Articles

First Synthesis of the Novel *Gelsemium* Alkaloids, Gelselegine, Gelsenicine, and Gelsedine Using a Biomimetic Approach

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Based on a suggested biogenetic sequence, a sarpagine-type indole alkaloid, gardnerine (**7**), was converted into three novel *Gelsemium* alkaloids, gelselegine (**4**), gelsenicine (**6**), and gelsedine (**5**). This first synthesis of these alkaloids involves stereoselective skeletal rearrangements, such as indole to oxindole transformations and conversion of humantenine-type compounds to gelselegine, as well as the synthesis of a characteristic N_a-methoxyoxindole function.

Introduction

Chemical studies of the toxic plant, *Gelsemium elegans* Benth., from which the Chinese folk medicine "Kou-Wen or Hu-Man-Teng" is derived, have been ongoing for many decades.[1] In recent years, several new indole and oxindole alkaloids have been isolated from this plant in these and other laboratories.[2] These alkaloids have highly strained polycyclic structures and can be classified into six groups, the sarpagine-, humantenine-, gelselegine-, gelsedine-, koumine-, and gelsemine-types, based on their skeletal types.[2a] Our interest in the relationship of the various skeletal structures of the *Gelsemium* alkaloids has led us to consider their biogenetic pathway and to investigate our proposal with a series of chemical transformations.[3] Among the *Gelsemium* alkaloids, a new oxindole type, gelselegine (**4**),[4] has a hydroxymethyl group at the C20 position, suggesting from a biogenetic point of view that the C21 carbon rearranges to the *exo* position on the D-ring of the humantenine-type alkaloids, such as rankinidine (**3**), which could be derived from the sarpagine-type indole alkaloid, koumidine (**1**), via the C/D-ring cleavage compound (19*Z*)-anhydrovobasinediol (**2**). Furthermore, gelsedine-type alkaloids, such as gelsenicine (**6**) and gelsedine (**5**), would arise from **4** by loss of the C21 carbon (Scheme 1). In this paper, we describe the first synthesis of these chemically and biogenetically unique oxindole alkaloids (**4**–**6**), in a manner consistent with this biogenetic sequence.

Results and Discussion

We chose a *Gardneria* indole alkaloid, gardnerine (**7**),[5] which has a basic sarpagine skeleton, as the starting material. The methoxy group on the indole ring of **7** was removed by a six-step sequence in 62% overall yield.[6] The resulting (19*E*)-koumidine (**8**) was converted to the C/D ring-opened compound **9** in 94% yield by treatment with β,β,β-trichloroethyl chloroformate in the presence of MgO in aqueous THF. Because of the higher susceptibility to osmium tetraoxide (OsO_4) oxidation of the ethylidene side chain than the indole nucleus, 2 equiv of OsO_4 were used to convert the indole ring to an oxindole function. Compound **11** having the *S* configuration at the C7 spiro center was produced in 39% yield, accompanied by the indole diol **10**, in 28% yield. The indole **10** was in turn treated with OsO_4 to give the oxindole **11**. The stereochemistry at the C7 position was comfirmed by a comparison of the CD spectrum with that of the humantenine-type alkaloids.[3j] The ethylidene side chain was reformed in 75% overall yield from the vicinal diol of **11** by a three-step operation (1. trimethyl orthoformate, PPTS, THF. 2. Ac_2O, reflux, 3.5% KOH aqueous MeOH) to give the humantenine-type compound **12**. The double bond migration from the C19–20 to the C20–21 position was accomplished in 94% yield, using NaI and TMSCl in MeCN[3f] at room temperature, to provide the enamine **13**, which was successively treated with OsO_4 (yield 82%) and then $NaBH_4$ (yield 97%) to produce the diol **14** stereoselectively. The stereochemistry at C20 could be deduced from a stereomodel analysis. The reagent (OsO_4) should

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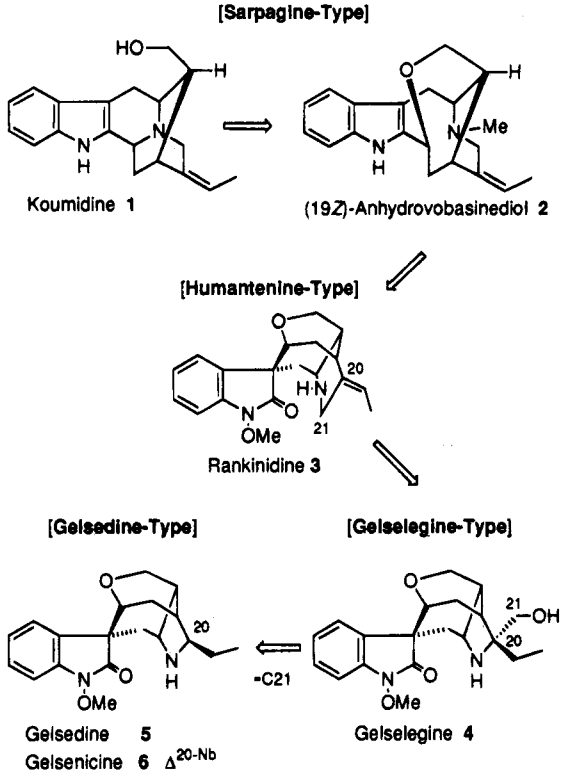
0022-3263/94/1959-4381$04.50/0

