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Zizimauritic acids A–C, three novel nortriterpenes from *Ziziphus mauritiana*

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ABSTRACT

Zizimauritic acids A–C (**1–3**), three novel nortriterpenes with a unique A-nor-E-seco spiro-lactone ceanothane-type triterpene skeleton, together with 3 known triterpenes ceanothenic acid (**4**), betulinic acid (**5**), and ceanothic acid (**6**), were isolated from the roots of *Ziziphus mauritiana*. Compounds **1–4** showed cytotoxicities with the IC_{50} values ranging from 5.05 to 11.94 μg/ml, and compounds **1** and **3** showed an inhibitory effect on the growth of *Staphylococcus aureus* with the IC_{50} values 2.17 and 12.79 μg/ml. A plausible biosynthetic pathway of compounds **1-3** was proposed.

The genus *Ziziphus* (Rhamnaceae) is widespread in tropical and subtropical area of the world and comprises about 170 species and 12 variants. They are important economic plants for their edible fruits and medicinal uses, and some of them are nectar plants or parasitic plants for lac insect.[1–3] *Ziziphus mauritiana* Lam. is distributed and cropped in low-latitudes of Asia, Africa and Australia. Its seeds were firstly cited in '*Dian-Nan-Ben-Cao*', which was the first monograph about herbal medicines in Yunnan province since Ming dynasty (1436 AD), and used as a substitute for the traditional Chinese medicine 'Suan-Zao-Ren' (seeds of *Ziziphus jujuba* var. *spinosae*) to treat insomnia. Futhermore, its barks and roots were used as anti-inflamatory and anti-infection agents for burn, scald and diarrhea in Yunnan province.[1] Previous chemical studies of this species dealt with the isolation of 11 new cyclopeptide alkaloids (mauritines A–F, H, J–M) together with 9 known ones,[4–10] beside lupane type triterpenes,[11,12] flavonoids,[13] steroids,[11,14] and aliphatic compounds.[12,15–17] It has been shown that lupane-type and ceanothane-type triterpenoids displayed antitumor and anti-HIV activities, especially betulinic acid and ceanothic acid.[18,19] As one part of our research for active principles of this plant, herein we report the isolation and structure elucidation of three A-nor-E-seco spiro-lactone ceanothane triterpenes, zizimauritic acids A–C (**1–3**), together with three known compounds, ceanothenic acid (**4**), betulinic acid (**5**) and ceanothic acid (**6**). Their cytotoxicity against three cancer cell lines as well as antimicrobial activity against *Staphylococcus aureus* (SA) and *Candida albicans* (CA) were evaluated. We also described a plausible biosynthetic pathway of compounds **1–3**.

The roots of *Z. mauritiana* were collected from Mengla, Yunnan Province, PRC, in October, 2008. The material was identified by associate Professor Shao-Tian Chen at Kunming Institute of Botany. The voucher specimen (No. 0864748) has been deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences. Air-dried and powdered roots (18 kg) of *Z. mauritiana* were extracted with 90% methanol to give a crude extract. The crude extract (1.5 kg) was acidified and partitioned with EtOAc to afford the EtOAc fraction.[20] Then the latter was subjected to repeated silica gel column chromatography (CC) and HPLC to afford three new nortriterpenes, zizimauritic acid A (**1**, 18 mg), B (**2**, 28 mg) and C (**3**, 20 mg), together with three known compounds, ceanothenic acid (**4**, 90 mg),[21] betulinic acid (**5**, 70 g),[22] and ceanothic acid (**6**, 120 g).[23] *Z. mauritana* contains high contents of compounds **5** and **6**, which could be used as a resource plant. The known compounds **4**–**6** were identified by comparison with the reported NMR data in the literatures.

