DOI: 10.1002/asia.200800021

Monoterpenoid Indole Alkaloids Bearing an N_4-Iridoid from *Gelsemium elegans*

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Abstract: Five new alkaloids, gelseganines A–D (**1–4**) and humantenine N_4-oxide (**5**), were isolated from the stems and leaves of *Gelsemium elegans*. Compounds **1–4** represent a rare class of monoterpenoid indole alkaloids that bear an N_4-iridoid unit. The structures of **1–5** were determined by spectroscopic analysis, single-crystal X-ray diffraction, and chemical correlation, and their absolute configurations were elucidated by CD analysis. A plausible biogenetic pathway for alkaloids **1–5** was also postulated.

Keywords: alkaloids · natural products · structure elucidation · terpenoids · X-ray diffraction

Introduction

Gelsemium elegans Benth. (Loganiaceae), a well-known toxic plant in Southeast Asia, is used as a Chinese traditional medicine for the treatment of pain, spasticity, and ulcers.[1] Pharmacological investigations into the crude or purified alkaloids of this plant demonstrated potent cytotoxic,[2] analgesic, and anti-inflammatory[3] activity. Previous chemical studies of this plant led to the isolation of more than 40 oxindole alkaloids based on about 10 different structural classes.[4–9] Recently, our research group reported four new alkaloids from *G. elegans*.[4] In our continuing chemical studies of this plant, we re-examined the stems and leaves of *G. elegans*, and five new additional alkaloids **1–5** were isolated (Scheme 1). Among them, compounds **1–4** represent a rare type of alkaloid with an N4–C11′ linkage between the monoterpenoid indole alkaloid core and the iridoid moiety. In this report, we describe the isolation and structural determination of the new oxindole alkaloids **1–5**.

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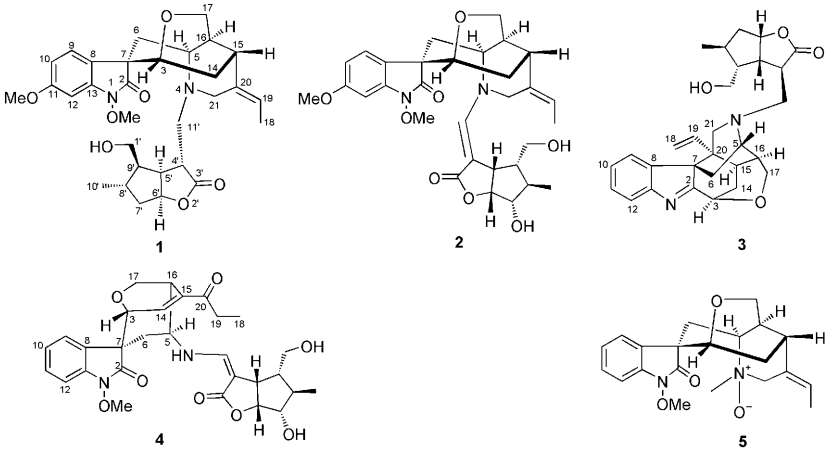
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200800021.

Results and Discussion

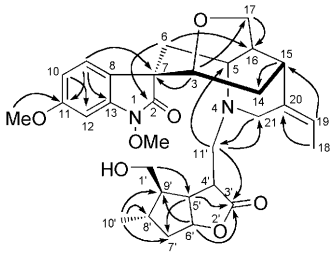
Gelseganine A (**1**) was obtained as a colorless crystal (m.p.: 126–127 °C). EI HRMS gave a molecular-ion peak at *m/z* 552.2816 $[M]^+$, consistent with the molecular formula $C_{31}H_{40}N_2O_7$, and a dominant fragment ion at *m/z* 370.1908 $[M-C_{10}H_{14}O_3]^+$, corresponding to $C_{21}H_{26}N_2O_4$, which is identical to the molecular ion of humantenirine (**6**),[5] a co-existing alkaloid in this plant. As the common *Gelsemium* alkaloids usually contain about 20 carbon atoms, compound **1** is thus supposed to bear an additional monoterpene unit. The ^{1}H NMR spectrum showed some readily assignable signals due to the alkaloid core of **6**, including those for three aromatic protons (δ_H = 7.22 (dd, 9-H), 6.60 (d, 10-H), 6.56 ppm (d, 12-H)), an N1 methoxy group (δ_H = 3.98 ppm (s, 3H)), an aromatic methoxy group (δ_H = 3.82 ppm (s, 3H)), three protons on oxygenated carbon atoms (δ_H = 3.58 (d, J = 7.0 Hz, 3-H), 4.05–4.07 ppm (m, 2H, 17-H)), an olefinic proton (δ_H = 5.52 ppm (q, J = 6.6 Hz, 19-H)), and an olefinic methyl group (δ_H = 1.67 ppm (d, J = 6.6 Hz, 3H, 18-H)). Furthermore, doublet methyl (δ_H = 0.95 ppm (d, J = 6.2 Hz, 3H, 10′-H)), hydroxymethyl (δ_H = 3.71 (dd, J = 12.3, 5.0 Hz, 1′-H_a), 3.33–3.37 ppm (m, 1′-H_b)), and oxymethine signals (δ_H = 4.97 ppm (dd, J = 7.3, 7.2 Hz, 6′-H)) were present and ascribable to an iridoid moiety. Analysis of the ^{13}C NMR spectrum of **1** demonstrated that the monoterpenoid indole alkaloid core and the iridoid appendage are the humantenirine and gelsamydine moieties, respectively, by comparison with literature data.[4,5] In a comparison of the ^{13}C NMR spectroscopic data of **1** with those of **6**, the severely downfield chemical shifts of C5 and C21 suggest that the gelsamydine moiety is probably attached to N4. This was



