Synthesis of a Novel Gelsedine-type *Gelsemium* Alkaloid, Gelsemicine

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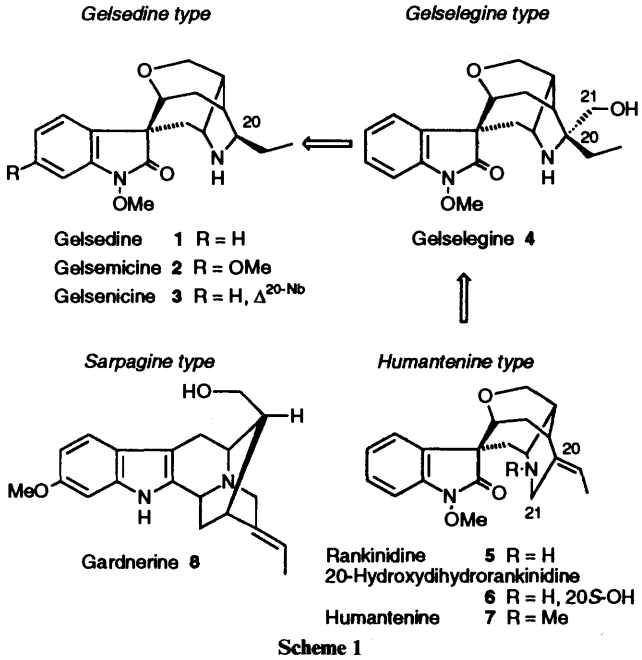
A *Gelsemium* alkaloid, gelsemicine is synthesized from a sarpagine-type indole alkaloid, gardnerine, *via* humantenine, gelselegine- and gelsenicine-type compounds.

The *Gelsemium* species, belonging to the family Loganiaceae, have been used as analgesic and antispasm agents in traditional folk medicine. Chemical investigation of the components of this plant has shown this genus to be a rich source of many skeletal types of monoterpenoid indole alkaloids having highly strained polycyclic structures.[1] Among them, an oxindole alkaloid, gelsemicine **2**, was first isolated from *Gelsemium sempervirens* Ait. as a minor constituent[2] and was later found in *Mostuea brunonis* Didr. var. *brunonis forma augustifolia*.[3] The molecular structure was determined by X-ray analysis using the hydroiodide of the N^b-methyl derivative.[4] The structures of the gelsedine-type oxindole alkaloids such as gelsedine **1**, gelsemicine **2** and gelsenicine **3**, are similar to those of humantenine-type alkaloids but lacking their C-21 carbon. Biogenetically, gelsedine-type alkaloids might be derived from corresponding humantenine-type oxindole alkaloids **5**–**7**. Recently, a new type of *Gelsemium* alkaloid, gelselegine **4** was isolated from *Gelsemium elegans* Benth,[5] which has a hydroxymethyl group at the C-20 position, which means that the C-21 carbon has rearranged to the *exo* position on the D-ring of the humantenine-type alkaloids. The oxidative bond cleavage of the 1,2-amino alcohol system in gelselegine **4** would give gelsenicine **3**. Therefore, gelselegine **4** can be considered to be a biogenetic intermediate between the humantenine-type alkaloids and gelsedine group (Scheme 1).

