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Six new indole alkaloids from *Gelsemium sempervirens* Ait. f.

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Abstract—One new yohimbane and five new sarpagine-type indole alkaloids were isolated from the radix of *Gelsemium sempervirens* Ait. f., and their structures were determined by spectroscopic analysis, chemical conversion or total synthesis. It was found that 2-acyl sarpagine-type alkaloids possessing an N_b-methyl group take a keto–amino structure or a transannular form in solution depending on the solvent.

In our recent study, we proved that the original plant of 'Yakatsu,' one of the ancient medicines stored for more than 1250 years in Shosoin repository in Japan, was *Gelsemium elegans* Benth.[1] The genus *Gelsemium*, which belongs to Loganiaceae, comprises three species: *G. elegans* Benth., *G. sempervirens* Ait. f., and *G. rankinii* Small, from which more than fifty indole alkaloids have been isolated.[2–4] In the course of our chemical studies on *Gelsemium* alkaloids, we investigated the constituents in the radix of *G. sempervirens*, and this has resulted in the isolation of one new yohimbane alkaloid (**1**) and five new sarpagine-type alkaloids (**2**–**6**). In this paper, we describe the structure elucidation of the new alkaloids as well as an interesting spectroscopic observation in the new sarpagine-type alkaloids.

The dried radix of *G. sempervirens* Ait. f. (413.7 g), that was cultivated in the medicinal plant garden of our university, was extracted with hot MeOH to give the MeOH extract (50.2 g). The crude alkaloidal fraction (4.88 g) obtained by a conventional procedure from the MeOH extract was purified by SiO_2 column chromatography to afford six new alkaloids, sempervilam (**1**, 17.8 mg), gelsempervine-A (**2**, 20.7 mg), -B (**3**, 7.6 mg), -C (**4**, 49.0 mg), -D (**5**, 5.3 mg), and 19*Z*-16-*epi*-voacarpine (**6**, 1.7 mg) (Fig. 1).

The high-resolution (HR)-FAB-MS spectrum of new alkaloid (**1**)[5] gave a molecular ion peak at *m*/*z* 288.1272 $[M]^+$ that corresponded to the molecular formula $C_{19}H_{16}N_2O$ (*m*/*z* 288.1263). The UV spectrum of **1** was similar to that of sempervirine (**8**).[6] The ^1H NMR spectrum[5] that showed signals corresponding to seven aromatic protons including one singlet and eight aliphatic protons was very similar to that of sempervirine (**8**) that possessed two singlet aromatic protons. The ^{13}C NMR spectrum[5] showed 15sp^2 carbons, including one carbonyl carbon at δ 58.8 and four sp^3 methylenes. Heteronuclear multiple bond connectivity (HMBC) correlations between H-5 and the carbon at δ 58.8 revealed that the carbonyl function existed at

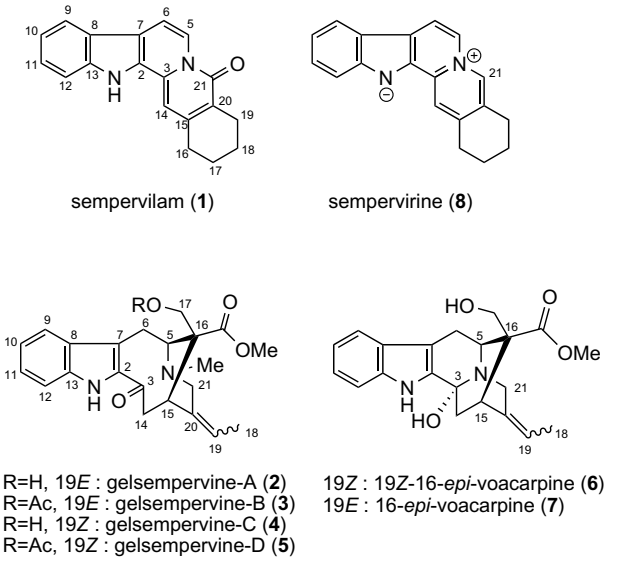

Figure 1. Structures of new alkaloids (**1**–**6**) and known alkaloids (**7**, **8**).

