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Synthetic Studies on Lythraceae Alkaloids. V.[1] Total Synthesis of (±)-Vertaline

Miyoji Hanaoka, Nobuo Ogawa, and Yoshio Arata

Faculty of Pharmaceutical Sciences, Kanazawa University[2]

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The first total synthesis of one of the *cis*-quinolizidine Lythraceae alkaloids, vertaline (IV), was described. The Mannich reaction of isopelletierine (V) with 6-bromoveratraldehyde (VI) in tetrahydrofuran in the presence of aqueous sodium hydroxide gave the *cis*- and *trans*-quinolizidine (VII and VIII) in the ratio of 5: 2. Reduction of VII with sodium borohydride afforded the axial alcohol (IX) along with the equatorial alcohol (X). The Ullmann condensation of the acetyl derivative (XI) from IX with methyl 3-(4-hydroxyphenyl)propionate furnished the biphenyl ether (XIII). Hydrolysis of XIII and lactonization of the resulting hydroxy-acid (XV) provided (±)-vertaline (IV).

Lactonic Lythraceae alkaloids[3] are classified into two groups, the biphenyl and biphenyl ether type, each of which is further classified into the *trans*- and *cis*-quinolizidine type. The *trans*-quinolizidine alkaloids such as decaline (I),[4,5] decinine (II),[6] and methyldecinine (III),[1,7,8] the methyl ether of II, were already synthesized. It is of value to establish a general synthetic method for the *cis*-quinolizidine alkaloids, because half of the lactonic alkaloids belongs to the *cis*-quinolizidine type.[9] In a preliminary communication,[10] we published the first total synthesis of one of the *cis*-quinolizidine alkaloids, vertaline, which had been isolated in 1962 from *Decodon verticillatus* (L.) Ell.[11] Its structure was assigned as IV by Ferris, *et al.*[12] and further confirmed by the X-ray analysis.[13] The present paper is concerned with a full account of our experiments.

It has been clarified[14] that the Mannich condensation of isopelletierine (V)[15] with an arylaldehyde under an alkaline condition affords initially *cis*-4-arylquinolizidin-2-one which then isomerizes to the corresponding *trans* isomer and that the solubility of an arylaldehyde and a solvent play important roles in the stereoselectivity of this reaction. Since the reaction with an alkali-soluble arylaldehyde such as 6-bromoisovanillin gave stereoselectively the

