Pergamon

Tetrahedron Vol. 50, No. 41, pp. 11813-11820, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00740-3

A Biomimetic Synthesis of a New Skeletal *Gelsemium* Alkaloid, 11-Methoxy-19(*R*)-hydroxygelselegine

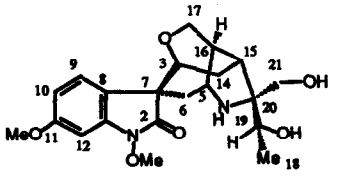
Hiromitsu Takayama, Mariko Kitajima and Shin-ichiro Sakai*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263, Japan

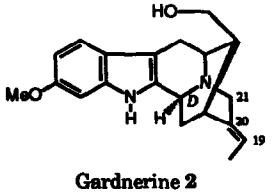
Abstract: Based on a suggested biogenetic sequence, a sarpagine-type indole alkaloid, gardnerine (**2**), was stereoselectively converted to a new skeletal type *Gelsemium* alkaloid, 11-methoxy-19(*R*)-hydroxygelselegine (**1**), via a biogenetically hypothetical aziridine intermediate (**17**).

Introduction

Biomimetic synthesis (or biogenetic-type synthesis) has been employed as one of the useful strategies for natural product synthesis, because this method has enabled one to attain overall efficiency of the synthetic scheme and to evaluate the mechanistic validity of a key step in the hypothetical biogenetic route. More than forty monoterpenoid indole alkaloids including six skeletal types have been isolated from the *Gelsemium* plants (Loganiaceae),[1] and their plausible biogenetic route was proposed based on the relationship of the chemical structures of the emerged alkaloids.[1a,2] Up to now, many kinds of *Gelsemium* alkaloids belonging to the sarpagine-,[3] koumine-,[4] humantenine-,[5] and gelsedine-groups[6] were synthesized in a biomimetic manner based on the suggested biogenetic sequence. In 1990, Cordell *et al.* found a new skeletal type of *Gelsemium* alkaloid, 11-methoxy-19(*R*)-hydroxygelselegine (**1**), from *G. elegans* Benth.,[7] the original plants of Chinese traditional medicine "Kou-Wen".[1b] We have planned the synthesis of this structurally unique alkaloid, whose C21 carbon is rearranged to the *exo* position of the D-ring in the common monoterpenoid indole alkaloids.



