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Four new tetracyclic alkaloids with *cis*-decahydroquinoline motif from *Myrioneuron effusum*

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ABSTRACT

Four new *Myrioneuron* alkaloids, mysumamides A–D (**1**–**4**), along with three known ones were isolated from the twigs and leaves of *Myrioneuron effusum*. All of these alkaloids possessed the tetracyclic skeleton and contained the decahydroquinoline (*cis*-DHQ) moiety. Their structures and relative configurations were elucidated on the basis of spectroscopic methods, especially 2D NMR techniques. The absolute configuration of **1** was determined by single-crystal X-ray diffraction. The cytotoxic activities of these compounds were also evaluated *in vitro*.

1. Introduction

Myrioneuron alkaloids elaborated specifically by plants of the genus *Myrioneuron* R. Br. (Rubiaceae) belong to the category of lysine-based structurally diverse natural products with various polycyclic skeletons (tricyclic-, tetracyclic-, pentacyclic-, hexacyclic-, octacyclic, and decacyclic-type), which have attracted much attention regarding their bioactivity and total synthesis [1–13]. In the past several years, we have isolated eighteen structurally unique and biosynthetically meaningful *Myrioneuron* alkaloids, including some with significant anti-hepatitis C virus (HCV) and antimicrobial activities [7–12]. In our continuing search for structurally unique and biologically active compounds, four new *Myrioneuron* alkaloids with *cis-DHQ* motif, mysumamides A–D (**1**–**4**) as well as three known ones, myrionamide (**5**), schoberine (**6**), and myrionidine (**7**) were isolated from the twigs and leaves of *Myrioneuron effusum* (Pitard) Li. Herein, we presented the isolation, structural elucidation, and bioactivity evaluation of these compounds.

2. Experimental

2.1. General experimental procedures

Optical rotations were measured with a Jasco P-1020 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for IR spectra as KBr pellets. 1D and 2D NMR spectra were recorded on Bruker spectrometer with TMS as internal standard. HRESIMS was performed on a triple quadrupole mass spectrometer. Semi-preparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Waters X-Bridge Prep Shield RP18 (10 × 150 mm) column. Column chromatography (CC) was performed using silica gel (100–200 mesh and 300–400 mesh, Qingdao Marine Chemical, Inc., Qingdao, PR China) and sephadex LH-20 (40–70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden).

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2.2. Plant material

The twigs and stems of *M. effusum* were collected from Guangxi Province, People's Republic of China, in November 2014. The plant samples were identified by Ligong Lei of Kunming Institute of Botany, Chinese Academy of Science (CAS). A voucher specimen (HXJ20141101) was deposited at the State Key Laboratory of Phytochemistry and Plant Resource in West China, Kunming Institute of Botany, Chinese Academy of Science (CAS).

2.3. Extraction and isolation

The air-dried, powdered leaves and twigs (57 kg) of *M. effusum* were extracted three times with MeOH at room temperature. The total extract (4.8 kg) was subjected to normal phase Si gel (100–200 mesh; $CHCl_3$/MeOH, 1:0 to 0:1) to obtain four major fractions (Fr. 1–4). Fraction 3 (212.3 g) was once again subjected to Si gel column chromatography (300–400 mesh) with $CHCl_3$/MeOH (15:1) to yield six sub-fractions (3a–3f). Fraction 3a (211.4 mg) was chromatographed over a sephadex LH-20 gel column, and then separated by semi-preparative HPLC (Waters XSelect Hss T3, 5 μm, 10 × 150 mm; MeOH-H_2O, 35:65; velocity of flow 2.5 mL/min) to give compound **1** (13.8 mg, retention time (t_R) = 27.5 min). Similarly, fraction 3e (96 mg) was separated to give compound **3** (1.8 mg, t_R = 20 min) by semi-preparative HPLC (Waters T3 column; MeOH-H_2O, 23:77; velocity of flow 2.0 mL/min). Fraction 3d (95 mg) was directly chromatographed over a sephadex LH-20 gel column to give compound **2** (15.2 mg). Fraction 2 (311.5 g) was also subjected to Si gel column chromatography with $CHCl_3$/MeOH (20:1) to yield four sub-fractions (2a–2d). Fraction 2c (90.0 g) was chromatographed over a RP-C18 silica gel with step-gradient of MeOH-H_2O (v/v, from 10:90 to 90:10) to obtain the crude alkaloids (51.4 g) and then separated to three fractions (2c-1–2c-3) by Si gel column chromatography (300–400 mesh, $CHCl_3$/MeOH, 20:1). Fraction 2c-1 (12.6 g) was separated by preparative HPLC (Waters XSelect CSH prep C18, 5 μm, 19 × 150 mm; MeOH-H_2O, from 30:70 to 90:10 in 20 mins; velocity of flow 10 mL/min) to obtained three fractions (2c-1a–2c-1c). Fraction 2c-1b (1.4 g) was chromatographed over a sephadex LH-20 gel column to give six fractions (2c-1b-1–2c-1b-6). Fraction 2c-1b-6 was separated by semi-preparative HPLC (Waters X-Bridge Prep Shield RP18, 5 μm, 10 × 150 mm; MeCN-H_2O, 17:83) to give compound **4** (3.1 mg, t_R = 28 min). Similarly, **5** (4.7 g) and **7** (38.5 mg) were obtained from fraction 2c-1b and **6** (1.0 mg) was obtained from fraction 2c-1c.

