Tetrahedron Letters 50 (2009) 3341–3344

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Spectroscopic analyses and chemical transformation for structure elucidation of two novel indole alkaloids from *Gelsemium elegans*

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ARTICLE INFO

Article history:
Received 10 January 2009
Revised 7 February 2009
Accepted 12 February 2009
Available online 20 February 2009

Keywords:
Gelsemium
Indole
Alkaloid
Gelsedine
Spectroscopy
Chemical transformation

ABSTRACT

Two new monoterpenoid oxindole alkaloids, gelsevanillidine (**1**) having an additional vanillin residue on gelsenicine-type alkaloid and gelseoxazolidinine (**2**) possessing an unusual oxazolidine ring, were isolated from *Gelsemium elegans*. To confirm their structures, the chemical transformation of a humantenine-type alkaloid into gelsevanillidine (**1**) and the deacetoxy derivative of gelseoxazolidinine was performed.

Gelsemium elegans Benth. (Loganiaceae) is a toxic plant that is widely distributed in Southeast Asia. *Gelsemium* plants are a rich source of indole alkaloids: more than 70 alkaloids have been isolated to this day, and they are classified into six types on the basis of their chemical structures.[1–3] *G. elegans* has been used in traditional Chinese medicine, and is the origin of 'Yakatsu', one of the ancient medicines stored in the Shosoin repository in Japan.[4] A number of pharmacological activities, including analgesic,[5] anti-inflammatory,[5] cytotoxic,[6,7] and antitumor[8] activities, of *G. elegans* alkaloids have been reported.

In our continuing chemical studies on the *Gelsemium* alkaloids,[6,9] we were able to isolate two novel gelsedine-related alkaloids, gelsevanillidine (**1**) and gelseoxazolidinine (**2**), from *G. elegans*. Gelsevanillidine (**1**) possesses a side chain with a vanillin residue, which is the first example of a monoterpenoid indole alkaloid. Gelseoxazolidinine (**2**) consists of a hexacyclic skeleton with an unprecedented oxazolidine ring. To confirm their unique structures, the chemical transformation of a known humantenine-type *Gelsemium* alkaloid, rankinidine (**4**), into new alkaloid **1** and the 14-deacetoxy derivative of new alkaloid **2** was performed (Fig. 1). In this Letter, we report the structure elucidation of these two new alkaloids **1** and **2** by means of spectroscopic analyses and chemical transformation.

New alkaloid **1**,[10] named gelsevanillidine,[11] was found to have the molecular formula $C_{27}H_{28}N_2O_5$ from HRFABMS [*m/z* 461.2075 (MH^+)]. UV spectroscopy (384, 314, 296 (sh), 247 (sh), 207 nm) suggested the presence of a long conjugated system. ^1H and ^{13}C NMR spectra (Table 1) showed readily assignable signals due to the gelsenicine (**5**) part, including signals of four aromatic protons [δ 7.58 (d, H-9), δ 7.30 (ddd, H-11), δ 7.12 (ddd, H-10), δ 6.96 (d, H-12)], an N_a-methoxy group [δ 3.89 (3H, s)], and oxygenated protons [δ 4.38 (br dd, H-17), δ 4.35 (dd, H-17), δ 3.70 (overlapped, H-3)], and confirmed the presence of a trisubstituted olefin group [δ_H 7.18 (br s, H-21), δ_C 130.9 (C-19), δ_C 139.6 (C-21)]. These spectral data were very similar to those of gelsecrotonidine,[9a] the exception being the existence of a 1,2,4-trisubstituted benzene ring system [δ_H 7.10 (br d, H-23), δ_H 7.01 (br dd, H-27), δ_H 6.85 (d, H-26), δ_C 148.7 (C-24), δ_C 148.3 (C-25), δ_C 129.8 (C-22), δ_C 124.8 (C-27), δ_C 116.2 (C-26), δ_C 114.6 (C-23)] instead of a methyl carboxylate group in gelsecrotonidine. Based on the allylic coupling of H-18 and H-21 as confirmed by ^1H–^1H COSY and the lack of H-19 protons, the olefin group was elucidated to be at C-19 position. Furthermore, the trisubstituted olefin group and the trisubstituted benzene ring system could be connected by HMBCs from the proton at δ 7.18 (H-21) to the carbons at δ 114.6 (C-23) and δ 124.8 (C-27) (Fig. 2). The substitution pattern of the benzene ring was presumed on the basis of NOE correlations (Fig. 2) from the proton at δ 7.18 (H-21) to the two protons at δ 7.10 (H-23) and δ 7.01 (H-27), and from the aromatic methoxy protons at δ 3.90 to the proton at δ

