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Syntheses of Erythrinan Alkaloids: (±)-Coccolinine, (±)-Isococculidine, (±)-Coccuvinine, and (±)-Cocculidine

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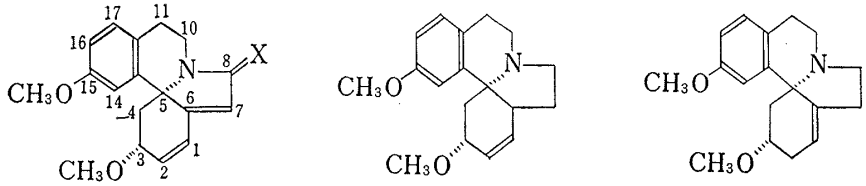
Total syntheses of 'abnormal-type' erythrinan alkaloids, (±)-coccolinine (**1**), (±)-isococculidine (**2**), (±)-coccuvinine (**3**) and (±)-cocculidine (**4**), are described. Mondon's glyoxylic ester synthesis was successfully applied in these syntheses. The key intermediate, 16-ethoxycarbamido-2,15-dimethoxyerythrinan-7,8-dione (**7**), was obtained by condensation of 3-ethoxycarbamido-4-methoxyphenylethylamine (**5**) with ethyl 4-methoxycyclohexanone-2-glyoxylate (**6**), followed by treatment with phosphoric acid. The ethoxycarbamido group at the C_{16} position was effectively employed as a regiospecific *para*-directing group in the isoquinoline ring closure.

Keywords——synthesis of erythrinan alkaloids; glyoxylic ester synthesis; ethoxycarbamido group; coccolinine; isococculidine; coccuvinine; cocculidine

Recently, Bhakuni *et al.* investigated the alkaloid constituents of the leaves of Indian *Cocculus laurifolius* DC. (Menispermaceae), which have hypotensive activity in the 50% aqueous ethanolic extract, and reported the isolation and structure elucidation of a number of new erythrinan- and dibenz[*d*,*f*]azonine-type alkaloids.[1] In contrast to Barton's biogenetic view of erythrinan alkaloids,[2] *i.e.*, that aromatic erythrinan alkaloids should possess an oxygen function at the C_{16} position, these erythrinan alkaloids isolated by Bhakuni *et al.* have no O-function at this position. In this sense, these erythrinan alkaloids are 'abnormal', and the biosynthetic route was clarified by Bhakuni *et. al.*[3] The synthesis of 'abnormal'-type erythrinan alkaloids is of interest because of the biological activity of some of these alkaloids; they have hypotensive and neuromuscular blocking action.[4]

The authors wish to report here the first total syntheses of (±)-coccolinine (**1**),[1a] (±)-isococculidine (**2**),[1b] (±)-coccuvinine (**3**),[1c] and (±)-cocculidine (**4**).[1b,5]



1 : X=O
3 : X=H_2

2

4

Chart 1

A route similar to that used in the glyoxylic ester method developed by Mondon *et al.*[6] was employed. The key step in applying this method to the synthesis of abnormal-type erythrinan alkaloids was to achieve isoquinoline ring closure at the *meta* position with respect to the methoxy group on the aromatic ring. Ishiwata *et al.*[7] have already reported syntheses of 6-amino-1-phenylisoquinolines by means of the Bischler–Napieralski reaction, in which the ethoxycarbamido group accelerates the ring closure reaction, and they also stated that the ring closure occurs selectively at the *para* position with respect to the ethoxycarbamido group. The ethoxycarbamido group, therefore, was assumed to be suitable for our syntheses, and the ease with which the ethoxycarbonyl group can be removed was also convenient.