2.4. Mysumamide A (*1*)

Colorless crystal. $[\alpha]_D^{24} = -50.1$ (c = 0.21, MeOH). UV (MeOH): 204 (3.93). IR (KBr): 3427, 2925, 2861, 1643, 1455, 1443, 1418, 1372, 1334, 1295, 1241, 1195, 1179, 1089 and 1026 cm^{-1}. ^1H and ^{13}C NMR data (see Tables 1 and 2). Positive ESIMS: m/z 249 $[M + H]^+$. Positive HRESIMS: $[M + H]^+$ m/z 249.1962, calcd 249.1961. Melting point: 128–130 °C.

2.5. Mysumamide B (*2*)

Colorless oil. $[\alpha]_D^{25} = +6.8$ (c = 0.39, MeOH). UV (MeOH): 204 (3.82). IR (KBr): 3426, 2931, 2865, 1664, 1443, 1419, 1369, 1333, 1295, 1260, 1184, 1162, 1088, 1054, 1011 and 976 cm^{-1}. ^1H and ^{13}C NMR data (see Tables 1 and 2). Positive ESIMS: m/z 265 $[M + H]^+$. Positive HRESIMS: $[M + H]^+$ m/z 265.1914, calcd 265.1911.

2.6. Mysumamide C (*3*)

Colorless oil. $[\alpha]_D^{24} = -12.9$ (c = 0.12, MeOH). UV (MeOH): 380 (1.68), 204 (3.67). IR (KBr): 3426, 2926, 2854, 1632, 1447, 1418, 1384, 1291, 1272, 1234, 1201, 1175, 1121, 1087, 1064 and 1035 cm^{-1}. ^1H and ^{13}C NMR data (see Tables 1 and 2). Positive ESIMS: m/z 265 $[M + H]^+$. Positive HRESIMS: $[M + H]^+$ m/z 265.1911, calcd 265.1911.

Table 1
^1H NMR spectroscopic data for 1 to 4.