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doi:10.1016/j.tetlet.2009.02.092

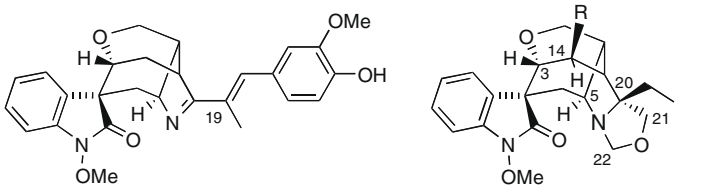


Figure 1. Structures of new alkaloids (**1** and **2**) and the 14-deacetoxy derivative of **2** (**3**).

Table 1
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for gelsevanillidine (**1**) in CD_3OD

Position	**1**	
	δ_H	δ_C
2		173.2
3	3.70 (overlapped)	76.3
5	4.56 (m)	73.2
6	2.59 (dd, 15.7, 4.8)	38.4
	2.20 (dd, 15.7, 1.9)	
7		57.6
8		133.3
9	7.58 (d, 7.7)	126.0
10	7.12 (ddd, 7.7, 7.7, 1.1)	124.7
11	7.30 (ddd, 7.7, 7.7, 1.1)	129.4
12	6.96 (d, 7.7)	107.8
13		139.1
14	2.39 (2H, overlapped)	29.6
15	3.70 (overlapped)	40.5
16	2.72 (m)	40.6
17	4.38 (br dd, 11.3, 1.4)	62.6
	4.35 (dd, 11.3, 3.0)	
18	2.32 (3H, br s)	15.1
19		130.9
20		184.2
21	7.18 (br s)	139.6
22		129.8
23	7.10 (br d,1.5)	114.6
24		148.7
25		148.3
26	6.85 (d, 8.2)	116.2
27	7.01 (br dd, 8.2, 1.5)	124.8
N_a–OMe	3.89 (3H, s)	63.9
24-OMe	3.90 (3H, s)	56.4