Scheme 1. Structures of the new alkaloids **1**–**5**.

demonstrated by the HMBC spectrum of **1**, in which the correlations 11′-H/C5 and C21 as well as 21-H/C11′ were observed, thus indicating the linkage of C11′ to the N4 nitrogen atom (Scheme 2). A single-crystal X-ray study further confirmed the structure of **1** (Figure 1) and allowed the determination of its relative stereochemistry, which was in good accordance with that assigned by its ROESY spectrum in solution.

Gelseganine B (**2**) was obtained as a white amorphous powder. EI HRMS showed the $[M]^+$ ion at m/z 566.2619, which corresponds to the molecular formula $C_{31}H_{38}N_2O_8$, thus implying that compound **2** is also a monoterpenoid indole alkaloid bearing an iridoid moiety. Comparison of the NMR spectroscopic data of **2** and **1** revealed that both compounds share a common humantenirine component, and the differences come from the iridoid moieties. In compound **2**, the iridoid component has an α,β-unsaturated lactone with a heteroatom (N or O) at the β position, as implied from the NMR resonances $\delta_H = 7.28$ (11′-H) and 4.66 ppm (6′-H), $\delta_C =$ 145.8 (C11′), 90.0 (C4′), 174.9 (C3′), and 82.1 ppm (C6′).[6] Furthermore, the C7′ atom of **2** was assigned as an oxygenated methine carbon atom ($\delta_H = 3.66$–3.70 ppm (m), $\delta_C =$ 79.4 ppm). The above structural deduction of **2** was further confirmed by its HMBC spectrum, in which the correlations 11′-H/C3′, C4′, C5, and C21 showed the linkage of C5, C21, and C11′ to the N4 atom, and the HMBC correlations from 10′-H and 8′-H to the oxygenated methine carbon atom revealed that C7′ bears a hydroxy group. The relative stereochemistry of **2** was established by analysis of the ROESY spectrum (Scheme 3). In particular, the *E* geometry of the



Scheme 2. Key HMBC correlations (H→C) of **1**.

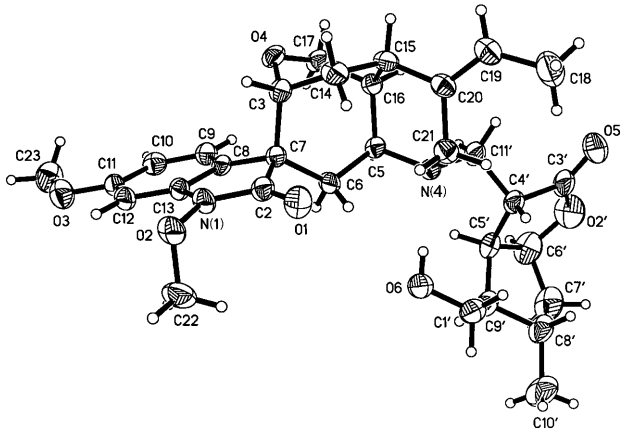
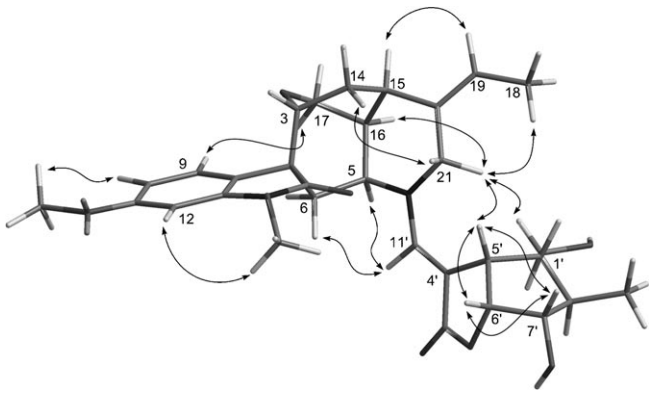


Figure 1. Single-crystal X-ray structure of **1**.



Scheme 3. Key ROESY correlations (↔) of **2**.

Δ4′(11′) double bond was determined by the ROESY correlations 11′-H/5-H and 6α-H as well as 21α-H/5′-H and 1′-H. The ROESY correlations from 7′-H to 5′-H and 6′-H indicate that these atoms are cofacial. The stereochemistry of the remaining part of **2** was assigned to be the same as that of **1** by comparing their NMR data.