Keywords: Indole alkaloid; *Gelsemium*; Structure elucidation; NMR; Total synthesis; Isomerization; Solvent effect.
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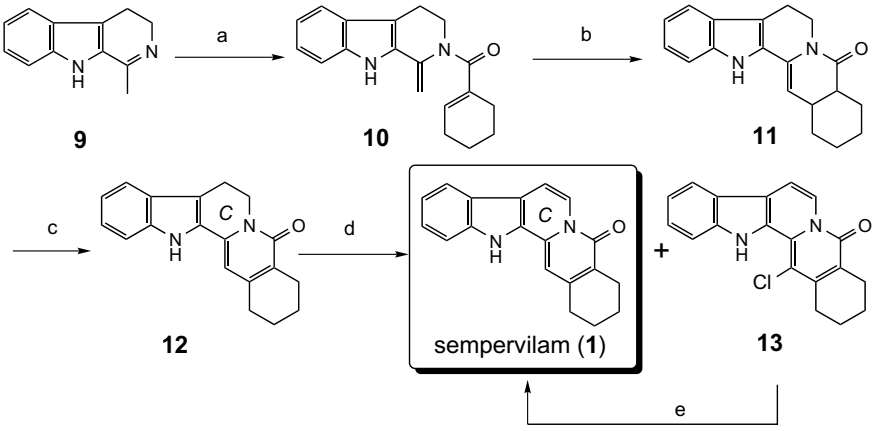
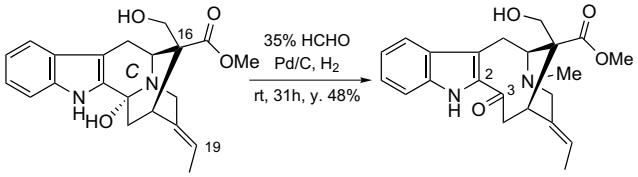


Scheme 1. Reagents and conditions: (a) cyclohexene-1-carboxylic acid, HOAT, EDCI, $^{i}Pr_2NEt$, CH_2Cl_2, rt, 4 h, 87% ; (b) hν, benzene, rt, 1 h, 36%; (c) DDQ, 1,4-dioxane, reflux, 20 min, 74%; (d) (1) $^{t}BuOCl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (2) DBU, toluene, reflux, 2 h, **1**: 28%, **14**: 24%; (e) *n*-Bu_3SnH, AIBN, toluene, reflux, 5.5 h, 74%.

C-21. The spectroscopic data led to the elucidation of structure **1** for the new alkaloid, sempervilam.

To confirm the structure, we planned the total synthesis of **1** (Scheme 1). 3,4-Dihydroharman (**9**), which was prepared from tryptamine by acetylation and subsequent Bishler–Napieralski reaction, was condensed with cyclohexene-1-carboxylic acid using HOAT and EDCI to give amide **10** in 87% yield. Photocyclization[7] of **10** gave cycloadduct **11** in 36% yield together with the recovered starting material (14% recovery). Oxidation of **11** with DDQ gave pyridone **12** in 74% yield. Next, to aromatize the C-ring, **12** was treated with $^{t}BuOCl$ and then with DBU to afford **1** in 28% yield together with 14-chloro derivative **13** (24% yield), the latter of which was treated with *n*-Bu_3SnH and AIBN to give **1** in 74% yield. The spectroscopic data (^1H NMR, ^{13}C NMR, and UV) of synthetic compound **1** were completely identical with those of the natural product.

The HR-FAB-MS spectrum of new alkaloid (**2**),[8] named gelsempervine-A, gave a protonated molecular ion peak at *m*/*z* 383.1935 ($[MH]^+$) that corresponded to the molecular formula $C_{22}H_{27}N_2O_4$ (*m*/*z* 383.1971). The ^1H NMR spectrum (in $CDCl_3$) showed significant signals characteristic of an ethylidene group at δ 5.28 (ddd, H-19) and δ 1.71 (3H, d, H_3-18), together with four aromatic protons of the indole system [δ 7.69 (d, H-9), 7.37 (d, H-12), 7.31 (dd, H-11), 7.15 (dd, H-10)], an N_b-methyl group at δ 2.29 (3H, s) and a carboxymethyl group at δ 3.68 (3H, s). The ^{13}C NMR data of **2** and the known sarpagine-type alkaloid, 16-*epi*-voacarpine (**7**),[9] are highly similar but for two exceptions, namely, the spectrum of **2** shows a signal due to the N_b-methyl group at δ 42.0 and does not exhibit a signal at the C-3 position, which is indicative of the hemiaminal function in **7**. Taking the molecular formula into consideration, new alkaloid **2** was deduced to be the N_b-methyl derivative of **7**. To reveal the structure, including the stereochemistry at C-16 and the geometry of the ethylidene side chain, **7** was converted into the N_b-methyl derivative by treating with formalin in the