Condensation of 3-ethoxycarbamido-4-methoxyphenylethylamine (**5**)[7] with ethyl 4-methoxycyclohexanone-2-glyoxylate (**6**)[8] followed by treatment with 85% phosphoric acid gave the keto-lactam (**7**),[9] which possesses the erythrinan skeleton. The isoquinoline ring closure occurred selectively at the *para* position with respect to the ethoxycarbamido group. Reduction of **7** with sodium borohydride gave the hydroxy-lactam (**8**). The hydroxyl group was expected to have the α-configuration, since the hydride attack would occur from the less-hindered side, and this assumption was confirmed by the oxido ring formation in the next stage. Thus, when warmed in concd. sulfuric acid, the hydroxy-lactam (**8**) gave the oxido-lactam (**9**). Hydrolysis of **9** with 20% hydrochloric acid under a nitrogen atmosphere gave the amino-lactam (**10**) in 54.6% yield. The amino group was then diazotized in the usual manner and subsequent treatment with hypophosphorous acid gave the 2,7-oxido-lactam (**11**). Treatment of **11** with *p*-toluenesulfonic acid in acetic anhydride gave the olefin acetate (**12**) in 80% yield. Epoxidation of **12** with *m*-chloroperbenzoic acid gave a single epoxide (**13**). The β-configuration of the epoxide ring was anticipated, since the reagent would attack the double bond from the less-hindered side. The epoxide (**13**) was transformed to the allyl alcohol (**14a**) by the method developed by Sharpless *et al.*[10] Allylic rearrangement of **14a**