Gelseganine C (**3**) was isolated as a colorless crystal (m.p.: 238–239 °C). The molecular formula $C_{29}H_{34}N_2O_4$ was established by the ESI HRMS peak at m/z 475.2599 $[M+H]^+$. The IR spectrum showed absorptions at 3425 (hydroxy) and 1755 cm^{-1} (five-membered lactone). The ^1H and

^{13}C NMR data showed the presence of four aromatic protons (δ_H=7.72 (d, 9-H), 7.28 (dd, 10-H), 7.36 (dd, 11-H), 7.59 ppm (d, 12-H)), a terminal vinyl group (δ_H=4.86 (d, 18-H$_a$), 4.84 (d, 18-H$_b$), 4.66 ppm (dd, 19-H); δ_C=116.5, 136.6 ppm), four sp^3-hybridized methylene carbon atoms (two of which bear heteroatoms), two heteroatom-bearing sp^3-hybridized methine carbon atoms (δ_C=70.9 (C3), 57.6 ppm (C5)), two sp^3-hybridized quaternary carbon atoms (δ_C=56.6 (C7), 44.9 ppm (C20)), and an imine carbon atom (δ_C=184.6 ppm (C2)). The aforementioned data of **3** show a remarkable resemblance to those of koumine (**7**),[7] which was also isolated in this study. The remaining 10-carbon unit was presumed to be an iridoid appendage with the characteristic doublet methyl (δ_H=1.01 (d, 3H, 10′-H); δ_C= 16.9 ppm), hydroxymethyl (δ_H=3.51–3.53 (m), 3.93 ppm (dd); δ_C=61.2 ppm (C1′)), oxygenated methine (δ_H=5.04–5.08 (m, 6′-H); δ_C=82.4 ppm), and lactone carbonyl signals (δ_C=177.8 ppm (C3′)). The koumine moiety and iridoid component are connected by the N4–C11′ bond, as determined by the HMBC correlations 5-H/C11′, 21-H/C11′, and 11′-H/C21. The single-crystal X-ray study of **3** (Figure 2) further confirmed its planar structure and allowed the determination of its relative stereochemistry, which is also in good accordance with that assigned by its ROESY spectrum in solution.

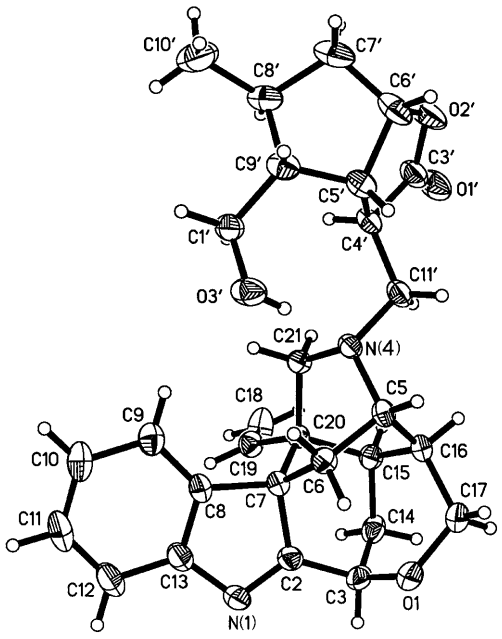
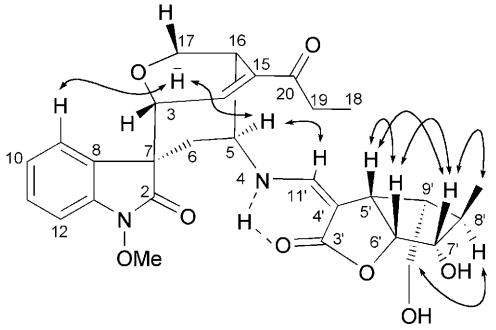


Figure 2. Single-crystal X-ray structure of **3**.

Gelseganine D (**4**), a colorless gum, gave an EI HRMS ion at *m*/*z* 538.2308 $[M]^+$, which corresponds to a molecular formula of $C_{29}H_{34}N_2O_8$, thus suggesting that **4** is an isomer of gelseiridone,[6] a known alkaloid previously isolated from the same plant. The ^{1}H and ^{13}C NMR data of **4** showed great similarities to those of gelseiridone, except for major differences that occurred for the iridoid moiety. In the NMR spectra of **4**, the signals for the oxygenated quaternary carbon atom (δ_C=83.7 ppm (C9′)) and methylene group (δ_C=39.0 ppm (C7′)) in gelseiridone were absent; instead, the signals for two additional methine carbon atoms (one oxygenated) were observed. This observation implies that the hydroxy group at C9′ of gelseiridone migrated to C7′ of **4**. In the HMBC spectrum of **4**, the correlations from 10′-Me to C7′ (δ_C=79.9 ppm) and C9′ (δ_C=48.0 ppm) confirm this conclusion. The relative stereochemistry of **4** was established by comparison of its NMR data with those of gelseiridone, and by analysis of its ROESY spectrum (Scheme 4).



