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New findings of cyclohexane-fused octahydroquinolizine alkaloids from *Myrioneuron faberi*

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ABSTRACT

Cyclohexane-fused octahydroquinolizine (COHQ) alkaloids present an unwonted carbon framework among alkaloids isolated from genus *Myrioneuron*, which featured with bridge-ring and hemiacetal groups. Continued chemical investigation of *Myrioneuron faberi* led to the isolation of four COHQ related structures, β-myrifabral C (**1**), α-myrifabral C (**2**), β-myrifabral D (**3**), and α-myrifabral D (**4**). **1** and **2** were inseparable hemiacetal epimers (cluster A), as did **3** and **4** (cluster B). The structures of **1**–**4** were elucidated on basis of MS and NMR spectra. In vitro, cluster A showed moderate inhibition activity against hepatitis C virus (HCV) replication with therapeutic index (CC_{50}/EC_{50}) of 74.0.

Myrioneuron alkaloids are a class of fast growing natural products elaborated by plants of the genus *Myrioneuron*. The lysine-based origination of *Myrioneuron* alkaloids was suggested,[1–3] and the reactive C_5 units derived from lysine constructed intricate polycyclic ring systems (tri-, tetra-, penta-, hexa-, and decacyclic types).[4–10] A number of these structural distinctive alkaloids exhibited antimalarial,[2] antimicrobial,[7] and anti-HCV activities,[7–11] and attracted great organic synthesis interests.[1,2,12–15] Recent phytochemical investigation of *M. faberi*, *M. effusum*, and *M. tonkinensis* resulted in several interesting carbon frameworks,[7–11,16–18] which bring new insights into the biogenetical pathway and structural diversity of *Myrioneuron* alkaloids.

Cyclohexane-fused octahydroquinolizine (COHQ) alkaloids are a group of metabolites obtained from *M. faberi*.[8] Its unique octahydroquinolizine (OHQ) core was differed from other *Myrioneuron* alkaloids, and also featured with a bridge-ring and a hemiacetal groups. However, COHQ alkaloids show no exception with other typical *Myrioneuron* alkaloids, they all holding '$n \times C_5$' carbon frameworks (C_{10}, C_{15}, C_{20}, and C_{35}).[3,7]

During our ongoing investigation of structurally unique and biologically interesting *Myrioneuron* alkaloids, two C_{20} COHQ structures (**1** and **2**) and two C_{15} ones (**3** and **4**) were obtained. **1** And **2** presented a new carbon skeleton bearing a '—$(CH_2)_5$—' straight chain attached to the previously reported C_{15} COHQ carbon framework (myrifabral A)[8] through carbon-carbon bond. **3** and **4** presented C-6 epimer of myrifabral A. These findings to some degree broadened our understanding of structural diversity of *Myrioneuron* alkaloids. In this work, we report the isolation, structure elucidation, bioactivity, and hypothesized biogenetical pathway of **1**–**4**.

Cluster A (**1** and **2**)[19] was obtained as colorless gum. The NMR spectrum of Cluster A exhibited a mixture of two compounds' resonance signals (S1.1–1.6 in Supporting Information), and the downfield '—CH—' signals ($\delta_{C-13} = 98.2$ and $\delta_{C-12} = 80.7$ in **1**; $\delta_{C-13} = 92.2$ and $\delta_{C-12} = 72.6$ in **2**) (Tables 1 and 2) suggested it to be a pair of hemiacetal epimers as myrifabral A.[8] Because **1** and **2** are isomers, their molecular formula $C_{20}H_{35}NO_3$ was revealed by HRESIMS data (m/z found 337.2635 for $[M]^+$; calcd. for $C_{20}H_{35}NO_3$, 337.2617). The molecular formula $C_{20}H_{35}NO_3$ indicated that **1** and **2** possessing four devices of hydrogen deficiency. The ^{13}C NMR, DEPT and HSQC spectra of the mixture of **1** and **2** (S1.2 and S1.4 in Supporting Information) revealed that there are 40 carbon signals comprising $2 \times (14 \times CH_2,\ 5 \times CH,\ 1 \times qC)$ carbon atoms (Fig. 1). In addition, the typical nitrogenated carbon atoms in COHQ alkaloids (C-2, C-6, and C-16, see Table 1), and highfield quaternary carbon atoms ($\delta_{C-11} = 32.1$ in **1**; $\delta_{C-11} = 32.6$ in **2**) were observed. The above featured NMR data and the four devices of hydrogen deficiency indicated **1** and **2** possessed the COHQ carbon framework.