Position	1[a]	2[a]	3[b]	4[b]
2	2.78 (dt, 13.7, 3.9)	3.08 (m)	–	–
	2.46 (td, 14.6, 4.0)	3.01 (m)		
3	1.78 (m)	1.68 (m)	2.70 (dd, 18.0, 4.8)	2.49 (ddd, 17.6, 5.3, 1.6)
	1.54 (m)	1.54 (m)	2.38 (dd, 11.9, 6.2)	2.36 (ddd, 17.6, 12. 8, 6.7)
4	1.93 (m)	2.39 (m)[c]	2.21 (ddd, 26.5, 13.0, 4.9)	1.99 (ddd, 26.1, 13.0, 5.3)
	1.31 (m)	1.69 (m)	1.50 (m)	1.48 (m)[c]
5	1.92 (m)	1.73 (m)	2.11 (m)[c]	2.10 (dt, 16.1, 5.2)
6	1.55 (m)	2.94 (m)	1.80 (m)	1.70 (m)
	1.42 (m)	0.99 (m)[c]	1.66 (m)	1.41 (m)[c]
7	1.56 (m)	1.58 (dd, 13.5, 4.3)	1.55 (m)	1.58 (m)
	1.39 (m)	1.37 (m)	1.46 (m)	1.41 (m)[c]
8	1.60 (m)	1.48 (m)	0.96 (dd, 25.0, 12.1, 3.4)	1.81 (m)
	0.85 (m)	0.99 (m)[c]	1.58 (m)	1.02 (ddd, 25.3, 12.8, 3.5)
9	2.05 (m)	2.06 (ddt, 23.5, 11.7, 4.2)	2.91 (m)[c]	1.77 (m)
10	2.67 (dd, 13.8, 5.7)	3.05 (m)	3.31 (dd, 11.2, 5.3)	3.47 (dd, 11.2, 5.2)
11	4.61 (dd, 16.0, 5.8)	4.71 (dd, 13.2, 4.7)	3.40 (t, 11.3)	2.76 (dd, 11.2, 5.2)
	2.21 (t, 15.3)	2.39 (m)[c]	2.91 (m)[c]	
13	4.41 (t, 8.6)	4.62 (dd, 7.7, 4.8)	5.78 (dd, 12.9)	5.39 (dd, 11.2, 2.8)
14	1.96 (m)	2.62 (m)	2.11 (m)[c]	1.48 (m)[c]
	1.63 (m)[c]	2.31 (dd, 12.0, 4.4)	1.84 (m)[c]	1.86 (m)
15	1.81 (m)	1.84 (m)	1.95 (d, 12.1)	1.29 (m)
	1.63 (m)[c]	1.72 (m)	1.73 (m)[c]	1.68 (dt, 18.2, 4.5)
16	2.29 (dd, 9.5, 7.3)	2.36 (dd, 7.4, 2.2)	1.84 (m)[c]	1.30 (m)
	1.82 (m)	1.85 (m)	1.73 (m)[c]	1.48 (m)[c]
17	–	–	3.52 (dd, 6.8)	3.18 (d, 13.9)
			3.64 (m)	2.80 (td, 13.2, 2.7)
18				3.75 (dd, 11.5, 3.7)
				3.63 (dd, 11.5, 2.1)

[a] Recorded in $CDCl_3$-d_1 at 500 MHz.
[b] Recorded in $CDCl_3$-d_1 at 600 MHz.
[c] Overlapped.

Table 2
^{13}C NMR spectroscopic data for 1 to 4.

Position	1[a]	2[a]	3[b]	4[b]
2	38.6	50.7	170.4	168.3
3	25.8	30.3	32.9	32.6
4	24.1	20.0	21.6	21.7
5	35.3	29.3	32.7	33.0
6	20.0	29.3	30.5	30.3
7	31.2	22.0	20.1	20.6
8	29.7	19.4	28.1	29.3
9	26.3	31.6	31.3	38.0
10	65.3	80.0	55.4	54.4
11	47.6	46.9	62.6	59.1
13	75.5	88.3	79.0	66.4
14	26.2	20.8	26.5	24.8
15	19.3	18.4	22.7	20.2
16	32.9	32.1	23.1	24.4
17	170.6	170.1	70.2	48.9
CH_2OH				58.1

[a] Recorded in $CDCl_3$-d_1 at 125 MHz.
[b] Recorded in $CDCl_3$-d_1 at 150 MHz.

2.7. Mysumamide D (**4**)

Colorless oil. $[\alpha]_D^{19} = +38.6$ ($c = 0.46$, MeOH). UV (MeOH): 204 (3.76); IR (KBr): 3420, 2930, 2858, 1633, 1448, 1420, 1377, 1323, 1299, 1226, 1204, 1173, 1058, and 1026 cm^{-1}. ^{1}H and ^{13}C NMR data (see Tables 1 and 2). Positive ESIMS: m/z 279 $[M + H]^+$; Positive HRESIMS: $[M + H]^+$ m/z 279.2066, calcd 279.2067.

3. Results and discussion

Mysumamide A (**1**) was obtained as colorless crystal, and its molecular formula $C_{15}H_{24}N_2O$ was established by positive HRESIMS (m/z 249.1962 $[M + H]^+$, calcd for $C_{15}H_{25}N_2O$, 249.1961), corresponding to 5 degrees of unsaturation. The IR absorption band at 1643 cm^{-1} showed the presence of carbonyl functionality. Analysis of the NMR data, including DEPT and HSQC spectra revealed the presence of 15 carbon resonances, corresponding to one amide carbonyl (δ_C 170.6), ten sp^3 methylenes, and four sp^3 methines (Table 2). Of these, one methine (δ_C 75.5) was typical carbon bearing two nitrogen atoms of *Myrioneuron* alkaloid; two methylenes (δ_C 38.6 and 47.6) and one methine (δ_C 65.3) were representative carbons bearing one nitrogen atom, respectively. The amide carbonyl accounted for one out of the five indices of hydrogen deficiency, requiring four rings in the structure.