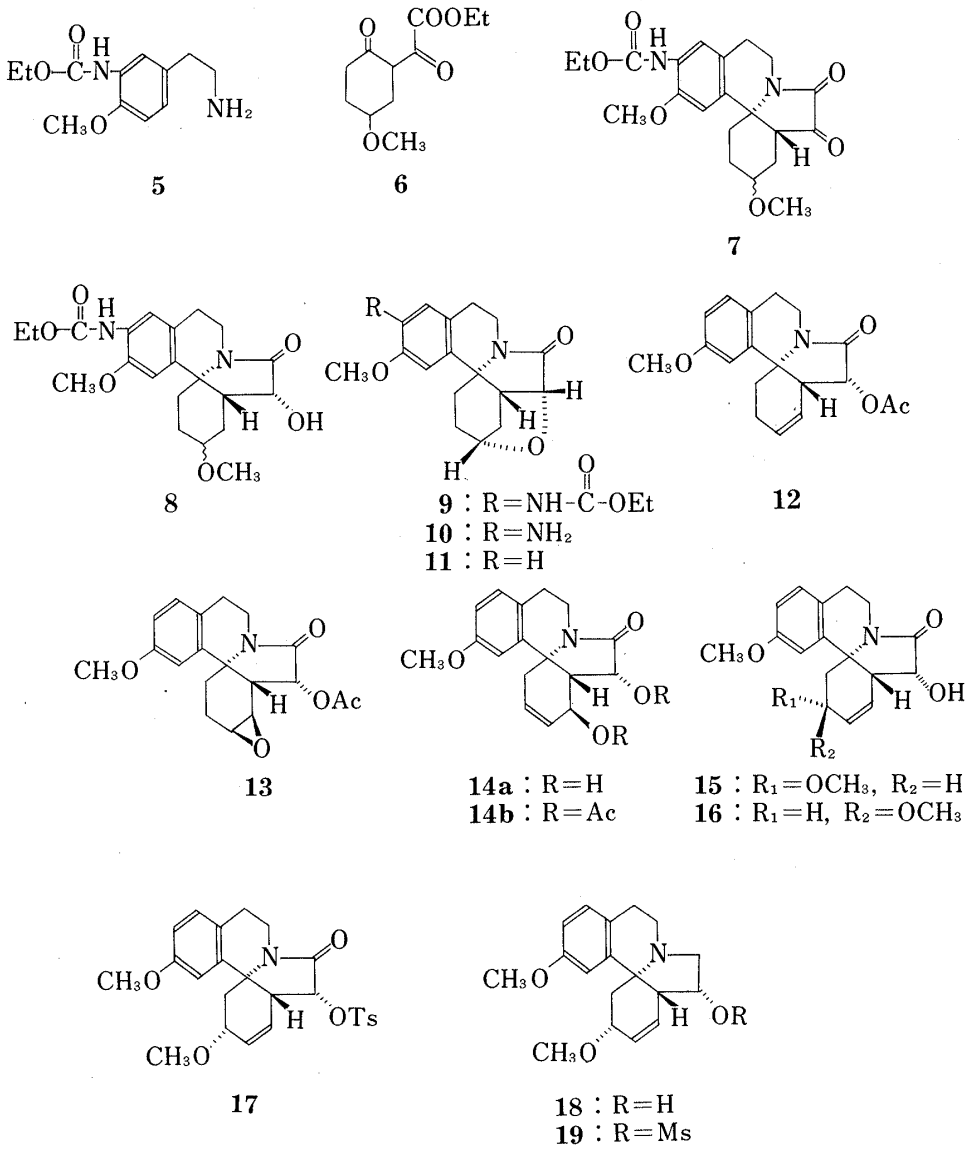


Chart 2

with 6N hydrochloric acid in methanol afforded two products epimeric at C_3, *i.e.*, the 3α-methoxy compound (**15**) and the 3β-methoxy compound (**16**), in a ratio of 1:1. Each configuration was established by proton nuclear magnetic resonance (NMR) spectroscopy by means of the homonuclear internuclear double resonance (INDOR) and nuclear Overhauser effect (NOE) techniques.[11] In the INDOR experiments on compound (**15**), a signal due to the C_{14} aromatic proton was observed at δ 6.94 with *meta* coupling (J=2.5 Hz), and signals attributable to the C_4 methylene protons were observed at δ 2.26 and δ 2.53 when the C_3 proton signal at δ 3.83 was monitored. On monitoring the aromatic proton signal at δ 6.94, the signal due to a proton attached to C_3 with its aliphatic methoxy group was observed at δ 3.83. These results suggest that the aromatic proton at C_{14} and the proton at C_3 are situated closely enough to permit observation of NOE. Thus, an NOE increment (about 10%) was observed at the signal of the aromatic proton at C_{14} upon irradiation of the proton signals at C_3 in compound (**15**). On the other hand, the same technique was applied to compound (**16**) but neither alteration of the signals in the INDOR spectrum nor signal increments in the NOE spectrum were observed between any aromatic protons and the C_3-proton. From these NMR analyses, it was concluded that the configuration of the C_3 methoxy group of compound (**15**) is α and that of compound (**16**) is β.

Compound (**15**), which has the natural α configuration of the C_3 methoxy group, was transformed to the tosylate (**17**), and the latter was detosylated with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) to give (±)-coccolinine (**1**). Reduction of **17** with lithium aluminum hydride provided (±)-isococculidine (**2**). These synthetic products were identical with the corresponding authentic natural samples on the basis of IR, NMR and mass spectral and TLC comparisons. Reduction of **15** with lithium aluminum hydride under an argon atmosphere gave compound (**18**). Treatment of **18** with methanesulfonyl chloride in pyridine gave the mesylate (**19**). Demesylation of **19** with potassium hydroxide provided (±)-coccuvinine (**3**). 1,4-Hydrogen addition of **3** gave (±)-cocculidine (**4**). The synthetic compounds were identical with the corresponding authentic natural specimens in terms of their IR, NMR and mass spectra and TLC behavior.

Consequently, the structures of these 'abnormal-type' erythrinan alkaloids were synthetically verified. The ethoxycarbamido group at the C_{16} position was successfully employed as a regioselective *para*-directing group in the synthesis of 'abnormal-type' erythrinan alkaloids, and the usefulness of this group was confirmed by its ready replacement with a hydrogen after the ring closure.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco IR-G spectrometer in $CHCl_3$. NMR spectra were measured on a Varian A-60 or a Hitachi R22 spectrometer with tetramethylsilane as an internal standard; chemical shifts are given in δ values. Mass spectra were taken on a Hitachi RMU-6 MG mass spectrometer. TLC was performed on silica gel (Kieselgel G nach Stahl) or alumina (Aluminium Oxyd G nach Stahl) with acetone–chloroform or acetone–methanol as a developing solvent. Unless otherwise specified, the extracts were dried over anhydrous magnesium sulfate.