Zizimauritic acid A (**1**)[24] was isolated as a colorless gum. Its molecular formula was determined as $C_{30}H_{44}O_5$ from the HRTOF-ESI-MS spectrum, which exhibited a pseudomolecular ion peak $[M-H]^-$ at *m/z* 483.3100 (calcd for $[C_{30}H_{44}O_5-H]^-$, 483.3110), indicating 9° of unsaturation. The IR spectrum showed absorption bands of hydroxyl (3421 cm^{-1}), carboxyl and ester carbonyl (1770, 1722 cm^{-1}) groups. The ^{13}C NMR spectrum (Table 1) showed the characteristic signals of seven methyls (with one methoxyl included), seven methylenes, eight methines [among which one acetal δ_C 103.64 (C-21) and three olefinic carbons δ_C 140.92 (C-2),

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Table 1
^{1}H and ^{13}C NMR data for zizimauritic acids A–C (**1–3**) (Pyridine-d_5)

No.	1		2		3	
	δ_C [a]	δ_H [b]	δ_C [a]	δ_H [b]	δ_C [c]	δ_H [b]
2	140.92	6.02 (d, 5.6)	140.92	6.03 (d, 5.6)	141.02/141.02	6.04 (d, 5.5)/6.04 (d, 5.5)
3	139.28	5.42 (d, 5.6)	139.30	5.42 (d, 5.6)	139.33/139.33	5.43 (d, 5.5)/5.43 (d, 5.5)
4	44.82		44.82		44.89/44.89	
5	63.07	1.44 (m)	63.07	1.44 (m)	63.13/63.13	1.46 (m)/1.46 (m)
6α	17.89	1.48 (m)	17.88	1.48 (m)	17.94/17.94	1.50 (m)/1.50 (m)
6β		1.44 (m)		1.44 (m)		1.47 (m)/1.47 (m)
7α	37.33	2.42 (m)	37.37	2.39 (overlap)	37.41/37.45	2.42 (m)/2.42 (m)
7β		1.79 (d, 13.1)		1.79 (d, 13.0)		1.81 (d, 13.1)/1.81 (d, 13.1)
8	41.98		41.94		42.05/42.00	
9	49.06	2.22 (overlap)	48.99	2.22 (overlap)	49.47/49.02	2.25 (overlap)
10	51.01		51.01		51.08/51.08	
11α	23.52	1.65 (m)	23.51	1.65 (m)	23.60/23.60	1.66 (overlap)/1.66 (overlap)
11β		1.71 (m)		1.71 (m)		1.74 (m)/1.74 (m)
12α	26.75	2.43 (m)	26.63	2.43 (m)	26.86/26.72	2.47 (m)/2.47 (m)
12β		1.76 (m)		1.71 (m)		1.78 (m)/1.78 (m)
13	37.66	2.93 (td like, 11.7, 4.1)	37.62	2.77 (td like, 12.7, 4.1)	37.87/37.78	3.01 (overlap)/2.82 (t like, 10.9)
14	58.17		58.04		58.32/58.14	
15α	25.36	2.22 (overlap)	25.25	2.20 (m)	25.48/25.48	2.24 (overlap)
15β		2.16 (td, 13.3, 3.1)		2.36 (overlap)		2.19 (m)
16α	34.32	2.00 (m)	34.84	2.03 (td like, 13.8, 3.1)	33.89/35.23	2.05 (m)/2.15 (m)
16β		2.11 (br d, 14.6)		2.36 (overlap)		2.21 (overlap)/2.58 (br d, 16.2)
17	48.48		46.27		49.14/47.29	
18	44.73	2.88 (t like, 10.6)	46.04	2.91 (t like, 10.8)	44.71/46.40	2.93 (t like, 10.6)/2.99 (t like, 10.8)
19	125.42	5.17 (br d, 10.1)	125.22	5.04 (br d, 10.6)	125.80/125.68	5.27 (br d, 10.0)/5.12 (br d, 10.5)
20	135.66		135.88		135.39/135.39	
21	103.64	5.45 (t like, 6.3)	103.35	5.22 (br d, 5.3)	98.02/97.46	6.24 (br s)/6.02 (br d, 3.5)
22α	42.28	2.24 (dd, 13.2, 6.9)	42.73	2.36 (overlap)	44.49/44.71	2.50 (overlap)/2.50 (overlap)
22β		1.97 (dd, 13.2, 5.9)		1.75 (d, 15.0)		2.10(m)/1.96 (d, 13.3)
23	29.71	0.88 (s)	29.71	0.88 (s)	29.78/29.78	0.90 (s)/0.90 (s)
24	21.68	0.90 (s)	21.68	0.90 (s)	21.75/21.75	0.91 (s)/0.91 (s)
25	20.23	1.01 (s)	20.22	1.01 (s)	20.33/20.33	1.02 (s)/1.02 (s)
26	18.39	1.29 (s)	18.36	1.30 (s)	18.48/18.44	1.32 (s)/1.32 (s)
27	177.96		177.99		178.08 [d]/178.14	
28	177.47		179.07		178.02 [d]/179.75	
29	25.79	1.60 (s)	25.80	1.66 (s)	25.89/25.81	1.60 (s)/1.69 (s)
30	18.86	1.59 (s)	18.92	1.65 (s)	18.92/18.99	1.53 (s)/1.66 (s)
OMe	57.29	3.39 (s)	56.63	3.35 (s)		

