ORGANIC LETTERS

2006
Vol. 8, No. 14
3085−3088

Four Novel Gelsenicine-Related Oxindole Alkaloids from the Leaves of *Gelsemium elegans* Benth.†

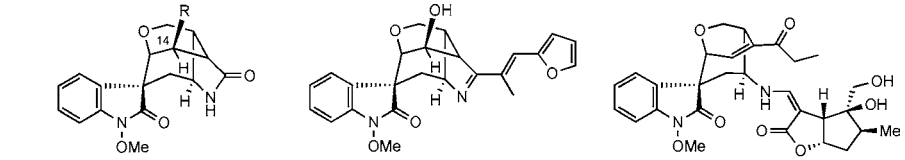
Noriyuki Kogure,‡ Naoko Ishii,‡ Mariko Kitajima,‡ Sumphan Wongseripipatana,§ and Hiromitsu Takayama*,‡

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan, and Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10500, Thailand

takayama@p.chiba-u.ac.jp

Received May 2, 2006

ABSTRACT



R=H, gelsedilam (**1**)
R=OAc, 14-acetoxygelsedilam (**2**)

gelsefuranidine (**3**)

gelseiridone (**4**)

New types of four gelsenicine-related oxindole alkaloids were isolated from the leaves of *Gelsemium elegans* Benth. Gelsedilam (1) and 14-acetoxygelsedilam (2) are the first examples of 18,19-nor-type monoterpenoid indole alkaloids. Gelsefuranidine (3) and gelseiridone (4) have, respectively, an additional furan residue or an iridoid unit on the gelsenicine-related monoterpenoid indole alkaloid.

Gelsemium elegans Benth. (Loganiaceae), which is widely distributed in Southeast Asia, is known as a toxic plant and has been used in traditional Chinese medicine. Our previous study has proven that the origin of "Yakatsu," one of the ancient medicines stored in the Shosoin repository in Japan, is *G. elegans*.[1] As this plant was used in traditional Chinese medicine as a remedy for certain kinds of skin ulcers, it is presumed to have been used as an external medication for dermatitis more than 1250 years ago in Japan. Recently, we found that among the structurally diverse *Gelsemium* alkaloids,[2] gelsedine and 14-acetoxygelsenicine, which belong to the gelsedine-type compounds, showed potent cytotoxic effects against A431 epidermoid carcinoma cells.[3] Further, the *Gelsemium* alkaloids have attracted the attention of many synthetic organic chemists as challenging target molecules due to their markedly diverse and complex monoterpenoid indole alkaloid architectures.[2,4] In our continuing chemical studies on the *Gelsemium* alkaloids,[5] we found new types of four monoterpenoid indole alkaloids, gelsedilam (**1**), 14-acetoxygelsedilam (**2**), gelsefuranidine (**3**), and gelseiridone (**4**), in the leaves of *Gelsemium elegans* growing in Thailand. In this paper, we describe the structure elucidation of these novel alkaloids.

The molecular formula of new alkaloid **1**,[6] named gelsedilam, was established as $C_{17}H_{18}N_2O_4$ from HRFABMS [*m*/*z* 315.1347 ([M + H]$^+$)], which possessed two carbons less than common *Gelsemium* alkaloids. UV and NMR spectra exhibited the characteristic N_a-methoxyoxindole chromophore. ^{1}H and ^{13}C NMR data (Table 1) revealed the presence of a nonsubstituted A ring of the oxindole system,

† Dedicated to Emeritus Professor Shin-ichiro Sakai on the occasion of his 77th birthday.

‡ Chiba University.

§ Chulalongkorn University.

(1) Kitajima, M.; Arai, Y.; Takayama, H.; Aimi, N. *Proc. Jpn. Acad., Ser. B* **1998**, *74*, 159−163.

(2) Takayama, H.; Sakai, S. *Gelsemium* Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1997; Vol. 49, Chapter 1, and references therein.

(3) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715−718.

(4) (a) Mardin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054−18065. (b) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073−4075. (c) Atarashi, S.; Choi, J.-K.; Ha, D. C.; Hart, D. J.; Kuzmich, D.; Lee, C. S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226−6241. (d) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812−9824. (e) Beyersbergen van Henegouhen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2214−2217.