The gross structure of **1** was constructed by 2D NMR experiment as a myrionamide-type alkaloid (See Fig. 1.). Analysis of the ^{1}H—^{1}H COSY and HSQC spectra revealed two structural fragments as drawn with bold bonds (see Fig. 2). The connectivity of the both structural fragments, nitrogen atoms and the carbonyl group was then established by the analysis of HMBC correlations. Particularly, the HMBC correlations of H_2-2 (δ_H 2.46, td, 14.6, 4.0) and H-10 (δ_H 2.67, dd, 13.8, 5.7) to C-13 (δ_C 75.5) indicated that C-2 (δ_C 38.6), C-10 (δ_C 65.3), and C-13 were connected *via* N-1; the HMBC correlations of H_2-11 (δ_H 2.21, t, 15.3) with C-13 revealed that C-11 (δ_C 47.6) and C-13 were connected through N-12. In addition, the chemical shifts and HMBC correlations from H-13 (δ_H 4.41, t, 8.55), H_2-16 (δ_H 2.29, dd, 9.5, 7.3) and H_2-11 (δ_H 4.61, dd, 13.8, 5.7) to C-17 (δ_C 170.6) indicated the presence of a carbonyl at C-17. Thus, the 2D structure of **1** was established as shown.

The structure and the relative configuration of **1** were further confirmed by X-ray crystallographic analysis. The ORTEP drawing, with the atom-numbering indicated, was shown in Fig. 3. In the crystal structure, all four rings adopted chair conformation. Then, the absolute configuration of **1** was unequivocally established as **5*S***, **9*S***, **10*R***, **13*R*** *via* the refinement of its CuKα data [Flack parameter: 0.0 (3)].

The molecular formula of mysumamide B (**2**) was established as $C_{15}H_{24}N_2O_2$ by positive HRESIMS (m/z 265.1914 $[M + H]^+$, calcd for $C_{15}H_{25}N_2O_2$, 265.1911) with five degrees of unsaturation. Comparison of the NMR data of **2** to those of **1** (Tables 1 and 2) showed that they were closely related analogues featuring identical carbon frameworks. The main distinction was that the carbon signals of C-2, C-10 and C-13 in **2** were shifted downfield by 12.1, 14.7, 12.8 ppm, respectively. All these data suggested that these three carbons should be attached to the N-oxide group, which was further confirmed by 2D-NMR experiments. The relative configurations of all the chiral carbons of **2** was consistent with those of **1** as determined by similar ROESY correlations. Moreover, by comparison of the NMR data of **2** with that of **1**, the resonance of the C-5 is 6.0 ppm to low frequency ($\Delta\delta_{C\text{-}5} = -6.0$ ppm), which indicated that the oxygen atom

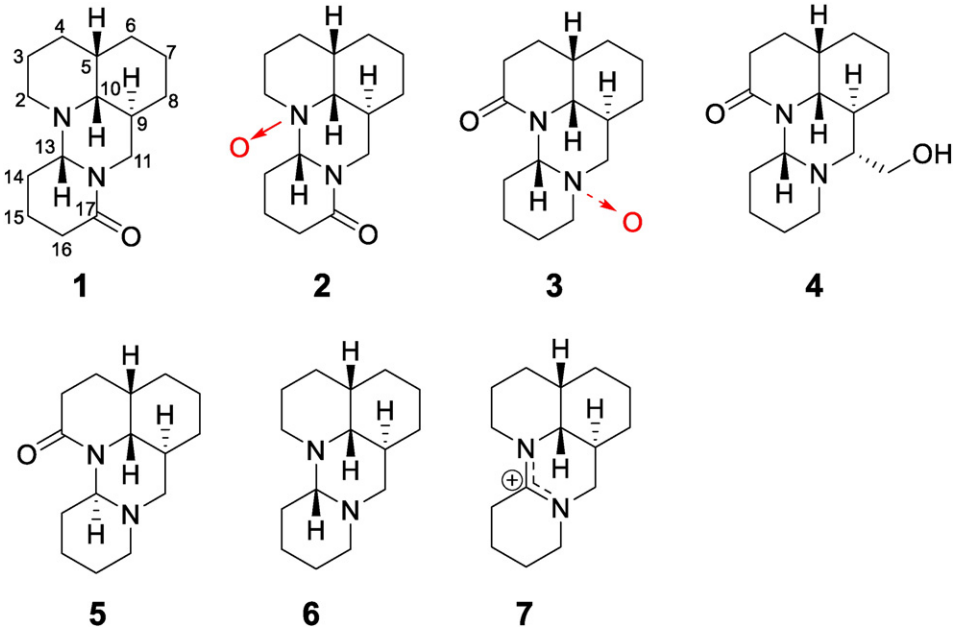

Fig. 1. Structures of **1** to **7**.