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2) Location: *13-1, Takara-machi, Kanazawa, 920, Japan.*
3) J.P. Ferris, C.B. Boyce, R.C. Briner, U. Weiss, I.H. Qureshi, and N.E. Sharpless, *J. Am. Chem. Soc.*, **93**, 2963 (1971) and references therein.
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13) J.A. Hamilton and L.K. Steinrauf, *Tetrahedron Letters*, **1966**, 5121; *idem*, *J. Am. Chem. Soc.*, **93**, 2939 (1971).
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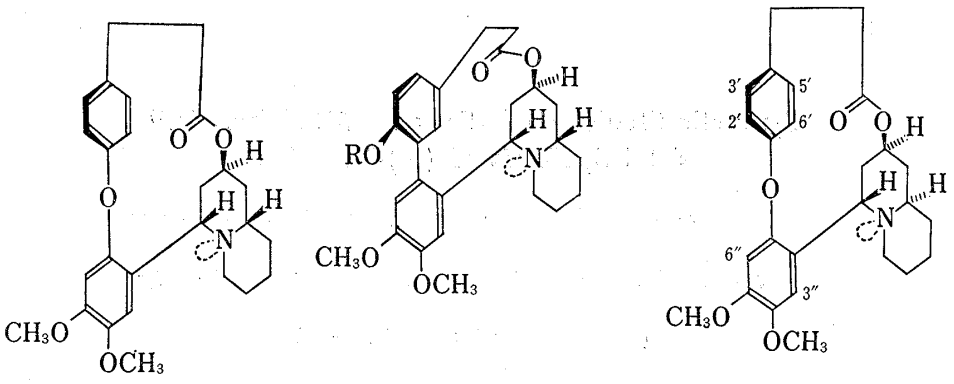
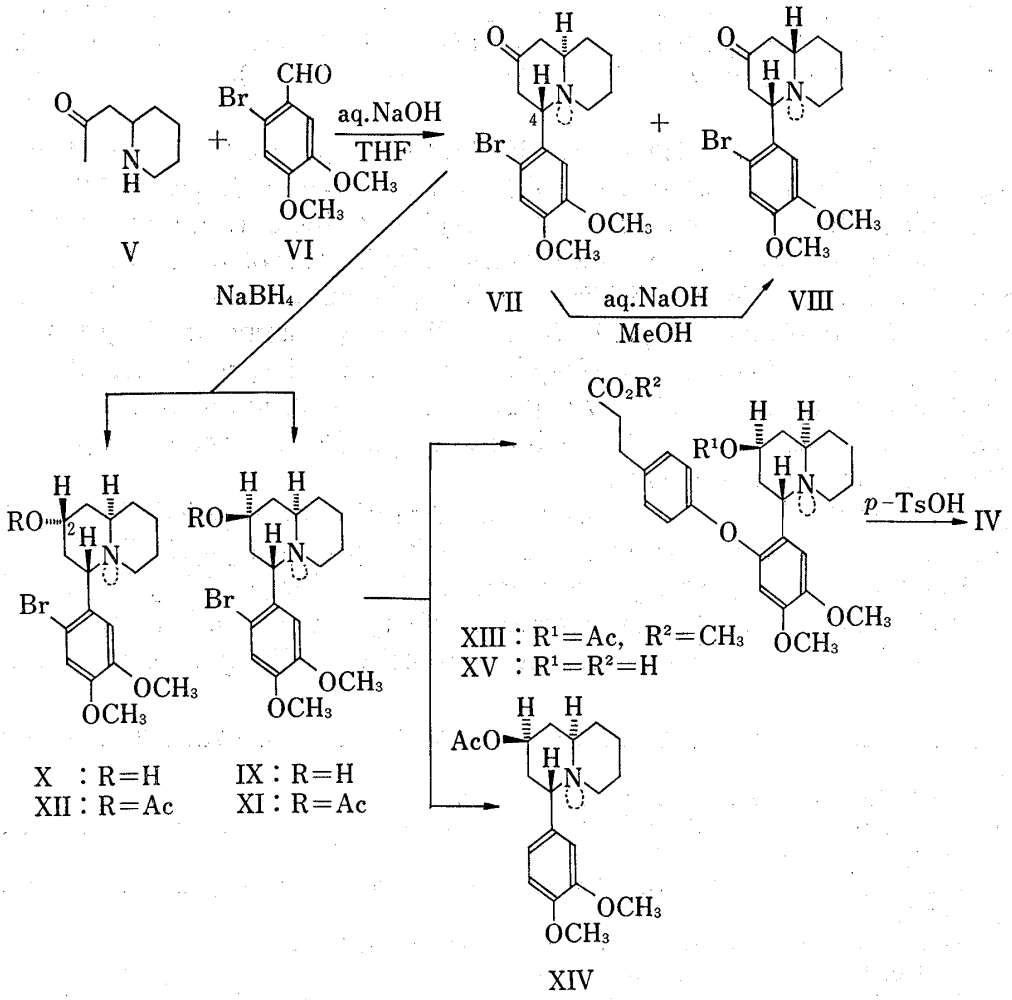
15) M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, **94**, 531 (1974).



I II : R=H III : R=CH_3 IV

Chart 1



V VI VII VIII IX : R=H XI : R=Ac X : R=H XII : R=Ac XIII : R^1=Ac, R^2=CH_3 XV : R^1=R^2=H XIV

Chart 2

trans-quinolizidine,[4] alkali-insoluble 6-bromoveratraldehyde (VI)[16] was chosen as the starting material in order to get the *cis*-quinolizidine.

Condensation of V with VI in tetrahydrofuran in the presence of methanolic aqueous sodium hydroxide afforded the expected *cis*-quinolizidine (VII), *m/e* 369, 367 (M^+, 1:1), and the *trans*-quinolizidine (VIII), *m/e* 369, 367 (M^+, 1:1), in the ratio of 3:2 in 42% yield.The

16) R. Pschorr, *Ann*, **391**, 23 (1912).

latter was identified with the authentic specimen[4] in all respects. The stereochemistry of the former was verified by the lack of the Bohlmann bands in its infrared (IR) spectrum and the chemical shift of the axial proton at C-4 [4.87 ppm (triplet, J=6.5 Hz)[17]] *ca.* 1 ppm lower[14,18] than that of the corresponding proton of VIII in the nuclear magnetic resonance (NMR) spectrum. The further confirmatory evidence for the *cis*-quinolizidine structure of VII arose from the fact that VII isomerized to the *trans*-quinolizidine (VIII) on treatment with aqueous sodium hydroxide in methanol.