Scheme 4. Key ROESY correlations (↔) of **4**.

In particular, the ROESY correlations from 5′-H to 6′-H and 7′-H allowed the assignment of 7′α-OH. The proton signal of N4H appeared clearly at δ_H=6.92 ppm (dd, J= 13.0, 9.2 Hz) in the ^{1}H NMR spectrum, which reveals the presence of a hydrogen bond between N4H and the C3′ carbonyl atom,[6] thus suggesting that the Δ4′(11′) double bond adopts *Z* geometry; this was corroborated by the ROESY correlation between 11′-H and 5-H. Thus, compound **4** was assigned to be the 7α-hydroxy-9-dehydroxy derivative of gelseiridone.

Humantenine N_4-oxide (**5**), a colorless gum, gave an EI HRMS molecular-ion peak at *m*/*z* 370.1895 $[M]^+$, corresponding to the molecular formula of $C_{21}H_{26}N_2O_4$, which has one more oxygen atom than humantenine (**9**),[5] a major alkaloid isolated in this study. The UV/Vis, IR, and NMR data of **5** are very similar to those of **9**, except for the downfield-shifted proton and carbon resonances for C5 methine (δ_H=3.85 ppm; δ_C=77.3 ppm), C21 methylene (δ_H=4.06 (d, J=14.1 Hz), 4.45 ppm (d, J=14.1 Hz); δ_C=60.1 ppm), and N_4-Me (δ_H=3.24 ppm (s, 3H); δ_C=57.4 ppm). This observation implies that **5** is an N_4-oxide derivative of **9**. Chemical transformation of humantenine (**9**) into humantenine N_4-oxide (**5**) was achieved by oxidation with *m*-chloroperbenzoic acid to confirm this conclusion. The ^{1}H and ^{13}C NMR data of **5** were completely assigned by 2D NMR spectroscopy (HSQC, HMBC).

The absolute stereochemistry of compounds **1**–**5** were determined by comparison of their CD spectra (Figure 3) with those of their analogues reported. Compounds **1**, **2**, and **5**, which share a common humantenine core, showed similar CD curves with those of humantenine,[10] which indicates

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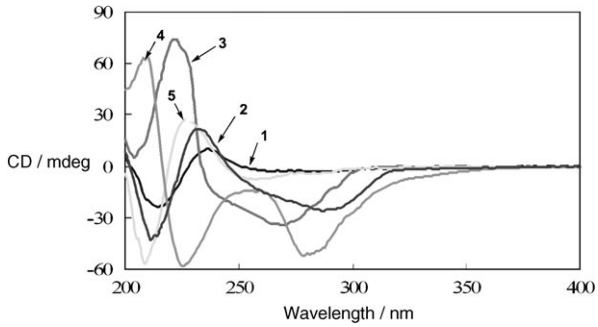


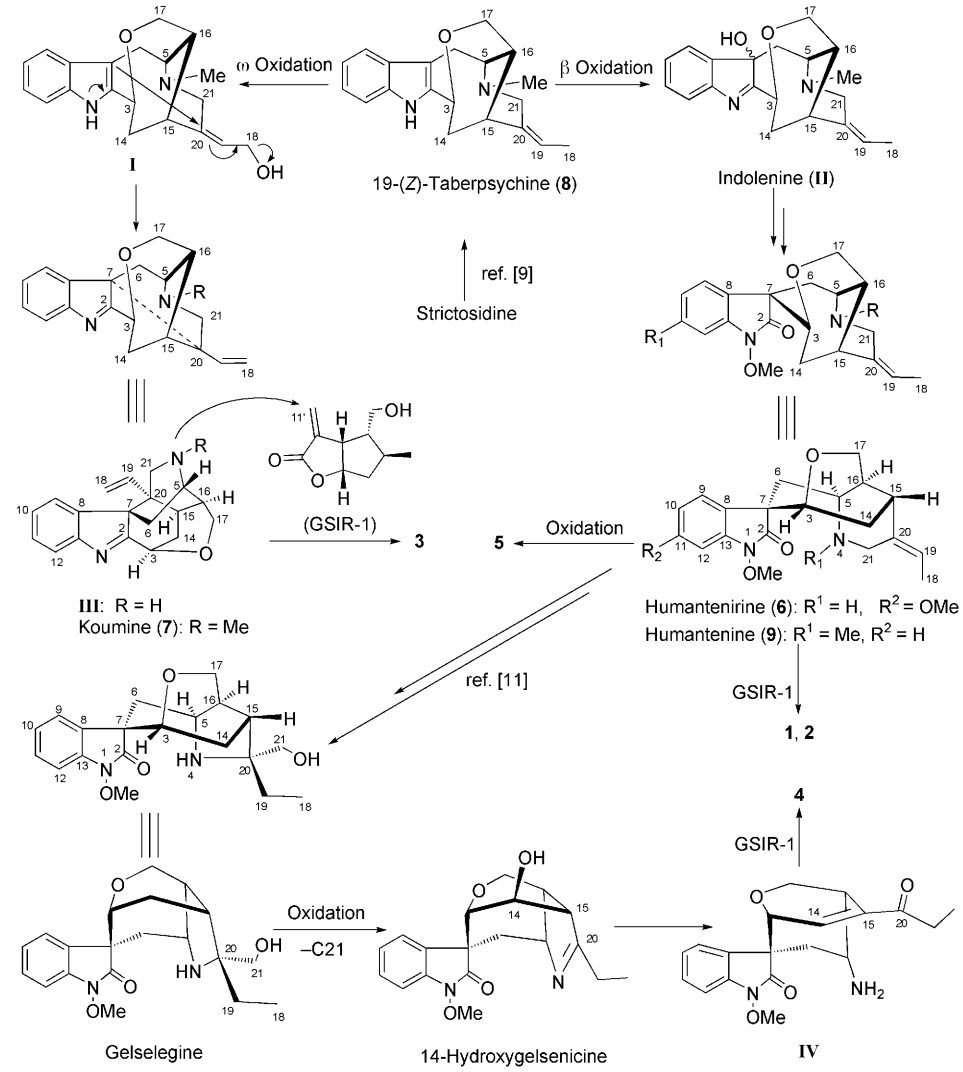
Figure 3. CD spectra of compounds **1**–**5**.