[a] ^{13}C NMR data were recorded at 125 MHz.
[b] ^{1}H NMR data were recorded at 500 MHz.
[c] ^{13}C NMR data were recorded at 100 MHz.
[d] Interchangeable signals.

139.28 (C-3), 125.42 (C-19)] and eight quaternary carbons [including one olefinic carbon δ_C 135.66 (C-20), one carboxyl δ_C 177.96 (C-27) and one ester carbonyl δ_C 177.47 (C-28)], revealing five rings in the structure of **1**. These data corroborated with the ^{1}H NMR spec-

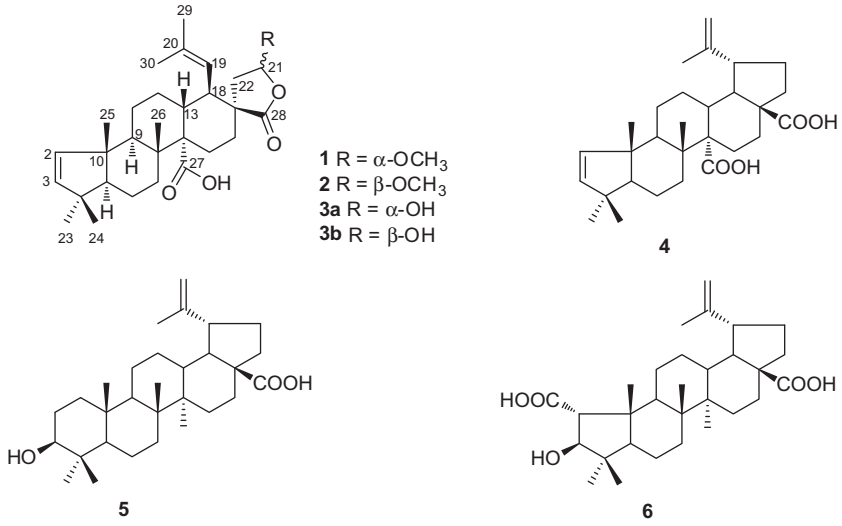


Figure 1. Structures of compounds **1–6** isolated from *Z. mauritiana*.