Scheme 2. Chemical conversion from 16-*epi*-voacarpine (**7**) to gelsempervine-A (**2**).

presence of catalytic Pd–C under H_2 atmosphere.[10] The product was completely identical with natural alkaloid, gelsempervine-A, demonstrating the 3-oxo, that is, 2-acyl indole structure of **2** (Scheme 2).

However, perusal of the UV spectrum of **2** revealed typical absorptions of the indole nucleus in MeOH (λ_{max}, 290.5, 282, 220.5 nm). The 2-acyl indole alkaloids are known to exhibit a characteristic absorption at around 310 nm.[11] In order to investigate this unusual observa-

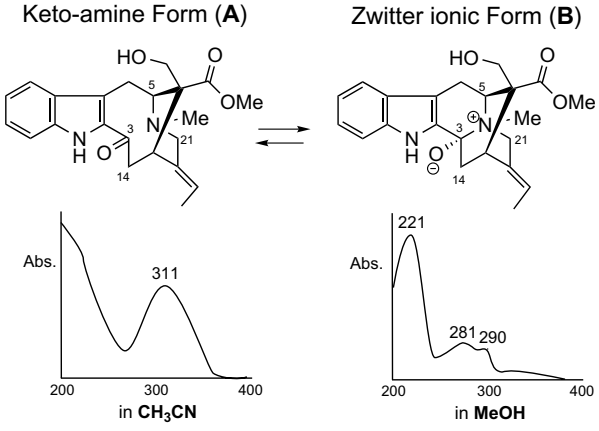


Figure 2. Two structural forms and UV spectra of gelsempervine-A (**2**).

Table 1. NMR data for **2**

Position	**2** in $CDCl_3$		**2** in CD_3CN		**2** in CD_3OD	
	^1H[a]	^{13}C[b]	^1H[c]	^{13}C[d]	^1H[e]	^{13}C[d]
2		133.9		133.6		136.5
3		—[*]		—[*]		—[*]
5	3.81 (d, 9.8)	57.7	3.59 (br s)	57.9	4.18 (d, 6.0)	62.5
6	3.63 (overlapped)	20.3	3.56 (d, 8.5)	20.3	3.39 (overlapped)	21.0
	3.23 (overlapped)		3.12 (d, 15.1)		3.41 (overlapped)	
7		117.0		119.0		112.2
8		128.1		128.3		128.3
9	7.69 (d, 7.7)	120.5	7.69 (d, 8.2)	120.7	7.52 (d, 8.1)	120.7
10	7.15 (dd, 7.7, 7.7)	120.3	7.05 (ddd, 8.2, 7.0, 1.2)	120.1	6.97 (ddd, 8.1, 7.0, 1.1)	120.7
11	7.31 (dd, 7.7, 7.7)	126.0	7.21 (ddd, 8.2, 7.0, 1.2)	125.6	7.10 (ddd, 8.1, 7.0, 1.1)	125.2
12	7.37 (d, 7.7)	112.1	7.35 (d, 8.2)	112.3	7.28 (d, 8.1)	112.9
13		135.9		136.3		138.1
14	3.20 (overlapped)	41.0	2.91 (dd, 14.3, 11.5)	40.0	2.51 (m)	42.4
	3.09 (br dd, 12.4, 11.3)		3.28 (br d, 14.3)		2.89 (dd, 14.2, 3.1)	
15	3.74 (br d, 11.3)	30.5	3.65 (br d, 11.5)	29.5	3.47 (dd, 7.1, 3.1)	33.1
16		57.1		57.1		57.8
17	3.90 (2H, m)	64.7	3.71 (d, 11.6)	64.1	3.65 (d, 11.0)	64.9
			4.03 (d, 11.6)		3.86 (d, 11.0)	
18	1.71 (3H, d, 6.6)	12.8	1.57 (3H, d, 6.9)	12.3	1.58 (3H, d, 7.0)	13.0
19	5.28 (ddd, 6.6, 6.6, 6.6)	120.5	5.08 (ddd, 6.9, 6.9, 6.9)	119.9	5.18 (ddd, 7.0, 7.0, 7.0)	120.4
20		133.8		136.4		133.6
21	3.00 (br d, 15.3)	54.2	2.71 (d, 14.8)	54.8	3.38 (overlapped)	56.3
	2.92 (d, 15.3)		2.63 (br d, 14.8)		3.08 (d, 15.4)	
N_a-H	9.26 (br s)		9.75 (br s)			
N_b-Me	2.29 (3H, s)	42.0	2.14 (3H, s)	41.8	2.36 (3H, s)	42.3
CO_2Me		175.3		174.7		176.0
CO_2Me	3.68 (3H, s)	52.3	3.49 (3H, s)	51.4	3.58 (3H, s)	52.8