11-Methoxy-19(*R*)-hydroxygelselegine **1**

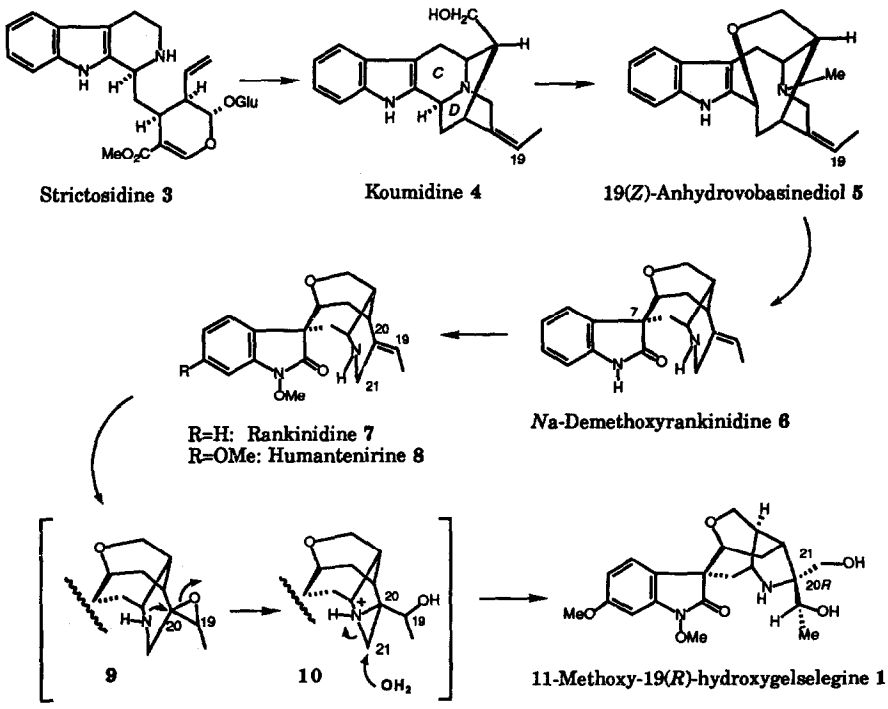


Gardnerine **2**

Results and Discussion

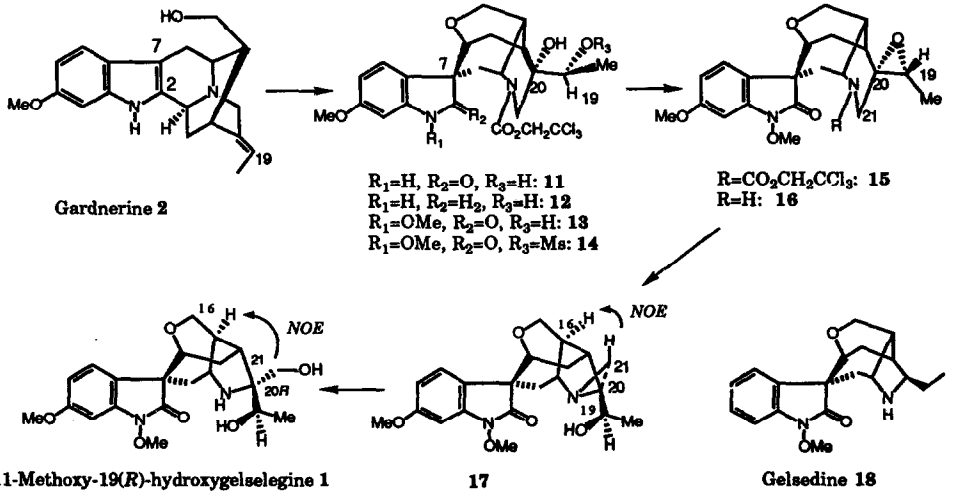
From a biogenetic point of view, a sarpagine-type indole alkaloid, koumidine (**4**), would be generated from strictosidine (**3**), which is an important pivotal intermediate to many kinds of monoterpenoid indole alkaloids.[8] Next, *via* the C/D-ring cleavage in (**4**) and subsequent oxidative transformation, the humantenine-type oxindole alkaloid, such as *N*a-demethoxyrankinidine (**6**),[9] would be produced. By introduction of an oxygen function onto the *N*a position, alkaloids (**7** and **8**) having an *N*a-methoxyoxindole function, which is one of the characteristics of *Gelsemium* alkaloids, would be formed. In the next stage, the double bond at the C19-20 position would be oxidized to form the epoxy derivative (**9**), and by the subsequent attack of the nitrogen (*N*b) to the C20 epoxy carbon, an aziridinium intermediate (**10**) would be generated.[7] Furthermore, a new skeletal type alkaloid (**1**), possessing a hydroxymethyl group at the C20 position, would arise from (**10**) by ring opening between the C21 and *N*b positions using water.

In order to realize the above mentioned biogenetic hypothesis using chemical means, a sarpagine-type indole alkaloid, gardnerine (**2**), one of the major constituents of *Gardneria nutans* (Loganiaceae) native to Japan,[10] was chosen as the starting material of the chemical transformation. The C/D-ring cleavage in **2** and stereoselective rearrangement to the oxindole derivative (**11**) was carried out according to the method previously reported in