that the absolute configuration of their spiro center at C7 is *S*. The CD spectra of **3** and **4** showed great similarity to those of koumine[7] and gelseiridone,[6] respectively, thus giving their absolute stereochemistry as shown in Scheme 1.

On the basis of the previous work of Ponglux et al.,[9] a plausible biosynthetic pathway for alkaloids **1**–**5** was proposed (Scheme 5). The key alkaloid 19-(*Z*)-taberpsychine (**8**), which originates from strictosidine, was rationalized as the precursor of humantenine- and koumine-type indole alkaloids. Oxidation of C18 of alkaloid **8** and subsequent intramolecular C–C bond formation between C7 and C20 would afford the key intermediate **III**. Michael addition of the secondary amine of **III** to the C11′ position of GSIR-1,[11] a coexisting major iridoid in this plant genus, would produce alkaloid **3**.[6] β Oxidation of the indole part of **8** would generate indolenine (**II**), which would further transform into the humantenine-type alkaloids humantenirine (**6**) or humantenine (**9**). As in the case for the formation of **3**, humantenirine (**6**) would be transformed into alkaloid **1** or **2** by Michael addition with GSIR-1. The humantenine-type alkaloids would also be transformed into gelselegine by breaking the N4–C21 bond and forming an N4–C20 bond.[12] 14-Hydroxygelsenicine would be generated from gelselegine by C14 oxidation and C21 degradation. After hydrolytic cleavage of the imine and dehydration, 14-hydroxygelsenicine would be transformed into the key intermidiate **IV**, which would further condense with GSIR-1 to produce **4**.

Conclusions

The monoterpenoid indole alkaloids bearing an iridoid moiety are very rare, and the iridoid components in the previously reported Gelsemium alkaloids were normally embedded in the alkaloid core by the C19–C11′ bond. Interestingly, gelseganines A–D (**1**–**4**) bearing the iridoid components by means of a rarely seen N4–C11′ linkage were isolated from *Gelsemium elegans* in the current study.



Scheme 5. Plausible biosynthetic pathway for compounds **1**–**5**.

Table 1. ^{1}H NMR spectroscopic data for compounds **1**–**5**.[a]

