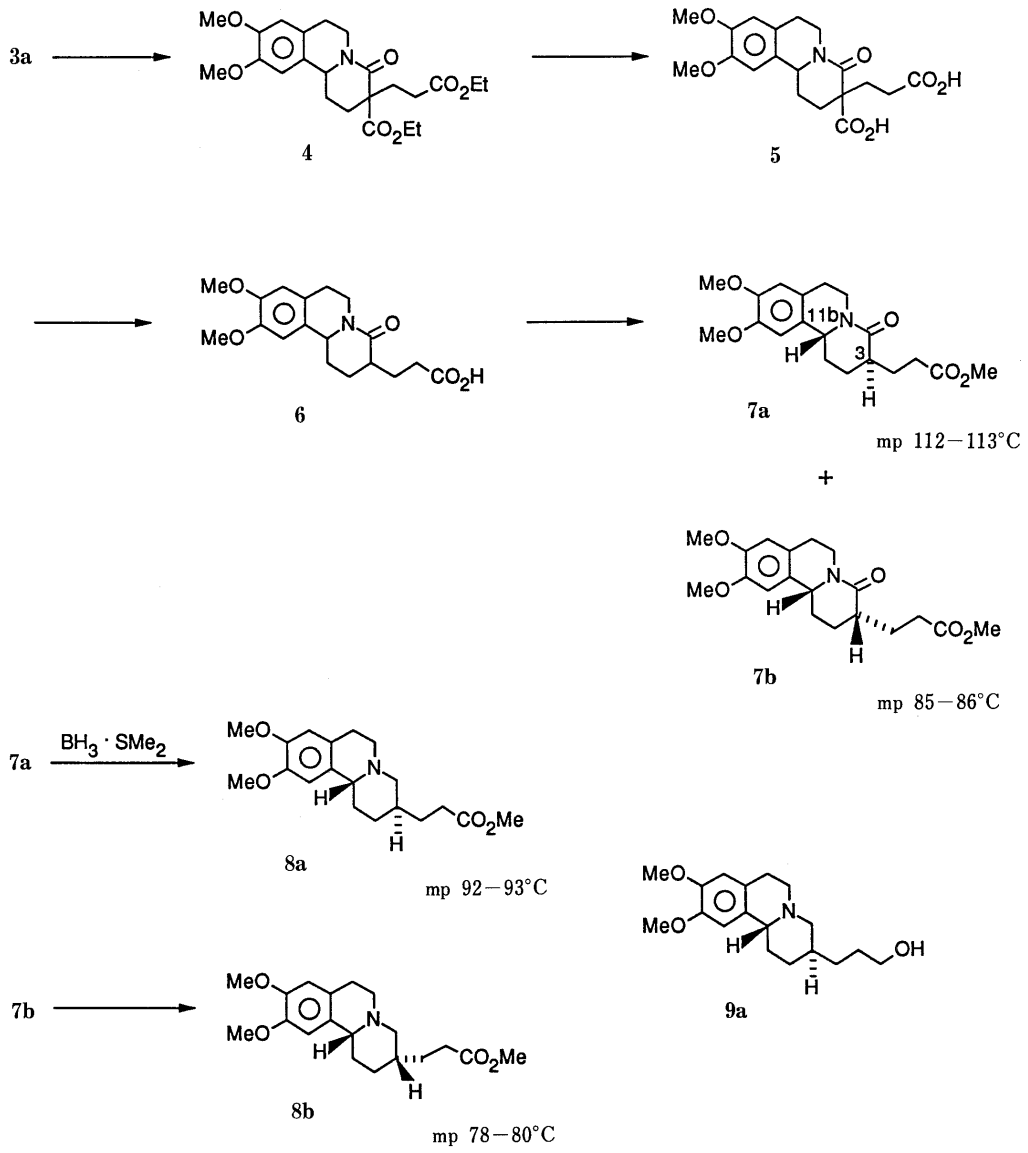


Chart 2

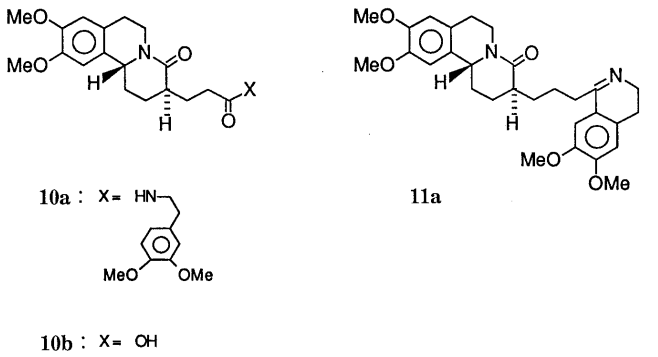
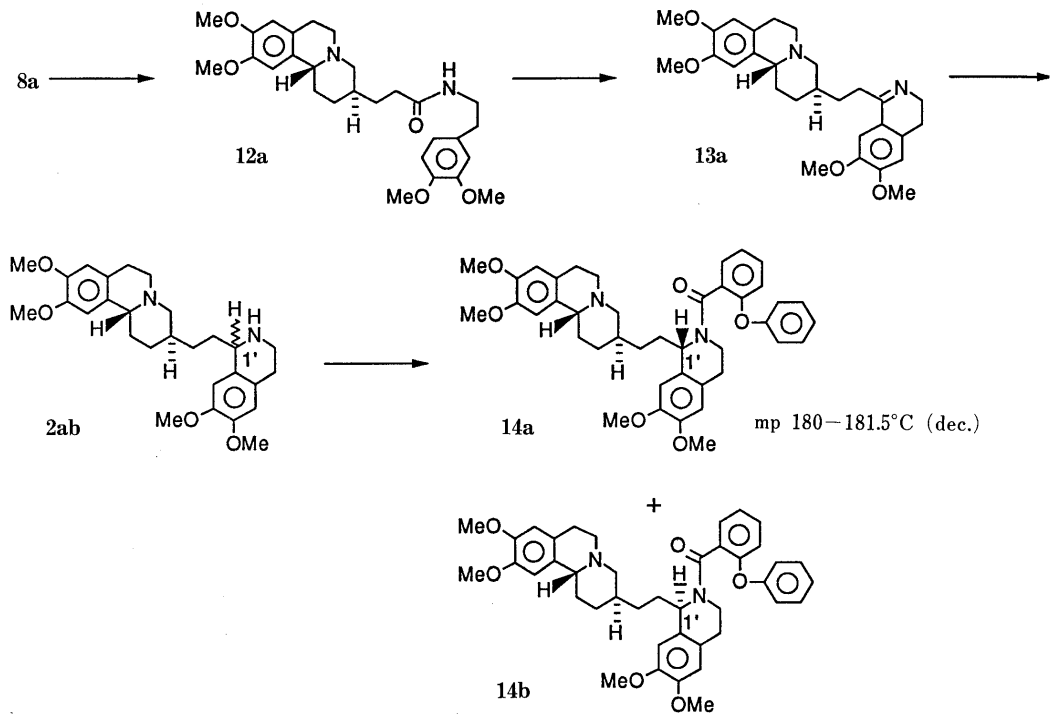


Chart 3

The *trans*-lactam acid (**10b**) was obtained without epimerization by alkaline hydrolysis of **7a**. Condensation of **10b** and homoveratrylamine using 1-hydrobenzotriazole (HOBT) and dicyclohexylcarbodiimide (DCC) afforded the lactam amide (**10a**) in 60% yield from **7a**. Attempts to cyclize **10a** with phosphorus oxychloride ($POCl_3$)[6] under a variety of conditions failed to furnish the *trans* lactam-imine (**11a**). The cyclization would proceed with epimerization of the product (**11a**), since on treatment with $POCl_3$ in refluxing benzene (C_6H_6), **7a** gave a mixture of **7a** and **7b**.[7]

Conversion of **8a** into **2a** and **2b** was, therefore, carried out through the sequence of reactions outlined in Chart 4.