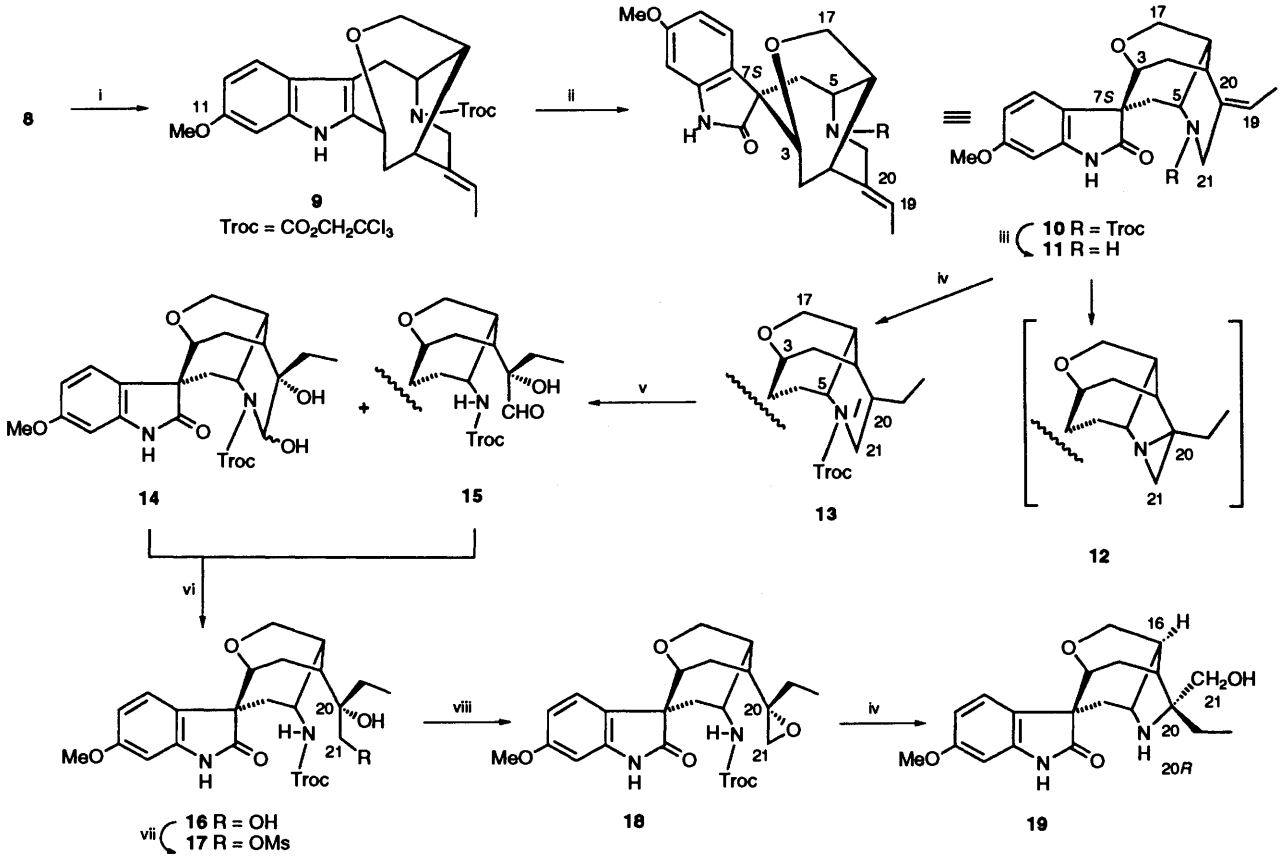


Scheme 1

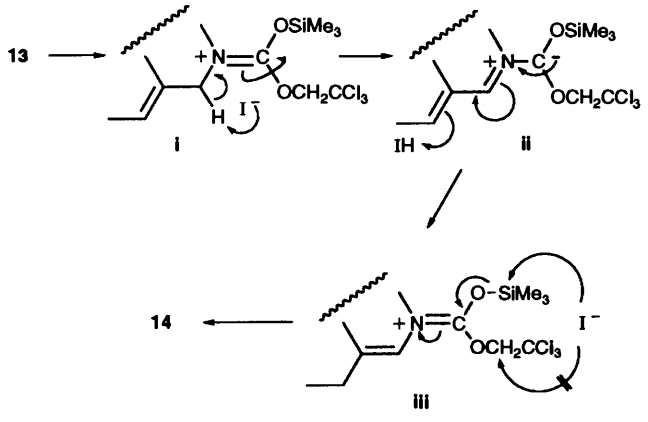
During chemical studies on the *Gelsemium* alkaloids,[6] we were interested in the synthesis of a novel oxindole alkaloid, gelsemicine **2** and, therefore, we considered a synthetic approach as indicated in Scheme 1.

Gardnerine **8**,[7] a major alkaloid of *Gardneria nutans*, was treated with 2,2,2-trichloroethyl chloroformate in aq. THF in the presence of a large excess of magnesium oxide to give the C/D ring-cleaved compound **9** (Scheme 2). This carbamate was regio- and stereo-selectively oxidized with 1 equiv. of osmium tetraoxide (OsO_4) in dry Py–dry THF at −70 °C to give the oxindole **10** which had the desired 7*S* configuration.[6j] The stereochemistry at C-7 was confirmed by a comparison of the CD spectrum with that of humantenine. In order to construct the gelselegine skeleton from the humantenine-type compound, bond formation between N^b and the C-20 position as well as bond cleavage between N^b and the C-21 position were required. Initial attempts to construct the aziridine ring (N^b–C-20–C-21) using the N^b-H derivative of compound **10** were unsuccessful. To reconstruct the D ring we utilized the C-19, -20 double bond in compound **10**. We found that treatment of compound **10** with trimethylsilyl chloride and sodium iodide in dry acetonitrile at room temperature resulted in alkene migration to afford the ene carbamate **13** in 97% yield. This unusual reaction was considered to occur *via* the siloxy immonium intermediate and conjugate immonium intermediates (Scheme 3). The double bond at the C-20, -21 position was oxidized again with OsO_4 (1 equiv.) in dry Py–dry THF to give the diol **14** and the aldehyde **15** in 84 and 15% yield, respectively. A mixture of the diol **14** and the aldehyde **15** was reduced with $NaBH_4$ in MeOH to give exclusively the diol **16**. The stereochemistry at the C-20 position in compounds **14**–**16** could be deduced using a Dreiding model analysis. Thus, OsO_4 should attack the double bond in **13** only from the less hindered convex side. The primary hydroxy group in the diol **16** was mesylated in 97% yield and the resultant mesylate **17** was converted into the epoxide **18** by treatment with potassium carbonate in MeOH in 93% yield. After removal of N^b-carbamate in compound **18** with Zn–AcOH, the resultant free amine was graudally transformed in 82% yield to the gelselegine-type compound **19** by standing at room temperature for 5 days. The primary amine attacked the epoxide at the C-20 position in a regio- and stereo-selective manner (5-*exo*-tetrahedral mode). The formation of a 20-hydroxydihydrorankinidine-type compound **6**, which would be derived by the 6-*endo*-tetrahedral mode, could not be observed. The ^1H and ^{13}C NMR spectra of compound **19** closely resembled those of gelselegine except for the signals of the oxindole moiety. The differential NOE experiment between 16-H and 21-H_2 suggested the desired 20*R* configuration. Thus, irradiation of 16-H (δ 2.73, m) led to 4% (δ 3.44, d, *J* 10.4) and 8% (δ 3.26, d, *J* 10.2) enhancement of 21-H_2. Other spectroscopic data (UV, IR, mass, HRMS and CD) also supported the structure of compound **19**.