(5) (a) Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. *Org. Lett.* **2003**, *5*, 2075−2078. (b) Kogure, N.; Nishiya, C.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2005**, *46*, 5857−5861. (c) Kitajima, M.; Urano, A.; Kogure, N.; Takayama, H.; Aimi, N. *Chem. Pharm. Bull.* **2003**, *51*, 1211−1214.

10.1021/ol061062i CCC: $33.50
Published on Web 06/16/2006

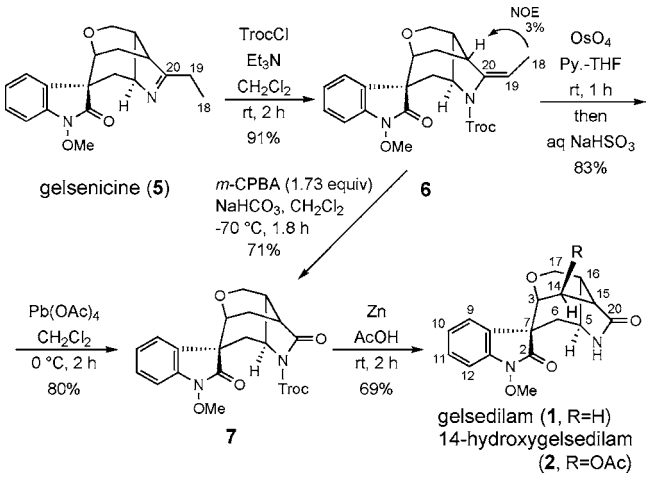
Table 1. ^{1}H and ^{13}C NMR Data for **1** and **2**

	gelsedilam (**1**)		14-acetoxygelsedilam (**2**)	
	δ_H (400 MHz)	δ_C (125 MHz)	δ_H (400 MHz)	δ_C (125 MHz)
2		171.6		170.7
3	3.80 (dd, 4.8, 2.0)	74.8	3.88 (br t, 1.7)	75.6
5	4.12 (m)	56.5	4.14 (m)	55.9
6	2.35 (dd, 15.6,3.9)	36.6	2.38 (dd, 15.6,3.2)	35.9
	2.03 (dd, 15.6,2.4)		2.17 (dd, 15.6,2.0)	
7		55.8		53.7
8		131.3		130.5
9	7.48 (d, 7.6)	124.4	7.43 (d, 7.6)	124.1
10	7.08 (t, 7.6)	123.4	7.07 (t, 7.6)	123.5
11	7.28 (t, 7.6)	128.4	7.28 (t, 7.6)	128.6
12	6.91 (d, 7.6)	107.0	6.89 (d, 7.6)	107.2
13		138.4		138.5
14	2.53 (br d, 15.4)	27.1	5.63 (d, 2.0)	69.2
	2.31 (m)			
15	2.65 (dd, 9.0, 8.2)	36.7	2.71 (dd, 8.5, 1.2)	42.8
16	2.86 (br t, 8.2)	35.6	3.48 (br t, 8.5)	35.5
17	4.24 (2H, m)	62.0	4.36 (dd, 11.2,3.2)	61.6
			4.28 (dd, 11.2,1.0)	
20		179.8		176.8
*N*a-OMe	3.95 (3H, s)	63.6	3.94 (3H, s)	63.3
*N*b-H	5.77 (br s)		6.30 (s)	
$OCOCH_3$				169.8
$OCOCH_3$			2.02 (3H, s)	21.1