Reaction of **8a** with homoveratrylamine–trimethylaluminum (Me_3Al) reagent[8] in boiling C_6H_6 afforded the amide (**12a**) in 74% yield. The Bischler–Napieralski (B.-N.) reaction of **12a** with 2 equimolar amounts of $POCl_3$ gave 3,11b-*trans* dehydro C-nor emetine Pyman (**13a**) in 95% yield. Reduction of **13a** with sodium borohydride ($NaBH_4$)[9] in methanol (MeOH) gave 3,11b-*trans* C-nor emetine Pyman (**2ab**) as an inseparable oily mixture (**2a**:**2b**=*ca.* 1:1). To achieve separation, the C_1-epimeric mixture (**2ab**) was converted into the amide derivatives (**14** and **16**) having bulky substituents in the amide moiety (Chart 5). Of these amides (**14** and **16**), the 2-phenoxybenzoyl derivative (**14**) was found to be most suitable for the separation of the epimers after examining the chromatographic properties of **14** and **16**. Acylation of **2ab** with 2-phenoxybenzoyl chloride and triethylamine (Et_3N) in dichloromethane (CH_2Cl_2), and



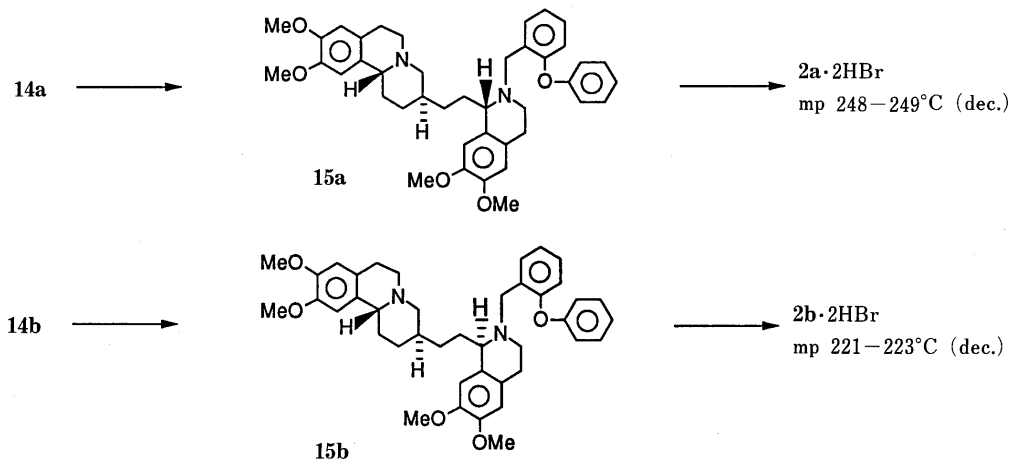


Chart 4

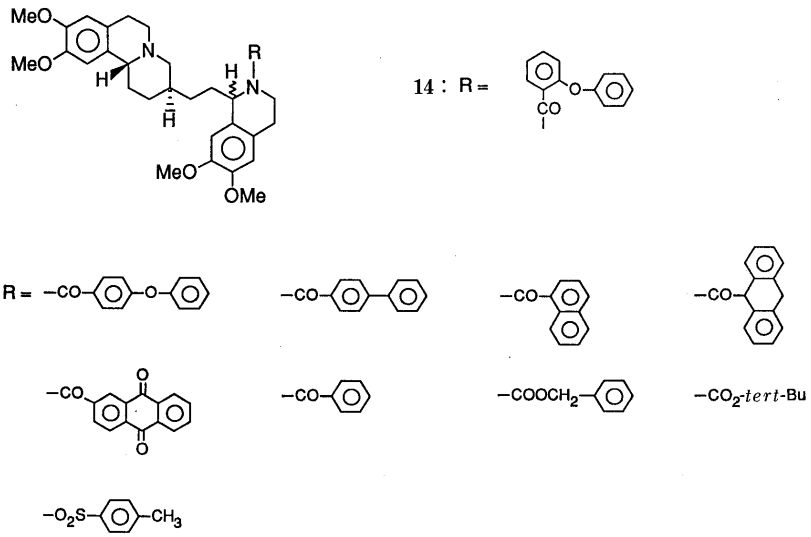


Chart 5

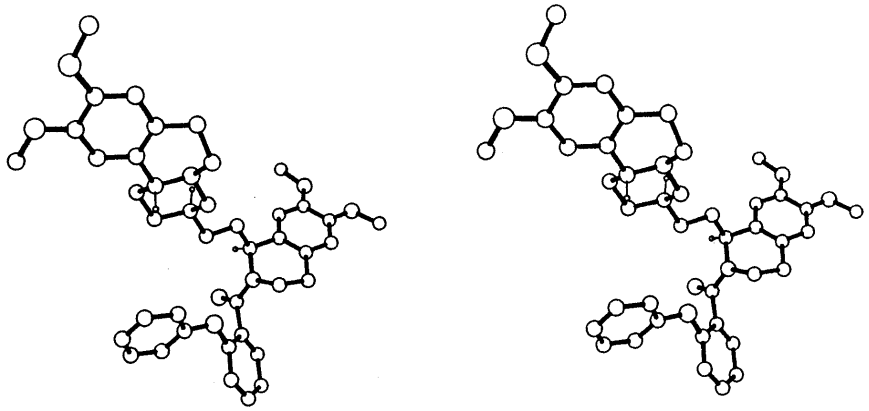


Fig. 1. Stereoview of the Structure of **14a**

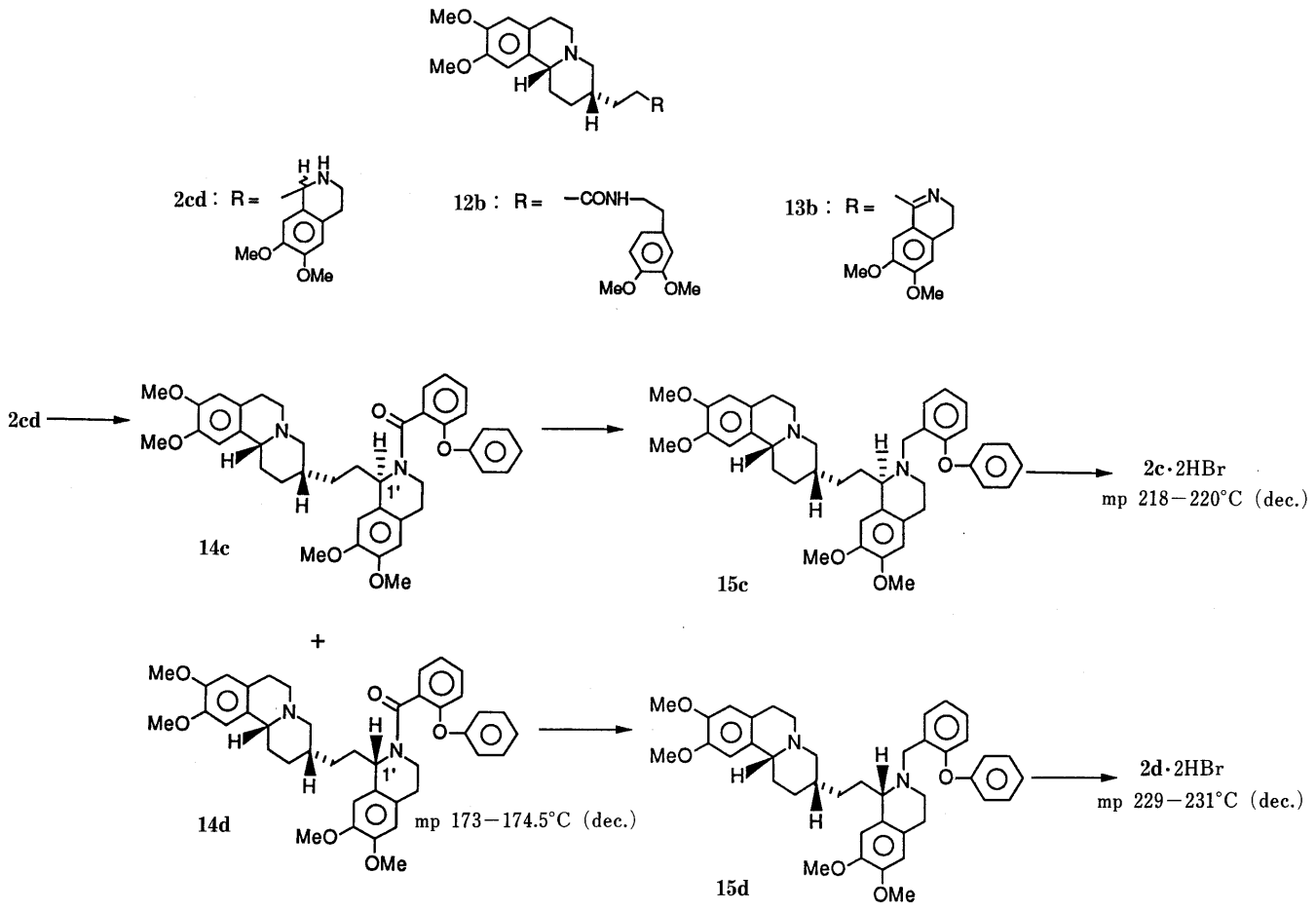


Chart 6

the subsequent separation by column chromatography provided C(1′*S**)-C-nor emetine Pyman amide (**14a**) (39% yield from **13a**) and the C(1′*R**)-isomer (**14b**) (35% yield from **13a**).[10] The C(1′*S**) configuration of **14a** was unambiguously defined by X-ray crystallographic analysis (Fig. 1).

Direct conversion of **14a** into **2a** by hydrolysis under acidic and alkaline conditions was unsuccessful. The hydrolysis led to the formation of intractable material, owing to the instability of the free base (**2a**). Removal of the 2-phenoxybenzoyl group from **14a** was achieved by a