Biotransformation of Jervine by *Cunninghamella echinulata*

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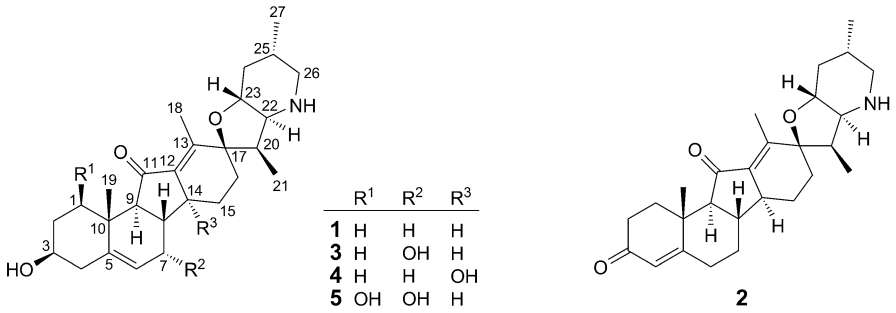
Biotransformation of jervine (**1**) by *Cunninghamella echinulata* (ACCC 30369) was carried out. Four biotransformation products were obtained, and three of them, **3**–**5**, were identified as new compounds. On the basis of their NMR and mass-spectral data, their structures were characterized as jervinone (**2**), 7α-hydroxyjervine (**3**), 14α-hydroxyjervine (**4**), and 1β,7α-dihydroxyjervine (**5**). The X-ray diffraction structure of **1** is also reported for the first time.

Introduction. – Microbial transformation is an effective method for the structural modification of bioactive natural compounds. Its application in asymmetric synthesis is increasing due to its versatility and ease [1]. A variety of transformations on natural products such as oxidation, reduction, hydrolysis, isomerization, epimerization, rearrangement, *D*-homoannulation, *Michael* addition, and reverse aldol reaction have been already performed [2]. *Cunninghamella echinulata*, a filamentous fungus, is recognized for its potential for steroid hydroxylation and has been noted for its ability to mimic mammalian hepatic metabolism with other substrates [3][4].

Veratrum alkaloids are a group of potent hypotensive agents that act by reflex suppression of the cardiovascular system [5][6]. Jervine (**1**) is one of the most important steroidal alkaloid derived from the *Veratrum* genus. Similar to cyclopamine, which also occurs in the *Veratrum* genus, it is a teratogen implicated in birth defects when consumed by animals during a certain period of their gestation [7–10]. Biotransformations of *Veratrum* alkaloids, such as rubijervine, jervine, and veratramine with various microorganisms have been reported previously [11–13].

In continuation of our studies on the phytochemistry of *Veratrum* alkaloids [14][15] and biotransformation studies on the *Veratrum* alkaloids [16], we now report the characterization of four metabolites of jervine (**1**) in cell suspension of *C. echinulata* (ACCC 30369). These metabolites were identified as jervinone (**2**), 7α-hydroxyjervine (**3**), 14α-hydroxyjervine (**4**) and 1β,7α-dihydroxyjervine (**5**) by spectroscopic methods (*Fig. 1*). We also report here the X-ray diffraction structure of jervine (**1**) for the first time.

Results and Discussion. – Compound **3** was obtained as a white amorphous powder, showing a positive reaction with *Dragendorff*'s reagent. The HR-ESI-MS (positive-ion