[*] Not detected.
[a] Measured at 500 MHz.
[b] Measured at 125 MHz.
[c] Measured at 400 MHz.
[d] Measured at 150 MHz.
[e] Measured at 600 MHz.

tion in the UV spectrum, we next measured the UV as well as NMR spectra in protic or aprotic solvents. As a result, we found that **2** exhibited the typical absorption patterns of indole and 2-acyl indole alkaloids in MeOH and CH_3CN, respectively, as shown in Figure 2. Quite interestingly, the signals of the protons and carbons at C-5 and C-21 in CD_3OD were observed in the low field compared with those in CD_3CN (see Table 1). On the other hand, the signals of H_2-14 were observed in the lower field in CD_3CN than in CD_3OD. These spectroscopic data suggest that as shown in Figure 2, gelsempervine-A (**2**) existed exclusively as a *C*/*D* ring-opening structure with the keto–amine form (**A**) in such aprotic solvents as CD_3CN, and as a transannular structure with the zwitter ionic form (**B**) in such protic solvents as CD_3OD.

The other three new alkaloids, gelsempervine-B (**3**),[12] -C (**4**),[13] and -D (**5**),[14] are the analogues of gelsempervine-A (**2**), that is, **3** is an acetyl derivative of the hydroxyl group at C-17 in **2**, **4** is a 19*Z* isomer of **2**, and **5** is an acetyl derivative of the hydroxyl group at C-17 in **4**, and were elucidated by comparison of the ^1H NMR and ^{13}C NMR data (Table 2) and differential NOE experiments, as shown in Figure 3. In these compounds, the above-described phenomena in the UV and NMR spectra for compound **2** were also observed.

Table 2. ^{13}C NMR data for **3**–**7** in $CDCl_3$ (at 125 MHz)

Position	**3**	**4**	**5**	**6**	**7**
2	133.2	135.5[**]	134.2	136.9	137.1
3	—[*]	—[*]	—[*]	80.7	80.5
5	57.5	57.9	58.4	57.4	57.5
6	20.5	21.4	21.4	21.4	21.3
7	118.2	111.6	113.3	107.1	107.0
8	128.4	127.3	127.7	125.8	125.7
9	120.7	119.9	120.1	118.6	119.5
10	120.5	119.9	120.2	119.6	115.7
11	126.4	124.6	125.3	122.2	122.0
12	112.1	111.9	112.1	110.9	110.9
13	135.8	135.6[**]	135.9	136.3	136.3
14	40.7	44.9	43.5	36.7	36.5
15	29.9	39.3	37.5	40.9	33.7
16	55.2	56.4	54.7	54.0	53.2
17	65.8	64.8	65.9	63.1	63.3
18	12.9	12.6	12.6	12.6	12.7
19	121.2	120.3	121.7	116.5	118.5
20	133.8	133.4	132.6	136.3	135.4
21	53.9	51.2	51.1	46.0	48.1
N_b-Me	42.2	41.1	42.0		
CO_2Me	173.9	175.4	173.9	175.8	175.8
CO_2Me	52.2	52.5	52.5	52.5	52.1
OCOMe	170.5		170.1		
OCO*Me*	20.7		20.7		

[*] Not detected.
[**] Interchangeable.