Scheme 1



approach the double bond of **13** from the less hindered, convex side, resulting in the formation of the C20(*S*) alcohol (Figure 1). At this stage, the N_a-methoxyoxindole function, which is one of the characteristics of many *Gelsemium* alkaloids, was introduced. The lactam of **14** was reduced in 77% yield with BH_3·SMe_2 complex and the resultant amine **15** was oxidized with urea–hydrogen peroxide complex, in the presence of a catalytic amount of sodium tungstate,[3a] followed by *O*-methylation with CH_2N_2 to yield the N_a-methoxyoxindole **16** in 61% overall yield from **15**. We next wished to prepare the epoxide from the diol **16**. Conventional reagents, including several MsCl/base combinations and the Mitsunobu system produced no useful results, but treatment of **16** with *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) and n-Bu_3P (a modified Mitsunobu reaction)[8] in DMF for 4 h at room temperature gave the epoxide **17** in 63% yield. Removal of the N_b-carbamate (Zn, AcOH) gave the primary amine **18**, which gradually transformed into the natural product, gelselegine (**4**), in 50% yield, upon standing for 5 days at room temperature. It appears that the primary amine regioselectively attacked the C20 position (5-*exo* tetrahedral mode) with complete inversion. The synthetic gelselegine (**4**) was identical with the natural compound in terms of physical (mp, $[\alpha]_D$) and spectroscopic (UV, ^{1}H- and ^{13}C-NMR, MS, CD) data.[4] The absolute configuration of the new alkaloid **4** is hereby chemically confirmed.

In keeping with the above biogenetic speculation, the C21 carbon of **4** was oxidatively cleaved with $NaIO_4$ in aqueous MeOH to yield gelsenicine (**6**)[9] in 64% yield. Furthermore, catalytic reduction of the imine function of **6** furnished gelsedine (**5**)[10] in quantitative yield.

Since the total synthesis of (+)-(19*E*)-koumidine (**8**) has been already accomplished by Magnus,[11] the present work completes the formal total synthesis of these three alkaloids.

Experimental Section

General. Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. IR spectra were measured with a Hitachi 260 spectrophotometer, and UV spectra were measured in methanol with a Hitachi U3400 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM A 500 (500 MHz) spectrometer with tetramethylsilane as internal standard. *J*-Values are given in hertz. ^{13}C NMR spectra were measured with a JEOL JNM A-500 (125.65 MHz) spectrometer with tetramethylsilane as internal standard. Mass spectra were taken with a Hitachi RMU-6E, an RMU-7M, a JEOL JMS-AM20, or a HX-110 spectrometer. CD spectra were measured with a JASCO J-500A spectrometer for solutions in MeOH. Thin-layer chromatography was performed on Merck precoated silica gel 60F-254 plates. Column chromatography utilized Merck silica gel 60 [70–230 and 230–400 mesh (for flash chromatography)] and prepacked column [Kusano CPS-HS-221-05 (for medium pressure column chromatography)].

Preparation of the Carbamate 9 from (19*E*)-Koumidine (8). 2,2,2-Trichloroethyl chloroformate (113.3 mL, 0.097 mol) was added to a stirred mixture of **8** (1.90 g, 6.46 mmol) and magnesium oxide (5.30 g, 0.129 mol) in THF (52.5 mL) and H_2O (17.5 mL) at 0 °C and the mixture was then stirred at room temperature for 15 h. The reaction mixture was filtered and the filtrate was concentrated and then acidified with 1 N HCl solution. The whole was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel flash column chromatography with ethyl acetate–hexane (3:7) to give the carbamate compound **9** (2.84 g, yield 94%) as an amorphous powder: ^{1}H-NMR ($CDCl_3$) δ 5.49 and 5.55 (1 H, each, q, J = 6.6 Hz, 19-H),[12] 5.06, 4.80, 4.78, 4.60 (2 H, each d, J = 12.0 Hz, OCH_2CCl_3),[12] 5.20 (1 H, d, J = 10.3 Hz, 3-H), 4.55 and 4.50 (1 H, each, m, 5-H),[12] 4.40 (1 H, dd, J = 15.8, 6.0 Hz, 17-H), 4.06 (1H, d, J = 15.8 Hz, 17-H), 1.71 and 1.70 (3 H, each, d, J = 6.6 Hz, 18-H);[12] UV (MeOH) λ_{max} 284, 223 nm; IR ($CHCl_3$) ν_{max} 3480, 2980, 1720, 1430, 1140 cm^{-1}; EI-MS *m/z* 470 (M^+ + 2, 12%), 468 (M^+, 10), 206 (12), 204 (7), 156 (73), 97 (63), 95 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{23}N_2O_3Cl_3$ 468.0774, found 468.0766.

Osmylation of the Carbamate 9. A solution of osmium tetraoxide (3.07 g, 12.1 mmol) in dry THF was added to a solution of the carbamate **9** (2.85 g, 6.07 mmol) in dry THF (30 mL) and dry pyridine (30 mL) at −78 °C and the mixture was stirred at the same temperature for 2.5 h. Aqueous sodium bisulfite solution (0.243 mmol) was added and the mixture was stirred at room temperature for 15 h. After the addition of ice–water the whole was extracted with chloroform. The organic layer was washed with 1 N HCl solution and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with ethyl acetate–hexane (17:2) to afford the oxindole **11** (1.23 g, 39%) and with ethyl acetate to give the diol **10** (850 mg, 28%). The oxindole **11**: an amorphous powder; ^{1}H-NMR ($CDCl_3$) δ 8.17 and 8.13 (1 H, each, br s, N_a-H), 4.83 (1 H, m, 5-H), 4.01 and 3.97 (1 H, each, q, J = 5.5 Hz, 19-H), 3.59 and 3.58 (1 H, each, d, J = 6.8 Hz,

(8) (a) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, 539–542. We thank Professors T. Tsunoda and S. Ito of Tokushima Bunri University for supplying the reagents and these experimental details.