an N_a-methoxy group (δ_H 3.95, δ_C 63.6), an oxymethine group (δ_H 3.80, δ_C 74.8, C-3), a methine group bearing nitrogen (δ_H 4.12, δ_C 56.5, C-5), and an oxymethylene group (δ_H 4.24, δ_C 62.0, C-17). Furthermore, in addition to the carbonyl carbon due to the oxindole nucleus at δ 171.6, an sp^2 quaternary carbon at δ 179.8 was observed in the ^{13}C NMR spectra. These spectral data were very similar to those of gelsenicine (**5**)[7] except for the lack of proton and carbon signals ascribable to the C18 and C19 positions. From the above data, **1** was deduced to be an 18,19-nor-20-lactam compound derived from gelsenicine (**5**). To confirm the structure of **1** proposed by spectroscopic analyses, partial synthesis from gelsenicine (**5**) was performed. Gelsenicine (**5**), a major alkaloid in the plant material of this study, was treated with trichloroethoxycarbonyl (Troc) chloride in the presence of Et_3N in CH_2Cl_2 to give enamine carbamate (**6**) in 91% yield. The double bond that migrated to the C19−C20 position was oxidatively cleaved in two steps [(i) OsO_4, Py-THF, then aq $NaHSO_3$, yield 83%; (ii) $Pb(OAc)_4$, CH_2Cl_2, yield 80%] to yield lactam (**7**). It was found that treatment of **6** with *m*-CPBA (1.73 equiv) also afforded lactam (**7**) in 71% yield. Finally, removal of the N_b-Troc group (Zn, AcOH) gave gelsedilam (**1**) in 69% yield. All of the spectroscopic data including the CD spectrum of synthetic **1** were identical with those of natural **1**, and therefore, the structure including the absolute configuration was established.

The molecular formula of alkaloid **2**[8] (see Scheme 1) was established as $C_{19}H_{20}N_2O_6$ from HRFABMS [*m*/*z* 373.1374 ([M + H] $^+$)]. In the ^{1}H NMR spectrum, the characteristic signals of an acetyl methyl group at δ 2.02 (3H, s) and a

Scheme 1



low-field methine proton at δ 5.63 (d, H-14) were observed. The ^{13}C NMR spectrum including the lactam carbonyl carbon signal at δ 176.8 (C-20) was very similar to that of gelsedilam (**1**) except for the existence of carbons due to the acetoxy group (δ 169.8 and 21.1) and a low field methine carbon at δ 69.2 (C-14). ^{1}H−^{1}H COSY correlation between the H-3 oxymethine proton at δ 3.88 and the low-field methine proton at δ 5.63 and HMBC correlations between the proton at δ 5.63 and the acetyl methyl protons (δ 2.02) and the carbon at δ 169.8 indicated that an acetoxy group was attached to C-14. The configuration of the acetoxy group at C-14 was shown to be β by the coupling constant ($J_{3,14}$ = 2.0 Hz) of the proton at C-14, as in the case of other compounds having a hydroxyl or an acetoxy group at C-14.[3] Therefore, the structure of alkaloid **2** was deduced to be 14-acetoxygelsedilam. The new alkaloids, gelsedilam (**1**) and 14-acetoxygelsedilam (**2**), are unprecedented 18,19-nor-type monoterpenoid indole alkaloids.

The HRFABMS spectrum of new alkaloid **3**,[9] named gelsefuranidine, gave a protonated molecular ion peak at *m*/*z* 421.1736 ([M + H]$^+$) that corresponded to the molecular formula $C_{24}H_{25}N_2O_5$ (*m*/*z* 421.1763). The ^{1}H NMR spectrum showed some readily assignable signals due to the 14-hydroxygelsenicine (**8**) part, such as four aromatic protons [δ 7.53 (d, H-9), δ 7.28 (t, H-11), δ 7.10 (t, H-10), δ 6.88 (d, H-12)], an N_a-methoxy group [δ 3.92, (3H, s)], and oxygenated protons [δ 4.51 (H-14 and H-17), δ 4.39 (d, H-17), δ 3.67 (br-s, H-3)]. In addition, four protons on sp^2 carbons [δ 7.50 (d, J = 1.8 Hz, H-5′), δ 6.97 (s, H-1′), δ 6.61 (d, J = 3.4 Hz, H-3′), δ 6.49 (dd, J = 3.4, 1.8 Hz, H-4′)] were observed. Based on the COSY spectrum (Figure 1) and the coupling constants of these protons as well as the chemical shifts of the related carbons (C2′-C5′), the presence

(6) Gelsedilam (**1**): UV (MeOH) λ_{max} nm (log ϵ) 257.0 (3.72), 209.5 (4.35); IR (KBr) 1679 cm^{-1}; FABMS (NBA) *m*/*z* 315 ([M + H]$^+$); HRFABMS (NBA/PEG) *m*/*z* 315.1347 ([M + H]$^+$, calcd for $C_{17}H_{19}N_2O_4$, 315.1345); CD (*c* = 0.229 mmol/L, MeOH, 24 °C) $\Delta\epsilon$ (nm) 0 (300), −5.86 (261), 0 (248), +8.91 (235), 0 (224), −26.98 (211).