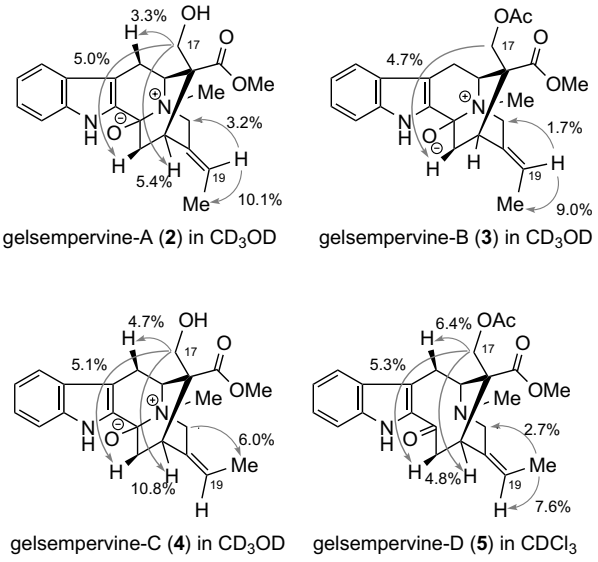


Figure 3. NOE experiments in **2**–**5**.

The molecular formula of new alkaloid (**6**)[15] was established to be $C_{21}H_{24}N_2O_4$, which was the same as that of 16-*epi*-voacarpine (**7**), from the HR-FAB-MS spectrum (*m*/*z* 369.1828 $[MH]^+$). The ^1H NMR and ^{13}C NMR spectra showed the existence of an ethylidene group, a carboxymethyl group and an indole skeleton (Table 2). A hemiaminal carbon was observed at δ 80.7 (C-3) in the ^{13}C NMR spectrum similar to 16-*epi*-voacarpine (**7**). The chemical shifts of C-15 (7.2 ppm lower field than that of **7**) and C-21 (2.1 ppm higher field than that of **7**) indicated that the double bond has a *Z*-configuration, which was confirmed by NOE experiments. From these data, new alkaloid (**6**) was concluded to be 19*Z*-16-*epi*-voacarpine.