Next, based on a biogenetic speculation, the C-21 carbon in compound **19** was removed by the oxidative cleavage of the 1,2-amino alcohol system by treatment with sodium periodate in MeOH to give the gelsenicine-type compound **20** in 41% yield (Scheme 4). In the ^{13}C NMR spectrum, the signal of C-20 in compound **20** was observed at δ 183.8. Catalytic



Scheme 2 *Reagents:* i, $ClCO_2CH_2CCl_3$, MgO, aq. THF; ii, OsO_4 (1 equiv.), dry Py–dry THF; iii, Zn, AcOH; iv, TMSCl, NaI, dry MeCN; v, OsO_4, dry Py–dry THF; vi, $NaBH_4$, MeOH; vii, MsCl, dry Py–dry CH_2Cl_2; viii, K_2CO_3, MeOH; iv, Zn, AcOH



Scheme 3

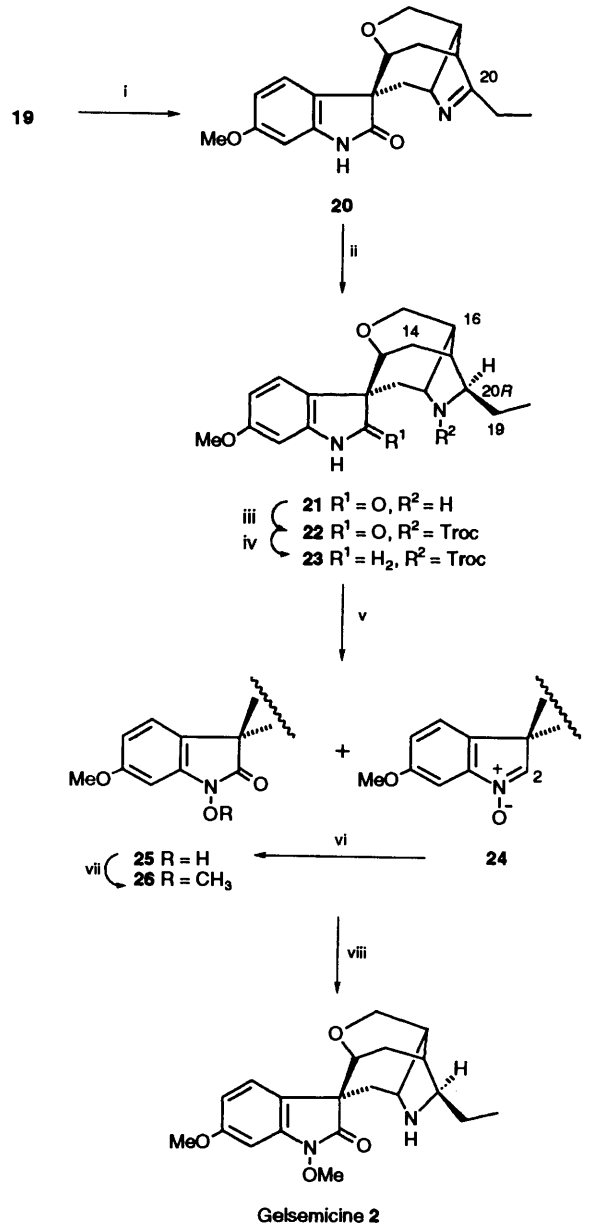
hydrogenolysis of the imine **20** (H_2, PtO_2, EtOH)[8] stereoselectively gave the gelsedine-type compound **21** in 98% yield. The stereochemistry at the C-20 position was unambiguously determined by differential NOE. By irradiation at one of the 19-H_2 (δ 1.72, m) and 20-H (δ 2.94, m), 4.5 and 5.9% enhancement of 14-Hα (δ 2.20, br d, J 15.4) and 16-H (δ 2.46, q like, J 4.5) were observed, respectively.

We next attempted the conversion of a oxindole moiety into an N^a-methoxyindole function to accomplish the gelsemicine synthesis. After protection of the free N^b group as the trichloroethyl carbamate, the lactam in the oxindole **22** was selectively reduced with excess borane–dimethyl sulfide complex in THF. The amine–borane complex formed in the last reduction reaction was decomposed by treatment with trimethylamine *N*-oxide[9] in MeOH to give the indoline **23** in 64% overall yield. The indoline **23** was treated with the urea hydrogen peroxide addition compound (H_2O_2·H_2NCONH_2, 15 equiv.) and sodium tungstate (Na_2WO_4·$2H_2O$, 0.6 equiv.)[6a] in aq. MeOH at room temperature to give the nitrone **24** and the hydroxamic acid **25** in 63 and 15% yield, respectively. In the ^1H NMR spectrum the signal for 2-H in compound **24** was observed at δ 7.68 and the signal of OH in compound **25** was observed at δ 10.13. The nitrone **24** was further oxidized with lead tetraacetate (1 equiv.)[10] in CH_2Cl_2 at $-15 \sim 0$ °C followed by treatment with potassium carbonate in MeOH to afford the hydroxamic acid **25** in 56% yield. The use of H_2O_2 as oxidant instead of $Pb(OAc)_4$ decreased the yield of hydroxamic acid **25**. The hydroxamic acid **25** was treated with diazomethane in MeOH to give the N^a-methoxyoxindole **26** in 65% yield. Finally, the protecting group on N^b was removed with Zn–AcOH to yield gelsemicine **2** {m.p. 161–164 °C, $[\alpha]_D^{26}$ −149 (*c* 0.1 in $CHCl_3$)}. All spectroscopic data (^1H, ^{13}C NMR, UV, IR, mass, HRMS and CD) supported the structure of synthetic gelsemicine **2**.

In conclusion, we report the first synthesis of the novel *Gelsemium* alkaloid, gelsemicine from the sarpagine-type alkaloid, gardnerine. This chemical conversion using a biomimetic approach includes unique stereoselective rearrangements and transformations.