(7) a) Du, X. B.; Dai, Y. H.; Zhang, C. L.; Lu, S. L.; Liu, Z. G. *Huaxue Xuebao* **1982**, *40*, 1137−1141. (b) Yan, J. S.; Chen, Y. W. *Yaoxue Xuebao* **1983**, *18*, 104−112. (c) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381−4385.

(8) 14-Acetoxygelsedilam (**2**): UV (MeOH) λ_{max} nm (log ϵ) 257.5 (3.65), 210.0 (4.31); FABMS (NBA) *m*/*z* 373 ([M + H]$^+$); HRFABMS (NBA/PEG) *m*/*z* 373.1374 ([M + H]$^+$, calcd for $C_{19}H_{21}N_2O_6$, 373.1400); CD (*c* = 0.232 mmol/L, MeOH, 24 °C) $\Delta\epsilon$ (nm) 0 (300), −5.07 (262), 0 (248), +7.72 (235), 0 (223), +15.10 (211).

(9) Gelsefuranidine (**3**): UV (MeOH) λ_{max} nm (log ϵ) 362.0 (sh, 2.77), 306.5 (4.14), 255.5 (sh, 3.67), 208.5, (4.21); FABMS (NBA) *m*/*z* 421 ([M + H]$^+$); HRFABMS (NBA/PEG) *m*/*z* 421.1736 ([M + H]$^+$, calcd for $C_{24}H_{25}N_2O_5$, 421.1763); CD (*c* = 0.305 mmol/L, MeOH, 24 °C) $\Delta\epsilon$ (nm) 0 (338), +0.85 (308), 0 (296), −4.90 (260), 0 (244), +2.15 (236), 0 (227), −11.91 (212).

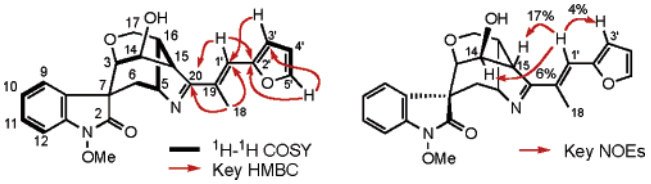
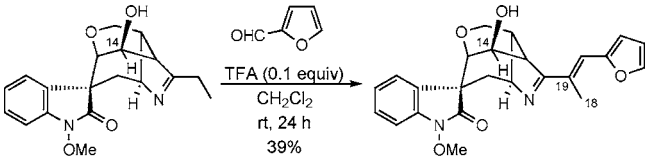


Figure 1. Gelsefuranidine (**3**).

of a 2-substituted furan residue was indicated. Furthermore, the presence of a propenyl group (C18, 19 and 1′) was inferred from ^{1}H and ^{13}C NMR spectra [δ_H 2.47 (3H, s) and 6.97 (1H, s), δ_C 15.0, 130.9, and 122.8]. The three units above, i.e., 14-hydroxygelsenicine, furan and propenyl group, could be connected by HMBC cross-peaks from the proton at δ 6.97 (H-1′) to the imine carbon at δ 176.9 (C-20) and the furan carbon at δ 152.8 (C-2′), and from the protons at C-18 to the carbons at C-20 and C-1′ (δ 122.8). The geometry of the double bond at C19−1′ was elucidated by NOE experiments, as shown in Figure 1. The configuration of the hydroxyl group at C-14 was shown to be β because H-14 was not coupled with H-15. To confirm the structure inferred by spectroscopic analyses above, the chemical transformation of 14-hydroxygelsenicine (**8**) into **3** was attempted (Scheme 2). Compound **8** was treated with furfural

Scheme 2



14-hydroxygelsenicine (**8**) gelsefuranidine (**3**)

in the presence of a catalytic amount of TFA in CH_2Cl_2 to give **3** in 39% yield. All of the spectroscopic data including the CD spectrum of semisynthetic **3** were identical with those of the natural product, thereby establishing the structure including the absolute configuration. Gelsefuranidine (**3**) is the first example of a monoterpenoid indole alkaloid having a furan residue on the side chain.