Acknowledgments

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References and notes

1. Kitajima, M.; Arai, Y.; Takayama, H.; Aimi, N. *Proc. Jpn. Acad.* **1998**, *74*, 159–163.
2. Takayama, H.; Sakai, S. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1997; Vol. 49, Chapter 1, and references cited therein.
3. Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. *Org. Lett.* **2003**, *5*, 2075–2078.
4. Kitajima, M.; Urano, A.; Kogure, N.; Takayama, H.; Aimi, N. *Chem. Pharm. Bull.* **2003**, *51*, 1211–1214.
5. Sempervilam (**1**), ocherous amorphous powder, EI-MS *m*/*z* (%): 288 (M^+, 100). HRFAB-MS (NBA/PEG) *m*/*z*: 288.1272 (M^+, calcd for $C_{19}H_{16}N_2O$ 288.1263). UV (MeOH) λ_{max} nm (logε): 409.0 (4.32), 387.5 (4.17), 349.0 (3.69), 319.0 (3.97), 255.0 (4.24), 221.5 (4.37). ^1H NMR (500 MHz, pyridine-d_5): δ 13.25 (1H, s, N_a-H), 9.21 (1H, d, $J = 7.4$ Hz, H-5), 8.16 (1H, d, $J = 7.6$ Hz, H-9), 7.65 (1H, d, $J = 7.6$ Hz, H-12), 7.63 (1H, d, $J = 7.4$ Hz, H-6), 7.48 (1H, dd, $J = 7.6$, 7.6 Hz, H-11), 7.37 (1H, dd, $J = 7.6$, 7.6 Hz, H-10), 6.91 (1H, br s, H-14), 2.93 (2H, dd, $J = 6.4$, 6.4 Hz, H_2-19), 2.52 (2H, dd, $J = 6.1$, 6.1 Hz, H_2-16), 1.68 (2H, m, H_2-17), 1.59 (2H, m, H_2-18). ^{13}C NMR (125 MHz, pyridine-d_5): δ 158.8 (C-21), 146.0 (C-15), 140.6 (C-13), 131.7 (C-2), 131.2 (C-3), 126.2 (C-11), 123.0 (C-8*), 120.9 (C-10), 120.7 (C-9), 119.1 (C-5), 117.8 (C-20), 116.8 (C-7), 112.4 (C-12), 108.1 (C-6), 98.1 (C-14), 30.0 (C-16), 25.0 (C-19), 23.0 (C-17), 22.5 (C-18). *: under C_5D_5N signal.
6. (a) Woodward, R. B. *J. Am. Chem. Soc.* **1949**, *71*, 379; (b) Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *44*, 3195–3202; (c) Chatterjee, A.; Sahu, A.; Saha, M.; Banerji, J. *Monatsh. Chem.* **1996**, *127*, 1259–1262.
7. Ninomiya, I.; Tada, Y.; Kiguchi, T.; Yamamoto, O.; Naito, T. *Heterocycles* **1978**, *9*, 1527–1531.
8. Gelsempervine-A (**2**), colorless amorphous powder, EI-MS *m*/*z* (%): 382 (M^+, 17), 180 (100). HRFAB-MS (NBA/PEG) *m*/*z*: 383.1935 (MH^+, calcd for $C_{22}H_{27}N_2O_4$ 383.1971). UV (MeOH) λ_{max} nm (logε): 290.5 (3.65), 282.0 (3.71), 220.5 (4.44). UV (CH_3CN) λ_{max} nm (logε): 311.5 (3.99), 224.5 (4.17). IR (ATR, cm^{-1}): 3492, 3385, 2923, 1720, 1648. IR ($CHCl_3$, cm^{-1}): 3451, 3342, 2951, 1732, 1639. CD ($c = 0.262$ mM, MeOH, 23 °C) $\Delta\varepsilon$ (λ nm): 0 (396), +1.91 (321), 0 (299), −1.51 (282), 0 (265), +1.12 (257), 0 (243), −10.32 (224), 0 (210), +3.55 (203).