	R^1	R^2	R^3
1	H	H	H
3	H	OH	H
4	H	H	OH
5	OH	OH	H

Fig. 1. *Structures of compounds* **1**–**5**

mode) provided the molecular formula $C_{27}H_{39}NO_4$ *m/z* 442.2952 ($[M+H]^+$). The IR spectrum exhibited absorptions for an OH group (3370 and 1070 cm^{-1}). The ^{13}C-NMR spectrum (*Table 1*) of **3** showed signals due to four Me, seven CH_2, ten CH groups, and six quaternary C-atoms, including one C=C bond (δ(C) 142.3 (C(5)), 123.4 (C(6))), and three O-bearing sp^3-C-atoms. The ^{1}H-NMR spectrum (*Table 2*) displayed resonances for four Me groups (δ(H) 0.85 (*d*, *J* = 6.6, Me(27)), 0.89 (*s*, Me(19)), 0.90 (*d*, *J* = 7.1, Me(21)), 2.01 (*s*, Me(18)), and the ^{13}C-NMR exhibited the signals of two C-atoms attached to an N-atom at δ(C) 65.4 (C(22)) and 56.7 (C(26)), which are characteristic for a jervine-type steroid alkaloid. The OH is located at C(7) due to the HMBCs between the H-atom resonating at δ(H) 4.61–4.67 (*m*, H–C(7)) and C(8) (δ(C) 37.0). Furthermore, the relative configuration of 7-OH was deduced as α by NOESY correlation between H–C(7) and the H-atom resonating at δ(H) 2.30–2.36 (*m*, H_β–C(8)). Therefore, the structure of **3** was elucidated as 7α-hydroxyjervine.

Table 1. *^{13}C-NMR Data of* **3**–**5**. At 125 MHz in CD_3OD; δ in ppm. Atom numbering as indicated in *Fig. 1*.

C-Atom	**3**	**4**	**5**	C-Atom	**3**	**4**	**5**
C(1)	38.2	38.1	74.3	C(15)	24.3	24.1	24.0
C(2)	29.6	29.5	29.5	C(16)	28.4	28.7	28.8
C(3)	67.9	68.1	67.2	C(17)	84.3	84.3	84.7
C(4)	31.1	30.8	31.3	C(18)	11.6	11.6	11.7
C(5)	142.3	141.9	143.2	C(19)	18.1	18.5	18.0
C(6)	123.4	122.3	124.5	C(20)	39.8	39.8	39.6
C(7)	68.8	32.6	69.5	C(21)	10.6	10.7	10.7
C(8)	37.0	36.8	38.2	C(22)	65.4	65.8	65.9
C(9)	61.6	61.9	61.7	C(23)	76.0	75.2	75.4
C(10)	34.8	34.9	34.8	C(24)	38.2	38.5	38.5
C(11)	206.3	206.9	206.6	C(25)	31.3	31.3	31.5
C(12)	138.5	138.4	138.4	C(26)	56.7	56.6	56.8
C(13)	147.1	146.5	146.7	C(27)	18.7	18.9	19.1
C(14)	46.3	77.8	45.5				

Compound **4** was obtained as a white amorphous powder, showing a positive reaction with *Dragendorff*'s reagent. The HR-ESI-MS (positive-ion mode) gave the

molecular formula $C_{27}H_{39}NO_4$ *m/z* 442.2956 ($[M+H]^+$). The IR spectrum exhibited absorptions for OH groups (3361 and 1073 cm^{-1}). The ^{13}C-NMR data of **4** were similar to those of jervine (**1**) except for the presence of a OH group. Therefore, **4** was determined as an oxidized analog of **1**. The OH was localized at C(14) due to the HMBCs between H-atom resonating at δ(H) 1.72–1.77 (*m*, 1 H, CH_2(15)) and C(14) (δ(C) 77.8). Comparing the spectra of **4** with those of compound **1**, the chemical shifts of C(8), C(12), C(13), and C(15) were similar to those found in compounds **1**, **3**, and **5**, indicating the relative α-configuration for 14-OH. Thus, the structure of **4** was identified as 14α-hydroxyjervine.

Compound **5** was obtained as a white amorphous powder, showing a positive reaction with *Dragendorff*'s reagent. The HR-ESI-MS (positive-ion mode) led to the molecular formula $C_{27}H_{39}NO_5$ (*m/z* 458.2906, $[M+H]^+$). The IR spectrum exhibited absorptions for OH groups (3361 and 1068 cm^{-1}) and C=C bonds (1624 cm^{-1}). The ^{13}C- (*Table 1*) and ^1H-NMR (*Table 2*), and ESI mass spectra suggested it to be a dihydroxylated jervine derivative. Three OH groups are localized at C(1) (δ(C) 74.3), C(3) (67.2), and C(7) (69.5), respectively, due to the HMBC correlations between the H-atom resonating at δ(H) 3.85–3.89 (*m*, H–C(1)) and C(2) (δ(C) 29.5), the H-atom resonating at δ(H) 3.86–3.92 (*m*, H–C(3)) and C(2) (δ(C) 29.5), C(4) (31.3), and the H-atom resonating at δ(H) 4.59–4.66 (*m*, H–C(7)) and C(6) (δ(C) 124.5), C(8) (38.2). The stereochemical relationship among the functional groups, *i.e.*, 3-OH, Me(19), Me(21), and Me(27), was established to be identical to that of the