On the other hand, though the reaction mixture separated in two layers, the same reaction without methanol as a cosolvent gave VII and VIII in the ratio of 5:2 in 73% yield.

Reduction of the *cis*-quinolizidin-2-one (VII) with sodium borohydride in methanol, followed by chromatographic separation of the crude product yielded the axial alcohol (IX), *m/e* 371, 369 (M^+, 1:1), and the equatorial alcohol (X), *m/e* 371, 369 (M^+, 1:1), in the ratio of 3:1 in 96% yield. In order to establish the stereochemistry of the hydroxyl group in IX and X, both alcohols were acetylated with acetic anhydride in pyridine to afford the axial and equatorial acetyl derivatives (XI and XII), in 92% and 81% yield, respectively. The NMR spectra of XI and XII showed the signal due to C_2–H at 5.16 (quintet, J=4.5 Hz) and 5.14 (multiplet, W_H=24 Hz), and that due to C_4–H at 4.76 (doublet of doublets, J=8; 4.5 Hz) and 4.57 ppm (doublet of doublets, J=11.5; 3 Hz), respectively, supporting well the assigned stereochemistry of XI and XII as depicted.

The Ullmann condensation of XI with methyl 3-(4-hydroxyphenyl)propionate[19] in pyridine using copper oxide in the presence of potassium carbonate furnished the biphenyl ether (XIII), *m/e* 511 (M^+), in 28% yield together with the debrominated product (XIV), *m/e* 333 (M^+), in 19% yield. In agreement with the structure XIII, the major product showed a band at 1727 cm^{-1} (C=O) in its IR spectrum and signals at 1.92 (3H, singlet, $OCOCH_3$), 3.73, 3.84, 3.98 (each 3H, singlet, $OCH_3\times3$), 4.62 (1H, triplet, J=6 Hz, CHAr), and 5.20 ppm (1H, quintet, J=5 Hz, CHOAc) in its NMR spectrum. Hydrolysis of XIII with aqueous sodium hydroxide in methanol afforded quantitatively the hydroxy-acid (XV), *m/e* 455 (M^+), which was shown to exist in a zwitterion from its IR spectrum: 2460 (broad, N^+H), 1590 cm^{-1} (CO_2^-).

A highly diluted solution of XV in benzene was heated with *p*-toluenesulfonic acid[1,4,20] to provide (±)-vertaline (IV), mp 224—225°, *m/e* 437 (M^+), in 46% yield from XIII. The product showed a band at 1720 cm^{-1} (C=O) and no Bohlmann bands in its IR spectrum, and signals at 3.48 (1H, doublet of doublets, J=11; 3.5 Hz, CHAr), 3.93, 3.97 (each 3H, singlet, $OCH_3\times2$), and 4.96 ppm (1H, multiplet, W_H=9 Hz, CHOCO) in its NMR spectrum.

The synthetic (±)-vertaline was proved to be completely identical with natural vertaline by IR (in $CHCl_3$), NMR, mass, ultraviolet (UV) spectral comparison and thin-layer chromatographic behavior.

The chemical shift (3.48 ppm) of the proton at C-4 of vertaline (IV) was *ca.* 1 ppm higher than those of the corresponding protons of the aforementioned synthetic intermediates. The diamagnetic shift of this proton in vertaline must be caused by the anisotropy of the benzene ring in the lactonized phenylpropionate moiety, suggesting the possible conformation of vertaline.

Thus, the total synthesis of (±)-vertaline was accomplished. This synthesis will provide a general synthetic method for the *cis*-quinolizidine Lythraceae alkaloids.

17) As pointed out in the previous paper,[14] the splitting pattern of this proton would indicate that the piperidone ring in VII exists in a flexible form rather than a chair form.
18) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.
19) E.N. Marvell, D. Sturmer, and C. Rowell, *Tetrahedron*, **22**, 861 (1966).
20) Lactonization of the active hydroxy-acid (XV) to vertaline in 67% yield using 2,2′-dipyridyl disulfide and triphenylphosphin has been recently reported: E.J. Corey, K.C. Nicolaou, and L.S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 654 (1975).