The HRFABMS spectrum of new alkaloid **4**,[10] named gelseiridone, gave a molecular ion peak at *m*/*z* 539.2410 ([M + H]$^+$) that corresponded to the molecular formula $C_{29}H_{35}N_2O_8$ (*m*/*z* 539.2393), showing that **4** possessed 10 carbons more than common *Gelsemium* alkaloids.[11] The ^{1}H NMR spectrum showed some readily assignable signals such as four aromatic protons [δ 7.39 (t, H-11), δ7.38 (d, H-9), δ 7.17 (t, H-10), δ 7.04 (d, H-12)], an N_a-methoxy group [δ 4.00, (3H, s)], an oxymethylene proton at δ 4.17 and 3.59 (H_2-17), and isolated ethyl protons [δ 3.03 (dq, H-19), δ 2.84 (dq, H-19), δ 1.20 (t, H_3-18)] due to the monoterpenoid indole alkaloid moiety, such as gelsenicine (**5**). The presence of an α,β-unsaturated ketone residue was suggested by the characteristic signals δ_H 7.45 (H-14), δ_C 201.1 (C-20), δ C 139.0 (C-14), and δ_C 138.6 (C-15). ^{1}H−^{1}H COSY and HMBC correlations (Figure 2), particularly from H-16 to

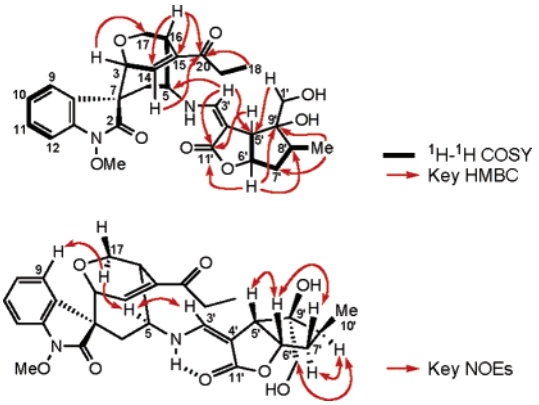


Figure 2. Gelseiridone (**4**).

C-14, 15, and 20 (δ 201.1), from H-14 to C-20, and from H-18 to C-20, suggested the gross structure of the monoterpenoid indole alkaloid part having an α,β-unsaturated ketone residue as well as the N_b-C20 seco-form.[5a] The configuration of the spiro-center at C-7 was deduced to be *S* by comparison of the CD spectrum with that of gelsenicine (**5**). NOE correlations of H-5/H-17α and H-17α/H-9 on the benzene ring suggested *S* configuration of the C-5 position. The remaining 10-carbon unit was easily considered to be a monoterpene having an iridoid skeleton with methyl, hydroxymethyl, and tertiary hydroxyl groups. In addition, the iridoid has an α,β-unsaturated ester (or lactone) with a heteroatom (N or O) at the β position, as inferred from the NMR signals δ_H 7.33 (H-3′), δ_H 4.89 (H-6′), δ_C 146.2 (C-3′), δ_C 91.3 (C-4′), δ_C 175.1 (C-11′), and δ_C 80.3 (C-6′). The gross structure of the iridoid part was assigned on the basis of ^{1}H−^{1}H COSY and HMBC correlations (Figure 2), particularly from H-3′ to C-11′ and C-5′; from H-6′ to C-11′, C-8′ and C-9′; from H-5′ to C-11′; and from H-1′ to C-5′. The relative stereochemistry of the sequential chiral centers (C-5′−C-9′) in the iridoid moiety was deduced from the NOE correlations, as shown in Figure 2. In the ^{1}H NMR spectrum, the signal of N_b-H appeared clearly at δ 6.87, the assignment of which was confirmed by spin−spin coupling with the proton at C-3′ as well as by D_2O addition experiments. The N_b-H proton is considered to be stabilized by the intramolecular hydrogen bonding with the ester carbonyl (C-11′), which fixed the *Z* configuration of the C-3′−C-4′ double bond. HMBC correlation between H-3′ proton (δ 7.33) of the iridoid and C-5 (δ 57.8) of the alkaloid unit indicates that the monoterpene unit was attached to N_b group, the fact of which was supported by the observation of a strong NOE between H-5 and H-3′. The iridoid part inferred by spectroscopic analysis above was considered to be derived from 7-deoxygelsemide (**9**), a coexisting iridoid in this plant,[12] by the addition of the primary amine in the indole alkaloid