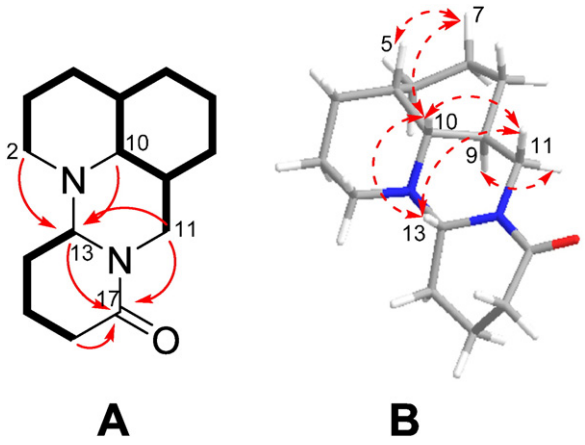

Fig. 2. (A) ^{1}H—^{1}H COSY (Bold) and key HMBC correlations (arrow, H → C) of **1**. (B) Key ROESY correlations of **1**.

at N-1 adopted β configuration as same as H-5 due to the obvious γ-gauche effect. [14–15].

Mysumamide C (**3**) was obtained as colorless oil. Its molecular formula, $C_{15}H_{24}N_2O_2$, was established by HRESIMS (*m/z* 265.1911 $[M + H]^+$, calcd for $C_{15}H_{25}N_2O_2$, 265.1911), which had one more oxygen atom than that of **5**. By comparing their NMR data (Tables 1 and 2), **3** were suggested to be the N-oxide derivatives of **5**. Subsequent 2D NMR data analyses defined its structure as myrionamide N-12-oxide. The relative configuration of **3** was shown to be identical to that of **5** based on their similar coupling constants and supported by the NOESY data. The up-field shift of the C-9 carbon ($\Delta\delta_{C\text{-}9} = -5.9$ ppm) compared with that of **5** revealed that oxygen atom at N-12 adopted α configuration as same as H-9 due to the γ-gauche effect.

Mysumamide D (**4**) was assigned the molecular formula $C_{16}H_{26}N_2O_2$ by HRESIMS at *m/z* 279.2066 $[M + H]^+$(calcd for $C_{16}H_{27}N_2O_2$, 279.2067), corresponding to five indices of hydrogen deficiency. Analysis of the NMR data (Tables 1 and 2), including

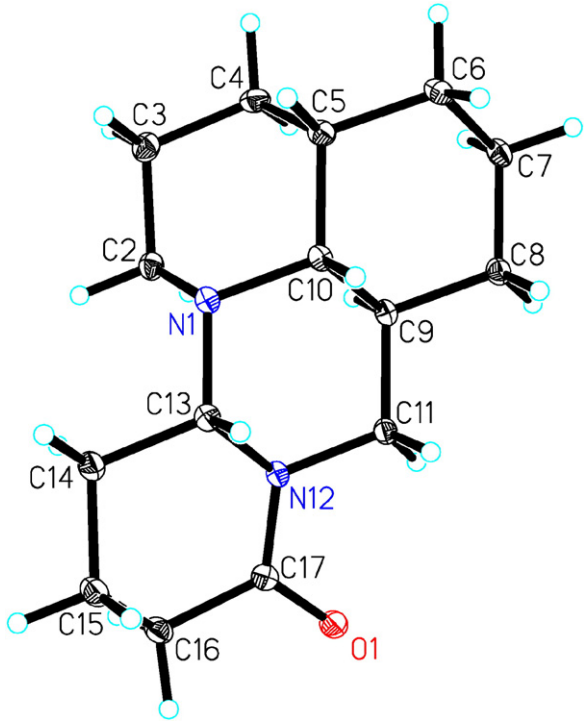

Fig. 3. X-ray ORTEP drawing of compound **1**.