Experimental

M.p.s 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 ethanol with a Hitachi U3400 spectrophotomer. ^1H NMR spectra were recorded on a JEOL JNM GSX400 (400 MHz) or a JEOL JNM A 500 (500 MHz) spectrometer with tetramethylsilane as



Scheme 4 *Reagents:* i, $NaIO_4$, MeOH; ii, H_2, PtO_2, EtOH; iii, $ClCO_2CH_2CCl_3$, dry Py–dry CH_2Cl_2; iv, BH_3·SMe_2, dry THF; $Me_3N{\rightarrow}O$·$2H_2O$, MeOH; v, H_2NCONH_2·H_2O_2, Na_2WO_4·$2H_2O$, aq. MeOH; vi, $Pb(OAc)_4$, CH_2Cl_2; K_2CO_3, MeOH; vii, CH_2N_2, MeOH; viii, Zn, AcOH

internal standard. *J* Values are given in Hz. ^{13}C NMR spectra were measured with a JEOL GSX400 (100.4 MHz) or a JEOL JNM A-500 (125.65 MHz) spectrometer with tetramethylsilane as internal standard. Mass spectra were taken with a Hitachi RMU-6E, a 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. Elemental analyses were measured with a Perkin-Elmer 240 elemental analyser. 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)]. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Compound **10** was prepared from gardnerine **8** according to the reported procedure.[6j]

Preparation of the Ene Carbamate **13** *from Compound* **10**.—Trimethylsilyl chloride (0.26 cm^3, 2.049 mmol) was added to a stirred mixture of compound **10** (345 mg, 0.669 mmol) and sodium iodide (306 mg, 2.041 mmol) in dry acetonitrile (9 cm^3) at 0 °C and the mixture was stirred at room temperature for 20 min. Cold 5% aq. sodium sulfite was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by silica gel flash column chromatography with ethyl acetate–hexane (2:3) to give the ene carbamate **13** (334 mg, 97%) as an amorphous powder (Found: M^+, 514.0824. $C_{23}H_{25}Cl_3N_2O_5$ requires *M*, 514.0829); λ_{max}(EtOH)/nm 292sh, 284sh and 217; ν_{max}($CHCl_3$)/cm^{-1} 3440, 1720, 1640, 1415, 1160, 1130 and 850; δ_H(500 MHz; $CDCl_3$) 6.52 (1 H, br s, 21-H), 3.801 and 3.799 (3 H, each s, OMe), 3.72 (d, *J* 6.1) and 3.70 (d, *J* 6.3) (1 H total, 3-H) and 1.15 and 1.14 (3 H, each t, *J* 7.4, 18-H_3); *m/z* 518 (M^+ + 4, 14%), 516 (M^+ + 2, 39), 514 (M^+, 39), 339 (21), 176 (100) and 163 (32). Gardnerine derivatives possessing a carbamate function in the molecule were often shown by the ^1H NMR spectra to occur as a mixture of rotation isomers.

Osmylation of the Ene Carbamate **13**.—Osmium tetraoxide (60 mg, 0.236 mmol) was added to a solution of compound **13** (110 mg, 0.214 mmol) in a mixture of dry tetrahydrofuran (THF) (2 cm^3) and dry pyridine (1 cm^3) at −15 °C. The mixture was stirred at −15–0 °C for 40 min. Aq. sodium hydrogen sulfite (443 mg in water, 3 cm^3) was added to the mixture and the mixture was then stirred at room temperature for 2 h. Water was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by MPLC with ethyl acetate–hexane (1:1) to afford the diol **14** (98 mg, 84%) and the aldehyde **15** (18 mg, 15%). Compound **14**: amorphous powder; λ_{max}(EtOH)/nm 293sh, 285sh, 259 and 215; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1710, 1640, 1310, 1120 and 845; δ_H(400 MHz; $CDCl_3$) 8.19 (1 H, s, N^a-H), 6.30 (1 H, br s, OH), 4.30 (1 H, d, *J* 10.8, 17-H), 4.11 (1 H, dd, *J* 10.8 and 4.9, 17-H), 3.80 (3 H, s, OMe), 3.71 (1 H, d, *J* 8.4, 3-H), 3.02 (1 H, s, OH) and 0.99 (3 H, t, *J* 7.5, 18-H_3); *m/z* 550 (M^+ + 2, 3%), 548 (M^+, 2), 339 (34), 337 (32), 176 (100) and 162 (51). Compound **15**: amorphous powder (Found: M^+, 548.0873. $C_{23}H_{27}Cl_3N_2O_7$ requires *M*, 548.0884); λ_{max}(EtOH)/nm 292sh, 285sh, 258 and 215; ν_{max}($CHCl_3$)/cm^{-1} 3470, 1750, 1655, 1530, 1145 and 840; δ_H(400 MHz; $CDCl_3$) 9.46 (1 H, d, *J* 1.5, 21-H), 7.73 (1 H, s, N^a-H), 4.32 (1 H, d, *J* 10.3, 17-H), 4.41 (1 H, d, *J* 0.9, OH), 4.07 (1 H, dd, *J* 10.3 and 4.4, 17-H), 3.81 (3 H, s, OMe), 3.67 (1 H, d, *J* 7.9, 3-H) and 0.84 (3 H, t, *J* 7.5, 18-H_3); *m/z* 550 (M^+ + 2, 4%), 548 (M^+, 4), 176 (100) and 162 (38).

