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Insect Antifeedants from *Munronia henryi*: Structure of Munroniamide

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A novel A,B-seco-tetranortriterpenoid lactam, named munroniamide (**1**), along with three known ceramides (**2**-**4**), was isolated from the methanolic extract of the whole bodies of *Munronia henryi*. The structure of **1** was established using spectroscopic methods. Compound **2** exhibited significant antifeeding activity, and **1** exhibited moderate activity, whereas **3** and **4** showed negative activity against *Pieris brassicae* L.

KEYWORDS: ***Munronia henryi*; tetranortriterpenoid lactam; ceramides; antifeedants; *Pieris brassicae***

INTRODUCTION

Recently, tetranortriterpenoids (limonoids) have attracted much attention because of the marked insect antifeeding and growth-regulating activity of azadirachtin. Tetranortriterpenoids are diverse and abundant in members of the family Meliaceae. Many papers about tetranortriterpenoids isolated from the family Meliaceae have discussed their roles in antifeeding (*1*−*3*), cytotoxicity (*4*−*6*), ichthyotoxicity (*7*), insect growth inhibition (*8*), inhibition of cell adhesion (*9*, *10*), and larval growth (*11*). The genus *Munronia* Wight (Meliaceae), comprising 13−15 species, is naturally distributed in China, Sri Lanka, India, Indonesia, and The Philippines. No chemical constituents have been published for this genus to the present. Three species of this genus have been found in Yunnan province. *M. henryi* Harms is a low, small semibush, which has been used for the treatment of many diseases such as tuberculosis, colds, indigestion, and sore throat in Chinese traditional medicine (*12*). Moreover, *M. henryi* is also used as a pest control agent in rural areas of Yunnan province.

As part of a program seeking novel antifeeding tetranortriterpenoids from Meliaceae plants (*13*−*18*), we undertook an investigation of *M. henryi*. A novel tetranortriterpenoid lactam, munroniamide (**1**), together with three known ceramides, 1-*O*-*β*-D-glucopyranosyl-(2*S*,3*S*,4*R*,8*Z*)-2-*N*-(2′-hydroxytetracosanoyl)-heptadecasphinga-8-ene (**2**) (*19*), (2*S*,3*S*,4*R*,8*E*)-2-*N*-(2′-hydroxytetracosanoyl)heptadecasphinga-8-ene (**3**) (*20*), and (2*S*,3*R*,4*E*)-2-*N*-(2′-hydroxytetracosanoyl)heptadecasphinga-4-ene (**4**) (*21*), was isolated from whole-plant material of *M. henryi*. The structure of **1** was elucidated on the basis of extensive 1D and 2D NMR experiments. Compounds **1**−**4** were subjected to an antifeedant assay of *Pieris brassicae* L.

MATERIALS AND METHODS

General Experimental Procedures. All of the melting points were obtained on an XRC-1 micromelting apparatus and are uncorrected. Optical rotations were measured with a Horiba SEAP-300 spectropolarimeter. UV spectra were measured with a Shimadzu double-beam 210A spectrophotometer in MeOH solution. IR (KBr) spectra were obtained on a Bio-Rad FTS-135 infrared spectrophotometer. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a Bruker AM-400 and a DRX-500 MHz NMR spectrometer with TMS as internal standard. MS spectral data were obtained on a VG Autospec-3000 spectrometer, 70 eV for EI. Silica gel (200−300 mesh) for column chromatography and GF_{254} for TLC were obtained from the Qindao Marine Chemical Factory, Qindao, People's Republic of China.

Extraction and Isolation. *M. henryi* plants were collected from Xishuangbanna, Yunnan, People's Republic of China, in December 2001, and identified by Prof. J. Y. Cui, Xishuangbanna Botany Garden, Academia Sinica. A voucher specimen (no. 3386) was deposited in the herbarium of the Department of Taxonomy, Kunming Institute of Botany, Academia Sinica, Kunming, People's Republic of China. Air-dried and powdered plant materials (4.5 kg) of *M. henryi* were extracted with MeOH three times at room temperature, and the solvent was evaporated in vacuo. The residue was partitioned in H_2O and extracted with EtOAc three times. The EtOAc extracts were concentrated in vacuo to afford 135 g of residue, which was subjected to column chromatography (CC) on a silica gel, using $CHCl_3/Me_2CO$ (from $CHCl_3$ to $CHCl_3/Me_2CO$ 1:1) as eluent. By combining the fractions with TLC (GF_{254}) monitoring, 11 fractions were obtained. Then, fraction 5 (15 g) was subjected to column chromatography (CC) on silica gel, eluted with $CHCl_3/Me_2CO$ (from 7:3 to 2:1), respectively, to give four subfractions (A−D). Fraction A (5.0 g) was subjected to CC on silica