Table 2. *^1H-NMR Data of* **3**–**5**. At 500 MHz in CD_3OD; δ in ppm, *J* in Hz. Atom numbering as indicated in *Fig. 1*.

H-Atom	**3**	**4**	**5**
CH_2(1)	2.51–2.53 (*m*), 2.12–2.17 (*m*)	2.47–2.52 (*m*), 2.10–2.13 (*m*)	3.85–3.89 (*m*)
CH_2(2)	1.80–1.85 (*m*), 1.70–1.74 (*m*)	1.80–1.84 (*m*), 1.70–1.75 (*m*)	2.29–2.34 (*m*), 1.92–1.96 (*m*)
H–C(3)	4.12–4.21 (br. *s*)	4.11–4.26 (*m*)	3.86–3.92 (*m*)
CH_2(4)	2.41–2.47 (*m*), 1.52–1.61 (*m*)	2.38–2.45 (*m*), 1.51–1.55 (*m*)	2.57–2.63 (*m*), 2.39–2.44 (*m*)
H–C(6)	5.35 (*d*, *J* = 5.1)	5.35 (*d*, *J* = 5.1)	5.62 (*d*, *J* = 5.1)
H–C(7)	4.61–4.67 (*m*)	2.21–2.27 (*m*), 2.05–2.09 (*m*)	4.59–4.66 (*m*)
H–C(8)	2.30–2.36 (*m*)	1.63–1.67 (*m*)	2.35–2.39 (*m*)
H–C(9)	1.90–1.97 (*m*)	1.81–1.85 (*m*)	2.04–2.07 (*m*)
H–C(14)	1.96–2.01 (*m*)	–	2.09–2.13 (*m*)
CH_2(15)	1.92–1.97 (*m*), 1.31–1.33 (*m*)	2.21–2.24 (*m*), 1.72–1.77 (*m*)	1.99–2.04 (*m*), 1.39–1.42 (*m*)
CH_2(16)	2.33–2.36 (*m*), 1.38–1.41 (*m*)	2.07–2.11 (*m*), 1.68–1.71 (*m*)	2.33–2.36 (*m*), 1.32–1.36 (*m*)
Me(18)	2.01 (*s*)	2.04 (*s*)	2.01 (*s*)
Me(19)	0.89 (*s*)	0.85 (*s*)	0.91 (*s*)
H–C(20)	2.53–2.57 (*m*)	2.57–2.62 (*m*)	2.55–2.61 (*m*)
Me(21)	0.90 (*d*, *J* = 7.1)	0.91 (*d*, *J* = 7.0)	0.91 (*d*, *J* = 7.0)
H–C(22)	2.68–2.71 (*m*)	2.64–2.69 (*m*)	2.67–2.70 (*m*)
CH_2(23)	3.43–3.50 (*m*)	3.66–3.69 (*m*)	3.62–3.66 (*m*)
CH_2(24)	2.26–2.30 (*m*), 1.17–1.22 (*m*)	2.23–2.26 (*m*), 1.13–1.16 (*m*)	2.24–2.27 (*m*), 1.09–1.13 (*m*)
H–C(25)	1.48–1.53 (*m*)	1.49–1.52 (*m*)	1.47–1.52 (*m*)
CH_2(26)	3.14–3.18 (*dd*, *J* = 12.0, 3.5), 2.34–2.38 (*m*)	3.07–3.11 (*dd*, *J* = 11.0, 3.5), 2.28–2.31 (*m*)	3.19–3.25 (*dd*, *J* = 12.0, 6.0), 2.29–2.34 (*m*)
Me(27)	0.85 (*d*, *J* = 6.6)	0.87 (*d*, *J* = 6.6)	0.86 (*d*, *J* = 6.0)

starting material **1** by NOESY analysis, and also by comparison of chemical shifts and coupling constants of **5** with those of **1**. The relative configuration of 1-OH and 7-OH was deduced as β/α, respectively, by the NOESY correlations between H–C(1) resonating at δ(H) 2.04–2.07 (*m*, H_α–C(9)) and H–C(7) resonating at 2.35–2.39 (*m*, H_β–C(8)) (*Fig. 2*). Therefore, the structure of **5** was identified as 1β,7α-dihydroxyjervine.