Scheme I A Biogenetic Hypothesis for the Alkaloid 1

this journal.[11] The conversion of the oxindole in **11** into the *N*a-methoxyoxindole derivative was accomplished by applying a new procedure developed by us.[12] Thus, the lactam in **11** was chemoselectively reduced with a borane dimethylsulfide complex to give the indoline (**12**) in quantitative yield. The secondary amine (**12**) was then oxidized with the urea hydrogenperoxide addition complex in the presence of sodium tungstate[13] followed by treatment of the resulting hydroxamic acid with ethereal diazomethane to produce the *N*a-methoxyoxindole derivative (**13**) in 40% overall yield. In the ^{1}H-NMR spectrum, the characteristic methoxy signal (d 3.99) of the *N*a-methoxyoxindole group was observed. Next, the diol on the side chain in **13** was converted to the epoxide (**15**) by a conventional method, *i.e.*, mesylation of the secondary alcohol with mesyl chloride (y. 93%) followed by treatment with potassium carbonate in methanol (y. 98%). Because the *Gardneria* alkaloids have a 19(*E*) ethylidene side chain, by using this procedure (inversion of the C19 stereochemistry), we could obtain the epoxide having the same relative stereochemistry between the C19 and 20 positions as that derived by the direct epoxidation of the 19(*Z*) ethylidene side chain in *Gelsemium* alkaloids such as **8**. By removal of the *N*b protecting group in **15** with zinc in AcOH, the secondary amine (**16**) was obtained in 82% yield. The amine-epoxide (**16**) was then heated in dioxane at 150°C for 6 h which produced the aziridine derivative (**17**) in 61% yield, which corresponded to the biogenetically hypothetical key intermediate.[7] In the ^{1}H-NMR spectrum, the protons on the C21 carbon were observed in the high-field region (d 1.62 and 1.58) due to the anisotropic effect of the aziridine ring.[14] The strong NOE (11.6%) between H-16 and H-21 revealed the C20(*S*) configuration in **17**, indicating that the secondary amine regioselectively attacked the C20 position with complete inversion. The stereochemistry at C19, which was already elucidated by X-ray



Scheme II Chemical Transformation of Gardnerine to the Alkaloid 1

analysis of the model compound (*N*a-demethoxy derivative of **17**)[15], could be considered to be (*R*) like that of the epoxide (**16**). Finally, the acid mediated cleavage of the aziridine ring in **17** was attempted. We previously succeeded in the regioselective ring opening of the aziridine ring with trifluoroacetic acid using a model compound (*N*a-demethoxy derivative of **17**).[15] But, the rearrangement of the oxygen function on the *N*a position of the oxindole onto the aromatic ring has been reported.[16] We then examined the behavior of the *N*a-methoxyoxindole function in gelsedine (**18**) upon treatment with CF_3CO_2H in THF under reflux conditions that resulted in the recovery of the starting material. Based on this result, the aziridine (**17**) was refluxed in THF with CF_3CO_2H for 0.5 h to furnish 11-methoxy-19(*R*)-hydroxygelselegine (**1**) in 77% yield (mp.236-238°C). The NOE observed between H-16 and H-21 demonstrated that the C20 position had an (*R*) configuration. The synthetic (**1**) was identical with the natural compound based on comparison of their spectroscopic data (^1H, ^{13}C-NMR, UV, mass, high-mass, CD, $[a]_D$ and m.p.) reported in the literature.[7]

In conclusion, we succeeded in the first synthesis of a new *Gelsemium* alkaloid, 11-methoxy-19(*R*)-hydroxygelselegine (**1**), from the sarpagine-type alkaloid, gardnerine (**2**), that provided the chemical support for the suggested biogenetic route. The absolute configuration of the new alkaloid is hereby chemically confirmed.

Experimental

M.p.s were measured on a Yanagimoto MP-S3 apparatus and are uncorrected. IR spectra were measured with a Hitachi 260 spectrophotometer, and UV spectra were measured in ethanol with a Hitachi U3400 spectrophotometer. ^1H NMR spectra were recorded on a JEOL JNM A 500 (500 MHz) spectrometer with tetramethylsilane as the internal standard. *J*-Values are given in Hz. ^{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 JEOL JMS-AM20 or a JEOL JMS-HX110 spectrometer. Optical rotation was measured on a JASCO DIP-140 polarimeter for solutions in MeOH. Thin layer chromatography was performed on Merck precoated Silica gel 60F-254 plates. Column chromatography utilized a Merck Silica gel 60 [70-230 mesh and 230-400 mesh (for flash chromatography)] and prepacked column [Kusano CPS-HS-221-05 (for medium pressure column chromatography) (MPLC)].