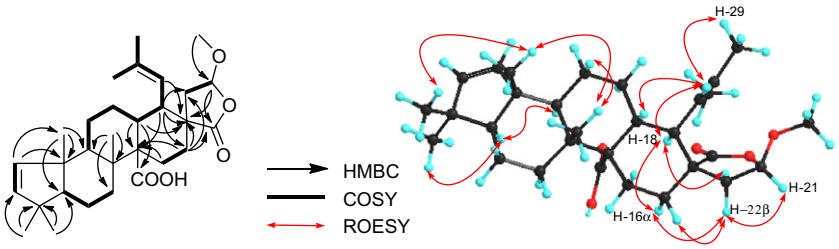
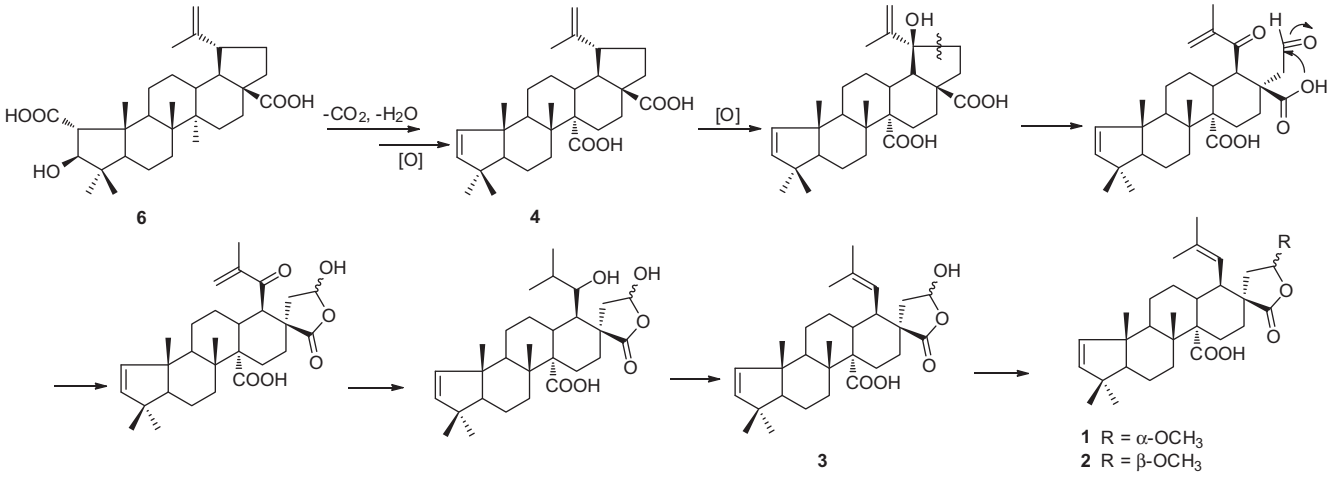


Figure 2. Key COSY, HMBC and ROESY correlations for zizimauritic acid A (**1**).



Scheme 1. Plausible biosynthetic pathway of **1–3.**

Table 2
IC_{50} values (μg/ml) for cytotoxicities on three cancer cell lines, antibacterial and antifungal activities

Compounds	A549	BGC-823	Hela	SA	CA
1	9.37	8.80	6.06	2.17	>10
2	5.05	6.24	5.36	>20	>10
3	11.94	10.06	9.25	12.79	>10
4	—	>10	7.55	>20	>10
Taxol	0.02	0.01	0.38	—	—
Ampicillin				0.04	
Miconazole nitrate					0.16

trum (Table 1) which displayed seven single peaks of methyl group at δ_H 0.88, 0.90, 1.01, 1.29, 1.59, 1.60, 3.39 (methoxyl), one acetal proton at δ_H 5.45 (t like, 6.3 Hz, 1H, H-21) and three olefinic protons at δ_H 6.02 (d, 5.6 Hz, 1H, H-2), 5.42 (d, 5.6 Hz, 1H, H-3), 5.17 (br d, 10.1 Hz, 1H, H-19). The comparison of 1D and 2D NMR data of compound **1** with those of ceanothenic acid (**4**) indicated that both compounds have similar fragments in ring A–C, suggesting the presence of an A-nor ceanothane triterpene skeleton.

The ^1H–^1H COSY spectrum (Fig. 2) clearly showed an allylic coupling with cross-peaks between two geminal methyls (H_3-29, δ_H 1.60, s and H_3-30, δ_H 1.59, s) and the olefinic proton (H-19); H-19 and H-18 (δ_H 2.88, t like, 10.6 Hz); H-18 and H-13 (δ_H 2.93, td like, 11.7, 4.1). Further pertinent cross-peaks were observed between H-21 and H-22, H-15 and H-16. In the HMBC spectrum (Fig. 2), the key correlations were observed from H-methoxyl to C-21; H-21 to C-17 and C-28; H-18 to C-14, C-16, C-17 and C-22; H-16 to C-14, C-17, C-22 and C-28; and H-13 to C-14, C-15 and C-27. On the basis of above data (COSY and HMBC), the planar structure was elucidated as 19,21-seco-19,20-ene-21,28-lactone ceanothenic acid, forming a spiro γ-methoxyl-γ-lactone at C-17. The absolute configuration of **1** was determined by ROESY as shown in Figure 2. The ROESY correlations of H-22α with H-18, H-22β with H-16α, H-16β and H-21, H-16α with H-18 revealed that the plane of spiro γ-methoxyl-γ-lactone is vertical to that of ring D, and H-21 is at a β orientation. Therefore, compound **1** was characterized as 19,21-seco-19,20-ene-21,28-lactone-21-*O*-α-methoxyl ceanothenic acid and named zizimauritic acid A (Fig. 1).