H	1	2	3	4	5
3	3.58 (d, 7.0)	3.63 (m)	5.02 (m)	4.31 (d, 5.9)	3.67 (d, 7.5)
5	3.40 (m)	4.03 (m)	3.01 (m)	3.70 (m)	3.85 (m)
6α	1.90 (m)	2.43 (m)	2.33 (m)	1.91 (dd, 13.5, 13.5)	2.15 (m)
6β	2.54 (dd, 15.3, 9.1)	1.80 (m)	2.33 (m)	1.64 (dd, 13.5, 4.5)	2.49 (dd, 15.0, 9.3)
9	7.22 (dd, 7.3, 1.5)	7.18 (d, 8.2)	7.72 (d, 7.3)	7.37 (m)	7.38 (m)
10	6.60 (d, 7.3)	6.62 (dd, 8.2, 2.4)	7.28 (dd, 7.3, 6.4)	7.16 (ddd, 7.6, 7.6, 1.0)	7.16 (td, 7.8, 1.2)
11			7.36 (dd, 7.5, 6.4)	7.38 (m)	7.34 (m)
12	6.56 (d, 1.7)	6.59 (d, 2.4)	7.59 (d, 7.5)	7.03 (br d, 7.6)	7.03 (dd, 7.8, 1.2)
14α	2.30 (m)	2.46 (m)	1.89 (ddd, 14.5, 2.0, 2.0)	7.44 (dd, 6.5, 1.8)	2.21 (m)
14β	2.25 (m)	2.46 (m)	2.59 (m)		2.31(m)
15	2.63 (m)	2.84 (t, 5.0)	2.62 (m)		2.76 (m)
16	2.30 (m)	2.35 (br d, 10.2)	2.86 (m)	3.51 (br s)	3.78 (m)
17α	4.06 (m)	4.14 (br d, 11.2)	3.56 (m)	4.16 (br d, 9.5)	4.18 (d, 3.0)
17β	4.06 (m)	4.05 (m)	4.25 (dd, 12.1, 4.6)	3.58 (dd, 9.5, 2.4)	4.18 (d, 3.0)
18	1.67 (d, 6.6, 3H)	1.70 (d, 6.6, 3H)	a: 4.86 (d, 18.0) b: 4.84 (d, 11.0)	1.18 (t, 7.3, 3H)	1.72 (d, 6.9, 3H)
19	5.52 (q, 6.6)	5.60 (q, 6.6)	4.66 (dd, 18.0, 11.0)	a: 2.82 (dq, 17.2, 7.3) b: 3.02 (dq, 17.2, 7.3)	5.72 (q, 6.9)
21α	3.34 (m)	4.60 (br d, 15.7)	2.85 (m)		4.06 (d, 14.1)
21β	3.80–3.82 (m)	4.29 (br d, 15.7)	3.56–3.61 (m)		4.45 (d, 14.1)
1′a	3.71 (dd, 12.3, 5.0)	3.55–3.62 (m)	3.52 (m)	3.47 (m)	
1′b	3.35 (m)	3.55–3.62 (m)	3.93 (dd, 11.7, 4.5)	3.89 (ddd, 9.4, 2.5, 2.5)	
4′	2.68 (m)		2.75 (m)		
5′	2.93 (ddd, 7.4, 7.4, 6.8)	3.81 (m)	3.03 (m)	3.37 (ddd, 7.2, 7.2, 1.1)	
6′	4.97 (dd, 7.3, 7.2)	4.66 (dd, 5.9, 4.4)	5.06 (m)	4.70 (dd, 7.2, 5.1)	
7′α	1.49 (m)	3.66–3.70 (m)	2.18 (dd, 14.2, 6.0)	3.46 (m)	
7′β	2.11 (dd, 14.4, 6.2)		1.56 (m)		
8′	1.61 (m)	1.65 (m)	1.67 (m)	1.33 (m)	
9′	1.85 (m)	1.81 (m)	1.98 (m)	1.72 (m)	
10′	0.95 (d, 6.2, 3H)	1.12 (d, 6.4, 3H)	1.01 (d, 6.3, 3H)	1.05 (d, 6.3, 3H)	
11′a	3.34 (m)	7.28 (s)	3.43 (m)	7.42 (m)	
11′b	2.38 (m)		2.75 (m)		
11-OMe	3.82 (s, 3H)	3.84 (s, 3H)			
N_1-OMe	3.98 (s, 3H)	3.96 (s, 3H)		4.00 (s, 3H)	4.00 (s, 3H)
			1′-OH: 6.38 (s)	7′-OH: 2.20 (d, 11.3) N_4-H: 6.92 (dd, 13.0, 9.2)	N_4-Me: 3.24 (s, 3H)

[a] Recorded in $CDCl_3$ at 400 MHz. Chemical shifts and coupling constants (in parentheses) are given in ppm and Hz, respectively.

Table 2. ^{13}C NMR spectroscopic data for compounds **1**–**5**.[a]

C	1	2	3	4	5
2	174.3	173.3	184.6	171.0	173.7
3	72.2	72.2	70.9	71.4	72.1
5	62.1	64.0	57.6	58.0	77.3
6	29.1	33.4	32.8	37.6	30.6
7	54.5	54.2	56.6	52.8	55.8
8	120.2	119.3	143.0	125.9	127.9
9	126.6	126.7	123.6	129.1	125.8
10	107.5	107.7	126.5	123.6	123.6
11	160.2	160.4	128.3	126.3	128.8
12	94.7	95.0	120.9	107.7	107.8
13	140.1	140.0	154.7	139.2	138.9
14	27.7	30.0	25.2	139.0	27.3
15	34.9	32.0	32.9	138.5	33.1
16	35.3	37.5	34.2	39.7	30.8
17	66.6	65.6	60.7	68.5	65.8
18	12.9	13.3	116.5	8.3	13.1
19	122.1	122.3	136.6	30.6	126.1
20	134.7	135.1	44.9	201.3	131.7
21	43.9	42.1	56.4		60.1
1′	60.8	62.5	61.2	61.0	N_4-Me:
3′	177.8	174.9	177.8	174.7	57.4
4′	38.8	90.0	39.1	90.2	
5′	47.8	41.1	47.5	40.9	
6′	82.2	82.1	82.4	79.5	
7′	42.2	79.4	42.3	79.9	
8′	32.5	40.2	32.6	37.9	
9′	52.6	50.0	52.8	48.0	
10′	16.9	16.3	16.9	14.7	
11′	58.8	145.8	62.7	147.0	
11-OMe	55.6	55.6			
N_1-OMe	63.4	63.4		63.6	63.6

[a] Recorded in $CDCl_3$ at 100 MHz. Chemical shifts are given in ppm.