Compound (**11**) was prepared from gardnerine (**2**) according to the reported procedure.[11]

Reduction of the Oxindole (11) Borane-methyl sulfide complex (10.0 M solution in THF, 10.2 ml, 102 mmol) was added to a solution of **11** (2815 mg, 5.120 mmol) in dry THF (50 ml) at 0 °C and the mixture was heated under reflux for 6 h. Cold 5% aq. sodium hydrogen carbonate solution was added to the mixture followed by extraction with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (50 ml) and trimethylamine *N*-oxide dihydrate (2845 mg, 25.598 mmol) was added to the solution. The reaction mixture was heated under reflux for 2 h. The solvent was

evaporated *in vacuo*. Cold 10% aq. sodium carbonate 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 SiO_2 flash column chromatography with ethyl acetate to yield the indoline (**12**) (2718 mg, quant.) as an amorphous powder. UV (EtOH) : 297, 241 (sh), 209 nm. IR ($CHCl_3$) : 3415, 1710, 1630, 1510, 1160, 1130 cm^{-1}. ^{1}H-NMR (500MHz, $CDCl_3$) δ : 3.75 (3H, s, OMe). MS *m/z* : 536 (M^++2, 16%), 534 (M^+, 16), 160 (100). High MS (Fab, NBA) Calcd for $C_{23}H_{30}N_2O_6Cl_3$ (MH), 535.1170. Found 535.1160.

Preparation of the N_a-Methoxyoxindole (13) Sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$, 6 mg, 0.018 mmol) and urea hydrogen peroxide addition compound ($H_2NCONH_2 \cdot H_2O_2$, 53 mg, 0.563 mmol) were added to a solution of the indoline (**12**) (30 mg, 0.056 mmol) in 10% aq. MeOH (1 ml) and the mixture was stirred at 18°C for 1 h. After the addition of further $H_2NCONH_2 \cdot H_2O_2$ (53 mg, 0.563 mmol) to the reaction mixture, the mixture was stirred at 18° for 4 h. Cold water was added to the mixture and the whole was extracted with 5% MeOH-chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The resulting hydroxamic acid was dissolved in methanol (1 ml) and an ether solution of diazomethane (1 ml) was added to the solution at 0 °C. The mixture was stirred at room temperature for 1.5 h. After the solution was evaporated under reduced pressure, the residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (4:1) to afford the N_a-methoxyoxindole (**13**) (12.9 mg, 40%) as an amorphous powder. UV (EtOH) : 292 (sh), 283, 257, 216 nm. IR ($CHCl_3$) : 3450, 1715, 1635, 1135 cm^{-1}. ^{1}H-NMR (500MHz, $CDCl_3$) δ : 3.98 and 3.97 [3H, each s, (5:9) N_a-OMe],[17] 3.84 (3H, s, Ar-OMe), 1.27 (d, *J* = 6.9 Hz) and 1.26 (d, *J* = 6.4 Hz) (3H total, 18-H_3). MS *m/z* : 580 (M^++2, 24%), 578 (M^+, 22), 174 (100). High MS (Fab, NBA) Calcd for $C_{24}H_{29}N_2O_8Cl_3$ (M), 578.0987. Found 578.1007.

Mesylation of the N_a-Methoxyoxindole (13) Mesyl chloride (6.4 μl, 0.083 mmol) was added to a stirred mixture of **13** (40 mg, 0.069 mmol) and triethylamine (15 μl, 0.108 mmol) in dry dichloromethane (0.8 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. Cold 10% sodium carbonate 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 separated by MPLC with ethyl acetate-hexane (3:1) to afford the mesyl compound **14** (42 mg, 93%) as an amorphous powder. UV (EtOH) : 292 (sh), 285, 218 nm. IR ($CHCl_3$) : 1710, 1630, 1175 cm^{-1}. ^{1}H-NMR (500MHz, $CDCl_3$) δ : 3.99 and 3.98 [3H, each s, (5:9) N_a-OMe],[17] 3.84 (3H, s, Ar-OMe), 3.15 and 3.11 (3H, each s, OSO_2Me), 1.54 (d, *J* = 6.4 Hz) and 1.53 (d, *J* = 6.3 Hz) (3H total, 18-H_3).