9. Ponglux, D.; Wongseripipatana, S.; Subhadhirasakul, S.; Takayama, H.; Yokota, M.; Ogata, K.; Phisalaphong, C.; Aimi, N.; Sakai, S. *Tetrahedron* **1988**, *44*, 5075–5094.
10. Gorman, M.; Sweeny, J. *Tetrahedron Lett.* **1964**, *5*, 3105–3111.
11. (a) Dolby, L. J.; Sakai, S. *Tetrahedron* **1967**, *23*, 1–9; (b) Sakai, S.; Yamanaka, E.; Dolby, L. *Yakugaku Zasshi* **1977**, *97*, 309–319.
12. Gelsempervine-B (**3**), colorless amorphous powder, EI-MS *m*/*z* (%): 424 (M^+, 96), 365 (56), 192 (100), 180 (96). HRFAB-MS (NBA/PEG) *m*/*z*: 425.2113 (MH^+, calcd for $C_{24}H_{29}N_2O_5$ 425.2076). UV (MeOH) λ_{max} nm (logε): 316.5 (3.65), 290.5 (3.72), 282.0 (3.74), 219.5 (4.46). UV (CH_3CN) λ_{max} nm (logε): 312.5 (3.92), 221.0 (4.07). ^1H NMR (500 MHz, $CDCl_3$): δ 8.96 (1H, br s, N_a-H), 7.73 (1H, dd, $J = 8.2$, 0.6 Hz, H-9), 7.35 (2H, overlapped, H-11, H-12), 7.17 (1H, ddd, $J = 8.2$, 6.4, 1.7 Hz, H-10), 5.29 (1H, ddd, $J = 6.9$, 6.9, 6.9 Hz, H-19), 4.59 (1H, d, $J = 11.9$ Hz, H-17), 4.29 (1H, d, $J = 11.9$ Hz, H-17), 3.80 (1H, br dd, $J = 11.8$, 2.4 Hz, H-15), 3.75 (1H, dd, $J = 15.9$, 9.2 Hz, H-6β), 3.69 (1H, br d, $J = 9.2$ Hz, H-5), 3.65 (3H, s, CO_2Me), 3.26 (1H, overlapped, H-14α), 3.23 (1H, overlapped, H-6α), 3.16 (1H, dd, $J = 14.3$, 11.8 Hz, H-14β), 2.90 (1H, d, $J = 15.0$ Hz, H-21β), 2.79 (1H, br d, $J = 15.0$ Hz, H-21α), 2.29 (3H, s, N_b-Me), 2.02 (3H, s, OCO*Me*), 1.75 (3H, dd, $J = 6.9$, 1.2 Hz, H_3-18). IR (ATR, cm^{-1}): 3313, 2925, 1742, 1640. CD ($c = 0.210$ mM, MeOH, 23 °C) $\Delta\varepsilon$ (λ nm): 0 (396), +2.29 (318), 0 (302), −1.64 (286), 0 (264), +1.24 (252), 0 (246), −8.38 (223), 0 (205).
13. Gelsempervine-C (**4**), colorless amorphous powder, FAB-MS (NBA) *m*/*z*: 383 (MH^+). HRFAB-MS (NBA/PEG) *m*/*z*: 383.1939 (MH^+, calcd. for $C_{22}H_{27}N_2O_4$ 383.1971). UV (MeOH) λ_{max} nm (logε): 290.0 (3.70), 281.0 (3.80), 221.0 (4.54). UV (CH_3CN) λ_{max} nm (logε): 309.5 (4.02), 227.5 (4.27). ^1H NMR (500 MHz, $CDCl_3$): δ 9.17 (1H, br s, N_a-H), 7.61 (1H, d, $J = 7.7$ Hz, H-9), 7.36 (1H, d, $J = 7.7$ Hz, H-12), 7.27 (1H, dd, $J = 7.7$, 7.7 Hz, H-11), 7.13 (1H, dd, $J = 7.7$, 7.7 Hz, H-10), 5.36 (1H, ddd, $J = 6.7$, 6.7, 6.7 Hz, H-19), 4.02 (1H, d, $J = 7.2$ Hz, H-5), 3.99 (1H, d, $J = 11.2$ Hz, H-17), 3.93 (1H, d, $J = 11.2$ Hz, H-17), 3.70 (3H, s, CO_2Me), 3.43 (1H, dd, $J = 17.6$, 7.2 Hz, H-6β), 3.31 (1H, d, $J = 17.6$ Hz, H-6α), 3.12 (1H, overlapped, H-21β), 3.10 (1H, overlapped, H-15), 3.09