$NaBH_4$ *Reduction of the Diol* **14** *and the Aldehyde* **15**.—Sodium borohydride (15 mg, 0.397 mmol) was added to a suspension of the diol **14** (43 mg, 0.078 mmol) and the aldehyde **15** (63 mg, 0.115 mmol) in methanol (1.5 cm^3) and the mixture was stirred at room temperature for 20 min. Water was added to the reaction mixture and the whole was extracted with 5% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was separated by MPLC with 3% methanol–chloroform to afford the diol **16** (110 mg, quant.) as needles, m.p. 162–164 °C (Found: C, 50.05; H, 5.6; N, 4.8. $C_{23}H_{29}Cl_3N_2O_7$ requires C, 50.1; H, 5.3; N, 5.1%); λ_{max}(EtOH)/nm 292sh, 285sh, 257 and 215; ν_{max}(KBr)/cm^{-1} 3660, 1720, 1700 and 1115; δ_H(500 MHz; $CDCl_3$) 8.72 (1 H, br s, N^a-H), 4.27 (1 H, d, *J* 10.2, 17-H), 4.00 (1 H, dd, *J* 10.2 and 4.1, 17-H), 3.80 (3 H, s, OMe), 3.73 (1 H, d, *J* 6.3, 3-H), 3.72 (1 H, m, 21-H), 3.60 (1 H, m, 21-H) and 0.86 (3 H, t, *J* 7.4, 18-H_3); *m/z* (FAB, NBA) 553 (M^+ + 3, 93%), 551 (M^+ + 1, 100), 460 (37), 217 (50), 176 (56), 120 (67) and 107 (94).

Mesylation of the Diol **16**.—Mesyl chloride (22 mm^3, 0.284 mmol) was added to a solution of compound **16** (131 mg, 0.237 mmol) in a mixture of dry pyridine (1.3 cm^3) and dry dichloromethane (1.3 cm^3) at 0 °C and the mixture was stirred at room temperature for 30 min. After the addition of further mesyl chloride (15 mm^3, 0.194 mmol) to the mixture at 0 °C the reaction mixture was stirred at room temperature for 30 min. Cold water was added to the mixture and the whole was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and then evaporated. The residue was separated by MPLC with 3% methanol–chloroform to afford the mesyl compound **17** (145 mg, 97%) as an amorphous powder; λ_{max}(EtOH)/nm 290sh, 279, 258 and 215; $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 1720, 1710, 1630, 1340 and 1110; δ_H(500 MHz; $CDCl_3$) 6.71 (1 H, d, *J* 9.8, N^b-H), 3.82 (3 H, s, OMe), 3.06 (3 H, s, OSO_2Me) and 0.93 (3 H, t, *J* 7.7, 18-H_3); *m/z* (FAB, thioglycerol + glycerol) 631 (M^+ + 3, 69%), 629 (M^+ + 1, 66), 628 (22), 454 (26), 437 (24), 185 (89), 176 (92), 162 (100) and 93 (69).

Preparation of the Epoxide **18**.—Potassium carbonate (125 mg, 0.904 mmol) was added to a solution of the mesyl compound **17** (70 mg, 0.111 mmol) in methanol (2 cm^3) at 0 °C and the mixture was stirred at the same temperature for 30 min. 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 then evaporated. The residue was separated by MPLC with ethyl acetate–hexane (3:2) to afford the epoxide **18** (55 mg, 93%) as prisms, m.p. 249–251 °C (Found: M^+, 532.0917. $C_{23}H_{27}Cl_3N_2O_6$ requires *M*, 532.0935); λ_{max}(EtOH)/nm 289sh, 280, 257 and 214; ν_{max}(KBr)/cm^{-1} 3400, 1710 and 1125; δ_H(500 MHz; $CDCl_3$) 5.89 (1 H, d, *J* 9.3, N^b-H), 4.28 (1 H, d, *J* 10.6, 17-H), 4.04 (1 H, dd, *J* 10.6 and 4.2, 17-H), 3.80 (3 H, s, OMe), 3.70 (1 H, d, *J* 8.4, 3-H), 2.72 (1 H, d, *J* 7.9, 21-H), 2.69 (1 H, d, *J* 7.9, 21-H) and 0.94 (3 H, t, *J* 7.6, 18-H_3); *m/z* 534 (M^+ + 2, 4%), 532 (M^+, 4), 176 (100), 175 (58) and 162 (23).

Preparation of the Gelselegine-type Compound **19**.—Zinc dust (250 mg, 3.824 mmol) was added to a solution of compound **18** (100 mg, 0.187 mmol) in acetic acid (5 cm^3) at room temperature and the mixture was stirred at the same temperature for 2.5 h. After the addition of further zinc dust (25 mg, 0.382 mmol) to the reaction mixture, the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and diluted with ice–water. The mixture was basified with cold aq. NH_4OH and the whole was extracted with 10% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. After the residue was left to stand for 5 days, it was purified by silica gel flash column chromatography with 5–10% methanol–chloroform to afford the gelselegine-type compound **19** (55 mg, 82%) as an amorphous powder (Found: M^+, 358.1893. $C_{20}H_{26}N_2O_4$ requires *M*, 358.1893); λ_{max}(EtOH)/nm 290sh, 267 and 217; $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1700, 1630, 1155 and 1120; δ_H(500 MHz; $CDCl_3$) 7.25 (1 H, d, *J* 8.8, 9-H), 6.59 (1 H, dd, *J* 8.4 and 2.3, 10-H), 6.42 (1 H, d, *J* 2.2, 12-H), 4.28 (1 H, dd, *J* 11.0 and 3.9, 17-H), 4.24 (1 H, dd, *J* 11.0 and 1.4, 17-H), 3.78 (3 H, s, OMe), 3.71 (1 H, br d, *J* 9.1, 5-H), 3.57 (1 H, d, *J* 6.3, 3-H), 3.44 (1 H, d, *J* 10.4, 21-H), 3.26 (1 H, d, *J* 10.2, 21-H), 2.73 (1 H, m, 16-H), 2.31 (1 H, d, *J* 15.4, 14-H), 1.99 (1 H, m, 15-H) and 0.91 (3 H, t, *J* 7.4, 18-H_3); δ_C(100.4 MHz; $CDCl_3$) 181.7 (s, C-2), 75.2 (d, C-3), 59.4 (d, C-5), 34.0 (t, C-6), 58.5 (s, C-7), 127.9 (s, C-8), 126.0 (d, C-9), 107.4 (d, C-10), 160.0 (s, C-11), 96.7 (d, C-12), 139.8 (s, C-13), 22.8* (t, C-14), 36.1 (d, C-15), 39.7 (d, C-16), 63.5 (t, C-17), 9.5 (q, C-18), 23.0* (t, C-19), 69.5 (s, C-20), 62.5 (t, C-21) and 55.5 (q, OMe). Assignments bearing the superscript * may be interchanged; *m/z* 358 (M^+, 3%), 340 (13), 327 (100) and 161 (11); CD $\Delta\varepsilon$/nm (*c* 0.28 mmol dm^{-3}, MeOH, 24 °C) −6.1 (264), +18.1 (235) and −18.9 (215).