16-Ethoxycarbamido-2,15-dimethoxyerythrinan-7,8-dione (**7**)——A solution of 65.7 g of 3-ethoxycarbamido-4-methoxyphenylethylamine (**5**) and 31.5 g of ethyl 4-methoxycyclohexanone-2-glyoxylate (**6**) in 700 ml of dry benzene was refluxed for 10 hr while water was azeotropically removed by a Dean–Stark apparatus. The solvent was evaporated off under reduced pressure, and the residue was dissolved in 1000 ml of MeOH and 1000 ml of 85% H_3PO_4. The mixture was refluxed for 20 hr under a nitrogen atmosphere, poured into ice-water and extracted with CH_2Cl_2. The extract was shaken with 5% NaOH solution and enolizable material was dissolved in the aqueous layer. The aqueous layer was made acidic with concd. HCl and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated to give 24.4 g of an oily compound. The residual oil was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with 5% acetone in CH_2Cl_2 gave a crystalline solid. Recrystallization from acetone gave the keto-lactam (**7**) as colorless needles. mp 214—218°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1710, 1660. NMR ($CDCl_3$, δ): 7.98 (1H, s), 7.18 (1H, br), 7.03 (1H, s), 4.24 (2H, q, J=7.0 Hz), 3.88, 3.46 (each 3H, s, OCH_3), 1.32 (3H, t, J=7.0 Hz). MS

m/e: 402 (M^+), 385, 342, 330, 329, 327. *Anal.* Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.36; H, 6.62; N, 6.88.

Hydroxy-lactam (8)——Sodium borohydride (4.24 g) was added to a solution of 29.88 g of the keto-lactam (**7**) in 300 ml of MeOH and 20 ml of H_2O under ice-cooling. The mixture was stirred overnight at room temperature, then the solvent was evaporated off under reduced pressure. The residual oil was extracted with CH_2Cl_2. The extract was successively washed with 10% HCl, 10% NaOH and H_2O, dried and concentrated to give 19.84 g of a crystalline solid. Recrystallization from acetone gave the hydroxy-lactam (**8**) as colorless needles. mp 228—230°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1700, 1680. NMR ($CDCl_3$, δ): 7.82 (1H, s), 7.15 (1H, s), 6.67 (1H, s), 4.23 (2H, q, J=7.5 Hz), 4.10 (1H, m, OH), 3.88, 3.40 (each 3H, s, OCH_3), 1.31 (3H, t, J=7.5 Hz). MS *m/e*: 404 (M^+), 332, 331 (base peak). *Anal.* Calcd for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.22; H, 7.08; N, 6.73.

Oxido-lactam (9)——A solution of 18.91 g of the hydroxy-lactam (**8**) in 30 ml of concd. H_2SO_4 was warmed at 40—50° for 3 hr with stirring. After cooling, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was successively washed with 10% HCl, 10% NH_4OH, and H_2O, then dried and concentrated to give 10.23 g of a crystalline solid. Recrystallization from acetone gave **9** as colorless needles. mp 189—190°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1715, 1680. NMR ($CDCl_3$, δ): 7.86 (1H, s), 7.17 (1H, br s), 6.71 (1H, s), 4.53 (1H, m), 4.23 (2H, q, J=7.0 Hz), 4.25 (1H, d, J=6.0 Hz), 3.89 (3H, s, OCH_3), 1.32 (3H, t, J=7.0 Hz). MS *m/e*: 372 (M^+), 343, 316, 315, 301. *Anal.* Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.30; H, 6.52; N, 7.53.

Amino-lactam (10)——A solution of 50 mg of the ethoxycarbamido compound (**9**) in 5 ml of 20% HCl was refluxed for 20 hr under a nitrogen atmosphere. After cooling, the reaction mixture was extracted with CH_2Cl_2 to remove a neutral compound, then the aqueous layer was made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated to give an oily compound. Purification through a silica gel column (acetone) gave a crystalline solid. Recrystallization from acetone gave 22 mg of the amino-lactam (**10**) as yellow needles. mp 185—189°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3350, 1680. NMR ($CDCl_3$, δ): 6.63 (1H, s), 6.45 (1H, s), 4.50 (1H, m), 4.24 (1H, d, J=6.0 Hz), 3.88 (3H, s, OCH_3), 3.47 (2H, s, NH_2). MS *m/e*: 300 (M^+), 271, 244, 243, 229. *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.21; H, 6.82; N, 9.34.

