[Chem. Pharm. Bull. 23(11)2478—2484(1975)]

UDC 547.834.2.04.057 : 547.539.3.04 : 547.622.04

Synthetic Studies on Lythraceae Alkaloids. IV.*,[1] Total Synthesis of (±)-Methyldecinine[2]

Miyoji Hanaoka, Hironori Sassa, Chieko Shimezawa, and Yoshio Arata

Faculty of Pharmaceutical Sciences, Kanazawa University[3]

(Received April 15, 1975)

The total synthesis of (±)-methyldecinine, the methyl ether of decinine, was described. The Ullmann reaction of 6-bromoveratraldehyde (IV) with the ester (V) gave the biphenyl (VI) along with the dimeric dialdehyde (VII) and the fluorenones (VIII and IX). The Mannich condensation of isopelletierine with VI afforded stereoselectively the *trans*-quinolizidin-2-one (XI), which, on treatment with the Henbest catalyst, furnished the axial alcohol (XII) together with the equatorial alcohol (XIII). Each of the alcohols was shown to be a mixture of two atropisomers from the dynamic nuclear magnetic resonance spectra. Hydrolysis of XII and lactonization of the resulting hydroxy-acid (XIV) provided (±)-methyldecinine (II) in an excellent yield.

Lactonic Lythraceae alkaloids[4] are classified into two groups, the biphenyl and biphenyl ether type as shown in decinine (I) and decaline (III), the latter of which was already synthesized.[1,5,6] Decinine, a representative of the biphenyl alkaloids, was first isolated in 1962 from *Decodon verticillatus* (L.) Ell.[7] and then from *Lagerstroemia indica* L.[8] and *Lythrum lanceolatum*,[9] and its structure was assigned as I by Ferris, *et al.*[10] We published the total synthesis of (±)-methyldecinine (II), the methyl ether of decinine, in a preliminary communication.[11] Another independent total synthesis of (±)-methyldecinine through the route similar to ours was reported.[12] The present paper deals with a full account of our experiments.

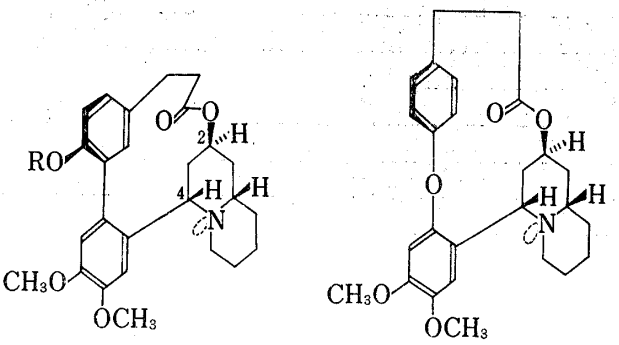
The synthesis consists of four parts; the synthesis of the unsymmetrical biphenyl (VI), the stereoselective formation of the *trans*-quinolizidin-2-one (XI) from VI, the stereoselective reduction of XI to the axial alcohol (XII), and the lactonization of the hydroxy-acid (XIV) derived from XII to (±)-methyldecinine (II).

The Ullmann reaction[13] of the activated halide,[13] 6-bromoveratraldehyde[14] (IV) with 2 molar equivalents of the ethyl ester (V) derived from 3-(3-bromo-4-methoxyphenyl)propionic

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part III: M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **23**, 2141 (1975).
2) A part of this work was presented at the 38th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, June 1974, Toyama, and at the 18th Symposium on the Chemistry of Natural Products, October 1974, Kyoto.
3) Location: *13–1, Takara-machi, Kanazawa 920, Japan.*
4) 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.
5) M. Hanaoka, N. Ogawa, and Y. Arata, *Tetrahedron Letters*, **1973**, 2355.
6) J.T. Wróbel and M.W. Gołębiewski, *Tetrahedron Letters*, **1973**, 4293.
7) J.P. Ferris, *J. Org. Chem.*, 27, 2985 (1962).
8) J.P. Ferris, R.C. Briner, and C.B. Boyce, *J. Am. Chem. Soc.*, **93**, 2958 (1971).
9) H. Wright, J. Clardy, and J.P. Ferris, *J. Am. Chem. Soc.*, **95**, 6467 (1973).
10) J.P. Ferris, C.B. Boyce, and R.C. Briner, *Tetrahedron Letters*, **1966**, 3641; *idem*, *J. Am. Chem. Soc.*, **93**, 2942 (1971).
11) M. Hanaoka, H. Sassa, C. Shimezawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **22**, 1216 (1974).
12) B. Loev, I. Lantos, and H. Van Hoeven, *Tetrahedron Letters*, **1974**, 1101.
13) P.E. Fanta, *Chem. Rev.*, **64**, 613 (1964); *idem*, *Synthesis*, **1974**, 9.
14) R. Pschorr, *Ann.*, **391**, 23 (1912).