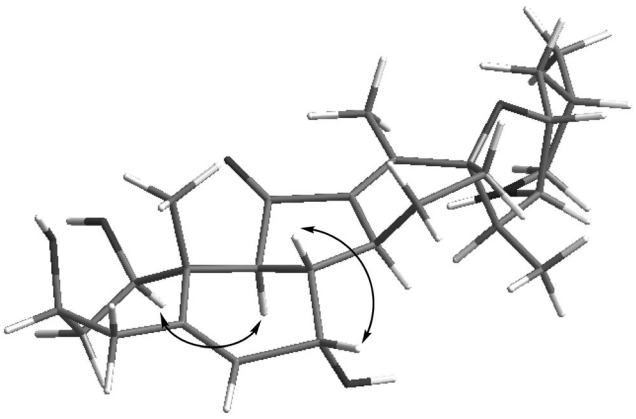


Fig. 2. *Key NOESY correlations of* **5**

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Experimental Part

General. Column chromatography (CC): *MCI* gel *CHP20P* (high-porous polymer 75–150 μm; *Mitsubishi Chemicals*, Japan), reversed-phase (RP) silica gel *RP-18* (40–63 μm; *Merck*, Germany), silica gel (SiO_2; 200–300 mesh; *Yantai*, P. R. China), and *Sephadex LH-20* (*Pharmacia Co., Ltd.*). TLC: SiO_2 plates; visualization by spraying with 10% H_2SO_4 in EtOH, followed by heating. Optical rotation: *Perkin-Elmer 341* polarimer. IR Spectra: *Nicolet-Compact-40-Bruker-Vector-22* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AVANCE^{II}-500* NMR, for ^1H at 500 and ^{13}C at 125 MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Varian MAT-212* mass spectrometer (for ESI) and *Q-Tof* micro mass spectrometer (for HR-ESI); in *m*/*z*.

Plant Material. The plants were collected in Yanbian, Jilin Province, P. R. China, in September 2005, and authenticated as *V. dahuricum* by Prof. *Yong-Zhen Liu*, School of Pharmacy, Yanbian University, China. A voucher specimen (No. 211) was deposited with the Herbarium of the School of Pharmacy, Shanghai Jiao Tong University, Shanghai, China.

Organisms. The stock culture of *C. echinulata* (ACCC 30369) was maintained on a potato dextrose agar slant. Four 1000-ml *Erlenmeyer* flasks, each containing 300 ml of liquid medium consisting of 0.1% peptone, 0.1% yeast extract, 0.1% beef extract, and 0.5% glucose were inoculated with freshly obtained *C. echinulata* cultured from the agar slant on a rotary shaker at 180 rpm. After cultivation at 28° for 72 h,

the *jervine* (**1**) soln. (50 mg of **1** dissolved in 250 µl of EtOH) was added to each flask, and the incubation was continued for 12 d.

Microbial Metabolism of Jervine (**1**). After 12 d of incubation, the incubation mixtures were pooled and filtered. The filtrate was passed through a *MCI-gel CHP20P* column, and washed with H_2O to remove sugars; then, successive extraction with 20% aq. MeOH, 60% aq. MeOH, and MeOH gave the *Fractions A*, *B*, and *C*, resp. Each fraction was evaporated to dryness *in vacuo* and analyzed by TLC ($CHCl_3$/MeOH/H_2O 65:35:10; visualization by spraying with 10% H_2SO_4 soln.). *Fr. C* was chromatographed repeatedly through a column on SiO_2 ($CHCl_3$/MeOH 10:1) to afford **2** (8.8 mg). *Fr. B* was subjected repeatedly to CC (SiO_2; $CHCl_3$/MeOH 5:1; *Sephadex LH-20*; 70% MeOH) to furnish **3** (4.6 mg) and **4** (6.1 mg). *Fr. A* was dissolved in 10% aq. MeOH and subjected to CC (RP SiO_2 (*ODS*); H_2O/MeOH 100:10 → 0:100) to give **5** (3.6 mg).