15-Methoxyerythrinan-8-one-2,7-oxide (11)——A solution of 0.63 g of $NaNO_2$ in 5 ml of H_2O was added to a solution of 100 mg of the amino-lactam (**10**) in 4 ml of 10% HCl at 5—0°. Then, a solution of hypophosphorous acid (2.64 g) was added and the whole was allowed to stand for 24 hr at 0°. The reaction mixture was extracted with CH_2Cl_2. The extract was washed with 10% NH_4OH and H_2O successively, dried and concentrated to give a crystalline solid. Recrystallization from acetone gave 28.9 mg of the 2,7-oxido-lactam (**11**) as colorless needles. mp 176—177°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. NMR ($CDCl_3$, δ): 7.08 (1H, d, J=9.5 Hz), 6.87 (1H, d, J=2.5 Hz), 6.78 (1H, d.d, J=9.5, 2.5 Hz), 4.26 (1H, d, J=6.0 Hz), 3.81 (3H, s, OCH_3), 4.50 (1H, m). MS *m/e*: 285 (M^+), 256, 229, 228, 214. *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.37; H, 6.79; N, 4.81.

7-Acetoxy-15-methoxyerythrinan-1-en-8-one (12)——*p*-Toluenesulfonic acid (0.87 g) was added to a solution of 1.28 g of the 2,7-oxido-lactam (**11**) in 35 ml of acetic anhydride and the reaction mixture was refluxed for 1.5 hr. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O, 2% $NaHCO_3$ solution and H_2O successively, then dried and concentrated. The oily residue was dissolved in CH_2Cl_2 and chromatographed on a silica gel column with CH_2Cl_2 as an eluent. The eluate was evaporated to dryness to give 1.177 g of 7-acetoxy-15-methoxyerythrinan-1-en-8-one (**12**) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1680. NMR ($CDCl_3$, δ): 7.11 (1H, d, J=9.0 Hz), 6.79 (1H, d.d, J=9.0, 2.5 Hz), 6.78 (1H, d, J=2.5 Hz), 6.17 (1H, m), 5.78 (1H, d.d, J=10.0, 4.0 Hz), 5.43 (1H, d, J=8.0 Hz), 3.77 (3H, s, OCH_3), 2.12 (3H, s, $COCH_3$). MS *m/e*: 327 (M^+), 285, 273, 268, 231.

7-Acetoxy-15-methoxyerythrinan-1,2-oxido-8-one (13)——*m*-Chloroperbenzoic acid (656 mg) was added to a solution of 415 mg of **12** in 50 ml of $CHCl_3$ and the mixture allowed to stand for 2 days at room temperature. After dilution of the reaction mixture with $CHCl_3$, the organic layer was washed with saturated sodium thiosulfate solution, 1% $NaHCO_3$ solution and H_2O successively. The extract was dried and concentrated to give an oily compound, which was purified by silica gel column chromatography to give 157 mg of the epoxide (**13**) as a crystalline solid. Recrystallization from acetone gave pale yellow plates. mp 145—146°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1700. NMR ($CDCl_3$, δ): 6.99 (1H, d, J=9.0 Hz), 6.75 (1H, d.d, J=9.0, 2.5 Hz), 6.78 (1H, d, J=2.5 Hz), 5.39 (1H, d, J=8.0 Hz), 4.25 (2H, m), 3.80 (3H, s, OCH_3), 2.20 (3H, s, $COCH_3$). MS *m/e*: 343 (M^+), 314, 272, 243. *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.62; H, 6.16; N, 3.95.

Diol-lactam (14a)——Sodium borohydride (43 mg) was added to a solution of 174.8 mg of diphenyl-diselenide in 5 ml of absolute EtOH, and 341 mg of the epoxide (**13**) was added to the resulting mixture. The whole was refluxed for 2 hr, then 2.5 ml of THF and 1.32 ml of 30% H_2O_2 was added dropwise to the reaction mixture under cooling and the mixture was stirred for 2 hr, then extracted with CH_2Cl_2. The extract was washed with saturated sodium thiosulfate solution and H_2O, dried and concentrated to give the diol-lactam (**14a**) as a crystalline solid. Recrystallization from acetone gave 95 mg of colorless needles. mp 207—208°. IR ν_{max}^{KBr} cm^{-1}: 3400, 1650. NMR (C_5D_5N, δ): 7.86 (1H, d, J=2.5 Hz), 7.08 (1H, d, J=