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Table 1. 1D and 2D NMR Spectral Data of Compound **1**[a]

no.	^{13}C NMR	^{1}H (HMQC)	HMBC	^{1}H–^{1}H COSY	NOESY
1	148.8 d	6.56 (1H, d, 11.7)	H-2, 9, 19	H-2	
2	125.9 d	6.54 (1H, d, 11.7)	H-1	H-1	
3	168.6 s		H-1, 2, 11		
4	87.2 s		H-5, 28, 29		
5	55.0 d	3.36 (1H, dd, 8.8, 4.5)	H-6, 9, 19, 28, 29	H-6α β	H-28
6	33.8 t	2.84 (1H, dd, 17.8, 4.5), 3.24 (1H, dd, 17.8, 8.8)	H-5	H-5	
		3.24 (1H, dd, 17.8, 8.8, H-6a)			
7	175.1 s		H-5, 6, 29		
8	136.9 s		H-9, 30		
9	57.3 d	3.78 (1H, d, 8.1)	H-19, 30	H-11	H-11
10	42.7 s		H-5, 6, 9, 11, 19		
11	80.7 d	4.93 (1H, dd, 10.8, 8.1)	H-9, 12	H-9, 12	H-9, 18
12	75.8 d	6.47 (1H, d, 10.8)	H-9, 11, 18	H-11	H-17, 19
13	45.8 s		H-12, 16, 18		
14	71.5 s		H-9, 18, 30		
15	59.8 d	3.84 (1H, s)	H-16		H-18
16	32.0 t	2.07 (1H, dd, 14.0, 7.3), 2.19 (1H, dd, 14.0, 11.1)	H-15, 17	H-17	
17	39.9 d	3.14 (1H, dd, 10.6, 7.3)	H-15, 18	H-16α β	H-12
18	13.7 q	0.94 (3H, s)	H-12, 17		H-11, 15
19	22.3 q	1.19 (3H, s)	H-1, 5, 9		H-12, 29
20	137.5 s		H-16, 17, 22, 23		
21	170.9 s		H-17, 22, 23		
22	139.5 d	6.74 (1H, s)	H-17, 23		
23	50.9 t	3.86, 3.78 (each 1H, s)	H-22		
28	30.9 q	1.36 (3H, s)	H-29		H-5
29	26.7 q	1.40 (3H, s)	H-28		H-19
30	120.5	5.28, 5.20 (each 1H, s)	H-9		
CH_3CO	170.6 s		H-12, CH_3CO		
			CH_3COO		
	21.2 q	1.96 (3H, s)			
1′	175.3 s		H-23, 2′		
2′	24.6 t	2.48, 2.02 (each 1H, m)	H-3′, NH	H-3′	
3′	42.0 t	3.57 (2H, m)	H-2′, NH	H-2′	
NH		2.47 (1H, m)		NH_2	
NH_2		2.00 (2H, m)		NH	

[a] Chemical shift values δ are in ppm, and coupling constant values J are in Hz; 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 500 MHz for 2D NMR in pyridine-d_5 with TMS as internal standard.

gel, eluted with $CHCl_3/Me_2CO$ (7:3), to give **4** (14 mg). Fraction C (2.2 g) was chromatographed over Sephadex LH-20 eluting with MeOH to afford **3** (26 mg). Fraction 8 was repeatedly subjected to CC on silica gel, eluted with $CHCl_3$/MeOH (12:1), to give **1** (36 mg). Fraction 9 was repeatedly subjected to CC on silica gel, eluted with $CHCl_3$/MeOH (9:1), to give **2** (21 mg).

Munroniamide 1: white powder; mp 338−339 °C; $[\alpha]_D^{27.1}$ -3.75 (*c* 0.27, pyridine); UV (MeOH) λ_{max} (log ϵ) 209 (4.39) nm; IR (KBr) ν_{max} 3443, 2981, 2943, 1731, 1681, 1642, 1466, 1388, 1370, 1271, 1237, 1174, 1060, 1035, 961 cm^{-1}; ^{1}H and ^{13}C NMR spectral data, see **Table 1**; EIMS, *m/z* 597 [M]$^+$ (2), 552 (0.6), 537 (2), 511 (2), 497 (2.5), 478 (3), 425 (1.5), 392 (2.5), 364 (3), 344 (10), 298 (11), 285 (7), 256 (6), 239 (10), 223 (20), 207 (17), 195 (27), 178 (25), 165 (24), 149 (26), 122 (31), 108 (35), 97 (70), 81 (57), 69 (100); HREIMS, *m/z* 597.2670 [M]$^+$ (calcd for $C_{31}H_{39}N_3O_9$ 597.2686, error = 1.6 ppm).