$NaIO_4$ *Oxidation of the Amine* **19**.—A solution of sodium periodate (27 mg, 0.126 mmol) in water (0.6 cm^3) was added to a solution of compound **19** (14.9 mg, 0.042 mmol) in methanol (1.8 cm^3) at −20 °C and the mixture was stirred at room temperature for 30 min. Cold 10% aq. sodium carbonate was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was separated by MPLC with 5% methanol–chloroform to afford the imine **20** (5.6 mg, 41%) as an amorphous powder [Found: MH^+, 327.1707. $C_{19}H_{23}N_2O_3$ requires *M*H, 327.1708 (FAB, NBA)]; λ_{max}(EtOH)/nm 292sh, 282sh, 261 and 215; $\nu_{max}(CHCl_3)/cm^{-1}$ 3430, 1705, 1630, 1155 and 1150; δ_H(500 MHz; $CDCl_3$) 8.34 (1 H, s, N^a-H), 7.37 (1 H, d, *J* 8.2, 9-H), 6.53 (1 H, dd, *J* 8.2 and 2.2, 10-H), 6.36 (1 H, d, *J* 2.2, 12-H), 4.39 (1 H, m, 5-H), 4.29 (1 H, dd, *J* 11.0 and 3.0, 17-H), 4.27 (1 H, dd, *J* 11.0 and 1.6, 17-H), 3.77 (3 H, s, OMe), 3.74 (1 H, dd, *J* 4.7 and 2.2, 3-H), 2.85 (1 H, t, *J* 9.4, 15-H), 2.67 (1 H, dq, *J* 16.8 and 7.4, 21-H), 2.55 (1 H, m, 16-H), 2.41 (1 H, dq, *J* 16.8 and 7.4, 21-H), 2.34 (1 H, dd, *J* 15.7 and 4.7, 6-H), 2.33 (1 H, m, 14-H), 2.28 (1 H, dd, *J* 15.7 and 2.5, 6-H) and 1.30 (3 H, t, *J* 7.4, 18-H_3); δ_C(125.65 MHz; $CDCl_3$) 178.7 (s, C-2), 75.4 (d, C-3), 72.6 (d, C-5), 38.0 (t, C-6), 57.3 (s, C-7), 128.8 (s, C-8), 125.4 (d, C-9), 107.1 (d, C-10), 159.8 (s, C-11), 96.0 (d, C-12), 140.0 (s, C-13), 26.8* (t, C-14), 42.5† (d, C-15), 39.8† (d, C-16), 62.1 (t, C-17), 10.0 (q, C-18), 25.7* (t, C-19), 183.8 (s, C-20) and 55.4 (q, OMe). Assignments bearing the same superscript (* or †) may be interchanged; *m/z* 326 (M^+, 100%), 151 (54) and 122 (56).

Hydrogenolysis of the Imine **20**.—A solution of compound **20** (114 mg, 0.349 mmol) in ethanol (9 cm^3) was hydrogenated in the presence of platinum oxide (47 mg, 0.207 mmol) for 1 h at room temperature. The catalyst was filtered off, and the filtrate was evaporated. The residue was purified by silica gel flash column chromatography with 1–3% methanol–chloroform (sat. NH_3) to afford compound **21** (113 mg, 98%) as prisms, m.p. 248 °C (decomp.) (Found: C, 69.3; H, 7.35; N, 8.4. $C_{19}H_{24}N_2O_3$ requires C, 69.5; H, 7.4; N, 8.5%); λ_{max}(EtOH)/nm 291sh, 274 and 218; ν_{max}(KBr)/cm^{-1} 3440, 1685, 1640, 1160 and 1120; δ_H(500 MHz; $CDCl_3$) 7.25 (1 H, d, *J* 8.3, 9-H), 6.57 (1 H, dd, *J* 8.3 and 2.5, 10-H), 6.39 (1 H, d, *J* 2.2, 12-H), 4.34 (1 H, dd, *J* 10.7 and 4.2, 17-H), 4.25 (1 H, d, *J* 10.7, 17-H), 3.77 (3 H, s, OMe), 3.67 (1 H, m, 5-H), 3.53 (1 H, d, *J* 6.8, 3-H), 2.95 (1 H, m, 20-H), 2.46 (1 H, m, 16-H), 2.22 (1 H, br d, *J* 15.1, 14-H), 2.15 (1 H, m, 15-H), 2.08 (1 H, dd, *J* 15.9 and 3.4, 6-H), 2.03 (1 H, dd, *J* 15.9 and 2.2, 6-H), 1.88 (1 H, ddd, *J* 15.3, 10.7 and 7.0, 14-H), 1.78 (1 H, m, 19-H), 1.71 (1 H, m, 19-H) and 1.00 (3 H, t, *J* 7.5, 18-H_3); δ_C(125.65 MHz; $CDCl_3$) 182.2 (s, C-2), 75.0 (d, C-3), 59.5 (d, C-5), 34.2 (t, C-6), 58.6 (s, C-7), 128.4 (s, C-8), 126.0 (d, C-9), 107.2 (d, C-10), 159.8 (s, C-11), 96.9 (d, C-12), 140.3 (s, C-13), 21.0 (t, C-14), 34.6 (d, C-15), 41.7 (d, C-16), 63.9 (t, C-17), 12.0 (q, C-18), 21.4 (t, C-19), 65.2 (d, C-20) and 55.5 (q, OMe); *m/z* 328 (M^+, 97%) and 152 (100); CD $\Delta\varepsilon$/nm (*c* 0.27 mmol dm^{-3}, MeOH, 22 °C) −29.4 (213), +25.3 (235) and −7.7 (264).