two-step reduction. Reduction of **14a** with $BH_3 \cdot SMe_2$ complex in tetrahydrofuran (THF) gave the 2-phenoxybenzyl derivative (**15a**) in 95% yield. Hydrogenation of **15a** over colloid-Pd[11] followed by treatment with hydrogen bromide–acetic acid (HBr–AcOH) afforded colorless crystals (**2a**·2HBr), mp 248—249 °C (dec.), in 72% yield from **14a**. Similarly, by this two-step reduction, the $C_{1'}$-isomer (**14b**) was converted into the free base (**2b**), which was treated with HBr–AcOH to form **2b**·2HBr, mp 221—223 °C (dec.) (70% yield from **14b**).[12]

The synthesis of 3,11b-*cis* C-nor emetine Pyman (**2c** and **2d**) was also achieved by a synthetic route similar to that used for the elaboration of **2a** and **2b** (Chart 6).

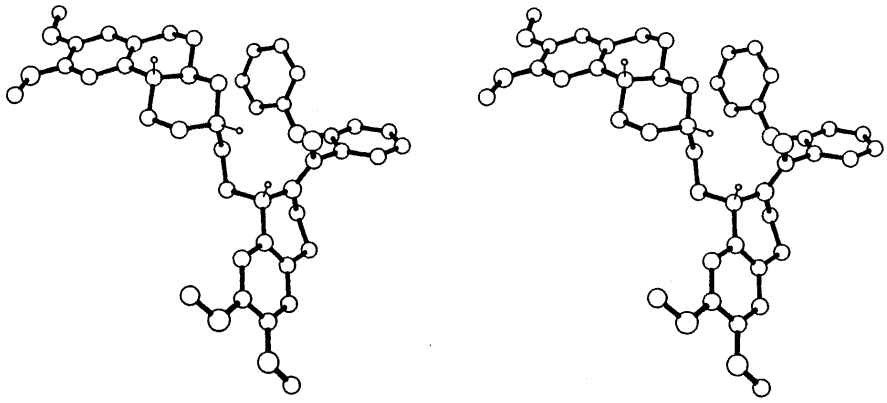


Fig. 2. Stereoview of the Structure of **14d**

Treatment of **8b** with homoveratrylamine–Me_3Al reagent and the B.-N. reaction of the resulting amide (**12b**) gave 3,11b-*cis* dehydro C-nor emetine Pyman (**13b**) in 76% yield from **8b**. $NaBH_4$ reduction of **13b** and acylation with 2-phenoxybenzoyl chloride afforded a mixture of 3,11b-*cis* C-nor emetine Pyman amides (**14c** and **14d**). Chromatographic separation gave the C(1′*R**) 3,11b-*cis* amide (**14c**) (39% yield from **13b**) and the C(1′*S**)-isomer (**14d**) (41% yield from **13b**).[10] The C(1′*S**) configuration for **14d** was also determined by X-ray crystallographic analysis (Fig. 2). Removal of the 2-phenoxybenzoyl group of **14c** by the two-step reduction and subsequent treatment with HBr–AcOH gave **2C**·2HBr, mp 218—220 °C (dec.), in 77% yield from **14c**. Similarly, **2d**·2HBr, mp 229—231 °C (dec.) was obtained in 70% yield from **14d**.[11] No significant pharmacological activities were observed for C-nor emetine Pyman (**2a—d**).