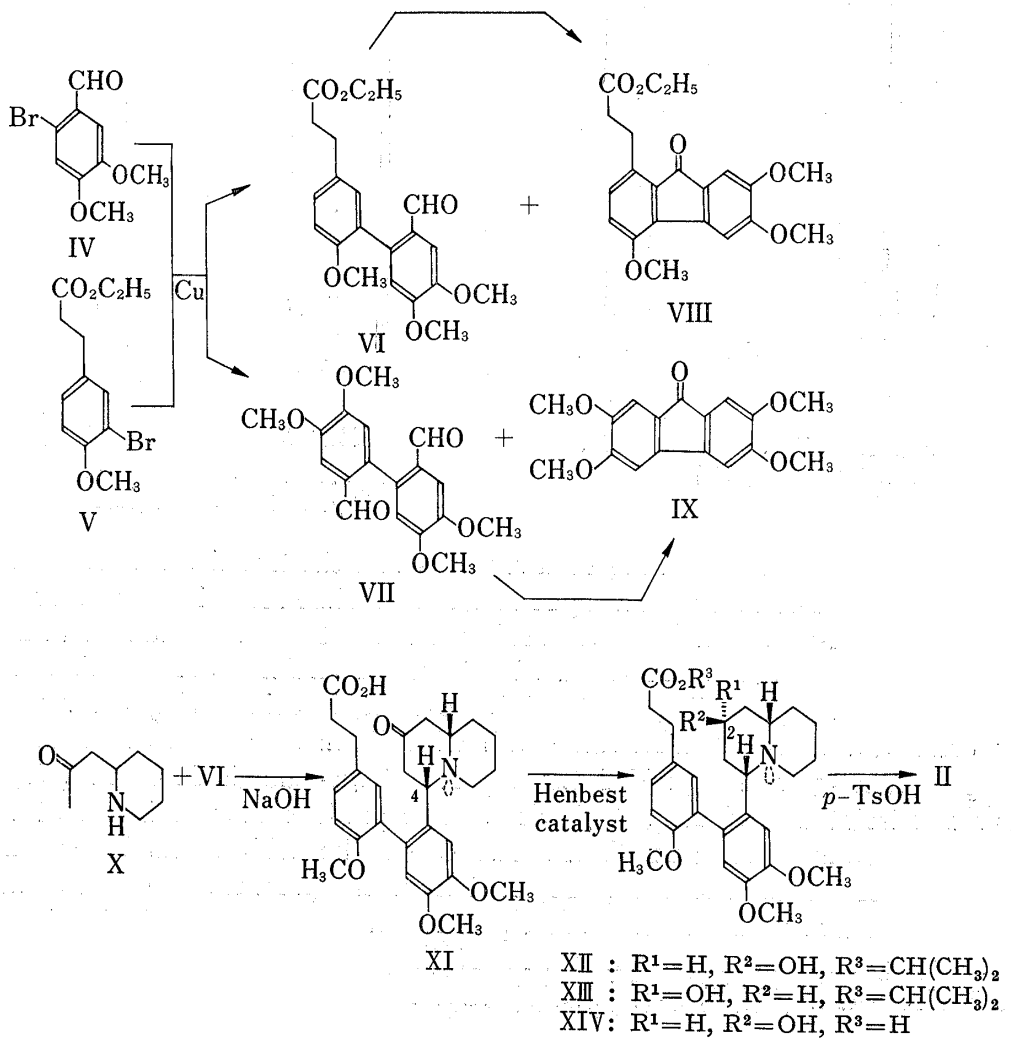
acid[15] in the presence of copper powder at 240° afforded the desired unsymmetrical biphenyl (VI), the dimeric dialdehyde (VII), and the fluorenones (VIII and IX) in 22, 17, 15, and 2.2% yield based on IV, respectively. The biphenyl (VI), *m/e*: 372 (M^+), showed bands at 1725 (ester) and 1673 cm^{-1} (aldehyde) in its infrared (IR) spectrum and peaks at 9.70 (1H, singlet, CHO), 3.76, 3.99, 4.02 (each 3H, singlet, $OCH_3 \times 3$), 4.16 (2H, quartet, $J=7$ Hz, $C\underline{H}_2CH_3$) and 1.23 ppm (3H, triplet, $J=7$ Hz, $CH_2C\underline{H}_3$) in its nuclear magnetic resonance (NMR) spectrum. The anticipated product, the dimeric dialdehyde (VII), *m/e*: 330 (M^+), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CHO), was already obtained[16] by the Ullmann reaction of IV itself. The fluorenones (VIII and IX) were assigned their structures from their spectral data (see Experimental) and sup-