Zizimauritic acid B (**2**)[25] was also isolated as a colorless gum. Its molecular formula was determined by the HRTOF-ESI-MS spectrum to be $C_{30}H_{44}O_5$, indicating that it is a positional isomer of **1**. This was confirmed by the ^{13}C NMR and ^1H NMR spectra (Table 1) which showed very similar signals. The main differences were observed in the ^{13}C NMR spectrum of **2** on the resonance signals at δ_C: 179.07 (C-28, Δ 1.60), 103.35 (C-21, Δ −0.29), 56.63 (OMe, Δ −0.66), 46.27 (C-17, Δ −2.21), 46.04 (C-18, Δ1.31), 42.73 (C-22, Δ0.45), 34.84 (C-16, Δ0.52), and in its ^1H NMR spectrum on the signals at δ_H: 5.22 (br d, 5.3 Hz, 1H, H-21), 5.04 (br d, 10.6 Hz, 1H, H-19), 2.91 (t like, 10.8 Hz, 1H, H-18), 2.77 (td like, 12.7, 4.1 Hz, 1H, H-13). Such observations were attributable to the difference of the H-21 orientation in both compounds. This assertion was confirmed by the COSY, HMBC and ROESY spectra. Thus, the structure of **2** was established and as shown in Figure 1.

Zizimauritic acid C (**3**)[26] was obtained as an inseparable mixture of a pair of epimers **3a**/**3b** with a ratio of ca. 1:1.6. The HRTOF-ESI-MS spectra established its molecular formula as $C_{29}H_{42}O_5$. The ^1H and ^{13}C NMR spectra showed two sets of resonance signals of nor-triterpene which are superimposable to **1** and **2**, except for the absence of the methoxyl group and appearance of one hydroxyl group at C-21. The complete assignment of ^1H and ^{13}C NMR were elucidated by the extensive 2D-NMR analysis. Thus, the structures of **3a/3b** were confirmed as shown in Figure 1.

A plausible biosynthetic pathway of compounds **1–3** is proposed as shown in Scheme 1. The pathway is involved in the precursor ceanothic acid (**6**) by decarboxylation and dehydration at the ring A, and oxygenation at C-27 to give ceanothenic acid (**4**). Subsequent oxidative cleavage of the C(19)–C(21) bond lead to give a 19-ketone and 21-aldehyde fragment, then the hydroxyl of C-28 carboxyl by a nucleophilic reaction with the carbonyl of aldehyde (C-21) form the spiro γ-hydroxyl-γ-lactone structure. In the last step, hydrogenation and dehydration of C-19 afford zizimauritic acid C (**3a/3b**), which via methyl esterification at the hemiacetal produce zizimauritic acid A (**1**) and B (**2**). This pathway route is unlike that of radermsinin A,[27] which has a similar structure except in ring A and C-27 carboxyl group, and was thought to be derived from the precursor H-18α oleanane triterpene.