Experimental Section

General

Melting points were measured with an SGW X-4 melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter, and CD spectra were obtained on a JASCO 810 spectrometer. UV/Vis spectra were obtained on a Shimadzu UV-2550 spectrophotometer. IR spectra were obtained on a Perkin–Elmer 577 spectrometer as KBr disks. NMR spectra were recorded on a Bruker-AM-400 spectrometer. EI MS and HRMS (70 eV) were performed on a Finnigan MAT-95 mass spectrometer. ESI LRMS was performed on a Finnigan LC Q^{DECA} instrument, and ESI HRMS was performed on a Waters-Micromass Q-TOF Ultima Global electrospray mass spectrometer. Semipreparative HPLC was performed on a Waters 515 pump equipped with a Waters 2487 detector (254 nm) and a YMC-Pack ODS-A column (250×10 mm, S-5 μm, 12 nm). All solvents used were of analytical grade (Shanghai Chemical Plant, Shanghai, China). Silica gel

(200–300 mesh), silica gel H60, Sephadex LH-20 (Amersham Biosciences), reversed-phase C18 silica gel (150–200 mesh, Merck), and MCI gel (CHP20P, 75–150 mm, Mitsubishi Chemical Industries, Ltd.) were used for column chromatography. Precoated silica gel GF254 plates (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China) were used for TLC.

Plant Material

The leaves and stems of *G. elegans* were collected from Xishuangbanna Tropical botanical Garden (XTBG), Chinese Academy of Sciences, Mengla County, Yunnan Province, China in June 2006. The plant was identified by Prof. You-Kai Xu of XTBG, where a voucher specimen (accession number: 033769a) was deposited.

Isolation

The air-dried leaves and stems of *G. elegans* (4.5 kg) were percolated three times with EtOH (95%, 9.0 L) at room temperature. The ethanolic extract (900 g) was dissolved in water (1.5 L) to form a suspension, which was acidified with 20% H_2SO_4 to around pH 4. The acidic suspension was first partitioned with EtOAc to remove the neutral compounds, and the aqueous phase was then basified with Na_2CO_3 to around pH 10 and extracted with $CHCl_3$ to give a crude alkaloid extract (40 g). The crude alkaloid was subjected to silica-gel column chromatography (CC; $CHCl_3$/MeOH = 40:1→1:1) to give four major fractions (A–D). Fraction A (500 mg) was subjected to chromatography over silica gel ($CHCl_3$/MeOH = 20:1) to afford a major component, which was further purified by preparative HPLC (CH_3CN/H_2O = 70:30, 3 mL min^{-1}) to give **1** (22 mg). Fraction B (12 g) was separated by silica-gel CC (petroleum ether/EtOAc = 10:1→0:1) to afford six fractions B1–B6. Fraction B3 was subjected to CC with C18 reversed-phase silica gel (MeOH/H_2O = 30:70→100: 0) followed by extensive CC over columns of LH-20, silica gel, and MCI gel to give **3** (15 mg) and **5** (12 mg). Fraction C was subjected to silica-gel CC with a solvent system of cyclohexane/EtOAc/Et_2NH (10:1:1) to give five fractions C1–C5. Fraction C5 was purified by preparative HPLC (CH_3CN/H_2O = 60:40, 3 mL min^{-1}) to give two major compounds, **2** (28 mg) and **4** (16 mg).

1: Colorless crystals (MeOH). M.p.: 126–127 °C; $[\alpha]_D^{20} = -123.0$ ($c = 0.170$, MeOH); CD (MeOH): λ ($\Delta\varepsilon$) = 336 (0), 283 (−2.6), 250 (0), 236 (+8.6), 228 (0), 215 nm (−19.9 M^{-1}cm^{-1}); UV/Vis (MeOH): λ_{max} (log ε) = 215 (4.54), 262 (3.64), 286 nm (3.64); IR (KBr): $\tilde{\nu}_{max}$ = 3438, 2912, 1753, 1726, 1631, 1500, 1450, 1350, 1217 cm^{-1}; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2; MS (EI): *m*/*z* (%) = 552 $[M]^+$ (16), 521 (20), 370 (88), 339 (50), 164 (100), 140 (30), 108 (60), 93 (24); HRMS (EI): *m*/*z* calcd for $C_{31}H_{40}N_2O_7$: 552.2836; found: 552.2816.