I : R=H
II : R=CH_3

III

Chart 1



XII : R^1=H, R^2=OH, R^3=$CH(CH_3)_2$
XIII : R^1=OH, R^2=H, R^3=$CH(CH_3)_2$
XIV: R^1=H, R^2=OH, R^3=H

Chart 2

15) T. Kametani, S. Takano, and K. Haga, *Chem. Pharm. Bull.* (Tokyo), **16**, 663 (1968).
16) S. Kobayashi and M. Azekura, *Tokushima Daigaku Kenkyu Nempo*, **18**, 11 (1969) [*Chem. Abst.*, **73**, 98558t (1970)].

posed to be produced *via* the biphenyls (VI and VII), respectively. In fact, VI and VII were converted into the fluorenones (VIII and IX) under the above Ullmann reaction condition, respectively.

A mechanism for the formation of VIII and IX may be considered as follows; VI is oxidized to the corresponding carboxylic acid which then cyclizes to the fluorenone (VIII), while VII is oxidized to the dicarboxylic acid, decarboxylative cyclization of which furnishes the symmetrical fluorenone (IX).

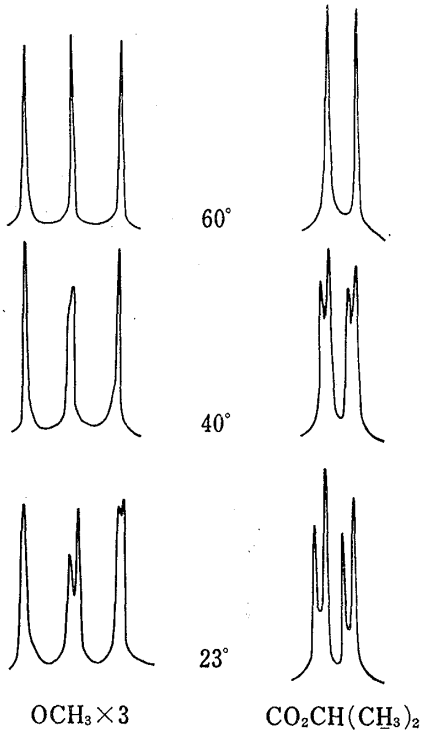


Fig. 1. NMR Spectrum of the Axial Alcohol (XII)

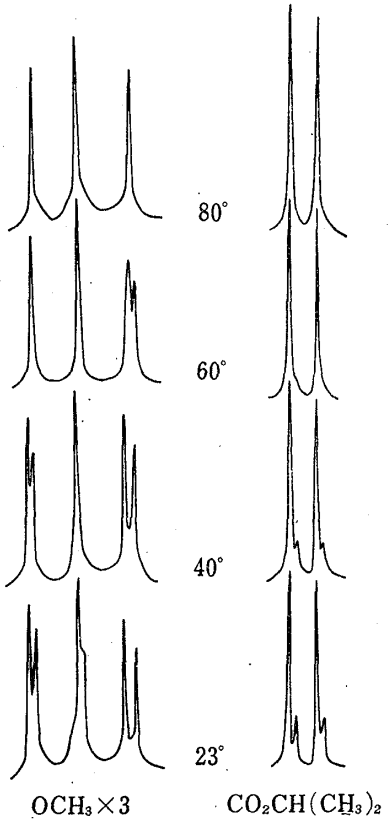


Fig. 2. NMR Spectrum of the Equatorial Alcohol (XIII)

In the previous papers,[1,17] it has been reported that the Mannich condensation of isopelletierine with an alkali-soluble arylaldehyde under an alkaline condition gives stereoselectively a *trans*-quinolizidin-2-one. On the basis of this generality, the condensation with the biphenyl ester (VI) would be also expected to afford a *trans*-quinolizidine because VI is presumably hydrolyzed to the corresponding alkali-soluble carboxylic acid during the reaction.

The condensation of isopelletierine[18] (X) with VI in an aqueous methanolic solution containing sodium hydroxide yielded the expected *trans*-quinolizidin-2-one (XI), *m/e*: 467 (M^+), as a sole isolated product in 75% yield. The product showed bands at 2780, 2740 (Bohlmann bands), and 1720 cm^{-1} (ketone and carboxylic acid) in its IR spectrum. The stereochemistry of XI was deduced as depicted from the presence of the Bohlmann bands and the fact that 4-aryl substituents are equatorial in 4-aryl-*trans*-quinolizidines.[1,17,19]