Preparation of the Carbamate **22**.—2,2,2-Trichloroethyl chloroformate (15 mm^3, 0.109 mmol) was added to a solution of compound **21** (30 mg, 0.091 mmol) in a mixture of dry pyridine (0.3 cm^3) and dry dichloromethane (0.15 cm^3) and the mixture was stirred at room temperature for 1 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 then evaporated. The residue was purified by MPLC with ethyl acetate–hexane (2:3) to afford the carbamate **22** (46 mg, quant.) as an amorphous powder [Found: MH^+, 503.0899. $C_{22}H_{26}Cl_3N_2O_5$ requires *M*H, 503.0907 (FAB, NBA)]; λ_{max}(EtOH)/nm 292sh, 281sh, 260 and 215; $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 and 1120; δ_H(500 MHz; $CDCl_3$) 9.29 and 8.84 (1 H, each

s, N^a-H), 3.81 and 3.80 (3 H, each s, OMe) and 0.91 (3 H, t, *J* 7.6, 18-H_3); *m/z* 504 (M^+ + 2, 13%), 502 (M^+, 11), 189 (35) and 176 (100).

Reduction of the Carbamate **22**.—Borane–methyl sulfide complex (10.0 mol dm^{-3} solution in THF; 0.36 cm^3, 3.60 mmol) was added to a solution of compound **22** (90 mg, 0.179 mmol) in dry THF (2 cm^3) at 0 °C and the mixture was heated under reflux for 6 h. Cold 10% aq. sodium carbonate was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was dissolved in methanol (3 cm^3) and trimethylamine *N*-oxide dihydrate (100 mg, 0.900 mmol) was added to the mixture. The reaction mixture was heated under reflux for 2 h. Cold 10% aq. sodium carbonate was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by MPLC with ethyl acetate–hexane (1:3) to yield the indoline **23** (58 mg, 64%) as an amorphous powder [Found: M^+, 488.1038. $C_{22}H_{27}Cl_3N_2O_4$ requires *M*, 488.1036 (FAB, NBA)]; λ_{max}(EtOH)/nm 297, 238sh and 208; ν_{max}($CHCl_3$)/cm^{-1} 3400, 1705 and 1125; δ_H(500 MHz; $CDCl_3$) 4.00 (1 H, d, *J* 5.6, 3-H), 3.74 (3 H, s, OMe), 3.57 and 3.23 (each 1 H, d, *J* 8.8, 2-H_2) and 0.91 (3 H, t, *J* 7.5, 18-H_3); *m/z* 490 (M^+ + 2, 38%), 488 (M^+, 49), 330 (43), 328 (40), 160 (100) and 137 (37).

Oxidation of the Indoline **23**.—Sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$, 17.8 mg, 0.054 mmol) and urea hydrogen peroxide addition compound ($H_2NCONH_2 \cdot H_2O_2$, 124 mg, 1.318 mmol) were added to a suspension of compound **23** (43 mg, 0.088 mmol) in 10% aq. methanol (1.65 cm^3) at 0 °C and the mixture was stirred at room temperature for 3 h. Cold water was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by MPLC with ethyl acetate–hexane (2:3 to 2:1) to afford the nitrone **24** (28 mg, 63%) and the hydroxamic acid **25** (7 mg, 15%). Compound **24**: amorphous powder [Found: MH^+, 503.0899. $C_{22}H_{26}N_2O_5Cl_3$ requires *M*H, 503.0907 (FAB, NBA)]; λ_{max}(EtOH)/nm 276, 235sh, 228sh and 218; ν_{max}($CHCl_3$)/cm^{-1} 3350, 1725, 1630 and 1110; δ_H(500 MHz; $CDCl_3$) 7.68 (1 H, s, 2-H), 3.87 (3 H, s, OMe), 3.64 (1 H, d, *J* 5.4, 3-H) and 0.93 (3 H, t, *J* 7.5, 18-H_3); *m/z* 504 (M^+ + 2, 8%), 502 (M^+, 9), 328 (40), 326 (42), 176 (100), 133 (83), 131 (76) and 95 (58). Compound **25**: amorphous powder [Found: MH^+, 519.0851. $C_{22}H_{26}Cl_3N_2O_6$ requires *M*H, 519. 0856. (FAB, NBA)]; λ_{max}(EtOH)/nm 294sh, 287 and 219; ν_{max}($CHCl_3$)/cm^{-1} 3300, 1700, 1630 and 1120; δ_H(500 MHz; $CDCl_3$) 10.13 (1 H, s, OH), 3.85 and 3.83 (3 H, each s, OMe) and 0.47 (t, *J* 7.5) and 0.39 (t, *J* 7.2) (3 H total, 18-H_3); *m/z* 520 (M^+ + 2, 14%), 518 (M^+, 14), 191 (68), 133 (63), 131 (64), 97 (61) and 95 (100).