2: White amorphous powder. $[\alpha]_D^{20} = -265.0$ ($c = 0.150$, MeOH); CD (MeOH): λ ($\Delta\varepsilon$) = 370 (0), 287 (−12.7), 246 (0), 232 (+10.7), 224 (0), 211 nm (−21.1 M^{-1}cm^{-1}); UV/Vis (MeOH): λ_{max} (log ε): 214 (4.41), 294 nm (4.28); IR (KBr): $\tilde{\nu}_{max}$ = 3427, 2929, 1716, 1604, 1498, 1360, 1219, 1130, 1032 cm^{-1}; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2; MS (EI): *m*/*z* (%) = 566 $[M]^+$ (24), 535 (34), 172 (100), 144 (64), 103 (42), 91 (38); MS (ESI+): *m*/*z* (%) = 589 $[M+Na]^+$ (60), 1155 $[2M+Na]^+$ (100); MS (ESI−): *m*/*z* (%) = 611 $[M+(HCOO)]^-$ (100); HRMS (EI): *m*/*z* calcd for $C_{31}H_{38}N_2O_8$: 566.2628; found: 566.2619.

3: Colorless crystals (MeOH). M.p.: 238–239 °C; $[\alpha]_D^{20} = -110.0$ ($c = 0.110$, MeOH); CD (MeOH): λ ($\Delta\varepsilon$) = 315 (0), 269 (−12.3), 232 (0), 221 nm (+26.7 M^{-1}cm^{-1}); UV/Vis (MeOH): λ_{max} (log ε) = 206 (4.71), 262 nm (3.75); IR (KBr): $\tilde{\nu}_{max}$ = 3425, 2952, 2920, 2864, 1755, 1589, 1454, 1190, 1078, 1036, 993 cm^{-1}; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2; MS (ESI+): *m*/*z* (%) = 475 $[M+H]^+$ (100); HRMS (ESI): *m*/*z* calcd for $C_{29}H_{35}N_2O_4$: 475.2597; found: 475.2599.

4: Colorless gum. $[\alpha]_D^{20} = -435.0$ ($c = 0.110$, MeOH); CD (MeOH): λ ($\Delta\varepsilon$) = 378 (0), 283 (−26.0), 256 (−4.7), 225 (−27.5), 217 (0), 210 nm (+30.4 M^{-1}cm^{-1}); UV/Vis (MeOH): λ_{max} (log ε): 205 (4.44), 288 nm (4.48); IR (KBr): $\tilde{\nu}_{max}$ = 3433, 2937, 1718, 1674, 1631, 1464, 1331, 1205, 1111, 1047 cm^{-1}; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2; MS (EI): *m*/*z* (%) = 538 $[M]^+$ (48), 369 (100), 173 (24); HRMS (EI): *m*/*z* calcd for $C_{29}H_{34}N_2O_8$: 538.2315; found: 538.2308.

5: Colorless gum. $[\alpha]_D^{20} = -108.0$ ($c = 0.060$, MeOH); CD (MeOH): λ ($\Delta\varepsilon$) = 350 (0), 260 (−2.0), 245 (0), 227 (+8.3), 220 (0), 209 nm (−17.6 M^{-1}cm^{-1}); UV/Vis (MeOH): λ_{max} (log ε): 205 (4.41), 256 (3.74), 339 nm (2.09); IR (KBr): $\tilde{\nu}_{max}$ = 3427, 2925, 1716, 1618, 1464, 1118, 1074, 752 cm^{-1}; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2; MS (EI): *m*/*z* (%) = 370 $[M]^+$ (40), 354 (70), 323 (100), 194 (62), 122 (40); HRMS (EI): *m*/*z* calcd for $C_{21}H_{26}N_2O_4$: 370.1893; found: 370.1895.

Oxidation of humantenine to **5**: 3-Chloroperbenzoic acid (12 mg) was added to a stirred solution of humantenine (10 mg) in $CHCl_3$ (2 mL) at 0 °C. The mixture was stirred at room temperature for 3 h and then evaporated. The resulting yellow solid was subjected to purification with silica-gel CC ($CHCl_3$/MeOH = 30:1) to give **5** (8 mg). Its $[\alpha]_D^{20}$ and ^{1}H NMR spectroscopic data are identical to those of the natural product.

Crystal data for **1**: $C_{31}H_{40}N_2O_7 \cdot H_2O$, orthorhombic, space group $P2_12_12_1$, a = 9.1725(8), b = 11.4638(10), c = 28.303 (2) Å, V = 2976.2(4) Å^3, Z = 4, D_{calcd} = 1.274 g cm^{-3}, T = 293 K, R = 0.0724, R_w = 0.0999. CCDC-664823 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for **3**: $C_{29}H_{34}N_2O_4$, monoclinic, space group $P2_1$, a = 9.3014(10), b = 11.7006(12), c = 11.8697(12) Å, V = 1191.5(2) Å^3, Z = 2, D_{calcd} = 1.323 g cm^{-3}, T = 293 K, R = 0.0512, R_w = 0.0919. CCDC-664824 (**3**) contains the supplementary crystallographic data for this papaer. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Financial support from the key project of the National Natural Science Foundation (Grant No. 30630072, 30721005) of the People's Republic of China is gratefully acknowledged. We thank Prof. You-Kai Xu for the collection and identification of the plant material.

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Received: January 22, 2008
Revised: April 4, 2008
Published online: July 4, 2008