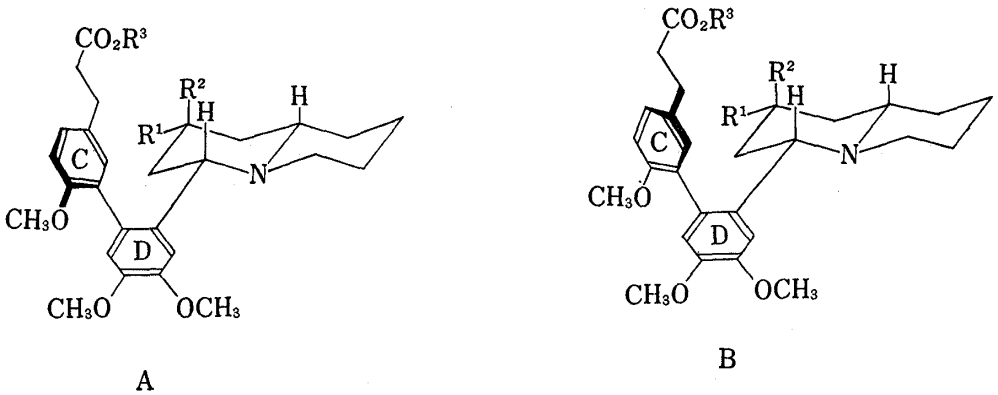
In order to get an axial alcohol, treatment of the quinolizidin-2-one (XI) with the Henbest catalyst[20] [$IrCl_4$–HCl–$(CH_3O)_3P$–iso–PrOH] effected reduction and partial esterification,

17) M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **23**, 1573 (1975).
18) M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, **94**, 531 (1974).
19) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.
20) H.B. Henbest and T.R.B. Mitchel, *J. Chem. Soc.* (*C*), **1970**, 785; E.L. Eliel, T.W. Doyle, R.O. Hutchins, and E.C. Gilbert, "Org. Syntheses", Vol. 50, 1970. p. 13.

giving the two isomeric alcohols (XII and XIII) in the 5:1 ratio in 35% yield along with a mixture of the isomeric hydroxy-acids, which, on subsequent esterification with isopropanol, furnished XII and XIII in the 5:1 ratio in 25% overall yield from XI. Each of the alcohols was shown to be homogeneous on the thin-layer chromatography (TLC) and their structures were verified from their spectral data; XII, *m/e*: 511 (M^+), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2800, 2760, 2720 (Bohlmann bands), 1720 (ester); XIII, *m/e*: 511 (M^+), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2800, 2750, 2720 (Bohlmann bands), 1718 (ester).

Since it has been reported that the Henbest reduction of non-hindered cyclohexanones gives predominantly axial alcohols[20] and that this generality is applicable to the quinolizidin-2-one system,[1] the major alcohol (XII) should be assigned to be the axial alcohol and the minor alcohol (XIII), the equatorial alcohol.

The NMR spectrum of XII at 23° revealed the signal due to the methyl of the isopropyl group at 1.17 (doublet, J=6.5 Hz) and 1.20 ppm (doublet, J=6.5 Hz), and the signal due to the three methoxyl groups at 3.65, 3.66, 3.77, 3.78, and 3.88 ppm as singlets as illustrated in Fig. 1. This observation suggests that the alcohol (XII) is a mixture of two atropisomers[21,22] (XIIA and XIIB) (Chart 3) caused by the restricted rotation around the pivot bond owing to the presence of the bulky quinolizidine moiety and the methoxyl group at *ortho* position in the D and C ring, respectively. In order to prove the above interpretation, the dynamic NMR spectrum[22,23] was measured at several temperatures. The NMR spectrum of XII at 60° showed one doublet at 1.19 ppm ($CO_2CH(C\underline{H}_3)_2$) and three singlets at 3.68, 3.81, and 3.90 ppm ($OCH_3\times3$) (Fig. 1), indicating the disappearance of atropisomerism in XII. The similar phenomenon was observed in the equatorial alcohol (XIII) (Fig. 2) and the quinolizidin-2-one (XI), whereas no atropisomerism was observed in the biphenyl (VI) from its NMR spectrum.



XI : $R^1+R^2=O$, $R^3=H$
XII : $R^1=H$, $R^2=OH$, $R^3=CH(CH_3)_2$
XIII : $R^1=OH$, $R^2=H$, $R^3=CH(CH_3)_2$
XIV: $R^1=H$, $R^2=OH$, $R^3=H$

Chart 3

Hydrolysis of the axial alcohol (XII) with aqueous sodium hydroxide in methanol furnished the hydroxy-acid (XIV), *m/e*: 469 (M^+), which was shown to exist in a zwitterion from its IR spectrum; 2460 (broad, N^+H) and 1574 cm^{-1} (CO_2^-), and as a mixture of two atropisomers from its NMR spectrum (see Experimental).

21) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGrau-Hill, New York, 1962, p. 156.
22) W.L. Meyer and R.B. Meyer, *J. Am. Chem. Soc.*, **85**, 2170 (1963); M. Ōki, H. Iwamura, and N. Hayakawa, *Bull. Chem. Soc. Japan*, **36**, 1542 (1963); *idem*, *ibid.*, **37**, 1865 (1964); I.O. Sutherland and M.V. J. Ramsay, *Tetrahedron*, **21**, 3401 (1965); L.D. Colebrook and J.A. Jahnke, *J. Am. Chem. Soc.*, **90**, 4687 (1968).
23) G. Binsch, "Topics in Stereochemistry," Vol. III, ed. by E.L. Eliel and N.L. Allinger, Interscience Publishers, New York, 1968, p. 97.

A highly diluted solution of the hydroxy-acid (XIV) in benzene was heated at reflux with *p*-toluenesulfonic acid[1] to provide the lactone (II), mp 215—216°, *m/e*: 451 (M^+), in 82% overall yield from XII. The product showed bands at 2790, 2720 (Bohlmann bands) and 1718 cm^{-1} (C=O) in its IR spectrum, and signals at 4.95 (1H, multiplet, W_H=8 Hz, C_2–H), 3.72, 3.84, and 3.89 ppm (each 3H, singlet, $OCH_3\times3$) in its NMR spectrum. The narrow half-height width of the C_2–H signal offered an unequivocal evidence for the stereochemistry at C_2 in II, as well as that in XII and XIII assigned above. The lactone (II) was confirmed to exist in only one of two possible atropisomers from its NMR spectrum. The formation of the single atropisomer can be reasonably explained by assuming that the hydroxy-acid (XIV) loses its atropisomerism under the reaction condition and then cyclizes to the stable isomer (II). The excellent yield of II and the disappearance of atropisomerism in XII at 60° may eliminate an alternative possibility that only one of two atropisomers in XIV cyclizes to II.

The synthetic lactone (II) was proved to be identical with methyldecinine derived from natural decinine by IR ($CHCl_3$), NMR ($CDCl_3$), ultraviolet (UV), and mass spectral comparison and TLC behaviour. The total synthesis of (±)-methyldecinine is thus completed. This synthesis will provide a general synthetic method for the biphenyl type Lythraceae alkaloids.

Experimental[24]

Ethyl 3-(3-Bromo-4-methoxyphenyl)propionate (V)——A solution of 3-(3-bromo-4-methoxyphenyl)-propionic acid[15] (16 g) in abs. EtOH (120 ml) was refluxed with conc. H_2SO_4 (17 ml) for 6 hr and evaporated *in vacuo*. To the cooled residue was added H_2O and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, saturated aq. $NaHCO_3$, and H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give V (15 g, 87%) as a colorless oil, bp 127—128°/0.17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (C=O). NMR δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.57 (2H, t with a fine structure, J=7.5 Hz, $CO\underline{CH}_2CH_2$), 2.87 (2H, t with a fine structure, J=7.5 Hz, $ArC\underline{H}_2CH_2$), 3.87 (3H, s, OCH_3), 4.11 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.79 (1H, d, J=8.5 Hz, Ar–H$^{5'}$), 7.09 (1H, d–d, J=8.5; 2 Hz, Ar–H$^{6'}$), 7.36 (1H, d, J=2 Hz, Ar–H$^{2'}$). Mass Spectrum *m/e*: 288, 286 (M^+, 1:1). High Resolution Mass Spectrum *m/e*: 288.016, 286.017. Calcd. for $C_{12}H_{15}O_3Br$: 288.018, 286.020.

The Ullmann Reaction of 6-Bromoveratraldehyde (IV) with the Ester (V) (Formation of Ethyl 3-[3-(2-Formyl-4,5-dimethoxyphenyl)-4-methoxyphenyl]propionate (VI), 4,4′,5,5′-Tetramethoxy-2,2′-bibenzaldehyde (VII), Ethyl 3-(4,6,7-Trimethoxy-9-oxofluoren-1-yl)propionate (VIII), and 2,3,6,7-Tetramethoxyfluoren-9-one (IX))——To a mixture of the ester (V, 20 g, 70 mmoles) and 6-bromoveratraldehyde[14] (IV, 8.5 g, 35 mmoles) was added Cu powder (10 g) at 220° with stirring. The reaction mixture was heated at 240° for 4 hr with stirring. The cooled reaction mixture was taken in $CHCl_3$ and filtered through the column packed with alumina (150 g) and the column was washed with $CHCl_3$. The filtrate and washings were combined and evaporated *in vacuo*. The residue was distilled at <165°/0.1 mmHg to give the ester (V) and veratraldehyde. The distillation residue was chromatographed on alumina (400 g, benzene: ether, 3: 1).

The first fraction gave the ester (V). The combined amount of V is 12.5 g (44 mmoles).