8.5 Hz), 6.88 (1H, d.d, J=2.5, 8.5 Hz), 6.53 (1H, m), 5.85 (1H, m), 3.77 (3H, s, OCH_3). MS *m/e*: 301 (M^+), 232, 231 (base peak), 214. *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.74; H, 6.50; N, 4.41. Diacetate (**14b**): colorless cubes. mp 81—82°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1690. NMR (90 MHz, $CDCi_3$, δ): 2.08, 2.12 (each 3H, s, $OCOCH_3$), 3.78 (3H, s, OCH_3), 3.01 (1H, d.d, J=7.5, 2.5 Hz, C_6–H), 5.33 (1H, m, C_1–H), 5.67 (1H, d, J=8.5 Hz, C_7–H), 5.99 (1H, d.d, J=9.0, 4.0 Hz, C_3–H), 6.15 (1H, d.d, J=2.5, 9.0 Hz, C_2–H), 6.76 (1H, d.d, J=9.0, 2.5 Hz, C_{16}–H), 7.03 (1H, d, J=9.0 Hz, C_{17}–H), 7.08 (1H, d, J=2.5 Hz, C_{14}–H). MS *m/e*: 385 (M^+), 274, 273, 232, 231. *Anal.* Calcd for $C_{21}H_{23}NO_6 \cdot 1/2H_2O$: C, 63.95; H, 6.13; N, 3.56. Found: C, 64.16; H, 6.20; N, 3.30.

Allylic Rearrangement of the Diol-lactam (14a)——A mixture of 237.5 mg of the diol-lactam (**14a**) in 107 ml of MeOH and 11 ml of 6 N HCl was refluxed for 20 hr. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated. The residual oil was dissolved in CH_2Cl_2 and chromatographed on a silica gel column. Elution with 5% acetone in CH_2Cl_2 gave 88.9 mg of the 3β-methoxy compound (**16**) and elution with 10% acetone in CH_2Cl_2 gave 96.4 mg of the 3α-methoxy compound (**15**). 3α-Methoxy compound (**15**): Recrystallization from acetone gave colorless cubes. mp 190—191°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1675. NMR (90 MHz, C_5D_5N, δ): 2.26 (1H, d.d, J=12.0, 10.0 Hz), 3.19, 3.70 (each 3H, s, OCH_3), 3.83 (1H, m), 4.57 (1H, d, J=7.0 Hz), 6.03 (1H, br, OH), 6.12 (1H, d.q, J=11.5, 1.5 Hz), 6.32 (1H, br d, J=11.5 Hz), 6.86 (1H, d.d, J=8.0, 2.5 Hz), 6.94 (1H, d, J=2.5 Hz), 7.09 (1H, d, J=8.0 Hz). MS *m/e*: 315 (M^+), 300, 283, 231 (base peak). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.94; H, 6.78; N, 4.35. 3β-Methoxy compound (**16**): Recrystallization from acetone gave colorless cubes. mp 175°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1680. NMR (90 MHz, C_5D_5N, δ): 1.97 (1H, d.d, J=10.0, 13.5 Hz), 3.27, 3.72 (each 3H, s, OCH_3), 3.82 (1H, m), 4.62 (1H, d, J=8.0 Hz), 5.38 (1H, br, OH), 6.18 (1H, br d, J=11.5 Hz), 6.37 (1H, d.q, J=11.5, 1.5 Hz), 6.88 (1H, d.d, J=8.0, 2.0 Hz), 7.02 (1H, d, J=8.0 Hz), 7.11 (1H, d, J=2.0 Hz). MS *m/e*: 315 (M^+), 300, 283, 231 (base peak). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.96; H, 6.75; N. 4.33.