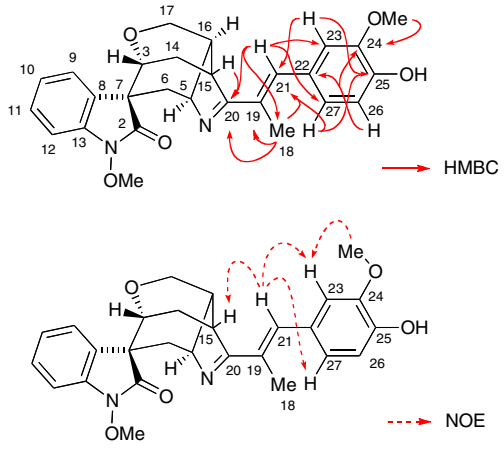
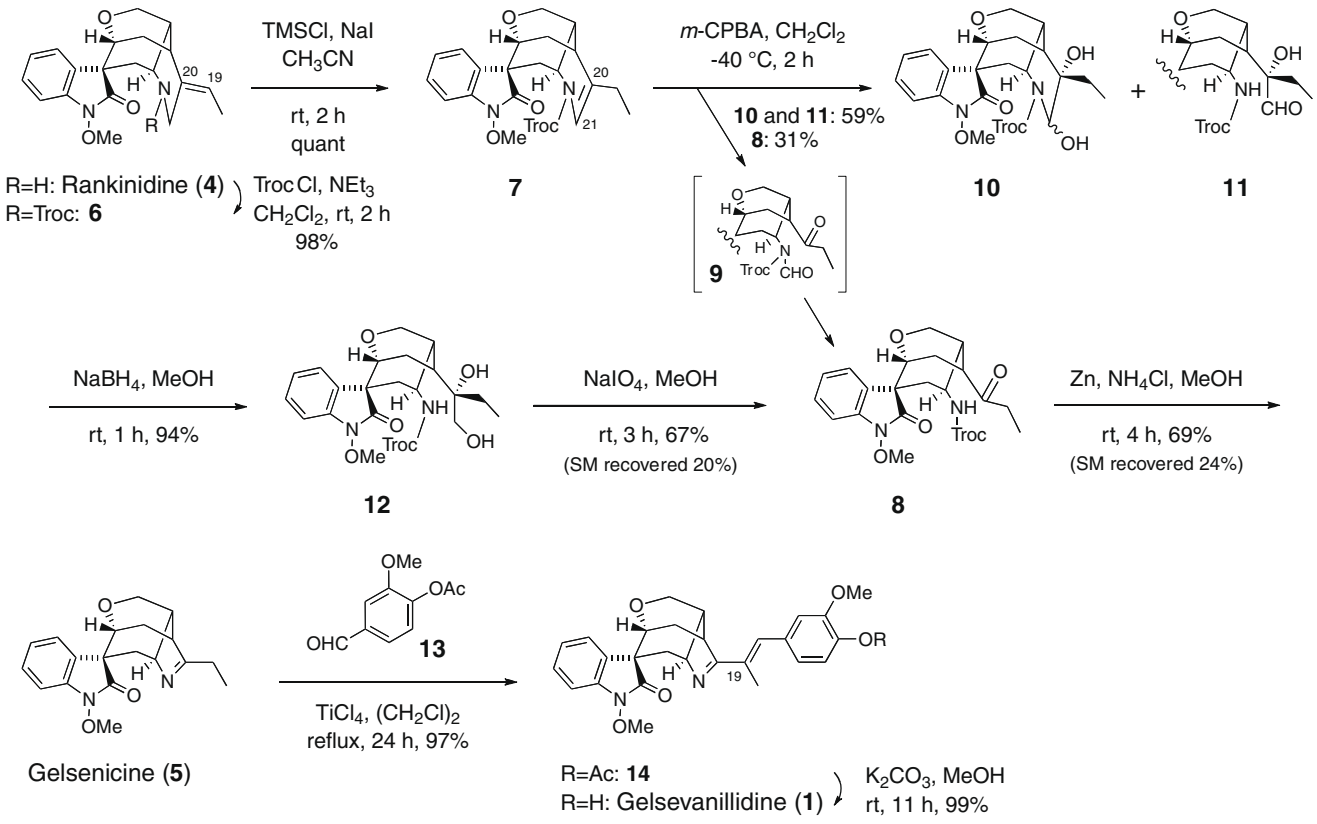


Figure 2. Selected HMBC and NOE correlation of gelsevanillidine (**1**).

7.10 (H-23), as well as of the HMBCs depicted in Figure 2. Considering all these factors as well as the chemical shifts, we proposed the presence of a *p*-hydroxy-*m*-methoxy-substituted benzene ring system. The double bond between C-19 and C-21 was elucidated to have the *E*-configuration based on the NOE correlation of the olefin proton (H-21) to the proton at δ 3.70 (overlapped, H-15). From these data, the structure of gelsevanillidine was deduced to be that shown as formula **1**.