Preparation of the Epoxide (15) Potassium carbonate (40 mg, 0.289 mmol) was added to a solution of the mesyl compound (**14**) (37 mg, 0.056 mmol) in MeOH (1 ml) 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 organic layer was

washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by MPLC with ethyl acetate-hexane (1:1) to yield the epoxide (**15**) (31 mg, 98%) as an amorphous powder. UV (EtOH) : 291 (sh), 285, 218 nm. IR ($CHCl_3$) : 1720, 1635, 1130 cm^{-1}. ^1H-NMR (500MHz, $CDCl_3$) δ : 3.99 and 3.98 [3H, each s, (3:5) N_a-OMe],[17] 3.840 and 3.837 (3H, each s, Ar-OMe), 3.63 (1H, d, J = 7.8 Hz, 3-H), 3.10 (1H, br-q, J = 5.6 Hz, 19-H), 1.44 and 1.41 (3H, each d, J = 5.6 Hz, 18-H_3). MS m/z : 562 (M^++2, 16), 560 (M^+, 15), 174 (100). High MS (Fab, NBA) Calcd for $C_{24}H_{28}N_2O_7Cl_3$ (MH), 561.0962. Found 561.0933.

Preparation of the Amine (16) Zinc dust (360 mg, 5.507 mmol) was added to a solution of the epoxide (**15**) (308 mg, 0.548 mmol) in acetic acid (5 ml) and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was filtered and diluted with ice-water. The mixture was basified with a cold aq. NH_4OH solution and the whole was extracted with 5% MeOH-chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 flash column chromatography with 3% methanol-chloroform to afford the amine (**16**) (173 mg, 82%) as prisms. m.p. 154-156 °C (AcOEt). UV (EtOH) : 292 (sh), 285, 218 nm. IR (KBr) : 3320, 1715, 1625 cm^{-1}. ^1H-NMR (500MHz, $CDCl_3$) δ : 7.32 (1H, d, J = 8.3 Hz, 9-H), 6.64 (1H, dd, J = 8.3 and 2.4 Hz, 10-H), 6.58 (1H, d, J = 2.4 Hz, 12-H), 4.28 (1H, d, J = 10.8 Hz, 17-H), 4.01 (1H, dd, J = 10.5 and 4.9 Hz, 17-H), 4.00 (3H, s, N_a-OMe), 3.84 (3H, s, Ar-OMe), 3.71 (1H, m, 5-H), 3.57 (1H, d, J = 8.3 Hz, 3-H), 3.42 (1H, d, J = 15.1 Hz, 21-H), 3.04 (1H, q, J = 5.6 Hz, 19-H), 2.78 (1H, d, J = 15.1 Hz, 21-H), 2.51 (1H, dd, J = 15.0 and 8.2 Hz, 14-H), 2.22 (1H, ddd, J = 15.1, 11.7, 8.5 Hz, 14-H), 2.24 (2H, d, J = 5.7 Hz, 6-H_2), 1.71 (1H, ddd, J = 11.5, 8.0, 3.9 Hz, 15-H), 1.36 (3H, d, J = 5.6 Hz, 18-H_3). MS m/z : 386 (M^+, 31), 355 (37), 180 (100), 80 (43). High MS (Fab, NBA) Calcd for $C_{21}H_{27}N_2O_5$ (MH), 387.1920. Found 387.1928.