Tosylation of (15)——*p*-Toluenesulfonyl chloride (300 mg) was added to a solution of 105.5 mg of the 3,15-dimethoxy-lactam (**15**) in 10 ml of pyridine under cooling with an ice-water bath and the mixture was allowed to stand in a refrigerator for 3 days. The reaction mixture was then poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated to give an oily residue. The residue was dissolved in CH_2Cl_2 and chromatographed on a silica gel column. Elution with CH_2Cl_2 afforded 102 mg of the tosylate (**17**) as a crystalline solid. Recrystallization from acetone–EtOH gave colorless needles. mp 158—159°. NMR ($CDCl_3$, δ): 1.77 (1H, d.d, J=10.0, 12.5 Hz), 2.45 (3H, s), 3.31, 3.77 (each 3H, s), 5.09 (1H, d, J=7.5 Hz), 6.00 (1H, m), 6.32 (1H, br d, J=10.5 Hz), 6.69 (1H, d, J=2.5 Hz), 6.79 (1H, d.d, J=8.5, 2.5 Hz), 7.12 (1H, d, J=8.5 Hz), 7.34 (2H, d, J=8.5 Hz), 7.88 (2H, d, J=8.5 Hz). MS *m/e*: 469 (M^+), 321, 297, 282. *Anal.* Calcd for $C_{25}H_{27}NO_6S$: C, 63.96; H, 5.80; N, 2.99. Found: C, 63.99; H, 5.80; N, 2.99.

(±)-Coccolinine (1)——A solution of 1,5-diazabicyclo-[5,4,0]-undecene-5 (300 mg) in 30 ml of dry benzene was added to a solution of 85.5 mg of the tosylate (**17**) in 30 ml of dry benzene. The mixture was refluxed for 4 hr, then the solvent was evaporated off under reduced pressure and the residue was extracted with CH_2Cl_2. The extract was washed with 5% HCl solution, dried and concentrated to yield an oily residue. The residue was dissolved in CH_2Cl_2 and purified on a silica gel column. Elution with the same solvent afforded 43.5 mg of (±)-coccolinine (**1**). Recrystallization from MeOH gave colorless needles. mp 179—180°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665. NMR ($CDCl_3$, δ): 1.70 (1H, d.d, J=10.5, 12.0 Hz), 3.34, 3.75 (each 3H, s, OCH_3), 6.03 (1H, s), 6.30 (1H, d.d, J=10.0, 2.0 Hz), 6.91 (1H, d.d, J=10.0, 3.0 Hz), 6.78 (1H, d.d, J=9.0, 2.5 Hz), 6.83 (1H, d, J=2.5 Hz), 7.18 (1H, d, J=9.0 Hz). MS *m/e*: 297 (M^+, base peak), 282, 266, 264, 254, 238, 236. The IR, NMR and mass spectra of synthetic (±)-coccolinine (**1**) were superimposable on those of natural coccolinine.

(±)-Isococculidine (2)——Lithium aluminum hydride (500 mg) was added to a suspension of 102 mg of the tosylate (**17**) in 50 ml of dry ether with stirring under ice-cooling. The reaction mixture was refluxed for 3 hr under an argon atmosphere. The excess reagent was decomposed with H_2O, then the reaction mixture was made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated. The residue was dissolved in CH_2Cl_2 and chromatographed on a silica gel column. Elution with 20% acetone in CH_2Cl_2 gave 9.5 mg of (±)-isococculidine (**2**) as an oil, followed by 17.2 mg of 7-hydroxy-3,15-dimethoxyerythrinan-1-ene (**18**). (±)-Isococculidine (**2**): colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1495. NMR (90 MHz, $CDCl_3$, δ): 1.69 (1H, d.d, J=10.5, 12.0 Hz), 3.23, 3.72 (each 3H, s, OCH_3), 5.87 (1H, d.d, J=10.5, 1.5 Hz), 6.04 (1H, d.q, J=10.5, 3.0 Hz), 6.73 (1H, d.d, J=8.5, 2.5 Hz), 6.75 (1H, d, J=2.5 Hz), 7.06 (1H, d, J=8.5 Hz). MS *m/e*: 285 (M^+), 270 (base peak), 254, 240. The IR, NMR and mass spectra and TLC behavior of synthetic (±)-isococculidine (**2**) were identical with those of natural isococculidine.