To confirm the structure inferred from the spectroscopic analysis above, we attempted to synthesize **1** from the known humantenine-type alkaloid rankinidine (**4**),[12] which is one of the major alkaloids in *Gelsemium rankinii* (Scheme 1). At the start of the synthesis, rankinidine (**4**) was treated with 2,2,2-trichloroethyl chloroformate (TrocCl) in the presence of triethylamine in CH_2Cl_2 to give carbamate **6** in 98% yield. Then, the double bond migration from C-19–C-20 position to C-20–C-21 position was achieved in a quantitative yield by using TMSCl and NaI[13] in CH_3CN to afford enamine-carbamate **7**. Enamine-carbamate **7** was then treated with *m*-CPBA (3 equiv) in CH_2Cl_2 to afford keto-carbamate **8** in 31% yield, which would be formed via oxidatively cleaved product N_b-formyl-carbamate **9**,[14] together with a mixture of aminal **10** and aldehyde **11** in 59% yield. The mixture of **10** and **11** could be converted into keto-carbamate **8** by $NaBH_4$ reduction (94% yield) followed by oxidative cleavage of resulting diol **12** with $NaIO_4$ in MeOH in 67% yield. Removal of the N_b-carbamate in **8** with Zn and ammonium chloride in MeOH gave a secondary amine that was spontaneously converted into gelsenicine (**5**)[13,15] in 69% yield. Condensation of gelsenicine (**5**) and vanillin acetate (**13**) under acidic conditions with $TiCl_4$ in $(CH_2Cl)_2$ afforded **14** in 97% yield *E*-selectively to avoid the steric hindrance between a bulky aromatic ring and the gelsenicine part. Finally, removal of the acetyl group in **14** (K_2CO_3, MeOH) gave gelsevanillidine (**1**) in 99% yield. Synthetic **1** was completely identical in all respects with the natural one, thereby establishing its structure including its absolute configuration {natural: $[\alpha]_D^{22}$ – 79.9 (*c* 0.24, MeOH), synthetic: $[\alpha]_D^{22}$ – 81.8 (*c* 0.12, MeOH)}.

New alkaloid **2**,[10] named gelseoxazolidinine,[16] was shown to have the molecular formula $C_{23}H_{28}N_2O_6$ from HREIMS [*m*/*z* 428.1937 (M^+)]. UV and NMR spectra indicated the presence of the characteristic N_a-methoxyoxindole chromophore. ^{1}H and ^{13}C NMR data (Table 2) revealed the presence of a nonsubstituted A ring of the oxindole system, an N_a-methoxy group (δ_H 4.04, δ_C 63.5), an oxymethine group (δ_H 3.61, δ_C 76.7, C-3), a methine group bearing nitrogen (δ_H 3.46, δ_C 69.8, C-5), two oxymethylene groups (δ_H 4.32, 4.26, δ_C 62.9, C-17 and δ_H 3.62, 3.41 δ_C 75.4, C-21), and an oxymethine group (δ_H 6.08, δ_C 67.7, C-14) to which an acetoxy group [δ_H 2.00 (3H, s), δ_C 170.2, 21.1] is attached. ^{1}H–^{1}H COSY correlation between the H-3 oxymethine proton at δ 3.61 and the low-field methine proton at δ 6.08 indicated that an acetoxy group was attached to C-14. This inference was confirmed on the basis of the HMBC between the proton at δ 6.08 (H-14) and the acetoxy carbonyl carbon at δ 170.2 (Fig. 3). The configuration of the acetoxy group at C-14 was shown to be β from the coupling constant of



Scheme 1.

Table 2
^{1}H (400 MHz) and ^{13}C (125 MHz) NMR data for gelseoxazolidinine (**2**) in $CDCl_3$

Position	**2**	
	δ_H	δ_C
2		171.5
3	3.61 (d, 1.8)	76.7
5	3.46 (m)	69.8
6	2.19 (dd, 15.7, 2.8)	37.4
	2.14 (dd, 15.7, 4.2)	
7		53.6
8		131.2
9	7.34 (d, 7.5)	125.0
10	7.08 (ddd, 7.5, 7.5, 1.1)	123.1
11	7.28 (ddd, 7.5, 7.5, 1.1)	128.3
12	6.93 (d, 7.5)	106.8
13		138.5
14	6.08 (br s)	67.7
15	2.44 (br d, 6.4)	45.8
16	2.66 (m)	35.7
17	4.32 (dd, 10.8, 4.2)	62.9
	4.26 (br d, 10.8)	
18	0.85 (3H, dd, 7.2, 7.2)	8.9
19	2.80 (dq, 14.1, 7.2)	26.6
	1.66 (dq, 14.1, 7.2)	
20		[a]
21	3.62 (d, 8.3)	75.4
	3.41 (d, 8.3)	
22	4.56 (d, 7.2)	89.3
	4.35 (d, 7.2)	
N_a–OMe	4.04 (3H, s)	63.5
14-OCOMe		170.2
14-OCO*Me*	2.00 (3H, s)	21.1