Experimental

Melting points were determined with a Yanaco MP-J2 hot stage microscope and a Büchi 535 digital melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were measured with a Hitachi R-90H, a JEOL JNM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Mass spectra (MS) were recorded with a Hitachi RMU-6 or JEOL JMS-HX 100 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240B C.H.N analyzer and a Yokokawa IC-100 ion chromatographic analyzer. Silica gel 60 K-230 (230—400 mesh) (Katayama) was used for column chromatography. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

Ethyl 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*]-quinolizine-3-carboxylate (3a) A solution of 4,4-bis(ethoxycarbonyl)-butanoyl chloride, prepared from 4,4-bis(ethoxycarbonyl)butanoic acid (8.90 g, 38.3 mmol), in Et_2O (80 ml) was added to a stirred mixture of homoveratrylamine (7.0 g, 38.6 mmol) and K_2CO_3 (5.4 g, 39 mmol) in H_2O (50 ml) and Et_2O (80 ml) at 0 °C. The mixture was stirred for 3 h at 0 °C, then AcOEt was added. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave 13.75 g (90%) of diethyl 2-[*N*-(3,4-dimethoxyphenethyl)carbamoyl]ethylmalonate (**17**), mp 69—70 °C. IR (Nujol): 3310, 1735, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t), 2.2 (4H, m), 2.76 (2H, t), 3.38 (1H, t), 3.54 (2H, t), 3.85 (3H, s), 3.86 (3H, s), 4.19 (4H, q), 5.60 (1H, br s), 6.7—6.8 (3H, m). $POCl_3$ (23.6 ml, 250 mmol) was added to a solution of **17** (10.0 g, 25.3 mmol) in C_6H_6 (100 ml). The mixture was refluxed for 80 min. After removal of the C_6H_6 and excess $POCl_3$, the residue was dissolved in 5% HCl, extracted with Et_2O, and basified to pH 9 with aqueous NH_4OH solution. The resulting oil was extracted with Et_2O. The Et_2O was washed with brine and dried. Removal of the Et_2O gave 8.64 g (91%) of diethyl 2-(6,7-dimethoxy-3,4-dihydro-1-isoquinolinyl)ethylmalonate (**18**) as an oil. IR (neat): 1745, 1730, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, t), 2.3 (2H, m), 2.61 (2H, t), 2.80 (2H, t), 3.56 (1H, t), 3.65 (2H, t), 3.91 (3H, s), 3.94 (3H, s), 4.20 (4H, q), 6.68 (1H, s), 7.12 (1H, s). $NaBH_4$ (0.87 g, 23 mmol) was added to a stirred solution of **18** (8.64 g) in EtOH (80 ml) at 0 °C. Stirring was continued for 30 min at 0 °C, then the EtOH was removed by evaporation at 60 °C. The residue was dissolved in a small amount of H_2O, neutralized with 10% HCl, saturated with NaCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to give 7.63 g (100%) of **3a** as a mixture of diastereomers. IR (neat): 1730, 1640 cm^{-1}. MS *m/z*: 333 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.22, 1.32 (3H, each t, J=7.2 Hz), 1.6—2.95 (8H, m), 3.39, 3.50 (1H, each m), 3.86 (3H, s), 3.87 (3H, s), 3.9—4.35 (2H, m), 4.67, 4.74 (1H, each m), 5.97 (1H, quasi s), 6.64 (1H, quasi s). **3a** was used in the next step without further purification.

Ethyl 3-Ethoxycarbonyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*]quinolizine-3-propanoate (4) KOH (150 mg) was added to a stirred solution of **3a** (7.93 g, 23.8 mmol) and ethyl acrylate (8.0 ml, 74 mmol) in *tert*-BuOH (75 ml) and THF (75 ml) at room temperature. After 3 h, the reaction was quenched by addition of saturated NH_4Cl solution and the solvent was removed. The residue was taken up in $CHCl_3$, washed with brine, and dried. Removal of the $CHCl_3$ gave a crude product which was purified by column chromatography on silica gel (× 10). Elution with hexane–AcOEt (1 : 1) gave 8.69 g (84%) of **4** as a mixture of diastereomers. IR (neat): 1735, 1640 cm^{-1}. MS *m/z*: 433 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.35 (6H), 1.75—2.95 (11H, m), 3.86 (3H × 2, s), 4.05—4.3 (4H, m), 4.55—4.85 (2H, m), 6.63 (2H, s). In another experiment under the same conditions, the Michael product (**4**) was obtained in 89% yield.

3-Carboxy-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]-quinolizine-3-propanoic Acid (5) A solution of **4** (22.04 g, 50.8 mmol), KOH (70 g, 1.25 mol) in EtOH (400 ml) and H_2O (200 ml) was stirred for 4 h at 60 °C. After removal of the EtOH, the residue was dissolved in H_2O, and extracted with Et_2O. The aqueous layer was acidified to pH 2 with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine and dried. Evaporation of the $CHCl_3$ gave 19.17 g (100%) of **5** as a foam. IR (Nujol): 2500—3500, 1730, 1720, 1610 cm^{-1}. MS *m/z*: 378 (M^+ + 1). ^{1}H-NMR ($CDCl_3$) δ: 1.7—3.0 (11H, m), 3.85 (6H, s), 4.70 (2H, m), 6.64 (2H, m), 9.88 (2H, br s), **5** was used in the next step without further purification.

Methyl *trans*-1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*]quinolizine-3-propanoate (7a) and *cis*-Isomer (7b) A solution of **5** (19.17 g, 50.8 mmol) in DMF (400 ml) was heated for 3.5 h at 130 °C. The DMF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 ml) containing *N*,*N*-diisopropylethylamine (26.5 ml) and methyl iodide (100 ml), and the mixture was stirred for 24 h at room temperature with protection from light. CH_2Cl_2 (500 ml) was added to the mixture, and the whole was washed with 5% HCl, saturated $NaHCO_3$ solution, H_2O and brine, and dried. Removal of the solvent gave a mixture of **7a** and **7b**, which was separated by column chromatography on silica gel (× 100). Elution with hexane–AcOEt (2 : 1) gave 7.45 g (42%) of **7a**, mp 112—113 °C (recrystallized from AcOEt–iso-Pr_2O). IR (Nujol): 1735, 1620 cm^{-1}. MS *m/z*: 347 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.63 (1H, m), 1.67 (1H, m), 1.89 (1H, dt, J=21.0, 7.7 Hz), 2.05 (1H, m), 2.29 (1H, m), 2.33 (1H, m), 2.51 (2H, t, J=7.7 Hz), 2.55 (1H, m), 2.62 (1H, m), 2.77 (1H, ddd, J=12.1, 11.7, 2.2 Hz), 2.88 (1H, ddd, J=12.0, 11.7, 4.7 Hz), 3.66 (3H, s), 3.86 (3H, s), 4.59 (1H, m), 4.87 (1H, ddd, J=12.1, 4.7, 2.2 Hz), 6.61 (1H, s), 6.65 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 25.7 (t), 27.5 (t), 28.5 (t), 30.7 (t), 32.0 (t), 39.8 (t), 41.0 (d), 51.6 (q), 55.9 (q), 56.1 (q), 56.9 (d), 108.1 (d), 111.5 (d), 127.2 (s), 129.3 (s), 147.7 (s), 147.8 (s), 171.1 (s), 174.0