Oxidation of the Nitrone **24**.—Lead tetraacetate (5.6 mg, 0.011 mmol) was added to a solution of compound **24** (5.5 mg, 0.011 mmol) in dry dichloromethane (0.2 cm^3) at −15 °C and the mixture was stirred for 4 h at −15–0 °C. Cold water was added to the mixture and the whole was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was dissolved in methanol (0.2 cm^3) and potassium carbonate (7.5 mg, 0.054 mmol) was added to the solution at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Cold aq. HCl (1 mol dm^{-3}) was added to the mixture and the whole was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by silica gel pencil-column chromatography with ethyl acetate–hexane (1:1) to give the hydroxamic acid **25** (3.2 mg, 56%).

Methylation of the Hydroxamic Acid **25**.—A diethyl ether solution of diazomethane (0.6 cm^3) was added to a solution of compound **25** (12.8 mg, 0.025 mmol) in methanol (0.5 cm^3) at 0 °C and the mixture was stirred at room temperature for 1.5 h. Cold water was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by MPLC with ethyl acetate–hexane (1:2) to afford the N^a-methoxy compound **26** (8.5 mg, 65%) as an amorphous powder [Found: MH^+, 533.1018. $C_{23}H_{28}N_2O_6Cl_3$ requires *M*H, 533.1013 (FAB, NBA)]; λ_{max}(EtOH)/nm 292sh, 286 and 217; ν_{max}($CHCl_3$)/cm^{-1} 3400, 1715, 1635, 1410 and 1120; δ_H(500 MHz; $CDCl_3$) 3.95 (3 H, s, N^a-OMe), 3.82 (3 H, s, OMe) and 0.89 (3 H, t, *J* 7.5, 18-H_3); *m/z* 534 (M^+ + 2, 5%), 532 (M^+, 5), 174 (61), 133 (81), 131 (87), 97 (60) and 95 (100).

Preparation of Gelsemicine **2**.—Zinc dust (25 mg, 0.382 mmol) was added to a solution of compound **26** (10.6 mg, 0.019 mmol) in acetic acid (0.8 cm^3) at room temperature and the mixture was stirred at the same temperature for 2 h. After the addition of further zinc dust (25 mg, 0.382 mmol) to the reaction mixture, the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered and diluted with ice–water. The mixture was basified with cold aq. NH_4OH and the whole was extracted with 10% methanol–chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by silica gel pencil-column chromatography with 15–30% methanol–chloroform to afford gelsemicine **2** (7 mg, quant.) as prism, m.p. 161–164 °C; $[\alpha]_D^{26}$ −149 (*c* 0.1 in $CHCl_3$) {lit.,[11] $[\alpha]_D^{25}$ −142 (*c* 0.945 in $CHCl_3$)} [Found: MH^+, 359.1966. $C_{20}H_{27}N_2O_4$ requires *M*H, 359.1971 (FAB, NBA)]; λ_{max}(EtOH)/nm 292sh, 284 and 219; δ_H(500 MHz; $CDCl_3$) 7.29 (1 H, d, *J* 8.3, 9-H), 6.63 (1 H, dd, *J* 8.3 and 2.5, 10-H), 6.54 (1 H, d, *J* 2.4, 12-H), 4.32 (1 H, dd, *J* 10.9 and 4.0, 17-H), 4.23 (1 H, d, *J* 10.8, 17-H), 3.99 (3 H, s, N^a-OMe), 3.83 (3 H, s, OMe), 3.75 (1 H, br d, *J* 9.5, 5-H), 3.49 (1 H, d, *J* 6.8, 3-H), 3.03 (1 H, m, 20-H), 2.50 (1 H, m, 16-H), 2.18 (1 H, m, 15-H), 2.17 (1 H, br d, *J* 14.2, 14-H), 2.10 (1 H, dd, *J* 16.1 and 3.7, 6-H), 2.01 (1 H, dd, *J* 16.1 and 2.9, 6-H), 1.93 (1 H, ddd, *J* 15.9, 11.0 and 7.0, 14-H), 1.85 (1 H, m, 19-H), 1.73 (1 H, m, 19-H) and 1.01 (3 H, t, *J* 7.5, 18-H_3); δ_C(125.65 MHz; $CDCl_3$) 175.0 (s, C-2), 74.9 (d, C-3), 59.5 (d, C-5), 34.0 (t, C-6), 56.8 (s, C-7), 123.5 (s, C-8), 126.1 (d, C-9), 108.2 (d, C-10), 160.2 (s, C-11), 94.6 (d, C-12), 139.0 (s, C-13), 21.2 (t, C-14), 34.5 (d, C-15), 41.5 (d, C-16), 63.8 (t, C-17), 11.9 (q, C-18), 21.3 (t, C-19), 65.3 (s, C-20), 63.5 (q, N^a-OMe) and 55.6 (q, OMe); *m/z* (FAB, NBA) 359 (M^+ + 1, 100%), 328 (8), 307 (11), 154 (36) and 136 (24); CD $\Delta\varepsilon$/nm (*c* 0.45 mmol dm^{-3}, MeOH, 22 °C) −5.4 (269), +20.1 (236) and −22.3 (216).

Acknowledgements

We are grateful to Mrs. H. Seki, Miss R. Hara and Mr. T. Kuramochi in the Analytical Center of Chiba University for measurement of spectral data and elemental analysis.

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Paper 4/01180E
Received 28*th February* 1994
Accepted 14*th March* 1994