Jervine (**1**). Colorless prisms. $C_{27}H_{39}NO_3$. ESI-MS: 426 ($[M+H]^+$). $[\alpha]_D^{23} = -58.2$ ($c = 3.08$, MeOH). *Jervine* (**1**) was isolated from the roots of *Veratrum dahuricum* with purity of 99.0% by HPLC analysis in our laboratory. The chemical structure was identified by detailed NMR analysis and comparing its data with those in the literature [17]. An X-ray diffraction analysis of (−)-varatrobasine (= jervine-11β-ol) has been reported previously [18]. We performed the X-ray-analysis of **1** (*Fig. 3*) to establish the absolute configuration of (−)-jervine.

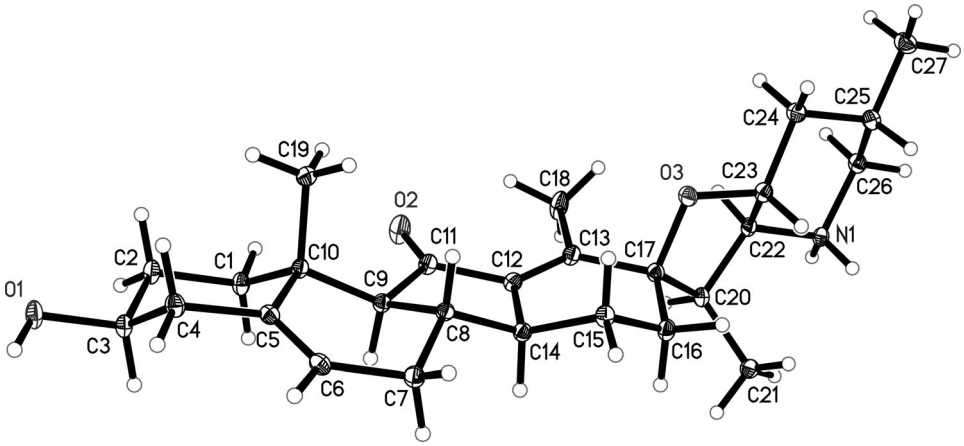

Fig. 3. *X-Ray crystal structure of* **1**

7α-Hydroxyjervine (= *(3β,7α,22*S,*23*R*)-3,7-Dihydroxy-17,23-epoxyveratraman-11-one* = *(3*S,*3′*R,*3a′*S,*6*S,*6′*S,*6a*S,*6b*S,*7a′*R,*9*R,*11a*S,*11b*R*)-2,3,3′a,4,4′,5′,6,6′,6a,6b,7,7′,7′a,8,11a,11b-Hexadecahydro-3,6-dihydroxy-3′,6′,10,11b-tetramethylspiro[9*H*-benzo[a]fluorene-9,2′(3′*H*)-furo[3,2-b]pyridin]-11(1*H*)-one*; **3**). White amorphous powder. $[\alpha]_D^{23} = -113.4$ ($c = 0.81$, MeOH). IR (KBr): 3370, 2951, 2177, 1623, 1070. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*, resp. 2D-NMR (HMBC; 500 MHz, CD_3OD): H–C(3)/C(4), H–C(7)/C(5), H–C(7)/C(8), H–C(15)/C(14). ESI-MS: 442 ($[M+H]^+$). HR-ESI-MS: 442.2952 ($[M+H]^+$, $C_{27}H_{40}NO_4^+$; calc. 442.2957).