(s). *Anal.* Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.57; H, 7.28; N, 3.98. Further elution with hexane–AcOEt (2:1) gave 6.63 g (38%) of **7b**, mp 85—86 °C (recrystallized from AcOEt–iso-Pr_2O). IR (Nujol): 1720, 1635 cm^{-1}. MS *m/z*: 347 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.67 (1H, m), 1.74 (1H, dt, J=21.0, 7.7 Hz), 1.81 (1H, m), 1.99 (1H, m), 2.11 (1H, m), 2.34 (1H, m), 2.49 (2H, t, J=7.7 Hz), 2.49 (1H, m), 2.64 (1H, ddd, J=12.1, 3.2, 2.5 Hz), 2.85 (2H, m), 3.66 (3H, s), 3.87 (3H×2, s), 4.58 (1H, dd, J=9.8, 4.7 Hz), 4.78 (1H, ddd, J=12.3, 4.7, 2.5 Hz), 6.61 (1H, s), 6.66 (1H, s). ^{13}C-NMR ($CDCl_3$): 24.5 (t), 27.3 (t), 27.9 (t), 28.6 (t), 32.2 (t), 39.8 (t), 39.8 (d), 51.5 (q), 55.9 (q), 56.0 (q), 56.1 (d), 108.3 (d), 111.6 (d), 127.3 (s), 128.9 (s), 147.8 (s), 147.9 (s), 171.9 (s), 173.8 (s). *Anal.* Calcd for $C_{19}H_{25}NO_5$: C, 65.59; H, 7.25; N, 4.03. Found: C, 65.49; H, 7.23; N, 4.01. Assignment of each signal of **7a** and **7b** was carried out by correlated spectroscopy (COSY). Stereochemistry was determined by phase-sensitive NOE spectroscopy (NOESY) and 1D-differential NOESY.

Methyl *trans*-1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]-quinolizine-3-propanoate (8a) A 2.0 M solution of $BH_3 \cdot SMe_2$ (55 ml, 110 mmol) in THF was added to a solution of **7a** (9.50 g, 27.3 mmol) in THF (100 ml) at −70 °C. The mixture was warmed to 11 °C and stirred for 5 h at the same temperature. Then MeOH (40 ml) was added followed by addition of a solution of oxalic acid (40 g) in MeOH (100 ml) under ice-cooling. The whole was stirred for 18 h at room temperature and refluxed for 1 h. The solvent was removed. Saturated $NaHCO_3$ solution was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel (×30). Elution with $CHCl_3$–MeOH (40:1) gave 7.91 g (87%) of **8a**, mp 92—93 °C (recrystallized from $CHCl_3$–iso-Pr_2O). IR (Nujol): 1730 cm^{-1}. MS *m/z*: 333 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (1H, m), 1.41 (1H, m), 1.60 (2H, t, J=7.8 Hz), 1.72 (1H, m), 1.99 (2H, quasi t), 2.26 (1H, m), 2.36 (2H, t, J=7.8 Hz), 2.56 (2H, m), 2.9—3.1 (4H, m), 3.68 (3H, s), 3.84 (6H, s), 6.57 (1H, s), 6.68 (1H, s). *Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.56; H, 8.18; N, 4.07. Further elution with $CHCl_3$–MeOH (40:1) gave 570 mg (7%) of **9a** as a foam. IR (neat): 3380 cm^{-1}. MS *m/z*: 305 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (1H, m), 1.32 (2H, m), 1.45 (1H, m), 1.63 (3H, m), 2.01 (2H, quasi t), 2.2—2.6 (4H, m), 2.9—3.1 (4H, m), 3.65 (2H, t, J=6.0 Hz), 3.84 (3H, s), 3.91 (3H, s), 6.57 (1H, s), 6.68 (1H, s).

Methyl *cis*-1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]-quinolizine-3-propanoate (8b) Reduction of **7b** (8.00 g, 23 mmol) with a 2.0 M solution of $BH_3 \cdot SMe_2$ (46 ml, 92 mmol) in THF was carried out under conditions similar to those described for the preparation of **8a**. Chromatography of the crude product on silica gel and elution with $CHCl_3$–MeOH (40:1) gave 6.90 g (90%) of **8b**, mp 78—80 °C (recrystallized from $CHCl_3$–iso-Pr_2O). IR (Nujol): 1730 cm^{-1}. MS *m/z*: 333 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, m), 1.86 (2H, m), 2.00 (1H, m), 2.33 (2H, t, J=7.8 Hz), 2.4—2.6 (3H, m), 2.71 (1H, br d, J=11 Hz), 2.85 (1H, dd, J=6, 11 Hz), 2.9—3.1 (3H, m), 3.66 (1H, s), 3.84 (6H, s), 6.57 (1H, s), 6.88 (1H, s). *Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.22; H, 8.15; N, 4.04.

***trans*-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*]quinolizine-3-propanamide (10a)** A 10% KOH solution (2.6 ml, 4.6 mmol) was added to a solution of **7a** (0.80 g, 2.3 mmol) in MeOH (5 ml). The mixture was stirred for 3 h at room temperature, then the MeOH was removed. The aqueous residue was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ was washed with brine and dried. Evaporation of the $CHCl_3$ gave 0.57 g (74%) of the lactam acid (**10b**), mp 142—144 °C (rinsed with Et_2O). IR (Nujol): 3520, 3440, 1720, 1620 cm^{-1}. MS *m/z*: 333 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.4—1.7 (2H, m), 1.8—2.3 (4H, m), 2.5—2.8 (4H, m), 3.2—3.9 (3H, br), 3.72 (3H, s), 3.73 (3H, s), 4.5—4.7 (2H, m), 6.70 (1H, s), 6.83 (1H, s). Treatment of **10b** with excess ethereal diazomethane gave **7a** in a quantitative yield, mp 110—112 °C. A mixture of **10b** (0.57 g), HOBT (0.27 g, 2 mmol), and DCC (0.41 g, 2 mmol) in CH_2Cl_2 (10 ml) and THF (5 ml) was stirred for 2 h under ice-cooling, then a solution of homoveratrylamine (0.31 g, 1.7 mmol) in THF (5 ml) was added. The mixture was stirred for 5 h, then CH_2Cl_2 (50 ml) was added. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution and brine, and dried. Removal of the CH_2Cl_2 gave a crude product, which was purified by column chromatography. Elution with $CHCl_3$–acetone (10:1) gave 0.69 g (60% yield from **7a**) of **10a** as a foam. IR ($CHCl_3$): 3440, 1660, 1610 cm^{-1}. MS *m/z*: 496 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.1 (6H, m), 2.2—2.5 (4H, m), 2.6—3.0 (5H, m), 3.48 (2H, br), 3.86 (6H, s), 3.87 (6H, s), 4.5—4.6 (1H, m), 4.7—4.8 (1H, m), 6.62 (1H, s), 6.66 (1H, s), 6.7—6.8 (3H, m).