Preparation of the Aziridine (17) A mixture of **16** (230 mg, 0.595 mmol) and 1,4-dioxane (5 ml) was heated at 150 °C for 6 h in a sealed tube. The solvent was evaporated. The residue was purified by SiO_2 flash column chromatography and MPLC with 5% MeOH-chloroform to give the aziridine (**17**) (140 mg, 61%) as prisms. m.p. 233-234 °C (Acetone). UV (EtOH) : 294 (sh), 285, 217 nm. IR (KBr) : 3260, 1730, 1625, 1495, 1215, 1110 cm^{-1}. ^1H-NMR (500MHz, $CDCl_3$) δ : 7.33 (1H, d, J = 8.3 Hz, 9-H), 6.58 (1H, dd, J = 8.3 , 2.5 Hz, 10-H), 6.52 (1H, d, J = 2.5 Hz, 12-H), 4.37 (1H, br-q, J = 6.6 Hz, 19-H), 4.28 (1H, dd, J = 11.1, 3.4 Hz, 17-H), 4.17 (1H, dd, J = 11.1, 1.3 Hz, 17-H), 3.98 (3H, s, N_a-OMe), 3.82 (3H, s, Ar-OMe), 3.63 (1H, dd, J = 5.4, 1.7 Hz, 3-H), 3.54 (1H, m, 5-H), 3.06 (1H, d, J = 15.8 Hz, 14-H), 2.85 (1H, dd, J = 9.9, 7.5 Hz, 15-H), 2.33 (1H, m, 16-H), 2.22 (1H, dd, J = 15.8, 2.6 Hz, 6-H), 2.18 (1H, dd, J = 15.8, 4.7 Hz, 6-H), 2.13 (1H, ddd, J = 15.7, 10.4, 5.4, 14-H), 1.62 (1H, d, J = 0.9 Hz, 21-H), 1.58 (1H, d, J = 0.8 Hz, 21-H), 1.31 (3H, d, J = 6.6 Hz, 18-H_3). MS m/z : 386 (M^+, 98), 355 (100), 343 (74), 312 (48). High MS (Fab, NBA) Calcd for $C_{21}H_{27}N_2O_5$ (MH), 387.1920. Found 387.1936.

Preparation of 11-Methoxy-19(*R*)-hydroxygelselegine (1) Trifluoroacetic acid (33 μl, 0.428 mmol) was added to a solution of **17** (8.2 mg, 0.021 mmol) in dry THF (1 ml) at 0 °C and the

mixture was refluxed for 30 min. After the addition of ice water the reaction mixture was basified with aq. NH_4OH and the whole was extracted with 5% MeOH-chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 open column chromatography with 10% MeOH-chloroform to afford 11-methoxy-19(*R*)-hydroxygelselegine (1) (6.6 mg, 77%) as prisms. m.p. 236-238 °C (Acetone) (lit.[7] 234-236 °C). $[\alpha]_D^{23}$ -107° (*c* 0.115 in MeOH) {lit. $[\alpha]_D$ -110° (*c* 0.02 in MeOH)}. UV (EtOH) : 292 (sh), 284, 219 nm. IR (KBr) : 3420, 3260, 1700, 1620, 1215 cm^{-1}. ^{1}H-NMR (500MHz, $CDCl_3$) δ : 7.30 (1H, d, *J* = 8.6 Hz, 9-H), 6.63 (1H, dd, *J* = 8.6, 2.5 Hz, 10-H), 6.55 (1H, d, *J* = 2.5 Hz, 12-H), 4.62 (1H, br-q, *J* = 6.4 Hz, 19-H), 4.32 (1H, dd, *J* = 11.1, 3.8 Hz, 17-H), 4.25 (1H, br-d, *J* = 11.0 Hz, 17-H), 4.00 (3H, s, N_a-OMe), 3.83 (3H, s, Ar-OMe), 3.70 (1H, m, 5-H), 3.69 (1H, d, *J* = 11.0 Hz, 21-H), 3.55 (1H, d, *J* = 6.4 Hz, 3-H), 3.47 (1H, d, *J* = 11.0 Hz, 21-H), 2.77 (1H, m, 16-H), 2.45 (1H, m, 15-H), 2.37 (1H, br-d, *J* = 15.9 Hz, 14-H), 2.17 (1H, ddd, *J* = 15.9, 10.7, 6.4 Hz, 14-H), 2.12 (1H, dd, *J* = 16.2, 3.7 Hz, 6-H), 1.98 (1H, dd, *J* = 15.9, 2.7 Hz, 6-H), 1.42 (3H, d, *J* = 6.4 Hz, 18-H_3). ^{13}C-NMR (125.65 MHz, $CDCl_3$) δ : 175.44 (s, C-2), 75.37 (d, C-3), 59.89 (d, C-5), 33.76 (t, C-6), 56.99 (s, C-7), 123.34 (s, C-8), 126.09 (d, C-9), 108.25 (d, C-10), 160.33 (s, C-11), 94.78 (d, C-12), 138.97 (s, C-13), 22.94 (t, C-14), 36.52 (d, C-15), 39.28 (d, C-16), 63.61 (t, C-17), 19.33 (q, C-18), 68.47 (d, C-19), 69.30 (s, C-20), 63.55 (t, C-21), 62.48 (q, N_a-OMe), 55.64 (q, Ar-OMe). MS *m/z* : 404 (M^+, 0.6), 374 (51), 373 (100), 343 (27), 342 (44), 299 (16). High MS Calcd for $C_{21}H_{28}N_2O_6$ (M), 404.1948. Found 404.1938.