(1H, overlapped, H-21α), 3.01 (1H, d, $J = 13.9$ Hz, H-14β), 2.78 (1H, dd, $J = 13.9$, 8.2 Hz, H-14α), 2.22 (3H, s, N_b-Me), 1.45 (3H, d, $J = 6.7$ Hz, H_3-18). IR (ATR, cm^{-1}): 3308, 2947, 1728, 1633. IR ($CHCl_3$, cm^{-1}): 3454, 3324, 2952, 1733, 1639. CD ($c = 0.225$ mM, MeOH, 23 °C) $\Delta\varepsilon$ (λ nm): 0 (377), +1.21 (320), 0 (301), −1.42 (289), −1.61 (281), 0 (263), +0.56 (252), 0 (247), −13.12 (226), 0 (216), +5.01 (209). In the 1D ^{13}C NMR spectrum, the signal due to C-3 in compounds **2**–**5** could not be observed under various experimental conditions (high or low temperature in various solvents; using prolonged pulse delay time). However, in the case of gelsempervine-C, HMBC correlations between the protons at H-21 and H-5 and the signal at δ 125.5 were observed in CD_3OD. These correlations enabled us to assign the chemical shift of C-3 in **4**, and the HMBC connectivities supported the transannular form in the protic solvent.

14. Gelsempervine-D (**5**), colorless amorphous powder, FAB-MS (NBA) m/z: 425 (MH^+). HRFAB-MS (NBA/PEG) m/z: 425.2059 (MH^+, calcd for $C_{24}H_{29}N_2O_5$ 425.2076). UV (MeOH) λ_{max} nm ($\log\varepsilon$): 315.0 (3.36), 290.5 (3.71), 282.0 (3.77), 220.0 (4.48). UV (CH_3CN) λ_{max} nm ($\log\varepsilon$): 311.5 (4.01), 221.5 (4.21). ^1H NMR (500 MHz, $CDCl_3$): δ 9.40 (1H, br s, N_a-H), 7.65 (1H, d, $J = 7.7$ Hz, H-9), 7.40 (1H, d, $J = 7.7$ Hz, H-12), 7.31 (1H, dd, $J = 7.7$, 7.7 Hz, H-11), 7.16 (1H, dd, $J = 7.7$, 7.7 Hz, H-10), 5.44 (1H, ddd, $J = 6.9$, 6.9, 6.9 Hz, H-19), 4.61 (1H, d, $J = 11.6$ Hz, H-17), 4.33 (1H, d, $J = 11.6$ Hz, H-17), 3.95 (1H, br d, $J = 7.8$ Hz, H-5), 3.67 (3H, s, CO_2Me), 3.59 (1H, dd, $J = 17.1$, 7.8 Hz, H-6β), 3.36 (1H, br d, $J = 7.0$ Hz, H-15), 3.20 (2H, overlapped, H-6α, H-21β), 3.14 (1H, dd, $J = 14.0$, 2.9 Hz, H-14β), 2.95 (2H, overlapped, H-14α, H-21α), 2.35 (3H, s, N_b-Me), 2.04 (3H, s, OCO*Me*), 1.44 (3H, d, $J = 6.9$ Hz, H_3-18). IR (ATR, cm^{-1}): 3344, 2923, 1736, 1636. IR ($CHCl_3$, cm^{-1}): 3451, 3316, 2928, 1737, 1641. CD ($c = 0.224$ mM, MeOH, 23 °C) $\Delta\varepsilon$ (λ nm): 0 (392), +1.46 (318), 0 (301), −1.36 (282), 0 (265), +1.10 (251), 0 (244), −6.99 (224), 0 (214), +3.15 (204).
15. 19*Z*-16-*epi*-Voacarpine (**6**), colorless amorphous powder, EI-MS m/z (%): 368 (M^+, 100), 265 (61), 184 (78). HRFAB-MS (NBA/PEG) m/z: 369.1828 (MH^+, calcd for $C_{21}H_{25}N_2O_4$ 369.1814). UV (MeOH) λ_{max} nm ($\log\varepsilon$): 290.5 (3.71), 282.5 (3.79), 225.5 (4.49). ^1H NMR (600 MHz, $CDCl_3$): δ 8.00 (1H, br s, N_a-H), 7.10 (1H, d, $J = 8.0$ Hz, H-12), 7.05 (1H, overlapped, H-11), 7.04 (1H, overlapped, H-9), 6.90 (1H, ddd, $J = 8.0$, 6.9, 1.1 Hz, H-10), 5.25 (1H, m, H-19), 4.46 (1H, d, $J = 5.7$ Hz, H-5), 4.16 (1H, d, $J = 17.6$, H-21), 3.70 (3H, s, CO_2Me), 3.43 (2H, m, H_2-17), 3.38 (1H, br d, $J = 17.6$ Hz, H-21), 2.86 (1H, dd, $J = 16.3$, 5.7 Hz, H-6α), 2.75 (1H, d, $J = 16.3$ Hz, H-6β), 2.69 (1H, br dd, $J = 2.9$, 2.9 Hz, H-15), 2.08 (1H, dd, $J = 14.1$, 2.9 Hz, H-14β), 1.84 (1H, dd, $J = 14.1$, 2.9 Hz, H-14α), 1.53 (3H, d, $J = 6.9$ Hz, H_3-18). IR (ATR, cm^{-1}): 3330, 2925, 1731. CD ($c = 0.272$ mM, MeOH, 23 °C) $\Delta\varepsilon$ (λ nm): 0 (319), +0.79 (271), 0 (244), −13.02 (230), 0 (215), +1.12 (211), +2.16 (206).