(9) The most toxic compound of the *Gelsemium* alkaloids: LD50 70 μg/kg (iv), 219 μg/kg (ip) in mice. These data were provided by Prof. K. Watanabe, Faculty of Pharmaceutical Sciences, Chiba University.

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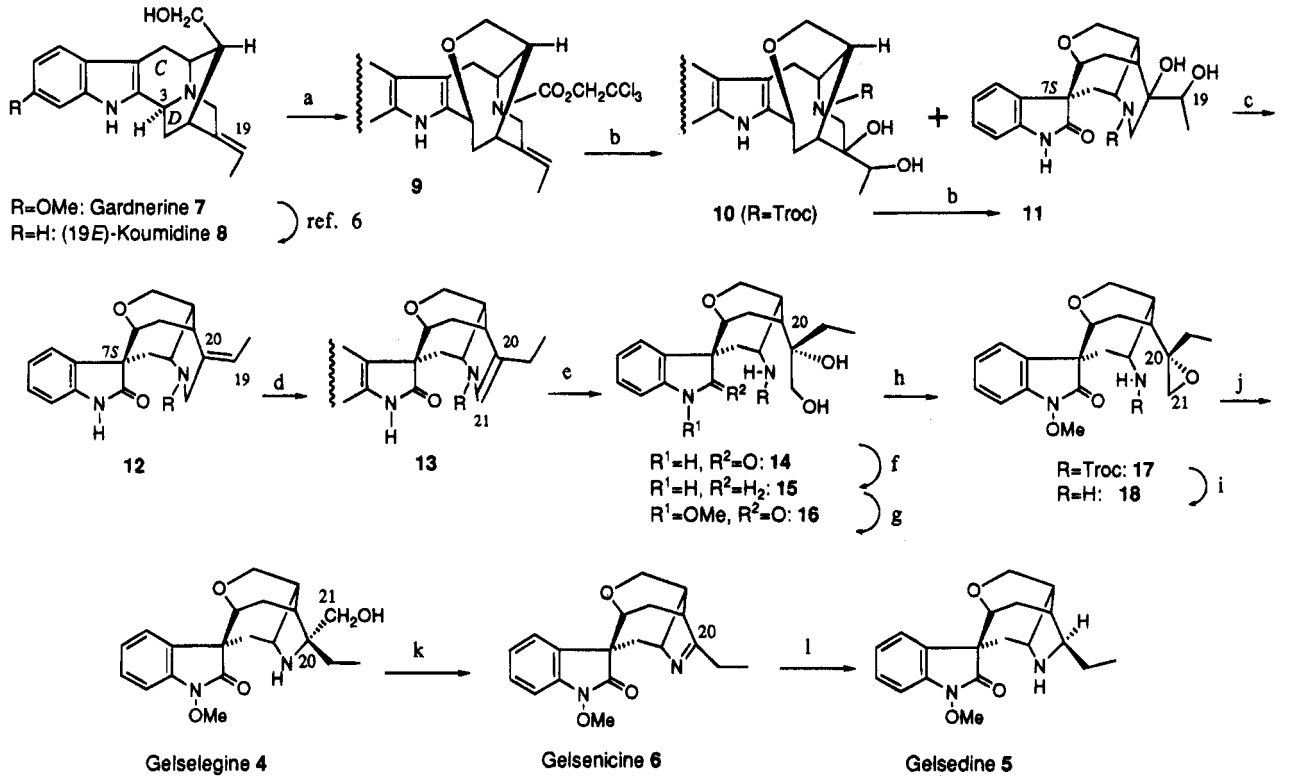
(12) Gardnerine derivatives possessing a carbamate function in the molecule were often shown by the ^{1}H-NMR spectra to occur as a mixture of rotation isomers.

Scheme 2



(a) TrocCl, MgO, aqueous THF, rt, 15 h; 94%. (b) OsO_4, py. THF, -78°C, then aq. $NaHSO_3$. (c) i, $CH(OMe)_3$, PPTS, THF, rt, 2 h. ii, Ac_2O, reflux, 3 h. iii, 5% aq. KOH, MeOH, rt, 2 h. 75% overall. (d) TMSCl, NaI, MeCN, rt, 1 h, 94%. (e) i, OsO_4, py, THF, rt, 2 h, then aq. $NaHSO_3$, 82%. ii, $NaBH_4$, MeOH, rt, 2 h, 97%. (f) BH_3•SMe_2, THF, reflux, 2 h, then $Me_3N{\rightarrow}O$, MeOH, reflux, 2 h, 77%. (g) i, urea•H_2O_2, cat. Na_2WO_4, aq. MeOH, rt, 4 h. ii, CH_2N_2, Et_2O, 61% overall. (h) TMAD, nBu_3P, DMF, rt, 4 h, 63%. (i) Zn, AcOH, rt, 4 h. (j) standing for 5 days, rt, 50% overall. (k) $NaIO_4$, aq. MeOH, rt, 2 h, 64%. (l) PtO_2, H_2, EtOH, rt, 1 h, quant.