Experimental[21]

4-(2-Bromo-4,5-dimethoxyphenyl)(*e*)-*cis*-quinolizidin-2-one(VII) and 4-(2-Bromo-4,5-dimethoxyphenyl)-(*e*)-*trans*-quinolizidin-2-one (VIII)——a) In Tetrahydrofuran (THF) and Methanol: To a solution of isopelletierine[15] (V, 7.0 g, 0.05 mole) and 6-bromoveratraldehyde[16] (VI, 12.5 g, 0.05 mole) in THF (150 ml) was added a solution (15 ml) of 20% aq. NaOH in MeOH (1: 3), and the reaction mixture was heated at 60° for 10 hr with stirring in a stream of N_2 and then evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was purified by filtration through the alumina-column using benzene as an eluent. The eluate was evaporated and the residue was chromatographed on silica gel using ether as an eluent. The first fraction gave a mixture (2.9 g) of VI and undefined products. The second fraction gave the *trans*-quinolizidine (VIII, 3.2 g, 17%), which was recrystallized from EtOH as colorless prisms, mp 143—144°. The product was identified with the authentic specimen[4] by IR spectrum, TLC, and mixed mp determination.

The third fraction gave the *cis*-quinolizidine (VII, 4.6 g, 25%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712 (C=O). NMR δ: 3.92 (6H, s, $OCH_3\times2$), 4.87 (1H, t, $J=6.5$ Hz, C_4–H), 6.95 (1H, s, Ar–H$^{3'}$), 7.07 (1H, s, Ar–H$^{6'}$). Mass Spectrum *m/e*: 369, 367 (M^+, 1: 1). High-resolution Mass Spectrum *m/e*: 369.072, 367.074. Calcd. for $C_{17}H_{22}O_3NBr$: 369.068, 367.070.

b) In THF: To a solution of V (540 mg, 3.5 mmoles) and VI (710 mg, 2.9 mmoles) in THF (15 ml) was added 1% aq. NaOH (30 ml) and the mixture was heated at 70° for 2 hr with stirring in a stream of N_2. The cooled reaction mixture was adjusted to neutral with aq. HCl and evaporated. The residue was made alkaline with 10% aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on silica gel using ether as an eluent in the same procedure as that described in 1) to give VIII (230 mg, 22% based on VI) and VII (530 mg, 51% based on VI), which were identical with VIII and VII obtained in 1), respectively, in IR spectrum and TLC comparison.

Isomerization of VII into VIII——A solution of the *cis*-quinolizidine (VII, 20 mg) and 5% aq. NaOH (0.4 ml) in MeOH (4 ml) was refluxed for 4.5 hr with stirring and evaporated. To the residue was added H_2O (2 ml) and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was purified by p-TLC (silica gel, ether) to give the *trans*-quinolizidine (VIII, 14 mg, 70%), which was identified with the authentic specimen obtained above by IR spectra and TLC. The starting *cis*-quinolizidine was detected on TLC, but was too minor to be isolated.

4-(2-Bromo-4,5-dimethoxyphenyl) (*e*)-*cis*-quinolizidin-2-ol (*a*) (IX) and 4-(2-Bromo-4,5-dimethoxyphenyl)-(*e*)-*cis*-quinolizidin-2-ol (*e*) (X)——To a solution of VII (5.6 g) in MeOH (100 ml) was added $NaBH_4$ (1.0 g), and a reaction mixture was stirred at room temperature for 2 hr and evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on alumina. The fraction eluted with ether gave the axial alcohol (IX, 4.1 g, 73%) as a colorless amorphous solid, mp 136—138°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). NMR δ: 3.93 (6H, s, $OCH_3\times2$), 4.17 (1H, quin, $J=5.5$ Hz, C_2–H), 4.79 (1H, t, $J=5.5$ Hz, C_4–H), 7.08 (1H, s, Ar–H$^{3'}$), 7.12 (1H, s, Ar–H$^{6'}$). Mass Spectrum *m/e*: 371, 369 (M^+, 1: 1). High-resolution Mass Spectrum *m/e*: 371.090, 369.094. Calcd. for $C_{17}H_{24}O_3NBr$: 371.092, 369.094.

The fraction eluted with $CHCl_3$ gave the equatorial alcohol (X, 1.3 g, 23%) as a colorless amorphous solid, mp 76—78°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). NMR δ: 3.90, 3.92 (each 3H, s, $OCH_3\times2$), *ca.* 4.04 (1H, m, C_2–H), 4.51 (1H, d-d, $J=11.5$; 3 Hz, C_4–H), 7.01 (1H, s, Ar–H$^{3'}$), 7.15 (1H, s, Ar–H$^{6'}$). Mass Spectrum *m/e*: 371, 369 (M^+, 1: 1). High-resolution Mass Spectrum *m/e*: 371.087, 369.090. Calcd. for $C_{17}H_{24}O_3NBr$: 371.092, 369.094.