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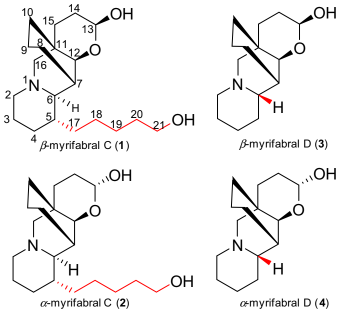
Table 1
^{13}C NMR data for **1**–**4** (δ in ppm).

No.	**1**[a]	**2**[a]	**3**[b]	**4**[b]
2	57.1 (CH$_2$)	57.1 (CH$_2$)	54.8 (CH$_2$)	54.7 (CH$_2$)
3	26.4 (CH$_2$)	26.4 (CH$_2$)	25.9 (CH$_2$)	26.1 (CH$_2$)
4	30.4 (CH$_2$)	30.4 (CH$_2$)	22.6 (CH$_2$)	22.5 (CH$_2$)
5	37.2 (CH)	37.3 (CH)	29.8 (CH$_2$)	29.9 (CH$_2$)
6	70.3 (CH)	70.8 (CH)	64.1 (CH)	64.5 (CH)
7	35.3 (CH)	35.0 (CH)	40.2 (CH)	40.0 (CH)
8	20.7 (CH$_2$)	20.5 (CH$_2$)	19.2 (CH$_2$)	19.4 (CH$_2$)
9	21.4 (CH$_2$)	21.5 (CH$_2$)	25.4 (CH$_2$)	25.4 (CH$_2$)
10	29.5 (CH$_2$)	28.6 (CH$_2$)	29.2 (CH$_2$)	28.4 (CH$_2$)
11	32.1(qC)	32.6 (qC)	31.9 (qC)	32.4 (qC)
12	80.7 (CH)	72.6 (CH)	74.3 (CH)	66.4 (CH)
13	98.2 (CH)	92.2 (CH)	98.2 (CH)	92.3 (CH)
14	30.6 (CH$_2$)	27.4 (CH$_2$)	30.7 (CH$_2$)	31.2 (CH$_2$)
15	34.2 (CH$_2$)	29.3 (CH$_2$)	35.9 (CH$_2$)	27.6 (CH$_2$)
16	69.1(CH$_2$)	69.6 (CH$_2$)	62.2 (CH$_2$)	62.9 (CH$_2$)
17	32.0 (CH$_2$)	32.0 (CH$_2$)		
18	26.6 (CH$_2$)	26.6 (CH$_2$)		
19	27.2 (CH$_2$)	27.2 (CH$_2$)		
20	34.2 (CH$_2$)	34.2 (CH$_2$)		
21	62.4 (CH$_2$)	62.4 (CH$_2$)		

[a] Recorded at 294 K.
[b] Recorded at 300 K.

The 2D structure of **1** was confirmed by 2D NMR (^{1}H–^{1}H COSY, HSQC, and HMBC) spectrums. Related to the downfield NMR signals, four ^{1}H–^{1}H spin fragments were figured out: H$_2$-2/H$_2$-3, H-5/H-6/H-7/H-12, H-13/H$_2$-14, and H$_2$-21/H$_2$-20 (Fig. 2). The location of CH$_2$-4 was elucidated by HMBC correlations from H$_2$-2 (δ_H 2.70, m; 1.67, m) to C-4 (δ_C 30.4), and H$_b$-4 (δ_H 0.84, m) to C-5 (δ_C 37.2) and C-6 (δ_C 70.3) (Fig. 2). Then the linkage of rings A and B through C-6 and N-1 was suggested by HMBC correlations from H-6 (δ_H 1.74, m) to C-2 (δ_C 57.1), C-12 (δ_C 80.7), and C-16 (δ_C 69.1). The existence of ring C and hemiacetal group was revealed by HMBC correlations from H-12 (δ_H 3.20, d, 3.0 Hz) to C-13 (δ_C 98.2), H$_2$-15 (δ_H 1.25, m) to C-12 and C-13. Finally, the bridge ring over CH-7 and qC-11 can be elucidated by HMBC correlations from H-7 (δ_H 2.16, br s) to C-8 (δ_C 20.7), as well as H-12 to C-8 and C-10 (δ_C 29.5). Thus a C$_{20}$ planar fragment harboring COHQ moiety of **1** was elucidated as in myrifabral A, whose structure was confirmed by single crystal X-ray analysis.[8]