***trans*-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-3-propanamide (12a)** A solution of **8a** (7.15 g, 21.4 mmol) in C_6H_6 (100 ml) was added to a solution of the homoveratrylamine–Me_3Al reagent, prepared from a 2 M solution of Me_3Al (65 ml, 130 mmol) in hexane and homoveratrylamine (23.5 g, 130 mmol) in C_6H_6 (70 ml),[8] at room temperature. The reaction mixture was refluxed for 2.5 h. A 5% HCl solution (120 ml) was added, and stirring was continued for 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel (×30). Elution with $CHCl_3$–MeOH (40:1) gave 7.65 g (74%) of **12a**, mp 133—135 °C (recrystallized from $CHCl_3$–iso-Pr_2O). IR (Nujol): 3290, 1640 cm^{-1}. MS *m/z*: 482 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (1H, m), 1.38 (1H, m), 1.57 (2H, quasi t), 1.65 (1H, m), 1.98 (2H, m), 2.18 (1H, t), 2.26 (1H, m), 2.46 (1H, m), 2.59 (1H, m), 2.76 (2H, t, J=6.8 Hz), 2.9—3.1 (4H, m), 3.50 (2H, t, J=6.8 Hz), 3.84 (3H×2, s), 3.86 (3H, s), 3.87 (3H, s), 5.46 (1H, br), 6.56 (1H, s), 6.68 (1H, s), 6.7—6.8 (3H, m). *Anal.* Calcd for $C_{28}H_{38}N_2O_5$: C, 69.68; H, 7.94; N, 5.80. Found: C, 69.47; H, 8.05; N, 5.79.

***cis*-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-3-propanamide (12b)** The reaction of **8b** (452 mg, 1.36 mmol) with amine–Me_3Al reagent, prepared from a 2.0 M solution of Me_3Al (2.7 ml, 5.4 mmol) and homoveratrylamine (975 mg, 5.4 mmol), was carried out under conditions similar to those described for the preparation of **12a**. Chromatography of the crude product on silica gel and elution with $CHCl_3$–MeOH (40:1) gave 595 mg (91%) of **12b** as a foam. IR (neat): 3300, 1645 cm^{-1}. MS *m/z*: 482 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.65 (4H, m), 1.88 (1H, m), 2.07 (1H, m), 2.18 (2H, quasi t), 2.4—2.6 (3H, m), 2.7—2.9 (4H, m), 2.9—3.1 (3H, m), 3.43 (2H, dd, J=13.0, 6.0 Hz), 3.84 (3H×4, s), 5.69 (1H, br), 6.56 (1H, s), 6.71 (4H, m).

***trans*-3-[2,(6,7-Dimethoxy-3,4-dihydro-1-isoquinolinyl)ethyl]-1,3,4,6,7,-11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (13a)** $POCl_3$ (3.2 g, 20.9 mmol) was added to a suspension of **12a** (5.0 g, 10.4 mmol) in C_6H_6 (250 ml) under ice-cooling. The reaction mixture was refluxed for 3.5 h and the C_6H_6 was removed. To the residue, saturated $NaHCO_3$ solution was added. The resulting oil was extracted with $CHCl_3$, washed with brine, dried and evaporated. The crude product was purified by column chromatography on silica gel (×10). Elution with $CHCl_3$–MeOH (50:1) gave 4.62 g (95%) of **13a** as a foam. IR (Nujol): 1605 cm^{-1}. MS *m/z*: 464 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (1H, m), 1.40 (1H, m), 1.63 (2H, quasi t), 1.80 (1H, m), 2.04 (2H, quasi t), 2.03 (1H, m), 2.47 (1H, m), 2.61 (3H, quasi t), 2.75 (2H, t, J=7.8 Hz), 2.9—3.1 (4H, m), 3.64 (2H, t, J=7.8 Hz), 3.85 (3H×2, s), 3.92 (3H×2, s), 6.57 (1H, s), 6.70 (2H, s), 7.00 (1H, s).

***cis*-3-[2-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolinyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (13b)** The B.-N. reaction of **12b** (2.70 g, 5.6 mmol) with $POCl_3$ (1.1 ml, 11.6 mmol) in C_6H_6 (100 ml) was carried out under conditions similar to those described for the preparation of **13a**. Chromatography of the crude product on silica gel and elution with $CHCl_3$–MeOH (30:1) gave 2.16 g (83%) of **13b** as a foam. IR (neat): 1605 cm^{-1}. MS *m/z*: 464 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (7H, m), 2.5—3.1 (11H, m), 3.61 (2H, t, J=7.3 Hz), 3.81 (3H, s), 3.83 (3H×2, s), 3.90 (3H, s), 6.55 (1H, s), 6.68 (2H, s), 7.00 (1H, s).

Preparation of 2-Phenoxy Benzoylamide (14a) and Its Isomer (14b) $NaBH_4$ (328 mg, 8.7 mmol) was added to a stirred solution of **13a** (1.34 g, 2.9 mmol) in MeOH (40 ml) under ice-cooling. Stirring was continued for 3 h at 0—5 °C, then the reaction was quenched by addition of acetone (3 ml) and the MeOH was evaporated off. The residue was taken up in $CHCl_3$, washed with brine, and dried. Removal of the $CHCl_3$ gave 1.38 g (100%) of **2ab** as an oil. Without purification, this oil (**2ab**) was dissolved in CH_2Cl_2 (50 ml) containing Et_3N (1.2 ml, 8.6 mmol). To the solution, 2-phenoxybenzoyl chloride, prepared from 2-phenoxybenzoic acid (1.26 g, 5.8 mmol) and $SOCl_2$ (15 ml), was added at 0 °C and the mixture was stirred for 2.5 h at room temperature. The CH_2Cl_2 was washed with H_2O, saturated $NaHCO_3$ solution, and brine, and dried. Removal of the CH_2Cl_2 gave a mixture of $C_{1'}$-epimers **14a** and **14b**, which were separated by column chromatography on silica gel (×300). Elution with hexane–AcOEt–MeOH (10:30:1) gave 0.75 g (39% yield from **13a**) of **14a**, mp 180—182 °C (dec.) (recrystallized from AcOEt–hexane). IR (Nujol): 1640 cm^{-1}. MS *m/z*: 662 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1 (1H, m), 1.4 (2H, m), 1.6 (1H, m), 1.8 (4H, m), 2.1—2.6 (4H, m), 2.7—3.1 (4H, m), 3.54 (1H, m), 3.64 (1H, m), 3.76 (1H, m), 3.83 (3H×2, s), 3.84 (3H, s), 3.87 (3H, s), 4.61, 4.75 (1H, each m), 5.76 (1H, m), 6.3 (1H, m), 6.55 (2H, quasi d), 6.65 (2H, quasi d), 6.89 (1H, quasi d), 6.96 (1H, m), 7.0—7.1

(3H, m), 7.2—7.4 (3H, m). *Anal.* Calcd for $C_{41}H_{46}N_2O_6$: C, 74.29; H, 7.00; N, 4.23. Found: C, 74.09; H, 7.02; N, 4.18. Further elution with hexane–AcOEt–MeOH (10 : 30 : 1) gave 0.66 g (35% yield from **13a**) of **14b** (purity 98%, HPLC) as a foam. IR (Nujol): 1640 cm^{-1}. MS *m/z*: 662 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1 (1H, m), 1.2—1.4 (3H, m), 1.6—1.7 (3H, m), 1.8—1.9 (2H, m), 2.2—2.6 (3H, m), 2.7—3.1 (4H, m), 3.54 (1H, m), 3.64 (1H, m), 3.76 (1H, m), 3.83 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 4.59, 4.78 (1H, each m), 5.57 (1H, quasi t), 6.4 (1H, m), 6.55 (2H, quasi d), 6.65 (2H, m), 6.87 (1H, m), 6.95 (1H, m), 7.0—7.2 (3H, m), 7.3—7.4 (3H, m). HPLC analysis was carried out under the following conditions: column, TSK-gel ODS-80TM (4.6 × 150 mm); mobile phase, CH_3CN–MeOH–20 mM phosphate buffer (pH 3.6) (25 : 25 : 50), 1 ml/min; detector, 280 nm; retention time, **14a** (22 min), **14b** (30 min).