(10) Gelseiridone (**4**): UV (MeOH) λ_{max} nm (log ϵ) 288.0 (4.28), 205.5 (4.33); FABMS (NBA) *m*/*z* 539 ([M + H]$^+$); HRFABMS (NBA/PEG) *m*/*z* 539.2410 ([M + H]$^+$, calcd for $C_{29}H_{35}N_2O_8$, 539.2393); CD (c = 0.195 mmol/L, MeOH, 24 °C) $\Delta\epsilon$ (nm) 0 (327), −12.0 (282), −1.0 (256), −14.3 (226), 0 (217), +17.0 (210).

(11) a) Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Ogata, K.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1988**, *29*, 5395−5396. (b) Lin, L. Z.; Cordell, G. A.; Ni, C. Z.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3199−3202.

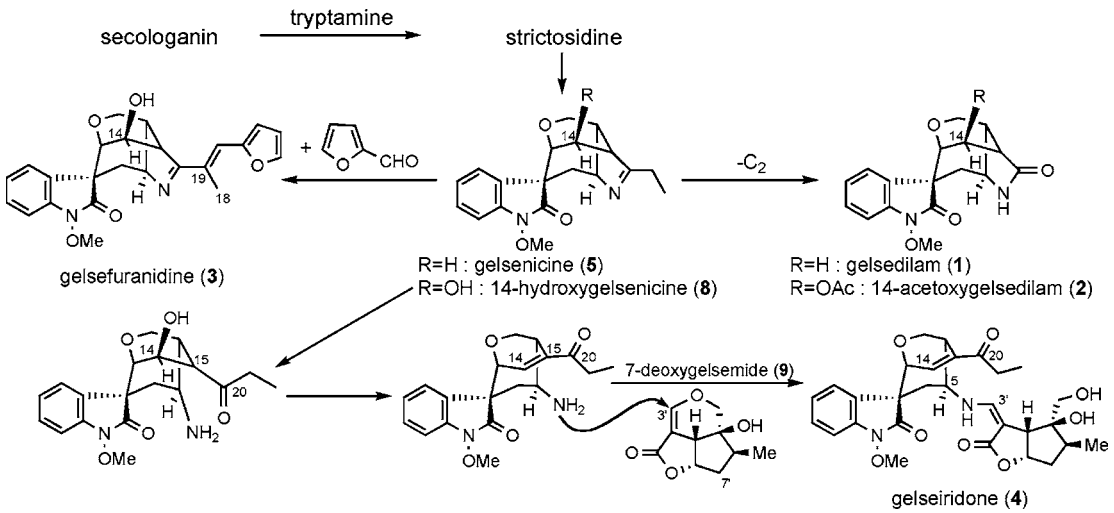


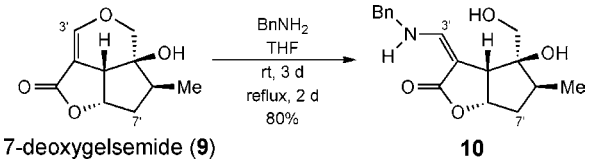
Figure 3. Possible biogenetic path of new alkaloids **1**−**4**.