The second fraction gave veratraldehyde. The combined amount is 1.2 g (21% based on IV). The product was identified with the authentic specimen by IR spectra and TLC.

The third fraction gave VI (2.7 g, 22% based on IV), which was distilled to give a pale yellow viscous oil, bp 185—190° (bath temp.)/5×10^{-4} mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (ester), 1673 (CHO). NMR δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.76, 3.99, 4.02 (each 3H, s, $OCH_3\times3$), 4.16 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 9.70 (1H, s, CHO). UV nm (ε): λ_{max} 315 infl. (6630), 283 (12500), 243 infl. (20400), 233 (21900); λ_{min}265 (7950), 221 (17400). Mass Spectrum *m/e*: 372 (M^+). High Resolution Mass Spectrum *m/e*: 372.158. Calcd. for $C_{21}H_{24}O_6$: 372.157.

The fourth fraction gave VIII (1.9 g, 15% based on IV), which was recrystallized from MeOH to give red needles, mp 133.5—135°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723 (ester), 1697 (ketone). NMR δ: 1.15 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.56 (2H, t, J=7 Hz, $CO\underline{CH}_2CH_2$), 3.16 (2H, t, J=7 Hz, $ArC\underline{H}_2CH_2$), 3.84, 3.86, 3.91 (each 3H, s, $OCH_3\times3$), 4.04 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.79, 6.89 (2H, AB–q, J=9 Hz, Ar–H$^{2',3'}$), 7.03 (1H, s, Ar–

24) Melting points were measured with a Yanagimoto Micro Melting Point Apparatus. Melting points and boiling points 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 TLC and preparative TLC (p-TLC). IR spectra were measured with a JASCO-IRG, NMR spectra in $CDCl_3$ with a JEOL-PS-100 using TMS as an internal standard, mass spectra with a JEOL-JMS-01SG, and UV spectra in MeOH with a Hitachi Model 323.

$H^{5'}$), 7.24 (1H, s, Ar–$H^{8'}$). UV nm (ε): λ_{max} 320 (6060), 308 (6380), 279 (39600), 271—274 plateau (38500), 263 sh (30200), 249 sh (17700); λ_{min} 315 (5210), 300 (4840), 226 (7070). Mass Spectrum *m/e*: 370 (M^+). *Anal.* Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.89; H, 6.10.

The fifth fraction gave VII (2.0 g, 17% based on IV), which was recrystallized from benzene to give colorless prisms, mp 206—207° (lit., mp 209—211.5°,[16] mp 215°,[25] bp 96°/0.67 mmHg[26]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CHO). NMR δ: 3.98, 4.02 (each 6H, s, $OCH_3\times4$), 6.79 (2H, s, Ar–$H^{6,6'}$), 7.54 (2H, s, Ar–$H^{2,2'}$), 9.63 (2H, s, $CHO\times2$). UV nm (ε): λ_{max} 315 (11800), 280 (20600), 241 (31300); λ_{min} 305 (11600), 262 (15000), 216 (15600). Mass Spectrum *m/e*: 330 (M^+). *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49 Found: C, 65.38; H, 5.51.

The sixth fraction gave IX (0.23 g, 2.2% based on IV), which was recrystallized from MeOH to give reddish orange needles, mp 207—208.5° (lit.,[27] mp 203°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1698 (C=O). NMR δ: 3.92, 4.01 (each 6H, s, $OCH_3\times4$), 6.86 (2H, s, Ar–$H^{4,5}$), 7.11 (2H, s, Ar–$H^{1,8}$). UV nm (ε): λ_{max} 282 (63900), 259 infl. (13800); λ_{min} 219—221 (6510). Mass Spectrum *m/e*: 300 (M^+). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.75; H, 5.25.

Transformation of VI to VIII——A mixture of VI (44 mg) and Cu powder (50 mg) was treated in the same procedure as that described in the Ullmann reaction to give the crude product. The product was separated by p-TLC (alumina, benzene: ether, 2: 1) to give the starting material (VI, 18 mg, 41%) and the fluorenone (VIII, 21 mg, 47%), the latter of which was identified with VIII obtained in the Ullmann reaction by IR spectra, TLC, and mixed mp.

Transformation of VII to IX——A mixture of VII (57 mg) and Cu powder (50 mg) was treated in the same procedure as that described in the Ullmann reaction to give the crude product. The product was separated by p-TLC (alumina, benzene: ether, 1: 2) to give the starting material (VII, 31 mg, 54%) and the fluorenone (IX, 19 mg, 37%), the latter of which was identified with IX obtained in the Ullmann reaction by IR spectra, TLC, and mixed mp.