Acknowledgment The financial support given to this work by "The Research Foundation for Pharmaceutical Sciences" and "The Iwaki Research Foundation" is gratefully acknowledged.

References and Footnotes

1) (a) Takayama, H.; Sakai, S. Recent advances in the chemistry of Gelsemium alkaloids. in *Studies in Natural Product Chemistry*, Rahman, A. Ed.; Elsevier: Amsterdam, Vol. 15, in press. (b) Liu, Z.-J.; Lu, R.-R. *The Alkaloids*; Brossi, A. Ed.; Academic Press: New York, **1988**, Vol. 33, Chap. 2. (c) Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Ogata, K.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1988**, *29*, 5395-5396, and references cited therein. (d) Lin, L.-Z.; Cordell, G. A.; Ni, C.-Z.; Clardy, J. *Phytochem.* **1991**, *30*, 1311-1315, and references cited therein. (e) Zhang, Z. -P.; Liang, X. -T.; Sun, F.; Lu, Y.; Yang, J.; Xing, Q. -Y. *Chinese Chemical Lett.* **1991**, *2*, 365-368, and references cited therein.

2) (a) Ponglux, D.; Wongseripipatana, S.; Subhadhirasakul, S.; Takayama, H.; Yokota, M.; Ogata, K.; Phisalaphong, C.; Aimi, N.; Sakai, S. *Tetrahedron* **1988**, *44*, 5075-5094. (b) Takayama, H.; Sakai, S. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 876-890.

3) Takayama, H.; Kitajima, M.; Wongseripipatana, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1075-1076.

4) (a) Takayama, H.; Kitajima, M.; Sakai, S. *Heterocycles* **1990**, *30*, 325-327. (b) Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongseripipatana, S.; Ponglux, D. *Tetrahedron Lett.* **1986**, *27*, 4585-4588.

5) (a) Takayama, H.; Kitajima, M.; Sakai, S. *Tetrahedron* **1994**, *50*, 8363-8370. (b) Phisalaphong, C.; Takayama, H.; Sakai, S. *Tetrahedron Lett.* **1993**, *34*, 4035-4038. (c) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1773-1779.

6) (a) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1990**, *38*, 5483-5486. (b) Takayama, H.; Horigome, M.; Aimi, N.; Sakai, S. *ibid*, **1990**, *38*, 1287-1290. (c) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1573-1578. (d) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, in press.

7) Lin, L.-Z.; Cordell, G. A.; Ni, C.-Z.; Clardy, J. *Phytochemistry* **1990**, *29*, 3013-3017.

8) Stöckigt, J. The Biosynthesis of Heteroyohimbine-Type Alkaloids. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D.; Zenk, M. H. Eds.; Academic Press, London, **1980**, pp.113-141.

9) Lin, L.-Z.; Cordell, G. A.; Ni, C.-Z.; Clardy, J. *J. Nat. Prod.* **1989**, *52*, 588-594.

10) Sakai, S.; Kubo, J.; Haginiwa, J. *Tetrahedron Lett.* **1969**, 1485-1488.

11) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327-1336.

12) Takayama, H.; Seki, N.; Kitajima, M.; Aimi, N.; Sakai, S. *Natural Product Lett.* **1993**, *2*, 271-276.

13) Murahashi, S.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, *55*, 1744-1749.

14) Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. 2nd Edition, Pergamon Press, Oxford, **1969**, pp. 98-101.

15) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 4583-4584.

16) Kikugawa, Y. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 749-757.

17) 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.

(*Received in Japan* 19 *July* 1994; *accepted* 12 *August* 1994)