Bioassay. The test compounds were dissolved in acetone (including ∼1% of DMSO for improvement of solubility) at concentrations of 1000 ppm, respectively. Leaf disks of *Brassica oleracea* L. (1.5 cm diameter) were dipped in the test solutions, and the control disks were in acetone (including 1% of DMSO) for 1 s. All of the leaf disks were dried before being presented to the insect. The test insects were third-instar larvae of *P. brassicae* L., which had been deprived of food for 6 h prior to being individually placed in a Petri dish. Five Petri dishes, each containing two larvae and three leaf disks, were used for each sample. After 48 h, the areas eaten were measured by an LI-3000 area-measurement apparatus. The antifeedant rate was calculated from $[(C - T)/C] \times 100\%$, where C and T are control disk areas eaten and treated disk areas eaten, respectively. After 6 days, the mortality of the test insects was calculated.

RESULTS AND DISCUSSION

Compound **1** exhibited a molecular ion peak at *m/z* 597 in its EIMS, which suggested an odd-number nitrogen atom in **1**. It possessed a molecular formula of $C_{31}H_{39}N_3O_9$ as determined by HREIMS, which was supported by the ^{13}C and DEPT NMR spectra. Its UV spectrum exhibited maximum absorption at 209 nm (α,β-unsaturated lactone).The IR spectrum of **1** showed absorption bands for −NH (3443 cm^{-1}), a carbonyl group (1731 cm^{-1}), an amide group (1681 cm^{-1}), and double bonds (1642 cm^{-1}). The ^{13}C NMR and DEPT spectra displayed signals for 31 carbons, namely, 26 skeleton carbons [including 4 tertiary methyl groups, 3 methylenes, 6 methines (2 of which were oxymethines), 4 quaternary carbons, 3 double bonds, and 3 carbonyl groups], an acetyl [δ_C 170.6 (s), 21.2 (q)], and an acyl radical moiety [δ_C 175.0 (s), 42.0 (t), 24.6 (t)]. The ^{1}H NMR spectrum showed five methyl singlets at δ_H 0.93, 1.19, 1.36, 1.40 (tertiary C-methyl groups), and 1.96 (acetate methyl) and bisubstituting olefinic signals at δ_H 5.28 and 5.20 (each 1H, s). All of these data suggested that **1** had a tetranortriterpenoid skeleton with a double bond between C-8 and C-30 (*17*, *22*−*24*).

The ^{13}C and ^{1}H NMR spectra showed an oxirane [δ_C 71.5 (s), 59.8 (d), δ_H 3.84 (1H, s)], which was assigned to be 14,15-epoxy as for other analogous tetranortriterpenoids (*4*, *14*, *24*). This was further supported by the HMBC spectrum (**Table 1**). A NOE interaction between δ_H 3.84 (1H, s, H-15) and δ_H 0.94 (3H, s, H-18) in the NOESY spectrum indicated 14β,15β-substituents. The olefinic carbons δ_C 120.5 (t) and 136.9 (s) and corresponding to protons δ_H 5.28 and 5.20 (each 1H, s) suggested an olefinic linkage between C-8 and C-30. This was confirmed by the HMBC spectrum, which showed correlations of δ_H 5.28 and 5.20 (each 1H, s, H-30) with δ_C 57.3 (d, C-9) and 71.5 (s, C-14). An acetoxyl was placed at C-12 by the