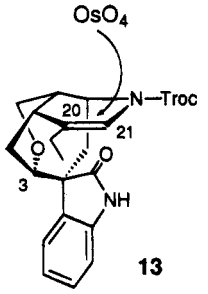


Figure 1.

3-H), 1.19 and 1.18 (3H, each, d, J = 6.5 Hz, 18-H); UV (MeOH) λ_{max} 251, 208 nm; IR ($CHCl_3$) ν_{max} 3440, 1710, 1120 cm^{-1}; EI-MS m/z 520 (M^+ + 2, 2%), 518 (M^+, 3), 146 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{26}N_2O_6Cl_3$ 519.0856, found 519.0829; CD $\Delta\epsilon$ nm (c 0.19 mmol/L, MeOH, 20 °C) −5.03 (265), +9.44 (229), −36.2 (209). The diol **10**: an amorphous powder; ^{1}H-NMR ($CDCl_3$) δ 5.18 and 5.17 (1 H, each, d, J = 10.3 Hz, 3-H), 4.60 (1H, m, 5-H), 1.33 and 1.32 (3 H, each, d, J = 5.4 Hz, 18-H); UV (MeOH) λ_{max} 285, 223 nm; IR ($CHCl_3$) ν_{max} 3650, 1795, 1520, 1220 cm^{-1}; EI-MS m/z 504 (M^+ + 2, 5%), 502 (M^+, 4), 131 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{25}N_2O_5Cl_3$ 502.0829, found 502.0822.

Preparation of the Oxindole 11 from the Diol 10. A solution of OsO_4 (39 mg, 0.150 mmol) in dry THF was added dropwise to a stirred mixture of the diol **10** (62.9 mg, 0.125 mmol), dry THF (1 mL), and dry pyridine (1 mL) at −18 °C and the mixture was stirred at room temperature for 2 h. Aqueous sodium hydrogen sulfite (5 mmol) was added to the mixture and the mixture was then stirred at room temperature for 15 h. Water was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with 1 N HCl solution and brine, dried ($MgSO_4$), and evaporated. The residue was separated by MPLC with ethyl acetate–hexane (9:1) to afford the oxindole **11** (31 mg, 47%) and the starting material **10** (12.4 mg, 20% recovery).

Preparation of the Orthoester from the Diol 11. Pyridinium p-toluenesulfonate (197 mg, 0.789 mmol) and trimethyl orthoformate (0.86 mL, 7.87 mmol) were added to a solution of **11** (818 mg, 1.57 mmol) in dry THF (12 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The solution was passed through a short column of silica gel with ethyl acetate–hexane (1:1) to give the orthoester (813 mg, 92%) as an amorphous powder: ^{1}H-NMR ($CDCl_3$) δ 5.80, 5.79, 5.76, and 5.73 (1 H, each, s, C*H*OMe), 3.38, 3.37, and 3.34 (3 H, each, s, OMe); UV (MeOH) λ_{max} 252, 209 nm; IR ($CHCl_3$) ν_{max} 3440, 1720, 1440, 1130 cm^{-1}; FAB-MS (NBA + NaCl) m/z 485 (M^+ − 75, 88%), 483 (M^+ − 77, 90), 154 (100), 136 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{22}N_2O_4Cl_3$ 483.0645, found 483.0653.

Preparation of the Olefinic Compound 12 from the Orthoester. A solution of the orthoester (1.79 g, 3.19 mmol) in acetic anhydride (20 mL) was refluxed under argon for 3 h. After the addition of cold water, the reaction mixture was basified with aqueous NH_4OH and the whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in methanol (15 mL), and 5% KOH solution (1 mL) was added to the solution. The mixture was stirred at room temperature for 2 h. After evaporation of methanol, the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with ethyl acetate–hexane (1:2) to give the olefinic compound **12** (1.26 g, 81%) as an amorphous powder: ^{1}H-NMR ($CDCl_3$) δ 5.65 and 5.63 (1 H, each, q, J = 7.0 Hz, 19-H), 1.77 and 1.76 (3 H, each, d, J = 7.0 Hz, 18-H); UV (MeOH) λ_{max} 249, 206 nm; IR ($CHCl_3$) ν_{max} 3440, 2925, 1710, 1420, 1130 cm^{-1}; FAB-MS m/z 487 (M^+ + 3, 100%), 485 (M^+ + 1, 96), 337 (22), 154 (90), 136 (64); high

resolution FABMS (NBA) calcd for $C_{22}H_{24}N_2O_4Cl_3$ 485.0801, found 485.0788.

Preparation of the Ene Carbamate 13 from 12. Trimethylsilyl chloride (989 μL, 7.80 mmol) was added to a stirred mixture of compound **12** (1.26 g, 2.60 mmol) and sodium iodide (1.16 g, 7.80 mmol) in dry acetonitrile (20 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. A cold 5% aqueous sodium sulfite solution was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with ethyl acetate–hexane (1:1) to give the ene carbamate **13** (1.18 g, 94%) as an amorphous powder: ^1H NMR ($CDCl_3$) δ 6.52 (1 H, s, 21-H), 3.76 and 3.75 (1 H, each, d, J = 7.2 Hz, 3-H), 1.15 and 1.14 (3 H, each, t, J = 7.5 Hz, 18-H); UV (MeOH) λ_{max} 228, 207 nm; IR ($CHCl_3$) ν_{max} 3425, 1710, 1620, 1420, 1120 cm^{-1}; FAB-MS (NBA) m/z 487 (M^+ + 3, 92%), 485 (M^+ + 1, 100), 146 (47); high resolution FABMS (NBA) calcd for $C_{22}H_{24}N_2O_4Cl_3$ 485.0801, found 485.0788.