Preparation of *cis*-Isomers (14c and 14d) $NaBH_4$ reduction and acylation with 2-phenoxybenzoyl chloride were carried out under conditions similar to those described for the preparation of **14a** and **14b**. Reduction of **13b** (2.75 g, 5.9 mmol) with $NaBH_4$ (670 mg, 17.7 mmol) gave 2.75 g (100%) of **2cd** as an oil. Acylation of **2cd** with 2-phenoxybenzoyl chloride, prepared from 2-phenoxybenzoic acid (2.7 g, 12.3 mmol) and $SOCl_2$, in the presence of Et_3N (2.5 ml, 17.9 mmol) gave a mixture of **14c** and **14d**, which were separated by column chromatography on silica gel (× 300). Elution with $CHCl_3$–MeOH (50 : 1) gave 1.53 g (39% yield from **13b**) of **14c** (purity 98%, HPLC) as a foam. IR (Nujol): 1640 cm^{-1}. MS *m/z*: 662 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, m), 1.5—1.9 (6H, m), 2.4—3.2 (7H, m), 3.5—3.8 (3H, m), 3.8—3.9 (12H, m), 4.56, 4.73 (1H, each m), 5.72 (1H, m), 6.4—7.4 (13H, m). Further elution with $CHCl_3$–MeOH (50 : 1) gave 1.60 g (41% yield from **13b**) of **14d**, mp 173—174.5 °C (dec.) (recrystallized from AcOEt–hexane). IR (Nujol): 1640 cm^{-1}. MS *m/z*: 662 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, m), 1.5—2.0 (6H, m), 2.4—3.1 (7H, m), 3.4 (1H, m), 3.5 (1H, m), 3.7 (1H, m), 3.8—3.9 (12H, m), 4.57, 4.72 (1H, each m), 5.72 (1H, m), 6.4—7.4 (13H, m). *Anal.* Calcd for $C_{41}H_{46}N_2O_6$: C, 74.29; H, 7.00; N, 4.23. Found: C, 74.05; H, 7.08; N, 4.20. HPLC analysis was carried out under the same conditions as described for **14a** and **14b**; retention time, **14c** (24 min), **14d** (36.6 min).

[3-(α)(1′*S), 11b(β)]-3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinyl)ethyl]-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]-quinolizine (2a)** A 2.0 M solution of $BH_3 \cdot SMe_2$ (15 ml, 30 mmol) in THF was added to a solution of **14a** (1.00 g, 1.51 mmol) in THF (50 ml) under ice-cooling. The mixture was refluxed for 4.5 h and worked up as described for the preparation of **8a**. Chromatography of the crude product on silica gel and elution with $CHCl_3$–MeOH (40 : 1) gave 0.93 g (95%) of **15a** as a foam. MS *m/z*: 648 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1 (1H, m), 1.3 (3H, m), 1.8 (6H, m), 2.2 (1H, m), 2.5 (2H, m), 2.7 (2H, m), 2.9 (3H, m), 3.1 (2H, m), 3.56 (1H, quasi t), 3.77 (2H, s), 3.83 (3H, s), 3.84 (3H × 3, s), 6.53 (3H, m), 6.68 (1H, s), 6.91 (3H, m), 7.1—7.3 (5H, m), 7.60 (1H, m). A solution of **15a** (0.93 g, 1.43 mmol) in AcOH (70 ml) was hydrogenated over colloid-Pd[11] (70 ml) catalyst at room temperature for 4 h under atmospheric pressure of hydrogen. After removal of the AcOH, the residue was dissolved in iso-PrOH–MeOH (1 : 1) and the catalyst was removed by filtration. Removal of the iso-PrOH–MeOH and treatment of the residue with HBr–AcOH gave colorless crystals, which were recrystallized from MeOH–AcOEt to give 0.68 g (72% from **14a**) of **2a**·2HBr, mp 248—249 °C (dec.). IR (Nujol): 3400—3600, 1605 cm^{-1}. MS *m/z*: 466 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.4—1.5 (3H, m), 1.65 (1H, m), 1.9 (1H, m), 2.0—2.2 (3H, m), 2.8 (1H, m), 2.9—3.1 (4H, m), 3.2—3.4 (3H, m), 3.4—3.5 (2H, m), 3.6 (1H, m), 3.74 (3H, s), 3.75 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 4.36 (1H, m), 4.43 (1H, br), 6.8—6.9 (4H, m), 8.8, 9.3, 9.75, 10.3 (3H, each br, D_2O-exchangeable). *Anal.* Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HBr \cdot H_2O$: C, 52.02; H, 6.55; Br, 24.72; N, 4.33. Found: C, 52.22; H, 6.61; Br, 24.42; N, 4.22.

3(α)(1′*R), 11b(β)-Isomer (2b)** Reduction of **14b** (1.00 g, 1.51 mmol) with $BH_3 \cdot SMe_2$ gave 0.88 g (90%) of **15b** as a foam. MS *m/z*: 648 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1 (1H, m), 1.25 (3H, m), 1.7 (4H, m), 1.9 (2H, m), 2.2 (1H, m), 2.5 (2H, m), 2.7 (2H, m), 2.9 (3H, m), 3.1 (2H, m), 3.56 (1H, quasi t), 3.77 (2H, s), 3.83 (3H, s), 3.84 (3H × 3, s), 6.51 (1H, s), 6.55 (2H, quasi d), 6.68 (1H, s), 6.89 (3H, m), 7.0—7.3 (5H, m), 7.60 (1H, m). Hydrogenation of **15b** (0.88 g, 1.36 mmol) over colloid-Pd catalyst[11] followed by treatment with HBr–AcOH gave colorless crystals, which were recrystallized from MeOH–AcOEt to give 0.66 g (70% from **14b**) of **2b**·2HBr, mp 221—223 °C (dec.). IR (Nujol): 3400—3600, 1605 cm^{-1}. MS *m/z*: 466 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.3—1.5 (3H, m), 1.65 (1H, m), 2.05 (4H, m), 2.8 (1H, m), 2.85—3.05 (4H, m), 3.2—3.4 (2H, m), 3.45 (2H, m), 3.6 (2H, m), 3.74 (3H, s), 3.75 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 4.35 (1H, m), 4.45 (1H, br), 6.8—6.9 (4H, m), 8.8, 9.3, 9.8, 10.3 (3H, each br, D_2O-exchangeable). *Anal.* Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HBr \cdot H_2O$: C, 52.02; H, 6.55; Br, 24.72; N, 4.33. Found: C, 52.23; H, 6.37; Br, 24.59; N, 4.23.