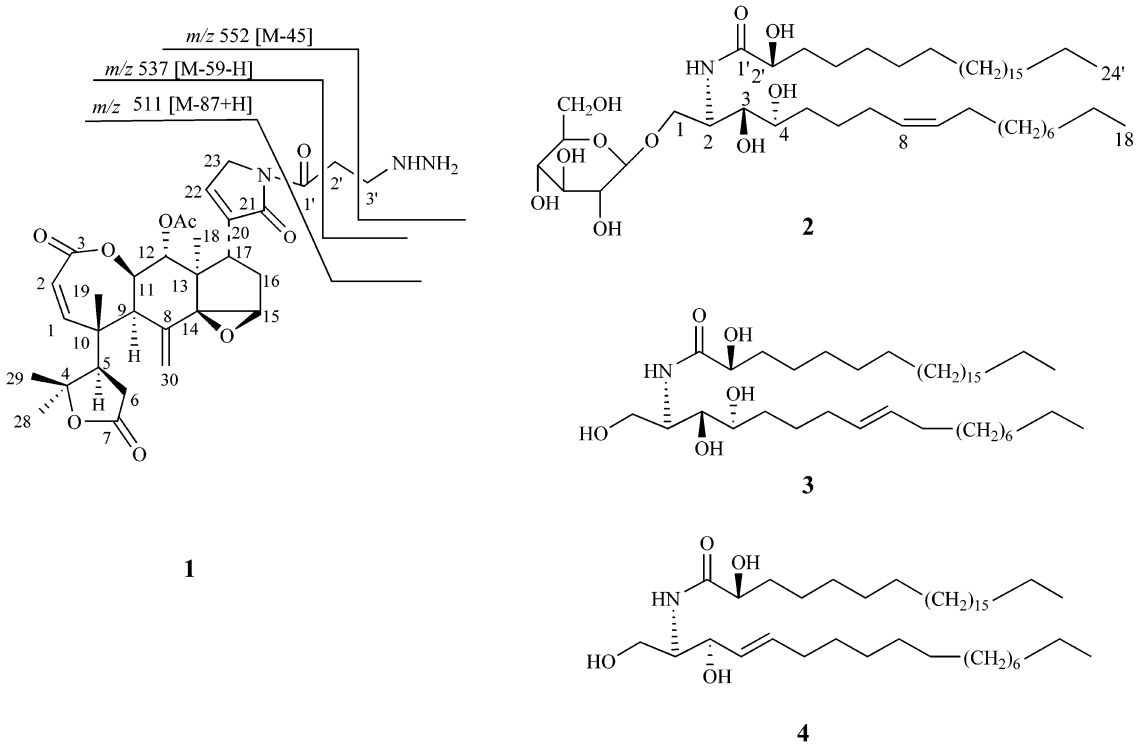

Figure 1. Structures of compounds **1**–**4**.

observation of cross-peaks between δ_C 170.6 (s, CH_3COO) and δ_H 6.47 (1H, d, $J = 10.8$ Hz, H-12) and δ_H 1.96 (3H, s, CH_3-COO), respectively, in the HMBC spectrum. In the $^1H-^1H$ COSY spectrum, the correlation between H-12 and δ_H 4.93 (1H, dd, $J = 10.8$, 8.1 Hz) was assigned to H-11. H-11 showed correlations with H-12 and δ_H 3.78 (1H, d, $J = 8.1$ Hz), which was assigned H-9. The assignment was further supported by the HMBC spectrum (**Table 1**). In the NOESY spectrum, NOE interactions between H-12 and H-17 and between H-12 and H-19 placed the acetyl at the 12α-position, whereas NOE interactions between H-11 and H-18 and between H-11 and H-9 suggested an 11*β*-substituent.

The carbon signals at δ_C 125.0 (d), 148.2 (d), and 167.8 (s) in the ^{13}C NMR spectrum of **1** and corresponding proton signals at δ_H 6.56 (1H, d, $J = 11.7$ Hz) and 6.54 (1H, d, $J = 11.7$ Hz) in the ^1H NMR spectrum were typical signals for an α,*β*-unsaturated lactone moiety in the A ring (*15*, *23*, *25*). These doublet signals were assigned to H-1 and H-2, respectively. In the HMBC spectrum, the correlations of δ_C 167.8 (s) with H-11, H-1, and H-2, respectively, allowed the assignment of δ_C 167.8 (s, C-3) and indicated a seven-membered ring lactone between C-3 and C-11 in compound **1**. The signal at δ_C 86.5 (s) was attributed to C-4 because the HMBC spectrum showed correlations of δ_C 86.5 (s) with δ_H 1.34 (3H, s, H-28) and 1.37 (3H, s, H-29). The B ring has been cleaved to form a *γ*-lactone between C-7 and C-4 on the basis of the observation of a weak cross-peak between H-29 and δ_C 174.4 (s, C-7) in the HMBC spectrum. NOE correlations of H-5 with H-28 and of H-19 with H-29 indicated their *cis*-relationships.