Osmylation of the Ene Carbamate 13. A solution of osmium tetraoxide (448 mg, 1.72 mmol) in dry THF was added to a solution of compound **13** (475 mg, 0.978 mmol) in a mixture of dry THF (5 mL) and dry pyridine (5 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. An aqueous sodium hydrogen sulfite (0.039 mol) solution was added to the mixture and the mixture was then stirred at room temperature for 15 h. Water was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with 1 N HCl solution and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with ethyl acetate–hexane (11:8) to afford a mixture of the aldehyde and the diol (416 mg, 82%). Only the aldehyde could be obtained as a pure state for characterization. The aldehyde: amorphous powder; ^1H NMR ($CDCl_3$) δ 9.49 and 9.46 (1 H, each, s, 21-H), 6.66 (1 H, d, J = 10.0 Hz, N_b-H), 4.34 (1 H, d, J = 10.5 Hz, 17-H), 4.08 (1 H, dd, J = 10.5, 4.4 Hz, 17-H), 3.70 (1 H, d, J = 8.0 Hz, 3-H), 2.10 (1 H, dq, J = 14.2, 7.2 Hz, 19-H), 1.77 (1 H, dq, J = 14.2, 7.2 Hz, 19-H), 0.84 (3 H, t, J = 7.2 Hz, 18-H); UV (MeOH) λ_{max} 250, 205 nm; IR ($CHCl_3$) ν_{max} 3450, 2950, 1730, 1120 cm^{-1}; FAB-MS (NBA) m/z 520 (M^+ + 2, 18%), 518 (M^+, 17), 503 (100), 501 (100), 473 (100), 471 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{25}N_2O_6Cl_3$ 518.0778, found 518.0793.

$NaBH_4$ Reduction of the Aldehyde and the Diol. Sodium borohydride (100 mg, 2.64 mmol) was added to a solution of a mixture of the aldehyde and the diol (343 mg, 0.659 mmol) in methanol (5 mL), and the mixture was stirred at room temperature for 2 h. Acetone was added to the reaction mixture and the mixture was stirred at room temperature for 15 min. After evaporation of the solvent, the residue was separated by silica gel flash column chromatography with 5% methanol–chloroform to afford the diol **14** (334 mg, 97%) as amorphous powder: ^1H NMR ($CDCl_3$) δ 7.59 (1 H, s, N_a-H), 6.96 (1 H, d, J = 10.0 Hz, N_b-H), 3.77 (1 H, d, J = 6.3 Hz, 3-H), 3.73 (1 H, d, J = 10.6 Hz, 21-H), 3.65 (1 H, d, J = 10.6 Hz, 21-H); UV (MeOH) λ_{max} 250, 207 nm; IR ($CHCl_3$) ν_{max} 3425, 3250, 2925, 1720, 1520, 1480, 1110 cm^{-1}; FAB-MS (NBA) m/z 523 (M^+ + 3, 65%), 521 (M^+ + 1, 60), 473 (26), 471 (26), 355 (45), 307 (34), 154 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{28}N_2O_6Cl_3$ 521.1013, found 521.1008.

Reduction of the Oxindole 14. Borane-methyl sulfide complex (182 μL, 1.97 mmol) was added to a solution of compound **14** (50 mg, 0.096 mmol) in dry THF (3 mL) at 0 °C, and the mixture was heated under reflux for 3 h. A cold 5% aqueous sodium hydrogen carbonate solution was added to the mixture and the whole was extracted with 3% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in methanol (1 mL) and trimethylamine N-oxide dihydrate (65 mg, 0.586 mmol) was added to the mixture. The reaction mixture was heated under reflux for 2 h. The solution was evaporated. The residue was passed through a short column of silica gel and purified by MPLC with ethyl acetate–hexane (1:4) to yield the indoline **15** (37.5 mg, 77%) as an amorphous powder: ^1H NMR ($CDCl_3$) δ 6.88 (1 H, d, J = 10.0 Hz, N_b-H), 4.87 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.60 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.50 (1 H, m, 5-H), 4.23 (1 H, d, J = 10.3 Hz, 17-H), 4.02 (1 H, d, J = 8.0 Hz, 3-H), 3.90 (1 H, dd, J = 10.3, 4.9 Hz, 17-H), 3.61 (1 H, d, J = 10.6 Hz, 21-H), 3.57 (1 H, d, J = 10.6 Hz, 21-H), 3.21 (1 H, d, J = 9.0 Hz, 2-H), 3.17 (1 H, d, J = 9.0 Hz, 2-H); UV (MeOH) λ_{max} 295, 243, 206 nm; IR ($CHCl_3$) ν_{max} 3375, 2975, 2950, 1740, 1120 cm^{-1}; EI-MS m/z 508 (M^+ + 2, 21%), 506 (M^+, 23), 167 (32), 130 (100); high resolution FABMS (NBA) calcd for $C_{22}H_{30}N_2O_5Cl_3$ 507.1220, found 507.1214.