[a] Under $CDCl_3$ signal.

the proton at C-14 ($J_{3,14}$ = 1.8 Hz), as in the case of other compounds having a hydroxyl or an acetoxy group at C-14.[7,9a,e,h] Furthermore, low-field methylene proton (δ 4.56, 4.35) and carbon

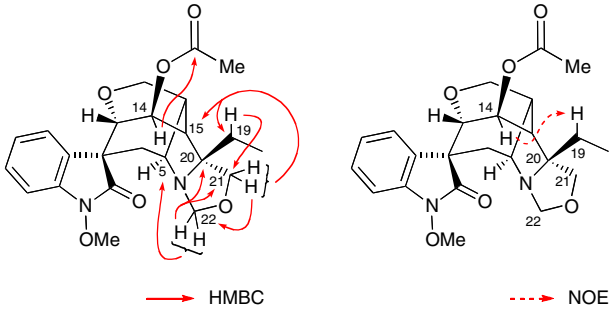
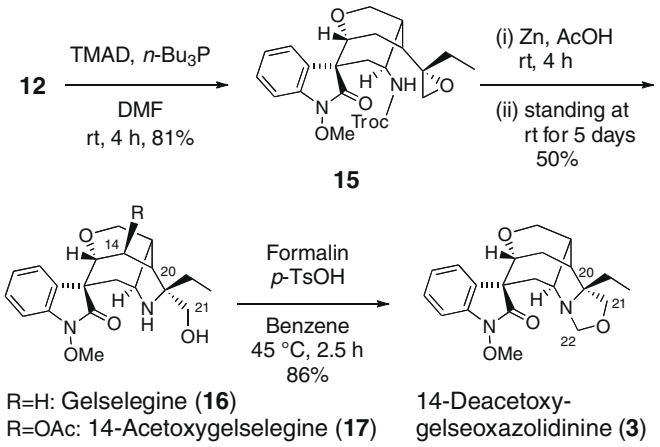


Figure 3. Selected HMBC and NOE correlation of gelseoxazolidinine (**2**).

signals (δ 89.3) were observed in the ^{1}H and ^{13}C NMR spectra, respectively, suggesting the existence of an hemiaminal methylene group (C-22). HMBCs between the hemiaminal protons and the oxymethylene carbon at δ 75.4 (C-21) and carbons bearing nitrogen (C-5 and C-20) implied the existence of an oxazolidine ring consisting of *N*-4, C-20, C-21, O, and C-22 positions. The NOE correlation of H-14 to H-19 revealed the β-ethyl configuration at C-20. Therefore, the structure of gelseoxazolidinine was deduced to be that shown as formula **2**.

As this kind of hexacyclic framework that includes an oxazolidine ring is the first instance of a natural product, we attempted to prepare the skeleton and to compare spectroscopic data. From a biogenetic point of view, gelseoxazolidinine (**2**) would be formed from 14-acetoxygelselegine (**17**)[6] by adding a C1 unit between N_b and C-21 primary alcohol. With compound **12** as the synthetic intermediate for gelsevanillidine (Scheme 1) in hand, we utilized it to construct the basic skeleton of gelseoxazolidinine, that is, the 14-deacetoxy derivative of gelseoxazolidinine. According to our previous study,[13] diol **12** was converted into epoxide **15** via



Scheme 2.

the modified Mitsunobu reaction [*N,N,N′,N′*-tetramethylazodicarboxamide (TMAD), *n*-Bu_3P, DMF] in 81% yield (Scheme 2). Removal of the N_b-Troc group (Zn, AcOH) afforded a primary amine, which was gradually cyclized at C-20 position to generate gelselegine (**16**).[17] Compound **16** was then treated with formalin in the presence of a catalytic amount of *p*-TsOH in benzene at 45 °C for 2.5 h to afford target molecule **3**[18] in 86% yield. The ^1H and ^{13}C NMR data and the CD spectral data of **3** resembled those of gelseoxazolidinine (**2**) well, except for the signals around C-14 position bearing a β-acetoxy group. Thus, we propose that the structure of gelseoxazolidinine is as shown in formula **2**.