In the HMBC spectrum, the correlations of δ_H 3.14 (1H, dd, $J = 10.6$, 7.3 Hz, H-17) with δ_C 136.9 (s), 170.9 (s), and 139.5 (d), and of δ_H 6.74 (1H, s) with δ_C 136.9 (s), 170.9 (s), and 50.9 (t) suggested that these signals [δ_C 136.9 (s), 170.9 (s), 139.5 (d), and 50.9 (t)] as a unit were attached to C-17. On the basis of a comparison of the ^{13}C NMR spectral data with those of tetranortriterpenoids in the literature carrying a 23-hydroxy-20(22)-ene-21,23-*γ*-lactone unit (*23*, *24*, *26*), a 20(22)-ene-21,23-*γ*-lactone mimic unit attached to C-17 in **1** [δ_C 136.9 (s, C-20), 170.9 (s, C-21), 139.5 (d, C-22), and 50.9 (t, C-23)] was proposed. C-23 was shifted upfield ∼20 ppm compared to normal oxymethylene. The data suggest a 20(22)-ene-21,23-*γ*-lactam unit rather than a 20(22)-ene-21,23-*γ*-lactone unit attached to C-17 in **1**, which is consistent with the molecular formula of the compound. The HMBC spectrum showing correlations of δ_H 3.86 and 3.78 (each 1H, s, H-23) with C-20, C-21, C-22, and C-1′ [δ_C 175.3 (s)] and its molecular formula supported the inference and suggested a substituent with two nitrogen atoms attached to the skeleton nitrogen.

The HMBC spectrum showing correlations of δ_H 2.48 and 2.02 (each 1 H, m, H-2′) with δ_C 175.3 (s, C-1′) and 42.0 (t, C-3′) and of δ_H 3.57 (2H, m, H-3′) with δ_C 24.6 (t, C-2′) and 175.3 (s, C-1′) and the $^1H-^1H$ COSY spectrum with a correlation of δ_H 2.48 (1H, m, H-2′) with δ_H 3.57 (2H, m, H-3′) indicated a $-CH_2CH_2-$ moiety attached to C-1′. The mass fragments at *m/z* 522 [M − 45], 537 [M − 59 − H], and 511 [M − 87 + H] in the EIMS suggested the loss of $-CH_2NHNH_2$, $-CH_3CH_2NHNH_2$, and $-COCH_2CH_2NHNH$ fragments, respectively. The correlation of δ_H 2.47 (1H, m, NH) with δ_C 42.0 (t, C-3′) and 24.6 (t, C-2′) in the HMBC spectrum and the correlation of δ_H 2.47 (1H, m, NH) with δ_H 2.00 (2H, m, NH_2) in the $^1H-^1H$ COSY spectrum supported the existence of a $-COCH_2CH_2NHNH_2$ substituting group linked to the nitrogen. On the basis of the above evidence, the structure of **1** was elucidated as shown (**Figure 1**), named munroniamide. All signals were assigned in **Table 1** on the basis of an analysis of 2D NMR data. The side chain of **1**, which was similar to ceramide derivatives, was unprecedented in tetranortriterpenoids.

Meanwhile, three ceramides (**2**−**4**) co-occurred in *M. henryi*. Their structures were identified by comparison with literature values (*19*−*21*). Ceramides are distributed ubiquitously in the members of eukaryotic cells (*27*), where they were previously thought to play a structural role. Marine organisms are a rich source of ceramides. Ceramides have also been isolated from plants, fungi, insects, and human skin (*28*−*31*). To our

Table 2. Antifeedant Activity of Compounds **1**–**4** Bioassayed with *P. brassicae* L.

compound	AR[a] (100%)	mortality (100%)
munroniamide (**1**)	27.6	10
1-*O*-*β*-D-glucopyranosyl-(2*S*,3*S*,4*R*,8*Z*)-2-*N*-(2′-hydroxytetracosanoyl)heptadeca-sphinga-8-ene (**2**)	62.0	50
(2*S*,3*S*,4*R*,8*E*)-2-*N*-(2′-hydroxytetracosanoyl)-heptadecasphinga-8-ene (**3**)	3.0	0
(2*S*,3*R*,4*E*)-2-*N*-(2′-hydroxytetracosanoyl)-heptadecasphinga-4-ene (**4**)	0	0
azadirachtin	99.5	100

[a] AR represents the antifeeding rate calculated from AR = $[(C - T)/C] \times 100\%$. *C* and *T* represent the areas eaten by the larvae of the control and treatment disks, respectively.

knowledge, no ceramides have previously been reported from the family Meliacea, except for a known ceramide from *Cipadessa baccifera* reported by our laboratory.

The antifeedant activities of compounds **1**−**4** were tested by the conventional leaf disk method against the larvae of *P. brassicae* L. The results indicated that **2** had significant activity by lower than that of the model compound azadirachtin (**Table 2**).

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