Preparation of the N_a-Methoxyoxindole 16. Sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$, 29.0 mg, 0.089 mmol) and urea–hydrogen peroxide addition compound ($H_2NCONH_2 \cdot H_2O_2$, 278 mg, 2.96 mmol) were added to a solution of compound **15** (150 mg, 0.296 mmol) in 10% aqueous methanol (5.5 mL) and the mixture was stirred at the room temperature for 2 h. After the addition of further $H_2NCONH_2 \cdot H_2O_2$, (278 mg, 2.96 mmol), the reaction mixture was stirred at room temperature for 2 h. Saturated NH_4Cl solution was added to the mixture and the whole was extracted with 3% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in methanol (2 mL). A ether solution of diazomethane (0.4 mL) was added to a solution at 0 °C and the mixture was stirred at room temperature for 1 h. After the evaporation of the solvent, the residue was crystallized from AcOEt and the mother liquid was further purified by MPLC with 3% methanol–chloroform to afford altogether 100 mg (61%) of the N_a-methoxy compound **16**: mp 247–249 °C (AcOEt); ^1H NMR ($CDCl_3$) δ 7.01 (1 H, d, J = 9.7 Hz, N_b-H), 4.84 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.55 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.41 (1 H, m, 5-H), 4.28 (1 H, d, J = 10.3 Hz, 17-H), 4.00 (1 H, dd, J = 10.3, 4.2 Hz, 17-H), 3.99 (3 H, s, OMe), 3.75 (1 H, d, J = 7.3 Hz, 3-H), 3.75 (1 H, d, J = 10.5 Hz, 21-H), 3.63 (1 H, d, J = 10.5 Hz, 21-H); UV (MeOH) λ_{max} 253, 207 nm; IR (KBr) ν_{max} 3450, 2950, 1740, 1710, 1520, 1220 cm^{-1}; EI-MS m/z 552 (M^+ + 2, 1%), 550 (M^+, 1), 503 (17), 501 (16), 485 (17), 483 (15), 176 (74), 144 (100); high resolution FABMS (glycerol) calcd for $C_{23}H_{30}N_2O_7Cl_3$ 511.1118, found 511.1111.

Preparation of the Epoxide 17. Method A. nBu_4NHSO_4 (3.7 mg, 0.011 mmol) and 20% aqueous K_2CO_3 were added to a solution of compound **16** (12 mg, 0.022 mmol) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 10 min. Mesyl chloride (12.5 μL, 0.033 mmol) was added to a reaction mixture and the mixture was stirred at room temperature for 1 h. A cold saturated sodium hydrogen carbonate solution was added to the mixture and the whole was extracted with 3% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was separated by MPLC with ethyl acetate-hexane (1:1) and then with 3% methanol–chloroform to afford the epoxide **17** (1.5 mg, 13%) and the starting material **16** (3 mg, 25% recovery). **Method B.** DEAD (2.8 μL, 0.027 mmol) was added to a mixture of the compound **16** (10 mg, 0.018 mmol) and PPh_3 (7.1 mg, 0.027 mmol) in dry THF (0.5 mL) at 0 °C and the mixture was stirred at room temperature for 3 h. After the addition of further DEAD (2.8 μL, 0.018 mmol) and PPh_3 (4.8 mg, 0.018 mmol) to the reaction mixture, the mixture was stirred at 50 °C for 12 h. Cold water was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was separated by MPLC with ethyl acetate–hexane (1:1) and then with 3% methanol–chloroform to afford the epoxide **17** (3.3 mg, 34%) and the starting material **16** (5.6 mg, 56% recovery). **Method C.** PBu_3 (33 μL, 0.054 mmol) and *N,N,N′,N′*-Tetramethylazodicarboxamide (TMAD, 7.8 mg, 0.054 mmol) were added to a solution of the compound **16** (20 mg, 0.036 mmol) in dry DMF (0.5 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. DMF was removed under reduced pressure and the residue was separated by MPLC with ethyl acetate–hexane (1:2) to afford the epoxide **17** (12 mg, 63%) and the starting material **16** (2 mg, 10% recovery). The epoxide **17**: an amorphous powder; ^1H NMR ($CDCl_3$) δ 7.39 (1 H, d, J = 7.5 Hz, 9-H), 7.33 (1 H, td, J = 7.6, 1.0 Hz, 11-H), 7.13 (1 H, td, J = 7.5, 1.2 Hz, 10-H), 7.00 (1 H, d, J = 7.6 Hz, 12-H), 5.90 (1 H, d, J = 9.5 Hz, N_b-H), 4..84 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.57 (1 H, d, J = 12.1 Hz, OCH_2CCl_3), 4.40 (1 H, m, 5-H), 4.29 (1 H, d, J = 10.2