2-Acetoxy (*a*)-4-(2-bromo-4,5-dimethoxyphenyl) (*e*)-*cis*-quinolizidine (XI)——A solution of IX (3.4 g) and Ac_2O (10 ml) in pyridine (10 ml) was kept standing overnight at room temperature and evaporated. To the residue was added aq. HCl and the mixture was washed with ether. The aqueous layer was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give XI (3.5 g, 92%) as a pale brown viscous oil, which was used in the following reaction without further purification. The sample for measuring the spectra was purified with p-TLC (alumina, $CHCl_3$–benzene 1: 1) to give a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729 (C=O). NMR δ: 2.11 (3H, s, $COCH_3$), 3.90, 3.93 (each 3H, s, $OCH_3\times2$), 4.76 (1H d-d, $J=8$; 4.5 Hz, C_4–H), 5.16 (1H, quin, $J=4.5$ Hz, C_2–H), 7.04 (1H, s, Ar-H$^{3'}$), 7.15 (1H, s, Ar-H$^{6'}$). Mass Spectrum *m/e*: 413, 411 (M^+, 1: 1). High-resolution Mass Spectrum *m/e*: 413.103 411.106. Calcd. for $C_{19}H_{26}O_4NBr$: 413.102, 411.104.

21) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The extracts were dried over anhyd. Na_2SO_4. Alumina (Brockmann grade II—III, Merck) and silica gel (Wako gel Q-23, 100—200 mesh, Wako) were used for column chromatography. Alumina (Aluminiumoxid GF_{254} Typ E, Merck) and silica gel (Kieselgel GF_{254} Typ 60, Merck) were used for thin-layer chromatography (TLC) and preparative TLC (p-TLC). IR spectra were measured with a JASCO-IR-G, NMR spectra in $CDCl_3$ with a JEOL-PS-100 using tetramethylsilan as an internal standard, mass spectra with a JEOL-JMS-01SG, and UV spectra in MeOH with a Hitachi Model 323.

2-Acetoxy (*e*)-4-(2-bromo-4,5-dimethoxyphenyl) (*e*)-*cis*-quinolizidine (XII)——A solution of X (120 mg) and Ac_2O (1 ml) in pyridine (1 ml) was treated by the same procedure as that described for XI and the crude product was purified with p-TLC (alumina, $CHCl_3$–benzene 1: 1) to give XII (108 mg, 81%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (C=O). NMR δ: 2.04 (3H, s, $COCH_3$), 3.90, 3.94 (each 3H, s, $OCH_3\times2$), 4.57 (1H, d-d, $J=11.5$; 3 Hz, C_4–H), 5.14 (1H, m, $W_H=24$ Hz, C_2–H), 7.01 (1H, s, Ar–H$^{3'}$), 7.14 (1H, s, Ar–H$^{6'}$). Mass Spectrum *m/e*: 413, 411 (M^+, 1: 1). High-resolution Mass Spectrum *m/e*: 413.105, 411.105. Calcd. for $C_{19}H_{26}O_4NBr$: 413.102, 411.104.

Methyl 3-[4-{2-(2-Acetoxy (*a*)-*cis*-quinolizidin-4-yl (*e*))-4,5-dimethoxyphenoxy}phenyl] propionate (XIII) and 2-Acetoxy (*a*)-4-(3,4-dimethoxyphenyl) (*e*)-*cis*-quinolizidine (XIV)——A mixture of XI (1.65 g, 4.0 mmoles) and methyl 3-(4-hydroxyphenyl)propionate[19] (1.08 g, 6.0 mmoles) and anhyd. K_2CO_3 (1.5 g) in pyridine (2 ml) was heated with stirring in a stream of N_2. To the mixture was added powdered CuO (800 mg) at 130° and the mixture was heated at 150° for 3 hr with stirring. To the cooled reaction mixture was added H_2O and $CHCl_3$, and the mixture was filtered. To the filtrate was added aq. NaOH and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on alumina. The fraction eluted with benzene–ether (1: 1) gave the debrominated product (XIV, 250 mg, 19%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (C=O). NMR δ: 2.05 (3H, s, $COCH_3$), 3.87, 3.89 (each 3H, s, $OCH_3\times2$), 4.07 (1H, t, $J=5$ Hz, C_4–H), 5.19 (1H, m, $W_H=17$ Hz, C_2–H), 6.80, 6.91 (2H, AB-q, $J=8.5$ Hz, Ar–H$^{5',6'}$), 6.89 (1H, s, Ar–H$^{2'}$). Mass Spectrum *m/e*: 333 (M^+). High-resolution Mass Spectrum *m/e*: 333.196. Calcd. for $C_{19}H_{27}O_4N$: 333.194.