Compounds **1–6** were evaluated for their cytotoxicity on three cancer cell lines (A549, BGC-823 and Hela) and for their antimicrobial activity against SA and CA.[28] All these compounds did not show any inhibitory activities against CA and compounds **5** and **6** were also inactive against the three cancer cell lines and SA (Table 2). Compounds **1–4** exhibited cytotoxicity against the three cancer cell lines with the IC_{50} values ranging from 5.05 to 11.94 μg/ml; the highest activity were recorded with compound **2** with the IC_{50} values of 5.05 (A549), 5.36 (Hela) and 6.24 (BGC-823) μg/ml. Compounds **1** and **3** showed an inhibitory effect on the growth of SA. The activity of **1** with an IC_{50} of 2.17 μg/ml was particularly noteworthy, while compound **2**, which is only the conformation difference of methoxyl group in the C-21 position, was inactive against SA at a concentration of 20 μg/ml.

Acknowledgments

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Supplementary data

Supplementary data (the experimental section and 1D, 2D NMR spectra and MS, IR, $[\alpha]_D$, UV, CD data of compounds **1–3** are supplied) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.074.

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20. Air-dried and powdered roots (18 kg) of *Z. mauritiana* were extracted for 4 times with 90% methanol under reflux, 3 h each time, and concentrated in vacuo. The crude extract (1.5 kg) was acidified by 1% HCl and partitioned with EtOAc to afford a EtOAc fraction. The EtOAc soluble fraction was subjected to silica gel CC and eluted with a stepwise gradient of petroleum ether/acetone to obtain seven fractions (A–G). Fraction B was further chromatographed over silica gel CC using petroleum ether/acetone in a ratio of 4:1 to afford four sub-fractions (B1–B4), and ceanothenic acid (**4**, 90 mg) was crystallized from the sub-fraction B2. The fractions C–F were pooled on the basis of their TLC profiles and subjected to repeated silica gel CC using a gradient of chloroform/methanol (50:1/30:1) to obtain a large amount of betulinic acid (**5**, 70 g) and ceanothic acid (**6**, 120 g). Then the compounds **5** and **6** free sub-fractions were combined and rechromatographed over silica gel CC, eluted with chloroform/methanol (50:1/30:1) to afford four sub-fractions (C-F1–C-F4). Sub-fraction C-F2 was finally purified by preparative HPLC, eluted with 85% MeCN/H_2O contained 0.5‰ TFA to yield compounds **1** (18 mg), **2** (28 mg), **3** (20 mg).
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24. *Zizimauritic acid A* (***1***): colorless gum; $[\alpha]_D^{13}$ +145.0 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.88) nm; CD (*c* 0.14, MeOH) λ (Δε) 210 (−0.46), 226 (1.82) nm; IR (KBr) ν_{max} 3421, 2949, 2866, 1770, 1722, 1687, 1641, 1452 cm^{-1}; ^1H NMR (500 MHz, Pyridine-d_5) and ^{13}C NMR (125 MHz, Pyridine-d_5), see Table 1; HRESIMS *m*/*z* 483.3100 $[M-H]^-$ (calcd for $C_{30}H_{43}O_5$, 483.3110).
25. *Zizimauritic acid B* (***2***): colorless gum; $[\alpha]_D^{14}$ +9.3 (*c* 0.14, MeOH); UV (MeOH) λ_{max} (log ε) 201 (3.80) nm; CD (*c* 0.14, MeOH) λ (Δε) 212 (−0.77), 223 (0.36) nm; IR (KBr) ν_{max} 3426, 2961, 2930, 2868, 1769, 1739, 1721, 1689, 1640, 1451, 1365 cm^{-1}; ^1H NMR (500 MHz, Pyridine-d_5) and ^{13}C NMR (125 MHz, Pyridine-d_5), see Table 1; HRESIMS *m*/*z* 483.3114 $[M-H]^-$ (calcd for $C_{30}H_{43}O_5$, 483.3110).
26. *Zizimauritic acid C* (***3a***/***3b***): colorless gum; $[\alpha]_D^{16}$ +38.8 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 201 (3.89), 254 (2.98) nm; CD (*c* 0.21, MeOH) λ (Δε) 211 (−0.54), 224 (0.83) nm; ^1H NMR (500 MHz, Pyridine-d_5) and ^{13}C NMR (100 MHz, Pyridine-d_5), see Table 1; HRESIMS *m*/*z* 469.2963 $[M-H]^-$ (calcd for $C_{29}H_{41}O_5$, 469.2953).
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