Hz, 17-H), 4.04 (1 H, dd, J = 10.2, 4.2 Hz, 17-H), 4.00 (3 H, s, OMe), 3.71 (1 H, d, J = 7.6 Hz, 3-H), 3.05 (1 H, d, J = 3.9 Hz, 21-H), 2.77 (1 H, d, J = 13.7 Hz, 6-H), 2.72 (1 H, d, J = 3.9 Hz, 21-H), 2.68 (1 H, m, 16-H), 2.49 (1 H, ddd, J = 11.2, 8.5, 3.2 Hz, 15-H), 2.25 (1 H, dd, J = 14.4, 8.5 Hz, 14-H), 2.09 (1 H, dq, J = 14.5, 7.5 Hz, 19-H), 1.94 (1 H, ddd, J = 14.4, 11.2, 7.6 Hz, 14-H), 1.61 (1 H, dd, J = 13.7, 6.7 Hz, 6-H), 1.50 (1 H, dq, J = 14.5, 7.5 Hz, 19-H), 0.94 (3 H, t, J = 7.5 Hz, 18-H); ^{13}C NMR ($CDCl_3$) δ 172.6 (s, C-2), 71.3 (d, C-3), 54.8 (d, C-5), 33.4 (t, C-6), 59.7 (s, C-7), 127.3 (s, C-8), 123.1* (d, C-9), 126.5* (d, C-10), 126.4 (d, C-11), 107.3 (d, C-12), 138.9 (s, C-13), 22.2** (t, C-14), 32.3 (d, C-15), 38.7 (d, C-16), 74.3*** (t, C-17), 9.8 (q, C-18), 26.7** (t, C-19), 53.9 (s, C-20), 49.4 (t, C-21), 63.4 (q, OMe), 153.6 (s, CO), 71.3*** (t, OCH_2CCl_3), 95.6 (s, CCl_3) (*, **, *** Assignments bearing the same symbols may be interchanged.); UV (EtOH) λ_{max} 252, 202 nm; IR ($CHCl_3$) ν_{max} 3400, 2950, 1730, 1520, 1120 cm^{-1}; EI-MS m/z 534 (M^+ + 2, 1%), 532 (M^+, 1), 485 (8), 483 (7), 176 (46), 144 (100); high resolution FABMS (NBA) calcd for $C_{23}H_{28}N_2O_6Cl_3$ 533.1013, found 533.1013.

Preparation of Gelselegine (4). Zinc dust (614 mg, 9.3 mmol) was added to a solution of compound **17** (62 mg, 0.116 mmol) in acetic acid (1 mL) and the mixture was stirred at room temperature for 4 h. The reaction mixture was filtered and diluted with ice–water. The mixture was basified with cold aqueous NH_4OH and the whole was extracted with 5% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. After the residue was permitted to stand for 5 days at room temperature, it was purified by silica gel column chromatography with 3% methanol–chloroform (saturated NH_3) and then by MPLC with benzene–ethyl acetate–Et_2NH (8:0.3:0.5) to afford gelselegine (**4**) (21 mg, 50%): mp 172–173 °C (AcOEt); $[\alpha]_D$ −94.6° (c 0.48 in MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40 (1 H, d, J = 7.5 Hz, 9-H), 7.30 (1 H, td, J = 7.5, 1.0 Hz, 11-H), 7.13 (1 H, td, J = 7.5, 0.7 Hz, 10-H), 6.96 (1 H, d, J = 7.6 Hz, 12-H), 4.28 (1 H, dd, J = 11.0, 3.6 Hz, 17-H), 4.25 (1 H, dd, J = 11.0, 1.3 Hz, 17-H), 4.01 (3 H, s, OMe), 3.64 (1 H, m, 5-H), 3.54 (1 H, d, J = 6.6 Hz, 3-H), 3.41 (1 H, d, J = 10.0 Hz, 21-H), 3.17 (1 H, d, J = 10.0 Hz, 21-H), 2.70 (1 H, m, 16-H), 2.29 (1 H, d, J = 15.6 Hz, 14-H), 2.13 (1 H, dd, J = 16.1, 2.8 Hz, 6-H), 2.08 (1 H, ddd, J = 15.6, 10.5, 6.5 Hz, 14-H), 2.01 (1 H, dd, J = 16.1, 3.8 Hz, 6-H), 1.95 (1 H, m, 15-H), 1.94 (1 H, dq, J = 14.4, 7.5 Hz, 19-H), 1.88 (1 H, dq, J = 14.4, 7.5 Hz, 19-H), 0.90 (3 H, t, J = 7.5 Hz, 18-H); ^{13}C NMR ($CDCl_3$) δ 174.7 (s, C-2), 74.8 (d, C-3), 59.3 (d, C-5), 34.0 (t, C-6), 57.3 (s, C-7), 131.6 (s, C-8), 125.5 (d, C-9), 123.7 (d, C-10), 128.3 (d, C-11), 107.2 (d, C-12), 137.9 (s, C-13), 23.1 (t, C-14), 36.0 (d, C-15), 39.9 (d, C-16), 63.6 (t, C-17), 9.5 (q, C-18), 23.1 (t, C-19), 69.1 (s, C-20), 63.4 (t, C-21), 62.5 (q, OMe); UV (MeOH) λ_{max} 257, 208 nm; EI-MS m/z 358 (M^+, 0.4%), 357 (0.6), 328 (40), 327 (100), 297 (29), 296 (66); high resolution FABMS (NBA) calcd for $C_{20}H_{27}N_2O_4$ 359.1971, found 359.1977; CD $\Delta\epsilon$ nm (c 0.28 mmol/L, MeOH, 20 °C) −8.25 (260), +21.3 (228), −27.2 (205).