14α-Hydroxyjervine (= *(3β,22*S,*23*R*)-3,14-Dihydroxy-17,23-epoxyveratraman-11-one* = *(3*S,*3′*R,*3a′*S,*6′*S,*6a*R,*6b*R,*7a′*R,*9*R,*11a*S,*11b*R*)-2,3,3′a,4,4′,5′,6,6′,6a,6b,7,7′,7′a,8,11a,11b-Hexadecahydro-3,6b-dihydroxy-3′,6′,10,11b-tetramethylspiro[9*H*-benzo[a]fluorene-9,2′(3′*H*)-furo[3,2-b]pyridin]-11(1*H*)-one*; **4**). White amorphous powder. $[\alpha]_D^{23} = -54.6$ ($c = 0.76$, MeOH). IR (KBr): 3361, 2947, 2170, 1617, 1073. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*, resp. 2D-NMR (HMBC; 500 MHz, CD_3OD): H–C(3)/C(4), H–C(7)/C(8), H–C(15)/C(14). ESI-MS: 442 ($[M+H]^+$). HR-ESI-MS: 442.2956 ($[M+H]^+$, $C_{27}H_{40}NO_4^+$; calc. 442.2957).

1β,7α-Dihydroxyjervine (= *(1β,3β,7α,22*S,*23*R*)-1,3,7-Trihydroxy-17,23-epoxyveratraman-11-one* = *(1*R,*3*R,*3′*R,*3a′*S,*6*S,*6′*S,*6a*S,*6b*S,*7a′*R,*9*R,*11a*S,*11b*R*)-2,3,3′a,4,4′,5′,6,6′,6a,6b,7,7′,7′a,8,11a,11b-Hexadeca-

*hydro-1,3,6-trihydroxy-3′,6′,10,11b-tetramethylspiro[9*H*-benzo[*a*]fluorene-9,2′(3′*H*)-furo[3,2-*b*]pyridin]-11(1*H*)-one*; **5**). White amorphous powder. $[\alpha]_D^{23} = -8.9$ ($c = 0.60$, MeOH). IR (KBr): 3361, 2937, 2155, 1624, 1068. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*, resp. 2D-NMR (HMBC; 500 MHz, CD_3OD): H–C(1)/C(2), H–C(3)/C(4), H–C(7)/C(5), H–C(7)/C(8). ESI-MS: 458 ($[M+H]^+$). HR-ESI-TOF-MS: 458.3304 ($[M+H]^+$, $C_{27}H_{40}NO_5^+$; calc. 458.2906).

X-Ray Diffraction Structure Analysis of Jervine[1]). Single crystal for analysis was obtained from $CHCl_3$/MeOH/H_2O. Data collection was performed with a *Bruker APEX2 CCD* and graphite monochromated CuK_α radiation ($\lambda = 1.54178$ Å) at 133(2) K. Crystallgraphic data: $C_{27}H_{39}NO_3 \cdot CH_3Cl \cdot 2\,H_2O$; M_r 512.11; crystal size $0.25 \times 0.20 \times 0.18$ mm, orthorhombic, space group $P2_12_12_1$; $a = 7.4412(10)$ Å, $b = 9.9446(10)$ Å, $c = 36.9172(3)$ Å, $\alpha = \beta = \gamma = 90°$; $V = 2731.86(5)$ Å^3; $Z = 4$; $D_x = 1.245$ g cm^{-3}; $F_{000} = 1112$; μ(CuK_α) 1.535 mm^{-1}. Cell refinement and data reduction: *Bruker SAINT*. Program used to solve and refine structure: SHELXS-97 and SHELXL-97, resp.; refinement on F^2 with full-matrix least-squares calculations. All non-H-atoms were filtered with anisotropic parameters, and all H-atoms were positioned by geometrical calculation and refined by ride-on method with relative isotropic parameters. Absorption correction were applied with semi-empirical from equivalents (maxmin transmission, 0.7679/0.7003). 12357 Reflections (4615 unique, $R_{int} = 0.0218$) were measured in the θ range of 2.39–66.56°; limiting indices, $8 \geq h \geq -8$, $11 \geq k \geq -11$, $41 \geq l \geq -43$. The final phase converged to $R_1 = 0.0289$ ($wR_2 = 0.0787$) for 4615 observed reflections ($I > 2\sigma(I)$) and 331 refined parameters, $R_1 = 0.0294$ ($wR_2 = 0.0790$) for all unique reflections; goodness-of-fit on F^2, 1.046.

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[1]) CCDC-889549 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.