β-myrifabral C (**1**)
β-myrifabral D (**3**)
α-myrifabral C (**2**)
α-myrifabral D (**4**)

Fig. 1. Structures of **1**–**4**.

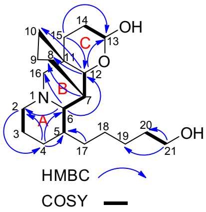


Fig. 2. ^{1}H–^{1}H COSY and Key HMBC correlations of **1**.

The rest five carbon atoms in structure of **1** all showed '—CH$_2$—' signals in DEPT135 spectrum indicating that this C$_5$ moiety to be a

Table 2
^{1}H NMR data for **1**–**4** Recorded in prydine-d_5 at 600 MHz, assigned based on HSQC.

No.	**1**[a]	**2**[a]	**3**[b]	**4**[b]
2	2.70 (m)	2.70 (m)	2.79 (m)	2.79 (m)
	1.67 (m)	1.67 (m)	2.41 (m)	2.41 (m)
3	1.53 (m)	1.53 (m)	1.66 (m)	1.66 (m)
	1.26 (m)	1.26 (m)	1.29 (m)	1.29 (m)
4	1.76 (m)	1.76 (m)	1.61 (m)	1.58 (m)
	0.84 (m)	0.84 (m)	1.23 (m)	1.23 (m)
5	1.53 (m)	1.53 (m)	1.60 (m)	1.60 (m)
			1.23 (m)	1.23 (m)
6	1.74 (m)	1.79 (m)	2.50 (m)	2.53 (m)
7	2.16 (br s)	2.06 (br s)	1.84 (m)	1.71 (m)
8	2.04 (m)	1.99 (m)	2.29 (m)	2.29 (m)
	1.62 (m)	1.62 (m)	1.50 (m)	1.50 (m)
9	2.73 (m)	2.78 (m)	2.10 (m)	2.10 (m)
	1.48 (m)	1.54 (m)	1.35 (m)	1.35 (m)
10	2.24 (m)	2.28 (m)	2.24 (m)	2.24 (m)
	1.21 (m)	1.21 (m)	0.99 (m)	1.03 (dd, 12.6, 5.4 Hz)
12	3.20 (d, 3.0 Hz)	4.20 (d, 2.4 Hz)	3.88 (m)	4.73 (d, 4.2 Hz)
13	5.14 (m)	5.75 (d, 2.4 Hz)	5.20 (dd, 9.6, 2.4 Hz)	5.70 (d, 3.0 Hz)
14	2.02 (m)	2.09 (m)	1.99 (m)	2.08 (m)
	1.88 (m)	1.78 (m)	1.87 (ddt, 13.2, 4.8, 2.4 Hz)	1.22 (m)
15	1.25 (m)	1.88 (m)	1.56 (m)	2.07 (m)
		1.10 (dd, 12.6, 4.2 Hz)	1.40 (m)	1.78 (m)
16	2.59 (m)	2.59 (m)	2.66 (d, 11.4 Hz)	2.74 (d, 11.4 Hz)
	1.80 (m)	1.98 (m)	2.38 (d, 11.4 Hz)	2.38 (d, 11.4 Hz)
17	1.41 (m)	1.41 (m)		
	1.00 (m)	1.00 (m)		
18	1.41 (m)	1.41 (m)		
19	1.78 (m)	1.78 (m)		
20	1.77 (m)	1.77 (m)		
21	3.90 (dd, 14.4, 6.8 Hz)	3.90 (dd, 14.4, 6.8 Hz)		

[a] Recorded at 300 K.
[b] Recorded at 313 K.