Preparation of Gelsenicine (6). Sodium periodate (5 mg, 0.025 mmol) was added to a solution of gelselegine (**4**) (6 mg, 0.017 mmol) in methanol (0.5 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h and at room temperature for 2 h. A cold 10% aqueous sodium carbonate solution was added to the reaction mixture and the whole was extracted with 3% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was separated by MPLC with 10% methanol–chloroform to afford gelsenicine (**6**) (3.5 mg, 64%): mp 169–171 °C (ether); ^{1}H NMR ($CDCl_3$) δ 7.53 (1 H, d, J = 7.0 Hz, 9-H), 7.25 (1 H, td, J = 7.5, 1.3 Hz, 11-H), 7.07 (1 H, td, J = 7.6, 1.0 Hz, 10-H), 6.87 (1 H, d, J = 7.9 Hz, 12-H), 4.40 (1 H, m, 5-H), 4.30 (1 H, dd, J = 11.0, 3.9 Hz, 17-H), 4.27 (1 H, dd, J = 11.0, 1.7 Hz, 17-H), 3.95 (3 H, s, OMe), 3.74 (1 H, dd, J = 4.7, 2.0 Hz, 3-H), 2.86 (1 H, t, J = 9.3 Hz, 15-H), 2.71 (1 H, dq, J = 17.1, 7.3 Hz, 19-H), 2.57 (1 H, m, 16-H), 2.41 (1 H, dq, J = 17.1, 7.3 Hz, 19-H), 2.40 (1 H, dd, J = 15.6, 5.0 Hz, 6-H), 2.39 (1 H, dd, J = 14.9, 2.2 Hz, 14-H), 2.29 (1 H, dd, J = 15.6, 2.2 Hz, 6-H), 2.13 (1 H, ddd, J = 14.9, 10.3, 4.6 Hz, 14-H), 1.29 (3 H, t, J = 7.3 Hz, 18-H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s, C-2), 74.9 (d, C-3), 72.5 (d, C-5), 37.7 (t, C-6), 55.8 (s, C-7), 132.3 (s, C-8), 124.7 (d, C-9), 123.3 (d, C-10), 128.0 (d, C-11), 106.6 (d, C-12), 138.1 (s, C-13), 25.7* (t, C-14), 42.5** (d, C-15), 39.8** (d, C-16), 62.1 (t, C-17), 10.0 (q, C-18), 27.0* (t, C-19), 184.4 (s, C-20), 63.3 (q, OMe) (*, ** Assignments bearing the same symbols may be interchanged.); UV (MeOH) λ_{max} 257, 207 nm; EI-MS m/z 326 (M^+, 55%), 295 (100), 150 (36), 122 (25); high resolution FABMS (NBA) calcd for $C_{19}H_{23}N_2O_3$ 327.1708, found 327.1704; CD $\Delta\epsilon$ nm (c 0.28 mmol/L, MeOH, 20 °C) −4.39 (262), +7.47 (235), −11.0 (205).

Preparation of Gelsedine (5). A solution of gelsenicine (**6**) (35 mg, 0 107 mmol) in ethanol (1 mL) was hydrogenated in the presence of platinum oxide (12 mg, 0.053 mmol) for 1 h at room temperature. The catalyst was filtered off, and the filtrate was evaporated. The residue was purified by silica gel column chromatography with ethyl acetate to afford gelsedine (**5**) (35 mg, quant.) as prisms: mp 172–175 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (1 H, dd, J = 7.7, 0.7 Hz, 9-H), 7.29 (1 H, td, J = 7.7, 1.2 Hz, 11-H), 7.13 (1 H, td, J = 7.6, 1.0 Hz, 10-H), 6.95 (1 H, br d, J = 7.7 Hz, 12-H), 4.34 (1 H, dd, J = 10.7, 4.1 Hz, 17-H), 4.26 (1 H, d, J = 10.8 Hz, 17-H), 4.00 (3 H, s, OMe), 3.68 (1 H, m, 5-H), 3.50 (1 H, d, J = 7.1 Hz, 3-H), 2.96 (1 H, m, 20-H), 2.48 (1 H, m, 16-H), 2.19 (1 H, dd, J = 15.4, 4.1 Hz 14-H), 2.16 (1 H, m, 15-H), 2.12 (1 H, dd, J = 15.8, 3.6 Hz, 6-H), 2.02 (1 H, dd, J = 15.8, 3.0 Hz, 6-H), 1.91 (1 H, ddd, J = 15.1, 10.3, 7.1 Hz, 14-H), 1.83 (1 H, m, 19-H), 1.71 (1 H, m, 19-H), 1.01 (3 H, t, J = 7.5 Hz, 18-H); ^{13}C NMR ($CDCl_3$) δ 174.4 (s, C-2), 74.5 (d, C-3), 59.7 (d, C-5), 33.8 (t, C-6), 57.3 (s, C-7), 131.7 (s, C-8), 125.3 (d, C-9), 123.6 (d, C-10), 128.1 (d, C-11), 107.1 (d, C-12), 137.9 (s, C-13), 21.2 (t, C-14)*, 34.6 (d, C-15), 41.7 (d, C-16), 63.8 (t, C-17), 12.0 (q, C-18), 21.4 (t, C-19)*, 65.5 (d, C-20), 63.3 (q, OMe); UV (EtOH) λ_{max} 257, 209 nm; CD $\Delta\epsilon$ nm (c 0.37 mmol/L, MeOH) −1.82 (277), −4.97 (260), +13.2 (228), −26.0 (210).

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Supplementary Material Available: ^{1}H NMR spectra for compounds **9**–**11**, cyclic orthoester derivative of **11**, **12**, **13**, the osmylation product of **13**, **14**–**17**, **4**, **6**, and **5** and ^{13}C NMR spectra for compounds **17**, **4**, **6**, and **5** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiilm version of the journal, and can be ordered from the ACS; see any current masthead page for information.