3-[3-{4,5-Dimethoxy-2-(2-oxo-*trans*-quinolizidin-4-yl(*e*))phenyl}-4-methoxyphenyl]propionic Acid(XI)——To a solution of isopelletierine[18] (X, 1.1 g, 7.8 mmoles) and VI (2.3 g, 6.1 mmoles) in MeOH (30 ml) was added 5% aq. NaOH (14 ml), and the reaction mixture was heated at 65° for 7 hr with stirring in a stream of N_2 and evaporated *in vacuo*. The residue was acidified to pH 5 with 10% HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was purified with chromatography (silica gel, 300 g, $CHCl_3$: EtOH, 50: 1) to give XI (2.2 g, 75%) as a colorless amorphous solid, mp 90—94°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780, 2740 (Bohlmann bands), 1720 (ketone and carboxylic acid). NMR δ: 3.68, 3.72, 3.81, 3.83, 3.93 (total 9H, each s, $OCH_3\times3$). Mass Spectrum *m/e*: 467 (M^+). High Resolution Mass Spectrum *m/e*: 467.228. Calcd. for $C_{27}H_{33}O_6N$: 467.231.

Isopropyl 3-[3-{2-(2-Hydroxy(*a*)-*trans*-quinolizidin-4-yl(*e*))-4,5-dimethoxyphenyl}-4-methoxyphenyl]-propionate (XII) and Isopropyl 3-[3-{2-(2-Hydroxy(*e*)-*trans*-quinolizidin-4-yl(*e*))-4,5-dimethoxyphenyl}-4-methoxyphenyl]propionate (XIII)——To a solution of XI (1.0 g) in iso-PrOH (30 ml) was added a solution prepared from $IrCl_4\cdot H_2O$ (150 mg), conc. HCl (2 ml), H_2O (5 ml), and $(CH_3O)_3P$ (1.5 ml), and the reaction mixture was refluxed for 40 hr and evaporated *in vacuo*. The residue was made alkaline with 10% aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina (130 g, $CHCl_3$: MeOH, 25: 1).

The first fraction gave the axial alcohol (XII, 0.31 g, 29%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2800, 2760, 2720 (Bohlmann bands), 1720 (C=O). NMR δ: 1.17, 1.20 (total 6H, each d, $J=6.5$ Hz, $CO_2CH(C\underline{H}_3)_2$), 3.65, 3.66, 3.77, 3.78, 3.88 (total 9H, each s, $OCH_3\times3$). (60°) δ: 1.19 (6H, d, $J=6.5$ Hz, $CO_2CH(C\underline{H}_3)_2$), 2.56 (2H, t, $J=7$ Hz, $COC\underline{H}_2CH_2$), 2.90 (2H, t, $J=7$ Hz, $ArC\underline{H}_2CH_2$), 3.68, 3.81, 3.90 (each 3H, s, $OCH_3\times3$), 4.97 (1H, septet, $J=6.5$ Hz, $CO_2C\underline{H}(CH_3)_2$). Mass Spectrum *m/e*: 511 (M^+). High Resolution Mass Spectrum *m/e*: 511.295. Calcd. for $C_{30}H_{41}O_6N$: 511.293.

The second fraction gave the equatorial alcohol (XIII, 64 mg, 6%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2800, 2750, 2720 (Bohlmann bands), 1718 (C=O). NMR δ: 1.17, 1.19 (total 6H, each d, $J=6.5$ Hz, $CO_2CH(C\underline{H}_3)_2$), 3.65, 3.67, 3.77, 3.78, 3.87, 3.88 (total 9H, each s, $OCH_3\times3$). (80°) δ: 1.19 (6H, d, $J=6.5$ Hz, $CO_2CH(C\underline{H}_3)_2$), 2.56 (2H, t, $J=7$ Hz, $COC\underline{H}_2CH_2$), 2.91 (2H, t, $J=7$ Hz, $ArC\underline{H}_2CH_2$), 3.68, 3.81, 3.91 (each 3H, s, $OCH_3\times3$), 4.99 (1H, septet, $J=6.5$ Hz, $CO_2C\underline{H}(CH_3)_2$). Mass Spectrum *m/e*: 511 (M^+). High Resolution Mass Spectrum *m/e*: 511.290. Calcd. for $C_{30}H_{41}O_6N$: 511.293.

The aqueous alkaline layer and washings were combined, adjusted to pH 5—6 with 10% HCl, and extracted with $CHCl_3$. The extract was dried and evaporated *in vacuo*. A solution of the residue (0.35 g) in iso-PrOH (15 ml) was saturated with dried HCl gas, refluxed for 6 hr, and evaporated *in vacuo*. The residue was made alkaline with saturated aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was separated by p-TLC (alumina, $CHCl_3$: MeOH, 75: 2)

25) R. Quelet and E.Matarasso -Tchiroukhine, *Compt. Rend.*, **244**, 467 (1957).
26) T. Kametani, K. Fukumoto, and T. Nakano, *Yakugaku Zasshi*, **82**, 1307 (1962).
27) R. Quelet and E.Matarasso -Tchiroukhine, *Compt. Rend.*, **246**, 1227 (1958); E.Matarasso-Tchiroukhine, (Paris), **3**, 405 (1958).

to give XII (0.23 g, 21% based on XI) and XIII (46 mg, 4% based on XI), which were identified with the corresponding samples obtained above by IR spectra and TLC.