Table 2. ^{1}H and ^{13}C NMR Data for **3** and **4**

	gelsefuranidine (**3**)		gelseiridone (**4**)	
	δ_H (500 MHz)	δ_C (125 MHz)	δ_H (400 MHz)	δ_C (125 MHz)
2		170.6		171.1
3	3.67 (br s)	79.5	4.32 (d, 6.3)	71.4
5	4.64 (m)	72.7	3.68 (m)	57.8
6	2.51 (dd, 15.6,4.9) 2.40 (dd, 15.6,2.1)	37.4	1.91 (br d, 13.5) 1.67 (dd, 13.5,4.5)	37.6
7		53.7		52.8
8		131.5		125.9
9	7.53 (d, 7.6)	124.6	7.38 (d, 7.6)	129.1
10	7.10 (t, 7.6)	123.5	7.17 (t, 7.6)	123.7
11	7.28 (t, 7.6)	128.4	7.39 (t, 7.6)	126.4
12	6.88 (d, 7.6)	106.8	7.04 (d, 7.6)	107.8
13		138.1		139.2
14	4.51 (overlapped)	67.6	7.45 (dd, 6.3,1.5)	139.0
15	3.43 (dd, 8.3, 1.2)	49.0		138.6
16	2.68 (ddd, 8.3, 8.3, 3.7)	38.3	3.53 (br s)	39.8
17	4.51 (dd, 11.0,3.7) 4.39 (d, 11.0)	61.9	4.17 (d, 8.4) 3.59 (br dd, 8.8, 2.4)	68.5
18	2.47 (3H, s)	15.0	1.20 (3H, t, 7.2)	8.4
19		130.9	3.03 (dq, 17.2,7.2) 2.84 (dq, 17.2,7.2)	30.7
20		176.9		201.1
*N*a-OMe	3.92 (3H, s)	63.4	4.00 (3H, s)	63.6
*N*b-H			6.87 (br dd, 13.0, 8.8)	
1′	6.97 (s)	122.8	3.72 (d, 10.2) 3.58 (br dd, 10.2, 2.6)	64.0
2′		152.8		
3′	6.61 (d, 3.4)	112.8	7.33 (dd, 13.0,1.4)	146.2
4′	6.49 (dd, 3.4, 1.8)	111.9		91.3
5′	7.50 (d, 1.8)	142.8	3.20 (br d, 5.7)	53.3
6′			4.89 (dd, 7.3, 5.7)	80.3
7′			2.05 (dd, 14.4,7.3) 1.94 (m)	39.0
8′			1.82 (m)	35.4
9′				83.7
10′			0.96 (3H, d, 6.6)	11.5
11′				175.1

moiety (see the biogenetic consideration below). To elucidate the structure of the iridoid part in **4**, a model compound (**10**) was prepared by condensation of 7-deoxygelsemide (**9**) and benzylamine (Scheme 3). The spectroscopic data (^{1}H and ^{13}C NMR) of the model compound were well correspondence with those of the iridoid part in **4** (see the table in the Supporting Information). From a biogenetic point of view, **4** would originate in 14-hydroxygelsenicine (**8**) and 7-deoxygelsemide (**9**) via the pathway shown in Figure 3, i.e., hydrolytic cleavage of the imine part in **8** to form a keto-amine intermediate, dehydration at C-14 and C-15 positions, 1,4-addition of primary amine to the C-3′ position in 7-deoxygelsemide, and ring opening of the dihydropyran moiety. Gelseiridone (**4**) is a new type of alkaloid having a nitrogen−carbon linkage between a gelsenicine-type monoterpenoid indole alkaloid and a monoterpene unit having an iridoid skeleton (Table 2).

Scheme 3



Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 16510156) from the Japan Society for the Promotion of Science.

Supporting Information Available: ^{1}H and ^{13}C NMR data of compounds **1**−**4** and experimental procedures for the preparation of **1**, **3**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061062I

(12) Takayama, H.; Morohoshi, Y.; Kitajima, M.; Aimi, N.; Wongseripipatana, S.; Ponglux, D.; Sakai, S. *Nat. Prod. Lett.* **1994**, *5*, 15−20.