In conclusion, the novel structures of two gelsedine-related oxindole alkaloids, gelsevanillidine (**1**) and gelseoxazolidinine (**2**), isolated from *G. elegans* were elucidated by spectroscopic and chemical methods. Gelsevanillidine is the first example of a monoterpenoid indole alkaloid with an additional vanillin residue, and gelseoxazolidinine is a novel skeletal type alkaloid consisting of a hexacyclic structure with an oxazolidine ring.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, the Research Foundation for Pharmaceutical Sciences, and The Uehara Memorial Foundation.

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10. The roots of *Gelsemium elegans* Benth. were collected in Phu Laung, Loei Province, Thailand, and were identified by Dr. Sumphan Wongseripipatana. A voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand. The roots of *G. elegans* (1353 g, dry weight) were extracted with MeOH to give a MeOH extract (109.7 g). The MeOH extract was dissolved in 20% MeOH/H_2O and was extracted successively with *n*-hexane, AcOEt, 5% MeOH/$CHCl_3$, and *n*-BuOH. The 5% MeOH/$CHCl_3$ extract (6.33 g) was separated by SiO_2 flash column chromatography with a $CHCl_3$/MeOH gradient to give seven fractions. The fraction eluted with 10% MeOH/$CHCl_3$ (164.5 mg) was purified by MPLC (3% MeOH/AcOEt and then 7% MeOH/$CHCl_3$) to give gelsevanillidine (**1**, 5.6 mg). Gelseoxazolidinine (**2**, 1.7 mg) was obtained from the crude base (6.76 g) that was prepared from the roots of *G. elegans* (600 g, dry weight) by a conventional method. The crude base was separated by amino silica gel open column chromatography with a $CHCl_3$/MeOH gradient, and then with an *n*-hexane/$CHCl_3$/MeOH gradient. The fraction that was eluted with 70–100% $CHCl_3$/*n*-hexane (552.5 mg) was purified by SiO_2 flash column chromatography ($CHCl_3$/MeOH gradient) and then by MPLC (5% MeOH/AcOEt) to give gelseoxazolidinine.
11. *Gelsevanillidine* (**1**): $[\alpha]_D^{22}$ −79.9 (*c* 0.24, MeOH); ^1H and ^{13}C NMR data, see Table 1; UV (MeOH) λ_{max} nm (log ε) 384 (3.57), 314 (4.05), 296 (sh, 4.01), 247 (sh, 4.02), 207 (4.46); IR (ATR) ν_{max} cm^{-1} 3263 (br), 2919, 1719, 1578, 1034; FABMS *m/z* 461 (MH^+); HRFABMS *m/z* 461.2075 (MH^+, calcd for $C_{27}H_{29}N_2O_5$, 461.2076); CD (*c* 0.219 mmol/L, MeOH, 24 °C) Δε (λ nm) 0 (352), +2.81 (306), 0 (278), −8.15 (258), 0 (243), +3.64 (236), 0 (227), −23.34 (211).
12. Rankinidine used in this study was isolated from *G. rankinii*: Schun, Y.; Cordell, G. A. *J. Nat. Prod.* **1986**, *49*, 806–808.
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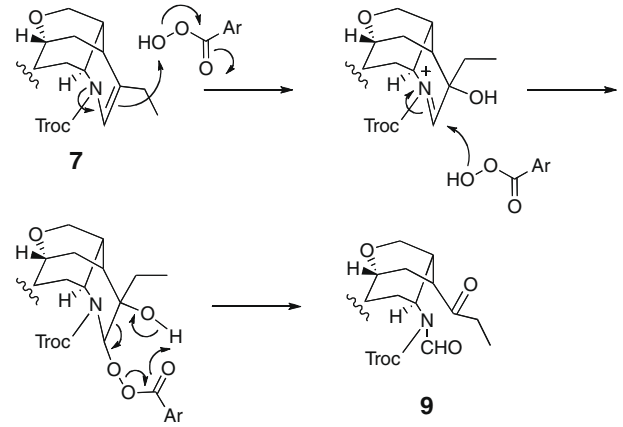
14. The possible mechanism for the oxidative cleavage of the enamine double bond with excess *m*-CPBA is shown below.