3-[3-{2-(2-Hydroxy(*a*)-*trans*-quinolizidin-4-yl(*e*))-4,5-dimethoxyphenyl}-4-methoxyphenyl]propionic Acid (XIV)——To a solution of XII (47 mg) in MeOH (2 ml) was added 5% aq. NaOH (2 ml), and the reaction mixture was refluxed for 1.5 hr and evaporated *in vacuo*. The residue was adjusted to pH 5—6 with 10% HCl and extracted with $CHCl_3$. The extract was dried and evaporated *in vacuo* to give XIV (43 mg) as a colorless amorphous solid, mp 140—142°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2460 br (N^+H), 1574 (CO_2^-). NMR δ: 3.63, 3.84, 3.86, 4.04 (total 9H, each s, $OCH_3 \times 3$). Mass Spectrum *m/e*: 469 (M^+). High Resolution Mass Spectrum *m/e*: 469.245. Calcd. for $C_{27}H_{35}O_6N$: 469.246.

The product was used in the following reaction without purification.

(±)-Methyldecinine (II)——In a flask equipped with the Dean-Stark water separator containing molecular sieves (3A 1/16, 2 g) a suspension of XIV (43 mg) in benzene (450 ml) was heated. After XIV was completely dissolved, *p*-TsOH·H_2O (450 mg) was added to the solution and the reaction mixture was refluxed for 135 hr. The cooled reaction mixture was washed with saturated aq. $NaHCO_3$ and H_2O. The combined aqueous layers were extracted with $CHCl_3$. The extract and the benzene layer were combined, dried, and evaporated *in vacuo*. The residue was purified by p-TLC (alumina, $CHCl_3$) to give colorless crystals (II, 34 mg, 82% from XII), which was recrystallized from MeOH to give colorless prisms, mp 215—216°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2720 (Bohlmann bands), 1718 (C=O). NMR δ: 3.72, 3.84, 3.89 (each 3H, s, $OCH_3 \times 3$), 4.95 (1H, m, $W_H = 8$ Hz, C_2–H). UV nm (ε): λ_{max} 293 (8120), 290 sh (7750), 250 sh (7310); λ_{min} 269 (3530). Mass Spectrum *m/e*: 451 (M^+). High Resolution Mass Spectrum *m/e*: 451.240. Calcd. for $C_{27}H_{33}O_5N$: 451.236. *Anal.* Calcd. for $C_{27}H_{33}O_5N$: C, 71.81; H, 7.37; N, 3.10. Found: C, 71.70; H, 7.21; N, 3.21.

The product was identified with methyldecinine derived from natural decinine by comparison with IR, NMR, UV, mass spectra and TLC behaviour.

Methyldecinine——To a solution of natural decinine[28] (20 mg) in MeOH (5 ml) was added an etherial solution (10 ml) saturated with diazomethane, and the reaction mixture was kept standing in refrigerator for 2 days and evaporated *in vacuo*. The residue was purified by p-TLC (alumina, $CHCl_3$) to give methyldecinine (14 mg, 67%), which was recrystallized from MeOH to give colorless prisms, mp 165—166°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2720 (Bohlmann bands), 1718 (C=O). NMR δ: 3.72, 3.84, 3.89 (each 3H, s, $OCH_3 \times 3$), 4.95 (1H, m, $W_H = 8$ Hz, C_2–H). UV nm (ε): λ_{max} 293 (7980), 290 sh (7570), 250 sh (7250); λ_{min} 269 (3530). $[\alpha]_D^{18}$ −151° ($c = 0.053$, $CHCl_3$). Mass Spectrum *m/e*: 451 (M^+). High Resolution Mass Spectrum *m/e*: 451.234. Calcd. for $C_{27}H_{33}O_5N$: 451.236.

Acknowledgement The authors are grateful to Prof. James P. Ferris, Department of Chemistry, Rensselaer Polytechnic Institute, for his generous gift of natural decinine and its IR spectrum. They are also indebted to Mr. Y. Itatani, Misses S. Toyoshima, and H. Hyuga of this Faculty for elemental analyses, NMR and mass spectral measurement.

28) Natural decinine was isolated from *Lagerstroemia indica* L. grown in Japan and identified with authentic natural decinine by IR spectra and TLC.