3(β)(1′*R), 11b(β)-Isomer (2c)** Reduction of **14c** (0.77 g, 1.16 mmol) with $BH_3 \cdot SMe_2$ gave 0.71 g (95%) of **15c** as a foam. MS *m/z*: 648 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.7 (8H, m), 2.0 (1H, m), 2.4—2.9 (8H, m), 3.15 (3H, m), 3.5 (1H, m), 3.74 (2H, s), 3.78 (3H, s), 3.83 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 6.51 (2H, quasi d), 6.57 (1H, s), 6.68 (1H, s), 6.86 (3H, s), 7.0—7.3 (5H, m), 7.60 (1H, m). Hydrogenation of **15c** (0.71 g, 1.09 mmol) over colloid-Pd catalyst followed by treatment with HBr–AcOH gave colorless crystals, which were recrystallized from MeOH–AcOEt to give 0.56 g (77% from **14c**) of **2c**·2HBr, mp 218—220 °C (dec.) IR (Nujol): 3400, 1605 cm^{-1}. MS *m/z*: 466 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.9 (1H, m), 1.3 (1H, m), 1.6—1.7 (1H, m), 1.9—2.0 (3H, m), 2.0—2.1 (2H, m), 2.6—2.8 (2H, m), 2.9 (3H, m), 3.1 (1H, m), 3.2—3.4 (3H, m), 3.5—3.6 (2H, m), 3.73 (3H × 2, s), 3.75 (3H, s), 3.76 (3H, s), 4.36 (1H, br s), 4.45, 4.77 (1H, each br), 6.75—6.90 (4H, m), 8.64, 8.81, 9.01, 9.25, 9.33, 10.41 (3H, each br, D_2O-exchangeable). *Anal.* Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HBr \cdot 0.7H_2O$; C, 52.46; H, 6.51; Br, 24.93; N, 4.37. Found: C, 52.50; H, 6.54; Br, 24.72; N, 4.12.

3(β)(1′*S), 11b(β)-Isomer (2d)** Reduction of **14d** (0.50 g, 0.75 mmol) with $BH_3 \cdot SMe_2$ gave 0.44 g (91%) of **15d** as a foam. MS *m/z*: 648 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.7 (8H, m), 2.0 (1H, m), 2.4—2.9 (8H, m), 3.1 (3H, m), 3.53 (1H, m), 3.74 (2H, s), 3.80 (3H, s), 3.83 (3H, s), 3.85 (3H × 2, s), 6.51 (2H, quasi d), 6.57 (1H, s), 6.69 (1H, s), 6.86 (3H, m), 7.0—7.3 (5H, m), 7.58 (1H, m). Hydrogenation of **13d** (0.44 g, 0.68 mmol) over colloid-Pd catalyst followed by treatment with HBr–AcOH gave colorless crystals, which were recrystallized from MeOH–AcOEt to give 0.33 g (70% from **14d**) of **2d**·2HBr, mp 229—231 °C (dec.). IR (Nujol): 3400, 1605 cm^{-1}. MS *m/z*: 466 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.9 (1H, m), 1.3 (1H, m), 1.7 (1H, m), 1.95 (3H, m), 2.1 (2H, m), 2.7 (2H, m), 2.9 (3H, m), 3.1 (1H, m), 3.2—3.4 (3H, m), 3.55 (2H, m), 3.73 (3H × 2, s), 3.76 (3H × 2, s), 4.35 (1H, br s), 4.45, 4.75 (1H, each br s), 6.75—7.0 (4H, m), 8.7, 8.8, 9.1, 9.25, 9.30, 10.4 (3H, each br, D_2O-exchangeable). *Anal.* Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HBr \cdot 0.7H_2O$: C, 52.46; H, 6.51; Br, 24.93; N, 4.37. Found: C, 52.49; H, 6.53; Br, 24.85; N, 4.37.

Reconversion of 2a·2HBr into 14a **2a**·2HBr (60 mg, 0.095 mmol) was dissolved in CH_2Cl_2 (10 ml) containing Et_3N (1 ml). Then, a solution of 2-phenoxybenzoyl chloride (54 mg, 0.23 mmol) in CH_2Cl_2 (1 ml) was added under ice-cooling, and the mixture was stirred for 2 h at room temperature. The CH_2Cl_2 was washed with H_2O, and dried. Removal of the CH_2Cl_2 and chromatography of the residue with a short column using $CHCl_3$–MeOH (50 : 1) as an eluent gave 60 mg (95%) of **14a**, mp 178—180 °C, shown by HPLC analysis to be >97% pure. In a similar manner, **2b—d**·2HBr were reconverted into the original amides (**14b—d**) (94—96% yield) and their purities (>97% pure) were confirmed by HPLC analysis.

Crystal Data of 14a $C_{41}H_{46}N_2O_6$; M_r = 662.83; monoclinic, space group $P2_1/a$; lattice constant: a = 28.118(2), b = 10.827(1), c = 14.914(1) Å, β = 128.80(1)°, U = 3538.6(6) Å^3, Z = 4, D_x = 1.24 g/cm^3, $F(000)$ = 1416, $\mu(CuK_\alpha)$ = 6.76 cm^{-1}. R = 0.065.

Crystal Data of 14d $C_{41}H_{46}N_2O_6$; M_r = 662.83; monoclinic, space group $P2_1/a$; lattice constant: a = 29.722(3), b = 12.858(2), c = 9.865(1) Å, β = 107.07(1)°, U = 3603.9(7) Å^3, Z = 4, D_x = 1.22 g/cm^3, $F(000)$ = 1416, $\mu(CuK_\alpha)$ = 6.64 cm^{-1}. R = 0.079.

References and Notes

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4) Of eight possible stereoisomers of **1**, two isomers whose stereochemistries are undefined have been synthesized (see ref. 4*e* and 4*g*).
5) *a*) Although methyl 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*] quinolizine-3-carboxylate (**3b**)[5b] is already known, we synthesized **3a** in just three steps from homoveratrylamine (see Experimental); *b*) T. Kametani, S. A. Surgenor, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 920.

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7) Treatment of **7b** with $POCl_3$ also gave a mixture of **7a** and **7b**.
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9) Reduction of **13a** was also examined by employing DIBAL, $NaBCNH_3$, and Pt-catalyst. We could not obtain **2a** or **2b** stereoselectively.
10) The 2-phenoxybenzoyl amides (**14a—d**) were found from their ^{1}H-NMR spectra to occur as mixtures of rotational isomers in the ratio of approximately 1 : 1.
11) Colloid-Pd (Pd 8 mg/ml) was prepared from $PdCl_2$ and polyvinylpyrrolidone K-40 according to the modified Skita's method. A Skita and W. A. Meyer, *Ber.*, **45**, 8579 (1912).
12) The free bases (**2a—d**) were unstable in air. The salts (**2a—d**·2HBr) were found from the ^{1}H-NMR spectra to occur as a mixture of rotational isomers. The purities of these HBr salts were confirmed by reconverting them into the original 2-phenoxybenzoyl amides (**14a—d**) and by elemental analyses of **2a—d**·2HBr (see Experimental).