DEPT and HSQC data of compound **4** revealed the presence of 16 carbon signals comprising one lactam carbonyl (δ_C 168.3), ten sp^3 methylenes (one oxygenated, and one nitrogenated), and five sp^3 methines (three nitrogenated). In addition to the one indice of hydrogen deficiency accounting for the lactam moiety, the remaining four indices of hydrogen deficiency were assumed to be due to the presence of a tetracyclic system in **4**. The ^{1}H and ^{13}C NMR data of compound **4** resembled those of **5,** indicating that both compounds are analogues. The main distinction was attributable to the presence of one additional hydroxymethyl (C-18, δ_C 58.1) in the former. ^{1}H—^{1}H COSY correlation of H_2–18 (δ_H 3.75, dd, 11.5, 3.7; δ_H 3.63, dd, 11.5, 2.1)/H-11 (δ_H 2.76, dd, 11.2, 5.2) suggested that the hydroxymethyl located at C-11 (δ_C 59.1), which was further confirmed by the HMBC correlations of H_2–18 to C-9 (δ_C 38.0) and C-11. ROESY correlations of H-10 (δ_H 3.47, dd, 11.2, 5.2)/H-11 and H-10/H-13 (δ_H 5.39, dd, 11.2, 2.8), and the correlations of H-6β (δ_H 1.70, m)/H-5 (δ_H 2.10, dt, 16.1, 5.2) and H-6β/H-10, indicated that these protons were cofacial as β-oriented (Fig. 4). Therefore, the structure of **4** was determined as shown.

Biogenetically, mysumamide D (**4**) should be derived from the deoxide (**8**) of mysumamide C as described in Scheme 1. **8** could be transformed into intermediate **9** *via* oxidation and dehydration. Then, intermolecular aldol condensation between **9** and formaldehyde yields intermediate **10**. Finally, compound **4** was generated by selective reduction.

Compounds **1–7** had been tested for their cytotoxicity against Hela, MCF-7, A549, MGC-803, and COLO-205 human cancer cell lines *in vitro*. The results indicated that only compound **5** exhibited weak cytotoxic activity against Hela, A549, and COLO-205 cell lines with IC_{50} of 38.3, 35.2, and 38.7 μM, respectively.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.fitote.2016.06.006.

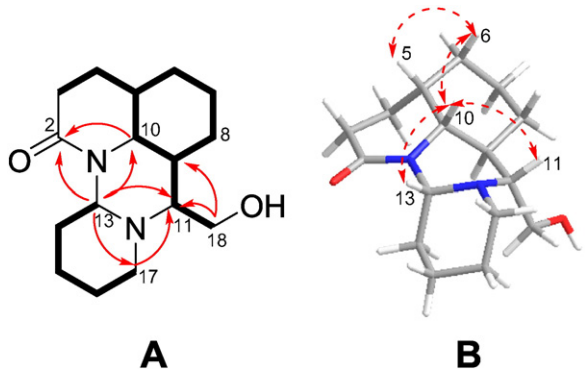
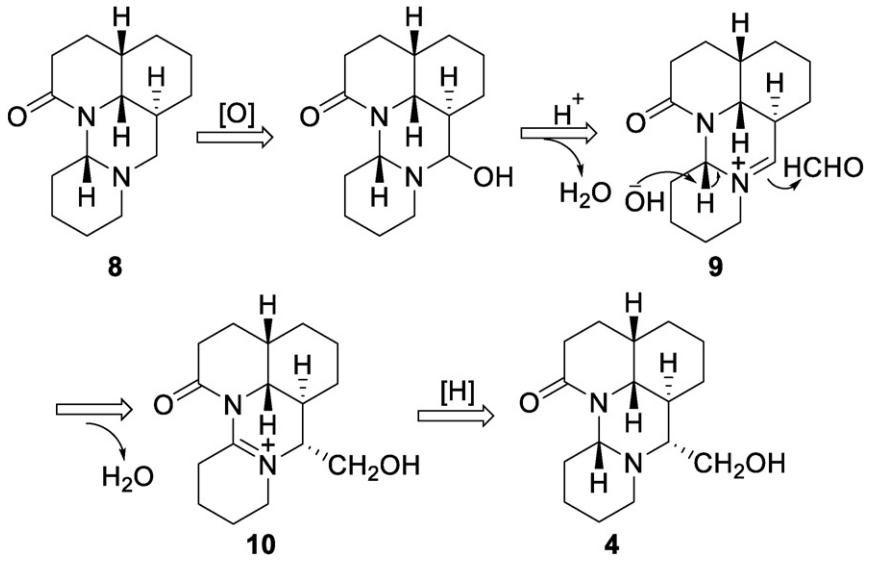


Fig. 4. (A) ^{1}H—^{1}H COSY (Bold) and key HMBC correlations (arrow, H → C) of 4. (B) Key ROESY correlations of **4**.



Scheme 1. Plausible biogenetic pathway of **4**.

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