7-Hydroxy-3,15-dimethoxyerythrinan-1-ene (18)——Lithium aluminum hydride (250 mg) was added portionwise to a suspension of 170 mg of the 3α-methoxy compound (**15**) in 30 ml of dry ether with ice-cooling and the mixture was refluxed for 6 hr under an argon atmosphere. The excess reagent was decomposed with H_2O, then the reaction mixture was made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated. The oily residue was dissolved in CH_2Cl_2 and chro-

matographed on silica gel. Elution with 20% acetone in CH_2Cl_2 gave 130.7 mg of **18** as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. NMR ($CDCl_3$, δ): 3.33, 3.77 (each 3H, s, OCH_3), 4.18, 6.10, 6.25 (each 1H, m), 6.61 (1H, d, J= 2.5 Hz), 6.71 (1H, d.d, J=8.0, 2.5 Hz), 7.03 (1H, d, J=8.0 Hz). MS *m/e*: 301 (M^+), 286, 270, 256.

7-O-Mesyl-3,15-dimethoxyerythrinan-1-ene (19)——Methanesulfonyl chloride (1 ml) was added to a solution of 55.5 mg of **18** in 2 ml of pyridine under ice-cooling. The reaction mixture was allowed to stand in a refrigerator for 2 days, then poured into ice-water, made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated to give an oily residue. The residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with 5% acetone in CH_2Cl_2 gave 31.5 mg of the mesylate (**19**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1335, 1170. NMR ($CDCl_3$, δ): 3.07 (3H, s, CH_3), 3.26, 3.76 (each 3H, s, OCH_3), 5.32, 5.94, 6.21 (each 1H, m), 6.67 (1H, d, J=2.5 Hz), 6.77 (1H, d.d, J=8.0, 2.5 Hz), 7.15 (1H, d, J=8.0 Hz). MS *m/e*: 379 (M^+), 284, 252.

(±)-Coccuvinine (3)——Potassium hydroxide (450 mg) was added to a solution of 45.5 mg of the mesylate (**19**) in 5.5 ml of ethyleneglycol monomethylether and the mixture was refluxed for 70 min under an argon atmosphere. The reaction mixture was made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated. The oily residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with 30% acetone in CH_2Cl_2 gave 10.9 mg of (±)-coccuvinine (**3**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1495. NMR (90 MHz, $CDCl_3$, δ): 1.83 (1H, t, J=11.0 Hz), 3.29, 3.71 (each 3H, s, OCH_3), 4.02 (1H, m, C_3–H), 5.71 (1H, m, C_7–H), 5.97 (1H, br d, J=10.0 Hz, C_1–H), 6.56 (1H, d.d, J=10.0, 2.0 Hz, C_2–H), 6.73 (1H, d.d, J=2.5, 8.5 Hz, C_{16}–H), 6.84 (1H, d, J=2.5 Hz, C_{14}–H), 7.07 (1H, d, J=8.5 Hz, C_{17}–H). MS *m/e*: 283 (M^+), 282, 268, 252 (base peak), 225, 223, 212, 199. The IR, NMR and mass spectra and TLC behavior of synthetic (±)-coccuvinine (**3**) were identical with those of natural coccuvinine.

(±)-Cocculidine (4)——(±)-Coccuvinine (**3**) (19.8 mg) was dissolved in 10 ml of MeOH and hydrogenated over 5% palladium-carbon. When absorption ceased, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with 50% acetone in CH_2Cl_2 gave 7.8 mg of (±)-cocculidine (**4**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1495. NMR (90 MHz, C_6D_6, δ): 1.89 (1H, t, J=12.0 Hz), 3.87 (1H, m, C_3–H), 3.01, 3.40 (each 3H, s, OCH_3), 5.41 (1H, m, C_1–H), 6.65 (1H, d.d, J=8.5, 2.5 Hz, C_{16}–H), 6.90 (1H, d, J=8.5 Hz, C_{17}–H), 6.93 (1H, d, J=2.5 Hz, C_{14}–H). MS *m/e*: 285 (M^+), 227 (base peak). The IR, NMR and mass spectra and TLC behavior of synthetic (±)-cocculidine were identical with those of natural cocculidine.

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