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16. *Gelseoxazolidinine* (**2**): $[\alpha]_D^{23}$ −93.8 (*c* 0.07, MeOH); ^1H and ^{13}C NMR data, see Table 2; UV (MeOH) λ_{max} nm (log ε) 284 (sh, 3.24), 256 (3.65), 209 (4.25); EIMS *m/z* (%) 428 (M^+, 17), 398 (78), 367 (77), 121 (100); HREIMS *m/z* 428.1937 (M^+, calcd for $C_{23}H_{28}N_2O_6$, 428.1947); CD (*c* 0.369 mmol/L, MeOH, 24 °C) Δε (λ nm) 0 (305), −4.46 (260), 0 (249), +7.81(236), 0 (222), −9.30 (212).
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18. *14-Deacetoxygelseoxazolidinine* (**3**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 7.4 Hz, H-9), 7.27 (1H, ddd, *J* = 7.4, 7.4, 1.2 Hz, H-11), 7.09 (1H, ddd, *J* = 7.4, 7.4, 1.2 Hz, H-10), 6.92 (1H, d, *J* = 7.4 Hz, H-12), 4.57 (1H, d, *J* = 7.3 Hz, H-22), 4.38 (1H, d, *J* = 7.3 Hz, H-22), 4.21 (1H, dd, *J* = 12.0, 2.8 Hz, H-17), 4.20 (1H, br d, *J* = 12.0 Hz, H-17), 4.01 (3H, s, N_a–OMe), 3.59 (1H, d, *J* = 7.8 Hz, H-21), 3.57 (1H, d, *J* = 6.4 Hz, H-3), 3.48 (br ddd, *J* = 9.2, 4.2, 3.1 Hz, H-5), 3.37 (1H, d, *J* = 7.8 Hz, H-21), 2.75 (2H, overlapped, H-14, H-19), 2.62 (1H, br dddd, *J* = 9.2, 6.0, 2.8, 2.8 Hz, H-16), 2.38 (1H, br ddd, *J* = 11.2, 6.0, 2.5 Hz, H-15), 2.14 (1H, dd, *J* = 15.8, 3.1 Hz, H-6), 2.11 (1H, dd, *J* = 15.8, 4.2 Hz, H-6), 2.04 (1H, ddd, *J* = 15.5, 11.2, 6.4 Hz, H-14), 1.60 (1H, dq, *J* = 14.4, 7.5 Hz, H-19), 0.87 (3H, dd, *J* = 7.5, 7.5 Hz, H_3-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C-2), 138.1 (C-13), 132.3 (C-8), 127.9 (C-11), 125.4 (C-9), 123.2 (C-10), 106.6 (C-12), 89.4 (C-22), 77.7 (C-20), 75.7 (C-21), 74.2 (C-3), 70.9 (C-5), 63.3 (N_a–OMe, C-17), 55.9 (C-7), 38.4 (C-15), 37.6 (C-16), 37.5 (C-6), 26.7 (C-19), 23.0 (C-14), 9.2 (C-18); UV (MeOH) λ_{max} nm (log ε) 257 (3.66), 208 (4.24); EIMS *m/z* (%) 370 (M^+, 33), 340 (95), 309 (100); HREIMS *m/z* 370.1892 (M^+, calcd for $C_{21}H_{26}N_2O_4$, 370.1892); CD (*c* 0.351 mmol/L, MeOH, 24 °C) Δε (λ nm) 0 (300), −1.46 (278), −5.73 (262), 0 (250), +11.08 (234), 0 (223), −19.82 (212).