The fraction eluted with ether gave the biphenyl ether (XIII, 580 mg, 28%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (C=O). NMR δ: 1.92 (3H, s, $COCH_3$), 3.73, 3.84, 3.98 (each 3H, s, $OCH_3\times3$), 4.62 (1H, t, $J=6$ Hz, C_4–H), 5.20 (1H, quin, $J=5$ Hz, C_2–H), 6.61 (1H, s, Ar–H$^{6''}$), 7.18 (1H, s, Ar–H$^{3''}$), 6.84, 7.20 (4H, AB-type-q, $J=9$ Hz, Ar–H$^{2',3',5',6'}$). Mass Spectrum *m/e*: 511 (M^+). High-resolution Mass Spectrum *m/e*: 511.255. Calcd. for $C_{29}H_{37}O_7N$: 511.257.

3-[4-{2-(2-Hydroxy (*a*)-*cis*-quinolizidin-4-yl (*e*))-4,5-dimethoxyphenoxy}phenyl]propionic Acid (XV)——A solution of XIII (410 mg) in MeOH (20 ml) was refluxed with 5% aq. NaOH (10 ml) for 2 hr and evaporated. The residue was adjusted to pH 6 with dil. aq. HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give XV (365 mg, quantitative) as a colorless amorphous solid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (br, OH), 2460 (br, N^+H), 1590 (CO_2^-). NMR δ: 3.83, 3.91 (each 3H, s, $OCH_3\times2$), 5.04 (1H, d-like, $W_H=20$ Hz, C_4–H), 6.63 (1H, s, Ar–H$^{6''}$), 6.75, 7.17 (4H, AB-type-q, $J=8$ Hz, Ar-H$^{2',3',5',6'}$), 7.76 (1H, s, Ar-H$^{3''}$). Mass Spectrum *m/e*: 455 (M^+). High-resolution Mass Spectrum *m/e*: 455.230. Calcd. for $C_{26}H_{33}O_6N$: 455.231.

(±)-Vertaline——In a flask equipped with the Dean-Stark water-separator containing molecular sieves (3A, 1/16), a mixture of XV (225 mg, 0.5 mmole) in benzene (1500 ml) was heated. After XV was completely dissolved, *p*-TsOH·H_2O (1.5 g) was added to the solution and the solution was refluxed for 92 hr. The cooled reaction mixture was washed with 10% aq. Na_2CO_3 and H_2O. The combined aqueous layers were extracted with $CHCl_3$. The extract was washed with H_2O. The extract and benzene layer were dried and evaporated. The residue was purified on p-TLC (alumina, $CHCl_3$–EtOH 100: 1) to give colorless crystals (IV, 100 mg, 46%), which was recrystallized from MeOH as colorless prisms, mp 224—225°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). NMR δ: 3.48 (1H, d-d, $J=11$; 3.5 Hz, C_4–H), 3.93, 3.97 (each 3H, s, $OCH_3\times2$), 4.96 (1H, m, $W_H=9$ Hz, C_2–H), 6.58 (1H, d with a fine structure, $J=8$ Hz, Ar–H$^{5'or6'}$), 6.86 (1H, s, Ar–H$^{6''}$), 7.00 (1H, s, Ar–H$^{3''}$), 7.04 (1H, d with a fine structure, $J=8$ Hz, Ar–H$^{6'or5'}$), 7.39 (2H, br-s, Ar–H$^{2',3'}$). Mass Spectrum *m/e*: 437 (M^+). UV nm (ε): λ_{max} 293 (6390), λ_{min} 264 (2110), λ_{infl} 280 (4360), 241 (9900), 223 (18100). *Anal.* Calcd. for $C_{26}H_{31}O_5N$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.58; H, 7.18; N, 3.50.

The product was identified with natural vertaline by comparison with IR (in $CHCl_3$), NMR (in $CDCl_3$), mass, UV (in MeOH) spectra and TLC behavior.

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